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MEDICINAL AND AROMATIC PLANTS FROM THE WILD FLORA OF DOBROGEA (ROMANIA)

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FOREWORD

The monograph, entitled *Medicinal and Aromatic Plants from the Wild Flora of Dobrogea* (Romania), is meant for specialists in the domain, for the students and PhD students in the fields of Biology, Pharmacy, Forestry, Agriculture or Food Industry, as well as for other persons interested to know more aspects referring to the botanical description, traditional use, chemical composition, pharmacological activity, recommendations, and possible adverse reactions when using these plants.

This monograph is the first work published in Romania, exclusively dedicated to the medicinal and aromatic plant species from the wild flora of Dobrogea, including the Danube Delta Biosphere Reserve, being achieved via a collaboration of specialists with remarkable results in the field. The work describes over 70 medicinal and aromatic plant species illustrated by original photos included in an annex of this work.

The authors of this monograph critically analyzed, synthesized and put up to date information from the specialty literature, inserting with scientific accuracy the original contributions, referring to bringing up to date the concept of the identified species diversity in the studied areal, and also new aspects that aim the chorology or the presence in certain habitats, as well as appreciations on the phenophases of the described species.

The expertise of the authors is sustained by national and international recognition, as a result of publishing scientific articles in prestigious journals, by the participation in many scientific meetings and the presence in the board of some congresses or scientific societies in Romania and abroad.

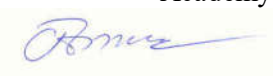
As the authors coordinate research projects with national and international financing, they are engaged in the finalization of these scientific researches and in the formation of young researchers ready to approach similar themes.

The monograph meets the present demands by multidisciplinary and polyvalent research directions that are considered to be current and of perspective in Pharmaceutical Botany, Pharmacognosy and Biochemistry, which are very useful in human and veterinary pathology.

Furthermore, by publishing this monograph, aspects less known in literature are completed, presenting specialists` present day researches from countries with tradition in the study of medicinal and aromatic plant diversity, plants from the spontaneous flora that could be transferred into cultivation by classical and modern technologies.

By the complexity of the approached problems, this work meets the demands of the special PhD training of the young PhD students in the field of Pharmacy as well as those of the ecosystem services and the sustainable use of natural resources.
Concluding, we recommend the including into the editorial plan and the acceptance for publication.

Professor univ. dr. Cătălin TĂNASE, corresponding member of the Romanian Academy



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The book, **entitled *Medicinal and Aromatic Plants from the Wild Flora of Dobrogea* (Romania)**, conceived as a result of studies that have been performed over a period of six years by a larger group of researchers, was elaborated in the framework of some research projects aiming to assess and characterize (biologically and chemically) the most important medicinal and aromatic plant species of Dobrogea (Romania), their use in traditional medicine, and their potential capitalization in modern medicine, respectively.

Along with Romanians, Dobrogea is inhabited by several ethnic groups such as Turks, Tartars, Lippovans, Russians, Greeks, Bulgarians, Italians and Aromanians, a fact that renders the region a cultural diversity also reflected in local ethnomedicine. As a result of the discussions with local people, important data on local ethnomedicine were collected, data that represented a starting point in the selection of the species to be investigated and to, further on, achieve the writing of the book.

Using these medicinal and aromatic plants of the studied area, one took into account the fact that the area comprises The Danube Delta Biosphere Reserve which is in a regime of a special biodiversity conservation. Out of the multitude of identified medicinal and aromatic plants, the authors made a selection of the most used ones, some of them being specific to Dobrogea, others being specific to the country and even to Europe.

As such, in this work, the authors present over 70 species; each of the species has a short monograph comprising aspects as: botanical description, traditional and present use, chemical composition and known pharmacological action (due to known literature).

This monograph collection has over 200 pages, with over 700 up-to-date bibliographical references, original photos taken in the investigated areas. This volume represents, as to our knowledge, the first data collection of this kind from the Dobrogea region, presented in a comprising enough monographic manner to become a reference bibliographic source for biologists and other specialists (pharmacists, doctors, chemists) interested by the subject. I must add, here, that from Valeriu Butura's 1979 Romanian Ethnobotanical Encyclopedia (Editura Stiintifica si Enciclopedica) such a work has not been written in the last 4 decades.

It is praiseworthy that the authors took their time to present an English version of the text so that it will be accessible to a great number of European specialists interested in the matter.

The text is clear, although scientific, it is easily to be followed and the photos taken by Dr. Elvira Gille are not only original but also of good quality.

Prof. Dr. Ursula Stănescu,
Member of the Romanian Academy of Medical Sciences

PREFACE

This monograph, **entitled *Medicinal and Aromatic Plants from the Wild Flora of Dobrogea* (Romania)**, is the result of the research activities performed over a period of six years within several research project implemented by The National Institute of Research and Development for Biological Sciences Bucharest/ „Stejarul" Biological Research Centre Piatra Neamt.

The information included in the present work is represented by the scientific data obtained following the ethnopharmaceutical surveys conducted in Dobrogea (including the Danube Delta area) and the developed experiments within the research projects (published and unpublished data), and also following the in depth analysis of the available scientific literature.

The starting point in the achievement of this work was the collection of the ethnopharmaceutical data from local population characterized by a high ethnic and cultural diversity (Dobrogea is inhabited by Romanians, Turks, Tartars, Lippovans, Russians, Greeks, Bulgarians, Italians and Aromanians), also reflected in the local ethnomedicine. The locals provided data on the medicinal and aromatic plants known in the studied area, including collection sites, and their use in specific diseases.

The special conservation status of The Danube Delta Biosphere Reserve was also taken into consideration when conceiving this monograph.

This work presents a selection of over 70 medicinal and aromatic plant species, some of them widely used in the traditional and modern medicine, and others less known and used. Each species has a short and comprehensive monograph comprising important aspects regarding the botanical description, traditional and current uses, chemical composition, pharmacological activities, and also precautions and adverse reactions on use.

This monograph collection has over 200 pages, with over 700 up-to-date bibliographical references and original photos of the selected species.

Due to the comprehensive nature of this work, the authors consider it as an important tool for specialists in many research fields such as Biology, Pharmacy, Agriculture and Food Industry, and also for students. Furthermore, it presents valuable information for the sustainable capitalization of the selected species, also through the transfer of the valuable species into culture.

The authors kindly thank ***Dr. Gheorghe COLDEA, corresponding member of the Romanian Academy*** for his special guidance in the identification of the selected medicinal and aromatic plant species.

The authors.

CONTENTS

Achillea clypeolata Sibth. et Sm. (yarrow, „coada șoricelului"), Asteraceae family

Syn. *Achillea alexandri-borzae* Prodán, *A. borzana* Prodán (Sarbu *et al.,* 2013).

Officinal products: flowering tops (similar with other *Achillea* species).

Botanical description

A. clypeolata is a perennial species, 20-60 cm high, covered with a compact, homogeneous, white-gray indumentum. Leaves are 2-3 cm wide, double penta-sectate. Var. *clypeolata* has 3.5-4 mm long anthodia and ligules of ¼ of the length of the anthodia. It blooms from July to August (Sarbu *et al*., 2013).

Distribution and habitat: through arid coastal meadows, rare, in the steppe and forest-steppe areas. *Achillea clypeolata* var. *clypeolata* is spread in Constanta and Tulcea counties (Sarbu *et al.,* 2013). In Dobrogea, the species is also found in the Danube Delta area (Dolosman, including Iancina Cape) (Doroftei *et al*., 2011).

Harvesting period: in full flowering (similar with other *Achillea* species), from July to August.

Traditional uses

Infusions from the aerial parts of *Achillea* species are used in Turkish folk medicine for their diuretic, emmenagogue and wound healing properties, against abdominal pain, diarrhoea and flatulence (Konyalioglu & Karamenderes, 2005). Ethnobotanical data also present the use of *Achillea* species as tonic, sedative, carminative, against inflammation, gastrointestinal disorders, hemorrhoids, hay fever (Mohammadhosseinia *et al*., 2017).

In Serbia, *A. clypeolata* was used as infusion for kidney disorders, to increase appetite and to sooth coughs (Jarić *et al*., 2015).

Chemical composition

The aerial parts of *A. clypeolata* contain essential oil, the main constituents being (E)-γ-bisabolene, 1,8-cineol, borneol, caryophillene-oxide, β-pinene, sabinene, germacrene D, camphor (Mohammadhosseinia *et al*., 2017; Simić *et al*., 2004). The presence of phytosterols (β-sitosterol, stigmasterol), sesquiterpene-lactones (guaianolides 3α,4α-epoxyrupicolin-A, 3α,4α-epoxyrupicolin-B), sesquiterpene alcohol (clypeotriol), diterpenes (sugeroside), flavonoids and coumarins was reported also for the aerial parts of *A. clypeolata* (Aljancic *et al*., 1996; Karaalp *et al*., 2009; Mohammadhosseinia *et al*., 2017; Todorova *et al*., 1998). Several diterpenes, namely 16α,17-epoxy-ent-kaurane, 16α,17-epoxy-19-acetoxy-ent-kaurane; 16α,17-epoxy-3α-acetoxy-ent-kaurane, were identified in roots (Aljancic *et al*., 1996).

Pharmacological activities

The methanol extract from *A. clypeolata* flower heads showed mild antibacterial activity against 2 strains of *Staphylococcus aureus* and *Bacillus cereus* (Karaalp *et al*., 2009). The essential oil had antibacterial activity against *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa* and *Staphylococcus aureus* (Mohammadhosseinia *et al*., 2017; Simić *et al*., 2004).

The infusion from the flower heads showed protective actions on antioxidant enzyme systems, glutathione and lipid peroxidation levels of erythrocytes and leucocytes

against oxidative damage, possibly due to flavonoid and phenolic acids in the extract (Konyalioglu & Karamenderes, 2005).

Current uses
Similar with other *Achillea* species.

Precautions and adverse reactions
No available data.

Achillea millefolium L. (yarrow, „coada șoricelului"), Asteraceae family

***Other common names*:** common yarrow, Devil's Nettle, Milfoil, Nose Bleed, Yarroway, Noble Yarrow, Knight's Milfoil (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia, the officinal product is *Milefolii herba* represented by whole or cut, dried flowering tops of *Achillea millefolium* (Eur. Ph. 8.0, 2013). The European Medicine Agency (EMA) and World Health Organization (WHO) mention the following officinal products: *Millefolii flos* and *Millefolii herba* (EMA/HMPC/143949/2010; EMA/HMPC/290284/2009; WHO, 2009). The collective drug *Millefolii flos* represents, depending on the area of origin, a mixture of several *Achillea* species (Stanescu *et al*., 2014).

Botanical description
Perrenial, herbaceous and erect plant with a lignified rhizome, from which underground stolons develop. The stem is simple, erect, 40-80 cm high and hirsute. Leaves are distributed spirally on the stem, bipinnate or tripinnate, liniar or lanceolate, with short acute tips and covered with long white hairs; their segments are incised into lanceolate particles. Lower leaves have a short petiole and the upper ones are long (8 cm), sessile, often with 2 or more small axillary leaves at the base. Numerous flowers, in dense terminal corymbs with small capitula; each capitulum consists of the receptacle, 4 or 5 white, pink or reddish ligulate ray-florets with 3-lobed ligules and 3–20 white or cream and androgynous tubular disc florets with a radial, 5-lobed corolla. The fruits are long achenes (1.5-2 mm), shiny, greyish-brown, slightly curved (Gruenwald *et al*., 2000; Parvu, 2006; Stanescu *et al*., 2014; WHO, 2009). It blooms from June to August (Parvu, 2006; Stanescu *et al*., 2014).
Distribution and habitat: from the plain to the mountain areas (Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Crisan, Sulina) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).
Harvesting period: from June to September, in full flowering (Oniga, 2007; Oroian, 2011).

Traditional uses
The European Medicine Agency - Committee on Herbal Medicinal Products refers to the following products from *Millefolii flos* with traditional use: infusion – internal use for temporary loss of appetite, the symptomatic treatment of mild gastrointestinal

complaints (including bloating and flatulence) and minor spasm associated with menstrual periods, external use for the treatment of small superficial wounds; liquid extract (in mild gastrointestinal complaints) (EMA/HMPC/143949/2010). In case of *Millefolii herba,* EMA mentions the traditional products for loss of appetite and gastrointestinal complaints (infusion, liquid extract and tincture), symptomatic treatment of mild menstrual spasms (infusion - internal use), treatment of superficial wounds (infusion - external use) (EMA/HMPC/290284/2009).

According to Plinius, the name of the *Achillea* genus comes from the Greek hero, Achilles, who used the flowers in the treatment of wounds (Prodan & Nyarady, 1964). In Romanian folk medicine, yarrow is used in different types of products with external (juice from fresh inflorescences, fresh plant and green leaves, ointment from dried plant powder or plant powder) and internal uses (infusion, decoction) (Stanescu *et al*., 2014). Herbal preparations for external use are indicated in some dermatological disorders (wounds and burns, abscesses, calluses, warts, impedigo etc.), as anti-perspiration, antihemorrhagic, in the treatment of hemorrhoids, in menstrual disorders (as baths). Internally, they are used in some digestive (gastric ulcer, intestinal colics, diarrhoea, gastroesophageal reflux, nausea, hepato-biliary complaints) and respiratory tract disorders (cough, asthma), in menstrual irregularities, leucorrhea and as diuretic (Ardelean & Mohan, 2008; Butura, 1979; Chevallier, 2016; Grigorescu & Silva, 1997).

Chemical composition

The inflorescences contain the following groups of bioactive compounds: essential oil (1,8-cineole, borneol, sabinene, camphor, eucalyptol, limonene, terpin-4-ol, terpineol, α-thujone, caryophyllene, achillicin, achillin, millefin and millefolide, azulene and chamazulene, β-pinene, β-caryophyllene etc.), phenolic acids (caffeoylquinic and dicaffeoylquinic acid derivatives), flavonoids (apigenin, luteolin and quercetin derivatives), triterpenoids, sterols, vitamins (K, E) (Barnes *et al*., 2007; Dias *et al.* 2013; Mohammadhosseini *et al*., 2017; Oniga, 2007; Oroian, 2011; EMA/HMPC/149343/2010). The main compounds in aerial parts are: essential oil (linalool, borneol, camphor, β-caryophyllene, 1,8-cineole, achillicin, achillin, leucodin and germacranolides etc.), flavonoids (apigenin, luteolin, isorhamnetin, rutin), aminoacids, fatty acids, phenolic acids (caffeic, salicylic), vitamins (ascorbic and folic acids), saponins, sterols (β-sitosterol), coumarins etc. (Barnes *et al*., 2007; Mohammadhosseini *et al*., 2017; EMA/HMPC/290284/2009). The European Pharmacopoeia requires for *Milefolii herba* min. 2 mL/kg essential oil (dried drug) and min. 0.02% proazulenes expressed as chamazulene (dried drug) (Eur. Ph. 8.0, 2013).

Pharmacological activities

In vitro studies have shown antibacterial (*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella penumoniae* etc.), antifungal (*Candida* strains), anti-inflammatory, antihemorrhagic, antispasmodic, antioxidant (Applequist & Moerman, 2011), choleretic (Benedek *et al*., 2006), antiparasitic (*Babesia gibsoni* and *Plasmodium malariae*) (Murnigsih *et al*., 2005), antitumoral (Pereira *et al*., 2018) and vasoprotective activities (Dall'Acqua *et al*., 2011). *In vivo* studies on animal models indicated anti-inflammatory, anxiolytic, hepatoprotective, gastroprotective, antiulcerogenic (Applequist & Moerman,

2011; Potrich *et al*., 2010), diuretic (de Souza *et al*., 2013) and anti-diabetic (Chávez-Silva *et al*., 2018) effects. Clinical trial data indicated the benefic effect of yarrow extract as adjuvant in the management of multiple sclerosis (Ayoobi *et al*., 2019) and in treating dysmenorrhea (Jenabi & Bita, 2015).

Current uses

The products with *A. millefolium* approved by the German Commission E are indicated in loss of appetite, liver and gallbladder complaints (Gruenwald *et al*., 2000). Yarrow products are indicated in acute gastritis, cough, bronchitis, hemorrhoids, as sedative in mentrual complaints (Oroian, 2011).

Precautions and adverse reactions

No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages. Its use is not recommended for children under 12 years of age. Due to its emmenagogue and uterotonic properties, it is contraindicated in pregnancy (Duke *et al*., 2002; EMA/HMPC/143949/2010; EMA/HMPC/290284/2009; Gruenwald *et al*., 2000). *Millefolii flos* preparations can cause allergic reactions (contact dermatitis) in pacients sensitive to Asteraceae plants, due to a sesquiterpene lactones (Oroian, 2011; WHO, 2009).

Other warnings

If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted (EMA/HMPC/143949/2010; EMA/HMPC/290284/2009).

Achillea setacea Waldst. et Kit. (yarrow, „coada șoricelului"), Asteraceae family

Syn. *Achillea millefolium* ssp. *setacea* (Waldst. & Kit.) Čelak. (Sarbu *et al*., 2013).

Officinal products: flowering tops (similar with other *Achillea* species).

Botanical description

A. setacea is a perennial species, roughly tomentaceous, with lanceolate leaves, pinnatisect, with linear lacinae. Calatidia are small, gathered in corymbs, 4-5 ligate white marginal flowers, and a few central tubular yellow flowers. The fruits are achenes without pappus. It blooms from June to August (Stefan & Oprea, 2007).

Distribution and habitat: frequent, from the steppe to the beech floor, through sunny, dry meadows (Andrei & Cristurean, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007). In Dobrogea, this species was reported in the Danube Delta area (Chituc, Histria) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (between Greci and Macin) (Andrei & Cristurean, 2006).

Harvesting period: in full flowering (similar with other *Achillea* species), from June to August.

Traditional uses

The aerial parts of *Achillea* species are used in folk medicines of many countries, for thousands of years, as wounds healing, emmenagogue, carminative, diuretic, sedative,

anti-inflammatory, appetizer agent, against abdominal pain, diarrhoea and colds (Konyalioglu & Karamenderes, 2005; Mohammadhosseinia *et al*., 2017; Turkmenoglu *et al*., 2015).

In Iran the *Achillea* species are used as diuretic, menstrual regulating, wound healing agents and against diarrhoea, flatulence and abdominal pain (Rezaei *et al*., 2017).

Chemical composition

The aerial parts of *A. setacea* contain 0.25-1.20% essential oil, the main constituents being nerolidol, α-cubenene, β-cadinene, 1,8-cineol, sabinene, α-pinene, camphor, lavandulyl acetate, caryophillene oxide, α-bisabolon oxide, hexadecanoic acid (Mohammadhosseinia *et al*., 2017; Rezaei *et al*., 2017; Turkmenoglu *et al*., 2015; Ünlü *et al*., 2002). Both the content and composition of *A. setacea* essential oil are influenced by the environmental factors (Rezaei *et al*., 2017; Ünlü *et al*., 2002). It contains 9.9% polyunsaturated fatty acids (linoleic and linolenic acids) and other fatty acids (palmitic, myristic, stearic, ligniceric acids etc.), and also phenolic compounds (gallic, caffeic, vanillic, p-coumaric, syringic, ferulic, synaptic and 4-hydroxy benzoic acids) (Rezaei *et al*., 2017).

Terpenoids such as sesquiterpene lactones (sintenin, rupicolin-A, rupicolin-B, 1-desoxy-1α-peroxy-rupicolin-A, 1-desoxy-1α-peroxy-rupicolin-b, 3α,4 α-epoxyrupicolni-A, 3α,4 α-epoxyrupicolni-B, rupin A etc.) and monoterpenes (8α-hydroxy-tanaparthin-α-peroxide, tanaparthin-α-peroxide, 1S,2R,4S-trihydroxy-*p*-methane) were also identified in *A. setacea* (Karaalp *et al*., 2009; Mohammadhosseinia *et al*., 2017).

Pharmacological activities

The infusion from the *A. setacea* flower heads showed protective actions on antioxidant enzyme systems, glutathione and lipid peroxidation levels of erythrocytes and leucocytes against oxidative damage, possibly due to flavonoid and phenolic acids present in the extract (Konyalioglu & Karamenderes, 2005).

A. setacea essential oil has a good *in vitro* antibacterial activity against *Clostridium perfringens*, *Acinetobacter lwoffii, Staphylococcus aureus, Streptococcus pneumoniae, Bacillus cereus* and *Mycobacterium smegmatis*, and anticandidal activity against *Candica albicans* and *Candida krusei* (Ünlü *et al*., 2002).

The hexane extract from *A. setacea* showed mild to low antibacterial activity against *Enterococcus faecalis* (Karaalp *et al*., 2009).

Sesquiterpene lactones (rupicolin B and 11,13-dehydrodeacetylmatricarin) isolated from *A. setacea* showed good anti-inflammatory activity (Zitterleglseer *et al*., 1991).

Current uses

Similar with other *Achillea* species.

Precautions and adverse reactions

No available data.

Adonis vernalis L. (spring pheasant's eye, "ruşcuţă de primăvară"), Ranunculaceae family

***Other common names*:** Pheasant's eye, Bird's eye, False Hellebore (Shang *et al*., 2019).

Officinal products: flowering aerial part (*Adonidis herba*), *Adonidis herba pulvis normatus* (Muntean *et al*., 2007).

Botanical description

It is a perennial plant, with a vertical, woody rhizome, of about 3 mm, dark brown, with numerous fibrous roots. Flower stems and sterile shoots grow from the rhizome. The flowering stem is erect, axial, 15-40 (50) cm high, straight, rarely branched, glabrous and foliate. The leaves are alternate, sessile, glabrous, 2-4 times pinnatisect. The flowers are solitary at the tip of the stem, large, composed of 5 sepals, 10-20 yellow-gold petals of 2-4 cm, numerous stamens and globular gynoecium. The fruits are globular nucules (polynucules) (Muntean *et al*., 2007; Stanescu *et al*., 2004a).

Distribution and habitat: frequent in steppe meadows (Sarbu *et al*., 2013). Protected species, declared a natural monument (Ardelean & Mohan, 2008).

Harvesting period: from the beginning of flowering to the fall of the fruit (Oroian, 2011).

Traditional uses

It is used in traditional medicine since the Middle Ages. In Romania the fibrous roots, crushed and macerated for 2-3 days in alcohol (home-made spirits), were used against headaches. The maceration in wine (25-30 ^{0}C) or the decoction in combination with lilac flowers was used to treat hernia. The root was used to treat the anthrax in animals – the root was inserted in the wound and kept for 2 hours (Butura, 1979; Grigorescu & Silva, 1997; Stanescu *et al*., 2014). The infusion was used as sedative, cardiotonic, diuretic, analgesic, in heart disorders and headaches (Segneanu *et al*., 2019; Tita *et al*., 2009).

Chemical composition

A. vernalis contains cardiotonic cardenolid glycosides, luteoline C-glycoside flavonoids (adonivertine, adonivernitin, orientin derivatives), saponins, resins, choline, palmitic acid, linoleic acid, phytosterols and minerals (Ardelean & Mohan, 2008; Chevallier, 2016; Oroian, 2011).

The main cardiotonic glycosides isolated from *A. vernalis* are cymarin, adonitoxin, 16-hydroxy-strophanthidin, acetyladonitoxin, vernadigin and 3-acetylstrophadogenin (Oniga, 2007; Shang *et al*., 2019). Other identified compounds: acetyl-adonitoxoside, K-strophantoside g, vernadiginoside, 3-epi-periplogenol (Stanescu *et al*., 2014).

Pharmacological activities

A. vernalis has sedative, cardiotonic, coronary-dilating and diuretic properties (Ardelean & Mohan, 2008; Chevallier, 2016; Segneanu *et al*., 2019). Adonidine is a low toxicity cardiotonic that does not accumulate; it is used in long-term treatments and is interposed between digitaline or ouabain treatments; it is also a good diuretic (Oroian, 2011). In the form of powder, infusion, tincture or extracts, it is used in heart failure and angina pectoris (Oniga, 2007).

Cardiotonic glycosides from *Adonidis herba* exhibit an action similar to those of *Digitalis lanata*, so they are used as substitutes for digoxin / digitoxin (Stanescu *et al*., 2014; Shang *et al*., 2019). The extract from *A. vernalis* shows anti-hyperlipidemic, hepatoprotective and anti-inflammatory action (Lateef *et al*., 2012; Shang *et al*., 2019), respectively analgesic, positive inotropic and venous tonic effect (Duke *et al*., 2002; Gruenwald *et al*., 2000). It is also used in tachycardia, extrasystole and neurovegetative disorders (Ardelean & Mohan, 2008).

Current uses

The extracts from *A. vernalis* were first introduced into medicine, as a cardiac stimulant, in 1879 by the Russian physician N.O. Buhnow. Due to its cardiotonic and diuretic properties, *A. vernalis* is used in stress, incipient and congestive heart failure. Due to the reduced toxicity and the reduced risk of accumulation in myocardial fiber, *A. vernalis* is used as a substitute for *Digitalis lanata* products (Stanescu *et al*., 2014; Shang *et al*., 2019; Lateef *et al*., 2012). The products with *A. vernalis* are approved by the Commission E (scientific advisory board of "Bundesinstitut für Arzneimittel und Medizinprodukte") for use in stress induced arrhythmias and heart disorders (Gruenwald *et al*., 2000). They are also indicated in cramps, dysmenorrhea, fever, nervousness, neuropathy and pain (Duke *et al*., 2002).

An extract from *Adonidis herba* is included in the composition of Miroton®, a combination preparation.

Precautions and adverse reactions

A. vernalis extracts are not recommended in patients with hypokalemia (due to the diuretic effect of the extract) and those taking digital glycosides (having similar effects). Due to adverse effects and drug interaction, co-administration with laxatives, saluretics, calcium, quinidine and glucocorticoids is not recommended as there is a risk of enhancing the cardiotonic action (Duke *et al*., 2002; Gruenwald *et al*., 2000).

The product is to be used only under medical supervision. Overdose causes heart disease, nausea and vomiting (Duke *et al*., 2002).

Other warnings

It can be replaced by *Adonis aestivalis* (summer pheasant's-eye) and *Adonis annua*, common in spontaneous flora, both with similar properties (Oroian, 2011).

Ajuga genevensis L. (blue bugle, „suliman, vinețică"), Lamiaceae family

***Other common names*:** Blue bugleweed (Ghita *et al*., 2012a).

Officinal products: aerial parts (*Ajugae genevensisae herba*) (Parvu, 2006).

Botanical description

A. genevensis is a tomentaceous, perennial plant, with a short, oblique rhizome, from which many roots start (Butura, 1979). The stem is erect, simple, sometimes slightly branched, with quadrangular cross-section. Leaves are more or less ovate, toothed or crenate, slightly hirsute, the lower ones attenuated into short petioles, the upper ones

sessile. The flowers are blue, rarely pink or white, bilaterally symmetrical, grouped in the axils of the leaves in dichasium. The fruits are reticulate-rough apocarpoid nucules (Parvu, 2006). It blooms from May to July (Andrei & Cristurean, 2006; Parvu, 2006; Sarbu *et al*., 2013).

Distribution and habitat: frequent, from the silvosteppe to the mountain area, grows through orchards, ruderal places, meadows, bushes (Andrei & Cristurean, 2006; Butura, 1979; Parvu, 2006; Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Letea) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: during flowering stage, from May to July (Parvu, 2006).

Traditional uses

In folk medicine, the aerial parts of *A. genevensis* are used (Parvu, 2006). Preparations such as infusion and tincture are used in inflammatory and rheumatic conditions, against diarrhoea, leucorrhoea, as hepatoprotective and healing agent (Ghita *et al*., 2012a). It is also used traditionally as sedative, anti-hemorrhagic and epithelization agent (Toiu *et al*., 2019). In Romanian folk medicine, the decoction from the flowering stems was used against indigestion (Butura, 1979).

Chemical composition

The flowers and aerial parts of *A. genevensis* are rich in phenolic acids (caffeic, p-coumaric and ferulic acids) and flavonoids (hyperoside, quercitrin, luteolin, apigenin) (Gavan *et al*., 2018; Rauca *et al*., 2019; Toiu *et al*., 2016; Toiu *et al*., 2019). In the aerial parts of *A. genevensis* several iridoids were identified, namely: harpagide, aucubin, catalpol, harpagoside, 8-O-acetyl-harpagide (Ghita *et al*., 2011; Paduraru *et al*., 2019; Rauca *et al*., 2019; Toiu *et al*., 2019). Among the phytosterols, ergosterol, stigmasterol, brassicasterol and campesterol were identified in the aerial parts of *A. genevensis* (Toiu *et al*., 2019). In the acetone extract from *A. genevensis*, 3 *neo*-cleronade diterpenes were identified, namely ajugavensins A, ajugavensins B and ajugavensins C (Malakov *et al*., 1991; Malakov *et al*., 1992). It also contains tannins and essential oil (Butura, 1979; Parvu, 2006).

A. genevensis aerial parts also contain essential oil (Gavril *et al*., 2016a).

Pharmacological activities

The alcohol extracts (ethanol and methanol) of *A. genevensis* showed good antioxidant activity, and the ethanol extract showed a good antimicrobial activity against *Staphylococcus aureus* (Rauca *et al*., 2019; Toiu *et al*., 2016). The ethanol extract showed anti-inflammatory properties, by inhibiting the transcription factor NF-kB-p65, decreasing oxidative stress, inhibiting phagocytosis, reducing polymorphonuclear leukocytes and total leukocytes (Toiu *et al*., 2019).

The aerial parts also have anti-hemorrhagic properties, support wound healing (promote epithelialization), and due to its tannins have anti-diarrhoeal properties (Parvu, 2006).

Current uses

The comminuted aerial parts of *A. genevensis,* as infusion or decoction, are used internally in treating diarrhoea, enteritis and hemorrhagic enteritis, and externally in the treatment of angina, leucorrhea, wounds (Parvu, 2006).

Precautions and adverse reactions
No available data.

Ajuga reptans L. (bugle, „vineriță"), Lamiaceae family

***Other common names*:** Bugula, Middle Comfrey, Middle Confound, Sicklewort, Carpenter's Herb (Gruenwald *et al*., 2000).

Officinal products: aerial parts (*Ajugae herba*) (Ardelean & Mohan, 2008; Chevallier, 2016; Gruenwald *et al*., 2000; Parvu, 2006), leaves (*Ajugae folium*), flowers (*Ajugae flos*) (Ardelean & Mohan, 2008; Parvu, 2006).

Botanical description
A. *reptans* is a perennial herbaceous species, with a short rhizome with many roots and stolons. The stolons have, on their nodes, adventitious roots. The stems are erect, simple, tetragonal, pubescent towards the top, up to 40 cm high. Leaves are opposite, petiolate, elliptical, glabrous, with a crenulated edge. Flowers are pentamerous, blue-azure, rarely pink or white, short petiolate, arranged in several vertices at the underside of the leaves at the top of the stem. The fruits are tetra-nucules (Ardelean & Mohan, 2008; Chevallier, 2016; Gruenwald *et al*., 2000; Istudor, 2001; Parvu, 2006). It blooms from April to August (Ardelean & Mohan, 2008; Parvu, 2006).
Distribution and habitat: frequent all over the country, from the plain area to the spruce floor, through bushes, meadows, ruderal places, forest edges, mountain meadows (Andrei & Cristurean, 2006; Ardelean & Mohan, 2008; Butura, 1979; Grigorescu *et al*., 1986; Istudor, 2001; Parvu, 2006; Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Chilia, Periprava) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).
Harvesting period: during flowering stage, from April to August (Ardelean & Mohan, 2008; Istudor, 2001; Parvu, 2006).

Traditional uses
In European folk medicine, it was used for centuries for its wound healing properties, to lower the pulse rate and for its benefic effects on the cardiovascular system (Chevallier, 2016).
In Romanian folk medicine, *A. reptans* was used externally, as fresh leaves, infusion and decoction for the local treatment of erysipelas (a type of skin infection), leucorrhea and uterine bleeding (Butura, 1979; Parvu, 2006). As ointment, it was used externally to treat skin ulcers, wounds, burns, bone fractures (Parvu, 2006). Internally, the decoction was used against genitor-urinary disorder, angina pectoris, pneumonia, asthma, hemoptysis (Butura, 1979; Parvu, 2006). This species was also used against mouth and larynx inflammation (Gruenwald *et al*., 2000). *A. reptans* is also known in folk medicine for its hepatoprotective properties (Toiu *et al*., 2017).

Chemical composition
In methanol and ethanol extracts from *A. reptans*, several phenolic acids and flavonoids were indentified, namely: caffeic, p-coumaric, rosmarinic and ferulic acids,

isoquercitrin, rutin, quercitrin, luteolin and apigenin (Ghita *et al.,* 2011; Gruenwald *et al*., 2000; Istudor, 2001; Toiu *et al*., 2017; Toiu *et al*., 2019). The following phytosterols were identified in the aerial parts of *A. reptans*: ergosterol, stigmasterol, brassicasterol, campesterol (β-sitosterol is the main compounds) (Toiu *et al*., 2019). Quantitatively, harpagide was the main iridoid in *A. reptans*, but aucubin, catalpol, harpagoside, 8-O-acetyl-harpagide were also identified and quantified (Paduraru *et al*., 2019; Ghita *et al.,* 2011; Grigoras *et al*., 2017; Istudor, 2001; Toiu *et al*., 2019).
A. reptans also contains tannins, resins, essential oil, anthocyanins (cyanidin and delphinidin glycosides), minerals (Ardelean & Mohan, 2008; Butura, 1979; Istudor, 2001; Parvu, 2006), phytoecdysone and diterpene bitter principles (Gruenwald *et al*., 2000; Chevallier, 2016).

Pharmacological activities
The extracts from *A. reptans* flowers showed a good antioxidant activity (due to their high content of phenolic acids and flavonoids), good antifungal activity against *Aspergillus niger* and *Candida albicans* and moderate antibacterial activity against *Staphylococcus aureus, Pseudomonas aeruginosa, Listeria monocytogenes, Escherichia coli* and *Salmonella typhimurium* (Toiu *et al*., 2017; Toiu *et al*., 2019). *A. reptans* also showed good anti-inflammatory potential, through several mechanisms (inhibition of the transcription factor NF-kB-p65, decrease of oxidative stress, inhibition of phagocytosis etc.) (Toiu *et al*., 2019).
A. reptans also has anti-diarrhoeal (due to tannins), anti-leucorrheic, wound healing (Grigorescu *et al*., 1986; Istudor, 2001; Parvu, 2006), antipyretic and mild analgesic properties (Chevallier, 2016; Duke *et al*., 2002).

Current uses
Internally, it is used against angina pectoris, respiratory disorders (pneumonia, bronchial asthma, bronchitis, cough), uterine bleeding, hemorrhoids, diarrhoea; externally, it is used in skin conditions (wounds, burns, skin ulcers, erysipelas) (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000, Istudor, 2001; Parvu, 2006).
Food supplements in the form of hydroalcoholic extracts are recommended for the normal functioning of the respiratory, cardiovascular and digestive systems.

Precautions and adverse reactions
No available data.

Allium ursinum L. (bear's garlic, „leurdă"), Liliaceae family

Syn. *Allium ucrainicum* (Kleopow & Oxner) Bordz. (Doroftei *et al*., 2011).
***Other common names*:** Ramsons, Broad-Leaved Garlic (Gruenwald *et al*., 2000).

Officinal products: leaves (*Allii ursini herba*) (Chevallier, 2016; Parvu, 2006; Stanescu *et al*., 2014; Stanescu *et al*., 2020; Tita *et al*., 2009), the bulb and the aerial part (*Allii ursini bulbus et herba*) (Istudor, 2001), bulbs (*Allii ursini bulbus*) (Chevallier, 2016; Parvu, 2006).

Botanical description

It is an herbaceous species, with a narrow and elongated bulb, which generates hairy roots, and with a straight flowering stem, 20-50 cm high. The leaves are wide, ovate-lanceolate, long petiolate, with two parallel ribs, dark-green on the upper side and light-green on the lower side. The star-like, white flowers are grouped in umbels. The fruit is a small capsule, with small black seeds. The whole plant has a characteristic garlic-like smell (Chevallier, 2016; Istudor, 2001; Parvu, 2006; Sarbu *et al*., 2013; Stanescu *et al*., 2002a; Stanescu *et al*., 2014; Stanescu *et al*., 2020; Stefan & Oprea, 2007). It blooms in April - May (June) (Andrei & Cristurean, 2006; Istudor, 2001; Parvu, 2006; Stefan & Oprea, 2007).

Distribution and habitat: *Allium ursinum* ssp. *ucrainicum* is frequent, from the plain region to the beech floor, through deciduous forests (Andrei & Cristurean, 2006; Istudor, 2001; Parvu, 2006; Stefan & Oprea, 2007; Sarbu *et al*., 2013). In Dobrogea this species was reported in the Danube Delta area (Caraorman, Sontea) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Greci, Macin, Balabancea, Cocos Monastery, Niculitel) (Andrei & Cristurean, 2006).

Harvesting period: aerial parts during flowering stage (April - May), bulbs in autumn (September-October) (Istudor, 2001; Parvu, 2006; Sobolewska *et al*., 2015).

Traditional uses

In the past, it was used as a garlic replacement and in traditional human and veterinary medicine (Parvu, 2006). In Romanian folk medicine, the plant was used in the treatment of gastrointestinal dysfunctions and dyspepsia, for its carminative and antibacterial properties (Stanescu *et al*., 2002a; Stanescu *et al*., 2004a; Stanescu *et al*., 2014). The leaves were consumed fresh in salads or added to certain foods against scurvy and for their stomachic properties, and also were used in the form of infusion as diuretic in kidney diseases and as depurative (Butura, 1979; Stanescu *et al*., 2014). Other ethnopharmacological data mention the use of infusion from aerial parts in digestive and urinary disorders, helminthiasis, wounds, furunculosis and insect bites (Tita *et al*., 2009).

A. ursinum was also used internally to reduce blood pressure and against atherosclerosis, for diarrhoea, colic, flatulence, indigestion, loss of appetite and externally for chronic rashes (Chevallier, 2016; Gruenwald *et al*., 2000).

Chemical composition

The sulfur compounds are the main bioactive constituents of *A. ursinum*. Alliins *(alkyleysteine sulphoxides)*, through hydrolysis, generate the specific sulfur compounds in the essential oil (Gruenwald *et al*., 2000; Sobolewska *et al*., 2015).

The organosulfur compounds are the main class of compounds of the essential oil (69.1-97.7%), and include mainly alk(en)yl disulfides, trisulfides, tetrasulfides, but also alk(en)yl and pentasulfides (Radulović *et al*., 2015).

It also contains lectins, alkanes, fatty acids (palmitic, linoleic, oleic, stearic, α-linolenic), sesquiterpenoids, polysaccharides (mainly fructans), aminoacids (asparagine, glutamine, aspartic and glutamic acids, arginine etc.), phytoestrogens, flavonoids (mainly kaempferol derivatives), phenolic acids (ferulic, vanillic, p-coumaric acids), steroid glycosides (diosgenin, β-sitosterol, 3-*O*-β-D-glucopyranoside) and carotenoids (Krivokapić *et al*., 2018; Pejatović *et al*., 2017; Radulović *et al*.,

2015; Sobolewska *et al*., 2015; Stanescu *et al*., 2014; Stanescu *et al*., 2020). Fresh plant contains condensed tannins, in higher amounts in leaves (2.15 mg/g) than in bulbs (1.59 mg/g) (Sahnoun *et al*., 2017).

Pharmacological activities

A. ursinum has benefic effects in the prevention and treatment of cardiovascular diseases. *In vitro* and *in vivo* studies showed that *A. ursinum* is exerting anti-aggregation effect, decreasing blood pressure (regulation of membrane function, inhibition of angiotensin 1-converting enzyme), serum cholesterol and triglyceride, and reducing oxidative stress (Duke *et al*., 2002; Gruenwald *et al*., 2000; Krivokapić *et al*., 2018; Sobolewska *et al*., 2015). Fresh leaves and bulbs extracts showed a good antioxidant activity, probably due to their content in phenolic and sulfur compounds (Pejatović *et al*., 2017; Sahnoun *et al*., 2017).

The extracts from *A. ursinum* have antimicrobial activity against several bacteria (*Bacillus subtilis*, *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Salmonella enteritidis*) and fungi (*Candida albicans, Aspergillus niger, Rhizopus nigricans, Geotrichum candidum*) (Lupoae *et al*., 2013; Pejatović *et al*., 2017; Sahnoun *et al*., 2017). The flower chloroform extract showed *in vitro* cytotoxic effect in murine melanoma and sarcoma cell lines (Krivokapić *et al*., 2018).

Current uses

The dried leaves are used as infusions or extracts in cardiovascular disease for their hypotensive, hypolipidemic, hypocholesterolemiant and antiplatelet effects (Istudor, 2001; Stanescu *et al*., 2014; Stanescu *et al*., 2020). It is also used in urinary conditions (hematuria, cystitis, nephritis), respiratory diseases (asthma, bronchitis, and emphysema) and against intestinal worms (Chevallier, 2016; Duke *et al*., 2002; Istudor, 2001; Parvu, 2006; Tita *et al*., 2009).

Precautions and adverse reactions

Gastric irritation has been reported for extracts (Stanescu *et al*., 2004a; Stanescu *et al*., 2014). Overdose can cause intoxication, with the following possible symptoms: hypersalivation, muscle tremors, anorexia, flatulence, heartburn (Duke *et al*., 2002; Parvu, 2006). *A. ursinum* can cause allergies (Duke *et al*., 2002).

Other warnings

It can be confused with the leaves of *Colchicum* species (Gruenwald *et al*., 2000).

Althaea officinalis L. (marsh-mallow, „nalbă mare"), Malvaceae family

Syn. *Althaea taurinensis* DC., *A. kragujevacensis* Panc.

Officinal products: According to the European Pharmacopoeia and the European Medicine Agency (EMA) the officinal products are *Althaeae radix* and *Althaeae folium* (EMA/HMPC/436679/2015; EMA/HMPC/436680/2015; Eur. Ph. 8.0, 2013). Literature also mentions the use of flowers (*Althaeae flos*) (Ardelean & Mohan, 2008).

Botanical description

It is a perennial plant, with fleshy root, 10-30 cm long, with few, thick branches, light-gray on the surface and white-yellow on the inside. The stem is 50-200 cm high, cylindrical, with few branches, lignified at the base and hirsute. The leaves are petiolate, the leaf blade with 3-5 lobes, 4-10 cm long and slightly smaller width, with very dense and soft trichomes. The flowers are arranged in racemes at the tip of the stem; the corolla consists of 5 triangular white-pink petals. The fruits consist of several mericarps, radially arranged in the persistent calyx. Each pericarp contains one reniform seed. It blooms from July to September (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu *et al*., 2006; Sarbu *et al*., 2013).

Distribution and habitat: frequent, from the plain area to the beech floor, through meadows, waterfront, ruderal areas (Sarbu *et al*., 2013, Stefan & Oprea, 2007). It is found throughout the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: leaves before flowering, flowers during blooming, roots in autumn (October - November) (Muntean *et al*., 2007; Parvu *et al*., 2006).

Traditional uses

The European Medicine Agency - Committee on Herbal Medicinal Products mentions the following traditionally-used preparations from the marsh-mallow roots: shredded plant product; aqueous liquid extract; macerate for syrup preparation; dry aqueous extract; liquid ethanol extract (EMA/HMPC/436679/2015).

Marsh-mallow is traditionally used since ancient times as follows: roots in the form of a decoction as a cicatrizing remedy (Hippocrates), in the treatment of diarrhoea, lithiasis, bee stings (Dioscorides), constipation, bronchial catarrh and gastritis; the flowers and the leaves in the form of infusions for internal use as emollient and external use as antiseptic; the leaves in the form of cataplasms for the treatment of skin inflammation; the flowers in the form of infusion as expectorant (Stanescu *et al*., 2014; Sharma *et al*., 2016). In folk medicine, the roots were most commonly used as a pectoral remedy (fluidization of bronchial secretions and improvement of respiratory tract disorders) and for the treatment of abdominal colic and gastric ulcer (Grigorescu & Silva, 1997; WHO, 2002).

Chemical composition

The characteristic chemical constituents differ depending on the officinal product. Thus, the roots mainly contain mucilages (5-11%, depending on the harvesting time and subsequent processing procedures) consisting of a mixture of polysaccharides, including arabinogalactans, arabinans, glucans and rhamnogalacturonans. Other identified constituents are: pectin (11%), starch (25-35%), 0.14-0.28% flavonoids (hypoletin-8-glucoside, kaempferol, quercetin, isoquercetin, astragalin, naringenin), phenolic acids (caffeic, p-coumaric, ferulic, salicylic, syringic and vanillic acids), coumarin (scopolatin), phytosterols, aminoacids (2% asparagine), tannins, mono- and di-saccharides (Al-Snafi, 2013; EMA/HMPC/436680/2015). The leaves contain mucilages (6-9%), consisting of arabinogalactans and galacturonorhamnans, flavonoids, phenolic acids, tannins and essential oil (Stanescu *et al*., 2002a). The flowers contain 6% mucilages (through hydrolysis they pass into galactose, rhamnose, glucose, galacturonic acid, arabinose and traces of xylose) and essential oil (Parvu, 2006).

Pharmacological activities

In vitro and *in vivo* (animal model) studies provide some evidence to support the use of marsh-mallow in the treatment of cough (emollient, anti-irritative and antitussive effects) and gastric inflammation. An *in vivo* experimental model on animals with induced cough revealed that the root extract and the polysaccharide fraction have antitussive effect superior to non-opioid antitussive drugs (prenoxdiazine, dropropizine) (Stanescu *et al*., 2014). The antitussive action is due to the bioadhesive properties of the polysaccharides in the mucous membranes, with local anti-irritant protective effect (efficiency in dry cough caused by the irritation of the pharyngeal and oral mucosa). The beneficial effects of root extracts from *A. officinalis* in the treatment of respiratory tract disorders are also due to the stimulation of the cellular regeneration of the epithelial cells and the inhibition of the tracheobronchial smooth muscle contractions (Deters *et al*., 2010; Alani *et al*., 2015; Sutovska *et al*., 2009). Polysaccharides and aminoacids form a biofilm on the surface of the gastric mucosa (protective effect - symptomatic treatment of minor gastric disorders). Marsh-mallow preparations can also be used in the treatment of moderate skin inflammation (Stanescu *et al*., 2014). In addition, the ethanol and methanol root extracts from *A. officinalis* have demonstrated antimicrobial potential, indicating possible uses in improving oral health (Chinsembu, 2016; Haghgoo *et al*., 2017). The aqueous root extract showed a protective effect against the oxidative stress induced by UVA radiation, thus suggesting the possible use in dermatological products (Curnow & Owen, 2016). Studies on animal models have also shown hypoglycemic, immunomodulatory and anti-inflammatory activities (Barnes *et al*., 2007).

Current uses

Marsh-mallow is included in various food supplements (singular or in combination with other species) used as adjuvant in respiratory, gastrointestinal and skin conditions. Due to its uses, *A. officinalis* is widely cultivated (Muntean *et al*., 2007).

Precautions and adverse reactions

There were no reported side effects associated with the correct administration of marsh-mallow preparations (Gruenwald *et al*., 2000). The use of marsh-mallow preparations is not recommended for children and adolescents under 18 years of age. The use during pregnancy and lactation is not recommended, in the absence of studies. The absorption of other medicines administered simultaneously may be delayed, thus, it should not be administrated ½-1 hour before or after other medicinal products. Administration to persons with hypersensitivity to active substances is not indicated (EMA/HMPC/436679/2015).

Other warnings

Not to be confused with other species of the *Althaea* genus (Gruenwald *et al*., 2000).

Althaea rosea (L.) Cav. (hollyhock, „nalbă de grădină"), Malvaceae family

Syn. *Alcea rosea* L. (Gruenwald *et al*., 2000).

***Other common names*:** Malva Flowers, Rose Mallow (Gruenwald *et al*., 2000).

Officinal products: *A. rosea* is not an officinal drug, but all parts of the plant were used in traditional medicine (Butura, 1979; Grigorescu & Silva, 1997; Gruenwald *et al*., 2000).

Botanical description

It is a perennial tomentaceous plant, with a robust stem, up to 300 cm high. The leaves are long petiolate, orbicular-cordate or rhombic, palmately lobed. The flowers are large (over 5 cm in diameter), subsessile, often involute, red, sometimes white or yellowish, blackish-purple, with a metallic luster, the calyx of 6-9 united hipsophils and the polycarpelate gynoecium. The fruits are polyachene, compressed in the middle, surrounded by a membranous margin, with glabrous mericarps. It blooms from July to October (Oroian, 2011; Stefan & Oprea, 2007).

Distribution and habitat: In the Danube Delta area, it has been identified on the island of Popina located in the north of the Razim liman (Doroftei *et al*., 2011).

Harvesting period: after the wilting of the flowers (Oroian, 2011).

Traditional uses

In Romanian folk medicine, it is used for its anti-inflammatory properties, as adjuvant in cough, dermatological conditions, for stopping metrorrhagia (Grigorescu & Silva, 1997). Thus, the leaves were placed on the sores and bumps. The infusion was used against cough (Butura, 1979). The aerial parts, roots and seeds are used internally and externally in coughs and pulmonary diseases. The flowers are used as mucilage in respiratory, gastrointestinal and urinary disorders, to reduce fever and thirst. Other traditional uses include the external application in skin inflammation and ulceration. The flower infusion and decoction were used as a gargle in pharyngeal inflammation (Gruenwald *et al*., 2000).

Chemical composition

It contains, like other related species: mucilages (consisting of a mixture of polysaccharides such as glucuronic acid, galacturonic acid, rhamnose and galactose), tannins, anthocyanins (althaeine) and mineral substances (Al-Snafi *et al*., 2013; Butura, 1979; Gruenwald *et al*., 2000; Oroian, 2011). The flowers contain flavonoids (quercetin and kaempferol) and phenolic acids (ferulic, p-coumaric, caffeic, vanillic and syringic acids) and in the aerial parts quercetin and kaempferol derivatives were identified (Kim *et al*., 2017). The aqueous extract from seeds has a high content of polysaccharides (Liu *et al*., 2014). The roots contain mucilages consisting of polysaccharides (galacturonorhamnans, arabinans, glucans, arabinogalactans), flavonoids (kaempferol, quercetin), coumarin, caffeic acid, calcium oxalate, fats and sterols, thus it can be used as a substitute for *Althaea officinalis* (Al-Snafi *et al*., 2013).

Pharmacological activities

The extracts from *A. rosea* flowers showed antimicrobial potential against pathogenic bacteria (*Escherichia coli*, *Salmonella typhimurium, Enterobacter cloacae, Enterococcus faecalis*) and fungi (*Candida albicans*), cardioprotective, vasoprotective, hypotensive, hypoglycaemic, antipyretic, anti-inflammatory and analgesic activities (Al-Snafi *et al*., 2013; Duke *et al*., 2002; Fahamiya *et al*., 2016; Ma *et al*., 2019).

In vitro experiments have shown the immuno-stimulatory effect of the aqueous extract from *A. rosea* flowers, rich in polysaccharides (Kim *et al*., 2017). The leaf extracts showed antimicrobial activity (Fahamiya *et al*., 2016), and the root extracts have

shown beneficial effects in urolithiasis, both in preventive and curative protocols (Al-Snafi *et al*., 2013; Ahmadi *et al*., 2012).

Current uses

The plant material is used as adjuvant in the treatment of respiratory disorders (pharyngitis, tracheitis), gastritis (Oroian, 2011), dermatoses, and also against abscesses, insect bites, constipation, dysmenorrhea, rheumatism and water retention (Duke *et al*., 2002).

Precautions and adverse reactions

There were no reported side effects associated with proper administration (Duke *et al*., 2002).

Angelica sylvestris L. (wild angelica, „angelică"), Apiaceae family

Syn. *Angelica reuteri* Boiss., *A. brachyradia* Freyn, *A. major* Lag., *A. pancicii* Vandas, *A. elata* Velen., *A. montana* Brot., *A. illyrica* K. Maly (Doroftei *et al*., 2011).

Officinal products: *A. sylvestris* is not an officinal drug, but the fruits, roots and aerial parts were traditionally used in European countries (Acimovic *et al*., 2007; Sarker *et al*., 2003).

Botanical description

A. sylvestris is a biannual or perennial plant. The stems are smooth and the terminal leaflet is usually undivided. The flowers are white to pink and grouped in umbels. The fruit is brown, with six black stripes, and the pericarp is attached to the seed (Dihoru *et al*., 2011). It blooms from July to September (Sarbu *et al*., 2013).

Distribution and habitat: frequent, from the plain to the spruce floor, through swampy meadows, meadows, bushes, waterfronts (Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Maliuc, Pardina, Sontea) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: fruits at ripening, roots in autumn, similar with other *Angelica* species (Parvu, 2006).

Traditional uses

It is traditionally used in indigestion, as antipyretic, analgesic, against arthritis and headache (Özek *et al*., 2008). The fruits (seeds) were used to increase appetite, and against anemia, migraine, vertigo, bronchitis; the roots were used to treat infections and the leaves as urinary antiseptic (Sarker *et al*., 2003).

Chemical composition

The fruits (seeds) of *A. sylvestris* var. *sylvestris* contain essential oil, consisting mainly of monoterpenes (monoterpene hydrocarbons) and sesquiterpenes (sesquiterpene hydrocarbons), the major compounds being α-pinene, bornyl acetate, β-phellandrene, limonene, myrcene, camphene, α-chamigrene, β-sesquiphellandrene (Acimovic *et al*., 2007; Özek *et al*., 2008).

The fruits (seeds) of *A. sylvestris* also contain coumarins, such as umbelliprenin, bergapten, isiomperatorin, xanthoxol, aviprin, byakangelicin, and in the roots imperatorin was identified (Murphy *et al*., 2004). Two coumarins were identified in the aerial parts of *A. sylvestris* var. *sylvestris*, namely angelicin and imperatorin (Erdogan Orhan *et al*., 2016).

Pharmacological activities
The dichloromethane extract from *A. sylvestris* fruits (seeds) showed antibacterial activity against methicillin resistant *Staphylococcus aureus* (MRSA) and *Citrobacter freundii* (Sarker *et al*., 2003). The methanol extract from *A. sylvestris* var. *sylvestris* aerial parts showed moderate acetylcholinesterase inhibitory effect (Erdogan Orhan *et al*., 2016). The ethanol extract from *A. sylvestris* roots demonstrated a good antimicrobial activity against *Bacillus subtilis, Enterococcus faecium, Listeria monocytogenes, Staphylococcus aureus* and *Staphylococcus epidermidis* (Canli *et al*., 2016).

Current uses
Similar with other *Angelica* species.

Precautions and adverse reactions
No available data.

Arctium lappa L. (burdock, „brusture"), Asteraceae family

Syn. *Arctium majus* Bernh., *Arctium chaorum* Klokov, *Lappa glabra* Lam., *Lappa major* Gaertn., *Lappa officinalis* All. (Doroftei *et al*., 2011; Duke, 2002; Grigorescu *et al*., 1986).

***Other common names*:** Beggars button, cockle-bur, cocklebutton, common burdock, greater burdock, hardock, stick-button, bat weed (Al-Sanfi, 2014).

Officinal products: According the European Medicine Agency (EMA) the officinal product is represented by roots (*Bardanae radix*) (EMA/HMPC/246763/2009 *Corr.1*). Literature also mentions the use of leaves (*Bardanae folium*) (Ardelean & Mohan, 2008).

Botanical description
It is an herbaceous, biannual, vigorous species. The root is pivoting, strong, fleshy, brown, up to 60 cm long. The stem, formed in the second year, is up to 2 m high, erect and branched. The leaves are large, up to 50 cm long, ovate-cordate, long petiolate, on the upper face glabrous, dark green, on the lower face whitish. The flowers are tubular, purple, in globular calatides, grouped in corymbs. The fruits are elongated achenes, black, with short pappus. It blooms from July to August (Stefan & Oprea, 2007).
Distribution and habitat: common ruderal weed, from the steppe area to the beech floor, through ruderal places, meadows, the waterfront (Sarbu *et al*., 2013). It is also found in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: for the second-year plants in February-March, and for first-year plants in October-November. The leaves are harvested without petiole in May-June, before flowering (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006).

Traditional uses

The European Medicine Agency - Committee on Herbal Medicinal Products mentions the following traditionally-used preparations from *A. lappa* roots: alcoholic fluid extract, aqueous soft extract, tincture. Also, the plant product is indicated for: increasing the amount of urine (diuretic effect), as an adjuvant in minor disorders of the urinary tract; temporary loss of appetite; different skin conditions (seborrheic skin) (EMA/HMPC/246763/2009 *Corr.1*).

On Romania's territory, burdock is known since antiquity (Geto-Dacians), being one of the most important medicinal plant used in our folk medicine (Fierascu *et al*., 2017). In traditional medicine, the roots are mainly used in skin conditions (dermatoses, furunculoses) (Stanescu *et al*., 2014). The chopped leaves were used for their antipruritic properties (Oroian, 2011). The scalp was washed with the plant decoction to enhance hair growth, and the root decoction was used internally for venereal diseases and skin rashes. The plant was used as an anti-inflammatory, disinfectant, antimicrobial, healing and detoxifying agent (Fierascu *et al*., 2017; Segneanu *et al*., 2019). The root decoction is used in colds, flu (as expectorant, antitussive, emollient), in digestive and renal disorders, hypertension, and as diuretic (Tita *et al*., 2009); the infusion is used in diabetes; hot maceration in sweat gland dysfunction (Parvu, 2006). In traditional medicine, *A. minus* Bernh. s.l. (*Lappa minor*) and *A. tomentosum* Mill. are also used (Grigorescu *et al*., 1986; Stanescu *et al*., 2014). The root is used in gastrointestinal disorders as diaphoretic (Gruenwald *et al*., 2000).

Chemical composition

The root contains fatty acids (linoleic, oleic, palmitic, stearic), phenolic acids (caffeic, chlorogenic acids), aldehydes, inulin (45-50%), mucilages, pectin and sugars, terpenoids (arctiol, β-eudesmol, arctiopicrina), thiophene (arctinone-a, arctinone-b, arctinol-a, arctinol-b), small amounts of essential oil, bitter substances (lappatin), resins, phytosterols (sitosterol and stigmasterol), tannin, lignans (arctiin, arctigenol) (Barnes *et al*., 2007; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Segneanu *et al*., 2019; Stanescu *et al*., 2014). The leaves of first-year plants contain sesquiterpenes, triterpenes, fatty acids, caffeic acid, ascorbic acid, mucilage, tannins. The mature fruits contain fatty acids, lignans and daucosterol. The roots contain essential oil (traces), polyacetylenes, phenolic acids (chlorogenic, isochlorogenic and caffeic acids), low amounts of tannins, triterpenes, fatty acids, inulin, vitamin C, γ-guanidino-n-butyric acid (EMA/HMPC/246764/2009).

Pharmacological activities

Studies showed many pharmacological effect of *A. lappa*, including anti-hepatotoxic (El-Kott & Bin-Meferij, 2015), anti-diabetic (e.g. regulation of blood glucose levels, decrease of serum urea and creatinine), antioxidant, anticancer (e.g. suppression cancer cell proliferation, induction of cell death *via* mitochondrial-mediated caspase-dependent apoptosis), anti-inflammatory (e.g. suppression of pro-inflammatory cytokine expression, inhibition of nuclear factor-kappa B pathway, inhibition of nitric oxide production), gastroprotective (e.g. reducing of gastric acid secretion),

hepatoprotective, antimicrobial (against *E. coli, Shigella flexneri, Shigella sonnei*, *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa*) and antiviral (against *Herpes simplex* virus-1) effects (Chan *et al*., 2011; Dias *et al*., 2017; Duke *et al*., 2002; Fierascu *et al*., 2018; Gao *et al*., 2018; Gurunanselage Don &Yap, 2019; Jiang *et al*., 2019; Segneanu *et al*., 2019).

In vitro and *in vivo* (animal model) studies highlighted burdock's antioxidant and anti-inflammatory actions, one essential mechanism being the activation of antioxidant enzymes and scavenging of free radicals (Al-Snafi, 2014). The lignans from the leaves and seeds of *A. lappa* inhibit nitric oxide (NO) production, which is associated with various inflammatory disorders (Chan *et al*., 2011).

The high contents of inulin and mucilages in the roots of *A. lappa* may be responsible for its anti-diabetic and gastroprotective effects (Duke *et al*., 2002). The lignans such as arctiin and arctigenol are responsible for its antiviral potential (Dias *et al*., 2017; Stanescu *et al*., 2014).

Current uses

A. lappa is used as adjuvant in gallstones, diabetes, eczema, enterocolitis, influenza, hypertension, and also externally in skin disorders (acne, eczema, inflammatory dermatoses, furunculosis) and herpes (Ardelean & Mohan, 2008; Barnes *et al*., 2007; Duke *et al*., 2002). The tinctures and the decoction are used in skin conditions. The root extract is indicated as a hypoglycemic agent (Muntean *et al*., 2007; Oroian, 2011) and as adjuvant in gastrointestinal and hepato-biliary disorders (Stanescu *et al*., 2014).

Precautions and adverse reactions

It is not recommended to be used by persons with hypersensitivity to *A. lappa* or other Asteraceae species. Anaphylactic shock has been reported but the frequency is unknown. Its use by children and adolescents under 18 years of age is not recommended. The concomitant use of synthetic diuretics is not recommended (EMA/HMPC/246763/2009 *Corr.1*). The uterine stimulation activity has been reported *in vivo*, thus it is not recommended to be used during pregnancy and lactation, in the absence of further studies (Barnes *et al*., 2007). The most common adverse reaction is contact dermatitis, induced either by contact with the plant material or with the extracts (Chan *et al*., 2011; Gruenwald *et al*., 2000).

Other warnings

The roots of *A. lappa*, product also known as *Radix Arctii*, *Radix Lappae* and *Radix Personatae*, can be mistaken with the roots of *Atropa belladonna* (deadly nightshade, belladonna) which are toxic due to their alkaloids L-hyoscyamine and scopolamine (Stanescu *et al*., 2014).

Artemisia absinthium L. (wormwood, „pelin alb"), Asteraceae family

***Other common names*:** bitter wormwood, grande absinthe (Nguyen & Németh, 2016; Nguyen *et al.*, 2018).

Officinal products: According to the European Pharmacopoeia and the European Medicine Agency (EMA) the officinal product is *Absinthii herba* consisting of basal leaves or lightly leafy flowering tips, or a mixture of the two dried parts of *Artemisia absinthium* L. (Eur. Ph. 8.0, 2013; EMA/HMPC/751490/2016; EMA/HMPC/751484/2016).

Botanical description

A. absinthium is a perennial subshrub. Short, sterile stems and long flowering stems develop from the lignified root. The flowering stem is erect, branched, about 30-100 cm high. The basal leaves on the sterile stems are petiolate, 3 times pinnatisect, and those on the flowering stems are sessile, 2 times pinnatisect. The leaves are silky pubescent on the lower side, greenish-gray on the upper side and silvery-grey on the lower side. The yellow flowers are grouped in small, grey calatides, placed under long bracts. The fruits are small, light brown achenes, without pappus. It blooms from August to September (Muntean *et al.*, 2007; Oroian, 2011; Parvu, 2006). The smell is strongly aromatic, characteristic, and the taste is very bitter (Grigorescu *et al*., 1986).

Distribution and habitat: frequent, through ruderal area, bushes, from the steppe area to the beech floor (Sarbu *et al*., 2013). It is a characteristic plant in the southern, sunny and warm areas (on hills), where it also meets the best cultivation conditions (Muntean *et al*., 2007). It is also found in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: for the extraction of essential oil at the beginning of flowering period (June-July), for extraction of bitter principles at full flowering (July-August) (Muntean *et al.,* 2007).

Traditional uses

The European Medicine Agency - Committee on Herbal Medicinal Products refers to the following products from *A. absinthium* aerial parts: herbal substance and herbal preparations such as powdered herbal substance, comminuted herbal substance, expressed juice from the fresh herb, tincture, with traditional use for gastrointestinal disorders, increasing appetite, in gastritis, hypoacidity, dyspepsia, in liver disease, diabetes, skin diseases, allergies, scabies, tetanus and as choleretic (EMA/HMPC/751490/2016; EMA/HMPC/751484/2016).

Wormwood was used since antiquity, as a remedy for jaundice (Hippocrate), fever and menstrual pain, as antiseptic, tonic, and against intestinal warms (Plinius, Dioscoride) (Oroian, 2011; EMA/HMPC/751484/2016). The infusion, extract and juice obtained from the freshly pressed plant were used internally to treat various digestive disorders such as dyspepsia, acid reflux, stomach ache, and as a digestive in chlorosis, anemia and scrofula. Externally, it was used in dermatoses and paralysis (Butura, 1979; Gruenwald *et al*., 2000; Stanescu *et al*., 2014). The Daco-Getae and the Daco-Romans used the plant in many ailments: fermented in wine as a digestive stimulant in anorexia, liver and gastrointestinal diseases; juices for washing wounds, against intestinal worms and colds (Parvu, 2006). In the Middle Ages it was used against tapeworm infestation. Paracelsus described it as having stomachic and anthelmintic actions (EMA/HMPC/751484/2016). Since the 18th century it is used to prepare the liqueur called absinthe, invented by a French doctor (Goud *et al*., 2015). In Romania, the flowers or flowering stems were used as infusions or fermented in wine in various

gastric and liver disorders. The juice from crushed green flowers and leaves was used against colds (Stanescu *et al*., 2014).

Chemical composition

The *A. absinthium* aerial parts contain essential oil in amounts of 0.1-1.46%, the content varying depending on the origin and source (harvested from the wild or cultivated) of the plant material (Chaieb *et al*., 2018; Ciocarlan *et al*., 2017; Nguyen & Németh, 2016). The main constituents of wormwood essential oil include α and β-thujone, myrcene, sabinene, chamazulene, camphor, β-pinene, artemisia ketone, bornyl acetate, 1,8-cineole. The ratio of essential oil constituents also depends on the plant origin (Bailen *et al*., 2013; Chaieb *et al*., 2018; Ciocarlan *et al*., 2017; Nguyen *et al*., 2018; Nguyen & Németh, 2016; EMA/HMPC/751484/2016). Wormwood also contains 0.15-0.4% bitter constituents, the main majority belonging to the sesquiterpene-lactones group, such as absinthin, anabsinthin, artabsin and matricin. The content of bitter constituents is influenced by the harvesting period, higher contents being obtained during flowering stage (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Oniga, 2007; EMA/HMPC/751484/2016). Other bioactive constituents of *A. absinthium* include flavonoids (quercetin, rutin, isoquercitrin), phenolic acids (caffeic and chlorogenic acids) and lignans (Ciocarlan *et al*., 2017; EMA/HMPC/751484/2016; Hussain *et al*., 2017; Oniga, 2007).

The European Pharmacopoeia requires a minimum essential oil content of 2 ml/kg dried drug (Eur. Ph. 8.0, 2013).

Pharmacological activities

The shikimic acid, a phenolic compound isolated from *A. absinthium*, showed anti-diabetic potential, by reducing the oxidative stress and glucose level, and preventing vascular damage in diabetic rats (Al-Malki, 2019). *A. absinthium* extracts showed *in vivo* hepatoprotective activity by increasing the activity of antioxidant enzymes, maintaining the integrity of the hepatocellular membrane and by inhibiting pro-inflammatory mediators and cytokines (Amat *et al*., 2010; Mohammadian *et al*., 2016). The extracts from the roots and the aerial parts of wormwood showed promising larvicidal activity against several mosquito species that are vectors for malaria, dengue fever and filariasis (Ali *et al*., 2018). *In vitro* studies highlighted the anticancer potential of wormwood (induction of apoptosis in human breast cancer cell) (Shafi *et al*., 2012). The essential oil showed *in vitro* antioxidant and antimicrobial activity against several pathogenic bacteria and fungi (Riahi *et al*., 2015). In a clinical trial, the powdered aerial parts of wormwood improved the symptoms of Crohn's disease patients, probably by its steroid-sparing effect (Omer *et al*., 2007). Wormwood also exhibited neuroprotective effects in rats (Bora & Sharma, 2010).

Current uses

The comminuted aerial parts of *A. absinthium*, in the form of infusion, tinctures and decoctions, are used internally in hepato-biliary and gastric disorders, to increase the appetite (anorexia), and against intestinal worms (Gruenwald *et al*., 2000; Oroian, 2011; Stanescu *et al*., 2014).

Precautions and adverse reactions

The high doses and long term use may have a neurotoxic effect due to the presence of thujone in the essential oil (Grigorescu *et al*., 1986; Parvu, 2006). It is contraindicated

for pregnant and lactating women, in acute intestinal disorders, in gastroduodenal ulcer (stimulates gastric secretion), and in biliary obstruction (Duke *et al*., 2002; Muntean *et al*., 2007; Parvu, 2006; Stanescu *et al*., 2014).
Due to insufficient data, the use by children and adolescents under 18 years of age has not been established. It may affect the ability to drive and use machines (EMA/HMPC/751490/2016).

Other warnings
Due to the neurotoxic effects and uterine stimulating activity of thujone, it is recommended to use chemotypes with low thujone content. Thus, the thujone content must be specified on the product, the daily dose being of maximum 6.0 mg (EMA/HMPC/751490/2016).

Caltha palustris L. (marsh marigold, „calcea calului"), Ranunculaceae family

Syn. *Caltha laeta* Sch., Ny et Ky (Ardelean & Mohan, 2008).
***Other common name*:** Cowslip, Kingcups, Water Blobs, Horse Blobs, Bull's Eyes, Leopard's Foot, Meadow Routs, Verrucaria, Solsequia, Sponsa Solis, Palsy Root, Water Dragon (Gruenwald *et al*., 2000).

Officinal products: aerial parts of the flowering plant (*Calthae herba*) (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Tita *et al*., 2009).

Botanical description
It is a perennial (Sarbu *et al*., 2013; Stefan & Oprea, 2007) herbaceous plant with numerous well developed, fibrous roots. The stem is erect, branched, glabrous, hollow, ascending or decumbent, 15-30 cm high, with many flowers. The leaves are dark-green, the basal ones are long-petiolate, reniform and the stem leaves are smaller and sessile. The flowers are yellow-golden, actinomorphic. The fruit is a follicle (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Parvu, 2006). It blooms from April to June (Parvu, 2006; Sarbu *et al*., 2013).
Distribution and habitat: common throughout the country, especially in hilly and mountainous areas, in wet places near swamps, on the edge of the streams, in swampy places (Ardelean & Mohan, 2008; Butura, 1979; Parvu, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007). It was reported in the Danube Delta area (Ciocarlan, 2011).
Harvesting period: during flowering stage, from April to June (Ardelean & Mohan, 2008).

Traditional uses
It is used traditionally against hepato-biliary disorders, as wound healing, laxative and diuretic agent (Gruenwald *et al*., 2000). In Canadian and Asian traditional medicine it was used to treat arthritis, rheumatism and gonorrhea (Suszko & Obminska-Mrukowicz, 2013). In Romanian folk medicine, the flowers were used against malaria (fever), being applied topically in the palm or wrist and at the lower end of the forearm. The flowering stems were also used as baths against hands and legs pain

(Butura, 1979). Other ethnopharmacological data mention the use of the plant (aerial part) as infusion in renal and digestive disorders (Tita *et al*., 2009).

Chemical composition

Several triterpenes were identified in *C. palustris*: sitosterol, hederagenic acid, hederagenin, 16,17-dihydroxykauran-19-oic acid, and palustrolide (Bhandari & Rastogi, 1984). It also contains protoanemonin and anemonin, bitter substances, polysaccharide, small amounts of berberine, isoquinoline alkaloids (Ardelean & Mohan, 2008; Butura, 1979; Gruenwald *et al*., 2000; Parvu, 2006).

Pharmacological activities

The polysaccharide fractions isolated from the aerial parts of *C. palustris* showed immunomodulatory effects through the modulation of the macrophage function, with benefic effects on collagen-induced arthritis in mice (Suszko & Obminska-Mrukowicz, 2013; Suszko & Obminska-Mrukowicz, 2017). The infusion from aerial parts has diuretic, laxative and sedative properties (Tita *et al*., 2009).

The methanol extract from *C. palustris* var. *alba* roots showed anthelmintic activity against gastrointestinal nematodes and antibacterial activity against *Bacillus subtilis, Staphylococcus aureus*, *Staphylococcus epidermidis, Pseudomonas aeruginosa* and *Proteus vulgaris* (Mubashir *et al*., 2014).

Analgesic, antiedemic, anti-inflammatory, antipyretic, antirheumatic, hyperglycemic, hypocholesterolemic, hypotensive and laxative properties were also reported for *C. palustris* (Duke *et al*., 2002; Gruenwald *et al*., 2000).

Current uses

The aerial parts are used for their diuretic, laxative and sedative effects (Parvu, 2006). Internally, it is also used in bronchitis, colds, cough, rheumatism, tuberculosis against gallstones and gout (Ardelean & Mohan, 2008; Duke *et al*., 2002).

Precautions and adverse reactions

A high degree of toxicity is reported for *C. palustris* in all vegetation phases (Gruenwald *et al*., 2000; Parvu, 2006), that can be reduced by boiling (Butura, 1979). Eating the raw plant led to poisoning (Duke *et al*., 2007). Due to its toxicity, it can also cause gastroenteritis and acute nephritis (Parvu, 2006). The prolonged skin contact with the fresh plant can lead to severe skin irritation (Gruenwald *et al*., 2000). Due to its toxicity, the plant is recommended to be used only topically as extract (Gruenwald *et al*., 2000).

Other warnings

Do not confuse it with toxic hellebores (Duke *et al*., 2007).

Capsella bursa-pastoris (L.) Medik. (shepherd's purse, „traista ciobanului"), Brassicaceae family

***Other common names*:** Shepherd's Scrip, Shepherd's Sprout, Lady's Purse, Poor Man's Parmacettie, Mother's Heart, Shepherd's Heart (Gruenwald *et al*., 2000).

Officinal products: According to the European Medicine Agency (EMA) the officinal product is represented by the blooming aerial part of shepherd's purse (*Bursae pastoris*

herba) (EMA/HMPC/262766/2010; EMA/HMPC/262767/2010). Literature also refers to *Herba Sanguinariae* (Stanescu *et al*., 2014).

Botanical description

Annual or biannual herbaceous plant with a simple tap root. The stem is erect, simple or branched, 6-60 (100) cm high, glabrous or sparsely hirsute. The basal leaves form a rosette, are lanceolate, entire-margined or sectate pinnatte, petioled, with a large terminal lobe, and with branched hairs. The stem leaves are entire-margined, sessile, sagittate, rare, increasingly smaller towards the top. The flowers are white, type 4, with 4 flat ovate or lanceolate sepals, white marginated, 4 obovate petals, androecium with 6 stamina, and are grouped in long terminal racemes. The inflorescence is extended after flowering. The fruit is 4 to 9 mm long and almost as wide. It is glabrous, flattened, long-stemmed, triangular and obcordate. The seeds are 0.8 to 1 mm long and red-brown, with a short style (Aksoy *et al*., 1998; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Istudor, 2005; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2014; Stefan & Oprea, 2007). It blooms from April to August (Ardelean & Mohan, 2008).

Distribution and habitat: frequent, from plain to mountain area (Parvu, 2006; Sarbu *et al*., 2013). It is a ruderal species (Stanescu *et al*., 2014), common throughout the country (Muntean *et al*., 2007). It was also reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: from May to August (Oroian, 2011).

Traditional uses

Shepherd's purse is used in Romanian folk medicine for dysmenorrhea and uterine bleeding. The infusion from the aerial parts was used against colds, and also as a diuretic in urinary tract infections (Stanescu *et al*., 2014). The infusion or maceration in wine was used to combat stomach ache and as a hemostatic in heavy menstruation (Butura, 1979). It is also used in haematemesis (vomiting with blood from an upper digestive hemorrhage), hematuria, diarrhoea and acute cystitis (Barnes *et al*., 2007). Shepherd's purse is a good remedy in preventing and stopping bleeding, being used especially for heavy uterine bleeding, but also for nose bleeding (Chevallier, 2016).

Chemical composition

C. bursa-pastoris aerial parts contain flavonoids (quercetin, kaempferol, luteolin, rutin, hesperidin and other luteolin and quercetin derivatives), phenolic acids (e.g. chlorogenic, syringic and vanillic acids), amines, aminoacids, essential oil, resin (Ardelean & Mohan, 2008; Butura, 1979; Chevallier, 2016; Grigorescu *et al*., 1986; EMA/HMPC/262767/2010; Istudor, 2005; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2014). *Bursae pastoris herba* also contains phytosterols (e.g. cholesterol, stigmasterol, β-sitosterol, lupeol), organic acids (oxalic, citric, malic, shikimic and fumaric acids), fatty acids (including polyunsaturated acids) and amines (acetylcholine, choline, aminoacids especially proline, histamine, tyramine) (Al-Snafi, 2015a; Barnes *et al*., 2007; Grosso *et al*., 2011). The seed oil is rich in unsaturated fatty acids (oleic, linoleic and linolenic acids) and the roots have high amounts of palmitic acid (Al-Snafi, 2015a).

Pharmacological activities

Antimicrobial, anticancer, anti-inflammatory, antioxidant, hepatoprotective, hemostatic, analgesic, antipyretic, anti-ulcer and diuretic activities were reported for *C. bursa-*

pastoris and its bioactive constituents (Al-Snafi, 2015a; Barnes *et al.*, 2007; Chevallier, 2016; Duke *et al*., 2002; Grosso *et al*., 2011; Ma *et al*., 2016). *C. bursa-pastoris* extracts have been proved to have antimicrobial activity against several pathogenic bacteria such as *Pseudomonas aeruginosa, Klebsiella pneumonia, Enterococcus faecalis, Staphylococcus aureus, Escherichia coli* (Al-Snafi, 2015a; Grosso *et al*., 2011). *In vivo* studies on animal model showed the antitumoral potential of shepherd's purse, probably due to its content in fumaric acid (Duke *et al*., 2002; Grigorescu *et al*., 1986; Parvu, 2006). *In vitro* studies suggest that the phenolic glycosides in shepherd's purse may be responsible for its anti-inflammatory activity in a neuroinflammatory model (Cha *et al*., 2017). The flavonoids from shepherd's purse showed moderate *in vitro* hepatoprotective activity (Ma *et al*., 2016). The methanol extract has a good free radical scavenging activity and moderate acetylcholinesterase inhibitory activity, thus its applicability in Alzheimer's disease could be further investigated (Grosso *et al*., 2011). The fumarates found in shepherd's purse showed a protective effect against autoimmune encephalomyelitis in mice (Al-Snafi, 2015a). *C. bursa-pastoris* has uterotrophic and hemostatic activities, reducing the heavy menstrual bleeding and duration of bleeding, probably due the presence of oxytocin-like polypeptides and flavonoids with anti-inflammatory potential (Danesh *et al*., 2019; Istudor, 2005; Stanescu *et al*., 2014).

A quaternary ammonium salt isolated from *Bursae pastoris herba* may be responsible for some of its activities (EMA/HMPC/262767/2010).

Current uses

The European Medicine Agency - Committee on Herbal Medicinal Products mentions the following preparations from the aerial part of the shepherd's purse: comminuted plant material and fluid extract. These are indicated for the reduction of menstrual bleeding in women with regular menstrual cycles, if other serious condition were excluded (EMA/HMPC/262766/2010; EMA/HMPC/262767/2010).

The plant product is administered in the form of extracts (infusion, fluid extract) for its hemostatic and vasoconstrictor action (Grigorescu *et al*., 1986). The extracts, comminuted or powdered plant material are included in products (e.g. tablets) used in dysmenorrhea, as a hemostyptic in prolonged menstrual bleeding, in the so-called "irritated bladder" in women (Stanescu *et al*., 2014). The aerial parts are used in dysmenorrhea, diarrhoea, hemorrhoids, varicose veins, venous insufficiency, bleeding wounds, heavy menstrual bleeding, as antihypertensive and vasoconstrictor (Ardelean & Mohan, 2008; Duke *et al*., 2002; Gruenwald *et al*., 2000; Istudor, 2005; Muntean *et al*., 2007; Oroian, 2011). The decoction and macerate is used against internal bleeding (stomach, lung) and hemophilia (Parvu, 2006).

Precautions and adverse reactions

The product is contraindicated in people with hypersensitivity to the active substances found in *C. bursa-pastoris*. The use by children and adolescents under 18 years of age is recommended only with a doctor's prescription. If side effects occur, a doctor or specialist should be consulted (EMA/HMPC/262766/2010). The potential interactions of shepherd's purse preparations with other concomitant medicinal products (in particular those with similar or opposite effects) should be considered (Barnes *et al*., 2007). Due to its content in oxalates, consumption by patients with kidney stones

should be avoided (Duke *et al*., 2002). The shepherd's purse is known as abortive and affects the menstrual cycle, thus its use during pregnancy and lactation should be avoided (Barnes *et al*., 2007; Duke *et al*., 2002).

Centaurea cyanus L. (cornflower, „albăstrele, vinețele"), Asteraceae family

Syn. *Centaurea cyanocephala* Velen. (Doroftei *et al*., 2011), *Cyanus segetum* Hill. (Lockowandt *et al*., 2019).

***Other common name*:** Centaurea, Bachelor's Buttons, Bluebonnet, Bluebottle, Blue Centaury, Cyani, Bluebow, Hurtsickle, Blue Cap and Cyani-flowers (Gruenwald *et al*., 2000).

Officinal products: marginal flowers (*Cyani flores*) (Grigorescu *et al*., 1986), also the entire anthodia (*Cyani flores cum receptaculi*) (Ardelean & Mohan, 2008), rarely only ligulate flowers (*Cyani flos sine receptaculis*) (Muntean *et al*., 2007), seeds and leaves (Chevallier, 2016).

Botanical description

It is an herbaceous, annual (rarely biennial) plant with a fusiform, whitish hairy root with numerous branches. Stem is erect (up to 100 cm), edged, simple or branched. The basal leaves are pinnatifid with narrow lobes, the upper leaves are entire-margined, linear-lanceolate, tomentaceous. The top of the stem and branches has an anthodium with funnel-shaped blue flowers. The tubular flowers are purple-violet and the ligulate ones are blue. The fruit is an achene with pappus (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Oroian, 2011; Stefan & Oprea, 2007). It blooms from July to September (Parvu, 2006).

Distribution and habitat: common from plain to mountain area, through grain crops, arid places (Ardelean & Mohan, 2008; Butura, 1979; Muntean *et al*., 2007; Sarbu *et al*., 2013). This species was reported in Macin Mountains and in the Danube Delta area (Andrei & Cristurean, 2006; Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: marginal flowers from July to August, anthodia from July to September (Ardelean & Mohan, 2008; Parvu, 2006; Stefan & Oprea, 2007).

Traditional uses

The medicinal properties of *C. cyanus* were mentioned for the first time in the 12th century by Hildegard of Bingen. The blue color of flowers was correlated with the health of eyes, this plant being used for eye complaints (Chevallier, 2016). Corn owers have been used in culinary decoration, in herbal teas and for pigmentation (Lockowandt *et al*., 2019).

The flowers are used in traditional medicine in the form of aqueous extract. In European traditional medicine, the aqueous extract from petals was used in the treatment of ocular, nervous, dermatological and gastric diseases, with diuretic, stimulant and tonic properties (Escher *et al*., 2018).

In Romanian folk medicine, the fresh flowers were applied on skin injuries. The decoction from cornflowers was used as eyewash (in the popular belief, this

preparation heals blue eyes). The plant soaked in wine or beer was taken as a diuretic, and comminuted as a purgative. The tea was used in colds and chest diseases. Also, inhalations were made against colds; the root juice was used in skin diseases, and the flower tea in kidney disease (Butura, 1979).

The infusion from aerial parts is used as eupeptic, astringent, diuretic, depurative and anti-inflammatory (Tita *et al*., 2009). Different preparations are used internally in renal and liver diseases (infusion, macerate), in diarrhoea, indigestion, dyspepsia, urinary disorders (infusion) (Parvu, 2006; Tita *et al*., 2009). Externally, the infusion was used in eye diseases (inflammation and conjunctivitis) and for scalp eczema (Gruenwald *et al*., 2000; Parvu, 2006). It was also used internally in fever, constipation, leucorrhea, menstrual complaints and in *Candida* vaginal infection, and for laxative, bitter, expectorant and tonic properties (Gruenwald *et al*., 2000). The decoction from leaves was used as a remedy to treat the rheumatic complaints (Chevallier, 2016).

Chemical composition

The flowers of *C. cyanus* contain anthocyans (e.g. centaurocyanin, cyanidine derivatives), flavonoids (apigenin, luteolin and quercetin derivatives, kaempferol), phenolic acids (chlorogenic, p-coumaric, caffeic and syringic acids), indole alkaloids (e.g. moschamine, centcyamine), tocopherols (α-tocopherol and γ-tocopherol), organic acids (e.g. oxalic, malic, shikimic, citric, succinic and fumaric acids) and bitter substances (Al-Snafi, 2015b; Fernandes *et al*., 2019; Gruenwald *et al*., 2000; Lockowandt *et al*., 2019; Marian *et al*., 2017).

Cornflower also contains sesquiterpene lactones (including cnicin), acetylenes, coumarins, polysaccharides (Chevallier, 2016; Escher *et al*., 2018), polyenes, tannins, mucilages, pectin (Ardelean & Mohan, 2008; Butura, 1979; Grigorescu *et al*., 1986; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006). Several indole alkaloids, namely moschamine, *cis*-moschamine, centcyamine and *cis*-centcyamine were identified in the seeds of *C. cyanus* (Sarker *et al*., 2001).

Pharmacological activities

Antibacterial, anti-inflammatory, antioxidant, gastroprotective, cytotoxic and diuretic activities were reported for *C. cyanus* and its bioactive constituents (Al-Snafi, 2015b; Chevallier, 2016; Gruenwald *et al*., 2000; Marian *et al*., 2017; Lockowandt *et al*., 2019). It also has antipyretic, astringent, cholagogue, diuretic, emmenagogue, expectorant, fungicide, hepatotonic, pectoral, stimulant and tonic properties (Duke *et al*., 2002; Stefan & Oprea, 2007; Tita *et al*., 2009).

The aerial parts (stems and leaves) showed *in vitro* antibacterial effect attributed to centaurocyanin (Gruenwald *et al*., 2000). Cnicin is a compound with moderate antibiotic activity (Chevallier, 2016).

The extract from *Centaurea flos* showed an important antioxidant activity, thus it can be used as a potential therapeutic agent with SOD-like and cytotoxic activities (Marian *et al*., 2017). The lower part of the capitulum has antioxidant and antibacterial activities (Lockowandt *et al*., 2019). The aqueous extract from *C. cyanus* petals showed *in vitro* antioxidant, anti-hemolytic, anti-hypertensive and antimicrobial properties (e.g. against *Pseudomonas aeruginosa, Listeria monocytogenes, Escherichia coli, Staphyloccocus aureus*) (Escher *et al*., 2018).

Current uses
The indications includ bacterial and fungic infections, cancer, cholecystosis, conjunctivosis, constipation, cough, dermatosis, diarrhoea, dysmenorrhea, eczema, fever, hepatosis, inflammation, jaundice, leucorrhea, mycosis, ophthalmia, pain, vaginosis and water retention (Duke *et al*., 2002). Internally, it is used in kidney and bladder disorders, anorexia, heart failure, phlebitis, edema, biliary dyskinesia and dyspepsia (Ardelean & Mohan, 2008; Stefan & Oprea, 2007). It is used externally as eye drops with anti-inflammatory action in eye conditions (e.g. dust irritations, conjunctivitis), and internally (infusion) as bitter tonic and diuretic (Muntean *et al*., 2007; Oroian, 2011).

Precautions and adverse reactions
No adverse reactions were reported at appropiate therapeutic doses (Duke *et al*., 2007; Gruenwald *et al*., 2000). It possesses a weak sensitization potential (Gruenwald *et al*., 2000).

Other warnings
Today, *C. cyanus* is rarely used as an inactive component in tea mixtures (Gruenwald *et al*., 2000).

Centaurium erythraea Rafn (centaury, „țintaură"), Gentianaceae family

Syn. *Centaurium minus* auct., *C. minus* auct. ssp. *minus*, *Erythraea centaurium* (L.) Pers. ssp. *centaurium* (Doroftei *et al*., 2011), *C. umbellatum* Gilib. (Barnes *et al*., 2007; Oniga, 2007).
***Other common name*:** common centaury, European centaury, Feverwort, Centaury Gentian, Centory, Bitter Herb, Bitterbloom, Bitter Clover, Wild Succory (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia and the European Medicine Agency (EMA) the officinal product is represented by the dried flowering aerial parts (*Centaurii herba*) of *C. erythraea* (EMA/HMPC/277493/2015; EMA/HMPC/277491/2015; Eur. Ph. 8.0, 2013). Literature also mentions the names *Herba Chironiae* or *Felis terrae* (Stanescu *et al*., 2002a).

Botanical description
It is an herbaceous, annual or biennial plant species (Sarbu *et al*., 2013), with pivoting root. The stem is erect (up to 30 high), thin, with four edges, simple, glabrous and branched at the top, with a rosette of ovate-elliptical basal leaves, short petiolate, and elongated-ovate or ovate-elliptical stem leaves, sessile, opposite. The flowers are pentamerous, tubular, red, rarely white, and grouped in cyme. The fruit is a yellow bilocular capsule with many small, brown seeds (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Stefan & Oprea, 2007). It blooms from July to September (Andrei & Cristurean, 2006).
Distribution and habitat: This species was reported in Macin Mountains and in the Danube Delta area (Andrei & Cristurean, 2006; Ciocarlan, 2011; Doroftei *et al*.,

2011). *C. erythraea* ssp. *turcicum* (Velen.) Melderis is found in Constanta, Tulcea (Sarbu *et al*., 2013) and in Danube Delta area (Lupilor and Saraturile marine grinds, Sacalin) (Doroftei *et al*., 2011) and *C. erythraea* Rafn. ssp. *erythraea* in Danube Delta area (Ciocarlan, 2011).
Harvesting period: during flowering stage (Istudor, 2001; Oniga, 2007; Parvu, 2006).

Traditional uses
The plant is used internally as a bitter, with aromatic and stomachic properties, against dyspepsia, to increase gastric secretions, to reduce blood pressure, and externally as a wound healing agent (Barnes *et al.,* 2007; Chevallier, 2016; Gruenwald *et al*., 2000). The aerial parts were used in Romanian folk medicine to increase appetite (in anorexia), in biliary dyskinesia, liver diseases, to decrease fever, against cold, flu, sciatica, pinworms, eczema and wounds (Parvu, 2006).

Chemical composition
The aerial parts of *C. erythraea* contain phenolic acids (e.g. caffeic, p-coumaric, ferulic acids), flavonoids (e.g. luteolin, apigenin, quercetin derivatives, rutin, isoquercitrin, kaempferol derivatives, astragalin, naringenin), xanthones (e.g. decussatin, eustomin, desmethyleustomin) and secoiridoids (e.g. sweroside, gentiopicrin, swertiamarin, loganin, secologanin) (Aberham *et al*., 2011; Chevallier, 2016; Đorđević *et al*., 2017; EMA/HMPC/277491/2015; Kachmar *et al*., 2019; Oroian, 2011; Stefkov *et al*., 2014).
The aerial parts also contain essential oil (0.02%) consisting of monoterpenes hydrocarbons, sesquiterpenes hydrocarbons, oxygenated monoterpenes, oxygenated sesquiterpenes, ketones, acids, aldehyde and alkanes, the major compounds being carvacrol, menthol, tricosane, isomenthone, piperitone, hexadecanoic acid, toluene, camphor and menthone (Bouyahya *et al*., 2019; Jerković *et al*., 2012).
C. erythraea has 11.80% water-soluble polysaccharides and 2.33% pectin substances (dry weight) (Stoiko *et al*., 2017). Alkaloids (gentianine, gentianidine), sterols, lactones, resins, fatty acids were also identified in *C. erythraea* (Ardelean & Mohan, 2008; Barnes *et al*., 2007; Gruenwald *et al*., 2000; Oniga, 2007; Parvu, 2006).

Pharmacological activities
The essential oil showed a good antimicrobial activity against several bacteria, namely *Staphylococcus aureus, Listeria monocytogenes, Proteus mirabilis, Escherichia coli, Salmonella enteritidis, Bacillus cereus* (Bouyahya *et al*., 2019; Jerković *et al*., 2012). The essential oil also showed *in vitro* anti-diabetic potential, by inhibiting the enzymes α-amylase, α-glucosidase and tyrosinase (Bouyahya *et al*., 2019). The anti-diabetic potential of the methanol extracts from *C. erythraea* was demonstrated *in vivo* (animal models), the administration of the extract leading to increased insulin level, decreased blood glucose, reduction of glycated hemoglobin concentration, regulation of serum lipids status (decrease of total cholesterol, triglyceride, HDL and LDL levels), decreased lipid peroxidation, reduction of oxidative stress (Đorđević *et al*., 2017; Stefkov *et al*., 2014).
An *in vivo* study showed the hepatoprotective potential of *C. erythraea* hydroalcoholic extract, by reducing fat accumulation in liver and improving liver steatosis (Hamza *et al*., 2015). The aqueous extract showed a good antioxidant and anti-inflammatory potential (inhibition of 5-lipoxygenase) in *in vitro* non-cellular systems (Kachmar *et*

al., 2019). The anti-inflammatory activity was also documented in animal models, gentiopicroside inhibiting tumor necrosis factor production (Barnes *et al*., 2007).
The bitter substances have tonic effect (stimulation of gastric secretion) and laxative action (Chevallier, 2016; Duke *et al*., 2002; Gruenwald *et al*., 2000; Istudor, 2001; Oniga, 2007; Oroian, 2011; Parvu, 2006). The active constituents of *C. erythraea* also have central nervous system depressant activity (Barnes *et al*., 2007; Istudor, 2001; Stanescu *et al*., 2002a).

Current uses
The European Medicine Agency - Committee on Herbal Medicinal Products refers to the following types of herbal preparations: comminuted herbal substance (herbal tea), tablets (with powdered plant material and/ or extract, singular or in combination with other medicinal plants), liquid extract, tincture and oral solutions (plant extract). These are used in the European countries in gastrointestinal disorders (stomachic, carminative and choleretic effects), prevention of renal gravel, against urinary tract infections and inflammation (EMA/HMPC/277493/2015; EMA/HMPC/277491/2015). Different preparations (soft extract, tincture, infusion) (Istudor, 2001; Oniga, 2007) are used in dyspeptic complaints, loss of appetite, anorexia (Gruenwald *et al*., 2000; Stanescu *et al*., 2002a). The plant is also included in infusion formulas used against hypertension, dysmenorrhea and cystitis, vomiting and bloating (Parvu, 2006).

Precautions and adverse reactions
No adverse reactions were reported for proper administration (Gruenwald *et al*., 2000). It is contraindicated to be used by individuals with gastro-duodenal ulcer, due to the stimulation of gastric secretion (Barnes *et al*., 2007; Gruenwald *et al*., 2000). Due to the lack of data, the use by pregnant and lactating women and by children and adolescents under 18 years is not recommended (Duke *et al*., 2007; EMA/HMPC/277493/2015).

Other warnings
It may be confused with other *Centaurium* varieties (Gruenwald *et al*., 2000) and with *Silene armeria* L. (Caryophyllaceae) during harvesting (Istudor, 2001; Stanescu *et al*., 2002a).

Chelidonium majus L. (greater celandine, „rostopască"), Papaveraceae family

***Other common names*:** celandine, celandine poppy, elon-wort, felonwort, rock poppy, swallow-wort, ascelandine (Biswas, 2013; Changizi-Ashtiyani *et al*., 2017; Maji & Banerji, 2015).

Officinal products: According to the European Pharmacopoeia and the European Medicine Agency (EMA) the officinal products is *Chelidonii herba* represented by dried *C. majus* L. aerial parts, whole or cut, harvested at flowering stage (EMA/HMPC/369801/2009; Eur. Ph. 8.0, 2013). Literature also mentions the use of *Chelidonii radix* (roots) (Stanescu *et al*., 2014), *Chelidonii herba et radix* (Aprotosoaie & Stanescu, 2010), and of latex (Chevallier, 2016).

Botanical description

It is an herbaceous, perennial plant with a dark brown, branched rhizome. The stem is branched and slightly tomentaceous, 50-80 cm in height. The leaves are large, alternate, glabrous, pinnatisect, green on the upper side, blue-greenish on the lower side. The basal and inferior leaves are petiolate and those on the upper part are sessile. The yellow flowers, with 2 sepals, 4 petals and numerous stamens, are grouped in a simple umbel. The fruit is a cylindrical, unilocular, multisperm capsule. The seeds are ovoid, black, shiny, with a well-developed appendage. The whole plant contains an yellow-orange latex which in contact with the air turns brown (Parvu, 2006; Stanescu *et al*., 2002a; Stanescu *et al*., 2004a; Stefan & Oprea, 2007). It blooms from April to September (Istudor, 2005; Oroian, 2011).

Distribution and habitat: common in shady places, ruderal areas, bushes, black locust forests, from the plains to the mountain areas (Ardelean & Mohan, 2008; Sarbu *et al*., 2013).

Harvesting period: roots preferably in autumn (when the alkaloid content is higher), aerial parts during flowering stage (Aprotosoaie & Stanescu, 2010; Istudor, 2005).

Traditional uses

C. majus is known since ancient times, being used in stomach and liver diseases, in the treatment of warts, etc. (Muntean *et al*., 2007). In folk medicine it is used internally for hepato-biliary disorders such as cholecystopathies, acute hepatitis, early stages of liver cirrhosis, gallstones, hepato-biliary colic and biliary dyskinesia, for cough, angina pectoris and as diuretic (Aprotosoaie & Stanescu, 2010; Oroian, 2011; Parvu, 2006; Tita *et al*., 2009). The aerial parts were mixed with field parsley, then boiled in milk and used against gonorrhea. Externally, the latex was used to treat warts (Istudor, 2005; Oroian, 2011; Stanescu *et al*., 2002a; Stanescu *et al*., 2004a); the infusions were used as washes for dermatophytosis and other dermatological conditions like psoriasis (Butura, 1979; Parvu, 2006; Stanescu *et al*., 2014).

Chemical composition

The main bioactive constituents of *C. majus* are isoquinoline alkaloids, in amounts of 3-4% in roots, 0.1-1.4 % in the aerial parts and 1.5% in the pericarp of the fruit (Aprotosoaie & Stanescu, 2010; Istudor, 2005; Stanescu *et al*., 2002a; Stanescu *et al*., 2004a). 25 alkaloids were identified and isolated, including chelidonine, chelerythrine, sanguinarine, berberine, coptisine, stylopine, protopine and coptisine (Aprotosoaie & Stanescu, 2010; Chevallier, 2016; Gilca *et al*., 2010; Gird *et al*., 2017; Mikołajczak *et al*., 2015). The aerial part also contains flavonoids, carotenoids, saponins, phenolic acids (caffeic, ferulic and p-coumaric acids), traces of essential oil, resins (Aprotosoaie & Stanescu, 2010; Ardelean & Mohan, 2008; Biswas, 2013; Changizi-Ashtiyani *et al*., 2017; Gilca *et al*., 2010; Maji & Banerji, 2015; Parvu, 2006; Stanescu *et al*., 2014). The roots also contain, in addition to alkaloids, choline, histamine, vitamin C, carotenoids, flavonoids and saponins (Aprotosoaie & Stanescu, 2010). The leaves have high vitamin C content (Muntean *et al*., 2007). The latex contains proteolytic enzymes, resins and alkaloids (Istudor, 2005; Stanescu *et al*., 2004a).

The European Pharmacopoeia requires a total alkaloid content, expressed as chelidonine, of minimum 0.6% (dried drug) (Eur. Ph. 8.0, 2013).

Pharmacological activities

Anti-inflammatory, analgesic, antimicrobial, antiviral, immunomodulatory, gastroprotective, choleretic, antitumoral, hypoglycemic and antioxidant activities were reported for *C. majus* extracts (Barnes *et al*., 2007; Biswas, 2013; Changizi-Ashtiyani *et al*., 2017; Duke *et al*., 2002; Gilca *et al*., 2010; Gird *et al*., 2017; Maji & Banerji, 2015; Mikołajczak *et al*., 2015; Parvu, 2006).

In vitro studies reveal significant antimicrobial activity of the aerial part and root extracts against bacteria (*Streptococcus mutans, Bacillus cereus, Salmonella enteritis, E. coli*), fungi (from *Fusarium* genus) and yeast (*Candida albicans*) (Aprotosoaie & Stanescu, 2010; Maji & Banerji, 2015). The crude extract inhibits the development of *Herpes simplex* type 1 and the alkaloids inhibit the reverse transcriptase enzyme of HIV-1 virus (Changizi-Ashtiyani *et al*., 2017; Maji & Banerji, 2015).

The alkaloids from greater celandine have anticancer potential in tumor cells, by inducing apoptosis through several mechanisms, such as: activating caspase 3, 7, 8 and 9; increase of pro-apoptotic and decrease of anti-apoptotic proteins formation; up-regulating the expression of apoptotic genes; inhibition of telomerase (Biswas, 2013; Gilca *et al*., 2010; Maji & Banerji, 2015).

The alkaloid chelidonine has papaverin-like antispasmodic activity on smooth muscles (Muntean *et al*., 2007; Stanescu *et al*., 2014). The alkaloids have cholecystokinetic properties and contribute to biliary drainage, pancreatic stimulation and good intestinal digestion (Aprotosoaie & Stanescu, 2010; Gilca *et al*., 2010). The anti-wart action is due to the presence of alkaloids, proteolytic enzymes and resins in the latex, with local antimitotic and irritative properties and with necrotizing action (Stanescu *et al*., 2014).

Current uses

It is used internally as comminuted dried aerial part for infusion, tincture, fluid extract and dried extract in biliary (chronic cholecystopathy, hepato-biliary colic, biliary dyskinesia, gallstones) and gastrointestinal dysfunctions (Aprotosoaie &Stanescu, 2010; Ardelean & Mohan, 2008; EMA/HMPC/369801/2009; Istudor, 2005). Due to its antimitotic properties, sanguinarine is being used as an antiplatelet agent in mouth washes and other dental preparations (Stanescu *et al*., 2002a; Stanescu *et al*., 2004a). *C. majus* is used in homeopathy against inflammation, chronic hepato-biliary disorders and rheumatism (Gruenwald *et al*., 2000; Oroian, 2011; Stanescu *et al*., 2014). Externally, it is used as tincture, ointment and gel, singular or in mixture with other medicinal plants, for the topical treatment of warts, *Herpes simplex* infections and psoriasis (EMA/HMPC/369801/2009).

Precautions and adverse reactions

Several adverse reactions were documented in connection to the internal use of *C. majus*, including abdominal pain, diarrhoea, nausea, increased hepatic enzymes, acute hepatitis, hepatocellular damage and jaundice (Barnes *et al*., 2007; EMA/HMPC/369801/2009; Pantano *et al*., 2017). This may be due to the alkaloid content in *C. majus*. The high frequency of hepato-biliary adverse reaction led to withdrawal of *C. majus* products in some EU Member States (or their use is restricted), the benefit-risk assessment of internal use of *C. majus* being considered

negative (Chevallier, 2016; EMA/HMPC/369801/2009; Pantano *et al*., 2017). Its use during pregnancy is not recommended (Gruenwald *et al*., 2000).

Cichorium intybus L. (chicory, „cicoare"), Asteraceae family

Syn. *Cichorium intybus* L. ssp. *glabratum* (C. Presl) Arcang., *Cichorium intybus* L. ssp. *sativum* (Bisch.) Janch., *Cichorium intybus* L. ssp. *foliosum* (Hegi) Janch. (Doroftei *et al*., 2011).

***Other common names*:** succory, hendibeh (Gruenwald *et al*., 2000).

Officinal products: According to the European Medicine Agency (EMA) the officinal product is represented by the dried roots (*Cichorii radix*) (EMA/HMPC/121816/2010; EMA/HMPC/113041/2010). Literature also mentions the use of the non-lignified aerial part in the flowering phase (*Cichorii herba*) or their mixture (*Cichorii radix et herba*) (Grigorescu *et al*., 1986; Istudor, 2001; Muntean *et al*., 2007; Oroian, 2011). The flowers are also used (Chevallier, 2016).

Botanical description

Cichorium intybus is a perennial plant with a well developed taproot. The stem is erect, 50-130 cm high, sparsely branched and often rough tomentaceous (Al-Snafi, 2016; Gruenwald *et al*., 2000; Singh & Chahal, 2018). The basal leaves are petiolate, dark green, matte, with an oval-lanceolate leaf blade, runcinately pinnatipartite, with a larger terminal lobe. Stem leaves are smaller, sessile, oval-lanceolate, with a cordate base. The flowers are ligulate, blue, grouped in calatides of 3-4 cm in diameter, solitary or in groups, sessile or with a short pedicle. The fruit is an obovate achene, 2-3 mm in length, with a short pappus. It blooms from July to September (Al-Snafi, 2016; Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Istudor, 2001; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013).

Distribution and habitat: from plain to mountain areas, on roadsides, ridges, meadows and near rivers (Butura, 1979; Istudor, 2001; Oroian, 2011). It is found in the Macin Mountains and throughout the Danube Delta area (Andrei & Cristurean, 2006; Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: the aerial part during flowering stage, in July-September, prior to the lignification of the stems, and the roots in September-November (Ardelean & Mohan, 2008; Istudor, 2001; Oroian, 2011; Parvu, 2006).

Traditional uses

The European Medicine Agency - Committee on Herbal Medicinal Products refers to the following products from *Cichorii radix* with traditional use: comminuted herbal substance as herbal tea for internal use for the relief of mild digestive disorders symptoms (bloating, flatulence, slow digestion) and temporary loss of appetite (EMA/HMPC/121816/2010; EMA/HMPC/113041/2010).

In Romanian folk medicine, the raw leaves and flowers, macerated in oil were used externally to treat wounds. The flower decoction was used against ophthalmological conditions, stimulation of liver and kidney functions (Butura, 1979; Parvu, 2006). The

flower infusion was used to treat liver conditions, fever, rheumatic pain, against stomach ache, constipation (Butura, 1979; Parvu, 2006). The flowers macerated in wine were used against headache and stomach ache (Parvu, 2006). The root decoction was used against chest pain and acute visceral pain (Butura, 1979). Externally, it was used to stimulate the healing of wounds and cuts, the raw leaves being applied over the affected area (Parvu, 2006). The roasted root was often used as a substitute for coffee (Chevallier, 2016).

Chemical composition

Bitter compounds, such as the sesquiterpenes lactones lactucin, lactucopicrin, guaianolid glycosides, are present in all parts of the plant (Gruenwald *et al*., 2000; Istudor, 2001; Oroian, 2011; Singh & Chahal, 2018; Al-Snafi, 2016). The main bioactive constituents present in the roots are: sesquiterpenes lactones, inulin (15-60%), tannins, alkaloids, flavonoids, phenolic acids and small amounts of essential oil (Al-Snafi, 2016; Chevallier, 2016; EMA/HMPC/113041/2010; Istudor, 2001; Grigorescu *et al*., 1986; Oroian, 2011; Parvu, 2006; Singh & Chahal, 2018). The leaves contain chicoric acid (main compound in the methanol extract), inulin, arginine, choline, caffeic acid, citric acid and flavonoids (isorhamnetine, apigenin, apigenin derivatives, luteolin, quercetin) (EMA/HMPC/113041/2010; Parvu, 2006; Street *et al*., 2013). The presence of coumarins (umbelliferon, esculetin) was identified in the stem (EMA/HMPC/113041/2010). The flowers contain anthocyanins responsible for their blue color (cyaniding and delphinidin derivatives), flavonoids, essential oil, methoxycoumarin (Al-Snafi, 2016; EMA/HMPC/113041/2010; Street *et al*., 2013). Several bioactive compounds were identified in the seeds: saponins, stigmasterol, phenolic acids and flavonoids (Al-Snafi, 2016; Singh & Chahal, 2018).

Pharmacological activities

Antimicrobial, antioxidant, anti-inflammatory, analgesic, anti-diabetic, hepatoprotective, anthelmintic, antimalarial, gastroprotective, tumor-inhibitory, antiallergic, immunomodulatory, wound healing and vasorelaxant activities were reported for *C. intybus* and its bioactive constituents (Al-Snafi, 2016; Chevallier, 2016; Duke *et al*., 2002; Istudor, 2001; Parvu, 2006; Saxena *et al*., 2014; Singh & Chahal, 2018; Street *et al*., 2013).

The ethanol and aqueous extracts from *C. intybus* showed significant *in vivo* hepatoprotective activity (animal model) by improving serological parameters and stimulating the regeneration of hepatocytes. The hepatoprotective activity of the aqueous extract was similar to that of silymarin (Nallamilli *et al*., 2013). The methanol root extract from chicory showed good larvicidal activity against several mosquito species that are vectors for several diseases such as malaria, dengue fever and filariasis (Ali *et al*., 2018). The addition of chicory in ruminant's diet was associated with antiparasitic activity, *in vitro* studies highlighting the potent effects of the sesquiterpenes lactones against helminthes and protozoa (Peña-Espinoza *et al*., 2018). A natural extract from chicory, rich in chicoric and caffeoylquinic acids showed anti-diabetic potential, improving the glucose tolerance and reducing the basal hyperglycemia in diabetic rats (Ferrare *et al*., 2018).

Current uses
It is used in digestive disorders (anorexia, bloating, slow digestion, cholecystopathy, flatulence), as mild laxative and depurative. It is also used in dietary nutrition of diabetics and as an adjunct in weight loss (Istudor, 2001; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006). It is also used as tablets (*C. intybus* powder mixed with other medicinal plants) for sustaining the hepato-biliary function. The tablets with *Chicory radix* powder are used for their laxative-purgative action, and *Cichorii herba* is used as depurative tea (Istudor, 2001). The dried aqueous extract from the roasted roots is used as a coffee substitute (Muntean *et al*., 2007; Oroian, 2011).

Precautions and adverse reactions
Its use by persons with hypersensitivity to the active substances or to other plants of the Asteraceae (Compositae) family is not indicated. Due to the lack of safety data, it is not recommended during pregnancy, lactation or by children under 12 years of age (EMA/HMPC/121816/2010).

Cirsium arvense (L.) Scop. (creeping thistle, "pălămidă"), Asteraceae family

Syn. *Cirsium setosum* (Willd.) M.Bieb., *Cirsium incanum* (S.G.Gmel.) Fisch., *Cnicus arvensis* (L.) Roth, *Cirsium horridum* (Wimm. & Grab.) Stankov, non (M. Bieb.) Fisch., *Cirsium argenteum* Peyer ex Vest (Doroftei *et al*., 2011).

Officinal products: *Cirsium arvense* is not an officinal drug.

Botanical description
It is an herbaceous, perennial plant species (Butura, 1979; Sarbu *et al*., 2013). The rhizome is well-developed, deep and superimposed. The stem is straight, almost glabrous, branched, with basal leaves that disappear before flowering. The leaves are pinnatisect with spiny tips, pubescent on the underside. The flowers are light purple, arranged in small, globular or ovoid calatides, solitary or in corymb-shaped panicles. The fruits are small achene, with a dirty-white pappus (Grigorescu *et al*., 1986). It blooms from July to August (Sarbu *et al*., 2013).
Distribution and habitat: widespread in all regions, frequent from lowlands to mountainous areas, sparse forests, ruderalized meadows, as weed in crops (Andrei & Cristurean, 2006; Grigorescu *et al*., 1986; Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).
Harvesting period: during flowering stage (Nazaruk, 2008).

Traditional uses
C. arvense was traditionally used as a tonic, diuretic and astringent agent, in the treatment of tuberculosis, against toothache, skin lesions, metrorrhagia, peptic ulcer, gastritis, diabetes and intestinal worms (Hossain *et al*., 2016; Hossain *et al*., 2017; Khan *et al*., 2011b; Khan *et al*., 2013). In Polish traditional medicine is used as diuretic, astringent and anti-inflammatory remedy (Nazaruk, 2008).

In Romanian folk medicine, the decoction was used against typhus, both internally and externally; the ripe root was used externally in tonsillitis; the plant mixed with other medicinal plants was used externally in baths against rheumatism (Butura, 1979).

Chemical composition

The aerial parts contain flavonoids (rutin hydrate, quercetin, kaempferol, hispidulin, luteolin, acacetin), phenolic acids (p-coumaric acid), coumarins (scopoletin, 6,7-dimethoxycoumarin), tannins, sterols (taraxasterol), alkaloids, mucilages, essential oil and carotenoids (Dutta & Ray, 1972; Grigorescu *et al*., 1986; Hossain *et al*., 2016; Hossain *et al*., 2017; Khan *et al*., 2011b; Khan *et al*., 2013).

Several flavonoids were identified in the leaves of *C. arvense*, namely tricin-5-*O*-glucoside, quercetin-3-*O*-digalactoside, quercetin-3-*O*-rhamnoglucoside, kaempferol-3-*O*-galactoside (Wallace, 1974).

Pharmacological activities

The methanol and ethanol extracts from the aerial parts, inflorescences and leaves showed *in vitro* antioxidant activity (Hossain *et al*., 2016; Nazaruk, 2008).

The ethanol extracts and bioactive compounds isolated from the aerial parts showed a high antibacterial activity against *Staphylococcus aureus, Staphylococcus pyogenes, Salmonella typhi*, *Bacillus subtilis, Shigella flexenari, Escherichia coli,* and a moderate antifungal activity against *Trichophyton longifusus, Candida albicans, Microsporum canis* and *Fusarium solani* (Hossain *et al*., 2017; Khan *et al*., 2011b; Khan *et al*., 2013). The ethanol extract also showed *in vitro* anthelmintic activity (Hossain *et al*., 2017). The hydroalcoholic extract induces an increase in bile secretion (Grigorescu *et al.,* 1986).

Current uses

It is used in hepato-biliary disorders (Grigorescu *et al*., 1986).

Precautions and adverse reactions

Its spines cause inflammation of the skin, and the pappus can cause eye irritation (Butura, 1979; Grigorescu *et al*., 1986).

Clematis vitalba L. (traveller's joy, „curpen de pădure"), Ranunculaceae family

Officinal products: leaves (*Clematis folium*) (Ardelean & Mohan, 2008; Butura, 1979; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Tita *et al*., 2009).

Botanical description

It is a perennial liana, with a length of 3-10 m, with striated and hairy vines. The rhizome is well-developed from which roots are generated. The stems are climbing, with prominent longitudinal edges towards the nodes. The leaves are simply pinnate-composed, with 3-9 petiolate, ovate or nearly cordate, entire leaflets, more or less irregularly crenate-lobed. The stem is climbing due to the petioles that are transformed into tendrils and are clinging. The white flowers are grouped in terminal or axillary cymes. The fruits are red-brown, long-tailed polyachene (Ardelean & Mohan, 2008;

Gruenwald *et al*., 2000; Sarbu *et al*., 2013; Stefan & Oprea, 2007). It blooms from June to September (Ardelean & Mohan, 2008; Parvu, 2006; Sarbu *et al*., 2013).

Distribution and habitat: widespread all over the country, in the plain and hilly areas, frequented in deciduous forests, bushes, meadows, from the steppe area to the beech floor, ruderal places (Ardelean & Mohan; Grigorescu *et al*., 1986; Parvu, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, Cardon, Letea) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: from June to September (Ardelean & Mohan, 2008).

Traditional uses

In Romanian folk medicine, it is used as diuretic, analgesic, anti-epileptic, anti-inflammatory, anti-malaric and antitussive agent, for hair growth and in dizziness (Grigorescu *et al*., 1986; Segneanu *et al*., 2019).

The plant was used externally as baths for skin conditions or as decoction to stimulate hair growth; internally, as tincture against hernia and acute infections, and as infusion against cough. The young vines were also used as condiment (Butura, 1979).

Other ethnopharmacological data mention the use of flowers and leaves, as infusion in wounds (external) and respiratory disorders (Tita *et al*., 2009).

Chemical composition

C. vitalba contains protoanemonin, anemonin, terpenoids, saponins (vitalboside A, vitalboside F, vitalboside D, vitalboside G, vitalboside H), alkaloids, sterols (β-sitosterol, campesterol), phenolic acids (caffeic, chlorogenic acids) and flavonoids (vitaboside) (Ardelean & Mohan, 2008; Buzzini & Pieroni, 2003; Chawla *et al*., 2012; Grigorescu *et al*., 1986; Parvu, 2006; Segneanu *et al*., 2019; Ulubelen, 1970).

Pharmacological activities

The extracts from the young shoots showed antimicrobial activity against several yeast and yeast-like microorganisms, especially against several *Prototheca* species (Buzzini & Pieroni, 2003).

The ethanol extract from aerial parts showed significant *in vivo* (animal models) anti-inflammatory, antinociceptive (analgesic) and antipyretic effects, in a dose-dependent manner; the anti-inflammatory effect may be due to the prostaglandin inhibition by vitalboside (Chawla *et al*., 2012; Yesilada & Kupeli, 2007). The ethanol extract also showed benefic effects as adjuvant in arthritis (Chawla *et al*., 2012).

C. vitalba also has vulnerar, antitussive, diuretic, cicatrizing, antirheumatic and anti-malaric properties (Duke *et al*., 2002; Parvu, 2006; Segneanu *et al*., 2019; Stefan & Oprea, 2007; Tita *et al*., 2009).

Current uses

C. vitalba is used in rheumatic pain and neuralgia (Ardelean & Mohan, 2008). Young vines, shortly boiled, are consumed as food in Italy (Chawla *et al*., 2012). *Clematis* species are used against edema, eye infections, gout, skin disease, and as antipyretic (Duke *et al*., 2002; Yesilada & Kupeli, 2007).

Internally, the tincture is used to treat urethral stricture, and the decoction against cough; externally, it is used as wound healing agent and against skin inflammation (Parvu, 2006).

Precautions and adverse reactions
Due to its content of alkaloids, the high intake of this plant can be toxic (Gruenwald *et al*., 2000; Parvu, 2006; Stefan & Oprea, 2007).
The fresh plant contains protoanemonines, thus the ingestion of raw plant can lead to severe irritation to the gastrointestinal tract, colic, severe diarrhoea and irritation of the urinary drainage passages (Duke *et al*., 2002; Gruenwald *et al*., 2000). The fresh plant applied topically can cause skin irritation (Chawla *et al*., 2012; Gruenwald *et al*., 2000). In the drying process, the toxic protoanemonin is degraded to a non-toxic compound (Chawla *et al*., 2012).

Cornus mas L. (Cornelian cherry, „corn"), Cornaceae family

***Officinal products*:** fruits (*Corni fructus*) (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986), bark (*Corni cortex*) (Grigorescu *et al*., 1986).

Botanical description
It is a shrub with a well-developed root system. The stem is tall (4-8 m), singular, often in the form of a bush with 4-5 stems. Bark with dry rhytidome. The leaves are ovate-elliptical, with curved ribs, hairy on both sides, and in the autumn turn red. The yellow flowers appear before leafing, are small, short-pedicellate, arranged in umbel-shaped cyme. The fruits are oval drupes, bright red to cherry red, reaching maturity in August-September (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Parvu, 2006; Sarbu *et al*., 2013). It blooms from February to March (Ardelean & Mohan, 2008).
Distribution and habitat: frequent from the plain to the hilly area (Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, C.A. Rosetti, Cardon, Letea) (Ciocarlan, 2011; Doroftei *et al*., 2011).
Harvesting period: fruits at full ripening (August - September) (Parvu, 2006).

Traditional uses
Traditionally, *C. mas* has been used against respiratory disorders (asthma, cough, bronchitis), gastrointestinal disorders, diarrhoea, liver and kidney diseases, viral infections (flu, measles and chicken pox), anemia, rheumatism, diabetes, cardiac problems, as diuretic, astringent, tonic, antipyretic, anti-inflammatory and wound healing agent, to increase immunity. In addition, it is also used to produce drinks, syrups and jams (Brindza *et al*., 2007; Czerwinska & Melzig, 2018; Dinda *et al*., 2016; Petkova & Ognyanov, 2018; Soltani *et al*., 2015; Yigit *et al*., 2018).
In Romanian folk medicine, the decoction from the dried leaves was used against diarrhoea, dysentery and intestinal worms; the fruits, fresh or as infusion, were used against cramps and diarrhoea; the decoction from the bark was used externally against skin conditions (Butura, 1979; Parvu, 2006).
Other ethnopharmacological data mention the use of the infusion and decoction from *Cornus* fruits, leaves and bark in diarrhoea, dysentery and fever (Tita *et al*., 2009).

Chemical composition

The fruits of *C. mas* have been found to contain a wide range of bioactive compounds such as anthocyanins, flavonoids (e.g. quercetin and kaempferol derivatives, catechin and epichatechin), phenolic acids (e.g. p-coumaric, caffeic, gallic, rosmarinic and ferulic acids), vitamins (ascorbic acid, α-tocopherol, biotin, riboflavin), organic acids, tannins (cornusiin A-G, camptothin A and B), iridoids, triterpenoids (ursolic acid), monoterpenoids and carotenoids (Bjić-Ljubičić *et al.,* 2018; Dinda *et al*., 2016; Moldovan *et al*., 2016; Rudrapaul *et al*., 2015). The anthocyanins include delphinidin 3-galactoside, cyanidin 3-galactoside, pelargonidin 3-galactoside, cyanidin 3-glucoside, pelargonidin 3-glucoside, delphinidin 3-*O*-β-galactopyranoside and cyanidin 3-*O*-β-galactopyranoside (Dinda *et al*., 2016; Hamid *et al*., 2011; Moldovan *et al*., 2016; Pantelidis *et al*., 2007). Among the iridoids, loganic acid, loganin, secologanin, sweroside, catalposide and cornuside were identified (Czerwinska & Melzig, 2018; Deng *et al*., 2013; Dinda *et al*., 2016; Sozanski *et al*., 2014; Szumny *et al*., 2015).

Pharmacological activities

In vitro and *in vivo* (animal model) studies showed the anti-inflammatory and antimicrobial activities of iridoids and phenolic compounds from *C. mas*, and their intraocular pressure reduction potential (also beneficial for the management of diabetic retinopathy) (Deng *et al*., 2013; Szumny *et al*., 2015). The methanol and aqueous extracts showed antimicrobial activity against several pathogenic bacteria and fungi, the strongest effect being observed against *Escherichia coli* (Yigit *et al*., 2018).

Cornelian cherry fruit extract showed significant *in vitro* and *in vivo* antioxidant and anti-inflammatory activities by inhibiting the formation of pro-inflammatory markers (TNF-α, IL-1β and IL-13) and enhancing the production of anti-inflammatory cytokines (IL-10) in Wistar rats (Hamid *et al*., 2011; Moldovan *et al*., 2016; Petkova & Ognyanov, 2018; Yigit *et al*., 2018). The fruits showed protective effects against hypertriglyceridemia and atherosclerosis in rats by the regulating oxidative stress and inflammation (Sozanski *et al*., 2014).

In vivo studies also showed anti-diabetic, anti-obesity, hypolipidemic, hepatoprotective, renalprotective, antiplatelet and cardioprotective effects of *C. mass* (Czerwinska & Melzig, 2018; Dinda *et al*., 2016). In a clinical trial with diabetic patients, the anti-diabetic activity of *C. mass* fruits was shown; the oral administration of the fruits determined an increase in insulin level, and a decrease in glycated hemoglobin and triglyceride levels (Soltani *et al*., 2015).

The infusion and decoction from *Cornus* fruits, leaves and bark have astringent, anthelmintic and antipyretic properties (Tita *et al*., 2009).

Current uses

The fruits of *C. mass* are consumed fresh or processed as juice, wine, jams, marmalade, compote and pickled (Bjić-Ljubičić *et al.,* 2018; Petkova & Ognyanov, 2018). They are also used as antiallergic, antimicrobial and antihistamine agent (Petkova & Ognyanov, 2018). Externally, they are used for cosmetic purposes, replacing synthetic astringent compounds (Hamid *et al*., 2011; Rudrapaul *et al*., 2015).

The leaves and fruits are used as infusion or decoction against gastrointestinal and hepatic disorders, and intestinal worms (Ardelean & Mohan, 2008; Parvu, 2006).

Precautions and adverse reactions
No available data.

Corylus avellana L. (European hazel, „alun"), Corylaceae family

***Other common names*:** hazel, hazelnut, common hazel (Cerulli *et al*., 2018; Esposito *et al*., 2017).

Officinal products: leaves (*Coryli folium*) (Grigorescu *et al*., 1986), bark (*Coryli cortex*) (Ardelean & Mohan, 2008).

Botanical description
C. avellana is a shrub, up to 6 m high, with gray-yellow and smooth bark. The stem is branched at the base, in the shape of a bush with a wide crown. The leaves are almost circular, dentate, short petiolate, broadly obovate, acuminate, hairy on both sides. Male flowers are nude, grouped in cylindrical catkins, pale yellow. The female flowers are like buds, solitary or grouped 2-3 at the top of the branches, accompanied by a cup-shaped involucre. The fruits are achenes with lignified pericarp (hazelnuts), wrapped in a cup of leaves divided up to the middle, approximately the length of the fruit (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006; Stefan & Oprea, 2007). It blooms before leafing, male flowers emerge in spring, female flowers in February - March (Ardelean & Mohan, 2008).
Distribution and habitat: frequent from hilly to mountainous areas, through deciduous forests or cultivated for its seeds (Muntean *et al*., 2007; Sarbu *et al*., 2013; Stefan & Oprea, 2007). In Dobrogea, this species is also found in Danube Delta area (Caraorman, Letea, Cardon) (Ciocarlan, 2011; Doroftei *et al*., 2011).
Harvesting period: the young leaves (*Coryli folium*) in June-July; the bark (*Coryli cortex*) in early spring or in the autumn from the young twigs; male flowers in the spring when they emerge (*Coryli flos*) (Parvu, 2006).

Traditional uses
Hazelnut has been used in traditional medicine against hemorrhoids, varicose veins, phlebitis, diabetes and gynecological disorders (Cerulli *et al*., 2018; Demirel *et al*., 2016).
In Romanian folk medicine, the young twigs were used externally against skin conditions, the crushed seeds were used topically against hernia, and the infusion from the flowers against pulmonary disorders, as sudorific and astringent (Butura, 1979; Parvu, 2006). The leaves, as aqueous or hydroalcoholic extract, were used as wound healing agent and the seeds against anemia and kidney stones (Parvu, 2006).
Other ethnopharmacological data mention the use of leaves (as infusion in wounds), male flowers (as infusion in diarrhoea), buds (as infusion in hepatitis, asthma, silicosis, pulmonary emphysema) and bark (as decoction in intermittent fever) (Tita *et al*., 2009).

Chemical composition

The fruits contain phenolic acids (e.g. caffeic, coumaric, gallic, dihydrosinaptic, ferulic, sinaptic and syringic acids), flavonoids (e.g. catechin, epicatechin, quercetin derivatives), alkaloids, proanthocyanidins, vitamins (folic acid, vitamin E, vitamins B1, B2, B6, B9), fatty acids (e.g. oleic, linoleic, palmitic, stearic acids, up to 10% polyunsaturated fatty acids) and phytosterols (genistein, daidzein, secoisolariciresinol) (Cappelli *et al*., 2018; Demirel *et al*., 2016; Mollica *et al*., 2018). The skin, hard shell, green leafy cover and leaves contain phenolic acids (protocatechuic, gallic, p-coumaric, ferulic and sinaptic acids) (Alasalvar *et al*., 2009). The leaves also contain flavonoids (kaempferol, quercetin, myricetin), cyclic diarylheptanoids and diaryletherheptanoids (giffonins A-P) (Cerulli *et al*., 2018; Parvu, 2006). In the shells, neolignans (e.g. lawsonicin, cedrusin, ficusal) and a cyclic diarylheptanoids (carpinontriol B) were also identified (Esposito *et al*., 2017). The seed oil contains phytosterols, such as β-sitosterol, campesterol and stigmasterol (Demirel *et al*., 2016). The alcohol extract from *C. avellana* bark, shells and leaves contain taxol and taxanes (e.g. cephalomannine, baccatin III) in amounts tenfold lower than in *Taxus*, but due to the faster growing rate and ease of cultivation, the hazelnut could be considered as a possible source of anticancer agents (Alasalvar *et al*., 2009; Gallego *et al*., 2017).

Pharmacological activities

Different parts (leaf, skin, kernel, green leafy cover) of *C. avellana* showed *in vitro* antioxidant activity (the lowest activity determined for the kernel and the highest activity for the leaf and skin), the hazelnut skin and green leafy cover being able to protect against LDL oxidation (Alasalvar *et al*., 2009). The ethanol extract from hazelnut showed *in vitro* antibacterial activity against *Staphylococcus aureus*, by enhancing human macrophage bactericidal response through increasing the expression of anti-inflammatory and iron metabolism genes (Cappelli *et al*., 2018).

The methanol extract from the shells showed antioxidant and cytotoxic activity in human malignant melanoma and human cervical cancer cell lines, by inducing apoptosis through caspase-3 activation (Esposito *et al*., 2017). The oil extracted from hazelnut had benefic effects against polycystic ovary syndrome, by regulating gonadotropins, steroids and serum lipid parameters, and also due to its antioxidant potential (Demirel *et al*., 2016). *In vivo* studies (animal model) showed that hazelnut consumption was associated with decrease in body weight, food intake, atherogenic index, lipid peroxidation, improvement of liver parameters and also had neuroprotective potential (Mollica *et al*., 2018). The ethanol extract from hazelnut has been demonstrated to stimulate the expression of low-density lipoprotein receptor through epigenetic mechanisms (Benassi *et al*., 2019).

Due to its content in taxanes, hazelnut could also be used in the treatment of various types of cancer (Alasalvar *et al*., 2009; Gallego *et al*., 2017).

Current uses

Internally, it is used as sudorific, astringent, and against hemorrhoids, varicose veins, foot edema, eczema, avitaminosis, pulmonary disorders (emphysema, silicosis, asthma), hepatitis; externally, it is used in ulcerations, periphlebitis, erythrocyanosis of the lower limbs (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006). It is

included in various tea formulas recommended in the treatment of hemorrhoids, periphlebitis, ulcerations (Grigorescu *et al*., 1986).

Precautions and adverse reactions
No available data.

Cotinus coggygria Scop. (smoke tree, „scumpie"), Anacardiaceae family

***Other common names*:** fustic, sumac (Rendeková *et al*., 2015).

Officinal products: leaves (*Cotini coggygriae folium*) (Ardelean & Mohan, 2008; Parvu, 2006; Grigorescu *et al*., 1986), bark (*Cotini coggygriae cortex*) (Ardelean & Mohan, 2008; Parvu, 2006).

Botanical description
C. coggygria is a shrub with a branched root and a stem up to 5 m high, covered with fine, scaly bark. The tendrils are reddish, glabrous, shiny, secreting milky juice when cut. The leaves are alternate, simple, elliptical to obovate (3-8 cm), with a cuneate base, rounded at the top or slightly marginal, with entire edges, when crushed they emit a carrot-like smell. The flowers are greenish-yellow, polygamous, small, grouped in large panicles. The fruit is a small, dry, obliquely-obovate drupe (Ardelean & Mohan, 2008; Parvu, 2006; Stefan & Oprea, 2007). It blooms in May-June (Ardelean & Mohan, 2008; Parvu, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007).
Distribution and habitat: spread sporadically, from the steppe area to the oak floor, at the edges of sparse forests (Butura, 1979; Parvu, 2006; Sarbu *et al*., 2013) or forming bushes on grassy coasts in Dobrogea, Banat and insular, in some areas of Oltenia, Muntenia, Moldova (Ardelean & Mohan, 2008; Parvu, 2006; Stefan & Oprea, 2007).
Harvesting period: the leaves are harvested during flowering, in beautiful, sunny weather; bark at the end of vegetation or in spring (March-April) until the leaves emerge, 2-3 year old branches being used (Parvu, 2006).

Traditional uses
C. coggygria was used traditionally in many countries as antipyretic, anti-inflammatory, anti-hemorrhagic, wound healing and antimicrobial agent, and to treat diarrhoea, gastric and duodenal ulcers, hepato-biliary conditions and to protect mucosal tissues (buccal, gastric, intestinal) (Aksoy *et al*., 2016; Matic *et al*., 2013; Matic *et al*., 2016; Rendeková *et al*., 2015).
In Romanian folk medicine, the decoction from young braches was used as gargle in syphilis, and also externally as cataplasm (Butura, 1979). It was also used as gargle in oral conditions for its astringent properties (Grigorescu *et al*., 1986).

Chemical composition
The phenolic compounds were identified in all parts of the plant: branches (1,2,3,4,6-penta-O-galloyl-β-D-glucose), heartwood (sulfuretin, fisetin, dustin, quercetin), flowers and leaves (gallic acid), whole plant (disulfuretin), stems (rosmarinic, coumaric, chlorogenic, ferulic and caffeic acids, myricetin, quercetin, kaempferol,

resveratrol and rutin) and leaves (quinic acid, galloyl hexose, gallic acid, trigalloyl hexoside, myricetin glucoside, myricetin rhamnoside and quercetin rhamnoside) (Ardelean & Mohan, 2008; Matic *et al*., 2013; Matic *et al*., 2016; Rendeková *et al*., 2015). The purple leaves contain anthocyanins such as delphinidin 3-galactoside, cyanidin 3-galactoside and petunidin 3-glucoside (Tanchev & Timberlake, 1969).
It also contains up to 15-30% tannins (mostly ellagic acid) and 0.1-0.2% essential oil (Grigorescu *et al*., 1986; Rendeková *et al*., 2015).

Pharmacological activities
The extracts from different plant parts showed anticancer, antioxidant, anti-inflammatory, antibacterial, antiviral, antigenotoxic, hepatoprotective properties, and acetylcholinesterase and α-glucosidase inhibitory activities (Matic *et al*., 2016).
The leaves extract showed antibacterial activity against several *Staphylococcus aureus* strains, the anti-biofilm potential also being demonstrated *in vitro* (Rendeková *et al*., 2015). The ethanol extract from the leaves of *C. coggygria* accelerated wound healing in diabetic rats, possibly due to its content in phenolic compounds with potent antioxidant and anti-inflammatory activities (Aksoy *et al*., 2016).
The methanol extract from the stem showed *in vivo* (animal model) antigenotoxic and hepatoprotective properties, probably due to the presence of myricetin (Matic *et al*., 2013). Flavonoids from *C. coggygria* showed *in vitro* tumor-inhibitory activity in glioblastoma cell lines (Wang *et al*., 2016).
The leaves and bark have antipyretic, hemostatic (through protein precipitation, reducing the inflammatory process), cicatrizing, antiseptic and astringent properties (Parvu, 2006).

Current uses
The decoction from dried leaves is used internally against fever, gastrointestinal conditions, diarrhoea, hepatic conditions, hemorrhoids, urinary incontinence, vomiting, and externally against oral conditions, gingivitis and external hemorrhoids (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Parvu, 2006).

Precautions and adverse reactions
No available data.

Crataegus monogyna Jacq. (hawthorn, „păducel roșu"), Rosaceae family

Syn. *Crataegus oxyacantha* L., nom. ambig. (Barnes *et al*., 2007; Doroftei *et al*., 2011), *C. apiifolia* Medik. non Michx., *C. oxyacantha* L. ssp. *monogyna* Lev., *Mespilus elegans* Poir., *M. monogyna* All., *M. monogyna* Ehrh. (WHO, 2002).

Officinal products: According to the European Pharmacopoeia (Eur. Ph. 8.0, 2013), the officinal product is represented by: dried false fruits (*Crataegi fructus*) of *C. monogyna* or *C. laevigata* (Poir.) DC. (syn. *C. oxyacantha* L.) or their hybrids or a mixture of these false fruits; whole or cut, dried flower-bearing branches (*Crataegi folium cum flore*) of *C. monogyna*, *C. laevigata* or their hybrids or, more rarely, other European *Crataegus* species including *C. pentagyna* Waldst. et Kit. ex Willd., *C.*

nigra Waldst. et Kit. and *C. azarolus* L. The officinal product *Crataegi folium cum flore* (dried flower-bearing branches of *C. monogyna*, *C. laevigata*, their hybrids or, more rarely, other *Crataegus* species) is also mentioned by other monographs (Barnes *et al*., 2007; EMA/HMPC/159075/2014; EMA/HMPC/159076/2014; WHO, 2002).

Botanical description

C. monogyna is a shrub up to 2-5 (-10) m high (Sarbu *et al.,* 2013). The stem is very branched, with thorns up to 1 cm long, reddish-brown. The leaves are oval or rhombic, pinnate-lobed or unevenly sectate, with 3-7 lobes, glossy on the adaxial surface, green, glabrous, and light-green, hirsute or glabrous on the abaxial surface. The white flowers are arranged in an erect corymb, with 5 persistent sepals, 5 free concave petals, and androecium with 15-20 stamens. The fruit is an oval or spherical drupe, red, fleshy, wrinkled after drying, and it has a persistent calyx at the anterior end; contains one seed (Ardelean & Mohan, 2008; Parvu, 2006; Stanescu *et al*., 2014; Stefan & Oprea, 2007). It blooms from May to June (Oroian, 2011).

Distribution and habitat: common, in forest edges, meadows, bushes, from the plain to the spruce floor (Ardelean & Mohan, 2008; Oroian, 2011; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, Cardon, Letea, Perisor) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: flowers (*Crataegi flos*) and bouquets of flowers with leaves (*Crataegi folium cum flore*) at the begining of the flowering stage, in April-May; leaves (*Crataegi folium*) in April-August; fruits (*Crataegi fructus*) when they turn red, from September to November (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006).

Traditional uses

It is used traditionally in many countries in cardiovascular disorders (heart failure, hypertension, myocardial injury, angina pectoris, arrhythmia, atherosclerosis), to improve blood circulation and to eliminate blood stasis, as an antispasmodic agent in the treatment of asthma, as diuretic, in gastrointestinal disorders, digestive stimulation, epigastric distension, abdominal pain, diarrhoea (Barnes *et al*., 2007; Nabavi *et al*., 2015; Wang *et al*., 2013; WHO, 2002; Yusuf & Meriçli, 2016).

In Romanian folk medicine, it was used internally as infusion (flowers) against insomnia, heart and liver diseases, and as decoction (fruit) with anti-diarrhoeal and diuretic properties; externally, the decoction from the leaves and the tips of the branches was used against corns on the soles (Butura, 1979; Grigorescu & Silva, 1997; Parvu, 2006; Stanescu *et al*., 2014).

Other ethnopharmacological data mention the use of the infusion and decoction from leaves, flowers and fruits in cardiac nervous disorders, sole wounds and pains (Tita *et al*., 2009).

Chemical composition

The main bioactive constituent of *Crataegi folium cum flore* include: crategic acid (a mixture of crategolic, neotegolic and acantolic acids), 1-3% flavan compounds (catechin, epicatechin), flavonoids (vitexin, isovitexin, orientin, hyperoside, rutin), triterpenes (ursolic and oleanolic acids), amines, sterols (β-sitosterol), catechin tannins and pectines (Ardelean & Mohan, 2008; Barnes *et al*., 2007; Chevallier, 2016; Cretu *et al*., 2011; EMA/HMPC/159076/2014; Hellenbrand *et al*., 2015; Miron, 2007; Oroian, 2011; Wang *et al*., 2013; WHO, 2002; Yusuf & Meriçli, 2016).

The leaves contain 1% flavon C-glycosides (vitexin-2"-rhamnoside and vitexin-4"'-acetil-2"- rhamnoside) and rutin, and the flowers contain approximately 1% hyperoside and traces of rutin. The fruits have a chemical composition similar with *Crataegi folium cum flore*, but are richer in hyperoside, and also contain carotenoids, anthocyanins, sugars and pectines (Ardelean & Mohan, 2008; Gavril *et al*., 2016b; Grigorescu *et al*., 1986; Nabavi *et al*., 2015; Stanescu *et al*., 2014; Stefanache *et al*., 2019; Tassell *et al*., 2010; Wang *et al*., 2013; WHO, 2002). The fruits also have high amounts of vitamin C (Ruiz-Rodríguez *et al.,* 2014; Edwards *et al.,* 2012; Stefanache *et al*., 2020; Tahirović *et al.,* 2012), between 210.4 mg and 287.0 mg/100 g dried plant material (Stefanache *et al*., 2019).

The European Pharmacopoeia requires for *Crataegi fructus* a content of minimum 0.06% procyanidins, expressed as cyanidin chloride (dried drug), and for *Crataegi folium cum flore* a content of minimum 1.5% total flavonoids, expressed as hyperoside (dried drug) (Eur. Ph. 8.0, 2013). WHO monographs mentions also, a minimum content of 0.6% flavon C-glycosides expressed as vitexin in fruits (WHO, 2002).

Pharmacological activities

Several *in vitro*, *in vivo* (animal model) and clinical studies have highlighted the pharmacological actions of *C. monogyna* extracts.

A clinical trial showed the benefic effect of a *C. oxyacantha* and *C. monogyna* standardized extract in the treatment of patients with congestive heart insufficiency, including the reduction of dyspnoea and fatigue (Degenring *et al*., 2003). Another clinical trial showed the increasing blood pressure effect in hypotensive patients induced by a drug with camphor and hawthorn extract (Csupor *et al*., 2019).

Several *in vivo* studies with hawthorn extracts have shown their applicability in the treatement of a variety of cardiovascular diseases, by lowering blood pressure, increasing coronary circulation, and through their endothelial protection, lipid reduction, vasodilatator, antiplatelet, antiarrhythmic, cardiotropic and inotropic effects (Suroowan & Mahomoodally, 2015; Wang *et al*., 2013; Yusuf *et al*., 2016). Its benefic effects on cardiovascular diseases are also due to the anti-inflammatory action (reduction of the expression of pro-inflammatory cytokines COX-2, TNF-α, IL-1β and IL-6) (Li & Wang, 2011).

The positive inotropic effect of hawthorn extract is due to the increased contraction of the papillary muscle bands in the left ventricle through a cAMP-independent mechanism (Schwinger *et al*., 2000).

Crataegus extract has an anti-hyperlipidemic effect by inhibiting the transformation of cholesterol, triglycerides and phospholipids into LDL and very low density lipoproteins, thus preventing the development of atherosclerosis (Suroowan & Mahomoodally, 2015). The polyphenolic extracts from *C. azarolus* and *C. monogyna* showed antitumor activity, having a cytotoxic effect against Caco-2 tumor cells (Belkhir *et al*., 2016).

Current uses

The hawthorn (leaves and flowers) extracts are administered in cardiovascular diseases such as stages I and II heart failure, angina pectoris, bradyarrhythmia and cardiac neurosis, due to its ability to reduce major risk factors such as inflammation, hypertension and thrombosis. In combination with other plant extracts they are also

used in the treatment of hypertension, atherosclerosis, mild forms of insomnia, and for memory improvement (Chevallier, 2016; Duke *et al*., 2002; Miron, 2007; Nabavi *et al*., 2015 ; Stanescu *et al*., 2014; Tassell *et al*., 2010; WHO, 2002; Yusuf & Meriçli, 2016).

Many hawthorn products are available on the market, either as food supplements (e.g. tinctures, extracts, teas, and tablets) or as medicines (with standardized extracts).

Precautions and adverse reactions

Clinical data and post-marketing surveillance studies suggest that hawthorn preparations are well tolerated if administrated properly (Barnes *et al*., 2007).

Not recommended in case of hypersensitivity to the active substance. Due to the lack of data, the use in adolescents under 18 years and children under 12 years is not recommended. In the absence of sufficient data, the use during pregnancy and lactation is not recommended (EMA/HMPC/159075/2014; EMA/HMPC/159076/2014).

Hawthorn products may potentiate the effects of digitalis and other cardiac medicines and it can interfere with cardiac, hypertensive, and hypotensive therapies (Duke *et al*., 2002).

Other warnings

The use should be limited to the functional symptoms of a healthy heart (EMA/HMPC/159076/2014).

Crataegus pentagyna Willd. (black hawthorn, „păducel negru"), Rosaceae family

Officinal products: *Crataegus pentagyna* is not an officinal drug, but the European Pharmacopoeia mentions the use of the whole or cut, dried flower-bearing branches of *C. pentagyna* as a possible substitute for *Crataegi folium cum flore* (Eur. Ph. 8.0, 2013).

Botanical description

C. pentagyna is a shrub up to 1-5 m high. The stems are dark brown, woody, bearing alternate, petiolate leaves, more or less deeply lobed (3-7 lobes) with slightly serrate or almost entire margins, glabrous or with only isolated trichomes; the adaxial surface is dark green or brownish-green, the abaxial surface is lighter grayish-green. The white flowers, grouped in corymbs, have a brownish-green tubular calyx composed of 5 free sepals, a corolla composed of 5 free, yellowish-white, rounded or broadly ovate and shortly unguiculate petals and numerous stamens. The ovary is fused to the calyx and consists of 5 or, rarely, 4 carpels, each with a long style and containing a single ovule. The fruit is black or black-purple, matte, and contains 5 seeds (EMA/HMPC/159076/2014; Eur. Ph. 8.0, 2013; Sarbu *et al.,* 2013). It blooms in May-June (Sarbu *et al.,* 2013).

Distribution and habitat: spread sporadically, from the plain to the oak floor, through forests edges and forest sparse, bushes, in the south and southeast regions of the country (Sarbu *et al.,* 2013).

Harvesting period: similar as for *C. monogyna*.

Traditional uses

The fruits are used traditionally in Iran to treat cardiovascular diseases (Rabiei *et al*., 2012). We did not identify data on its traditional use in Romania.

Chemical composition

Several flavonoids were identified in *C. pentagyna*, namely: vitexin, vitexin-2"-*O*-rhamnoside, acetylvitexin-2"-*O*-rhamnoside, isovitexin, isovitexin-rhamnoside, isoquercitrin, quercetin-3-*O*-galactoside, rutin, orientin-orientin-2"-*O*-rhamnoside, isoorientin, isoorientin-2"-*O*-rhamnoside in flowers; isovitexin, isovitexin-rhamnoside, crateside (quercetin derivative), glocoside (herbacetin derivative) in leaves (Edwards *et al*., 2012; Prinz *et al*., 2012). In the fruits, chlorogenic and caffeic acids, hyperoside, isoquercitrin and rutin were identified (Ebrahimzadeh *et al*., 2018; Stefanache *et al*., 2019; Stefanache *et al*., 2020).

In the leaves extract, the total phenolic content was of 206.94 mg gallic acid equivalent per g of extract, the total flavonoids content of 57.08 mg (+)-catechin equivalents per g of extract and the proanthocyanidin content of 68.92 mg cyanidin per g of extract; for the flowers, the total phenolic content was of 184.62 mg gallic acid equivalent per g of extract, the total flavonoids content of 67.04 mg (+)-catechin equivalents per g of extract and the proanthocyanidin content of 97.70 mg cyanidin per g of extract (Giurescu Bedreag *et al*., 2014).

Total phenolic content in the fruits was of 721.1 mg gallic acid equivalents per g of extract, while the total flavonoid content of 87.92 quercetin equivalents per g extract (Ebrahimzadeh *et al*., 2018). Fruits also contain high amounts of vitamin C (350.2-428.3 mg/100 g dried plant material) (Stefanache *et al*., 2019).

Pharmacological activities

The extracts from leaves, flowers and fruits showed a good antioxidant activity, the leaves extract having a higher antioxidant potential in comparison with the leaves of other *Crataegus* species (Ebrahimzadeh *et al*., 2008; Giurescu Bedreag *et al*., 2014; Özyürek *et al*., 2012; Rabiei *et al*., 2012; Tusa *et al*., 2016).

The fruit extract from *C. pentagyna* showed *in vivo* anti-hypoxic activity in mice (Ebrahimzadeh *et al*., 2018). The leaves extract showed a dose-dependent *in vitro* negative chronotropic effect and prolonged the field potential duration, thus having anti-arrhythmic potential (Pahlavan *et al*., 2018).

Current uses

No data were identified on the current use of *C. pentagyna*, but the European Pharmacopoeia mentions the use of *C. pentagyna* as a possible substitute for *Crataegi folium cum flore* (Eur. Ph. 8.0, 2013).

Precautions and adverse reactions

Similar as of *C. monogyna*.

Echium vulgare L. (viper's bugloss, „limba șarpelui"), Boraginaceae family

Syn. *Echium argenteum* Pau, *E. granatense* Coincy, *E. hispanicum* Asso (Doroftei *et al*., 2011).

Officinal products: aerial parts (*Echii herba*) (Ardelean & Mohan, 2008; Parvu, 2006; Tita *et al*., 2009), flowering tops (Chevallier, 2016).

Botanical description

E. vulgare is a biennial herbaceous species, with a pivoting, black root. The stem, up to 1 m in hight, is erect, rigid, unbranched or branched at the base, covered with short, soft hairs and among them long hairs. The leaves are lanceolate, acute; the basal ones are arranged in a rosette and attenuated in the petiole; the stem leaves are sessile, uninerve and tomentaceous. The flowers are blue, zygomorphic, arranged in scorpioid buds, gathered racemiformly. The fruits are nucules (Ardelean & Mohan, 2008; Chevallier, 2016; Parvu, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007). It blooms from June to August (Andrei & Cristurean, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007).

Distribution and habitat: frequent, through meadows, ruderal places, bushes, pebbles, from the plain area to the mountain floor (Ardelean & Mohan, 2008; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, Cardon, Crisan, Maliuc, Periprava, Sfantu Gheorghe, Sulina) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: during flowering stage, from June to August (Ardelean & Mohan, 2008).

Traditional uses

The common name, viper's bugloss, was given because *E. vulgare* was considered a remedy (for treatment and prevention) for viper bite. Viper's bugloss was also used to treat pulmonary conditions, as its mucilage soothes dry coughs and encourages expectoration (Chevallier, 2016).

In Romanian folk medicine, the dried plant, finely ground, was mixed with butter to obtain an ointment used for eczema. The decoction was used against toothache and pellagra, and the tea was used against diarrhoea, fatigue, anemia and epilepsy (Butura, 1979). Internally, the infusion was used to treat dysentery, diarrhoea, colds and cough. Externally, the infusion and the ointment made with butter were used to treat wounds (Parvu, 2006).

Chemical composition

The aerial parts of *E. vulgare* contain pyrrolizidine alkaloids such as 3′-acetylechimidine, 7-angeloylretronecine, 9-angeloylretronecine, 9-tigloylretronecine, 7-angeloyl-9-(2- methylbutyryl)retronecine, echimidine being the major alkaloid (El-Shazly *et al*., 1996). They also contain flavonoids (kaempferol 3-O-neohesperidoside), phenolic acids (rosmarinic acid), sterones, naphthoquinones, uridine, mucilages, allantoin, resins, alkannins (Ardelean & Mohan, 2008; Chevallier, 2016; Grigorescu *et al*., 1986; Kuruuzum-Uz *et al*., 2004; Parvu, 2006). Viper's bugloss flowers contain up to 25.36% polysaccharides (Tahmouzi, 2014). The seeds of *E. vulgare* have high amounts of lipids (27.40%), tocopherols (e.g. α-, β-, γ- and δ-tocopherol, 20.2 mg/100

g total tocopherol), phytosterols (e.g. stigmasterol, campesterol, sitosterol, avenasterol, 7.4 mg/g total sterols), phenolic compounds (Nogala-Kalucka *et al*., 2010). The roots contain mucilages and alkaloids (Butura, 1979).

Pharmacological activities

The seeds of *E. vulgare* showed a good antioxidant activity, probably due its content in phenolic compounds and phytosterols. Avenasterol, a phytosterols found in high levels in viper's bugloss, was proven to have a notable antioxidant activity (Nogala-Kalucka *et al*., 2010). The polysaccharide fraction of *E. vulgare* had: a good *in vitro* antioxidant activity; antilisterial activity, very good against *L. ivanovii* and *L. monocytogenes* and moderate against *L. seeligeri* and *L. marthii* (Tahmouzi, 2014). The ethanol root extract was proven to have a good *in vivo* wound healing effect (in mice), by promoting collagen fibers (Eruygur *et al*., 2016). The aqueous extract (low doses) and the ethanol extract (high doses) of *E. vulgare* showed significant *in vivo* (mice) antidepressant effects, comparable to imipramine (a well-known antidepressant agent) (Moallem *et al*., 2007). The alkannins have antimicrobial properties and allantoin has wound healing properties (Chevallier, 2016). The high mucilage content in viper's bugloss is also helpful in treating skin conditions (Chevallier, 2016).

Current uses

As infusion, it is used for its calming, antiseptic, sudorific, emollient and healing properties (Grigorescu *et al*., 1986; Parvu, 2006; Stefan & Oprea, 2007). It is also used as emollient, antitussive, expectorant, diuretic, depurative, antilithiasis and anti-inflammatory agent, and in respiratory and urinary disorders (cystitis), dysentery, diarrhoea, anemia (Ardelean & Mohan, 2008; Tita *et al*., 2009).

Precautions and adverse reactions

The isolated fraction of pyrrolizidine alkaloids from viper's bugloss could cause hepatotoxicity and renal toxicity (Chevallier, 2016; El-Shazly *et al*., 1996; Moallem *et al*., 2007), so high doses or long-term use of this plant should be avoided (Nogala-Kalucka *et al*., 2010). Thus, it is not recommended to be used internally. It can be safely used externally on wounds (unbroken skin) (Chevallier, 2016).

Epilobium palustre L. (marsh-willowherb, „pufulița de baltă"), Onagraceae family

Officinal products: aerial parts (*Epilobii herba*) (Parvu, 2006; Tita *et al*., 2009), rhizomes and stolons (*Epilobii palustre rhizoma et sarmentum*) (Parvu, 2006). The plant product could also consist of fragments of pubescent leaves or stem with dimensions of 1-3 cm, and only rarely flowers or fruits (Stanescu *et al*., 2004a; Stanescu *et al*., 2014).

Botanical description

E. palustre is an herbaceous perennial species, with a branched rhizome with aerial or semi-subterranean stolons that are thick, fleshy, reddish, ending with a bud. The stems are cylindrical, rigid, without longitudinal stripes, decurrent, sometimes with 2 lines of hairs. The leaves are linear to linear-lanceolate, sessile or with a very short petiole,

heavily tomentaceous, with a revolute edge (Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013). The flowers have 4 purple or pink petals, 8 stamens and a stigma with 4 lobes. The fruit is an elongated capsule containing seeds covered with numerous silky hairs (Stanescu *et al*., 2014). It blooms in June-August (Sarbu *et al*., 2013).

Distribution and habitat: sporadically, from the hilly area to the spruce floor, through swampy meadows, peat bogs, waterfronts, pebbles (Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Doroftei *et al*., 2011).

Harvesting period: the rhizomes and stolons during flowering stage or in autumn, the upper aerial parts at flowering stage (Parvu, 2006).

Traditional uses

In Romanian folk medicine, the aerial parts of *Epilobium* species are used due to its emollient and astringent properties, but also to treat urinary disorders associated with the benign prostatic hyperplasia (Stanescu *et al*., 2004a; Stanescu *et al*., 2014). Other ethnopharmacological data mention the use of the aerial part infusion in prostatitis and prostate adenoma, hepatitis, ulcer, enteritis, cirrhosis and urinary disorders (Tita *et al*., 2009).

In the villages of the Teleajen basin, the rhizomes, stolons and upper parts of the stem are used in hepatic and digestive disorders, to treat wounds, angina pectoris and also in avitaminosis (Parvu, 2006).

Chemical composition

E. palustre aerial parts contain flavonoids (quercetin-3-*O*-rhamnoside, quercetin-3-*O*-glucoside, quercetin-3-*O*-galactoside, quercetin-3-*O*-arabinoside, myricetin-3-*O*-rhamnoside, myricetin-3-*O*-glucoside, myricetin-3-*O*-galactoside, myricetin-3-*O*-arabinoside), high amounts of gallic acid derivatives, pectines, polysaccharides and tannins (Granica *et al*., 2014; Remmel *et al*., 2012; Stanescu *et al*., 2004a; Stanescu *et al*., 2014).

Pharmacological activities

The extracts from *E. palustre* showed antitumor potential through its antiproliferative activity, and also anti-diarrhoeal activity by inhibiting muscular contractibility and mobility (unspecific protein denaturation by tannins) (Granica *et al*., 2014).

The infusion from aerial parts has depurative, diuretic, choleretic-cholagogue, astringent, anti-inflammatory, hemostatic, antimicrobial, anti-inflammatory, cytostatic and regenerative properties (Parvu, 2006; Stanescu *et al*., 2014; Tita *et al*., 2009).

Current uses

The extract and infusion of *E. palustre* are used in Romania as a remedy for urinary, hepatic and chronic biliary disorders, in benign prostatic hyperplasia and as a diuretic Stanescu *et al*., 2004a; Stanescu *et al*., 2014).

It is also used internally to treat enteritis, gastroduodenal ulcer, diarrhoea, and externally to treat wounds and thrush (Parvu, 2006).

Precautions and adverse reactions

The long-term administration of *Epilobium* preparations could cause arrhythmias (Stanescu *et al*., 2014).

Epilobium parviflorum Schreb. (willow-herb, „pufulița de zăvoi"), Onagraceae family

***Other common names*:** Blood Vine, Blooming Sally, Rose Bay Willow Herb, Willow-Herb (Gruenwald *et al.*, 2000).

Officinal products: According to the European Medicine Agency (EMA) the officinal product is represented by the aerial parts of *E. parviflorum* (*Epilobii herba*) (EMA/HMPC/712510/2014; EMA/HMPC/712511/2014). Literature also mentions the use of the roots (Gruenwald *et al*., 2000).

Botanical description

E. parviflorum is a perennial herbaceous plant with a thick rhizome (Ardelean & Mohan, 2008; Sarbu *et al*., 2013). The stem is tall, cylindrical, with hairs; the base has short shoots. The leaves are narrow-lanceolate, small and sharply toothed, the lower and middle ones opposite, rarely alternate or verticilate, short-hirsute or rough-hirsute. The flowers are smaller, red-purple (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013) with 4 petals, 8 stamens and a stigma with 4 lobes. The fruit is an elongated capsule containing seeds covered with numerous silky hairs (Parvu, 2006). It blooms in June-August (Sarbu *et al*., 2013).

Distribution and habitat: frequent, on the waterfronts, through brooks, valleys, from the plain to the mountainous region, often through forest cuts, in wet meadows (Ardelean & Mohan, 2008; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: during flowering stage (Parvu, 2006).

Traditional uses

In Romanian folk medicine, the aerial parts of *Epilobium* species are used due to its emollient and astringent properties, and also to treat urinary disorders that are associated with the benign prostatic hyperplasia (Stanescu *et al*., 2004a; Stanescu *et al*., 2014). Other ethnopharmacological data mention the use of the aerial part infusion in prostatitis and prostate adenoma, hepatitis, ulcer, enteritis, cirrhosis and urinary disorders (Tita *et al*., 2009).

E. parviflorum is used traditionally for its depurative, choleretic, cholagogue, astringent, hemostatic, anti-inflammatory and antimicrobial properties, and also in the treatment of prostatitis, prostate hypertrophy (adenoma), urinary tract disorders, prostate and bladder cancer, liver disorders and gastroduodenal ulcer (Parvu, 2006).

Chemical composition

The *E. parviflorum* aerial parts contain flavonoids (kaempferol, kaempferol-3-*O*-rhamnoside, kaempferol-3-*O*-glucoside, quercetin, quercetin-3-*O*-rhamnoside, quercetin-3-*O*-glucoside, quercetin-3-*O*-galactoside, quercetin-3-*O*-arabinoside, quercetin-3-*O*-glucunoride, myricetin, myricetin-3-*O*-rhamnoside, myricetin-3-*O*-glucoside, myricetin-3-*O*-galactoside, myricetin-3-*O*-arabinoside), phenolic acids (ellagic, gallic, protocatechuic, syringic, vanillic, cinnamic, caffeic and ferulic acids), tannins (oenothein A, oenothein B), sterols (β-sitosterol, β-sitosterol glucoside, β-sitosterol propionate, β-sitosterol capronate, β-sitosterol palminate), fatty acids (oleic, linoleic, α-linolenic, palmitic, stearic and arachidonic acids) and tocopherols (α-tocopherol, γ-tocopherol) (Ardelean & Mohan, 2008; EMA/HMPC/712510/2014;

Granica *et al*., 2014; Gruenwald *et al*., 2000; Stanescu *et al*., 2014; Tóth *et al*., 2009). It also contains essential oil, the main classes of constituents being fatty acids, aldehydes and ketones, esters, furans, monoterpenes, diterpenes, sesquiterpenes (Bajer *et al*., 2017). In the seeds, sterols, fatty acids and tocopherols were identified (Granica *et al*., 2014).

Pharmacological activities

Different types of extracts from *E. parviflorum* showed depurative, choleretic-cholagogue, astringent, anti-inflammatory, hemostatic, antimicrobial, antitumor (inhibition of cell proliferation on prostate cancer cell line), regenerative and anti-diarrhoeal (inhibition of muscular contractibility and mobility) properties (EMA/HMPC/712510/2014; Granica *et al*., 2014; Gruenwald *et al*., 2000; Roman *et al*., 2010; Stanescu *et al*., 2014; Tita *et al*., 2009).

The extracts from *E. parviflorum* showed inhibitory activity against 5-α-reductase, an enzyme involved in the synthesis of testosterone (probably due to oenothein B content), thus having a benefic effect on benign prostate hyperplasia (Granica *et al*., 2014). *In vitro* studies showed potent antioxidant and anti-inflammatory (inhibition of hyaluronidase and lipoxygenase, inhibition of COX-1 and COX-2, inhibition of prostaglandin biosynthesis) activities of *E. parviflorum* extracts that are probably related with their content in phenolic acids, flavonoids and oenothein B (EMA/HMPC/712510/2014; Balázs *et al*., 2003; Granica *et al*., 2014; Kiss *et al*., 2011; Tóth *et al*., 2009). The essential oil isolated from *E. parviflorum* showed a potent antimicrobial effect against *Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans* (Bajer *et al*., 2017).

Current uses

According to the European Medicine Agency - Committee on Herbal Medicinal Products, the following types of products are used in the European countries: comminuted herbal substance (herbal tea) for oral use in the symptomatic treatment of benign prostatic hyperplasia; *Epilobium parviflorum herba* (tablets) for the symptomatic relief of benign prostatic hyperplasia; herbal tea and oral drops, in combination with other medicinal plant species for bladder inflammation, irritable bladder, prevention and treatment of prostate related disorders (EMA/HMPC/712510/2014; EMA/HMPC/712511/2014).

The extracts and infusion of *E. palustre* are used in Romania as a remedy for urinary, hepatic and chronic biliary disorders, in benign prostatic hyperplasia and as a diuretic (Stanescu *et al*., 2004a; Stanescu *et al*., 2014).

Precautions and adverse reactions

The long-term administration of *Epilobium* preparations could cause arrhythmias (Stanescu *et al*., 2014). Adverse reaction could occur due to hypersensitivity to the active substances (EMA/HMPC/712511/2014). A doctor should be consulted if fever, spasm, blood in urine, painful urination or urinary retention occurs during its use (EMA/HMPC/712511/2014).

Equisetum arvense L. (horsetail, „coada calului"), Equisetaceae family

Syn. *Allosites arvense* Brongn.; *Equisetum boreale* (L.) Börner (EMA/HMPC/278089/2015).

***Other common names*:** Bottle-Brush, Corn Horsetail, Dutch Rushes, Field Horsetail, Horse Willow, Paddock-Pipes, Pewterwort, Scouring Rush, (Gruenwald *et al*., 2000).

Officinal products: According to European Pharmacopoeia and the European Medicine Agency (EMA) the officinal product is *Equiseti herba*, representing whole or cut, dried sterile aerials parts of *E. arvense* (EMA/HMPC/278091/2015; EMA/HMPC/278089/2015; Eur. Ph. 8.0, 2013).

Botanical description

It is a perennial herbaceous plant, with numerous adventitious roots starting from a blackish, articulated rhizome, with tubers that are the size of a peanut. Annually fertile spring and sterile summer stems emerge from the rhizomes. The fertile stem emerge in March-May and is small, articulated, unbranched, light reddish-brown, juicy, at nodes with brown scaly leaves united in a sheath. It has a terminal sporiferous spike. The sterile stem is green, assimilating, erect, and it is formed after the disappearance of the fertile stem, in May-June. It is articulated, at nodes with small, uninervous leaves, united in a toothed sheath. Also, several secondary branches (that give the appearance of a horsetail) start vertically from the nodes (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Oniga, 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013; Stanescu *et al*., 2014).

Distribution and habitat: frequent, from the steppe area to spruce floor, in meadows, sandy places, fields, the edge of mountain waters (Sarbu *et al.,* 2013; Oroian, 2011). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, Cardon, Dranov, Erenciuc, Maliuc, Letea, Sulina) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: sterile stems in July-October (Ardelean & Mohan, 2008).

Traditional uses

In Romanian folk medicine, *E. arvense* was used internally as decoction and infusion against diarrhoea, urinary disorders, stomach ache, colds, respiratory disorders (including tuberculosis), leucorrhea and other gynecological conditions, as diuretic, astringent, hemostatic, and as a source of minerals (Butura, 1979; Parvu, 2006; Stanescu *et al*., 2014). Externally, it was used against rheumatism, skin disorders (impedigo, furunculosis) and as wound healing agent (Butura, 1979). Foot baths were made against edema, in order to reduce swelling (Stanescu *et al*., 2014).

Other ethnopharmacological data mention the use of the aerial part infusion in the treatment of renal disorders (hematuria) (Tita *et al*., 2009).

Chemical composition

The sterile stems of *E. arvense* contain flavonoids (mainly kaempferol and quercetin glycosides, luteolin, apigenin, apigenin-5-*O*-glucoside, luteolin-5-O-glucoside, epicatechin), phenolic acids (di-*E*-caffeoyl-*meso*-tartaric acid, methyl esters of protocatechuic and caffeic acids, caffeic, gallic and ferulic acids), alkaloids (palustrine, palustrinine and traces of nicotine), phytosterols (cholesterol, campesterol, epicholestanol, β-sitosterol) and triterpenes (germanicol, ursolic acid, oleanolic acid,

betulinic acid) (Ardelean & Mohan, 2008; Asgarpanah & Roohi 2012; EMA/HMPC/278089/2015; Gruenwald *et al*., 2000; Gründemann *et al*., 2014; Hancianu *et al*., 2008; Pallag *et al*., 2016; Sandhu *et al*., 2010). The sterile stems also contain high amounts of minerals, including silicic acid and silicates (5-8% total content, of which 10% are water-soluble), potassium and calcium (Gruenwald *et al*., 2000; Chevallier, 2016; EMA/HMPC/278089/2015; Sandhu *et al*., 2010).

The fertile stems contain phenolic glycosides such as equisetumoside A, equisetumoside B and equisetumoside C (Asgarpanah & Roohi 2012; Sandhu *et al*., 2010).

The European Pharmacopoeia requires for *Equiseti herba* a minimum 0.3% of total flavonoids, expressed as isoquercitroside (dried drug) (Eur. Ph. 8.0, 2013).

Pharmacological activities

Anti-inflammatory, antioxidant, antimicrobial (against gram-positive cocci), antiviral, anti-hemorrhagic, astringent, diuretic, vasorelaxant, anticancer (inducing apoptotic cell death) and sedative properties were determined for *E. arvense* (Asgarpanah & Roohi 2012; Dos Santos *et al*., 2005; Duke *et al*., 2002; Mohammed *et al*., 2017; Pallag *et al*., 2018; Sandhu *et al*., 2010).

The hydroalcoholic extract from *E. arvense* showed sedative and anticonvulsant effect in rats, reducing the severity of convulsions and the percentage of animals that developed convulsions (Dos Santos *et al*., 2005). The extracts from the sterile stems of *E. arvense* showed good antioxidant capacity and reducing power (Nagai *et al*., 2005; Pallag *et al*., 2016). The hydroalcoholic extracts have *in vitro* and *in vivo* (animal model) antinociceptive properties and significant anti-inflammatory activity through the inhibition of lymphocyte activation, inducing IL-2 surface receptor expression and IL-2, INF-γ and TNF-α production (Do Monte *et al*., 2004; Gründemann *et al*., 2014).

A food supplement based on silicon extracted from *E. arvense* and calcium showed benefic affects against osteoporosis, improving, both qualitatively and quantitatively, the bone remodeling process (Saudelli *et al*., 2018).

E. arvense increases the strength of connective tissue, thus it has positive effects on peripheral circulation and in the treatment of rheumatic conditions (Hancianu *et al*., 2008; Oniga, 2007; Stanescu *et al*., 2014).

Current uses

According to the European Medicine Agency - Committee on Herbal Medicinal Products, several herbal medicinal products are used to increase the amount of urine (flushing of the urinary tract), as an adjuvant in minor urinary complaints, and for the supportive treatment of superficial wounds, namely: comminuted herbal substance as herbal tea or in solid dosage forms for oral use; herbal preparations in liquid (aqueous and ethanol extracts, in liquid, soft and dry forms) or solid dosage forms for oral use; comminuted herbal substance for the preparation of decoction for cutaneous use; herbal preparations in liquid dosage forms for cutaneous use (EMA/HMPC/278091/2015; EMA/HMPC/278089/2015).

E. arvense is approved by the German Commission E in infections of the urinary tract, kidney and bladder stones, wounds and burns (Gruenwald *et al*., 2000).

Equiseti herba is part of medicinal tea formulas with diuretic action, and the extracts can be included in combination diuretic preparations (Hancianu *et al*., 2008; Stanescu

et al., 2014). The extract from the fresh aerial parts is included, in combination with other 6 extracts, in a homeopathic medicine used in the prophylaxis and treatment of recurrent respiratory infections (Stanescu *et al*., 2014).

Precautions and adverse reactions

Horsetail is contraindicated in patients who have edema due to impaired heart and kidney function, where a reduced fluid intake is recommended (EMA/HMPC/278091/2015; Gruenwald *et al*., 2000). For preparations other than infusions, an appropriate fluid intake should be ensured (EMA/HMPC/278091/2015). In the absence of sufficient data, the use in children under 12 years of age, and during pregnancy and lactation is not recommended (EMA/HMPC/278091/2015; Duke *et al*., 2002).

Other warnings

Not to be confused with other *Equisetum* species, such as *E. palustre, E. hyemale*, *E. fluviatile*, *E. sylvaticum*, that could be toxic, thus only controlled products (from pharmacies) should be used (EMA/HMPC/278089/2015; Gruenwald *et al*., 2000; Hancianu *et al*., 2008; Muntean *et al*., 2007).

Erodium cicutarium (L.) L'Hér. (heron's-bill, „pliscul cocorului"), Geraniaceae family

Syn. *Erodium viscosum* sensu Samp., vix (Mill.) Steud. (Doroftei *et al*., 2011).

***Other common names*:** alfilaria, common crowfoot, common erodium, common stork's-bill (Al-Snafi, 2017a).

Officinal products: aerial parts (*Erodii cicutarii herba*) (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Parvu, 2006).

Botanical description

E. cicutarium is an annual herbaceous plant (Sarbu *et al*., 2013), with fasciculate root and branched stem, up to 50 cm high, hirsute. The leaves are pinnate at the place of attachment to the stem. The flowers are pink-lilac, rarely white, arranged in long inflorescences. The fruit is a beak-shaped capsule that unfolds at maturity into five valves and a twisted central piece in a spiral shape, which ensures the catapult of the seeds (Ardelean & Mohan, 2008; Butura, 1979; Grigorescu *et al.,* 1986; Parvu, 2006). It blooms from April to October (Sarbu *et al*., 2013).

Distribution and habitat: frequent, from the plain to the mountain area, through meadows and fields, vineyards, parlors, gardens, rocky coasts, bushes (Ardelean & Mohan, 2008; Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Pardina, Sireasa) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: during flowering stage (Parvu, 2006).

Traditional uses

E. cicutarium is traditionally used as astringent, hemostatic (uterine bleeding), abortifacient, anti-diarrheic, diuretic, diaphoretic, stomachic remedy, to treat animal bites, skin infections and rheumatism (Al-Snafi, 2017a; Al-Snafi, 2017b).

In Romanian folk medicine, *E. cicutarium* is used as anti-inflammatory, diuretic hemostatic, in regulating the menstrual cycle and as oxytocin-like agent (Grigorescu *et al*., 1986; Parvu, 2006). The flowering tips were used as bath for topical treatment of pain or as decoction in rheumatic disorders (Butura, 1979).
Other ethnopharmacological data mention the use of *E. cicutarium* aerial parts as infusion in urinary and genital disorders, with diuretic and anti-inflammatory properties (Tita *et al*., 2009).

Chemical composition
The following bioactive compounds were identified in the aerial parts of *E. cicutarium:* phenolic acids (gallic, protocatechuic and ellagic acids), flavonoids (rutin, hyperin and isoquercitrin), tannins, potassium salts, aminoacids, tyramine, histamine and vitamins (K and C) (Al-Snafi, 2017a; Al-Snafi, 2017b; Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Parvu, 2006). The aerial parts also contain essential oil, the major classes of constituents being the fatty acids and their derived compounds, oxygenated sesquiterpenoids and diterpenoids (Radulović *et al*., 2009).

Pharmacological activities
The essential oil showed antibacterial and antifungal potential, and different extracts (with methanol, ethanol and hexane) showed antioxidant, antiproliferative, anti-inflammatory and analgesic effects, and negative inotropic action (Al-Snafi, 2017a; Al-Snafi, 2017b).
The aqueous and alcohol extracts from *E. cicutarium* exhibited antiviral activity against myxoviruses, Herpes virus type 1, vesicular stomatitis and vaccinia virus (Zielińska-Jenczylik *et al*., 1987) and the methanol extract showed interferogenic and antiviral effects (Zielińska-Jenczylik *et al*., 1988).

Current uses
E. cicutarium is used in regulating the menstrual cycle and as oxytocin-like agent (Ardelean & Mohan, 2008). The infusion and decoction are used internally to stimulate the onset of delayed menstruation (Parvu, 2006).

Precautions and adverse reactions
Due to its oxytocin-like action (abortifacient effect) and the effect on the menstrual cycle, the use during pregnancy and lactation should be avoided.

Eryngium campestre L. (eryngo, „scaiul dracului"), Apiaceae family

Syn. *Eryngium campestre* L. ssp. *contractum* (Micheletti) Degen, *Eryngium latifolium* Hoffmanns. & Link (Doroftei *et al*., 2011).
***Other common names*:** Eringo, Sea Holly, Sea Holme, Sea Hulver (Gruenwald *et al*., 2000).

Officinal products: rhizomes (*Eryngii campestre rhizoma*) (Ardelean & Mohan, 2008; Parvu, 2006; Tita *et al*., 2009), root (*Eryngii campestre radix*) (Muntean *et al*., 2007), dried leaves, dried flowers and dried roots (Gruenwald *et al*., 2000).

Botanical description

E. campestre is a perennial herbaceous, thorny plant, with a fusiform rhizome, vertical, up to 1 cm thick, 1-15 cm long, from which adventitious roots emerge. The stem is cylindrical, globulous-branched, whitish, up to 50 cm high. The leaves are stiff, 2-3 pinnatisect with spiky leaflets, the basal ones long-petiolate, and the stem ones are sessile and surround the stem. The flowers are blue-green, grouped in an ovoid capitulum, the calyx with lanceolate teeth, longer than the corolla; corolla with narrow petals. The fruit is a thorny diachena (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006). It blooms from July to August (Parvu, 2006; Sarbu *et al.,* 2013; Stefan & Oprea, 2007).

Distribution and habitat: frequent, from the plain to the beech floor, on arid, stony places, through meadows and dry pastures, stony shores, forest thickets, bushes, on fields and ruderal places (Ardelean & Mohan, 2008; Butura, 1979; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: from March-April or October-November (Ardelean & Mohan, 2008; Parvu, 2006).

Traditional uses

In Romanian folk medicine, it was used as depurative, diuretic and carminative. The roots were extracted in alcohol and used against enteritis and pulmonary tuberculosis. The decoction was used as mouth wash against toothache and periodontitis, and the aerial parts as infusion for its laxative effect, and against stomach ache and gastric ulcer (Butura, 1979). The rhizome was used externally as wound healing agent and internally in anorexia (to stimulate appetite), stomach ache, diarrhoea, periodontitis, tooth decay and gastric ulcer (Parvu, 2006).

Other ethnopharmacological data mention the use of the rhizome decoction in abdominal distention, urinary lithiasis, anorexia, gastric ulcer, convulsive cough and wounds (Tita *et al*., 2009).

Chemical composition

The aerial parts and roots contain essential oil. The main constituents of the essential oil are: (*E)*-caryophyllene, (*E*)-β-farsene, β-bisabolene, spathulenol, (Z)-*α-trans*-bergamotol, hexahydrofarnesyl acetone, germacrene D, β-elemene (in aerial parts); hexanoic acid, *n*-undecane, nonanoic acid, (*E*)-anethole, (*2E,4E*)-decadienal (in roots) (Cianfaglione *et al*., 2017; Matejic *et al*., 2018). The aerial parts also contain sterols (e.g. β-sitosterol, stigmasterol and cholesterol), phenolic acids (chlorogenic and rosmarinic acid) and flavonoids (e.g. quercitrin, isoquercitrin, rutin, astragalin, kaempferol derivatives and luteolin-7-*O*-β-D-glucopiranoside) (Conea *et al*., 2015; Gruenwald *et al*., 2000; Wang *et al*., 2012). *E. campestre* also contains coumarins, such as aegelinol benzoate, agasyllin and aegelinol (in the roots), monoterpenes, triterpenoid saponins, D-mannitol, rosmarinic acid derivatives (Kartal *et al*., 2005; Wang *et al*., 2012).

The rhizomes and roots contain saponoids, tannins, caffeic and chlorogenic acids, small amounts of essential oil, minerals (Ardelean & Mohan, 2008; Parvu, 2006).

Pharmacological activities

The aqueous and methanol extracts from the aerial parts and roots have antioxidant activity, and the essential oil has potent antimicrobial activity against *Klebsiella pneumoniae, Proteus mirabilis* and *Staphylococcus aureus*. The essential oil isolated from aerial parts had a higher antimicrobial activity compared to the one isolated from the roots (Matejic *et al*., 2018). The essential oil isolated from the aerial parts also has potent cytotoxic activity (human colon carcinoma cell line) and weak acetylcholinesterase inhibitory potential (Cianfaglione *et al*., 2017).

The hexane extract from *E. campestre* aerial parts showed a strong antitrypanosomal activity, but the selectivity was moderate (Medbouhi *et al*., 2018). A tincture from *E. campestre* showed anti-inflammatory activity in experimental rat periodontitis, by lowering total leukocytes count (reduction of neutrophils and monocytes), increasing serum total antioxidant response, and decreasing nitric oxide production and oxidative stress index, probably due to the synergic activity of the sterols, triterpenoid saponins and polyphenols (Conea *et al*., 2015).

Current uses

E. campestre is used in tea formulas for urinary disorders such as kidney stones (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Muntean *et al*., 2007). The decoction from rhizomes is used for its detoxifying, diuretic, cicatrizing, eupeptic, carminative and sedative properties (Tita *et al*., 2009).

The rhizome decoction is used externally to treat periodontitis, dental caries and wounds (Parvu, 2006).

The root is used in tea mixtures, extracts, decoctions and tinctures, while the aerial parts are administered as an extract (Gruenwald *et al*., 2000).

Precautions and adverse reactions

No hazards and/or adverse reactions were recorded for the proper therapeutic use (Duke *et al*., 2002; Gruenwald *et al*., 2000).

Eryngium planum L. (sea-holly, „scai vânăt"), Apiaceae family

***Other common names*:** Flat sea holl (Thiem *et al*., 2010).

Officinal products: aerial part (*Eryngii plani herba*) (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Oniga, 2007; Oroian, 2011).

Botanical description

E. planum is an herbaceous, perennial plant, blue-purple in color (more obvious during flowering), 25-100 cm high, with a fusiform rhizome. The stem is branched at the top, with 3-5 terminal branches, with spikes. The leaves are stiff; the basal ones have a long petiole, are more or less ovate, whole, serrate, with a cordate base; the stems leaves have a short petiole, the upper ones are sessile, palmately sectate, with the tip of the lobes spiny. The flowers are arranged in umbels in the form of a blue, ovoid capitulum, 15 mm long, with linear lanceolate involucre leaflets, long, exceeding the capitulum, toothed spiky (Ardelean & Mohan, 2008; Muntean *et al*.,

2007; Oniga, 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013). The fruits are diachene, spiny on the dorsal part (Oniga, 2007; Oroian, 2011; Parvu, 2006). It blooms from July to August (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013).

Distribution and habitat: frequently spread, from the plain to the beech floor, through meadows, in direct light, on light, sandy soils, forest edges, waterfronts, ruderal places (Butura, 1979; Muntean *et al*., 2007; Oniga, 2007; Parvu, 2006; Sarbu *et al.,* 2013).

Harvesting period: entire aerial part during flowering stage (Oniga, 2007; Oroian, 2011; Parvu, 2006).

Traditional uses

In Romanian folk medicine, the aerial parts were used, as infusion and decoction, against whooping cough and as diuretic; the decoction was also used as mouth wash against toothache, periodontitis and dental caries (Butura, 1979; Muntean *et al*., 2007; Parvu, 2006). Externally, it was used against skin infection, arthritis and rheumatism (Butura, 1979).

Other ethnopharmacological data mention the use of *E. planum* aerial parts as infusion in bronchitis, cough, urinary disorders, wounds, scars and burns (Tita *et al*., 2009).

Chemical composition

The leaves and roots of *E. planum* contain triterpenoids (R_1-barringenol, A1-barringenol, erynginol A, barringtogenol C) and the leaves contain flavonoids (kaempferol derivatives) (Wang *et al*., 2012). The aerial parts also contain sterols, such as β-sitosterol, stigmasterol and cholesterol, phenolic acids (chlorogenic, p-coumaric and ferulic acids) and flavonoids (isoquercitrin, quercitrin) (Conea *et al*., 2014; Conea *et al*., 2015). The roots contain phenolic acids (derivatives of p-coumaric, ferulic, caffeic and rosmarinic acids), triterpenoid saponins with berrigenol skeleton, D-glucose and 1-kestose, the flowers and seeds contain steroids (*cis*-chrysanthenyl esters) (Ozarowski *et al.,* 2015; Wang *et al*., 2012).

Pharmacological activities

The ethanol extract from the aerial parts showed anti-inflammatory activity in experimental rat periodontitis and in rat model of acute inflammation, reducing the edema, lowering total leukocytes count (reduction of neutrophils and monocytes), lowering circulating phagocytes proliferation, increasing serum total antioxidant response, and decreasing the nitric oxide production and the oxidative stress index, probably due to the synergic activity of the sterols, triterpenoid saponins and polyphenols (Conea *et al*., 2014; Conea *et al*., 2015; Conea *et al*., 2016).

The ethanol extract from *E. planum* leaves and roots showed potent antimycotic activity against *Candida albicans, C. glabrata, Trichophyton mentagrophytes* and *Cryptococcus neoformans* and moderate antibacterial activity against *Staphylococcus aureus* (Thiem *et al*., 2010).

The ethanol extract from *E. planum* roots showed significant *in vivo* (animal model) acetylcholinesterase and butyrylcholinesterase inhibitory activity in cortex and hippocampus, improving long-term memory in rats (Ozarowski *et al*., 2015).

The alcohol extracts from the fruits significantly induced apoptosis in 2 human leukemic cell lines (Wang *et al*., 2012).

Current uses
It is used internally against bronchitis, whooping cough, acute tracheo-bronchitis and urinary retention (Ardelean & Mohan, 2008; Oniga, 2007; Oroian, 2011; Parvu, 2006). It is included in expectorant tea and syrup formulas (Oniga, 2007; Oroian, 2011). The infusion from the aerial parts is used for its emollient, expectorant, antiseptic, spasmolytic, diuretic and cicatrizing properties (Tita *et al*., 2009). Externally, the decoction is used against periodontitis and skin infections (Parvu, 2006).

Precautions and adverse reactions
No available data.

Fumaria officinalis L. (fumitory, „fumariță"), Papaveraceae family

***Other common names*:** Earth Smoke, Hedge Fumitory, Beggary, Fumus, Vapor, Wax Dolls (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia and the European Medicine Agency (EMA), the officinal product is *Fumariae herba* represented by whole or fragmented, dried aerial parts of *Fumaria officinalis* L. harvested in full bloom (EMA/HMPC/574766/2010; EMA/HMPC/576232/2010; Eur. Ph. 8.0, 2013).

Botanical description
F. officinalis is an annual herbaceous plant, with pivoting root and erect, branched, glabrous stem, up to 30 cm high, glaucous and furrowed plate. The green-blue leaves are alternate, petiolate, bi- or tripinnate with narrow, linear segments. The flowers are small, pink, with a crimson tip, spurred, grouped in terminal racemes (Aprotosoaie & Stanescu, 2010; Ardelean & Mohan, 2008; Istudor *et al*., 2005; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2014). The fruit is a light-green, globular siliqua (Aprotosoaie & Stanescu, 2010; Oroian, 2011). Depending on the number of flowers in the inflorescence and the size of the sepals, *F. officinalis* has 2 subspecies: *F. officinalis* ssp. *officinalis* Sell. and *F. officinalis* ssp. *wirtgenii* (Koch) Arcangeli (Aprotosoaie & Stanescu, 2010; Istudor *et al*., 2005). It blooms from May to September (Aprotosoaie & Stanescu, 2010; Ardelean & Mohan, 2008; Istudor *et al*., 2005; Sarbu *et al.,* 2013).
Distribution and habitat: sporadic, in cultivated, ruderal places, on the water banks, in the oak area - sessile oak floor (Sarbu *et al.,* 2013; Stanescu *et al*., 2014).
Harvesting period: during full flowering stage, from May to September (Eur. Ph. 8.0, 2013; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006).

Traditional uses
In the European folk medicine, the plant was used in the treatment of liver and biliary diseases (Stanescu *et al*., 2014). It was also used for skin diseases (chronic eczema, cutaneous eruptions and other dermatological conditions), constipation, cystitis, arteriosclerosis, rheumatism, arthritis, as a blood purifier, for hypoglycemia, infections and in conjunctivitis (EMA/HMPC/576232/2010).

In Romanian folk medicine, *F. officinalis* was used as anti-inflammatory, antiarrhythmic, diuretic and laxative agent, in biliary and digestive disorders, and for the improvement of renal function, as well as in the treatment of skin conditions (Aprotosoaie & Stanescu, 2010; Parvu, 2006; Stanescu *et al*., 2004a; Stanescu *et al*., 2014). The infusion was used externally on areas with eczema and ringworm, and the decoction was used as gargle in gingivitis. The infusion was also used internally as depurative and in liver and biliary diseases (Stanescu *et al*., 2014). The aerial parts boiled in milk were used for dental diseases (Butura, 1979).
Other ethnopharmacological data mention the use of the infusion from aerial parts in urinary, cardiac and digestive disorders (Tita *et al*., 2009).

Chemical composition
The aerial parts of *F. officinalis* contain alkaloids, terpenoids, phytosterols, aminoacids, saponins, fixed oils, steroids, tannins, mucilages, organic acids (fumaric acid) (Aprotosoaie & Stanescu, 2010; Ardelean & Mohan, 2008; Al-Snafi, 2020b; Dutta *et al*., 2019; Latif *et al*., 2012; Muntean *et al*., 2007; Stanescu *et al*., 2014).
Among the alkaloids, protopine (fumarine), cryptopine, (±)-stylopine, (±)-scoulerine, (-)-scoulerine (aurotensine), fumaricine, fumaritine, fumariline, fumarofine, fumarophycine**,** cryptocavine, N-methylhydrasteine, oxo-*N*-methylhydrasteine, N-methylhydrastine and sanguinarine were identified in the aerial parts (EMA/HMPC/576232/2010; Khamtache-Abderrahim *et al*., 2016; Mardirossun *et al*., 1983; Paltinean *et al*., 2016). In addition, the following phenolic acids and flavonoids were identified in *F. officinalis*: cynarin, ferulic, isochlorogenic, chlorogenic, caffeic acids, isovitexin, rutin, isoquercitrin and quercitrin (Aprotosoaie & Stanescu, 2010; Barnes *et al*., 2007; EMA/HMPC/576232/2010; Istudor *et al*., 2005; Paltinean *et al*., 2016).
The European Pharmacopoeia requires for *Fumariae herba* a minimum 0.40% of total alkaloids, expressed as protopine (dried drug) (Eur. Ph. 8.0, 2013).

Pharmacological activities
Analgesic, antipyretic, antioxidant, amphocholeretic, antibacterial, antihelmintic, anti-diabetic, antiallergic, antispasmodic, hepatoprotective, cytoprotective, hypotensive and acetylcholinesterase inhibitory activities were revealed for different extracts from aerial parts (Al-Snafi, 2020b; Dutta *et al*., 2019; EMA/HMPC/576232/2010).
Isoquinoline alkaloid fractions isolated from the aerial parts of *F. officinalis* showed *in vitro* antioxidant and antibacterial activity against *Propionibacterium acnes* and *Acinetobacter calcoaceticus* (Khamtache-Abderrahim *et al*., 2016).
The ethanol extract showed *in vivo* (animal model) hepatoprotective activity, reducing the serum enzymes levels (glutamic pyruvic transaminase, glutamic-oxaloacetic transaminase, alkaline phosphatase) and also the elevated levels of bilirubin, cholesterol and triglycerides (Sharma *et al*., 2012). The ethanol extract from the aerial parts also showed analgesic effects in rats and mice, in several experimental models (Sharma *et al*., 2014).
The alkaloids isolated from *F. officinalis* have amphocholeretic (regulates the biliary flow) and spasmolytic properties (Aprotosoaie & Stanescu, 2010; Istudor *et al*., 2005; Parvu, 2006). Fumaric acid, also isolated from *F. officinalis*, has benefic effects in the treatment of several dermatologic conditions, synthetic fumaric acid being included in

some medicinal products used in the treatment of psoriasis (Stanescu *et al*., 2004a; Stanescu *et al*., 2014).

Current uses

According to the European Medicine Agency - Committee on Herbal Medicinal Products, the herbal medicinal products, such as comminuted herbal substance, powdered herbal substance, dry aqueous extract, liquid ethanol extract, tincture in ethanol, juice of the fresh plant, are used to increase the bile flow for the relief of symptoms of indigestion (such as the sensation of fullness, flatulence and slow digestion) (EMA/HMPC/574766/2010; EMA/HMPC/576232/2010).

The use of *F. officinalis* as a traditional herbal remedy is recognized for over 30 years by the specific regulatory bodies in several European countries such as France, United Kingdom and Germany (EMA/HMPC/576232/2010).

The use of fumitory is approved by the German Commission E in the treatment of liver and gallbladder complaints, spastic discomfort in the area of the gallbladder and bile ducts, and the gastrointestinal tract (Gruenwald *et al*., 2000).

The extracts are included in several preparations produced at industrial scale (e.g. tablets) recommended for gastrointestinal and biliary-tract disorders (Aprotosoaie & Stanescu, 2010; EMA/HMPC/576232/2010; Stanescu *et al*., 2014).

Precautions and adverse reactions

Not recommended in case of hypersensitivity to the active substances. Due to its amphocholeretic properties, the use in case of bile ducts obstructions, cholangitis, gallstones and other biliary diseases and hepatitis, is not recommended. Due to the lack of sufficient data, the use in children and adolescents under 18 years of age, and also during pregnancy and lactation is not recommended (EMA/HMPC/574766/2010; EMA/HMPC/576232/2010).

Other warnings

Not to be confused with other *Fumaria* species such as *F. vaillanti* and *F. schleicheri* (Gruenwald *et al*., 2000).

Galium aparine L. (cleavers, „turiță, lipicioasă"), Rubiaceae family

Syn. *Galium spurium* L. ssp. *tenerum* (Schleich.) Nyman (Doroftei *et al*., 2011).

***Other common names*:** Clivers, Goosegrass, Barweed, Hedgeheriff, Hayriffe, Eriffe, Grip Grass, Hayruff, Catchweed, Scratweed, Mutton Chops, Robin-Run-in-the-Grass, Love-Man, Goosebill, Everlasting Friendship, Bedstraw, Coachweed, Cleaverwort, Goose Grass, Gosling Weed, Hedge-Burs, Stick-a-Back (Gruenwald *et al*., 2000).

Officinal products: aerial parts (*Galii aparinis herba*) (Barnes *et al*., 2007; Chevallier, 2016; Gruenwald *et al*., 2000; Parvu, 2006).

Botanical description

G. aparine is an annual herbaceous species, with bent thorns, 60 to 150 cm high. The stem is decumbent or climbing through stiff trichomes, sharply quadrangular, often

branched, usually hirsute at the nodes. The leaves are linear, arranged in false whorls of 6 or 8. The flowers are white, small, tetrameric, with a short corolla tube, arranged in axillary, peduncled cymes. The fruits are pseudo-diachene, 4-7 mm wide, with dense hooked prickles (Chevallier, 2016; Gruenwald *et al*., 2000; Parvu, 2006; Sarbu *et al.,* 2013; Stefan & Oprea 2007). It blooms from May to September (Andrei & Cristurean, 2006; Sarbu *et al.,* 2013; Stefan & Oprea 2007).

Distribution and habitat: frequent, in cultivated and ruderal places, bushes, pebbles, forests and forest rarities, ravines, from the steppe area to the beech floor (Andrei & Cristurean, 2006; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Chilia, Cardon, Letea, Pardina, Sontea) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: aerial parts during flowering stage (Gruenwald *et al*., 2000; Parvu, 2006).

Traditional uses

Dioscorides considered this species as being useful for countering weariness (Chevallier, 2016).

G. aparine is used in German, French and Romanian folk medicines, as diuretic in kidney disease, atherosclerosis, against obesity, skin diseases, tonsillitis, pharyngitis, as a sedative and to promote sweating (Parvu, 2006).

In Romanian folk medicine, the infusion from dried and crushed flowering stems was used as gargle for sore throat with dry cough (Butura, 1979).

Chemical composition

The aerial parts of *G. aparine* contain anthraquinones, iridoids (asperulosidic acid and 10-deacetylasperulosidic acid), alkanes, flavonoids (quercitrin, quercetin, luteolin), tannins, phenolic acids (3,4-dihydroxybenzoic, p-hydroxycinnamic, gallic, chlorogenic, caffeic, cinnamic and p-coumaric acids), phytosterols (β-sitosterol, daucosterol), vitamins (e.g. vitamin C, vitamin B6, vitamin B5), carotenoids, carboxylic acids (dicarboxilic, aromatic, saturated and unsaturated fatty acids), esculetin and coumarin (Al-Snafi, 2018a; Atmaca *et al*., 2016; Barnes *et al*., 2007; Chevallier, 2016; Gruenwald *et al*., 2000; Mocan *et al*., 2006; Parvu, 2006; Shi *et al*., 2016; Vasilevna *et al*., 2016).

G. aparine aerial parts also contain essential oil, the main constituents, obtained by acid hydrolysis during distillation, being: hexadecanoic acid, tetradecanal, neophytadiene, hexahydrofarnesylacetone, tetradecanoic acid, linolenic acid and isophytol (Baser *et al*., 2004). The major classes of volatile constituents include aldehyde compounds and fatty acids (Atmaca *et al*., 2016).

Pharmacological activities

Antimicrobial, antioxidant, anticancer and hepatoprotective effects were reported for *G. aparine* (Al-Snafi, 2018a).

The lipophilic fraction isolated from the aerial parts of *G. aparine* showed high to very high antimicrobial activity against *Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis* and *Candida albicans*, and low antimicrobial activity against *Proteus vulgaris* (Vasilevna *et al*., 2016).

G. aparine methanol extract and its fractions showed a good *in vitro* antioxidant activity, the aqueous fraction being more potent (Bokhari *et al*., 2013).

The methanol extract from *G. aparine* aerial parts exhibited *in vitro* anticancer potential against breast cancer cell lines without impairing normal breast epithelial cells, inducing both apoptotic and non-apoptotic cell death (Atmaca *et al*., 2016).
Three compounds isolated from *G. aparine* (β-sitosterol, daucosterol and phthalate butyl) showed antiproliferative activity on leukemia cell line K562, phthalate butyl being more potent (Shi *et al*., 2016).

Current uses
It is used internally as infusion for the treatment of urinary tract conditions (lithuresis, calculosis, bladder catarrh and retention of urine), as diuretic, in atherosclerosis, skin diseases and obesity; externally, for the treatment of tonsillitis, pharyngitis (gargle with decoction), ulcers, festering glands, breast lumps, skin rashes and psoriasis (Barnes *et al*., 2007; Chevallier, 2016; Gruenwald *et al*., 2000; Parvu, 2006).
In Great Britain, *Galii aparinis herba* (herbal product or extracts) is used as a mild diuretic and astringent, and it is part of medicinal teas or herbal preparations with analgesic, antirheumatic and anti-psoriatic effects (Stanescu *et al*., 2014).

Precautions and adverse reactions
No side effects were recorded following the proper administration of designated therapeutic dosages (Gruenwald *et al*., 2000). Due to the lack of data, the use of cleavers during pregnancy and lactation should be avoided (Barnes *et al*., 2007). Like other iridoids, asperuloside is a mild laxative (Duke *et al*., 2002).

Galium verum L. (lady's bedstraw, „sânziene galbene"), Rubiaceae family

Syn. *Galium minutum* L. pro parte (Doroftei *et al*., 2011).
Other common names: Yellow Galium, Cheese Rennet, Curdwort. Maid's Hair, Yellow Cleavers, Petty Mugget, Cheese Renning (Gruenwald *et al*., 2000).

Officinal products: aerial parts (*Galii veri herba*) (Ardelean & Mohan, 2008; Chevallier, 2016; Muntean *et al*., 2007; Parvu, 2006; Stanescu *et al*., 2014).

Botanical description
G. verum is an herbaceous perennial species, with a thin, branched rhizome, from which adventitious roots emerge. The stem is erect or ascending, cylindrical, with four edges that are less obvious, 30-100 cm high, short-hirsute or glabrous. The leaves are linear, very narrow (0.5-1 mm wide), sharp, glabrous on the upper face, hirsute on the lower face, arranged in vertices, 8-12 at a node, with prominent ribs. The flowers are small, golden-yellow, pleasantly fragrant (honey scent), densely grouped in terminal panicles. The fruits are smooth, small nucules (up to 1.5 mm), grouped in pairs (Ardelean & Mohan, 2008; Istudor, 2001; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013; Stanescu *et al*., 2014; Stefan & Oprea 2007). It blooms from May to September (Andrei & Cristurean, 2006; Istudor, 2001; Sarbu *et al.,* 2013; Stefan & Oprea 2007).
Distribution and habitat: frequently spread, through meadows, bushes, forest edges and clearings, ruderal places, from plain to the spruce floor (Ardelean & Mohan, 2008;

Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: aerial parts during flowering stage (Gruenwald *et al*., 2000; Muntean *et al*., 2007; Oniga, 2007; Parvu, 2006).

Traditional uses

G. verum was used in folk medicine as a diuretic for bladder and kidney irritation, to promote wound healing, and also applied on burns to alleviate inflammation (Chevallier, 2016; Gruenwald *et al*., 2000).

In Romanian folk medicine, *G. verum* was used for its sedative, antispasmodic, diuretic and laxative properties, and against cystitis, gout, rheumatism, minor sleep disorders (as infusion, tincture, freshly pressed juice) (Oniga, 2007). Macerated in alcohol, the plant was used against hernia (Butura, 1979). The infusion was used as diuretic, diaphoretic and spasmolytic, and the tincture for diminishing the size of the thyroid nodules (Stanescu *et al*., 2014).

Chemical composition

G. verum aerial parts contain iridoid glycosides (asperuloside, asperulosidic acid, monotropein, daphylloside, scandoside, giniposidic acid), phenolic acids (chlorogenic, caffeic and coumaric acids), flavonoids (rutin, quercetin-7-glucoside, luteolin-7-glucoside, palustroside, cynaroside, isoquercitrin, astragalin, diosmetin, catechin, epicatechin), essential oil, tannins, monoterpene glycosides (betulalbuside A, (2E)-2,6-dimethyl-2,7-octadien-1,6-diol-6-O-β-glucopyranoside) and phytosterols (β-sitosterol, campesterol) (Al-Snafi, 2018b; Ardelean & Mohan, 2008; Bojthe-Horvath *et al*., 1982; Bradic *et al*., 2017; Farcas *et al*., 2018; Ghita *et al*., 2012b; Gruenwald *et al*., 2000; Istudor, 2001; Muntean *et al*., 2007; Parvu, 2006).

The aerial parts also contain essential oil, the main compounds being caryophyllene, caryophyllene oxide and germacrene-D (Al-Snafi, 2018b).

Pharmacological activities

Antioxidant (*in vivo* and *in vivo* studies), cytotoxic (in neck cancer cell lines HLaC78 and FADU), antimicrobial (against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Proteus vulgaris, Candida albicans*), hepatoprotective and antihemolytic activities were reported for *G. verum* extracts (Al-Snafi, 2018b; Bradic *et al*., 2017; Farcas *et al*., 2018; Lakić *et al*., 2010).

G. verum decoction showed *in vitro* cytotoxic effect on several laryngeal carcinoma cell lines: chemosensitive Hep-2 and HLaC79, and chemoresistant P-glycoprotein-overexpressing Hep2-Tax and HLaC79-Tax (Schmidt *et al*., 2014).

Two hydrogels loaded with *G. verum* essential oil showed *in vitro* bactericidal effect against *Staphylococcus aureus* and *Escherichia coli* (Gherman *et al*., 2018).

G. verum extracts showed hepatoprotective activity on carbon tetrachloride-induced liver injury in rats, decreasing the activities of the serum enzymes alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase (Goryacha *et al*., 2017).

Diosmetin extracted from *G. verum* has *in vivo* (animal model) protective effects on the thymus gland, inhibiting tumor growth and protecting tumor-induced apoptosis of

the thymus, the mechanism being closely associated with reduced cell death in the thymus and a Fas-FasL-dependent pathway (Zhao *et al*., 2011).
G. verum hydroalcoholic extract showed protective potential on the thyroid and ovarian morphological parameters in rats under anakinetic conditions (Roman & Puica, 2013).

Current uses
It is administered as an infusion from finely powdered plant product. The tincture (1:10, 50% alcohol) is administered to control the size of the thyroid nodules (Stanescu *et al*., 2014). It is also used internally as diuretic, for kidney stones, bladder stones, and other urinary conditions (including cystitis), and externally for skin conditions (skin rashes, psoriasis, erysipelas) and rheumatism (Ardelean & Mohan, 2008; Chevallier, 2016; Muntean *et al*., 2007; Parvu, 2006).

Precautions and adverse reactions
The extracts obtained from *Galii veri herba* are well tolerated, being free of toxicity. When administered to control the size of the thyroid nodules, the hormonal dosing should be performed according to a specialist (Stanescu *et al*., 2014).

Geranium robertianum L. (Herb Robert, „năpraznic"), Geraniaceae family

***Other common names*:** Dragon's Blood, Storkbill, Wild Crane's-Bill (Gruenwald *et al*., 2000), Crane's-Bill (Ardelean & Mohan, 2008).

Officinal products: aerial parts (*Geranii robertiani herba*) (Ardelean & Mohan, 2008; Chevallier, 2016; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Oroian, 2011) and roots (*Geranii robertiani radix*) (Chevallier, 2016).

Botanical description
G. robertianum is an annual or biennial herbaceous plant, with a height of 10-50 cm (Sarbu *et al.,* 2013). The root is pivoting. The stem is green (later turns reddish) and glandular-haired, with a pungent sour smell. It is straight or creeping with ascending tips, thickened at the nodes, heavily branched. The leaves are long petiolate, opposite, triangular in shape, with 3-5 segments, pinnatisect or pinnately compound, with glandular trichomes on both sides. The flowers are arranged 2 on a common peduncle, having the calyx formed by lanceolate sepals, provided with long edges and three ribs. The petals are red or pink, with three lighter ribs, often whole. The pubescent fruit is a capsule sharp at the top, and the seeds are finely dotted. The fruit lobes burst off from the central column without the awn (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013). It blooms from May to September (Parvu, 2006; Sarbu *et al.,* 2013).
Distribution and habitat: frequently spread, from plain to the subalpine floor, through beech and spruce forests, shrubs, meadows (Oroian, 2011; Sarbu *et al.,* 2013).
Harvesting period: in June-August (Oroian, 2011), at the beginning of the flowering stage (Parvu, 2006).

Traditional uses

G. robertianum was used traditionally for liver and gallbladder diseases, inflammation of the kidney, against diabetes, diarrhoea, gastritis, gout, sinus diseases and hypertension, for inflammation of the oral mucous membrane, tonsillitis and to promote wound healing (Graca *et al*., 2016; Gruenwald *et al*., 2000).

In Romanian folk medicine, the decoction from *G. robertianum* was used externally as washes or compresses for pangs, intestinal colic, rheumatic pain and pellagra, and internally for its antihemorrhagic action (Butura, 1979). The aerial parts were used in the treatment of contusions, stomatitis, oropharyngeal diseases, as an anti-diarrhoeal, antihemorrhagic and diuretic agent, in inflammation of the skin, eye diseases, to combat sterility, in leucorrhea, rheumatism and diseases of the excretory system (Parvu, 2006).

Other ethnopharmacological data mention the use of the infusion from aerial parts of *G. robertianum* in hemorrhagic cystitis, diarrhoea, bronchitis, hemorrhagic enteritis, leucorrhoea, tracheitis, pharyngitis and stomatitis (Tita *et al*., 2009).

Chemical composition

The aerial parts of *G. robertianum* contain tannins (geraniin, isogeraniin, β-penta-O-galloylglucose), bitter substances, traces of essential oil, citric acid, resins, alkaloids, saponins and oxalate (Ardelean & Mohan, 2008; Chevallier, 2016; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Igwenyi & Elekwa, 2014; Oroian, 2011; Parvu, 2006). Among the phenolic compounds, several constituents were identified: gallic, caffeic, ferulic, p-coumaric, syringic and ellagic acids, rutin, luteolin, quercetin, isoquercitrin, quercitrin, hyperoside, kaempferol and astragalin (Neagu *et al*., 2017; Graca *et al*., 2016; Parvu, 2006). The main constituents of the essential oil isolated from the aerial parts are represented by linalool, γ-terpinene, germacrene-D, limonene, geraniol, α-terpineol and phytol (Graca *et al*., 2016).

Several vitamins (A, B_1, B_2, B_3, C and E) were identified and quantified in leaves (Igwenyi & Elekwa, 2014).

Pharmacological activities

Several biological activities were reported for the extracts and essential oil isolated from *G. robertianum* aerial parts, namely: antioxidant (methanol extract), antimicrobial (essential oil and aqueous extract), anti-inflammatory (ethanol and aqueous extracts), anti-hyperglycemic (decoction) and cytotoxic (ethanol and aqueous extracts) (Ferreira *et al*., 2010; Graca *et al*., 2016; Neagu *et al*., 2010; Neagu *et al*., 2017; Paun *et al*., 2012).

The concentrated extracts showed *in vitro* antioxidant and cytostatic activity on human epidermoid carcinoma of larynges cell line (Neagu *et al*., 2010; Neagu *et al*., 2017; Paun *et al*., 2012).

G. robertianum leaf decoctions had anti-diabetic effects after oral administration in diabetic rats, lowering the plasma glucose levels, improving liver mitochondrial respiratory parameters and increasing oxidative phosphorylation efficiency (Ferreira *et al*., 2010).

The extract from the fresh herb has been shown to have a mild antiviral activity against the vesicular stomatitis virus (Gruenwald *et al*., 2000).

The aerial parts have antihypertensive, astringent, antihemorrhagic, diuretic, depurative, emollient, antiseptic and tonic properties (Duke *et al*., 2002; Parvu, 2006; Tita *et al*., 2009).

Current uses

It is used in the treatment of chronic diarrhoea, rheumatism, tuberculosis, leucorrhea, against stomach ulcers and inflammation of the uterus, and also in the form of gargles in herpes angina and stomatitis (Ardelean & Mohan, 2008; Chevallier, 2016; Grigorescu *et al*., 1986). Externally, it is used against eczema and to promote wound healing (Ardelean & Mohan, 2008).

Internally, the infusion is used as a diuretic and adjuvant in urinary and gastrointestinal conditions, and the decoction is used against diabetes, rheumatism and pulmonary diseases; externally, it is used as mouth wash or gargle against inflammation (Parvu, 2006).

Precautions and adverse reactions

No side effects were recorded following the proper administration of designated therapeutic dosages (Gruenwald *et al*., 2000).

Other warnings

Not to be confused with *Geranium palustre* and *Geranium pratense* which are frequently used as an adulteration (Gruenwald *et al*., 2000).

Glaucium flavum Crantz (horned-poppy, „mac cornut galben"), Papaveraceae family

***Other common names*:** yellow hornpoppy (Bournine *et al*., 2013b).

Officinal products: aerial parts (*Glaucii flavi herba*) (Ardelean & Mohan, 2008; Istudor, 2005; Parvu, 2006; Tita *et al*., 2009).

Botanical description

G. flavum is an annual, biennial or rarely perennial herbaceous plant, with pivoting root. The stem is green-blue, erect, branched, scattered hirsute or glabrous (Istudor, 2005; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013). The basal leaves are long petiolate. The lower segments are small, more or less entire, and the upper ones are hard-toothed. The stem leaves are small, ovate, penta-lobed and amplexicaul, glabrous or dispersed hirsute. The flowers are solitary, more or less peduncled, terminal or axillary, lemon-yellow or golden-yellow in color, with 2 slightly hirsute or glabrous sepals, 4 wide ovate petals and yellow stamens. The ovary is tuberculate, thin towards the top. The fruit is a capsule, linearly cylindrical, more or less curved, rough or smooth (Ardelean & Mohan, 2008; Istudor, 2005; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006). The plant product has a bitter taste and a characteristic faint odor (Aprotosoaie & Stanescu, 2010). It blooms from June to August (Ardelean & Mohan, 2008; Sarbu *et al.,* 2013).

Distribution and habitat: rarely spread, especially in sandy and arid places, in the steppe area - oak floor (Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was

reported in Constanta (Harsova, Cernavoda) and Tulcea (Sulina) counties (Ardelean & Mohan, 2008), and also in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011). In addition, the following subspecies were reported in the Danube Delta: *Glaucium flavum* Crantz ssp. *flavum* and ssp. *leiocarpum* (Boiss.) Ciocarlan (Ciocarlan, 2011).

Harvesting period: aerial parts (*Glaucii flavi herba*) during full flowering stage and at the beginning of fructification (Aprotosoaie & Stanescu, 2010; Ardelean & Mohan, 2008; Oroian, 2011; Muntean *et al*., 2007; Parvu, 2006).

Traditional uses

G. flavum is used in different regions and countries as laxative (seed powder), antitusive (infusion from aerial parts), antiseptic, wound healing and cicatrizing agent, to remove warts (stem latex), as detersive, hypotensive and pectoral (Bournine *et al*., 2013b).

In Romanian folk medicine, the dry petal infusion is used to treat cough, acute and chronic bronchitis, acute laryngitis, flu, and to increase diuresis; in some villages, the dried petals are used to treat respiratory diseases and to increase diuresis (Parvu, 2006).

Other ethnopharmacological data mention the use of the infusion from aerial parts in renal and respiratory disorders (Tita *et al*., 2009).

Chemical composition

The aerial parts and roots of *G. flavum* contain alkaloids, the main constituents being glaucine (in the aerial parts, especially in petals), protopine, magnoflorine, chelidonine, sanguinarine and chelerythrine (in roots) (Aprotosoaie & Stanescu; Ardelean & Mohan, 2008; Bournine *et al*., 2013a; Bournine *et al*., 2013b; Daskalova *et al*., 1988; Istudor, 2005; Muntean *et al*., 2007; Opletal *et al*., 2014; Oroian, 2011; Parvu, 2006). The fruits are also rich in glaucine (Muntean *et al*., 2007; Parvu, 2006).

Pharmacological activities

The alkaloid fraction from *G. flavum* aerial parts showed low antimicrobial activity against three Gram-positive bacteria, namely *Enterorococcus faecalis*, *Staphylococcus aureus* and *Staphylococcus hyicus* (Opletal *et al*., 2014).

The crude extract and alkaloid fraction from the aerial parts of *G. flavum* exhibited cytotoxic effect on human colon adenocarcinoma cell lines (HT-29, Caco-2) (Hadjiakhoondi *et al*., 2012).

The alkaloid extract from *G. flavum* roots exibited antitumoral effects, inhibiting the cell proliferation on breast cancer cell line (inducing G2/M phase cycle arrest and apoptosis) and significantly reducing the growth and vascularization of human glioma tumors (Bournine *et al*., 2013a).

The infusion from aerial parts has diuretic and antitussive properties (Tita *et al*., 2009). The antitussive and expectorant properties are similar with those of codeine from *Papaver somniferum* (Aprotosoaie & Stanescu, 2010; Muntean *et al*., 2007; Parvu, 2006).

Current uses

It is used as diuretic, against renal calculi and dermal tumors (Aprotosoaie & Stanescu, 2010; Ardelean & Mohan, 2008; Oroian, 2011). It is also used againt cough of various etiologies and in dermal disorders (Istudor, 2005).

Precautions and adverse reactions
Similar as for other species rich in alkaloids.

Glechoma hederacea L. (ground ivy, „rotungioară"), Lamiaceae family

Syn. *Glechoma hederacea* L. ssp. *glabriuscula* (Neilr.) Gams, *Nepeta glechoma* Benth., *Glechoma hederacea* L. ssp. *sardoa* (Bég.) Soó, *Glechoma hindenburgiana* Graebn. (Doroftei *et al*., 2011), *Nepeta hederacea* (L.) Trevis (Barnes *et al*., 2007).
***Other common names*:** Alehoof, Gill-Go-over-the-Ground, Lizzy-Run-up-the-Hedge, Gill-to-by-the-Hedge, Robin-Run-in-the-Hedge, Catsfoot, Hedgemaids, Tun-Hoof, Haymaids, Turnhoof, Creeping Charlie, Cat's-Paw (Gruenwald *et al*., 2000).

Officinal products: aerial parts (*Glechomae herba*) (Ardelean & Mohan, 2008; Barnes *et al*., 2007; Chevallier, 2016; Istudor, 2001; Parvu, 2006).

Botanical description
G. hederacea is an herbaceous perennial plant, 15 to 60 cm high. The root is lignified and poorly developed. The stem is repent, slightly hairy, generating numerous ascending flowering shoots. The leaves are petiolate, opposite, reniform or cordate-ovate, with crenate edges. The flowers are blue-violet, rarely red-lilac or white, short-pedicellate, grouped 3-10 in false whorls in the axils of the foliage leaves. The fruits are ellipsoidal, smooth, brown, small nucules (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Istudor, 2001; Parvu, 2006; WHO, 2009). It blooms from April to June (Andrei & Cristurean, 2006; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013).
Distribution and habitat: frequent throughout the country, through bushes and forest edges, wet and shady places, from silvo-steppe to beech floor (Ardelean & Mohan, 2008; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, C.A. Rosetti, Cardon, Letea, Sontea) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).
Harvesting period: during flowering stage (Gruenwald *et al*., 2000; Istudor, 2001; Muntean *et al*., 2007; Parvu, 2006).

Traditional uses
Traditionally, it has been used internally in inflammation of gastrointestinal mucous membranes and diarrhoea, in mild respiratory complaints (bronchitis, chronic bronchial catarrh, coughs), bladder and kidney diseases (as diuretic in kidney stones, cystitis), and externally to promote wound healing, ulcers and other skin conditions, and also against arthritis and rheumatism (Barnes *et al*., 2007; Gruenwald *et al*., 2000). It was also used against tinnitus (Barnes *et al*., 2007; Chevallier, 2016).
In Romanian folk medicine, *G. hederacea* was used internally in urinary tract, respiratory, digestive tract and liver diseases, and externally for poorly healed wounds and skin conditions (Parvu, 2006). It was also used as baths against rheumatic pains and varicose veins (Butura, 1979).

Chemical composition

G. hederacea aerial parts contain 0.02-0.08% essential oil, the main constituents being germacrene-D, γ-elemene, β-elemene, phytols, (Z)-β-ocimene, 1,8-cineole, trans-3-pinanone, β-caryophyllene and spathulenol, both the content and composition being influenced by the origin of the plant material (Chou *et al*., 2018; Mockute *et al*., 2005; Mockute *et al*., 2007). It also contains phenolic acids (rosmaric, caffeic, chlorogenic and ferulic acids), flavonoids (cymaroside, cosmosyin, hypersoside, isoquercitrin), proanthocyanidins, tannins, saponins, bitter substances and terpenoids (oleanolic, α-ursolic and β-ursolic acids) (Ardelean & Mohan, 2008; Barnes *et al*., 2007; Belscak-Cvitanovic *et al*., 2014; Gruenwald *et al*., 2000; Istudor, 2001; Muntean *et al*., 2007; Parvu, 2006; Uritu *et al*., 2018; Wang *et al*., 2017).

Pharmacological activities

Preclinical data indicate that *G. hederacea* has antibacterial, anti-inflammatory, anticancer, insecticidal and platelet-stimulating activities (Uritu *et al*., 2018).

G. hederacea essential oil showed good *in vitro* antioxidant and anti-inflammatory (related to the enzymes iNOS, COX-2, HO-1 and the inflammatory cytokine TNF-α) activities, and also markedly decreased melanin production *in vitro* (Chou *et al*., 2018).

Ground ivy water extracts (infusion, decoction and macerate) showed a good antioxidant activity and potent cytotoxic effects on HEp2 cells (Human Laryngeal Carcinoma) (Belscak-Cvitanovic *et al*., 2014).

The oral administration of a water decoction had hepatoprotective effects in rats, improving the serum parameters, ductular reaction, oxidative stress, inflammation (attenuated inflammatory cell infiltration/accumulation, NF-κB and AP-1 activation, and inflammatory cytokine production) and fibrosis (Wang *et al*., 2017). The anti-inflammatory potential of *G. hederacea* water decoction was also revealed in *in vitro* models, through the inhibition of interferon-γ (IFN- γ) and lipopolysaccharide (LPS)-induced production of nitric oxide (NO), and also of interleukin-12p70 and Tumor Necrosis Factor alpha (TNF-α) production (An *et al*., 2006).

G. hederacea hot water extract showed *in vitro* antioxidant (scavenging free radicals, reducing power and chelating metal ions) and anti-mutagenic potential (Chou *et al*., 2012).

Oleanolic and ursolic acids were found to inhibit tumour production by TPA in mouse skin, with activity comparable to that of retinoic acid, a known tumour-promoter inhibitor (Barnes *et al*., 2007).

Ursolic acid also demonstrates cytotoxic activity against lymphocytic leukemia, human lung carcinoma, and marginal activity against human colon and mammary tumors (Duke *et al*., 2002).

Current uses

G. hederacea is used internally in digestive (anorexia, cholecystitis, diarrhoea, intestinal parasitosis, ulcer, gastritis and acid indigestion), hepatic, urinary (lithiasis, mild forms of dropsy) and respiratory (e.g. bronchial catarrh, cough) disorders, and externally to promote wound healing (as cicatrizating) (Ardelean & Mohan, 2008; Chevallier, 2016; Duke *et al*., 2002; Istudor, 2001; Muntean *et al*., 2007; Parvu, 2006).

For this purposes, several types of preparations are used, such as infusion, liquid extract (25% ethanol) and plant fresh juice (Barnes *et al*., 2007; Duke *et al*., 2002; Gruenwald *et al*., 2000).
It is also used in homeopathy against diarrhoea and hemorrhoids (Gruenwald *et al*., 2000).

Precautions and adverse reactions
Side effects following the proper administration of designated therapeutic dosages are not recorded (Gruenwald *et al*., 2000). Ground ivy essential oil contains many terpenoids which irritate the gastrointestinal tract and kidneys. Due to the lack of toxicity data and the possible irritant and abortifacient action of the essential oil, the use of ground ivy during pregnancy and lactation should be avoided (Barnes *et al*., 2007; Duke *et al*., 2002).

Other warnings
Excessive doses may irritate the gastrointestinal mucosa and should also be avoided by individuals with existing renal diseases (Barnes *et al*., 2007).

Helichrysum arenarium (L.) Moench (sandy everlasting, „siminoc"), Asteraceae family

Syn. *Antennaria arenarium* L., *Gnaphalium arenarium* (WHO, 2010).
***Other common names*:** Common Shrubby Everlasting, Eternal Flower, Goldilocks, Yellow Chaste Weed (Gruenwald *et al*., 2000).

Officinal products: According to the European Medicine Agency (EMA) and the World Health Organization (WHO), the officinal product is represented by the aerial part of the flowering plant (*Helichrysi flos*) (EMA/HMPC/41108/2015; EMA/HMPC/41109/2015; WHO, 2010). Literature also mentions the names *Flores Stoechados citrinae* or *Flores Gnaphalii arenarii* (Stanescu *et al*., 2002a).

Botanical description
H. arenarium is an herbaceous perennial plant with a woody, pivoting root. The stem is erect, unbranched, covered with small, silver trichomes, and up to 30 (50) cm high. The leaves are oblanceolate, sessile, alternate and whitish-green due to the numerous small, silvery trichomes that cover them, giving a pasty appearance. The flowers are yellow and grouped in globular calatides, and they are gathered in a corymb-shaped panicle. The flower stalks are also covered with numerous trichomes. The fruits are small achenes (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Parvu, 2006; Stanescu *et al*., 2002a; Stanescu *et al*., 2014). It blooms from July to October (Ardelean & Mohan, 2008; Parvu, 2006; Sarbu *et al.,* 2013).
Distribution and habitat: frequent from the steppe to the oak floor, through meadows, forest thickets, stony shores, sands (Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, C.A. Rosetti, Letea) (Doroftei *et al*., 2011). *Helichrysum arenarium* (L.) Moench ssp. *ponticum* (Velen.) Clapham [syn. *H. arenarium* (L.) Moench ssp. *arenarium* var. *ponticum* Velen.] was reported in Constanta and Tulcea (Caraorman, C.A. Rosetti, Cardon and Letea)

counties (Ciocarlan, 2011; Doroftei *et al*., 2011; Sarbu *et al.,* 2013). It is also found in Macin Mountains (Pricopan Peak, Nifon, Greci) (Andrei & Cristurean, 2006).
Harvesting period: flowering tops at the beginning of the flowering stage (Stanescu *et al*., 2014; WHO, 2010).

Traditional uses

H. arenarium was used in the European folk medicine in the treatment of dyspepsia, chronic cholecystitis and spastic biliary disorders, as water extracts, infusions and decoctions (EMA/HMPC/41109/2015; Stanescu *et al*., 2014). It was also used as a diuretic and for jaundice, gout, rheumatism, kidney complaints, dropsy and indigestion, as well as for loss of appetite (Gruenwald *et al*., 2000; WHO, 2010).
In Romanian folk medicine, the flowers were used in the treatment of hepato-biliary disorders, hepatitis, gastrointestinal disorders, gout, rheumatism and against intestinal worms (Grigorescu *et al.,* 1986; Parvu, 2006). The alcohol decoction and macerate was used in the treatment of jaundice (Butura, 1979; Stanescu *et al*., 2014).

Chemical composition

The inflorescences of *H. arenarium* contain flavonoids (naringin, helichrysin A, helichrysin B, salipurposide, eriodictyol, luteolin, luteolin-7-*O*-glucoside, galuteolin, astragalin, kaempferol, apigenin, hispidulin), phenolic acids (caffeic, chlorogenic, neochlorogenic, *p*-coumaric and ferulic acids), coumarins (scopoletin, umbelliferon and aesculetin) and sterols (campesterol, β-sitosterol, stigmasterol) (Ardelean & Mohan, 2008; Babota *et al*., 2018; EMA/HMPC/41109/2015; Gille *et al*., 2018; Gruenwald *et al*., 2000; Jarzycka *et al*., 2013; Mao *et al*., 2017; Pljevljakušic *et al*., 2018; Gruenwald *et al*., 2000; WHO, 2010). Two pyrone derivatives (yellow pigments) were also isolated from *H. arenarium*, namely arenol and homoarenol (Vrkoc *et al*., 1971).
The inflorescences contain 0.04-0.09% essential oil, the most abundant group of constituents being the aliphatic acids (dodecanoic and decanoic acids), ester methyl palmitate and aromatic compounds (carvacrol and anethol) (Pljevljakušic *et al*., 2018).
Several constituents were identified in roots, namely: methylene-*bis*-4-hidroxy-2H-pyran-2-one derivatives, helipyrone, norhelipyrine, bisnorhelipyrone, galangin, naringenin and kaempferol-3-glucoside (Vrkoc *et al*., 1975).

Pharmacological activities

Several biological effects were reported for *H. arenarium* extracts, fractions or isolated compounds, namely: diuretic, mild choleretic and spasmolytic, stimulation of bile, gastric and pancreatic secretion and antispasmodic (on smooth muscles and isolated *ex vivo* gallbladders) (Duke *et al*., 2002; EMA/HMPC/41109/2015; Parvu, 2006; Pljevljakušic *et al*., 2018; Stanescu *et al*., 2014).
The 70% ethanol extract from *H. arenarium* showed a good antioxidant activity and a moderate antimicrobial effect against several bacteria and fungi species (Babota *et al*., 2018). The methanol extract from *H. arenarium* inflorescences showed *in vitro* antimicrobial activity against several lower respiratory tract pathogenic bacteria, such as *Streptococcus pneumoniae, Staphylococcus aureus* and *Moraxella catarrhalis* (Gradinaru *et al*., 2014).
Helichrysi flos water extracts and lyophilized water extracts showed *in vitro* antioxidant activity (Czinner *et al*., 1999; Czinner *et al*., 2000).

The flavonoids isolated from flowers showed *in vitro* anti-atherosclerotic activity through its anti-inflammatory effects, the flavonol aglycone being more active than its glycoside (Mao *et al*., 2017).
Sunscreen formulations containing *H. arenarium* showed *in vitro* photoprotectivity and photostability on a broad UV spectrum (Jarzycka *et al*., 2013).

Current uses
According to the European Medicine Agency - Committee on Herbal Medicinal Products, several herbal preparations are used in Europe: comminuted herbal substance (for infusion and decoction) as choleretic in mild dyspeptic disorders, liquid extract (in combination with other medicinal plants) as choleretic for symptoms of indigestion. Several products with sandy everlasting flowers are marketed in Russia and Ukraine: tablets with dry extract containing flavonoids, dry extract in granulated form, fluid extract and decoction; these products are used in chronic liver inflammation, diseases of the gallbladder and biliary ways (cholecystitis, cholangitis and hepato-cholecystitis) (EMA/HMPC/41108/2015; EMA/HMPC/41109/2015).
The German Commission E approved its use in dyspeptic complaints (Duke *et al*., 2002; Gruenwald *et al*., 2000).
In Europe, *H. arenarium* is used in the treatment of various conditions such as cystitis, arthritis, rheumatism and gout, as well as for stimulating gastric secretion and in the treatment of gallbladder disorders (Pljevljakušic *et al*., 2018).
In Romania, it is used for the same purposes, in the form of infusion, decoction and dry extract in granulated form or tablets (Ardelean & Mohan, 2008; Grigorescu *et al.,* 1986; Parvu, 2006; Stanescu *et al*., 2014).

Precautions and adverse reactions
It is not recommended in case of hypersensitivity to the active substance and to plants from the Asteraceae (Compositae) family. Due to the possible stimulation of bile secretion, *Helichrysi flos* is not recommended in case of obstruction of the bile duct, cholangitis, liver disease and gallstones. Due to the lack of adequate data, the use in children and adolescents under 18 years of age, and also during pregnancy and lactation is not recommended (Duke *et al*., 2002; EMA/HMPC/41108/2015; WHO, 2010).

Other warnings
Not to be confused with the capitula of *Helichrysum stoechas* and *Helichrysum angustifolium* (Gruenwald *et al*., 2000).

Heracleum sphondylium L. (hogweed, „brânca ursului"), Apiaceae family

***Other common names*:** Masterwort (Gruenwald *et al*., 2000).

Officinal products: aerial part, but the herbal medicine also uses the whole plant (especially leaves, buds, roots and seeds) (Gruenwald *et al*., 2000).

Botanical description

H. sphondylium is an herbaceous, vigorous, biennial or perennial plant, 50-150 (-200) cm high. It has a strong tuberous, whitish-yellow root. The stem is erect, angular, grooved, hollow, stiff-haired and branched above. The leaves are pinnate, rarely incompletely pinnate or only lobed. The basal leaves are very large and have grooved petioles, which gradually merge into leaf sheaths, the basal and stem foliage being clasping. The flowers are grouped in flat umbels with no involucre. The petals have cordate margins with indented lobes. They are irregular, often pubescent on the outside, whitish or greenish, green-yellow or yellowish and sometimes pink. The fruit is compressed, flat, 8 mm long and 5 mm wide, roundish-oval and brownish yellow (Butura, 1979; Gruenwald *et al*., 2000; Sarbu *et al.,* 2013). It blooms from June to September (Sarbu *et al.,* 2013).

Distribution and habitat: frequently spread, from the plain to the subalpine floor, through meadows, thickets and forest edges, bushes, grassy rocks (Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (C.A. Rosetti) (Doroftei *et al*., 2011); *Heracleum sphondylium* L. ssp. *sibiricum* (L.) Simonkai (syn. *H. flavescens* Willd.) in Histria and Letea (Doroftei *et al*., 2011), and *H. sphondylium* L. ssp. *flavescens* (Willd.) Soó (Ciocarlan, 2011).

Harvesting period: the leaves and buds from April to October, the whole during flowering stage, the roots in spring and autumn (Fierascu *et al*., 2017).

Traditional uses

It is used traditionally to relieve muscle cramps, against stomach disorders, digestion complaints, diarrhoea, gastrointestinal catarrh and diarrhoea following a cold (Gruenwald *et al*., 2000). Other ethnobotanical uses are: as antihypertensive, sedative, wound healing, stomachic, digestive, aphrodisiac, and against diarrhoea, dysentery menstrual complaints and dyspepsia (Bahadori *et al*., 2016).

In Romanian folk medicine, it was used against headache (in the form of compresses); the flowering stems were used as baths in rheumatic diseases (Butura, 1979).

It is also known as "Romanian Ginseng" due to its extremely intense vitalizing effects (Fierascu *et al*., 2017).

Chemical composition

Several phenolic compounds were identified in different plant parts of *H. sphondylium*: caffeic acid (in leaves, flowers and fruits), chlorogenic acid (in roots, stems, leaves, flowers and fruits), gentisic acid (in flowers), p-coumaric acid (in roots, leaves, flowers and fruits), ferulic acid (in roots, leaves and flowers), isoquercitrin (in stems, leaves and flowers), rutin (in roots, stems, leaves, flowers and fruits), quercitrin (in leaves and flowers), quercetin (in roots, stems, leaves, flowers and fruits), luteolin (in flowers) and apigenin (in flowers) (Benedec *et al*., 2017).

In the fruits of *H. sphondylium*, several classes of chemical constituents were identified: monoterpene hydrocarbons (α-pinene, β-pinene, myrcene, limonene, *trans*-β-ocimene), sesquiterpene hydrocarbons (β-caryophyllene, *trans*-β-farnesene, germacrene-D), esters, alcohols, aldehydes and furocoumarins (bergapten, xanthotoxin, isopimpinellin, imperatorin, heraclenin, byak-angelicol), β-sitosterol (Bicchi *et al*., 1990; Gruenwald *et al*., 2000; Lawrie *et al*., 1968).

The main class of constituents in the essential oil isolated from fruits are represented by aliphatic esters, among them octyl acetate and octyl butyrate being the most abundant (Maggi *et al*., 2014).

Pharmacological activities

Several biological effects were reported for *H. sphondylium*: vasorelaxant, antioxidant, antimicrobial and cytotoxic (Bahadori *et al*., 2016).

The dichloromethane extract exhibited vasorelaxant properties on rat isolated thoracic aortic rings, through endothelium-independent mechanisms involving the inhibition of Ca2+ mobilization and changes in Kv channel conductances (Senejoux *et al*., 2013).

The essential oil isolated from the fruits of *H. sphondylium* showed cytotoxic activity against two tumor cell lines - human malignant melanoma (A375) and human colon carcinoma (HCT116), its major compound responsible for this effect being octyl butyrate (Maggi *et al*., 2014).

The aqueous extract from *H. sphondylium* exhibited antimicrobial activity against *Staphylococcus aureus* and *Shigella* strains, and the ethanol extract showed antimicrobial activity only on *Staphylococcus aureus* (Ergene *et al*., 2006).

Current uses

Several types of products are available on the Romanian market: tablets (with dry extract and powdered plant material), tincture and comminuted plant material for infusion. These products are recommended for their vitalizing and aphrodisiac effects in sterility and impotence, to increase the vitality of the body, to normalize the secretory activity of the male and female sexual glands, and also against hypertension, renal failure and rheumatism.

Precautions and adverse reactions

Due to the phototoxic effects of furanocoumarins (causing blistering and exfoliation), the exposure to UV radiation should be avoided following the intake of *H. sphondylium* products or the contact with the freshly bruised plant (Duke *et al*., 2002; Gruenwald *et al*., 2000).

Hippophaë rhamnoides L. (sea buckthorn, „cătină"), Elaeagnaceae family

***Other common names*:** Sallow Thorn (Gruenwald *et al*., 2000).

Officinal products: ripe, yellow-red berries (false fruit) (*Hippophae fructus*) (Ardelean & Mohan, 2008; Chevallier, 2016; Gruenwald *et al*., 2000; Muntean *et al.,* 2007; Oniga, 2007; Oroian, 2011).

Botanical description

H. rhamnoides is a thorny, dioecious, whitish shrub, 1-6 m tall and very branched. The roots are superficial with nitrogenous nodules. The stem has a dark-brown bark that turns into a furrowed rhytidome. The leaves are alternate, entire, linear-lanceolate, with obvious median vein, short petiolate, green-gray on the upper side and silver on the lower side, with rusty scales. The flowers are unisexual dioecious, small and

yellow-rusty in color. The male flowers are sessile, have 2 sepals and 4 stamens, and are grouped in globular inflorescences; the female flowers are short pedicellate, with an elongated receptacle, with 2 small sepals and a filiform ovary, and are grouped in racemes. The fruit is a bright orange (brown when dry), globular, ellipsoid, false berry, containing one seed (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Istudor, 2001; Muntean *et al.,* 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013). It blooms from April to May (Sarbu *et al.,* 2013). The fruits reach maturity in August-September (Muntean *et al.,* 2007). Different cultivars were developed. Thornless forms were also obtained, with superior properties regarding the color, shape and size of the fruit, productivity and quality; the plant material from the spontaneous flora could also be used for propagation purposes, by selecting plants with many fruits and as few thorns as possible (Muntean *et al.,* 2007).

Distribution and habitat: it grows in clumps or extensive bushes, on sands and gravels, on pebbles along rivers, islets, coasts, rocks, on lands subject to erosion (Ardelean & Mohan, 2008; Istudor, 2001; Oniga, 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, it is found insular in the Danube Delta area (Ardelean & Mohan, 2008; Muntean *et al.,* 2007; Parvu, 2006) and sporadically, from the Black Sea coast to the beech floor (Istudor, 2001; Sarbu *et al.,* 2013). In the Danube Delta, it was reported in Caraorman, C.A. Rosetti, Cardon, Letea, and in the sea side area (Ciocarlan, 2011; Doroftei *et al*., 2011); *H. rhamnoides* L. ssp. *fluviatilis* Van Soest was reported in Sfantu Gheorghe (Doroftei *et al*., 2011).

Harvesting period: fruits at full ripening, from August until the first frost (Gruenwald *et al*., 2000; Istudor, 2001; Oniga, 2007; Oroian, 2011; Parvu, 2006).

Traditional uses

Traditionally, *H. rhamnoides* is used internally in the prophylaxis of infections, especially before spring and during periods of convalescence; externally, it is used in the treatment of radiation damage, sunburns, and its fatty oil is used as wound healing agent (Gruenwald *et al*., 2000).

H. rhamnoides was used in Russia and the Himalayan region for treatment of skin diseases, jaundice, asthma, for gastrointestinal conditions and for the treatment of rheumatism; in the Central Asia, for the treatment of hypertension, digestive system (gastritis, stomach ulcers) and skin diseases (Suryakumar & Gupta, 2011).

In the folk medicine of Tibet, *H. rhamnoides* has been used for relieving cough, aiding digestion, invigorating blood circulation and alleviating pain (Wang *et al*., 2015).

Chemical composition

H. rhamnoides contains high amounts of bioactive compounds, such as flavonoids, phenolic acids, vitamins (E, K, B, C, folic acid), carotenoids (α, β, δ-carotene, lycopene), phytosterols (β-sitosterol, ergosterol, stigmasterol, lansterol), organic acids (malic acid, oxalic acid), aminoacids, polyunsaturated fatty acids and minerals (calcium, phosphorus, magnesium, potassium, sodium, iron) (Ardelean & Mohan, 2008; Ciesarová *et al*., 2020; Gille *et al*., 2016b; Guo *et al*., 2017a ; Guo *et al*., 2017b; Pang *et al*., 2008; Oroian, 2011; Parvu, 2006; Suryakumar & Gupta, 2011; Sytařová *et al*., 2020; Tkacz *et al*., 2020). The fruits and leaves are very rich in vitamin C (0.98-3.65 g/kg in fruits and 22.81-46.32 g/kg in leaves) and vitamin E (6.98-29.91 g/kg in

fruits and 71.54-153.99 g/kg in leaves) (Sytařová *et al*., 2020). The fruits also contain polysaccharides (Wang *et al*., 2015).

The fruits of *H. rhamnoides* contain high amounts of phenolic compounds, the main constituents being isorhamnetin and its derivatives (e.g. isorhamnetin-3-O-rutinoside, isorhamnetin-3-O-glucoside), quercetin and its derivatives (e.g. quercetin-3-O-rutinoside, quercetin-3-O-glucoside), kaempferol and its derivatives (kaempferol-3-O-sophoroside-7-O-rhamnoside), catechin, epicathin, and also gallic, protocatechuic and ferulic acids (Guo *et al*., 2017a). High amounts of phenolic compounds are also present in leaves, the main constituents being rutin, epigallocatechin, epicatechin, catechin, resveratrol, and also gallic, syringic, protocatechuic, ellagic, hydroxycinnamic, caffeic, ferulic, chlorogenic, neochlorogenic and p-coumaric acids (Sytařová *et al*., 2020).

In branches, three phenolic compounds [(+)-catechin, (+)-gallocatechin and (-)-epigallocatechin] and one triterpenoid (ursolic acid) were identified (Yasukawa *et al*., 2009). Several ellagitannins were identified in leaves, namely pedunculagin, stachyurin, hippophaenin B and C, and casuarictin (Ma *et al*., 2019).

The seed oil has high amounts of essential fatty acids (omega-3 and 6) and the pulp oil contains high levels of omega-7; β–Sitosterol is the main phytosterol in the oil (Suryakumar & Gupta, 2011).

Pharmacological activities

Antioxidant, immunomodulatory, anticancer, hepatoprotective, anti-stress and adaptogenic activities, and also cardioprotective, anti-atherogenic, antibacterial, antiviral and wound healing properties were reported for *H. rhamnoides* (Suryakumar & Gupta, 2011).

A polysaccharide isolated from *H. rhamnoides* significantly inhibited tumor growth in an animal model (mouse with Lewis lung carcinoma), possibly through immunological effects (e.g. increasing lymphocytes proliferation, enhancing phagocytosis and cytotoxicity of macrophages, boosting the nitric oxide and TNF-α levels) (Wang *et al*., 2015). Polysaccharides from *H. rhamnoides* also exhibited anti-inflammatory activity and immunomodulatory properties in intestinal porcine epithelial cells, by enhancing the intestinal barrier integrity and reducing the pro-inflammatory cytokine levels (Zhao *et al*., 2020).

The ethanol extract from *H. rhamnoides* branches showed anti-inflammatory effects and prominent antitumor activity in an *in vivo* model (mice with induced skin tumors) (Yasukawa *et al*., 2009).

The fruit extracts, rich in phenolic acids and flavonoids, showed *in vitro* (non-cellular and cellular systems) antioxidant and antiproliferative potential on human cancer HepG2 cells (Guo *et al*., 2017a). The antioxidant activity was also highlighted for the hydroalcoholic extract from fruits and leaves, the extract exhibiting, in addition, *in vitro* neuroprotective effect on human neural cell line (Shivapriya *et al*., 2015). Furthermore, the leaf infusion (rich in flavonoids and ellagitannins) showed a good antioxidant activity (Ma *et al*., 2019).

The seed oil exhibited *in vitro* and *in vivo* antioxidant activity (Ting *et al*., 2011), while the fruit oil isolated had *in vivo* hepatoprotective activity in chickens exposed to aflatoxin B1 (Solcan *et al*., 2013).

The extracts from shoots with leaves and from the fruit press cake (resulted after juice extraction) showed antimicrobial activity against *Bacillus spp*., *Salmonella spp*., *Escherichia coli*, *Yersinia pestis*, *Klebsiella* and *Shigella* (Radenkovs *et al*., 2018). The aqueous seed extract had a good antioxidant activity and antibacterial effect on *Listeria monocytogenes* and *Yersinia enterocolitica*, thus it can be considered a potential natural preservative (Chauhan *et al*., 2007).

The leaf extracts obtained by differential extraction with different polarities solvents, exhibited *in vitro* antioxidant, wound healing and anticancer properties on prostate cancer cell lines, the end-phase aqueous fraction being the most potent (Masoodi *et al*., 2020).

The fruit hydroalcoholic extract showed anticholinergic properties, probably due to its content in flavonols and carotenoids (Tkacz *et al*., 2020).

H. rhamnoides has been shown to have significant cardioprotective activity, inhibiting the blood aggregation, lowering the cholesterol levels and blood pressure, and also through its antioxidant potential (Olas, 2016). Total flavones extracted from *H. rhamnoides* seed residues exerted antihypertensive effects in rats with a diet high in sucrose, partially by improving the insulin sensitivity and also by blocking the angiotensin signal pathway (Pang *et al*., 2008). Clinical trials revealed that the dietary supplementation with *H. rhamnoides* fruits and extracts led to a significant decrease of total cholesterol, triacylglycerol and LDL-cholesterol and to a significant increase of HDL-cholesterol in subjects with cardiovascular risks, these effects being probably attributed to its content in flavonoids and β-sitosterol (Guo *et al*., 2017b).

Several polyphenolic bioproducts obtained from the bark of *H. rhamnoides* shrub exhibited *in vitro* (cellular model) cytostatic and cytotoxic potential, and *in vivo* (animal model) immunomodulatory, normolipemiant and hypocholesterolemiant effects, and also antineoplastic potential (Gherghel *et al*., 2009; Mihai *et al*., 2008; Rotinberg *et al*., 2008).

Current uses

The fruits of *H. rhamnoides* are widely used as functional food supplement, as foods (jams) and food coloring material in food industry (Guo *et al*., 2017).

The fruits, fresh and dry, or conditioned as syrup, infusion and juice, are used in the treatment of hypo- and avitaminosis (Gruenwald *et al*., 2000; Istudor, 2001; Oniga, 2007; Oroian, 2011). The drug is also used in hepatic disorders (epidemic and chronic hepatitis, and liver cirrhosis), rheumatism, atherosclerosis, ophthalmic conditions, scurvy, hypertension and diarrhoea (Ardelean & Mohan, 2008; Istudor, 2001; Muntean *et al.,* 2007; Oniga, 2007; Parvu, 2006).

The oil is used, both internally and externally, in the treatment of burns, gynecological conditions, as hepatoprotective, ulcer-protective and wound healing agent (Gruenwald *et al*., 2000; Oniga, 2007). Thus, it is included in numerous pharmaceutical preparations for internal and external use, such as capsules, sprays, ophthalmic solutions and creams (Istudor, 2001; Oniga, 2007).

Precautions and adverse reactions

No side effects were reported in conjunction with the proper administration of designated therapeutic dosages (Gruenwald *et al*., 2000).

Other warnings
Not to be confused with tamarix (*Tamarix ramosissima*) (Grigorescu *et al*., 1986).

Hypericum perforatum L. (St. John's Wort, „sunătoare"), Hypericaceae family

Syn. *Hypericum veronense* Schrank, *H. noeanum* Boiss. (Barnes *et al*., 2007; Doroftei *et al*., 2011), *Hypericum officinarum* Crantz, *Hypericum officinale* Gater ex. Steud., *Hypericum vulgare* Lam. (WHO, 2002; WHO, 2010).
***Other common names*:** Hardhay, Amber, Goatweed, Klamath Weed, Tipton Weed, St. Johnswort (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia and the European Medicines Agency (EMA) (EMEA/HMPC/745582/2009; EMA/HMPC/101304/2008; EMA/HMPC/101303/2008; Eur. Ph. 8.0, 2013), the officinal product is *Hyperici herba* represented by whole or fragmented, dried flowering tops of *Hypericum perforatum* L. The drug must have few fructifications and lignified parts of the stem (Stanescu *et al*., 2014).

Botanical description
H. perforatum is a perennial herbaceous plant, with a short rhizome from which many adventitious roots emerge. The stem is erect, 10-100 cm high, woody at the bottom, branched at the top, with two longitudinal edges on which black dots are observed; many sterile branches emerge from the axils of the leaves. The leaves are small, sessile, ovate to elliptical, glabrous, opposite, with many translucent points (they give the appearance of small and numerous perforations due to the glands with essential oil, hence the name *perforatum*). The flowers are yellow, grouped in corymbs, consisting of 5 free, entire lanceolate sepals, 5 free petals that are 2 times longer than the sepals, each provided on the edges with small black dots, and with numerous long and prominent stamens. The fruit is a dry trilocular capsule, containing numerous blackish-brown seeds (Ardelean & Mohan, 2008; Eur. Ph. 8.0, 2013; Muntean *et al*., 2007; Oroian, 2011; Sarbu *et al.,* 2013; Stanescu *et al*., 2014; Stefan & Oprea, 2007). It blooms in June-September (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013; Stefan & Oprea, 2007).
Distribution and habitat: frequently spread, from plain to the spruce floor, through meadows, bushes, fields, in forest cuttings, at the edge of roads and forests (Ardelean & Mohan, 2008; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Letea, Perisor, Periteasca, Vadu including the Corbu area) (Ciocarlan, 2011; Doroftei *et al*., 2011).
Harvesting period: during flowering stage, in June-September (Ardelean & Mohan, 2008; Eur. Ph. 8.0, 2013; Gruenwald *et al*., 2000; Parvu, 2006; WHO, 2002; WHO, 2010).

Traditional uses
H. perforatum is considered a valuable medicinal plant (for over 2000 years), in European folk medicine being used as diuretic, cicatrizating and analgesic agent, in

depression, melancholy, anxiety, insomnia, menstrual disorders, intestinal parasites, gastritis, edema, skin inflammation and hemorrhoids. In Romanian folk medicine, the flowers macerated in oil were used externally to treat cuts, wounds, eczema, dermatological conditions and burns. The infusion was used externally against hair loss. The plant macerated in alcohol was used internally in dysentery, hernia, biliary disorders and jaundice; the decoction was used internally in the treatment of leucorrhea (Butura, 1979; Stanescu *et al*., 2014). It was also used against the inflammation of the bronchial and the genitourinary tracts, and as antihemorrhagic, antihemorrhoidal, antineuralgic, cicatrizating in the treatment of burns (Parvu, 2006).

Chemical composition

H. perforatum aerial parts contain several bioactive compounds classes, namely: naphthodianthrone (0.03-0.3% hypericin and pseudohypericin and their derivatives), phloroglucinol (2.0-4.5% hyperforin, and its precursors and derivatives), 2-4% flavonoids (quercetin, myricetin, luteolin, kaempferol, catechin, epicatechin, rutin, hyperoside, quercitrin, isoquercitrin, kaempferol 3-O-glucoside, kaempferol 3-rutinoside), phenolic acids (chlorogenic, neochlorogenic, caffeic, shikimic, p-coumaric and ferulic acids), 0.05-0.9% essential oil, xanthones, alkaloids, proanthocyanidins (procyanidin B2) and tannins (Cretu *et al*., 2011; Greeson *et al*., 2001; Gruenwald *et al*., 2000; Ionescu *et al*., 2018a; Ionescu *et al*., 2018b; Patočka, 2003; Saddiqe *et al*., 2010; Stanescu *et al*., 2014; Tebrencu *et al*., 2018c; Tebrencu *et al*., 2018d; Velingkar *et al*., 2017; WHO, 2010; Wirz, 2000; Yousuf *et al*., 2012). Other constituents include: acids (isovalerianic, nicotinic, myristic, palmitic, stearic), carotenoids, choline, nicotinamide, pectin, β-sitosterol, straight-chain saturated hydrocarbons (C16, C30) and alcohols (Barnes *et al*., 2007). Regarding the essential oil composition, the major constituent is methyl-2-octane (minimum 30%); other constituents include: *n*-nonane, methyl-2-decane and *n*-undecane, α- and β-pinene, α- terpineol, geraniol, traces of myrcene and limonene, caryophyllene and humulene (Barnes *et al*., 2001). A study showed that the optimum harvesting time (when the bioactive compounds content is higher) is at floral budding stage (Sun *et al*., 2018).

The European Pharmacopoeia requires: for *Hyperici herba* (dried drug) minimum 0.08% total hypericins (expressed as hypericin); for the quantified dry extract (*Hyperici herbae extractum siccum quantificatum* - anhydrous extract) 0.10-0.30% total hypericins expressed as hypericin, minimum 6.0% flavonoids expressed as rutin, maximum 6.0% hyperforin and not more than the content stated on the label (Eur. Ph. 8.0, 2013).

According to the European Medicines Agency, the extracts should be quantified with respect to hypericin, and the amounts of hyperforin and flavonoids should be declared (EMA/HMPC/101304/2008).

Pharmacological activities

The extracts, fractions and isolated compounds from *H. perforatum* have been reported to have antidepressant, antiparkinsonian, anticonvulsant, anxiolytic, antioxidant, antibacterial, antifungal, antiviral, wound healing, anti-inflammatory, analgesic, anti-diabetic, antiangiogenic and anticancer activities (Asgarpanah, 2012; Butterweck *et al*., 2001; Gruenwald *et al*., 2000; Patočka, 2003; Shrivastava & Dwivedi, 2015; Silva *et al*., 2005; Velingkar *et al*., 2017).

The antibacterial activity was reported for several types of extracts, fractions, isolated compounds and products with *H. perforatum*, against multiple bacterial strains: *Micrococcus luteus*, *Moraxella catarrhalis*, *Escherichia coli, Enterococcus faecalis, Staphylococcus oxford* and *S. aureus* (including methicillin-resistant strains of *S. aureus*), *Streptococcus mutans, S. sanguis, S. pyogenes* and *S. viridans*, *Pseudomonas aeruginosa*, *Helicobacter pylori, Bacillus subtilis* and *Salmonella typhi* (Saddiqe *et al*., 2010; Yousuf *et al*., 2012).

Numerous clinical trials highlighted the antidepressant activity of *Hypericum* extracts, but a lack of consensus in the medical community regarding its efficacy and the absence of standardization guidelines is observed (Barnes *et al*., 2001; Greeson *et al*., 2001). The clinical trials showed the efficacy of St. John's wort on patients with mild-to-moderate depression (comparable with selective serotonin reuptake inhibitors), but its long-term efficacy and safety and the beneficial effects on patients with severe depression are yet to be established (Ng *et al*., 2017). Several mechanisms were identified as being responsible for its antidepressant effect, these involving several neurotransmitters (inhibiting their metabolism and modulating their receptors density and sensitivity) and hormones: inhibiting the monoamine oxidase, the synaptosomal reuptake of serotonin, norepinephrine and dopamine, and increasing the cortisol levels (Anonymous, 2004; Barnes *et al*., 2001; Barnes *et al*., 2007; Bennett *et al*., 1998; Greeson *et al*., 2001; Mennini & Gobbi, 2004). Regarding the endocrine effects of *H. perforatum* in patients with depression, changes in the hypothalamic-pituitary-adrenal axis were observed, animal studies showing reduced plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone (Butterweck *et al*., 2001).

The standardized extract from *H. perforatum* exerted benefic effects on disorders associated with metabolic syndrome, significantly lowering the total cholesterol and low-density cholesterol in normal rats, inhibiting weight gain in high-fat-fed rats, normalising dyslipidemia induced by fructose feeding and improving the insulin sensitivity (Husain *et al*., 2011).

Extracts, fractions and isolated compounds (hypericin and pseudohypericin) from *H. perforatum* showed antiviral activity against herpes simplex virus 1 and 2, HIV, influenza virus and hepatitis C (Barnes *et al*., 2001; Chevallier, 2016; Stanescu *et al*., 2014).

H. perforatum fractions and isolated constituents (hyperforin, hypericin, and hyperoside) exhibited antispasmodic, bronchodilator and cardiovascular-modulatory effects *in vitro* (isolated animal tissues) (Khan *et al*., 2011a).

Current uses

Regarding the traditional use, the European Medicine Agency - Committee on Herbal Medicinal Products, mentions the following herbal preparations: (a) dry extract (extraction with 38% ethanol); (b) liquid extract (extraction with vegetable oil); (c) tincture (extraction with 45-50% ethanol); (d) liquid extract (extraction with 50% ethanol); (e) expressed juice from fresh herb; (f) comminuted herbal substance (herbal tea for oral use); (g) powdered herbal substance. Herbal preparations (a) and (g) in solid dosage forms, and also the preparations (b)-(e) in liquid dosage forms have oral use. The herbal preparations (b), (c) and (f) (liquid or semi-solid dosage forms) have cutaneous use. These herbal preparations are indicated for internal use for the relief of

temporary mental exhaustion and for the symptomatic relief of mild gastrointestinal discomfort, and for external use are indicated in healing of minor wounds (EMEA/HMPC/745582/2009).

Regarding the well-established use, EMA mentions the following herbal preparations: (a) dry extract (extraction with 80% methanol); (b) dry extract (extraction with 80% ethanol); (c) dry extract (extraction with 50-68% ethanol). The pharmaceutical forms are represented by herbal preparations in solid forms for oral use and are indicated for the treatment of mild to moderate depressive episodes (EMA/HMPC/101304/2008).

The German Commission E approved the use in anxiety, depressive moods, inflammation of the skin, blunt injuries, wounds and burns (Gruenwald *et al*., 2000).

According to the World Health Organization monographs, the uses include symptomatic treatment of mild and moderate depressive episodes (supported by clinical data) and external use for the treatment of minor cuts, burns, skin ulcers (uses reported in pharmacopoeias and in traditional medicine systems); the preparations include dried crude drug for decoction, powdered drug or extracts in capsules, tablets, tinctures, drops (internal use), oil, infusions, compresses, gels and ointments (external use) (WHO, 2002; WHO, 2010).

The amount of hyperforin has to be specified in the herbal preparations for oral use, since the daily intake is limited to 1 mg (EMEA/HMPC/745582/2009).

Several *Hypericum* standardized extracts (in hypericin or hyperforin) are included in numerous industrial preparations (singular or in combination), such as dragees, drops and ampoules, prescribed in the treatment of mild to moderate somatogenic and psychogenic depressions, preclimacteric and climacteric depressions, in states of anxiety, excessive nervousness and psychovegetative disorders (Muntean *et al*., 2007; Stanescu *et al*., 2002b; Stanescu *et al*., 2014). *Hypericum* oil (plant maceration in oil) is used in burns, wounds and other skin conditions, but also in the treatment of gastric ulcer (Muntean *et al*., 2007; Parvu, 2006).

Precautions and adverse reactions

Toxicity studies did not show signs of toxic effects and no signs of mutagenicity could be detected in *in vitro* and *in vivo* tests (EMA/HMPC/101304/2008; EMEA/HMPC/745582/2009). No health hazards are known in conjunction with the proper administration of designated therapeutic dosages (Gruenwald *et al*., 2000). Due to the lack of sufficient data, the use during pregnancy and lactation is not recommended (EMEA/HMPC/745582/2009). Due to the lack of data, the use in children under 12 years of age is not recommended (EMEA/HMPC/745582/2009; EMA/HMPC/101304/2008). *Hyperici herba* is contraindicated in cases of known allergy to plants from the *Hypericaceae* family and hypersensitivity to the active substance (EMEA/HMPC/745582/2009; EMA/HMPC/101304/2008; WHO, 2002; WHO, 2010).

Photosensitization reactions (due to photoactive hypericin) may occur with prolonged exposure to the sun or UV radiation, but normally the therapeutically active doses are lower than the photosensitizing doses (EMEA/HMPC/745582/2009; Stanescu *et al*., 2014).

Due to drug interaction, the concomitent use of *Hypericum* preparation with other drugs, such as other antidepressants (fluoxetine, fluvoxamine, sertraline), digoxin,

theophylline, warfarin anticoagulants, oral contraceptives, cyclosporine, indinavir, tacrolimus, amprenavir and irinotecan is not recommended (EMA/HMPC/101304/2008; Gruenwald *et al*., 2000; Stanescu *et al*., 2002b; Stanescu *et al*., 2014; WHO, 2002; WHO, 2010). Pharmacokinetic interactions between conventional medicines and *Hypericum* preparation could also be possible due to its effect on gastric motility (Capasso *et al*., 2008).

The most commonly reported side effects were: gastrointestinal irritations, anorexia, nausea, allergic reactions, fatigue, restlessness and headache (Greeson *et al*., 2001; Gruenwald *et al*., 2000).

Other warnings

Not to be confused with other *Hypericum* species, such as *H. barbatum*, *H. hirsutum*, *H. maculatum*, *H. montanum* and *H. tetrapterum* (Gruenwald *et al*., 2000).

Inula helenium L. (elecampane, „iarbă mare"), Asteraceae family

***Other common names*:** Alant, Elfdock, Elfwort, Horse-Elder, Horseheal, Inula, Scabwort, Wild Sunflower, Yellow Starwort, Velvet Dock (Barnes *et al*., 2007; Gruenwald *et al*., 2000).

Officinal products: rhizome (*Inulae rhizoma*), root (*Inulae radix*) (Barnes *et al*., 2007; Gruenwald *et al*., 2000; Istudor, 2001; Muntean *et al*., 2007; Oniga, 2007), rhizome and root (*Inulae rhizoma cum radicibus/ Inulae rhizoma et radix*) (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Oroian, 2011).

Botanical description

I. helenium is an herbaceous, perennial, robust plant, 80 to 180 cm high (Gruenwald *et al*., 2000; Sarbu *et al.,* 2013). In the first year it forms only a rosette of basal leaves. It has tuberous roots, thick at the top, from which secondary roots, up to 50 cm long, gray-brown, start annually. The stem is erect, edged, hirsute, simple or branched; the flowering stem appears in the second year of vegetation. The basal leaves are large, elliptical, long-petiolate, the stems ones are ovate-amplexical, with the petiole shorter and shorter, up to the sessile, cordate at the base, with uneven teeth on the edge, on the upper face are green, rough, short and rigidly hirsute, and on the lower face gray-tomentaceous. The yellow flowers are grouped in calatides; the female lateral florets are narrowly linguiform and the androgynous disc florets are tubular. The receptacle is flat, slightly pitted and glabrous. The calatides are reunited in a loose corymb. The inflorescences are protected with large, hirsute and nested bracts. The fruits are small achenes with long pappus (Ardelean & Mohan, 2008; Butura, 1979; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Oniga, 2007; Parvu, 2006; Stefan & Oprea, 2007). It blooms from June to September (Ardelean & Mohan, 2008; Oroian, 2011; Sarbu *et al.,* 2013; Stefan & Oprea, 2007).

Distribution and habitat: frequent through wet meadows, meadows, on the edge of forests, on the waterfront, sporadic from the hilly area to the beech floor (Sarbu *et al.,*

2013). In Dobrogea, this species was reported in the Danube Delta area (Maliuc, Sontea) (Doroftei *et al*., 2011).

Harvesting period: rhizomes and roots of 2-3 years old plants in autumn (starting from September) (Istudor, 2001; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006).

Traditional uses

I. helenium was used traditionally to treat bronchitis, whooping cough and cough associated with pulmonary tuberculosis, bronchial and tracheal catarrh, as a gently warming and tonic herb, as a stomachic, diuretic, carminative and cholagogue, and for menstrual complaints (Barnes *et al*., 2007; Chevallier, 2016; Gruenwald *et al*., 2000).

In Romanian folk medicine, the decoction from *I. helenium* roots was used for the treatment of bronchitis, asthma, cough of various etiologies, chronic urinary tract diseases, gout, biliary dyskinesia, allergies, ascariasis, anemia, rheumatism, leucorrhea, and also as sedative. Externally, the root decoction was used for the treatment of eczema, purulent wounds, ulcers, varicose ulcers, rheumatism and the ointment was used to treat ray (Parvu, 2006). It was also used against hernia, gastric complaints and intestinal colic in young children (Butura, 1979).

Other ethnopharmacological data mention the use of the root decoction in pulmonary disorders and intestinal worms (Tita *et al*., 2009).

Chemical composition

Several sesquiterpene lactones were identified in the roots of *I. helenium*, namely: eudesmanes (alantolactone, isoalantolactone, 11a,13-dihydroalantolactone, 11a,13-dihydro-isoalantolactone, 5-epoxyalantolactone), germacrane (isocostunolide), elemane (igalane) (Amin *et al*., 2013; Chen *et al*., 2007; Huo *et al*., 2010; Kaur *et al*., 2014; Konishi *et al*., 2002; Seca *et al*., 2014). The mixture of alantolactone derivatives is also known as helenin or elecampane camphor (Grigorescu *et al*., 1986; Gruenwald *et al*., 2000).

The roots also contain essential oil (with a relatively high amount of sesquiterpenoids), the main constituents being alantolactone, isoalantolactone and diplophyllin (Bourrel *et al*., 1993; Stojanović-Radić *et al*., 2012).

I. helenium is a valuable source of inulin (up to 44% in roots) (Barnes *et al*., 2007; Grigorescu *et al*., 1986; Stojanović-Radić *et al*., 2012).

In leaves and flowers, several phenolic compounds were identified: gentisic acid (leaves), caffeic acid (leaves and flowers), chlorogenic acid (leaves and flowers), p-coumaric acid (leaves), isoquercitrin (flowers), rutin (leaves), quercitrin (leaves and flowers), quercetin (flowers) and kaempferol (flowers) (Nan *et al*., 2011).

The leaves and flowers also contain carotenoids, such as neoxanthin, violaxanthin, lutein, β-criptoxanthin, β–carotene (in leaves), and neoxanthin, violaxanthin, lutein-5,6-epoxide, anteraxanthin, lutein, β-criptoxanthin, β–carotene (in inflorescences); the total carotenoids content being: in leaves 4.87 mg/100 g fresh weight (f.w.), in ligulate flowers 47.7 mg/100 g f.w., in tubular flowers 9.9 mg/100 g f.w., in inflorescences 11.78 mg/100 g f.w. (Nan *et al*., 2012).

Pharmacological activities

Antioxidant, antimicrobial, antiproliferative, hypotensive, hyperglycemic (large doses) and hypoglycemic (smaller doses) activities were reported for *I. helenium* extract and

its bioactive compounds (Akthar, 2016; Amin *et al*., 2013; Barnes *et al*., 2007; Kaur *et al*., 2014; Istudor, 2001).

The *n*-hexane fraction isolated from the roots of *I. helenium*, in which seven sesquiterpenes were identified, showed a strong antiproliferative activity against chronic myeloid leukemia (MK-1), human cervical cancer (HeLa) and murine melanoma (B16F10) cells (Konishi *et al*., 2002). Sesquiterpene lactones isolated from the roots of *I. helenium* also showed antitumor potential (in addition to HeLa) on several other tumor cell lines, namely: human endometrial adenocarcinoma (HEC-1), human ovarian serous cystadenocarcinoma (SHIN3), human ovarian adenocarcinoma (HOC-21) and human ovarian clear cell adenocarcinoma (HAC-2) (Li *et al*., 2012).

Isocostunolide, a sesquiterpene lactone isolated from roots, effectively induced cytotoxicity in three cancer cell lines: human amelanotic melanoma (A2058), human colon adenocarcinoma (HT-29) and human hepatoblastoma (HepG2), in human melanoma cells inducing mitochondrial membrane depolarization and caspase-dependent apoptosis (Chen *et al*., 2007).

The essential oil isolated from the roots of *I. helenium* exhibited a good antimicrobial activity against *Staphylococcus aureus*, by inducing cell membrane damage (increased permeability, followed by lysis of the exposed cells), the most active constituents being alantolactone, isoalantolactone and diplophyllin (Stojanović-Radić *et al*., 2012).

The hydroalcoholic extract from roots showed a moderate to high antimicrobial activity against several bacterial strains (*Escherichia coli, Bacillus cereus, Staphylococcus aureus* and *Enterococcus faecalis*) and fungi (*Candida albicans, Candida parapsilosis* and *Candida lipolytica*) (Diguta *et al*., 2014).

I. helenium extract and isolated sesquiterpenes exhibited *in vivo* (animal model) anti-inflammatory activity, and the oral intake alleviated the paw swelling and arthritic severity in rat arthritis models, these effects suggesting their possible use in the prevention and treatment of rheumatoid arthritis (Gao *et al*., 2017).

Inulin, found in high amounts in *I. helenium,* has mucilaginous qualities that help soothe the bronchial linings (Chevallier, 2016).

Current uses

The extract is included in numerous pharmaceutical preparations recommended for gastrointestinal diseases, gout, as diuretics and expectorant (Gruenwald *et al*., 2000).

As infusion, decoction, tincture, capsules (with powdered plant material, extract or essential oil), syrup, essential oil, *I. helenium* is used internally for mucopurulent catarrhal bronchitis, bronchial catarrh, chronic cough in the elderly, emphysemic bronchitis, asthma, intestinal parasitosis, atonic and hypotonic biliary dyskinesia, chronic urinary tract disorders, rheumatism, bronchitis, for regulating blood pressure and in menstrual disorders (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Istudor, 2001; Muntean *et al*., 2007; Oroian, 2011; Oniga, 2007). Externally, it is used in eczema, purulent wounds, ulcers, varicose ulcers, rheumatism and scabies (Ardelean & Mohan, 2008).

I. helenium is used in homeopathy for stomach ulcers and chronic cough (Gruenwald *et al*., 2000).

Precautions and adverse reactions
There is a lack of clinical safety and toxicity data on *I. helenium*. Elecampane has been reported to cause allergic contact dermatitis, due to essential oil and sesquiterpene contents (Barnes *et al*., 2007). Prolonged treatment or repetition at short intervals is not recommended, leading to severe irritation of mucous membranes, vomiting, diarrhoea and spasms (Gruenwald *et al*., 2000; Istudor, 2001). Not to be used during pregnancy (Gruenwald *et al*., 2000).

Other warnings
It can be confused with *Telekia speciosa* Baumg., which has similar flowers (Muntean *et al*., 2007; Oniga, 2007).

Lamium album L. (white deadnettle, „urzică moartă albă"), Lamiaceae family

***Other common names*:** Blind Nettle, Dumb Nettle, Dead Nettle, Deaf Nettle, Bee Nettle, Archangel, Stingless Nettle, White Archangel (Gruenwald *et al*., 2000).

Officinal products: flowers (*Lamii albi flos*) (Ardelean & Mohan, 2008; Grigorescu *et al.*, 1986; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Oniga, 2007; Stanescu *et al*., 2014), leaves (*Lamii albi folium*) (Grigorescu *et al.*, 1986; Gruenwald *et al*., 2000; Stanescu *et al*., 2014), flowering tops (Chevallier, 2016), flowering aerial parts (*Lamii albi herba*) (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Oniga, 2007).

Botanical description
L. album is an herbaceous perennial plant, up to 30-50 cm high. The rhizome is elongated, horizontal, from which adventitious roots and underground stolons start. The aerial stems start from the stolons, are quadrangular, grooved, hollow, noded, hirsute, erect and unbranched. The leaves are opposite, triangular-ovate, acuminate and scattered on both sides, petiolate, with serrated edges, large teeth, dark green on the upper surface and lighter green on the lower one. The white or pale yellow, fairly large bilabiate flowers are located in axillary false whorls of 6 to 16 flowers. The tube of the corolla is bent like a knee and the upper lip is curved like a helmet with a ciliate margin. There are 2 long and 2 short stamens under the upper lip. The fruits are truncated nucules, brown, grouped 4 in the persistent calyx (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013). It blooms from April to June (Sarbu *et al.,* 2013).
Distribution and habitat: frequent through shady places, forest edges, orchards, bushes, meadows, near fences and roads, from the hilly to the mountainous area (Ardelean & Mohan, 2008; Istudor, 2001; Parvu, 2006; Sarbu *et al.,* 2013).
Harvesting period: flowers without calyx and upper aerial parts during flowering stage (Parvu, 2006; Stanescu *et al*., 2004b).

Traditional uses
Traditionally, *L. album* was used internally for catarrh of the upper respiratory passages, complaints of the urogenital tract and gastrointestinal disorders (gastritis, sensation of bloating and flatulence), and externally for mild inflammation of the

mucous membranes of the mouth and throat, leucorrhea and superficial inflammation of the skin (Gruenwald *et al*., 2000).

In Romanian folk medicine, the infusion from flowers was used in colds, cough, whooping cough, leucorrhea, dysmenorrhea, in the treatment of prostate hypertrophy and for normalizing blood pressure; the infusion from underground stolons was used against gastric ulcer (Butura, 1979; Grigorescu *et al*., 1986; Muntean *et al*., 2007; Oroian, 2011). Decoctions or tinctures were administered orally as a decongestant (intestinal catarrh), emollient, vasoconstrictor, astringent (in diarrhoea), and externally, as wash in leucorrhea and local application in epitasis (Stanescu *et al*., 2014).

Chemical composition

The aerial parts of *L. album* contain iridoids, such as lamalbide, caryoptoside, alboside A and B, shanzhiside methyl ester (Alipieva *et al*., 2006; Czerwinska *et al*., 2018; Gruenwald *et al*., 2000).

It also contains phenylpropanoid glycosides (phlinoside D, lamalboside, acteoside and isoacteoside), phenolic acids (chlorogenic, caffeic, rosmarinic, ferulic, vanillic and protocatechuic acids), flavonoids (apigenin and quercetin glycosides, luteolin-7-O-glucoside, naringenin-7-O-rutinoside, astragalin, isoscutellarein derivatives), phytoecdysteroids (abutasterone, inokosterone, polypodine B and pterosterone), terpenes (ursolic and oleanolic acids), mucilages, small amounts of essential oil and tannins (Ardelean & Mohan, 2008; Chevallier, 2016; Czerwinska *et al*., 2018; Pereira *et al*., 2012; Pereira *et al*., 2013; Stanescu *et al*., 2014; Veleva *et al*., 2015; Yordanova *et al*., 2014).

Pharmacological activities

Antioxidant, antiviral, antimicrobial, cytoprotective, anticancer and anti-inflammatory activities were reported for *L. album* (Armatu *et al*., 2010; Veleva *et al*., 2015; Yordanova *et al*., 2014).

The hydroalcoholic extract from *L. album* aerial parts, standardized in total phenols, induced an *in vitro* relaxant effect on tracheal smooth muscle, thus being a candidate for the management of chronic respiratory diseases such as asthma and obstructive pulmonary diseases (Arefani *et al*., 2018).

Phenylpropanoid glycosides, iridoids and flavonoids isolated from *L. album* herb exerted anti-inflammatory potential, by inhibiting cytokine (IL-8 and TNF-α) and Reactive Oxygen Species (ROS) production in human neutrophils (Czerwinska *et al*., 2018). *L. album* ethanol purified extract showed cytoprotective activity on liver cells, having high capacities in counteracting ROS formation in oxidative stress conditions in HepG2 cells (Pereira *et al*., 2013).

Different types of extracts (chloroforms, alcohol and water) from *in vivo* and *in vitro* propagated plants of *L. album* showed antibacterial and antifungal activity (Chipeva *et al*., 2013). The methanol and chloroform extracts from *Lamium album* L. have anticancer potential exhibiting cytotoxic effect on the lung cancer cell line A549 (Moskova-Doumanova *et al*., 2012).

The butanolic extract from *L. album* aerial parts exhibited *in vivo* (animal model) hemostatic activity, probably due to the presence of iridoids such as 8-*O*-acetylshanzhiside methyl ester (Bubueanu *et al*., 2019).

The biological activity of *L. album* is due, in part, to iridoids, but pharmacological investigations performed on animal models have also shown a weak diuretic action and very good anti-inflammatory activity of the saponoid fraction (Stanescu *et al*., 2014).
Due to the presence of mucins and saponins, *L. album* has expectorant effects and the tannins confer astringent properties (Gruenwald *et al*., 2000).

Current uses
The German Commission E approved the use of *L. album* in inflammation of the skin, cough/bronchitis and inflammation of the mouth and pharynx (Gruenwald *et al*., 2000).
It is used internally (as tincture, fluid extract, infusion, syrup) in respiratory (bronchitis), digestive (diarrhoea, enteritis), vascular (varicose ulcer, varicose veins), endocrine (menopausal disorders), genital and urinary (nephritis, cystitis, prostate hypertrophy, leucorrhea, metrorrhagia) disorders; and externally (infusion as washings, local baths, compresses, poultices) against mucosal and skin disorders (skin ulcers, purulent wounds, boils), gout, hemorrhoids and vaginitis (Ardelean & Mohan, 2008; Chevallier, 2016; Istudor, 2001; Oniga, 2007; Parvu, 2006; Stanescu *et al*., 2014).

Precautions and adverse reactions
No side effects were reported in conjunction with the proper administration of designated therapeutic dosages (Gruenwald *et al*., 2000).

Lamium purpureum L. (red deadnettle, „urzică moartă roșie"), Lamiaceae family

***Other common names*:** purple deadnettle (Jones *et al*., 2012).

Officinal products: aerial parts (*Lamii purpureum herba*) (Ardelean & Mohan, 2008; Parvu, 2006).

Botanical description
L. purpureum is an annual herbaceous plant, with a height of 15-30 cm. The root is fibrous and well developed. The stem is branched at the base with ascending branches, pubescent from the middle upwards. The lower leaves are broad-ovate, deeply cordate, serrate, long-petiolate, the upper ones being cordate-ovate, with serrate-toothed edge, pubescent on the upper face, glabrescent on the lower one; the bracts are crenulate or crenulate-serrate. The flowers are red-purple, smaller (corolla tube about 1 mm in diameter), arranged in a pyramidal inflorescence, the calyx is slightly bilabiate, hairy, tubular-campanulate, the corolla is 10-18 mm long, tubular, slightly curved, bilabiate, with a hairy ring inside. The fruits are nucules with 4 edges (Ardelean & Mohan, 2008; Butura, 1979; Parvu, 2006; Sarbu *et al.,* 2013; Stefan & Oprea, 2007). It blooms from March to September (Andrei & Cristurean, 2006; Ardelean & Mohan, 2008; Parvu, 2006; Sarbu *et al.,* 2013).
Distribution and habitat: frequent as ruderal and segetal weed, in sunny areas, cultures, through gardens, near fences and roads, bushes, from steppe to beech floor

(Andrei & Cristurean, 2006; Butura, 1979; Sarbu *et al.,* 2013; Stefan & Oprea, 2007). In Dobrogea, this species was reported in the Danube Delta area (C.A. Rosetti, Ilgani, Maliuc, Sontea, Somova-Parches complex) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (frequent in Macin Mountains National Park) (Andrei & Cristurean, 2006).

Harvesting period: aerial parts during flowering stage (Ardelean & Mohan, 2008; Parvu, 2006).

Traditional uses

The aerial parts of *L. purpureum* were used in Romanian folk medicine to treat epilepsy, rheumatism, abscesses and wounds (Parvu, 2006). The flowering stems were boiled in wine, which was administrated 3 times a day against rheumatism and externally was used as baths against epilepsy and tachycardia (Butura, 1979).

Chemical composition

Small amounts of essential oil were isolated from the aerial parts of *L. purpureum*, between 0.01-0.08 mg% per fresh weight, the main constituents being germacrene D, (*E*)-caryophyllene and β-pinene (Flamini *et al*., 2005; Jones *et al*., 2012).

The whole plant of *L. purpureum* contains iridoids, such as lamiusides A, B, C, D and E, acteoside, leucosceptoside A, isoacteoside, 6-*O*-b-D-glucopyranosylmartynoside, shanzhiside methyl ester, caryoptoside, lamiol, 5-deoxylamiol and lamalbide (Alipieva *et al*., 2007; Ito *et al*., 2006).

Among the polyphenolic compounds, chlorogenic and caffeic acids, rutin, quercetin and hyperoside were identified in *L. purpureum* aerial parts (Bubueanu *et al*., 2013).

It also contains benzoxazinoids, aminoacids, phytoecdysteroids and fatty compounds (Bubueanu *et al*., 2019).

Pharmacological activities

The phenylethanoid glycosides isolated from whole plants of *L. purpureum* showed a good *in vitro* antioxidant activity (Ito *et al*., 2006). Antioxidant activity was also highlighted for the butanolic extract from *L. purpureum* (Bubueanu *et al*., 2013).

The butanolic extract from the aerial parts exhibited hemostatic activity, by decreasing the bleeding time in a hemostatic test (tail bleeding time determination) (Bubueanu *et al*., 2019).

Current uses

L. purpureum is used internally for the treatment of epilepsy (freshly comminuted plant macerated in honey, infusion from comminuted dried plant), rheumatism (decoction in wine of flowering stems) and externally for treating abscesses (dressing with ground fresh plant, directly on the abcess; local washes and compresses with decoction) (Ardelean & Mohan, 2008; Parvu, 2006).

Precautions and adverse reactions

No available data.

Malva neglecta Wallr. (dwart mallow, „cașul popii"), Malvaceae family

Syn. *Malva vulgaris* Fr. (Doroftei *et al*., 2011), *Malva rotundifolia* auct. plur., non L. (Doroftei *et al*., 2011; Grigorescu *et al*., 1986; Muntean *et al.,* 2007; Sarbu *et al.,* 2013).

***Other common names*:** neglected mallow (EMA/HMPC/749518/2016).

Officinal products: According to the European Pharmacopoeia and the European Medicines Agency (EMA), the officinal product is *Malvae folium* represented by whole or fragmented, dried leaf of *Malva sylvestris* L., *Malva neglecta* Wallr., or a mixture of both species (EMA/HMPC/749518/2016; Eur. Ph. 8.0, 2013). Literature also mentions the officinal products: *Malvae neglectae folium* (*M. neglecta* leaves) (Ardelean & Mohan, 2008; Muntean *et al.,* 2007; Parvu, 2006), *Malvae neglectae flos* (*M. neglecta* flowers) (Parvu, 2006; Tita *et al*., 2009). Roots are also used in traditional medicine (Tita *et al*., 2009).

Botanical description

M. neglecta is an annual herbaceous plant, with a height of 10-60 cm. The root is pivoting, thin. The stem is cylindrical, branched, ascending or lying, scattered-hirsute. The leaves are alternate, dense, long-petiolate, hirsute, with reniform to cordate-round leaf blade, cordate base, provided with 5-7 lobed teeth on the edge. The flowers are white-pink, long-peduncled (2-4 cm), arranged 1-6 at the axils of the leaves. The calyx is double, consisting of 3 free, small external sepals, and 5 larger and united internal sepals. The corolla consists of 5 emarginated, white-pink petals. The fruit is a flattened, disciform capsule with persistent calyx, which unfolds at maturity in several segments. The seeds are reniform (Ardelean & Mohan, 2008; Muntean *et al.,* 2007; Parvu, 2006; Stefan & Oprea, 2007). It blooms from June to September (Sarbu *et al.,* 2013; Stefan & Oprea, 2007).

Distribution and habitat: frequent throughout the country, from the plains to the mountain area, in ruderal, uncultivated places, roadsides, in fields, parlors (Ardelean & Mohan, 2008; Muntean *et al.,* 2007; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, Letea) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: flowers with the calyx at the beginning of the flowering stage, from May to September; mature leaves before and after flowering stage, but if they are not infected by *Puccinia malvacearum*, harvesting is indicated only after flowering (Parvu, 2006; Stanescu *et al*., 2002a; Stanescu *et al*., 2004b).

Traditional uses

It has been used in food since ancient times. The ancient writings (Horatius, Plinius, Scribonius) mention it as a food plant and recommend it as a vegetable (Butura, 1979; Oroian, 2011; Parvu, 2006). The plant was used by the Greeks and Romans for its emollient and laxatives properties (EMA/HMPC/749518/2016).

In Romanian folk medicine, it was used externally against swelling and sores, tonsillitis (in the form of compresses or gargle), head, hand and foot pain (topical application of decoction), against cough, hoarseness and chest pain (decoction from root, leaf and flower) (Parvu, 2006; Butura, 1979). In folk medicine, the product was

also used externally as poultices in the treatment of wounds and furunculosis (Stanescu *et al*., 2002a; Stanescu *et al*., 2004b).

Other ethnopharmacological data mention the use of the decoction and cataplasm with decoction from roots, leaves and flowers in pulmonary, intestinal, urinary, digestive, ophthalmic and skin disorders, against asthma, cough, hemorrhoids, hemorrhages, ascitis, wounds, burns and abscesses (Tita *et al*., 2009).

Chemical composition

The aerial parts of *M. neglecta* contain phenolics, tannins, alkaloids and aminoacids (Alqurashy, 2017).

Phenolic compounds (e.g. quinic, malic, protocatechuic, caffeic, p-coumaric, 4-hydroxybenzoic and salicylic acids), fatty acids (e.g. palmitic, linoleic, linolenic, myristic and stearic acids) and essential oil are present in the whole plant (roots and aerial parts) (Hasimi *et al*., 2017). Among the flavonoids, malvidin catechin, delphinidin and apigenin were identified in different plant parts (Khalid & Saleem, 2018).

Proteins, lipids, cellulose, Na, K, Ca, P, vitamin C, mucilages, tannins, phytosterols were also reported for *M. neglecta* (Ardelean & Mohan, 2008; Muntean *et al.,* 2007).

Pharmacological activities

Antioxidant, anti-inflammatory, antimicrobial, anticholinesterase, anti-urolithiatic and anti-ageing activities were reported for *M. neglecta* (EMA/HMPC/749518/2016; Khalid & Saleem, 2018).

The crude methanol extract from *M. neglecta* and its fractions exhibited a good antimicrobial activity against 3 bacteria (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Bacillus cereus*) and 2 fungi strains (*Aspergillus niger*, *Fusarium solani*) (Alqurashy, 2017). The ethanol extract from flowers also showed a good antimicrobial activity, especially against *Staphylococcus epidermidis* (Seyyednejad *et al*., 2010).

Different fractions of the methanol extract from the whole plant showed antioxidant and moderate anticholinesterase effects, and antimicrobial activity against *Escherichia coli, Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas aeruginosa* and *Candida albicans* (Hasimi *et al*., 2017). The hydroalcoholic extract from the leaves and flowers of *M. neglecta* and the aqueous extract from the aerial parts also showed antioxidant potential (Güder & Korkmaz, 2012; Mavi *et al*., 2004.).

The aqueous extract from *M. neglecta* leaves exhibited benefic effects in preventing the formation of kidney stones induced by ethylene glycol and ammonium chloride in rats (Saremi *et al*., 2015).

The decoction from the roots, leaves and flowers of *M. neglecta* has emollient, expectorant, antitussive, anti-inflammatory, diuretic, depurative, laxative, astringent and cicatrizing properties (Tita *et al*., 2009).

Due to its content in mucilage, the product has emollient and expectorant properties, and it is indicated in the treatment of upper respiratory tract, oral mucosa and gastrointestinal tract inflammation (Muntean *et al.,* 2007; Stanescu *et al*., 2002a; Stanescu *et al*., 2004b).

The leaves have similar properties to those from other *Malva* species (Oroian, 2011).

Current uses
According to the European Medicine Agency - Committee on Herbal Medicinal Products, the herbal medicinal product (comminuted herbal substance) is used as herbal tea (oral use) or decoction (oromucosal use) for the symptomatic treatment of oral or pharyngeal irritation, associated dry cough and for the symptomatic relief of mild gastrointestinal discomfort (EMA/HMPC/749518/2016).
It is used internally in cough, bronchitis, laryngitis, tracheitis, kidney and urinary tract diseases (nephritis, pyelitis, urethritis, cystitis), and externally in dental abscesses, tonsillitis, hemorrhoids and furunculosis (Ardelean & Mohan, 2008; Parvu, 2006).
The herbal product is a component of some preparation recommended for bronchial complaints, and the extract is part of instant teas with the same use (Stanescu *et al*., 2002a; Stanescu *et al*., 2004b). It is also used as syrup, decoction and macerate as expectorant and emollient (Grigorescu *et al*., 1986; Muntean *et al.,* 2007).

Precautions and adverse reactions
Due to the lack of adequate data, the internal use by children under 12 years of age is not recommended. Also, in the absence of sufficient data, the use during pregnancy and lactation is not recommended (EMA/HMPC/749518/2016).

Malva sylvestris L. (common mallow, „nalbă de pădure"), Malvaceae family

Syn. *Malva ambigua* Guss., *Malva erecta* C. Presl (Doroftei *et al*., 2011), *M. mauritiana* L. (Chevallier, 2016; Doroftei *et al*., 2011), *M. sylvestris* var. *incanescens* Griseb. (Chevallier, 2016).

***Other common names*:** High Mallow**,** Mallow, Blue Mallow, Mauls, Cheeseflower (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia and the European Medicines Agency (EMA) the officinal product is *Malvae sylvestris flos* represented by whole or fragmented dried flower of *Malva sylvestris* L. or its cultivated varieties (EMA/HMPC/749511/2016; EMA/HMPC/749518/2016; Eur. Ph. 8.0, 2013), and *Malvae folium* represented by whole or fragmented, dried leaf of *Malva sylvestris* L., *Malva neglecta* Wallr. or a mixture of both species (EMA/HMPC/749518/2016; Eur. Ph. 8.0, 2013). Other monographs refers to flowers (*Malvae flos*) from *Malva sylvestris* L. or/and *Malva sylvestris* subsp. *mauritiana* (L.) Asch. Et Graebn. (Stanescu *et al*., 2002a; Stanescu *et al*., 2004b). Literature also mentions the use of roots (Chevallier, 2016; Tita *et al*., 2009).

Botanical description
M. sylvestris is a biennial or perennial species, with a height of 20-120 cm (Sarbu *et al.,* 2013). The root is pivoting, fleshy. The stem is straight, branched and cylindrical. The leaves are alternate, long petiolate, palmately-lobed, with 3-7 semicircular or triangular lobes, with unevenly toothed and hairy edges. The abaxial surface of the lamina bears more hairs and shows a more prominent venation than the adaxial surface. The flowers are pink-purple, arranged in axillary cymes, long-peduncled (1-3

cm), with double, external calyx, formed by 3 free hipsophils. The fruit is a disc-shaped capsule that breaks into 9-11 wrinkled and glabrous mericarps (Ardelean & Mohan, 2008; EMA/HMPC/749518/2016; Eur. Ph. 8.0, 2013; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2004b; Stefan & Oprea, 2007). It blooms from May to October (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013).

Distribution and habitat: frequently spread, from plain to the beech floor, through meadows, bushes, thickets and forest edges, parlors, ruderal places, fields (Parvu, 2006; Sarbu *et al.,* 2013; Stefan & Oprea, 2007). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, Cardon, Letea) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: April-May (leaves), May-October (flowers) (Ardelean & Mohan, 2008; Parvu, 2006).

Traditional uses

M. sylvestris was used for the past thousand years in Europe, due to its high mucilage content, for treating the symptoms of oral or pharyngeal irritations, associated dry cough and gastrointestinal discomfort (EMA/HMPC/749518/2016).

Traditionally, *Malvae flos* and *M. folium* were used internally (as infusion and decoction) against the inflammation of upper respiratory tract and throat, in gastroenteritis, constipation; as gargle and mouth was used for the inflammation of the mouth and throat mucous membranes, sensitive gums, toothache; as a poultice and bath was used externally against skin redness, furuncles, itching and for its wound healing properties (EMA/HMPC/749518/2016).

Worldwide, different plant parts of *M. sylvestris* are traditionally used as infusion, decoction, bath/wash, gargle, ointment and cataplasm against gastrointestinal disturbance, dermatological ailments, menstrual pains, vaginal diseases, hemorrhoids, inflammation, urological disorders, respiratory complaints, pain and oral diseases (Gasparetto *et al*., 2011).

In the Dacian culture, *M. sylvestris* was used for its anti-inflammatory, cicatrizating and laxative effects, and also in respiratory disorders (Segneanu *et al*., 2019).

In Romanian folk medicine, the raw leaves and flowers or their decoction were used for blisters, swelling and abscesses. The leaves were used externally, in the form of poultices, in the treatment of wounds and boils. The decoction from the whole plant (including roots) was used externally against the swelling of the feet. The infusion and decoction from flowers, leaves and roots were used internally against cough and chest pain. The leaf infusion was used internally against kidney pain. The decoction and infusion from leaves and flowers were used against leucorrhea and as hemostatic (Butura, 1979; Stanescu *et al*., 2002a; Stanescu *et al*., 2004b).

Other ethnopharmacological data mention the use of the decoction, maceration and infusion from roots, leaves and flowers in pulmonary, intestinal, urinary, digestive, ocular and skin disorders, asthma, cough, hemorrhoids, hemorrhages, ascitis, wounds, burns and abscesses (Tita *et al*., 2009).

Chemical composition

Several bioactive compounds classes, such as polysaccharide, coumarins (scopoletin and 5,7- dimethoxycoumarin), flavonoids, phenolic acids, vitamins (A, C, E), tannins, sesquiterpenes, diterpenes and monoterpenes were reported in *M. sylvestris* (Ardelean

& Mohan, 2008; Gasparetto *et al*., 2011; Paul, 2016; Samavati & Manoochehrizade, 2013; Segneanu *et al*., 2019).

The flowers are rich in flavonoids, e.g. malvidin 3,5-diglucoside, malvidin 3-O-glucoside, delphinidin 3-O-glucoside, malvidin 3-O-(6″-O-malonylglucoside)-5-O-glucoside, delphinidin, genistein, myricetin, apigenin, quercetin and kaempferol derivatives (Gasparetto *et al*., 2011). The flowers also contain tannins, alkaloids, saponins, triterpenoids, sterols and anthocyanins (Mohajer *et al.*, 2016; Mohamadi Yarijani *et al*., 2019; Stanescu *et al*., 2004b). The flowers have up to 0.039% (w/w) essential oil, the main components being hexadecanoic acid, 2-methoxy-4-vinylphenol and pentacosane (EMA/HMPC/749518/2016).

The leaves, flowers and roots have high amount of mucilages, consisting mainly of glucuronic acid, galacturonic acid, rhamnose, galactose, fructose, glucose and sucrose (Butura, 1979; Gasparetto *et al*., 2011).

Several flavonoids and phenolic acids were identified in leaves, namely rutin, hyperoside, quercetin-3-D-glucoside, luteolin, apigenin, quercetin, chlorogenic, rosmarinic, p-coumaric, ferulic and caffeic acids (EMA/HMPC/749518/2016; Gruenwald *et al*., 2000; Terninko *et al*., 2017).

Pharmacological activities

Antioxidant, anti-inflammatory, anticancer, wound healing, laxative, hepatoprotective, antinociceptive, immunomodulatory, anti-ulcerogenic and antimicrobial activities were reported for *M. sylvestris*, following *in vitro* and *in vivo* studies (Gasparetto *et al*., 2011; Jabri *et al.*, 2017; Mohajer *et al.*, 2016; Paul, 2016).

The methanol macerate from *M. sylvestris* whole plant exhibited cardioprotective effects in myocardial ischemic/ reperfused rats, by reducing oxidative stress and inflammatory response (decreasing the levels of nitric oxide, aspartate transaminase, lactate dehydrogenase, C-reactive protein, macrophage inflammatory protein 1 alpha and pro-inflammatory cytokines) (Zuo *et al*., 2017).

The hydroalcoholic flower extract showed *in vivo* (animal model) protective effects on kidneys against toxic effects of gentamicin and decreased the harmful effects of nephrotoxicity on remote organs such as the liver (Mohamadi Yarijani *et al*., 2019).

A gel with *M. sylvestris* hydroalcoholic leaf extract showed benefic effects when applied to animals with inflammatory pathologies, by significantly decreasing the inflammation index and exudation rate, thus having potential use in treating dermatological diseases (Terninko *et al*., 2017).

The polysaccharide fraction isolated from the leaves of *M. sylvestris* exhibited antioxidant activity in a concentration dependent manner (Samavati & Manoochehrizade, 2013).

A pre-clinical study (on mice) highlighted the potential use of *M. sylvestris* in the treatment of psoriasis, the leaf hydroalcoholic extract exhibiting benefic effects on chronic inflammation and hyperproliferative response, by reducing edema, leukocyte migration and keratinocyte hyperproliferation (Prudente *et al*., 2017).

Due to the mucilage content, flowers have emollient properties (Stanescu *et al*., 2004b).

Current uses
According to the European Medicine Agency - Committee on Herbal Medicinal Products, the herbal medicinal product (comminuted herbal substance) is used as herbal tea (oral use) or decoction (oromucosal use) for the symptomatic treatment of oral or pharyngeal irritation, associated dry cough and for the symptomatic relief of mild gastrointestinal discomfort (as mild astringents in gastroenteritis) (EMA/HMPC/749518/2016).
The German Commission E approved the use of *Malva* leaf and flower in cough, bronchitis and inflammation of the mouth and pharynx (Gruenwald *et al*., 2000).
The flowers are frequently included in tea formulas for respiratory tract complaints (internal use) and in diseases of the oral cavity (as gargle) (Stanescu *et al*., 2002a; Stanescu *et al*., 2004b).

Precautions and adverse reactions
No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages (Duke *et al*., 2002; Gruenwald *et al*., 2000). Due to the lack of adequate data, the internal use by children under 12 years of age is not recommended. Also, in the absence of sufficient data, the use during pregnancy and lactation is not recommended (EMA/HMPC/749511/2016; EMA/HMPC/749518/2016).

Other warnings
Not to be confused with other varieties of *Malva* and with the leaves of *Althaea officinalis* (Gruenwald *et al*., 2000).

Matricaria recutita L. (chamomile, „mușețel"), Asteraceae family

Syn. *Chamomilla recutita* (L.) Rauschert (Ardelean & Mohan, 2008; Chevallier, 2016; Doroftei *et al*., 2011; Eur. Ph. 8.0, 2013; Istudor, 2001; Sarbu *et al.,* 2013; WHO, 1999; WHO, 2010), *Matricaria chamomilla* L. (Andrei & Cristurean, 2006; Duke *et al*., 2002; Istudor, 2001; Sarbu *et al.,* 2013; WHO, 1999; WHO, 2010), *M. suaveolens* L. (WHO, 1999; WHO, 2010), *Chamomilla vulgaris* Koch. (Istudor, 2001).
***Other common names*:** Pin Heads, Chamomilla, Single Chamomile, Hungarian Chamomile (Gruenwald *et al*., 2000), Scented Mayweed, Sweet False Chamomile, Wild Chamomile (Barnes *et al*., 2007), German chamomile (Tsivelika *et al*., 2018).

Officinal products: According to the European Pharmacopoeia, the European Medicines Agency (EMA) and the World Health Organization (WHO), the officinal products are: the dried capitula (*Matricariae flos*) of *Matricaria recutita* L. (*Chamomilla recutita* (L.) Rauschert); the blue essential oil (*Matricariae aetheroleum*) obtained by steam distillation from the fresh or dried flower-heads or flowering tops of *M. recutita*; liquid extract (*Matricariae extractum fluidum*) from *Matricaria* flower (EMA/HMPC/278814/2010; EMA/HMPC/55843/2011; EMA/HMPC/55837/2011; Eur. Ph. 8.0, 2013; WHO, 1999). Literature also mentions the names *Chamomillae*

flos, *Flos Chamomillae vulgaris*, *Flores Chamomillae germanicae* or *Anthodium Chamomillae* (Stanescu *et al*., 2002a).

Botanical description

M. recutita is an annual herbaceous plant, with a height of 10-50 (Sarbu *et al.,* 2013). The root is pivoting, superficially branched. The stem is glabrous, erect or ascending, often branched at the base, each branch ending with an inflorescence. The leaves are alternate, glabrous, pinnatisect and have a narrow thorny tip. The flowers are arranged in terminal semi-globular green inflorescences (capitula, up to 1.5 cm in diameter), on a conical, fistulous receptacle. Each capitulum consists of 12-18 ligulate marginal flowers (towards the end of flowering are oriented towards the ground), tridentate, female, white; the central flowers are tubular, hermaphrodite, yellow-golden. The involucre has biserial bracts that are elongated ovate, green, membranous white bordered. At maturity, the receptacle becomes conical and hollow inside. The fruits are slightly curved achenes, very small, light brown-gray, with 4-5 ribs on the ventral face and a very short or absent pappus (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Istudor, 2001; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2014; WHO, 2010). It blooms from May to June (Andrei & Cristurean, 2006; Oniga, 2007; Oroian, 2011; Sarbu *et al.,* 2013).

Distribution and habitat: frequent, from the steppe area to the beech floor, through meadows, vineyards, acacia plantations, parlors, ruderal places, salted lands (Ardelean & Mohan, 2008; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, C.A. Rosetti, Letea, Sulina) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: the inflorescences are collected in May-August, when the ligulate flowers are arranged horizontally and the tubular ones are in bloom, when the essential oil content is higher (Istudor, 2001; Muntean *et al*., 2007; Oniga, 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2014).

Traditional uses

M. recutita is one of the most popular medicinal plants in Europe, its traditional use being reported since ancient times (EMA/HMPC/55837/2011).

In folk medicine, it is used as an antibacterial, antiviral, emetic and emmenagogue agents, and also to relieve eye strain, to treat urinary infections and diarrhoea (WHO, 1999; WHO, 2010). It was also used externally for furuncles, hemorrhoids, abscesses, eczema and acne (Chevallier, 2016; Gruenwald *et al*., 2000).

In Romanian folk medicine, *M. recutita* decoction was used externally against hemorrhoids, eczema and as wound healing agent, and internally against stomach ache, and as gargle againt toothache. The infusion was used internally against cough, coulds and rheumatism (Butura, 1979). Internally, the flower infusion, maceration-infusion and tincture were used for the treatment of hyperacid gastritis, in gastric ulcer, enterocolitis, abdominal colic, diarrhoea, flu, colds, painful periods, asthma and to stimulate the liver function. Externally, the infusion was used in the treatment of gingivitis, dental abscesses, tonsillitis, stomatitis (as gargle and mouth wash), rheumatism, eczema, varicose ulcers, hemorrhoids, in boils, wounds, purulent wounds, ulcers and leucorrhea (as baths, poultices, vaginal washings); the tincture was used to treat burns (Parvu, 2006).

Other ethnopharmacological data mention the use of the infusion from flowers in gastritis, enterocolitis, diarrhoea, cough and flu (Tita *et al*., 2009).

Chemical composition

The most important bioactive compound classes present in chamomile are: sesquiterpenes, flavonoids, coumarins, polyacetylenes and essential oil (Singh *et al*., 2011).

The main bioactive constituents identified in flowers include: phenolic compounds (apigenin, quercetin, patuletin, luteolin and their glucosides, salicylic, caffeic, chlorogenic, syringic and vanillic acids), coumarins and dicycloethers (Gupta *et al*., 2010; Oniga, 2007; Stanescu *et al*., 2014).

Chamomile inflorescences contain 0.2-1.5% essential oil, the main constituents being E-β-farnesene, α-bisaboloxide B, (-)-α-bisabolol, chamazulene and bisaboloxide A (Göger *et al*., 2018; Gruenwald *et al*., 2000; Istudor, 2001; Necula *et al*., 2016; Necula *et al*., 2017; Oniga, 2007; Romero *et al*., 2012; Stanescu *et al*., 2014; WHO, 1999; WHO, 2010). The chmamomile essential oil was classified in four chemotypes, based on the ratios of the main constituents, namely Type A (α-bisabolol oxide B > α-bisabolol oxide A > α-bisabolol), Type B (α-bisabolol oxide A > α-bisabolol oxide B > α-bisabolol), Type C (α-bisabolol > α-bisabolol oxide B > α-bisabolol oxide A), Type D (α-bisabolol oxide B, α-bisabolol oxide A and α-bisabolol in equal amounts) (Tsivelika *et al*., 2018). There are also chemovarieties rich in essential oil but lacking azulene, and poor in essential oil but with high content of azulene (Istudor, 2001). The European Pharmacopoeia mentions 2 types of matricaria oil which are characterised as rich in bisabolol oxides or rich in (-)-α-bisabolol (Eur. Ph. 8.0, 2013).

The essential oil has a blue color determined by the presence of chamazulene (sesquiterpene compounds) (Oroian, 2011; Stanescu *et al*., 2014).

In leaves and flowers, the following coumarins were identified: skimmin (umbelliferone 7-O-b-D-glucoside), daphnin (daphnetin-7-O-b-D-glucoside), daphnetin, umbelliferone, herniarin, (Z)- and (E)-b-D-glucopyranosyloxy-4-methoxycinnamic acids (Barnes *et al*., 2007; EMA/HMPC/55837/2011; Petrulová-Poracká *et al*., 2013). Several sesquiterpene lactones (eudesmanolide, germacranolide and guaianolide types) and phenolic compounds (chlorogenic, caffeic, p-coumaric and salicylic acids, rutin, apigenin-7-glucoside, quercetin, luteolin, apigenin, kaempferol, isorhamnetin) were also identified in the aerial parts (Haghi *et al*., 2014; Zaiter *et al*., 2007).

The European Pharmacopoeia requires for *Matricariae flos* a content in blue essential oil of minimum 4 mL/kg (dried drug) and in total apigenin 7-glucoside of minimum 0.25% (dried drug) and for liquid extract minimum 0.30% blue residual oil. The extract is produced using a mixture of 2.5 volumes of a 10% (m/m) solution of ammonia (NH3), 47.5 volumes of water and 50 volumes of ethanol (96%, V/V) (EMA/HMPC/55837/2011; Eur. Ph. 8.0, 2013).

Pharmacological activities

Anti-inflammatory, immunomodulatory, antispasmodic, anti-diarrhoeal, antioxidant, antidepresive, anticarcinogenic, hepatoprotective, antimicrobial, wound healing and anti-diabetic (antihyperglycemic) effects were reported for chamomile extracts and

essential oil (Gupta *et al*., 2010; Hameed *et al*., 2018; Miraj & Alesaeidi, 2016; Stanescu *et al*., 2014).

The essential oil isolated from the inflorescences of chamomile showed larvicidal activity against the larvae of the parasitic nematode *Anisakis simplex* (Romero *et al*., 2012). Combinations between *M. recutita* essential oil fractions and antimicrobial agents had synergistic effect on clinic isolates of *S. aureus* and *C. albicans*, with no cytotoxic effects on the healthy cell line (Göger *et al*., 2018).

The chamomile hydroalcoholic extract decreased cisplatin-induced pain and inflammation in mice, better than morphine (Namvaran Abbas Abad *et al*., 2011).

A pilot clinical trial showed that the topical use of chamomile essential oil improved the symptomatic and functional status of patients with severe carpal tunnel syndrome (Hashempur *et al*., 2015). Another clinical trial highlighted the benefic effects of chamomile essential oil on patients with knee osteoarthritis, its topical application leading to a decrease of analgesic demand, an improvement of physical function and reduced stiffness (Shoara *et al*., 2015).

The cicatrizing effects of the topical use of chamomile preparations is explained by the favorable influence on skin metabolism, by stimulating the oxidative phosphorylation processes, activating the epithelialization and the appearance of granulation tissue after burns (Stanescu *et al*., 2002a; Stanescu *et al*., 2014). Chamomile preparations have also been found to be beneficial in the treatment of radiation mucositis caused by the head and neck radiation and systemic chemotherapy (WHO, 1999; WHO, 2010).

The essential oil has anti-ulcerogenic properties, α-bisabolol contributing to a faster healing of ulceration areas in the ventricular ulcer. Bisaboloxides and α-bisabolol stimulate the local endogenous synthesis of prostaglandins, thus strengthening the mucosal protective barrier against the aggressive effect of gastric juice (Parvu, 2006; Stanescu *et al*., 2002a; Stanescu *et al*., 2014).

Chamazulene exerts anti-inflammatory effects through the inhibition of leukotriene B4 formation (Gruenwald *et al*., 2000).

Current uses

The European Pharmacopoeia mentions the following products used in therapy: herbal substance, blue essential oil (*Matricariae aetheroleum*), liquid extract (*Matricariae extractum fluidum*) (EMA/HMPC/55837/2011; Eur. Ph. 8.0, 2013).

According to the European Medicine Agency - Committee on Herbal Medicinal Products, the herbal preparations are represented by: comminuted herbal substance; essential oil; different types of liquid extract in ethanol (38.5-96% ethanol); liquid extract (extraction with propan-2-ol 48%); dry extracts (different concentrations of ethanol). These herbal preparations are recommended for internal, oromucosal or cutaneous use, as bath additives and steam inhalation for: the symptomatic treatment of minor gastrointestinal complaints (bloating and minor spasms), common cold, treatment of minor ulcers and inflammations of the mouth and throat, adjuvant therapy of skin and mucosa (anal and genital region) irritations, the treatment of minor inflammation of the skin (sunburn), superficial wounds and small boils (furuncles) (EMA/HMPC/55843/2011; EMA/HMPC/55837/2011). The essential oil is used as a

bath additive for adjuvant therapy of irritations of skin and mucosa in the anal and genital region (EMA/HMPC/278814/2010).
The German Commission E approved its use in cough/bronchitis, fevers and colds, inflammation of the skin, mouth and pharynx, tendency to infection, wounds and burns (Gruenwald *et al*., 2000).
The fluid extract is included in some association preparations with carminative, spasmolytic and digestive action. Externally, in the form of steam inhalations, gargles, mouth washes, poultices, enemas, baths or ointments, chamomile is used in the treatment of inflammation of the skin and oral, nasal, pharyngeal, anal and genital mucosa, as well as in inflammation and irritation of the respiratory tract. The essential oil is used in aromatherapy and also in the cosmetic products (lotions, soaps, creams, shampoos, toothpastes) and perfumes (Stanescu *et al*., 2002a; Stanescu *et al*., 2014).

Precautions and adverse reactions
It is not recommended in case of hypersensitivity to the active substance and to other plants of the Asteraceae (Compositae) family. Baths are contraindicated in cases of open wounds, large skin injuries, acute skin diseases, high fever, severe infections, severe circulatory disturbances and cardiac insufficency. Hypersensitivity reactions, including severe allergic reaction, were reported following the mucosal contact with the liquid chamomile preparations (EMA/HMPC/278814/2010; EMA/HMPC/55843/2011). The allergic reaction may be due to the sesquiterpene lactones (Oniga, 2007; Stanescu *et al*., 2014).
Due to the lack of adequate data, the use in children under 12 years of age has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended (EMA/HMPC/278814/2010).

Other warnings
During harvesting, contamination with other *Matricaria* species and also *Anthemis* species may occure: *M. suaveolens* (syn. *M. discoidea* D.C.), *M. perforata* Merat. (syn. *M. inodora* L.), *Anthemis nobilis* L., *A. arvensis* L., *A. tinctoria* L., *A. cotula* L (Istudor, 2001; Muntean *et al*., 2007; Oniga, 2007; Oroian, 2011; Stanescu *et al*., 2014).

Melilotus officinalis (L.) Pall. (sweet clover, „sulfină"), Fabaceae family

Syn. *Melilotus petitpierreana* Willd., *Melilotus melilotus-officinalis* Asch. & Graebn. (Doroftei *et al*., 2011), *Melilotus arvensis* Wallr. (Chevallier, 2016; Doroftei *et al*., 2011; Duke *et al*., 2002), *M. officinalis* var. *micranthus* O. E. Schulz, *M. vulgaris* Hill, *Trifolium officinale* L. (Duke *et al*., 2002).
***Other common names*:** Melilot, King's Clover, Yellow Sweet Clover, Hay Flowers, Sweet Lucerne, Wild Laburnum, Hart's Tree (Gruenwald *et al*., 2000), common melilot (Ardelean & Mohan, 2008).

Officinal products: According to the European Pharmacopoeia and the European Medicines Agency (EMA), the officinal product is *Meliloti herba* represented by

whole or cut, dried aerial parts of *Melilotus officinalis* (L.) Lam. (EMA/HMPC/44166/2016; EMA/HMPC/44165/2016; Eur. Ph. 8.0, 2013). Other monographs refers to *Meliloti herba* from *Melilotus officinalis* and/or *Melilotus altissimus* (Gruenwald *et al*., 2000; Stanescu *et al*., 2004b; Stanescu *et al*., 2014). Flowers (*Meliloti flos*) are also used (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006).

Botanical description

M. officinalis is a biennial herbaceous plant, 40-250 cm long. The root is pivoting, well developed, with nodules. The stem is vigorous, erect or ascending, cylindrical, glabrous, branched. The leaves are alternate, trifoliate, with short peduncled leaflets, with serrated edges. The lower ones are obovate, at the base cuneate, at the tip obtuse; the upper ones are lanceolate, at the apex obtuse or truncated. At the base, the leaves have narrow, entire-margined, 6-7 mm long stipules. The flowers are yellow, with a coumarin scent, small and numerous, grouped 30-70 in simple, loose, elongated racemes, arranged at the base of the leaves. The fruits are compressed, ovoid, small, brownish-blackish, indehiscent, glabrous, brown, transversely rough pods, with a single greenish-yellow seed, about 2 mm long (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013; Stanescu *et al*., 2014; Stefan & Oprea, 2007). It blooms from June to September (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013; Stefan & Oprea, 2007).

Distribution and habitat: frequently spread, from the plain to the mountain area, through meadows, bushes, sowings, vineyards, on rocky coasts, ruderal places (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013; Stefan & Oprea, 2007). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: flowers or aerial parts with flowers and leaves, during flowering stage (Parvu, 2006); the plant product consists only of the upper parts of the stems and must not contain fruits (Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

Traditional uses

Traditional formulas under the name of *Emplastrum Meliloti* (monocomponent - *Herba Meliloti* and combination products - *Herba Meliloti* and other additional components) were used in many European countries, in the 18th century, in arthritis, rheumatoid swelling, skin ulcers, varices, skin inflammations, superficial burns, and as anti-inflammatory and wound healing agent (EMA/HMPC/44165/2016).

In Romanian folk medicine, *M. officinalis* was used against headache (as decoction), neuropsychiatric disorders, insomnia and asthma (as infusion) and leucorrhea (decoction) (Butura, 1979; Stanescu *et al*., 2014). The product was used for its emollient, digestive and analgesic properties, the extracts being administered internally in diarrhoea, colic, flatulence and externally in rheumatic and abdominal pain, ulcers (Stanescu *et al*., 2004b; Stanescu *et al*., 2014). It was also used internally to treat vascular diseases, as stimulant of liver function, in chronic hepatitis, liver cirrhosis, kidney diseases (kidney stones, hematuria, cystitis, pyelitis, pyelonephritis, urethritis), hypertension, rheumatism, gout, gastritis, varicose veins, thrombophlebitis, bronchitis (infusion from dried flowers); externally, it was used for the treatment of gingivitis, dental abscesses, canker sores (gargle with infusion from dried flowers),

laryngitis, tracheitis (gargle with infusion from the dried plant) and skin diseases (baths with infusion from the dried plant) (Parvu, 2006). It has been used for a long time in the form of ophthalmic lotions (Grigorescu *et al*., 1986).
Other ethnopharmacological data mention the use of the infusion from aerial parts in arthritis, hepatitis, renal lithiasis, gut, leucorrhoea and uterine disorders (Tita *et al*., 2009).

Chemical composition
The main bioactive constituents of *M. officinalis* aerial parts (*Meliloti herba*) are: coumarins (coumarin, melilotoside, melilotin, scopoletin, umbelliferone), phenolic acids (caffeic, chlorogenic, ferulic, o-coumaric, p-coumaric, rosmarinic and salicylic acids), flavonoids (robinin, luteolin, quercetin, rutin, umbelliferone, isoquercitrin), triterpenes, mucilages, tannins and essential oil (Al-Snafi, 2020a; Ardelean & Mohan, 2008; Chevallier, 2016; EMA/HMPC/44165/2016; Eur. Ph. 8.0, 2013; Liu *et al*., 2018; Martino *et al*., 2006; Paun *et al*., 2020; Sheikh *et al*., 2016; Sheikh & Desai, 2017; Stanescu *et al*., 2014; Tebrencu *et al*., 2014a; Tebrencu *et al*., 2014b). Among the main constituents of the essential oils, the following were mentioned: camphor, terpinene-4-ol, farnesane, spathulenol, globulol, β-eudesmol, bisabolon oxide, hexahydrofarnesylacetone, methyl linolenate and phytol (Al-Snafi, 2020a).
Melilot herb also contains oleanane type saponins: soyasapogenin I, astragaloside VIII, vistariasaponin D, melilotus-saponin (EMA/HMPC/44165/2016; Gruenwald *et al*., 2000).
The European Pharmacopoeia requires a minimum of 0.3% coumarin (dried drug) (Eur. Ph. 8.0, 2013).

Pharmacological activities
Antibacterial, antifungal, antioxidant, hypotensive, hepatoprotective, neuroprotective, sedative, anxiolytic, anticoagulant, anti-inflammatory, anti-diabetic, antitumor, wound healing and cicatrizing effects were reported for *M. officinalis* (Al-Snafi, 2020a; Stanescu *et al*., 2004b; Stanescu *et al*., 2014).
The aqueous extract from *M. officinalis* aerial parts has been shown to ameliorate the apoptosis of brain tissues in cerebral ischemic rats by decreasing the cerebral thrombosis, oxidative stress and inflammatory mediators (Zhao *et al*., 2017). The 70% methanol extract from the aerial parts exhibited hepatoprotective effects against paracetamol and carbon tetrachloride induced hepatotoxicity in mice, by improving serum liver parameters (reducing the levels of alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total albumin and total bilirubin) (Alamgeer *et al*., 2017).
Several coumarins, phenolic acids and flavonoids isolated from *M. officinalis* showed antioxidant, anti-inflammatory and antitumor effects (Liu *et al*., 2018).
M. officinalis crude and concentrated extract (in 50% ethanol) showed anti-diabetic (significant inhibition of α-amylase and α-glucosidase), antioxidant and anti-inflammatory effects in *in vitro* non-cellular models (Paun *et al*., 2020).
Coumarin has shown antitumor action (in clinical trials) due to the stimulation of cellular immunity (at low doses) and direct cytotoxicity (at high doses) and dicumarol has shown anticoagulant properties (Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

Mucilages have emollient action (beneficial in treating gastric diseases) and local hemostatic effect through protein precipitation (Parvu, 2006).

Current uses

According to the European Medicine Agency - Committee on Herbal Medicinal Products, the herbal preparations are represented by: comminuted herbal substance, powdered herbal substance, liquid extract (extraction with 70% ethanol and rapeseed oil). *Meliloti herba* preparations are often used in combinations with other herbal substances/ herbal preparations or various chemically defined substance (vitamins, minerals) (EMA/HMPC/44165/2016; EMA/HMPC/44166/2016). EMA mentions two indications: *(a)* to relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances; *(b)* for the treatment of minor inflammations of the skin (EMA/HMPC/44165/2016; EMA/HMPC/44166/2016).

The German Commission E approved the use of *M. officinalis* in blunt injuries, hemorrhoids and venous conditions (Gruenwald *et al*., 2000).

The flowers are used in gastric diseases, varicose veins, thrombophlebitis, hepatitis, liver cirrhosis, kidney diseases, gout, rheumatism, kidney stones, hematuria, cystitis, pyelitis, pyelonephritis, urethritis, hypertension, abscesses, canker sores, wounds, contusions, ulcers and skin diseases (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Parvu, 2006). The extracts are included in several preparations with antiflebitic action (creams, ointments) (Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

Precautions and adverse reactions

Do not use in case of hypersensitivity to the active substance(s). Due to the lack of adequate data, the use in children and adolescents under 18 years of age has not been established. The use during pregnancy and lactation is not recommended due to the absence of sufficient data. Gastrointestinal complaints (for oral use) and allergic reactions (for cutaneous use) have been reported (EMA/HMPC/44166/2016).

Co-administration of *Meliloti herba* extracts with anticoagulants (aspirin, warfarin or injectable anticoagulants) is not recommended. The use of *Meliloti herba* is contraindicated for patients with liver dysfunction (Gruenwald *et al*., 2000; Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

Administration of the drug in higher dosages can lead to headache, stupor and transitory liver damage (Gruenwald *et al*., 2000).

Mentha aquatica L. (water mint, „izma broaștei”), Lamiaceae family

Syn. *Mentha litoralis* (Hartm.) Neuman, *Mentha hirsuta* Huds., *Mentha braunii* Oborny (Doroftei *et al*., 2011), *M. palustris* Mill. (Duke *et al*., 2002).

***Other common names*:** Wild Mint, Marsh Mint, Hairy Mint (Gruenwald *et al*., 2000).

Officinal products: leaves (*Menthae aquaticae folium*) **(**Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Parvu, 2006) and aerial parts (*Menthae aquaticae herba*) (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006).

Botanical description

M. aquatica is a perennial herbaceous plant, with a height of 10-120 cm and a thin rhizome with long internodes. The stem is ascending, simple or branched, finely hirsute, glabrous at the bottom. The leaves are ovate, ovate-elliptical and slightly serrate on the edge, with a rounded-truncated base. The flowers are light purple, lilac-red, rarely white, grouped at the top of the stems and branches in capitulum-like inflorescences, with a hirsute ring inside; also, under them, there are 1-2 whorls or lax axillary capitula. The fruits are ovoid, light-brown nucules (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013). It blooms from June to September (Andrei & Cristurean, 2006; Sarbu *et al.,* 2013).

Distribution and habitat: present in floodplain, meadows, streams, reeds, swampy ruderal places, waterfront, near springs, from steppe to beech floor (Andrei & Cristurean, 2006; Butura, 1979; Sarbu *et al.,* 2013). In Dobrogea, this species occupies large areas in the Danube Delta and the floodplain of the Danube (Ardelean & Mohan, 2008; Ciocarlan, 2011; Doroftei *et al*., 2011; Parvu, 2006); it was also reported in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: during flowering stage, from June to July (Ardelean & Mohan, 2008).

Traditional uses

In literature, there are limited data on the use of *M. aquatica* but, in general, *Mentha* species are used as herbal medicines for their analgesic, antigenotoxic, spasmolytic, antibacterial and astringent properties (Venditti *et al*., 2017).

The aerial parts of the plant have empirical therapeutic uses in Romanian folk medicine (Parvu, 2006). The tea from the flowering stems was used as a stimulant in convalescence and against palpitations. It was also used against diarrhoea (Butura, 1979).

Other ethnopharmacological data mention the use of the leaf infusion in anorexia, colic, diarrhoea and enterocolitis (Tita *et al*., 2009).

Chemical composition

The aerial parts and roots of *M. aquatica* are rich in steroids and triterpenoids (Ferhat *et al*., 2017).

The aerial parts contain essential oil, the main constituents being menthofuran, limonene, trans-β-ocimene, ledol, β-caryophyllene, cis-β-ocimene, β-myrcene, β-pinene, 1,8-cineole, borneol, germacrene-D (Andro *et al*., 2013; Gruenwald *et al*., 2000; Malingre & Maarse, 1974; Muntean *et al*., 2007; Sutour *et al*., 2011). Phenolic acids and flavonoids were also identified in the aerial parts: caffeic, rosmarinic and salicylic acids, luteolin, luteolin-*O*-glucoside, apigenin, apigenin-7-*O*-glucoside, pebrellin, gardenin B, salvigenin, eriocitrin (Pereira & Cardoso, 2013; Venditti *et al*., 2017).

Pharmacological activities

In vitro studies (non-cellular models) revealed the antioxidant potential of *M. aquatica* root extracts, the anti-cholinesterase effects (inhibition of butyrylcholinesterase) and antibacterial activity (against *Morganella morganii*, *Salmonella heidelberg*, *Klebsiella pneumoniae*) of the aerial part and root extracts (Ferhat *et al*., 2017).

The 70% ethanol extract from *M. aquatica* aerial parts and (S)-naringenin isolated from it inhibit monoamine oxidase *in vitro*, which may explain its traditional use for depression-like conditions (Olsen *et al*., 2008).
The infusion from leaves has appetizer, spasmolytic, astringent, antimicrobial and anti-inflammatory properties (Tita *et al*., 2009).
The active compounds have bacteriostatic, carminative, antispasmodic, anti-diarrhoeal, diuretic, astringent, antitussive and antirheumatic properties (Duke *et al*., 2002; Gruenwald *et al*., 2000; Parvu, 2006).

Current uses
The plant is used internally for the empirical treatment of tachycardia, abdominal colic, flatulence, rash (infusion of leaf powder), and externally for the treatment of rash, rheumatism and as a general comforter of the body (dry decoction, added to bath water) (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Parvu, 2006).

Precautions and adverse reactions
No health hazards or side effects were reported in conjunction with the proper administration of designated therapeutic dosages (Duke *et al*., 2002; Gruenwald *et al*., 2000).

Nigella arvensis L. (black bread weed, „negruşcă"), Ranunculaceae family

Other common names: wild fennel (Chahardoli *et al.*, 2018b).

Officinal products: *Nigella arvensis* is not an officinal drug. Seeds are used in traditional medicine (Butura, 1979).

Botanical description
N. arvensis is an annual species, with a glabrous, erect stem, bi- or trisectate leaves (with linear-filiform leaflets). The flowers are actinomorphic, blue, with bilabiate nectarines and with carpels partially overgrown at the bottom. The fruits are follicles grown two-thirds of their length or full, resulting in a capsule (Sarbu *et al*., 2013; Stefan & Oprea, 2007). It blooms from May to August (Sarbu *et al*., 2013).
Distribution and habitat: frequent, in the steppe area - oak floor, segetal and ruderal (Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Crisan, Ilgani, Maliuc) (Doroftei *et al*., 2011).

Traditional uses
The plants within the *Nigella* genus have a long history (over 2000 years) of use as food ingredients and as medicinal plants for the treatment of several diseases (Bicak *et al*., 2017; Chahardoli *et al.*, 2018a; Heiss *et al.*, 2012).
In Romanian folk medicine, the decoction from seeds is used against cough. The seeds are also used in roundworm infection (Butura, 1979).

Chemical composition
N. arvensis contains terpenoids (β-sitosterol, campesterol, stigmasterol), flavonoids (quercetin-O-α-rhamnosyl-triglucoside) and phenolic acid derivatives (Bicak *et al*., 2017; Chahardoli *et al.*, 2017; Chahardoli *et al.*, 2018a; Farag *et al.*, 2014; Nicolis *et al*., 2010). The roots contain oleanane-type triterpene glycosides (Bicak *et al*., 2017).
The whole plant contains alkaloids such as glaucine, oxoglaucine, predicentrine, bracteoline, isoboldine, N-methylglaucine, N-methyllaurotetanine and asimilobine (Philipov *et al*., 2004) and proteins (Chahardoli *et al.*, 2017). The main phenolic compounds in seed flour are: gallic acid, syringic acid, synaptic acid, protocatechuic acid, hesperidin, quercetin, epicatechin, catechin (Alu'datt *et al*., 2016). The seeds contain volatile compounds, sesquiterpenes being the dominant class (β-elemene, (*Z,E*)-α-farnesene, (*E*)-α-bergamotene, α-muurolene), and also containing estragole, thymoquinone, α-phellandrene (Farag *et al.*, 2017).

Pharmacological activities
N. arvensis extracts have antimicrobial (against gram-positive bacteria and yeast strains) and anti-inflammatory activities (inhibition of COX-1 and COX-2) (Landa *et al.,* 2009).
The seed extract inhibited the expression of interleukin-8 (pro-inflammatory neutrophil chemokine) in cystic fibrosis bronchial epithelial IB3-1 cells exposed to *Pseudomonas aeruginosa* (mainly due to its content in β-sitosterol), thus β-sitosterol could be considered as a therapeutic agent in reducing excessive lung inflammation in cystic fibrosis patients (Nicolis *et al.,* 2010). Also, the seed extract has been shown to have a stimulating effect on Na^+ transport in renal epithelium (Atia *et al.,* 2002).
The hydrolyzed protein fractions from *N. damascena* and *N. arvensis* showed angiotensin converting enzyme inhibitory potential, hypoglycemic and antioxidant activities (Alu'datt *et al*., 2017).
The silver nanoparticles with *N. arvensis* seed extract showed antimicrobial (against gram-positive and gram-negative human pathogens) and cytotoxic effects (human breast cancer cell line and human colorectal adenocarcinoma cell line) (Chahardoli *et al*., 2017). The gold nanoparticles with *N. arvensis* leaf extract also showed significant cytotoxic and antibacterial activities (Chahardoli *et al*., 2018b).

Current uses
It is used in antiparasitic, antiallergic, antiviral and anti-inflammatory treatments **(**Chahardoli *et al.*, 2017; Chahardoli *et al.*, 2018b).

Precautions and adverse reactions
No available data.

Nuphar lutea Sm. (yellow water-lily, „nufăr galben"), Nymphaeaceae family

Syn. *Nymphosanthus luteus* (L.) Fernald, *Nymphaea lutea* L. (Doroftei *et al*., 2011), *Nuphar luteum* (L.) Sm. (Grigorescu *et al*., 1986; Tita *et al*., 2009).
Other common names: yellow pond-lily (Duman & Obali, 2008).

Officinal products: rhizomes (*Nupharis rhizoma*) (Istudor, 2005; Oroian, 2011; Parvu, 2006; Tita *et al*., 2009), flowers (*Nupharis flos*) (Parvu, 2006; Tita *et al*., 2009).

Botanical description

N. lutea is a heterophilic aquatic plant that produces both sunken and floating leaves (Kordyum & Klimenko, 2013). It is an herbaceous, perennial plant with a horizontal and well developed rhizome. The flower stems are submerged, long and end directly with alternate, long petiolate leaves, with a floating, orbicular-ovate or cordiform leaf blade. The flowers are large, solitary, yellow, radially symmetrical, with a strong smell, with 5 (4-7) free sepals, large, ovate, slightly concave, greenish on the outside, white-green on the inside and numerous free petals, ovate, smaller than the sepals. Conical, fleshy fruit (Istudor, 2005; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007). It blooms from June to July (Oroian, 2011; Sarbu *et al*., 2013; Stefan & Oprea, 2007).

Distribution and habitat: stagnant or smooth running water in the plain area (Parvu, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007), found throughout the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: the flowers at flowering stage (only petals), rhizomes at the end of the vegetation period (Parvu, 2006).

Traditional uses

N. lutea is traditionally used to treat conditions such as arthritis, fever, pain and inflammation (Ozer *et al.,* 2015).

In Romanian folk medicine, it was used internally in the treatment of lung diseases (including tuberculosis), against diarrhoea, genital diseases (leucorrhea, gonorrhea) and as emollient and astringent agent (Butura, 1979; Grigorescu *et al*., 1986; Istudor, 2005; Parvu, 2006). Externally, it was used in skin disorders (sunburns, insect bites and mycosis) and oral complaints (gingivitis, stomatitis, pharyngitis) (Istudor, 2005). The inhabitants of the Danube Delta are using the fruits as food (Parvu, 2006).

Other ethnopharmacological data mention the use of the decoction and infusion from roots and flowers in diarrhoea, fever and pulmonary disorders (Tita *et al*., 2009).

Chemical composition

Nuphar species contain alkaloids, such as thiobinupharidine derivatives (Iwanow *et al*., 1986) and ellagic acid (Bate-Smith, 1968).The leaves contain alkaloids, mainly sesquiterpene thioalkaloids such as 6-hydroxythiobinupharidine and 6-dihydroxythiobinupharidine B (El-On *et al.,* 2009; Ozer *et al.,* 2010).

The rhizomes are rich in alkaloids, including lutenurin, whose main constituent is thiobinupharidine (Grigorescu *et al*., 1986; Oroian, 2011). They also contain tannins, anthraquinone and cardiac glycosides, terpenoids, saponins, flavonoids (Istudor, 2005; Kaur & Mukhtar, 2016).

Pharmacological activities

Anti-leishmanial, antimicrobial, anticancer and anti-inflammatory properties were reported for *N. lutea* (Kaur & Mukhtar, 2016).

The crude extract and partially purified extract (alkaloids) of *N. lutea* leaves showed a good anti-leishmanial activity (against *Leishmania major*), through the activation of NF-kB and subsequent increased nitric oxide (NO) production (El-On *et al.,* 2009; Ozer *et al.,* 2010).

The leaf extracts have anti-inflammatory effect in mice (acute septic shock model), through phosphorylation of ERK1/2 and downregulation of NF-kB (Ozer *et al.,* 2015). Thioalkaloids from *N. lutea* have anti-inflammatory properties through the inhibition of NF-kB pathway, and they also induce apoptosis and have synergistic cytotoxicity with known cytostatic agents, with possible application in cancer therapy (Ozer *et al*., 2009). The semi-purified leaf extract showed *in vitro* anti-metastatic effect, inhibiting the cell migration through the inhibition of NF-kB pathway (Ozer *et al*., 2017).
The decoction and infusion from the roots and flowers have astringent and febrifuge properties (Tita *et al*., 2009). The alkaloids have antimicrobial properties, thiobinupharidine being active against *Trichomonas* (Grigorescu *et al*., 1986; Oroian, 2011; Parvu, 2006). The flowers have sedative and astringent properties (Parvu, 2006).

Current uses
It is used internally as decoction and fluid extract for poultices, gargling, and as homeopathic remedy against diarrhoea (Istudor, 2005). The rhizome extract and decoction are used against vaginal infections (Grigorescu *et al*., 1986; Parvu, 2006).
The infusion from petals is used as an adjuvant against pulmonary tuberculosis, and the decoction from rhizome against diarrhoea (Parvu, 2006).

Precautions and adverse reactions
Caution is required due to the presence of alkaloids present in this species.

Nymphaea alba L. (white water lily, „nufăr alb"), Nymphaeaceae family

Syn. *Nymphaea minoflora* (Simonk.) E. D. Wissjul., *Nymphaea occidentalis* (Ostenf.) Moss, *Castalia alba* (L.) Wood (Doroftei *et al*., 2011).
Other common names: European white water lily, white lotus (Raju *et al*., 2016).
Officinal products: rhizome (*Nymphaeae albae rhizoma*) and flowers (*Nymphaeae albae flos*) (Chevallier, 2016; Istudor, 2005; Oroian, 2011; Parvu, 2006).

Botanical description
N. alba is an aquatic, perennial, herbaceous plant. It has a well-developed rhizome, creeping on the bottom of the basin. The submerged, long stems are ending in alternate leaves, long-petiolate, sub-round, full-edged, floating and heart-shaped; the basal lobes of the leaf with the main veins almost straight or only slightly curved, in the first third always almost straight. The flowers are large (14 cm in diameter), solitary, white, radially symmetrical, with almost rounded base, with free sepals, deciduous, smaller than the petals, greenish on the outside, white-green on the inside, free petals, elliptical-lanceolate, numerous carpels and stamens. The fruit is spherical or oval, with a rounded, fleshy base, on which the traces of stamens can be seen (Istudor, 2005; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007). It blooms in June-September (Parvu, 2006; Sarbu *et al*., 2013).
Distribution and habitat: stagnant or smoothly flowing waters, frequent in the steppe area - oak floor (Butura, 1979; Parvu, 2006; Sarbu *et al*., 2013; Stefan & Oprea,

2007), found throughout the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: the flowers at flowering stage (only petals), rhizomes at the end of the vegetation period (Parvu, 2006).

Traditional uses

In the system of traditional herbal medicine, different parts of *N. alba* have been used as emollient and anti-inflammatory (Adnaik *et al*., 2009).

In Romanian folk medicine, it was used internally in the treatment of lung diseases (including tuberculosis), against diarrhoea, genital diseases (leucorrhea, gonorrhea), in heart failure, and as emollient and astringent agent (Butura, 1979; Grigorescu *et al*., 1986; Istudor, 2005; Parvu, 2006). The rhizome preserved in honey was used against cough, and the syrup or flower jam had calming effects (Butura, 1979). Externally, it was used in skin disorders (sunburns, insect bites and mycosis) and oral complaints (gingivitis, stomatitis, pharyngitis) (Istudor, 2005).

The inhabitants of the Danube Delta are using the fruits, which they name "pond figs", as food (Butura, 1979).

Other ethnopharmacological data mention the use of the decoction and infusion from roots and flowers in diarrhoea, fever and pulmonary disorders (Tita *et al*., 2009).

Chemical composition

N. alba is rich in phenolic acids, flavonoids, alkaloids, sterols, glycosides and hydrolyzable tannins (Pareek & Kumar, 2016; Rodrigues *et al*., 2008).

Several phenolic compounds were identified in *N. alba*: caffeic, p-coumaric, chlorogenic, vanillic, gallic, ferulic and cinnamic acids, quercetin, naringin, naringenin, kaempferol, orientin, apigenin, luteolin, isoquercitrin and hyperoside in flowers; quinic, vanillic, gallic, p-coumaric and chlorogenic acids, rutin, naringin, naringenin, catechin, epicatechin, quercetin, luteolin, brevifolin and orientin in leaves; quinic, vanillic, gallic, caffeic and p-coumaric acids, rutin, naringenin, naringin, catechin, epicatechin, apigenin, brevifolin and orientin in roots (Cudalbeanu *et al*., 2018; Jambor & Skrzypczak 1991; Selvakumari *et al*., 2016).

The rhizome also contains tannins, sesquiterpenic alkaloids, starch and fats (Istudor, 2005; Oroian, 2011; Parvu, 2006; Stefan & Oprea, 2007).

Pharmacological activities

N. alba leaf extracts showed *in vivo* (animal model) antihyperlipidemic properties, significantly reducing in cholesterol level and also reversing the Triton induced hyperlipidemia in rats (Raju *et al*., 2016). The ethanol flower extract also showed a significant antioxidant activity (Madhusudhanan *et al*., 2011).

The ethanol extract from flowers had hepatoprotective activity in rats, by inhibiting the morphological changes (liver weight and liver weight to body weight ratio) and maintaining the normal levels of serum biochemical parameter (total bilirubin, cholesterol, alanine amino transferase, aspartate amino transferase and alkaline phosphatase) (Paharia & Pandurangan, 2013). The ethanol extract from the whole plant showed anxiolytic and muscle relaxant properties (Thippeswamy *et al*., 2011). *N. alba* also showed antiproliferative activity (Selvakumari *et al*., 2016).

The flower crude extracts and purified fractions showed antiviral activity against hepatitis C virus, specifically targeting NS3 protease and viral replication in Huh-7 cells used as *in vitro* model (Rehman *et al*., 2018).
The bioactive compounds in flowers have nervous-sedative properties (with good results in insomnia) and also anaphrodisiac, tonic-nutritive and astringent effects (Chevallier, 2016; Grigorescu *et al*., 1986; Oroian, 2011; Parvu, 2006).

Current uses
Various pharmaceutical forms, such as decoction and fluid extract, are used internally and as poultices and gargling, and also in homeopathy as a remedy for diarrhoea (Istudor, 2005).
Internally, the infusion from flowers is used against insomnia, the decoction from flowers is used to treat sexual hyperexcitability, the decoction from rhizome is used to treat diarrhoea and heart failure, the sherbet or jam from petals in pulmonary tuberculosis and heart failure (Chevallier, 2016; Parvu, 2006).
A study on the ethanol extract from *N. alba* suggests that it can be used to combat anxiety (Thippeswamy *et al.*, 2011).

Precautions and adverse reactions
Caution is required due to the presence of alkaloids in this species.

Onosis spinosa L. (restharrow, „osul iepurelui"), Fabaceae family

Syn. *Ononis vulgaris* Rouy pro parte (Doroftei *et al*., 2011).
Other common names: spiny restharrow (Benedec *et al.,* 2012; EMA/HMPC/138316/2013), Cammock, Petty Whin, Stayplough, Wild Liquorice, Stinking Tommy, Ground Furze, Land Whin (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia and the European Medicine Agency (EMA), the officinal product is *Ononidis radix* represented by the whole or cut, dried root of *Ononis spinosa* L. (EMA/HMPC/138316/2013; EMA/HMPC/138317/2013; Eur. Ph. 8.0, 2013). Another monograph mentions the roots and flowering branches as officinal products (Gruenwald *et al*., 2000).

Botanical description
O. spinosa is a subshrub, perennial species. The rhizome continues with a flexible, long, cylindrical, gray root. The aerial stem is erect, with a lignified base, richly branched, up to 70 cm long, spiny and hirsute. The branches have rigid spines, one terminal and 2-3 lateral. The lower leaves are trifoliate, with oval leaflets, toothed on the edge, glandular-hirsute. The upper leaves are simple. The flowers are solitary, papillate, pink with darker stripes, arranged towards the top of the stem, at the axils of the bracts. The fruit is a small, hirsute pod with 1-2 sub-spherical seeds (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Oniga, 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al.* 2014). It blooms from June to July (Parvu, 2006; Sarbu *et al*., 2013).
Distribution and habitat: in the steppe area - oak floor, through meadows, bushes, pastures and arid meadows, on sandy soils, spread especially in the south of the

country (Oltenia, Dobrogea) (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, Perisor) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: roots in spring (March-April) when the first shoots appear, and in autumn (September/October-November) (Ardelean & Mohan, 2008; Oniga, 2007; Oroian, 2011; Parvu, 2006); leaves (*Ononidis folium*) and aerial parts (*Ononidis herba*) during flowering stage (Parvu, 2006).

Traditional uses

In traditional medicine, the extracts from the roots of *O. spinosa* were used as an adjuvant in various diseases of the urinary tract (Addotey *et al*., 2018). In Central Asia and Russia, the roots were used against skin irritations, itching, wounds and dermatitis (Mamedov *et al.,* 2005). The dried roots are traditionally used for their diuretic, anti-inflammatory and wound healing effects (Öz *et al*., 2018).

It was traditionally used for the treatment of kidney and bladder disorders (as diuretic, anti-inflammatory, prevention of gravel and small stones formation) (EMA/HMPC/138316/2013).

In Romanian folk medicine, it was used against typhoid fever and hernia (infusion and decoction from root) (Butura, 1979; Stanescu *et al.* 2014). The root was also used as diuretic and in the treatment of rheumatic diseases, gout and chronic dermatitis (Stanescu *et al.* 2004b). The infusion from the aerial parts was used against stomach ache and the infusion from the roots was used against kidney ache (Butura, 1979).

Other ethnopharmacological data mention the use of the root decoction in urinary disorders, gut and rheumatism (Tita *et al*., 2009).

Chemical composition

Several isoflavone derivatives were identified in the roots of *O. spinosa*, namely: trifolirhizin, ononin, medicarpin-3-O-glucoside, onogenin-7-O-glucoside, sativanone-7-O-glucoside, daidzin, genistin, formononetin (Benedec *et al.,* 2012; Gampe *et al*., 2018; Öz *et al*., 2018). The roots also contain triterpenes (α-onocerin), sterols (β-sitosterol, stigmasterol, campesterol, cholesterol and α-spinasterol), triterpenoid saponins, phenolic acids (e.g. p-hydroxybenzoic, vanillic, caffeic, syringic, p-coumaric, cinnamic and gentisic acids) and small amounts of essential oil (Chevallier, 2016; EMA/HMPC/138316/2013; Gruenwald *et al*., 2000).

In the branch tips of *O. spinosa*, isoflavonoids (onocerin, ononin, biochanin and fermonentin), coumarins and phenolic acids (hydroxi benzoic acid, p-coumaric acid and caffeic acid) were identified (Fayyazi *et al*., 2017).

Pharmacological activities

Antiedemic, antiseptic, cardiotonic, depurative, diuretic, estrogenic, hemolytic, litholytic properties were attributed to *O. spinosa* (Duke *et al*., 2002).

The dichloromethane extract from *O. spinosa*, rich in isoflavonoids, has a strong inhibitory effect on Human Hyaluronidase Hyal-1, thus having potential use in the treatment of many cancerous and non-cancerous diseases (Orlando *et al*., 2015). Fractions and isolated compounds (isoflavones) from *O. spinosa* roots showed anti-inflammatory and wound healing activities by inhibiting hyaluronidase and elastase enzymes, ononin and sativanone-7-O-glucoside being the most active compounds (Öz *et al*., 2018). The extracts from *O. spinosa* roots have diuretic properties (inhibition of

hyaluronidase) mainly due to their isoflavonoids, such as onogenin, sativanone, medicarpin and calycosin (Addotey *et al*., 2018).
Isoflavonoids may play an important role in the prevention and treatment of hormone-dependent cancer, osteoporosis, cardiovascular disorders and diseases as metabolic syndrome or polycystic ovary syndrome (Wiseman, 2006).
The diuretic action (elimination of urea and chlorides) is due to the synergism of action of saponins, flavonoids, terpenes and the volatile fractions (Grigorescu *et al*., 1986; Oniga, 2007; Parvu, 2006; Stanescu *et al*., 2004b; Stanescu *et al*., 2014).
The isoflavonoid derivative medicarpin has inhibitory action on 5-LOX (anti-inflammatory effect) (Stanescu *et al*., 2014). The isoflavonoid genistein has a diuretic action comparable to furosemide, and it was reported to produce a mild estrogenic effect (EMA/HMPC/138316/2013).

Current uses
According to the European Medicine Agency - Committee on Herbal Medicinal Products, the herbal preparations (single herbal tea or combination herbal tea) are used as adjuvants to increase the amount of urine in minor urinary problems (EMA/HMPC/138317/2013). The different extracts are included in combination products authorized/ registered in the EU Member States: ethanol dry extract, aqueous dry extract, ethanol liquid extract (EMA/HMPC/138316/2013).
The German Commission E approved its use in infections of the urinary tract, kidney and bladder stones (Gruenwald *et al*., 2000).
The roots are used against the inflammation of the urinary tract and kidney sand, as well as an adjuvant in the treatment of bacterial infections of the urinary tract (ESCOP, 2015). On the Romanian market, the plant material is included in the composition of diuretic teas and also in teas for weight loss (Stanescu *et al.* 2014).
The plant is also included in various tea formulas for treating atherosclerosis, biliary dyskinesia, cystitis, kidney stones, gout, in the preparation of urinary disinfectants and aqueous diuretics (Parvu, 2006).

Precautions and adverse reactions
It is not recommended in case of hypersensitivity to the active substances of *O. spinosa* and in conditions where a reduced fluid intake is recommended (severe cardiac or renal diseases). Due to the lack of sufficient data, the use by children under 12 years of age, and also during pregnancy and lactation is not recommended (EMA/HMPC/138317/2013).

Other warnings
In generally *O. spinosa* root infusions should be used on a short-term basis as the diuretic effect will decrease with continued use (EMA/HMPC/138316/2013; Stanescu *et al.* 2014).

Origanum vulgare L. (oregano, „sovârf"), Lamiaceae family

Syn. *Origanum vulgare* L. ssp. *viride* (Boiss.) Hayek, *Origanum puberulum* (Beck) Klokov, *Origanum virens* Hoffmanns. & Link ssp. *siculum* Nyman, *Origanum viride* (Boiss.) Halácsy, *Origanum dilatatum* Klokov (Doroftei *et al*., 2011; WHO, 2010).

Other common names: wild marjoram, pot marjoram (Beltran *et al.*, 2018; Ivask *et al.*, 2005), Mountain Mint, Origano, Winter Marjoram, Wintersweet (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia, the officinal drug is *Origani herba*, representing dried leaves and flowers separated from the stems of *O. onites* L. or *O. vulgare* L. subsp. *hirtum* (Link) Ietsw., or a mixture of both species (Eur. Ph. 8.0, 2013). According to the World Health Organization (WHO), the officinal product is *Origani herba*, consisting of the whole or cut dried aerial parts of *O. vulgare* collected during the flowering phase (WHO, 2010). The essential oil (*Origani aetheroleum*), isolated from the fresh or dried leaves by steam distillation, is also an officinal product (Chevallier, 2016; Gruenwald *et al*., 2000; Istudor, 2001; Stanescu *et al*., 2014).

Botanical description

O. vulgare is a perennial herbaceous plant, with an aromatic scent. The rhizome is horizontal, brown-gray, with underground stolons and numerous filiform roots. The aerial stem is erect, lignified at the base, with four slightly protruding edges, branched at the top, reddish-brown, covered with tector trichomes, and 30-50 (-80) cm high. The leaves are opposite, petiolate, entire, ovate, hirsute especially on the underside, at the base suddenly attenuated in the petiole. The leaves have weakly crenate-serrate edges, on both sides glandularly dotted. The flowers are bilabiate, pink-purple, grouped in corymb-shaped inflorescences, protected by reddish or purple bracts. The fruits are brown ovoid nucules, in groups of four (Ardelean & Mohan, 2008; Istudor, 2001; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013; Stanescu *et al*., 2014). It blooms in July-August (Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013).

Distribution and habitat: bushes, meadows, grassy cliffs, ruderal places, forest edges, from the plain area to the subalpine floor (Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Dolosman, Ilgani, Popina Island) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: aerial parts during flowering stage (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Oniga, 2007; Parvu, 2006; Stanescu *et al*., 2014; WHO, 2010).

Traditional uses

O. vulgare aerial parts were used traditionally in respiratory disorders (coughs, inflammation of the bronchial mucous membranes and as expectorant), dyspepsia, painful menstruation, rheumatoid arthritis, scrofulosis, urinary tract disorders and as a diaphoretic (Gruenwald *et al*., 2000; WHO, 2010).

In Romanian folk medicine, *Origani herba* was used as infusion and decoction, in the treatment of gastritis and other gastric diseases, whooping cough, pharyngitis, tracheitis, bronchitis, asthma, to increase appetite (anorexia), and in dermal diseases, wounds and burns. The infusion was used as gargle to remove the bad breath in periodontal diseases. It was also used as baths against rheumatism (Butura, 1979; Stanescu *et al*., 2014).

Chemical composition

Origani herba contains a wide range of bioactive compounds, including essential oil, tannins, anthocyanins (peonidin, malvidin), flavonoids (apigenin, luteolin and kaempferol derivatives, naringenin), phenolic acids (rosmarinic, caffeic, vanillic, syringic, ferulic and p-coumaric acids), triterpenes (ursolic and oleanolic acids), sterols, bitter compounds and vitamins (Gutiérrez-Grijalva *et al*., 2018; Istudor, 2001; Masoudi & Saiedi, 2017b; Oniga, 2007; Pezzani *et al*., 2017; Stanescu *et al*., 2014; WHO, 2010).

The essential oil (mono- and sesquiterpenes as main classes of constituents) is found in high amounts in *O. vulgare*, thymol and carvacrol being the main compounds, but γ-terpinene, p-cymene, limonene, 4-terpineol, β-caryophyllene, germacrene D, germacrene D-4-ol, caryophyllene oxide, sabinene, cis-sabinene hydrate were also detected in appreciable amounts (Chevallier, 2016; Bozin *et al.,* 2006; Brondani *et al*., 2018; Gruenwald *et al*., 2000; Lukas *et al.,* 2013; Sarikurkcu *et al.,* 2015; WHO, 2010). The composition of the essential oil varies depending on the geographic origin of the plant and on the chemotype (Bisht *et al*., 2009; Lukas *et al.,* 2013; Sarikurkcu *et al.,* 2015).

The leaves of *O. vulgare* contain phenolic compounds such as protocatechuic acid, caffeic acid, rosmarinic acid, a phenyl glycoside and 2-caffeoyloxy-3-[2-(4-hydroxybenzyl)-4,5-dihydroxyphenyl]propionic acid (Chis *et al.,* 2017). Protocatechuic acid ester derivatives (origanol A and B) and sterols (ursolic acid, oleanolic acid, β-sitosterol) were also identified in leaves (Rao *et al*., 2011).

The European Pharmacopoeia requires for *Origani herba* a minimum of 25 mL/Kg essential oil (anhydrous drug), and the sum of carvacrol and thymol contents of minimum 60% in the essential oil (Eur. Ph. 8.0, 2013).

Pharmacological activities

In vitro and *in vivo* studies showed that *O. vulgare* extracts have antioxidant, antimicrobial, anti-inflammatory, anticancer (inducing apoptotic cell death through morphologic changes), anti-hyperglycemic, anxiolytic, antinociceptive, antiurolitic, hepatoprotective and memory enhancing properties (Aelenei *et al*., 2016; Masoudi & Saiedi, 2017b; Pezzani *et al*., 2017; Singh *et al*., 2018; WHO, 2010).

The essential oil has a strong antimicrobial effect (against a wide range of bacteria and fungi, including antibiotic-resistant strains) and anticancer (against human breast and human colon adenocarcinoma cell lines) activity (Masoudi & Saiedi, 2017b; Oniga, 2007; Pezzani *et al*., 2017; Stanescu *et al*., 2014).

A mixture of oregano and cranberry aqueous extracts inhibited the *in vitro* development of *Helicobacter pylori*, probably through urease inhibition and disruption of energy production, thus having potential use in the treatment of gastric ulcer (Lin *et al*., 2005). The methanol crude extract, fractions, and two of the isolated compounds

from the leaves of *O. vulgare* showed a tyrosinase inhibitory activity, origanol A being the most potent compound (Rao *et al*., 2011). A study performed on male Wistar rats showed that the hydroalcoholic extract from *O. vulgare* has an analgesic effect (Arzi *et al.,* 2009).

The essential oil isolated from *O. vulgare* showed significant antiproliferative activity, anti-inflammatory effect (decreasing the levels of inflammatory biomarkers, such as monocyte chemo-attractant protein, vascular cell adhesion molecule 1, interferon gamma-induced protein 10), tissue remodeling and immunomodulatory activities in inflamed human skin cells (Han & Parker 2017). The essential oil also had anticancer activity in human stomach cancer cell lines by inhibiting the pathogenesis of lipogenesis, the activation of BAX (anti-apoptotic protein) and down-regulation of BCL2 (proapoptotic proteins) (Balusamy *et al.*, 2018).

Oregano essential oil significantly reduced the production of the phospholipase enzyme produced by *Candida albicans* strains, thus attenuating its virulence (Brondani *et al.,* 2018). The essential oil has anti-yeast activity against several *Candida, Pichia*, *Rhodotorula rubra* and *Saccharomyces cerevisiae* strains, so it could be used as alternative antimicrobial compound to be applied in food conservation (Souza *et al*., 2007). Essential oils also exhibited inhibitory effect on the bacterial growth, the biofilm formation and on the formed biofilm of *Streptococcus pyogenes*, underlining its alternative use against streptococcal pharyngitis (Wijesundara & Rupasinghe, 2018).

The aqueous extract from leaves has *in vivo* (animal model) hypoglycemic effect, without affecting the level of plasma insulin concentration (Oniga, 2007; Stanescu *et al*., 2014).

The essential oil blocks (*in vitro*) the adhesion of the Herpes Simplex Virus 1 to other cells, reducing its efficiency by up to 99% (destroys the viral lipid envelope, preventing its adhesion to the host cell) (Stanescu *et al*., 2014).

Current uses

O. vulgare is used as infusion, decoctions, fluid extracts, freshly pressed juice, and in the form of herbal powder tablets or as isolated essential oil in respiratory tract diseases (infections, whooping cough, cough, bronchitis, asthma, tracheitis, rhino-bronchopneumopathy, oropharyngitis) and digestive conditions (dyspeptic syndromes, infections). It is also used in urinary and genital infections and as sedative (Ardelean & Mohan, 2008; Istudor, 2001; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2014).

Precautions and adverse reactions

Due to its frequent use in diet, the plant has been designated by the FDA as generally safe (Stanescu *et al.,* 2014). The use during pregnancy is not recommended, since the concentrated teas may cause uterine contractions (Chevallier, 2016; WHO, 2010). Do not take essential oil internally. Also, external use may cause skin irritation (Chevallier, 2016; Istudor, 2001).

Paliurus spina-christi Mill. (Christ's thorn, „spinul lui Hristos"), Rhamnaceae family

Syn. *Paliurus australis* Gaertn., *Paliurus aculeatus* Lam. (Doroftei *et al*., 2011).

Officinal products: *P. spina-christi* is not an officinal drug, but the seed and fruits were traditionally used (Bulut & Tuzlaci; Sargin *et al.,* 2013).

Botanical description

P. spina-christi is an evergreen shrub. The stem is up to 3 m high, richly branched, with fine reddish-gray annual shoots, with buds wrapped in two unequal and hirsute scales. The leaves are alternate, simple, wide-ovate-elliptical, asymmetrical, with a very small crenate-serrated edge, short petiolate, with the upper surface dark green and shiny, and the lower surface pale-green and with obvious veins. The stipules from the base of the leaves are transformed into two spines, one straight, the second smaller and slightly curved. The flowers are yellow-green, bisexual, arranged in racemes at the axils of the leaves and have 5 very small petals. The fruit is 2-3 cm in diameter, and it has circular radial nerved winglet around and a woody seed. The fruit is dry, characteristically yellow, all around winged (Burda *et al*., 2006; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013). This species is protected by law (Parvu, 2006). It blooms from May to August (Parvu, 2006).

Distribution and habitat: rare, in the steppe and silvosteppe areas, in the counties of Arad, Caras-Severin, Mehedinti, Dolj, Giurgiu, Ilfov, Ialomita, Constanta, Tulcea (Sarbu *et al*., 2013), sporadically, isolated or in clusters, on stony, dry places, from the steppe and silvosteppe of Dobrogea (Parvu, 2006). In the Danube Delta area, it was reported in Dolosman (including the Iancina Cape) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Traditional uses

Christ's thorn is used as a diuretic, and against diarrhoea and rheumatism in traditional Croatian herbal medicine (Grlic, 1986). In Turkey, *P. spina-christi* was traditionally used against diarrhoea and rheumatism and the seed decoction was used against diabetes, kidney stones, pain and as diuretic (Kayalar *et al*., 2016; Sargin *et al.,* 2013), and the decoction from fruits was used against kidney stones (Bulut & Tuzlaci, 2013). Christ's thorn is also used in Iran as antimicrobial agent (Esmaeili *et al*., 2009).

P. spina-christi was also traditionally used as antirheumatic, hypocholesterolemic and tonic as well as in inflammation, diarrhoea, and chronic obstructive pulmonary disease (Brantner & Males 1990).

Chemical composition

The leaves, flowers, and fruits of *P. spina-christi* contain flavonoids (hyperoside, isoquercitrin and other quercetin derivatives, rutin, naringenin-*C*-diglycoside, kaempferol-3-glucoside), tannins (epigallocatechol, gallocatechol, catechol, gallocatechin, epicatechin, catechin, epigallocatechin and catechin hydrate), phenolic acids (gallic, syringic and caffeic acids), coumarins, aminoacids, fatty acids and alkaloids (Ahmed *et al*., 2013; Brantner & Males, 1990; Sen, 2018; Zor *et al*., 2017).

Quercetin 3-*O*-rhamnoglucoside 7-*O*-rhamnoside and rutin have been shown to be the main flavonoids in the leaves, flowers and fruits (Brantner & Males, 1999).

Catechin hydrate, proanthocyanidin B dimer, naringenin-C-diglycoside, 5-caffeoyl quinic acid, 5-p-coumaroylquinic acid, quercetin, isoquercitrin, rutin and hyperoside were also identified in fruits (Kayalar *et al*., 2016; Kustrak *et al*., 1990).
The seeds contain fatty acids (myristic, behenic, arahic, palmitic, oleic, linoleic and stearic acids) and aminoacids (alanine, glycine, isoleucine, leucine, valine, proline, aspartic acid, tyrosine, tryptophan) (Burda *et al*., 2006; Kemertelidze *et al*., 1999).
Aminoacids, alkaloids and sterols were found in the bark and in the fruits of *P. spina-christi* (Brantner & Males, 1999).

Pharmacological activities
The ethanol and ethyl acetate extracts from the leaves and branches of *P. spina-christi* showed good *in vitro* antioxidant and anti-inflammatory activities (Sen, 2018). The methanol extract from fruits also showed remarkable antioxidant activity (Kayalar *et al*., 2016).
The methanol crude extract from *P. spina-christi* and several isolated compounds (catechin, gallocatechin and rutin) may have beneficial effects in oxidative DNA damage (Zor *et al*., 2017). The aqueous extract from fruits showed *in vivo* (animal model) anti-hyperlipidemic potential, by lowering the serum levels of cholesterol and triglycerides (Mosaddegh *et al*., 2004).
An aqueous-ethanol tincture from fruits was found to possess bile-expelling and hepatoprotective properties (Kemertelidze *et al*., 1999).
The aerial parts showed antiplasmodial activity and cytotoxic effect against *Plasmodium falciparum* (Esmaeili et al., 2009).

Current uses
No available data.

Precautions and adverse reactions
No available data.

Papaver rhoeas L. (wild poppy, „mac de câmp”), Papaveraceae family

Syn. *Papaver strigosum* (Boenn.) Schur, *Papaver tenuissimum* Fedde, *Papaver tumidulum* Klokov, *Papaver intermedium* Beck, *Papaver roubiaei* Vig., *Papaver insignitum* Jord., *Papaver trilobum* Wallr., *Papaver commutatum* Fisch. & C. A. Mey. (Doroftei *et al*., 2011).
Other common names: Corn poppy (Aghaali *et al.*, 2019), Copperose, Corn Rose, Cup-Puppy, Headache, Headwark, Red Poppy (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia (Eur. Ph. 8.0, 2013), the officinal product is *Papaveris rhoeados flos* represented by dried, whole or fragmented petals of *Papaver rhoeas* L. The use of seeds is also mentioned (Gruenwald *et al*., 2000).

Botanical description

It is an annual herbaceous species, with multiple stems, 25-90 cm high. The root is pivoting, whitish. The stem is erect, simple or branched, with stiff hairs. The basal leaves are lanceolate, pinnatisect, petiolate, hirsute, and the stem leaves are deeply indented and sessile. The flowers are terminal or axillary, solitary, up to 10 cm in diameter. It has 2 green sepals and 4 intense red, orbicular petals, usually with a deep-black mark at the base. The fruit is a globular capsule with a persistent stellate stigma, with numerous reniform, dark brown seeds (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013; Stefan & Oprea, 2007). It does not contain latex (Oroian, 2011). It blooms from May to July (Parvu, 2006; Sarbu *et al*., 2013).

Distribution and habitat: frequent all over the country, in the steppe area - oak floor, trough straw crops, ruderal places, parlors, stubble, on dry, fertile, clayey, sandy soils (Ardelean & Mohan, 2008; Istudor, 2005; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Chilia, Ilgani, Maliuc, Pardina, Rusca, Sireasa) (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: petals, at the beginning of flowering, immediately after the flower opens (Ardelean & Mohan, 2008; Istudor, 2005; Muntean *et al*., 2007; Oroian, 2011).

Traditional uses

In traditional medicine, *P. rhoeas* was used for gastrointestinal complaints (poor digestion, nervous digestive disorders, diarrhoea), respiratory problems (bronchial complaints and coughs, asthma), insomnia, in inflammation and minor painful conditions and as sedative (Ghoshooni & Sahraei, 2014; Hasplova *et al*., 2011; Oh *et al*., 2018; Saeed-Abadi *et al*., 2012; Zargari, 1995).

In Romanian folk medicine, the petals were used in the treatment of heart rhythm disorders in adults, in the symptomatic treatment of neurotonic disorders in adults and children, especially for minor insomnia (Istudor, 2005). It was also used in acute bronchitis, flu, acute laryngitis, cough, measles, scarlet fever and for sore throats (Butura, 1979; Parvu, 2006).

Other ethnopharmacological data mention the use of the infusion from flowers in respiratory disorders (Tita *et al*., 2009).

Chemical composition

P. rhoeas contains alkaloids (influenced by chemotype), the main alkaloids being rhoeadine, N-methylasimilobine, rhoeagenine, and the minor ones include protopine, isorhoeadine, isorhoeagine and papaverrubines (Istudor, 2005; Oh *et al*., 2018; Rey *et al*., 1992). It also contains flavonoids (kaempferol, quercetin, luteolin, isoquercetin, astragaline and hyperoside), anthocyanins (e.g. cyanine, mecocyanin), mucilages and tannins (Ardelean & Mohan, 2008; Chevallier, 2016; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Hasplova *et al*., 2011; Hillenbrand *et al.,* 2004; Istudor, 2005; Matysik & Benesz, 1991; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006).

Pharmacological activities

In vitro and *in vivo* studies with *P. rhoeas* extracts highlighted their antinociceptive, antioxidant, anti-inflammatory and antimicrobial activities, antidepressant and stress amelioration properties, and the improvement of stress-induced memory impairment

in mice (Coban *et al*., 2017; El & Karakaya, 2004; Ghoshooni & Sahraei, 2014; Osanloo *et al*., 2016).
The plant extracts from *P. rhoeas* possess a high antioxidant activity (Hasplova *et al*., 2011). The ethanol extract from the whole plant showed *in vivo* (animal model) analgesic effects through opioid, glutamate and/ or nitric oxide mechanisms and anti-inflammatory activity (Saeed-Abadi *et al*., 2012).
The hydroalcoholic extract showed antidepressants effect in mice, by increasing plasma corticosterone concentration (Osanloo *et al*., 2016).
The alkaloids from *P. rhoeas* have antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* (Coban *et al*., 2017).
The infusion from flowers has anti-inflammatory, antitussive, expectorant and emollient properties (Tita *et al*., 2009).

Current uses
P. rhoeas is used internally (as infusion, tincture, capsules or syrup) in respiratory tract disorders (cough, acute and chronic bronchitis, acute laryngitis), against flu, as sedative (against insomnia) and as analgesic (Ardelean & Mohan, 2008; Chevallier, 2016; Duke *et al*., 2002; Grigorescu *et al*., 1986; Istudor, 2005; Parvu, 2006). It is used in homeopathy for states of agitation and excitation (Gruenwald *et al*., 2000).

Precautions and adverse reactions
Due to low alkaloid content, it is non-toxic, however cases of poisoning in children were reported after the intake of aerial parts (Chevallier, 2016; Gruenwald *et al*., 2000). Poisoning symptoms include vomiting and stomach pain (Gruenwald *et al*., 2000).

Other warnings
It may be confused with *Papaver dibium* and *Papaver argemone* (Gruenwald *et al*., 2000; Muntean *et al*., 2007). It can also be unpurified with *Paeonia officinalis* L. ex Willd. (Ranunculaceae) and *Papaver dubium*, both species containing the toxic alkaloid aporein (Istudor, 2005).

Phragmites australis (Cav.) Trin. ex Steud. (common reed, „stuf, trestie"), Poaceae family

Syn. *Phragmites vulgaris* Samp., *P. pumila* Willk., *P. gigantea* J. Gay, *P. loscosii* Willk. (Doroftei *et al*., 2011), *Arundo phragmites* L., *P. communis* Trin. (Doroftei *et al*., 2011; Duke *et al*., 2002), *Arundo vulgaris* Lam., *P. communis* var. *longivalvis* (Steud.) Miq., *P. longivalvis* Steud., *P. vulgaris* var. *longivalvis* (Steud.) W. Wight (Duke *et al*., 2002).
***Other common names*:** reed (Köbbing *et al*., 2013).

Officinal products: flowering tops (*Phragmites flos*), rhizomes (*Phragmites rhizoma*) (Parvu, 2006).

Botanical description

P. australis is a perennial plant, with a branched rhizome. The numerous underground stolons are repent, long, thick and sometimes floating on water. The stem is up to 4 m high, 2-2.5 cm thick, glabrous, fistulous, foliate. The leaves are linear-lanceolate, flat, rigid, 1-3 cm wide. The flowers are grouped in a loose panicle, 20-30 (50) cm long, consisting of linear-lanceolate, dark-brown spikelets, with 3-7 laterally compressed flowers. The fruits are yellow-brown caryopsis (Parvu, 2006). It blooms from July to September (Andrei & Cristurean, 2006; Parvu, 2006). *P. australis* ssp *chrysantha* (Mabille) Soják (*P. australis* ssp. *altissimu*s Benth.) W.D. Clayton, *P. communis* ssp. *pseudodonax* (Rabenh.) Roth. has a stem up to 5 m tall, leaves 3-6 cm wide, panicle 30-40 (-50) cm long, with light-brown spikelets, usually sterile (Sarbu *et al.,* 2013).

Distribution and habitat: frequent from the steppe area to the beech floor, through swamps, on the bank of running waters, shallow stagnant waters, in crops (Andrei & Cristurean, 2006; Sarbu *et al.,* 2013). In Dobrogea, *P. australis* was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (sporadically in Macin Mountains National Park) (Andrei & Cristurean, 2006). *P. australis* ssp. *chrysantha* is sporadic in the Danube Delta, on the edge of the channels (Sarbu *et al.,* 2013), in Chilia, Histria, Portita, Vadu (including Corbu area) (Doroftei *et al*., 2011; Sarbu *et al.,* 2013).

Harvesting period: flowering tops in July-August, rhizomes in October (Parvu, 2006).

Traditional uses

The flowering tips and rhizomes have therapeutic uses in Romanian folk medicine. During the drought of 1947, in Romania, the rhizomes were used as food by locals. They were boiled and consumed. By drying and grinding, flour for food use was obtained (Parvu, 2006).

Chemical composition

There are limited data in the literature regarding the chemical composition of *P. australis*.

The rhizomes of *P. australis* contain tannins, terpenoids, glycosides and flavonoids (Derouiche *et al*., 2017). Several flavonoids were identified in flowers: rhamnetin-3-*O*-rutinoside, rhamnetin-3-*O*-glucoside, swertiajaponin-3'-*O*-gentiobioside, swertiajaponin-3'-*O*-β-D-glucoside, swertiajaponin and isoswertiajaponin (Nawwar *et al*., 1980).

The stem contains cellulose, lignin and pectines (Parvu, 2006).

Pharmacological activities

There are limited data in the literature regarding the pharmacological activities of *P. australis*.

The aqueous extract from *P. australis* rhizome exhibits a benefic effect in diabetic rats, by normalizing blood glucose, serum biochemical profile (triglycerides, cholesterol) and pancreas histo-morphology (Derouiche *et al*., 2017).

The flowering tips and rhizomes have anti-inflammatory, anti-rheumatic, decongestant, antiemetic, diaphoretic, diuretic, emetic, expectorant and litholytic properties (Duke *et al*., 2002; Parvu, 2006).

Current uses
The flowering tips and rhizomes of *P. australis* are used externally to treat ankylosing spondylitis (decoction from flower tips and rhizomes, in the form of baths), swelling, wounds, inflammation (poultices, with a paste from boiled, applied to the affected area), and in the treatment of swelling and inflammation (decoction from flowering tops, in the form of local washes and dressings soaked in decoction) (Parvu, 2006).

Precautions and adverse reactions
No available data.

Plantago lanceolata L. (English plantain, „pătlagină îngustă"), Plantaginaceae family

Syn. *Plantago glabriflora* Sakalo (Doroftei *et al*., 2011).
Other common names: ribwort (Duke *et al*., 2002; Hesarinejad *et al.*, 2018), buckhorn, Chimney-Sweeps, Headsman, Narrow-Leaved Plantain, Ribgrass, Ripplegrass, Soldier's Herb (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia and the European Medicine Agency (EMA), the officinal product is *Plantaginis lanceolatae folium* represented by the whole or fragmented, dried leaf and scape of *Plantago lanceolata* L. s.l. (EMA/HMPC/437858/2010 *Corr.;* EMA/HMPC/437859/2010; Eur. Ph. 8.0, 2013). The collective drug *Plantaginis folium* is also used, consisting of the leaves of the species *P. major* L., *P. media* L. and *P. lanceolata* L. (Muntean *et al*., 2007; Stanescu *et al*. 2014).

Botanical description
P. lanceolata is a rosette-forming perennial herb, up to 5-50 cm high. The rhizome is short and thick and with numerous fasciculate roots. The stem is leafless. The basal rosette consists of lanceolate to linear-lanceolate leaves, 10-20 cm long and 2-3.5 cm wide, with 3-7 primary veins, almost parallel, and with multicellular conical tector trichomes and multicellular glandular trichomes. The flowers are very small, yellow-brown, type 4, grouped in an ovoid or short cylindrical spike; the inflorescence is 5-8 mm thick, more or less globular. The fruit is an ovoid capsule, 3-4 mm long, with 2 blackish seeds (Ardelean & Mohan, 2008; EMA/HMPC/437859/2010; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al*., 2013; Stanescu *et al*. 2014; Stefan & Oprea, 2007). It blooms from May to September (Ardelean & Mohan, 2008; Oroian, 2011; Sarbu *et al*., 2013).
Distribution and habitat: frequent from the plain to the mountain area, through ravines, forest thickets, vineyards, swamps, pebbles, ruderal places, in grassy, dry places, roadsides (Ardelean & Mohan, 2008; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).
Harvesting period: the leaves with flower scape during flowering stage, when they have the highest aucubin content (Oroian, 2011; Parvu, 2006).

Traditional uses

P. lanceolata is used in folk medicine for the treatment of wounds, as mucilage drug and mild expectorant against dry cough caused by pharyngitis. It is recommended in moderate irritative cough (internal use) as well as in cases of inflammation of the skin and mucosa (topical application) (EMA/HMPC/437859/2010).

In Romanian folk medicine, the fresh or crushed leaves and the pressed juice were used externally as hemostatic, in traumas, inflammations and boils. The poultices from the leaves were used in some dermatological diseases, especially erysipelas, but also in the treatment of inflamed, rheumatic joints. The infusions, decoctions, macerates and pressed juice were used internally against intestinal worms, as diuretic, antitussive, in lung diseases (pneumonia, tuberculosis) and liver conditions (Butura, 1979; Grigorescu & Silva, 1997; Parvu, 2006; Stanescu *et al*., 2014). The decoction from the roots was taken against stomach ache (Butura, 1979). The infusion was used as eye baths in combating conjunctivitis and blepharitis, and also as gargle in the treatment of laryngitis and tracheitis. The juice obtained from fresh plantain leaves was used in the treatment of chronic non-acid gastritis (Stanescu *et al*., 2014).

Other ethnopharmacological data mention the use of the leaf infusion in bronchitis, laryngo-tracheal catarrh, diarrhoea and wounds (Tita *et al*., 2009).

Chemical composition

P. lanceolata aerial parts contain phenylethanoids (acteoside, β-hydroxy-acteoside, isoacteoside, plantamajoside and lavandulifolioside), iridoid glycosides (aucubin, catalpol, geniposidic acid, asperuloside), flavonoids (luteolin, luteolin-7-glucoside, luteolin-7-glucuronide and luteoline-3'7-diglucuronide), phenolic acids (caffeic acids derivatives, ferulic, syringic, coumaric and vanillic acids), carotenoids, vitamins (A, C, K), tannins, pentacyclic triterpenes (ursolic and oleanolic acids) and small amounts of essential oil (Ardelean & Mohan, 2008; EMA/HMPC/437859/2010; Fleer & Verspohl, 2007; Grigorescu & Silva, 1997; Jankovi *et al*., 2012; Mazzutti *et al.*, 2017a; Stanescu *et al*., 2014). The iridoid glycoside concentrations vary widely between populations and also from plant to plant (Ianovici *et al*., 2010).

P. lanceolata leaves also contain approximate 6.5% mucilage, consisting of polysaccharides such as L-arabinose, D-galactose, D-glucose, D-manose, L-manose, D-galacturonic acid, D-glucuronic acid (Grigore *et al*., 2015).

The seeds contain mucilage, consisting of arabinose, rhamnose, xylose, galactose, glucose, mannose, galacturonic acid and glucuronic acid (Hesarinejad *et al.*, 2018).

The European Pharmacopoeia requires for *Plantaginis lanceolatae* a minimum 1.5% of total ortho-dihydroxycinnamic acid derivatives expressed as acteoside (dried drug) (Eur. Ph. 8.0, 2013).

Pharmacological activities

For *P. lanceolata* leaves and aerial parts several biological activities were reported: antioxidant, anti-inflammatory (inhibition of COX-1, 12-LOX, NF-kB), wound healing, anti-obesity (inhibition of pancreatic lipase, activating lipolysis in visceral fat), anti-ulcer, procoagulant, antiviral, immunostimulant and epithelizing (Dalar *et al.*, 2012; EMA/HMPC/437859/2010; Goncalves & Romano, 2016; Mazzutti *et al.*, 2017a; Mazzutti *et al.*, 2017b; Muntean *et al*., 2007; Parvu, 2006).

The phenylethanoid acteoside from *P. lanceolata* has anti-inflammatory properties, reducing edema in mice (Murai *et al*., 1995). The crude ethanol extract and isolated compounds from the aerial parts showed antispasmodic activity; the crude extract inhibited the contractions of the guinea-pig ileum and the trachea contractions; luteolin, acteoside and plantamajoside inhibited the acetylcholine-induced contractions of the ileum, while luteolin and acteoside reduced the barium-induced contractions of the trachea (Fleer & Verspohl, 2007).

The aqueous and methanol extracts from leaves have significant *in vivo* antioxidant and anti-inflammatory activities, and the aqueous extract showed wound healing effects (both in incision and excision models) (Kuranel *et al*., 2016).

The crude extract from *P. lanceolata* leaves showed a good antimicrobial activity against several Gram-positive (*Staphylococcus aureus* and *Streptococcus agalactiae)* and Gram-negative bacteria (*Escherichia coli* and *Salmonela thyphei*) and 2 fungi (*Aspergillus niger* and *Fusarium solani*), the extract being slightly more potent against the Gram-negative bacteria (Fayera *et al*., 2018).

The mucilages have immunostimulatory properties, which explain the cicatrizing action of *P. lanceolata* in treating wounds, as well as its antiseptic activity; the iridoids have hepatoprotective effects (Grigorescu & Silva, 1997; Stanescu *et al*., 2014).

The emollient action of the aqueous extracts is due to the mucilage that covers the inflamed mucosa with a protective film. The tannins have anti-inflammatory, spasmolytic, hemostatic, antimicrobial and anti-diarrhoeal properties. Vitamin K also contributes to the hemostatic action of plantain (Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

Current uses

According to the European Medicine Agency - Committee on Herbal Medicinal Products, several herbal preparations, such as herbal substance (comminuted or powdered), dry, liquid and soft extracts, expressed juice from the fresh herb, syrup, and tablets, are used to improve digestion, to sooth irritations, as expectorant, antimicrobial and astringent agents (EMA/HMPC/437858/2010 *Corr.;* EMA/HMPC/437859/2010).

The German Commission E approved its use in common cold, cough/bronchitis, fevers, inflammation of the mouth and pharynx, inflammation of the skin (Gruenwald *et al*., 2000).

P. lanceolata is currently used internally to treat mouth, throat and upper respiratory tract conditions, and externally as topical remedy for skin diseases (Goncalves & Romano, 2016).

P. lanceolata leaves are also used in cosmetic products such as creams, lotions and solution for spa use to optimize skin appearance, enhancing collagen production and wound healing, and also for their antioxidant effects (Grigore *et al*., 2015).

On the Romanian market, many medicinal preparations with *Plantaginis folium* extracts (syrup, tablets), and also tinctures and teas, are available. The syrups and tablets are used for their expectorant action. The leaf tincture is used in the treatment of minor dysfunctions of the gastrointestinal tract and in inflammatory dermal diseases (with local application) (Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

Precautions and adverse reactions
It is not recommended in case of hypersensitivity to the active substances. Due to the lack of adequate data, the oral use in children under 3 years of age and the oromucosal use in children and adolescents under 18 years of age are not recommended. In the absence of sufficient data, the use during pregnancy and lactation is not recommended (EMA/HMPC/437858/2010 *Corr.;* EMA/HMPC/437859/2010).
Aucubin can cause gastroenteritis and central palsy following oral administration (EMA/HMPC/437859/2010; Stanescu *et al*., 2014).

Other warnings
Not to be confused with the leaves of *Plantago major*, *Plantago media* or *Digitalis lanata* (EMA/HMPC/437859/2010; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Stanescu *et al*. 2004b).

Potentilla anserina L. (silverwood, „coada racului"), Rosaceae family

Other common names: Potentilla, Cinquefoil, Crampweed, Goosegrass, Goose Tansy, Moor Grass, Silver Cinquefoil, Goosewort, Prince's Feathers, Trailing Tansy, Wild Agrimony (Gruenwald *et al*., 2000), anserina (Duke *et al*., 2002).

Officinal products: aerial parts (*Anserinae herba*) (Ardelean & Mohan, 2008; Chevallier, 2016; Muntean *et al*., 2007; Parvu, 2006; Stanescu *et al*., 2004a; Stanescu *et al*., 2014; Tita *et al*., 2009); leaves and flowers (Gruenwald *et al*., 2000); root (Chevallier, 2016).

Botanical description
P. anserina is an herbaceous perennial plant with a thick, cylindrical rhizome, from which adventitious fibrous roots emerge. The basal stem is thick and has repent, long, thin lateral stems that are rooted at the nodes (stolons). The basal leaves are elongated-ovate, unevenly paired, with elongated ovate leaflets, serrate-dentate on the edges, green on the upper side and gray-silver on the underside. Large, membranous and multifidate stipules are present at the base of the leaves. The flowers are solitary on long pedicles, on type 5, 1.5 to 3 cm wide. The calyx is double and the corolla has free petals, golden-yellow in color, twice as long as the sepals. The fruits are small poly-achenes with persistent styles (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2004a; Stanescu *et al*., 2014). *Potentilla anserina* ssp. *anserina* is a perennial plant, 15-50 cm high, with stolons, and petals longer than the sepals (Sarbu *et al.,* 2013). It blooms from May to August (Sarbu *et al.,* 2013; Stanescu *et al*., 2014).
Distribution and habitat: common in wet, sandy places, on the banks of rivers and lakes, in wet meadows, ditches, from the plain to the mountain area (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Oroian, 2011). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, Letea, Sfantu Gheorghe, Sulina) (Ciocarlan, 2011; Doroftei *et al*., 2011). *P. anserina* ssp.

anserina is frequently spread from the plain to the spruce floor, in wet meadows, waterfront, on alluvium, pebbles, ruderal places (Sarbu *et al.,* 2013).
Harvesting period: aerial parts, during flowering stage (Gruenwald *et al*., 2000; Parvu, 2006).

Traditional uses

In Romanian folk medicine, *P. anserina* was used as infusion for its antispastic and anti-diarrhoeal properties. The plant was also used externally to treat wounds, sprains, eczema (as baths, poultices), gingivitis (infusion, decoction), stomatitis (decoction from roots) and internally against stomach ache and colds (infusion from aerial parts or leaves), anemia, arthritis, heavy menstruation, gastric colic, enterocolitis, diarrhoea, kidney stones (as decoction or infusion) (Butura, 1979; Parvu, 2006; Stanescu *et al*., 2014).
Other ethnopharmacological data mention the use of the infusion from aerial parts in digestive, renal and uterine disorders, gingivitis and leucorrhoea (Tita *et al*., 2009).

Chemical composition

P. anserina herb contains: catechins (e.g. catechin, epicatechin, ellagic acid), phenolic acids (e.g. gallic, *p*-coumaric, caffeic, ferulic and chlorogenic acids), coumarins (umbelliferon, scopoletin), flavonoids (e.g. myricetin, isorhamnetin-3-*O*-β-D-glucuronide, isoquercitrin, quercitrin, astragalin, rutin), aliphatic compounds, proanthocyanidins and polysaccharides (Olennikov *et al*., 2015; Stanescu *et al*., 2004a; Tomczyk *et al*., 2010).
The rhizomes contain triterpenoid saponins (Zhao *et al*., 2008). Several triterpenes (e.g. potentillanosides A–F, pomolic acid, rosamutin, euscaphic acid), sterols (β-sitosterol, β-daucosterol), isoflavones and polysaccharides (D-rhamnose, D-arabinose, D-glucose and D-galactose) were identified in roots (Chen *et al*., 2010; Morikawa *et al*., 2014; Qin *et al*., 2012).

Pharmacological activities

Triterpenoid saponins isolated from the rhizomes of *P. anserina* exhibited *in vivo* (animal model) antiviral activity against hepatitis-B virus (Zhao *et al*., 2008).
A methanol extract from the tuberous roots of *P. anserina* and several isolated triterpenes showed hepatoprotective activity in mice (Morikawa *et al*., 2014). The *n*-butanol extract from roots had neuroprotective activity in a hypoxic injury model (hippocampal neurons) (Qin *et al*., 2012). The polysaccharide fraction isolated from roots exhibited *in vitro* and *in vivo* immunomodulatory activity (Chen *et al*., 2010).
An *in vitro* study highlighted the anticariogenic activity of the water extracts from several *Potentilla* species, including *P. anserina* (Tomczyk *et al*., 2010).
Due to its tannin content, it has astringent, anti-diarrhoeal, antiseptic and hemostatic properties. Studies performed on isolated organ have shown, for *Anserinae herba* extracts, the ability to increase the tone and frequency of uterine contractions (Stanescu *et al*., 2004a; Stanescu *et al*., 2014).

Current uses

The German Commission E approved the use of *P. anserina* in diarrhoea, inflammation of the mouth and pharynx and premenstrual syndrome (Gruenwald *et al*., 2000).

Internally, it is used in acute, nonspecific diarrhoea (with gastrointestinal cramps) and also in dysmenorrhea; externally, in inflammation of the oral mucosa and upper respiratory tract, vaginal infections, uterine and vaginal hemorrhages, gingivitis and stomatitis. The plant product and the extracts are included in medicinal preparations used in spastic dysmenorrhea, insomnia or as a diuretic (Ardelean & Mohan, 2008; Stanescu *et al*., 2004a; Stanescu *et al*., 2014).
It is also used externally as a lotion or ointment for bleeding hemorrhoids (Chevallier, 2016).

Precautions and adverse reactions
Commission E reports no contraindications, adverse effects, or interactions, for the proper use of *P. anserina*, except for gastric irritation (Duke *et al*., 2002; Gruenwald *et al*., 2000), thus its administration to people with gastric sensitivity is not recomended (Stanescu *et al*., 2004a; Stanescu *et al*., 2014). For internal use, it is contraindicated in people with chronic liver and kidney diseases (Parvu, 2006).
Use internally for no more than 3-4 weeks at a time (Chevallier, 2016).

Other warnings
Substitutions with other *Potentilla* species (e.g. *P. reptans*) are possible (Muntean *et al*., 2007).

Potentilla recta L. (cinquefoils, „buruiană de cinci degete"), Rosaceae family

***Other common names*:** sulfur cinquefoil (Bazylko *et al*., 2013; Ökdem *et al*., 2018).

Officinal products: aerial parts (Grigorescu *et al*., 1986).

Botanical description
P. recta is a perennial herbaceous species, with a height of 30-70 cm. *P. recta* ssp. *recta* has dentate or sectate leaflets up to half of the leaf blade. It blooms from May to July (Sarbu *et al.,* 2013).
Distribution and habitat: frequently spread, from the plain to the beech floor, through meadows, bushes, orchards, in fields, forest edges, grassy rocks (Butura, 1979; Sarbu *et al.,* 2013). *P. recta* ssp. *recta* and *P. recta* ssp. *laciniosa* (Kit. Ex Nestl.) Soó were reported in the Danube Delta area (Ciocarlan, 2011).
Harvesting period: during flowering stage.

Traditional uses
In traditional medicine, *P. recta* was used as an astringent, styptic, stomachic, anti-inflammatory, analgesic, antipyretic and tonic agent (Bazylko *et al*., 2013).
In the traditional medicine of Turkey, *P. recta* is used for its antibacterial, anti-inflammatory effects and as a tonic (Ökdem *et al*., 2018).
In Romanian folk medicine, the decoction was used in skin and respiratory diseases (Butura, 1979).

Chemical composition
Several phenolic acids and flavonoids were identified in the aerial parts of *P. recta*: 4-hydroxybenzoic, vanillic, syringic, chlorogenic, *p*-coumaric, ferulic, salicylic and cinnamic acids, kaempferol, quercetin, quercetin-3-*O*-*β*-glucopyranoside, quercetin-3-*O*-*β*-glucuronide, kaempferol-3-*O*-rutinoside, rutin and apigenin-7-O-glucoside (Bazylko *et al*., 2013; Ökdem *et al*., 2018; Söhretoglu & Kırmızıbekmez, 2011; Tomczyk, 2011). It also contains tannins, triterpenoids (e.g. tormentic, oleanolic and ursolic acids), neolignans, coumarins and saponins (Butura, 1979; Ökdem *et al*., 2018; Sut *et al*., 2019; Şöhretoğlu *et al*., 2015).

Pharmacological activities
The 70% methanol extract from *P. recta* aerial parts, rich in phenolic compounds, exhibited *in vitro* (cellular mode) anti-inflammatory effects, by decreasing the levels of nitric oxide and of pro-inflammatory cytokines (TNF-α and IL-1β) (Ökdem *et al*., 2018).
Different extracts from *P. recta* aerial parts showed *in vitro* (cellular and non-cellular models) antioxidant and cytotoxic effects (Şöhretoğlu *et al*., 2015). The crude extracts, fractions and isolated compounds from *P. recta* exhibited *in vitro* (non-cellular models) antioxidant and anti-inflammatory activities (Bazylko *et al*., 2013).
The aqueous, methanol and ethyl acetate extracts have *in vitro* enzyme inhibitory effects (acetylcholinesterase, butyrylcholinesterase, tyrosinase, α-amylase, α-glucosidase) and antioxidant properties (Sut *et al*., 2019)

Current uses
The aerial part is used as a decoction for the treatment of pyoderma (Grigorescu *et al*., 1986).

Precautions and adverse reactions
No available data.

Prunus spinosa L. (blackthorn, „porumbar"), Rosaceae family

***Other common names*:** Sloe, Wild Plum (Gruenwald *et al*., 2000).

Officinal products: flowers (*Pruni spinosae flos*) (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2014), fruits (*Pruni spinosae fructus*) (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Muntean *et al*., 2007; Oroian, 2011). In traditional medicine, the leaves (*Pruni spinosae folium*), thinner roots (*Pruni spinosae radix*), root and the young branches bark (*Pruni spinosae cortex*) are also used (Parvu, 2006). Literature data also mention the name *Flores acaciae germanicae* or *nostratis* (Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

Botanical description
P. spinosa is a thorny shrub, 1-3 m tall, with numerous lateral branches, with dark-gray bark, slightly cracked. The root is deep and branched. The branches are usually

thorny, with thorns up to 4-8 cm long. It has young matte tendrils, usually more or less pubescent. The leaves are elliptical to oblong obovate, 2-4 cm long and wide at the middle, glabrous or sometimes hirsute, crenate-serrate, and have petioles with toothed stipules at the base, usually longer than the petioles. The flowers are small, 1-1.5 cm, long pedicellate, solitary, on type 5, with small sepals of 1-2 mm, white petals, numerous stamens and lower unicarpelar gynoecium. The fruits are globose drupes, 1-1.5 cm in diameter, blue-blackish, frosted and glabrous, with a single stone. The pulp of the fruit, green in color, has an astringent taste and it is adherent to the stone (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013; Stanescu *et al*., 2014). It blooms from April to May, before the leaves emerge (Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013). *P. spinosa* ssp. *spinosa* has glabrous flowering peduncles (Sarbu *et al.,* 2013).

Distribution and habitat: spread from the plain to the beech floor, through bushes, meadows, forest edges, roads, rocks, sunny shores (Ardelean & Mohan, 2008; Butura, 1979; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area: Caraorman, C.A. Rosetti, Cardon (including the forest), Dolosman, Dranov, Letea, Perisor, Popina Island and Sulina (Doroftei *et al*., 2011).

Harvesting period: flowers in April-May, fruits in October-November (Ardelean & Mohan, 2008; Oroian, 2011); leaves until July; thinner roots, bark of roots and bark of young branches in autumn, at the end of the vegetation season (Parvu, 2006).

Traditional uses

In folk medicine, the fruit juice was used as a gargle for mouth, throat and gum inflammation (Gruenwald *et al*., 2000).

In Romanian folk medicine, the roots and root bark decoctions were used as mouth wash against toothache. The fruit decoction was used internally against diarrhoea and the juice from the unripe fruits was used against indigestion (Butura, 1979; Stanescu *et al*., 2014). The stem bark was used against angina pectoris and the flowers were used as anti-diabetic, anti-asthmatic and anti-inflammatory agent (Grigorescu *et al*., 1986; Parvu, 2006).

Chemical composition

The main bioactive compounds classes identified in the fruits of *P. spinosa* are: flavonoids (quercetin-3-*O*-glucoside, quercetin rhamnosylhexoside, quercetin-3-*O*-rutinoside, kaempferol-3-*O*-rutinoside), phenolic acids (protocatechuic, gallic and caffeic acids, 3-*O*-caffeoylquinic acid, 4-*O*-caffeoylquinic acid, 3-*O*-feruloylquinic acid), anthocyanins (cyaniding-3-rutinoside, cyaniding-3-glucoside, peonidin-3-*O*-glucoside, peonidin-3-*O*-rutinoside), coumarins, vitamins (B1, B2, PP, C), fatty acids, tannins (Babalau-Fuss *et al*., 2018; Balta *et al*., 2019; Gille *et al*., 2016a; Gruenwald *et al*., 2000; Meschini *et al*., 2017; Pinacho *et al*., 2015; Ruiz-Rodríguez *et al*., 2014). Numerous polyphenols (e.g. caffeic acid derivatives, quercetin and kaempferol derivatives) and several A-type proanthocyanidins were identified in flowers (Kolodziej *et al*., 1991; Marchelak *et al*., 2017; Parvu, 2006; Stanescu *et al*., 2014).

In branches, protocatechuic, gallic and caffeic acids, kaempferol and quercetin derivatives were identified (Pinacho *et al*., 2015).

Pharmacological activities

Blackthorn fruit extracts showed antioxidant activity and flower extracts showed antioxidant and anti-inflammatory activitis (Marchelak *et al.*, 2017; Marchelak *et al*., 2019; Popović *et al*., 2020). The leaves and branches have also been shown to have antioxidant activity (Pinacho *et al*., 2015).

P. spinosa fruit extracts exhibited a good antiproliferative activity against several human cancer cell lines (Meschini *et al*., 2017; Popović *et al*., 2020). The antiproliferative activity was also determined for the blossom ethanol extract (Murati *et al*., 2019).

The fruit extract exhibited inhibitory potential towards two enzymes relevant to type 2 diabetes, namely α-amylase and α-glucosidase (Popović *et al*., 2020).

The flowers have diuretic, diaphoretic, laxative and expectorant properties, and the leaves have astringent and diuretic effects (Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

Current uses

P. spinosa fruits are approved by the German Commission E in inflammation of the mouth and pharynx (Gruenwald *et al*., 2000).

Blackthorn is mainly used as a traditional remedy in the treatment of kidney (edema, renal colic), gastrointestinal (colic, flatulence), respiratory, dermatological (rash) diseases and in convalescence. The fruits are manily used in the treatment of diarrhoea, as aqueous extract. The fruits are also used as juice, syrup, wine and jam, the juice being used in inflammation of the upper respiratory tract (Duke *et al*., 2002; Parvu, 2006; Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

The flowers are used as a sedative and as a diuretic in the treatment of diseases of the excretory system (nephritis, cystitis, hemorrhagic cystitis), enteritis. The leaves are used in skin rashes, and in kidney and bladder diseases (Parvu, 2006).

In homeopathy, *P. spinosa* is used for cardiac insufficiency and nervous headaches (Gruenwald *et al*., 2000).

Precautions and adverse reactions

No health hazards or side effects were reported in conjunction with the proper administration of designated therapeutic dosages (Gruenwald *et al*., 2000).

Other warnings

Rare cases of contamination with the flowers of *Prunus padus* L. (syn. *Padus avium* Mill.) have been reported (Stanescu *et al*., 2004b).

Rosa canina L. (dog rose, „măceș"), Rosaceae family

Syn. *Rosa heterostyla* Chrhan, *Rosa canina* L. ssp. *dumalis* (Bechst.) Arcang. pro parte, *R. willibaldii* Chrshan, *R. sarmentacea* J. Woods pro parte, *R. dumalis* Bechst, *R. prutensis* Chrshan, *R. canina* L. ssp. *vulgaris* (Mert.&W.D.J. Koch) Gams, *R. communis* Rouy ssp. *canina* (L.) Rouy) (Doroftei *et al*., 2011), *R. lutetiana* Léman (Duke *et al*., 2002).

***Other common names*:** Brier Hip, Hip, Rose Hip, Sweet Briar, Brier Rose, Eglantine Gall, Hogseed, Dog-Berry, Sweet Brier, Wild Brier (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia, the officinal product is *Rosae pseudo-fructus* represented by Rose hips made up by the receptacle and the remains of the dried sepals of *Rosa canina* L., *R. pendulina* L. and other *Rosa* species, with the achenes removed (Eur. Ph. 8.0, 2013). Literature also mentions the name *Cynosbati fructus* (Ardelean & Mohan, 2008; Butura, 1979; Istudor, 2001; Muntean *et al*., 2007; Oniga, 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2014).

Botanical description

R. canina is a 2-3 m tall shrub, with a branched stem that forms a bush with thorny branches. The thorns are wide at the base and curved at the top, 3-10 mm long. The leaves are alternate, imparipinnate-compound, with 5-7 leaflets, oval, elliptical, 2-4 cm long and 1-2 cm wide, sharp or rounded at the tip, simple or imperfectly bi-serrate at the edges and glabrous on the back. The petioles are glabrous or more or less hirsute, sometimes with small thorns, and 2 small overgrown stipules at the base. The flowers are large (4-5 cm in diameter), solitary or grouped 2-3 in inflorescences at the top of the branches and have sectate sepals. The receptacle is cup-shaped, the calyx consists of 5 sepals inserted on the edge of the receptacle orifice, and the corolla of 5 light-pink, white or dark red petals. The fruits are achenes, improperly called seeds (true fruits), that are strongly hairy, unispermous; are closed in the fleshy, ellipsoidal receptacle (false fruit called enduvia), bright in color at first, red-orange or bright red at maturity, with a glossy outer surface (becomes wrinkled by drying), and the inner part covered by numerous rough hairs, yellow in color (Muntean *et al*., 2007; Oniga, 2007; Oroian, 2011; Parvu, 2006; Stanescu *et al*., 2004a; Stanescu *et al*., 2014; Stefan & Oprea, 2007). It blooms from May to June (Istudor, 2001; Sarbu *et al.,* 2013).

Distribution and habitat: from the plain to the beech floor, through forests, thickets and forest edges, bushes, meadows (Ardelean & Mohan, 2008; Istudor, 2001; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: the fruits in August-October, when fully ripe (they acquire a brick-red color) (Ardelean & Mohan, 2008; Istudor, 2001; Oniga, 2007; Oroian, 2011; Stanescu *et al*., 2004a; Stanescu *et al*., 2014).

Traditional uses

The rose species have been traditionally used for food (teas, jellies, jams, custards, soups, alcoholic beverages) and medicinal purposes – treatment of various ailments such as colds, flu, inflammations, vitamin C deficiency, chronic pain, ulcers, urinary tract disorders and rheumatic conditions (Czyzowska *et al*., 2015; Gruenwald *et al*., 2000; Patel, 2017). Dog rose was valued as the source of a widely used folk remedy for chest problems (Chevallier, 2016).

In Romanian folk medicine, the fruit (pseudofruit) tea was used to treat cough and hoarseness, to combat abdominal colic in children, and also against stomach, kidneys and liver pain. The leaf decoction was used in the form of compresses in ear aches. The fruits were also used in the preparation of vitamin jams (Oniga, 2007; Stanescu *et al*., 2004a; Stanescu *et al*., 2014). The dog rose decoction mixed with *Galium erectum*

was taken against diarrhoea. Dried fruits were mixed with raspberry flower stalks and the tea was used against angina pectoris (Butura, 1979).
Other ethnopharmacological data mention the use of the decoction and infusion from fruits, leaves and flowers in anemia, anorexia, avitaminosis, colitis, diabetes, convulsive cough, urinary, gastric and cardiac disorders (Tita *et al*., 2009).

Chemical composition

R. canina fruits contain several bioactive compounds classes, such as: vitamins (C, E, provitamin A), organic acids, saturated and polyunsaturated fatty acids, anthocyanins (cyaniding-3-O-glucoside), carotenoids (lycopene, β- and α-carotene, lutein), phenolic acids (gallic, syringic, chlorogenic, p-coumaric, caffeic and ferulic acids), flavonoids (apigenin, isoquercitrin, kaempferol, rutin, quercetin, hyperoside), triterpenes acids (ursolic, oleanolic and betulinic acids), sugars (fructose, glucose, sucrose), proanthocyanidins (epicatechin, catechin, quinic acid), pectines and tannins (Al-Yafeai *et al*., 2018; Barros *et al*., 2011; Cretu *et al*., 2016; Cretu *et al*., 2020; Czyzowska *et al*., 2015; Gruenwald *et al*., 2019; Istudor, 2001; Kerasioti *et al*., 2019; Nađpal *et al*., 2016; Oniga, 2007; Patel, 2017; Stanescu *et al*., 2004a; Stanescu *et al*., 2014). Dog rose in considered a valuable natural source of vitamin C (500-1000 mg%) (Czyzowska *et al*., 2015; Nađpal *et al*., 2016; Patel, 2017). Furthermore, it is considered that the organic acids and flavonoids prevent the oxidation of vitamin C, enhancing its stability and bioavailability (Nađpal *et al*., 2016). The achenes contain 5.45-9.2% fatty oil (relative to dry plant material), the main constiutuents being palmitic, stearic, oleic, linoleic and linolenic acids (Muntean *et al*., 2007).
The European Pharmacopoeia requires for *Rosae pseudo-fructus* minimum 0.3% ascorbic acid (dried drug) (Eur. Ph. 8.0, 2013).

Pharmacological activities

In vitro (cellular and non-cellular models) and *in vivo* studies (animal models) highlighted the antioxidant, anti-inflammatory activities, and cytotoxic, anti-diabetic and anti-obesity potential of dog rose fruits (Fetni *et al*., 2020; Lattanzio *et al*., 2011; Nađpal *et al*., 2016; Ninomiya *et al.,* 2007; Oprica *et al*., 2016; Patel, 2017; Paunović *et al*., 2019).
In vitro studies on human cell lines suggest the enhancement of β-cells proliferation as the major anti-diabetic mechanism of dog rose fruits (Fattahi *et al*., 2017).
Dog rose showed an antioxidant activity correlated with its content in polyphenols, vitamins (C, E, B) and carotenoids, which act synergistically (Mármol *et al*., 2017). *In vitro* and *in vivo* studies showed the anti-inflammatory (reduction of pro-in ammatory cytokines and chemokines, reduction of NF-kB signaling, inhibition of pro-inflammatory enzymes) activity of dog rose extracts (Gruenwald *et al*., 2019; Lattanzio *et al*., 2011; Patel, 2017).
The fruit extract exhibited *in vitro* anticancer potential on human colon cancer cell line, having selective cytotoxicity in the colon cancer cell line compared to the normal colon cells (Turan *et al*., 2018).
The 80% aqueous-acetone extracts from the seeds of *R. canina* showed anti-obesity potential, having an inhibitory effect on the gain of body weight and visceral fat weight without affecting the food intake in mice (Ninomiya *et al*., 2007).

Several clinical trials highlighted the benefic effects of *R. canina* in the treatment of osteoarthritis, mainly due to its antioxidant and anti-inflammatory properties (Gruenwald *et al*., 2019).
Several polyphenolic bioproducts obtained from the bark of *R. canina* shrub exhibited *in vitro* (cellular model) cytostatic and cytotoxic potential, and *in vivo* (animal model) immunomodulatory, normolipemiant and hypocholesterolemiant effects and antineoplastic potential (Gherghel *et al*., 2009; Mihai *et al*., 2008; Rotinberg *et al*., 2008).

Current uses
The Complete German Commission E Monographs mentions *R. canina* as a medicinal plant, suggesting the use of the seed and shells in the treatment of arthritic conditions, gout, sciatica, and diseases of the kidney and lower urinary tract (Winther *et al*., 2016).
R. canina fruits are used as vitaminizing, astringent, anti-diarrhoeal, cholagogue, choleretic, arterial vasodilator and antilithiasis agent, and also in intestinal inflammation and various respiratory tract conditions (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006).
The fruits are used as infusion, decoction and tincture with tonic, diuretic, antispasmodic, anti-inflammatory action (Muntean *et al*., 2007; Oniga, 2007). The fruits are also included in several vitamin C food supplements, in the form of powders, tables, capsules, and in food supplements recommended in osteoarthritis of medium severity (Stanescu *et al*., 2014).

Precautions and adverse reactions
No side effects were reported in conjunction with the proper administration of designated therapeutic dosages (Duke *et al*., 2002; Gruenwald *et al*., 2000).
However, in some patients, the administration was accompanied by digestive complaints and, in rare cases, allergic reactions. However, gastrointestinal complaints disappear if enough fluid is given (Stanescu *et al*., 2014).

Rubus caesius L. (dewberry, „mur de miriște, mure negre"), Rosaceae family

***Other common names*:** blackberry, bramble (Rejewska *et al*., 2013).

Officinal products: young leaves (*Rubi caesii folium*) (Ardelean & Mohan, 2008; Tita *et al*., 2009), roots, buds (Tita *et al*., 2009).

Botanical description
R. caesius is a shrub, 30-80 cm high (Sarbu *et al.,* 2013). The root is deep. The stem has numerous repent shoots, 1-3 m long, thin, cylindrical, frosted, glabrous, rarely short-hairy, with short spines. The leaves are trifoliate, on the upper side scattered-hirsute, on the lower side tomentaceous, on the edge irregular-serrate. The flowers are white, small, grouped in short racemes. The fruits are fleshy, globular, black-purple poly-drupes, difficult to detach from the stem (Ardelean & Mohan, 2008; Parvu, 2006;

Stefan & Oprea, 2007). It blooms from May to September (Parvu, 2006; Sarbu *et al.,* 2013).

Distribution and habitat: frequent, from plain to the beech floor (rare in the region of hills and mountains), through ditches, meadows, fields, forest edges, bushes (Parvu, 2006; Sarbu *et al.,* 2013), through bushes, next to fences (Butura, 1979). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011).

Harvesting period: from May to July (Ardelean & Mohan, 2008).

Traditional uses

Similar with *Rubus fruticosus*, in Romanian folk medicine, the leaves, buds, roots and fruits of *R. caesius* have therapeutic uses. Internally, it is used in treating bronchitis, diarrhoea, enterocolitis, kidney diseases (leaf infusion), pulmonary diseases, diarrhoea, gastrointestinal diseases (leaf decoction), and as laxative (fruit syrup). Externally, the leaves are used as gargle (infusion or decoction) in gingivitis, stomatitis and laryngo-pharyngeal inflammation, as washes or local poultices (infusion) to treat leucorrhea, hemorrhoids, anal fissures and psoriasis (Parvu, 2006).

The leaves and roots, dried and ground, were mixed with white wine and taken against back pain (Butura, 1979).

Other ethnopharmacological data mention the use of the leaf infusion in diarrhoea, bronchitis, urinary disorders, gingivitis, stomatitis, leucorrhoea, hemorrhoids and psoriasis, and also of the decoction and infusion from roots and buds in pulmonary and laryngo-pharyngeal disorders (Tita *et al*., 2009).

Chemical composition

The fruits contain phenolic acids (caffeoyl hexoside, chlorogenic and p-coumaric acids), flavonoids (quercetin, kaempferol, luteolin and apigenin derivatives), anthocyanins (cyaniding-3-*O*-glucoside, cyaniding-3-*O*-diglucoside cyaniding-3-*O*-xyloside, cyanidin-3-*O*-rutinoside) and ellagitannins (Oszmiańsk *et al*., 2015; Rejewska *et al*., 2013). The fruits are also rich in vitamin C (Butura, 1979; Ardelean & Mohan, 2008).

Phenolic acids (gallic and p-coumaric acids, ellagic acid and its derivatives), flavonoids (mainly quercetin and kaempferol derivatives) and ellagitannins were identified in leaves (Grochowski *et al*., 2016).

Pharmacological activities

Antioxidant and antibacterial (against *Proteus mirabilis*, *Bacillus cereus, Staphylococcus aureus* and *Staphylococcus epidermidis*) activities were reported for *R. caesius* (Oszmiańsk *et al*., 2015; Rejewska *et al*., 2013).

Extracts and fractions from the leaves of *R. caesius* exhibited antioxidant and anticancer activities on two colon cancer cell lines (Grochowski *et al*., 2016). Ethanol leaf extract showed *in vivo* (animal model) hypoglycemic activity (Schädler & Dergatschewa, 2017).

The leaves, buds and roots have astringent, anti-diarrhoeal, disinfectant, stomachic and spasmolytic properties (Parvu, 2006).

The leaf infusion has astringent properties. The infusion and decoction from roots and buds have emollient and antiseptic properties (Tita *et al*., 2009).

Current uses
R. caesius is used as an adjuvant in the treatment of acute inflammatory bowel disease, and as laxative and stomachic (Parvu, 2006; Stefan & Oprea, 2007). Internally, it is also used in bronchitis, diarrhoea, enterocolitis, gastroenteritis and kidney diseases. Externally, it is used in gingivitis, stomatitis, leucorrhea, hemorrhoids, anal fissures and psoriasis (Ardelean & Mohan, 2008).

Precautions and adverse reactions
No available data.

Salvia glutinosa L. (sage, „cinsteț"), Lamiaceae family

Officinal products: aerial parts (*Salviae glutinosae herba*) (Parvu, 2006; Tita *et al*., 2009), inflorescences (*Salviae glutinosae flos*) (Parvu, 2006), leaves (*Salviae glutinosae folium*), roots and flowering stems (Ardelean & Mohan, 2008).

Botanical description
S. glutinosa is a perennial herbaceous plant, with a thick oblique rhizome, 50-100 cm long (Sarbu *et al.,* 2013). The stems are simple, sometimes branched, with articulated trichomes, at the top mixed with glandular-viscous trichomes. The leaves are simple, cordate-hastate-sagittate, reticulate-ribbed, with serrated edge, sharp basal lobes and pointed tip, with long and hirsute petiole. The flowers are yellow, with brown dots, rich in nectar, grouped in a simple inflorescence. The fruits are ovoid or ellipsoidal nucules, brown and smooth (Ardelean & Mohan, 2008; Butura, 1979; Parvu, 2006; Sarbu *et al.,* 2013). It blooms from June to August (Ardelean & Mohan, 2008; Parvu, 2006; Sarbu *et al.,* 2013).
Distribution and habitat: through humid and shady forests and forest cuts, besides streams, valleys, ravines, especially in mountainous regions, from the oak to the spruce floor (Ardelean & Mohan, 2008; Butura, 1979; Parvu, 2006; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011).
Harvesting period: in June, during the flowering stage (Ardelean & Mohan, 2008).

Traditional uses
This plant was known in Antiquity by the Getae, Dacians, Geto-Dacians. The aerial parts of the plant were used in human and veterinary folk medicine to treat various diseases (Parvu, 2006).
In Romanian folk medicine, the decoction was used as wash against headache and as baths against rheumatism (Butura, 1979).
Other ethnopharmacological data mention the use of the infusion from aerial parts in foot-and-mouth disease, wounds and bites (Tita *et al*., 2009).

Chemical composition
The flowers contain triterpenes (α-amyrin and ursolic acid), and the aerial parts contain phenolic acids (rosmarinic, caffeic, p-coumaric and chlorogenic acids) and

flavonoids (apigenin, kaempferol and quercetin derivatives) (Coisin *et al*., 2012; Lu & Foo, 2002; Wollenweber, 1974).
The aerial parts also contain essential oil, the main constituents being 1-octadecanol, nonanal, β-burbonene, linalool, bornyl acetate, β-elemene, β-caryophyllene, α-humulene, germacrene-D, borneol, germacrene-B and caryophyllene oxide (Kaya *et al*., 2003; Parvu, 2006; Velickovic *et al*., 2003).
In roots, several diterpenes were identified, e.g. tanshinone IIa, cryptotanshinone, tanshinone I, 1,2-dihydrotanshinone and isotanshinone II (Senol *et al*., 2017).

Pharmacological activities
Rosmarinic acid and several diterpenes isolated from the roots of *S. glutinosa* showed *in vitro* and *in silico* butyrylcholinesterase inhibitory activity (Senol *et al*., 2017).
The essential oil isolated from the aerial parts of *S. glutinosa* exhibited *in vitro* antimicrobial activity against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus* and *Aspergillus niger* (Velickovic *et al*., 2003).
The infusion from the aerial parts has antimicrobial, immunostimulant, anti-inflammatory, astringent, vermifuge and cicatrizing properties (Parvu, 2006; Tita *et al*., 2009).

Current uses
S. glutinosa is used internally to remove dizziness (root decoction), and for the treatment of cough and abdominal pain (infusion from the aerial parts); externally, it was used against headache and rheumatism (decoction from aerial parts) (Ardelean & Mohan, 2008; Parvu, 2006).

Precautions and adverse reactions
No available data.

Sambucus nigra L. (common elder, „socul negru"), Caprifoliaceae family

Syn. *Sambucus nigra f. alba* (Weston) Rehder, *f. aurea* (Sweet) Schwer., *f. lanciniata* (L.) Zabel, *f. pendula Dippel.* (Duke *et al*., 2002), *S. arborescens* Gilib., *S. medullina* Gilib., *S. vulgaris* Lam. (Stanescu *et al*., 2014; WHO, 2002).
***Other common names*:** Black Elder (Barnes *et al*., 2007; Gruenwald *et al*., 2000), Black-Berried Alder, Boor Tree, European Elder, Bountry, Ellanwood, Ellhorn (Gruenwald *et al*., 2000), Sambucus (Barnes *et al*., 2007).

Officinal products: According to the European Pharmacopoeia, European Medicines Agency (EMA) and World Health Organization (WHO) (EMA/HMPC/611512/2016, EMA/HMPC/611504/2016; Eur. Ph. 8.0, 2013; WHO, 2002), the officinal product is *Sambuci flos* represented by the dried flowers of *Sambucus nigra* L. Literature also mentions the use of fruits (*Sambuci fructus*) (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Parvu, 2006; Stanescu *et al*., 2014); traditionally, both bark (*Sambuci cortex*) and leaves (*Sambuci folium*) were used (Stanescu *et al*., 2014).

Botanical description

S. nigra is a shrub or a small tree. The root is branched. The stem is 4-10 m high, irregularly branched, with branches directly at the base, long and straight, gray bark with cracked rhytidoma. The crown is globular, quite thick. The vines are thick, greenish-gray or brown, with prominent lentils and spongy, and white-yellow marrow. The buds are opposite, large, ovoid-sharp. The leaves are imparipinnate-compound, with 5-7 elliptical or ovate-elliptical leaflets, acute, short petiolate, with irregular-sharp-serrate edges, on the lower face dispersed-hirsute along the veins, with an unpleasant odor. The flowers are actinomorphic, on type 5, small, white, grouped in large umbel-shaped or corymb-shaped tops, with 5 main branches, terminal, flat, large, strongly fragrant. The fruits are pseudo-drupes (berries), black, glossy, spherical, sweet-sour taste, with red juice, and with brown ovoid seeds (Ardelean & Mohan, 2008; Costica *et al*., 2019; Muntean *et al*., 2007; Parvu, 2006; Sarbu *et al.,* 2013; Stanescu *et al*., 2014; Stefan & Oprea, 2007). It blooms from May to July (Parvu, 2006; Stefan & Oprea, 2007) and the fruits ripen in August - September (Muntean *et al*., 2007).

Distribution and habitat: frequent, through edges and sparse forests, streams, bushes (Butura, 1979; Oroian, 2011; Sarbu *et al.,* 2013; Stefan & Oprea, 2007), in the undergrowth of hill and plain forests, in clearings or forest edges, near fences, from the plain to the lower part of the mountains (Muntean *et al*., 2007; Parvu, 2006). In Dobrogea, this species was reported in the Danube Delta area (Caraorman, C.A. Rosetti, Cardon, Letea) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: flowers in May-July, fruits in August-October (at full ripening) (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Oroian, 2011; Stanescu *et al*, 2004b); bark in spring (before the leaves emerge) or in autumn (Parvu, 2006).

Traditional uses

According to the European Medicine Agency - Committee on Herbal Medicinal Products, the dried flowers (as infusion, decoction, liquid extract and tincture) were used as diaphoretic in the treatment of common cold, against catarrhal conditions such as laryngitis, bronchitis, cough, whooping cough, beginning of pneumonia and other feverish conditions (EMA/HMPC/611504/2016). The World Health Organization mentions the following traditional uses of *S. nigra*: in the treatment of conjunctivitis, constipation, diabetes, diarrhoea, dry skin, headaches and rheumatism (WHO, 2002).

In Romanian folk medicine, the infusion from *S. nigra* flowers was used as emollient in the treatment of pharyngeal irritations (as gargle or mouth wash), against rheumatism, cough and respiratory diseases, and as compresses or local baths in the treatment of dermal and eye diseases. The leaves were used as infusion with depurative and antirheumatic action. The fruits were used as a diaphoretic, diuretic, laxative, expectorant and depurative agent. The bark decoction was used as laxative, emetic, diuretic, anti-inflammatory and anti-rheumatic agent (Butura, 1979; Stanescu *et al*., 2014).

The flowers were also used for their diuretic and diaphoretic effects, for the treatment of neuralgia, influenza, rhinitis, kidney diseases (Parvu, 2006; Stanescu *et al*, 2004b).

A traditional fermented beverage („socată") is prepared from the fresh flowers, mixed with water, lemon and sugar, and is consumed for its depurative properties (Grigorescu *et al*., 1986).

Chemical composition

The flowers contain flavonoids and phenolic acids, e.g. quercetin 3-O-rutinoside, quercetin 3-O-glucoside, kaempferol 3-O-glucoside, kaempferol 3-O-rutinoside, isorhamnetin 3-O-rutinoside, isorhamnetin 3-O-glucoside, neochlorogenic and chlorogenic acids (Młynarczyk *et al*., 2018; Sidor & Gramza-Michałowska, 2015; Stanescu *et al*., 2014). The flowers also contain 0.11% phytosterols, such as campesterol, β-sitosterol and stigmasterol, tannins, mucilage, pectine and minerals (EMA/HMPC/611504/2016; Stanescu *et al*., 2014).

The fruits are rich in bioactive compounds such as flavonoids (quercetin, kaempferol, isorhamnetin, quercetin 3-O-rutinoside, quercetin 3-O-glucoside, kaempferol 3-O-glucoside, kaempferol 3-O-rutinoside, isorhamnetin 3-O-rutinoside, isorhamnetin 3-O-glucoside), phenolic acids (neochlorogenic and chlorogenic acids), anthocyanins (cyanidin-3-glucoside, cyanidin-3-sambubioside, cyanidin 3-rutinoside, pelargonidin 3-glucoside, delfinidine-3-rutinoside) and vitamins (A, B, E, C) (Chevallier, 2016; Młynarczyk *et al*., 2018; Muntean *et al*., 2007; Olejnik *et al*., 2016; Parvu, 2006; Sidor & Gramza-Michałowska, 2015; Stanescu *et al*., 2014; Ulbricht *et al*., 2014).

The fruits and flowers also contain essential oils, the main constituents of the flower essential oil being hotrienol, rose oxides, nerol oxide, linalool oxides, a-terpineol and linalool (Młynarczyk *et al*., 2018; Salvador *et al*., 2017).

The bark contains triterpenoids such as α-amyrenone, α-amyrin, betulin, oleanolic acid and β-sitosterol (Lawrie *et al*., 1964; Ulbricht *et al*., 2014). The leaves also contain triterpenoids, e.g. ursolic and oleanolic acids, α-amyrin, β-amyrin (Inoue & Sato, 1975). The seeds contain oil rich in unsaturated fatty acids (linolenic, linoleic and oleic acids) (Młynarczyk *et al*., 2018; Petrut *et al*., 2017; Sidor & Gramza-Michałowska, 2015).

The European Pharmacopoeia requires for *Sambuci flos* a content of minimum 0.08% flavonoids, expressed as isoquercitroside (dried drug) (EMA/HMPC/611504/2016; Eur. Ph. 8.0, 2013).

Pharmacological activities

Antioxidant, anti-inflammatory, hypoglycemic, antimicrobial, immunomodulatory, antitumor, anti-obesity, laxative and diuretic activities, and also benefic effects on cardiovascular system were reported for *S. nigra* (Anonymous, 2005; Chevallier, 2016; Młynarczyk *et al*., 2018; Sidor & Gramza-Michałowska, 2015; Ulbricht *et al*., 2014).

The cytoprotective effect of elderberry extracts against oxidative damage was demonstrated in *in vitro* models (Olejnik *et al*., 2016; Petrut *et al*., 2017).

S. nigra fruit juice exhibits benefic effects in the treatment of flu, both directly by blocking the viral glycoproteins and indirectly by increasing the expression of inflammatory cytokines IL-6, IL-8, and TNF (Torabian *et al*., 2019).

Clinical trials showed that the supplementation with an elderberry extract significantly reduced the total duration and severity of upper respiratory symptoms in flu and common colds (Hawkins *et al*., 2019).

The elderberry extracts have immunomodulatory potential via cytokine production, both in healthy individuals and in those with viral infections or other diseases characterized by immunosuppression (Anonymous, 2005).
The secretolytic action has been demonstrated for preparations obtained from *S. nigra* flowers, and includes a diaphoretic and stimulating effect on bronchial secretion (Barnes *et al*., 2007; Gruenwald *et al*., 2000; Stanescu *et al*., 2014).
An ethanol extract from *Sambuci flos* had moderate anti-inflammatory activity in rats (WHO, 2002).
A lectin isolated from the bark of *S. nigra* was found to be a lactosespecific haemagglutinin. *In vitro*, phytohaemagglutinin stimulated the production of an interferon-like substance in human leukocytes (Barnes *et al*., 2007).

Current uses
According to the European Medicine Agency - Committee on Herbal Medicinal Products, *S. nigra* is used in several pharmaceutical forms (comminuted herbal substance as herbal tea for oral use, herbal preparations in liquid dosage forms for oral use – liquid extract and tincture) for the relief of early symptoms of common cold (EMA/HMPC/611504/2016; EMA/HMPC/611512/2016).
According to the World Health Organization, *S. nigra* is used as a diaphoretic for the treatment of fever and chills, as an expectorant for the treatment of mild inflammation of the upper respiratory tract, and also for the symptomatic treatment of the common cold (WHO, 2002).
The German Commission E approved the use of. *S. nigra* in cough and bronchitis, fevers and colds (Gruenwald *et al*., 2000).
The flowers are included in herbal medicines recommended for the treatment of rhino-sinusitis. Also, several preparations with fruit and flower extracts are available on the market, recommended for maintaining the health of the respiratory tract and the normal functioning of the immune system.
The infusions are administered in flu as diaphoretic and in colds accompanied by fever (Gruenwald *et al*., 2000; Stanescu *et al*., 2014).

Precautions and adverse reactions
It is not recommended in case of hypersensitivity to the active substance. The use in children under 12 years of age is also not recommended. In the absence of sufficient data, the use during pregnancy and lactation is not recommended (EMA/HMPC/611504/2016; EMA/HMPC/611512/2016).
The roots, stems, leaves, flowers and unripe berries, are stated to contain a poisonous alkaloid and a cyanogenic glycoside causing nausea, vomiting and diarrhoea. The flowers and ripe fruit are stated to be edible without harm (Barnes *et al*., 2007; Duke *et al*., 2002).

Other warnings
Not to be confused with other *Sambucus* species, such as *S. ebulus* and *S. racemosa* (Gruenwald *et al*., 2000; Muntean *et al*., 2007).

Scirpoides holoschoenus (L.) Soják (roundhead bulrush, „dicop"), Cyperaceae family

Syn. *Holoschoenus vulgaris* Link, *Scirpus holoschoenus* L. (Doroftei *et al*., 2011; Sarbu *et al.,* 2013).

***Other common names*:** salmiac (Gille *et al*., 2015a).

Officinal products: *S. holoschoenus* is not an officinal drug.

Botanical description

S. holoschoenus is a perennial species, with a height of 30-90 cm, forming tussocks. The rhizome is short, woody, emitting tillers. The leaves are reduced to sheaths. The stem ends with several spikelets; it has at the distal end one or several dense, spherical capitula (about 1 cm in diameter). One capitulum is sessile, and the other ones are pedunculate (Gille *et al*., 2015a; Popescu *et al*., 2016; Sarbu *et al.,* 2013). It blooms from July to August (Sarbu *et al.,* 2013).

Distribution and habitat: sporadic, in plain and hilly areas, on continental and maritime sands, on dunes (Sarbu *et al.,* 2013; Popescu *et al*., 2016). In Dobrogea, this species was reported in the Danube Delta area (Letea, Histria, Vadu, Caraorman, Sf. Gheorghe, Tulcea) (Ciocarlan, 2011; Doroftei *et al*., 2011; Popescu *et al*., 2011).

Traditional uses

Its rhizome has been used as a traditional medicine to eliminate kidney stones and for liver protection, and the roots were used to treat hemorrhoids (Oussaid *et al*., 2017). The leaves were used in toothache, colds and also as diuretic (Benítez *et al*., 2012).

The species is used in the ethnomedicine of Dobrogea region (Romania) by the locals as decoction (boiled rhizomes) for its hepatoprotective activity (Popescu *et al*., 2011; Popescu *et al*., 2016). The fishermen and sailors in the Danube Delta and the Black Sea coast use *S. holoschoenus* as decoction, for its energizing, hepatoprotective and anti-diarrhoeal effects (Gille *et al*., 2015c).

Chemical composition

Phytochemical studies on *S. holoschoenus* rhizomes revealed the presence of wide range of phenolic compounds such as 3,5,40-trimethoxystilbene, 2-prenyl-3,5,40-trimethoxystilbene, 2-prenyl-3-hydroxy-5,40-dimethoxystilbene, 2-prenyl-3,40-dihydroxy- 5-methoxystilbene, vanillin, E-resveratrol, Z-resveratrol, chlorogenic acid, caffeic acid, cinnamic acid, ferulic acid, gallic acid, p-coumaric acid, luteolin, β-sitosterol and stigmasterol (Abdel-Mogib *et al*., 2001; Arraki, 2014; Gille *et al.,* 2018; Popescu *et al*., 2011; Popescu *et al*., 2016; Oussaid *et al*., 2017; Oussaid *et al*., 2018; Tebrencu *et al*., 2018a; Tebrencu *et al*., 2018b).

Chlorogenic and ferulic acids, luteolin and β-sitosterol were also identified in the aerial parts (Tebrencu *et al*., 2018a).

Pharmacological activities

Different type of rhizome extracts showed antioxidant capacity and antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*, possibly due to its content in phenolic compounds, especially tannins (Gille *et al*., 2015b; Popescu *et al*., 2016; Oussaid *et al*., 2017).

The ethyl acetate fraction of *S. holoschoenus* underground parts exhibited antibacterial activity against *Pseudomonas aeruginosa* (Oussaid *et al*., 2018).

Current uses
The decoction of *S. holoschoenus* is a recognized remedy in the Danube Delta area, but it is not used in the modern therapy (Tebrencu *et al*., 2018a).

Precautions and adverse reactions
No available data.

Other warnings
Morphologically, it could be easily confused with *Juncus* species that are devoided of the characteristic solid three-angled stem of *Scirpus*, having instead a hollow cylindrical stem (Abdel-Mogib *et al*., 2001).

Solidago virgaurea L. (European goldenrod, „splinuță"), Asteraceae family

Syn. *Amphiraphis leiocarpa* Benth., *Amphiraphis pubescens* DC., *Dectis decurrens* (Lour.) Rafin., *Doria virgaurea* L. (Scop.) (EMEA/HMPC/285759/2007).
***Other common names*:** Aaron's Rod, Woundwort, Goldenrod (Gruenwald *et al*., 2000).

Officinal products: According to the European Pharmacopoeia and European Medicine Agency (EMA) (EMEA/HMPC/285758/2007; EMEA/HMPC/285759/2007; Eur. Ph. 8.0, 2013) the officinal product is *Solidaginis virgaureae herba* represented by whole or fragmented, dried, flowering aerial parts of *Solidago virgaurea* L. Literature also mentions *Virgaureae herba* (Ardelean & Mohan, 2008; Hancianu *et al*., 2008; Oniga, 2007; Stanescu *et al*., 2004b; Stanescu *et al*., 2014) and *Solidaginis summitates* (flowering tips) (Grigorescu *et al*., 1986; Parvu, 2006).

Botanical description
S. virgaurea is an herbaceous perennial plant. The stem is erect, simple or branched, round, with marrow inside, longitudinally striated, sometimes slightly pubescent at the top, purple, purple or brown at the bottom, up to 1 m high. The leaves are serrated, glabrous on the upper side and pubescent on the lower side. The basal ones are oblanceolate or obovate, with a winged petiole. The stem ones have shorter and shorter petioles, are linearly lanceolate or elliptical and acute. The inflorescences are anthodia grouped in a simple or multilateral paniculated raceme, yellow in color. The involucral bracts are imbricate and arranged in numerous rows. The ray florets are narrow, ligulate and female. The disc florets are tubular, 5- tipped and hermaphrodite. Each anthodium has 6-12 ligulate flowers and 10-30 tubular flowers, all yellow. The receptacle is flat and glabrous. The fruits are small achenes with a pappus (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013; Stanescu *et al*., 2014). It blooms from July to September (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013).
Distribution and habitat: frequent, in bushes, glades, meadows, forest cuts, rocky coasts, from the plain region to the lower alpine floor (Ardelean & Mohan, 2008; Butura, 1979; Grigorescu *et al*., 1986; Oniga, 2007; Oroian, 2011; Parvu, 2006; Sarbu

et al., 2013). In Dobrogea, this species was reported in Macin Mountains (Suluc Mountain, Greci) (Andrei & Cristurean, 2006).
Harvesting period: from July to September, during the flowering stage (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Oniga, 2007; Oroian, 2011; Parvu, 2006).

Traditional uses
Solidago has been used for treatment of different diseases in Europe since medieval times (EMEA/HMPC/285759/2007). It was used, both internally and externally, as a diuretic (by people suffering from kidney stones), and also in chronic nephritis, arthritis, menorrhagia, chronic dermatitis (eczema), wounds, inflammation of the mouth and pharynx (Stanescu *et al*., 2014). It was also used internally for rheumatism, gout, diabetes, hemorrhoids, prostatic hypertrophy, nervous bronchial asthma, internal bleeding, pulmonary tuberculosis and enlargement of the liver (Gruenwald *et al*., 2000).
In Romanian folk medicine, the flowering tips were used against kidney conditions and edema (Butura, 1979; Parvu, 2006).

Chemical composition
The aerial parts contain flavonoids (kaempferol-3-O-rhamnogalactoside, rutin, quercitrin, astragalin, kaempferol, kaempferol-3-O-rutinoside, kaempferol-3-O-robinobioside, isorhanmetin-3-O-rutinoside, quercetin, hyperoside), phenolic acids (e.g. chlorogenic, caffeic, p-coumaric, gallic, neochlorogenic, vanillic and ferulic acids) and anthocyanidins (EMEA/HMPC/285759/2007; Gruenwald *et al*., 2000; Hancianu *et al*., 2008; Oroian, 2011; Paun *et al*., 2016b; Pietta & Gardana, 1991; Stanescu *et al*., 2004b).
The aerial parts also contain clerodane diterpenes (solidagoic acids C-I, cleroda-3,13(14)-dien-16,15:18,19-diolide, cleroda-3,13(14)-dien-15,16:18,19-diolide) (Starks *et al*., 2010). Clerodane diterpenes (elongatolide C and E, solidagolactone II, III, V and VII) were also identified in roots (Goswami *et al*., 1984).
The aerial parts also contain triterpene saponins (0.2-0.3%), acetylenes, tannins, polysaccharides, carotenoids, phenol glucosides (leicarposide, virgaureoside A) and essential oil (0.4-0.5%), the main constituents of the essential oil being α-pinene, β-pinene, limonene, δ-elemene, γ-cadinene, β-phellandrene, myrcene (Ardelean & Mohan, 2008; Chevallier, 2016; EMEA/HMPC/285759/2007; Gruenwald *et al*., 2000; Stanescu *et al*., 2014).
The European Pharmacopoeia requires for *Solidaginis virgaureae herba* a content of minimum 0.5% and maximum 1.5% flavonoids, expressed as hyperoside (dried drug) (Eur. Ph. 8.0, 2013).

Pharmacological activities
In vitro and *in vivo* (animal model) studies highlighted for *S. virgaurea* extracts, fractions and isolated compounds, diuretic, anti-inflammatory, antioxidant, analgesic, spasmolytic, antibacterial, antifungal, anticancer and immunomodulatory activities (EMEA/HMPC/285759/2007; Hancianu *et al*., 2008; Oniga, 2007; Stanescu *et al*., 2004b; Stanescu *et al*., 2014).
The diuretic, spasmolytic, anti-inflammatory and analgesic activities and the benefic effects in urinary tract diseases, dysuria, pollakisuria and tenesmus were also observed in clinical trials, but not confirmed (EMEA/HMPC/285759/2007).

Several clerodane diterpenes isolated from the aerial parts exhibited a moderate *in vitro* antibacterial activity against *Staphylococcus aureus* (Starks *et al*., 2010).
The water decoction of *S. virgaurea* stems/leaves showed antiviral activity against Herpes simplex type 2, if added in the early phase of the infection, possibly by interfering with the viral DNA synthesis (Mendes *et al*., 2016).
The ethanol extract from *S. virgaurea* aerial parts, tested *in vitro*, exhibited high antioxidant and tyrosinase inhibitory activities, and moderate acetylcholinesterase inhibitory effect, thus having potential use in preventing neurodegenerative diseases (Paun *et al*., 2016b).
The drug has a diuretic effect due to the leiocarposide and the phenol glycosides (Gruenwald *et al*., 2000). The flavonoids decrease capillary permeability, a favorable effect on venous circulation (Oroian, 2011).

Current uses
According to the European Medicine Agency - Committee on Herbal Medicinal Products, *S. virgaurea* is used as a traditional herbal medicine (action not confirmed by clinical trials), in the form of infusion, liquid extract and tincture, to increase the amount of urine - as adjuvant in treatment of minor urinary complaints (EMEA/HMPC/285758/2007; EMEA/HMPC/285759/2007).
The German Commission E approved its use in infections of the urinary tract and kidney and bladder stones (Gruenwald *et al*., 2000).
The plant product is also used as infusion, decoction and syrup (Parvu, 2006).
An herbal medicine (fixed combination of extracts from *Populus tremula*, *Fraxinus excelsior* and *Solidago virgaurea*) is used as an antirheumatic remedy, due to its anti-inflammatory, anti-edematous, antioxidant and analgesic properties (Gundermann & Müller, 2007; Stanescu *et al*., 2014).
S. virgaurea extracts are part of anti-edematous drugs administered in cardiac and renal diseases. The plant product or its extracts are part of many drugs used especially in urological conditions (Chevallier, 2016; Duke *et al*., 2002; Hancianu *et al*., 2008; Oniga, 2007; Stanescu *et al*., 2004b; Stanescu *et al*., 2014).
Internally, it is also used in the treatment of diarrhoea and enteritis, due to the astringent effect of the tannins (Chevallier, 2016; Duke *et al*., 2002; Oroian, 2011).
Externally, it is used as an astringent, to reduce inflammation in the throat and mouth, and to promote wound healing (Ardelean & Mohan, 2008; Hancianu *et al*., 2008; Oroian, 2011; Stanescu *et al*., 2014; Duke *et al*., 2002).

Precautions and adverse reactions
The use is not recommended in case of hypersensitivity to the active substance or to plants of the Asteraceae (Compositae) family. No relevant data are available on toxicology of *Solidago virgaurea*, except of acute toxicity of leiocarposide. Its use is not recommended for children below 12 years of age. Due to the lack of sufficient data, the use during pregnancy and lactation cannot be recommended. Hypersensitivity reactions or gastrointestinal disorders may occur (frequency not known) (EMEA/HMPC/285759/2007; EMEA/HMPC/285758/2007).
Irrigation therapy is contraindicated in cases of edema resulting from reduced cardiac and/or kidney function (Duke *et al*., 2002; Gruenwald *et al*., 2000).

Because the product contains sesquiterpene lactones, there is a possibility of developing a contact allergy (Stanescu *et al*., 2014). Allergic rhinitis with congestion may also occur (Chevallier, 2016).

Other warnings

Not to be confused with other *Solidago* species, such as *S. canadensis* and *S. gigantea* (Hancianu *et al*., 2008; Oniga, 2007; Stanescu *et al*., 2004b), and with *Senecio* species (Gruenwald *et al*., 2000).

There are no specific data on pharmacokinetics of *S. virgaurea*. However, some interactions are possible due to the influence on CYP3A4 genes expression (EMEA/HMPC/285759/2007).

Stachys officinalis (L.) Trevis. (wood betony, „vindecea"), Lamiaceae family

Syn. *Betonica officinalis* L. (Andrei & Cristurean, 2006; Chevallier, 2016; Duke *et al*., 2002; Istudor, 2005; Sarbu *et al.,* 2013), *Stachys betonica* Benth. (Duke *et al*., 2002).

***Other common names*:** Betony, Bishopswort (Gruenwald *et al*., 2000).

Officinal products: aerial parts (*Stachysi herba*) (Ardelean & Mohan, 2008; Chevallier, 2016; Gruenwald *et al*., 2000; Parvu, 2006), leaves (*Stachysi folium*) and roots (*Stachysi radix*) (Oroian, 2011).

Botanical description

S. officinalis is an herbaceous perennial plant, with a height of 30-100 cm. The rhizome is short, from which adventitious roots start. The aerial stem is thin, erect, straight, unbranched, quadrangular, bristly-haired and usually has only 2 distal pairs of leaves. The basal leaves are rosette-like. The leaves are elongate-ovate with a cordate base and crenate. The lower ones are larger and long-petioled, and the upper ones are smaller and shorter. The flowers are purple, arranged spiciformly, in multicolored, compact vertices. The calyx, with 5 even, triangular tips, has long ciliate hairs and is shorter than the corolla tube. The corolla is curled downwards, and the white tube has no ring of hair. The fruit is an elongated, ovoid, smooth, brown nucule (Ardelean & Mohan, 2008; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Istudor, 2005; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013). It blooms from June to August (Andrei & Cristurean, 2006; Istudor, 2005; Parvu, 2006; Sarbu *et al.,* 2013).

Distribution and habitat: in meadows, bushes, forest edges, roadsides and orchards, from the plain to the spruce floor (Andrei & Cristurean, 2006; Ardelean & Mohan, 2008; Butura, 1979; Sarbu *et al.,* 2013). In Dobrogea, this species was reported in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: during flowering stage (Chevallier, 2016; Gruenwald *et al*., 2000; Istudor, 2005; Parvu, 2006).

Traditional uses

S. officinalis was used traditionally for cough, bronchitis asthma, inflammatory diseases, sore throat, liver disorders, headache, and also as sedative, anti-diarrhoeal, carminative agent (Chevallier, 2016; Gruenwald *et al*., 2000; Sliumpaite *et al*., 2013).

In Romanian folk medicine, the leaves were used in rhinitis and the decoction from aerial parts was used as washes against headache (Butura, 1979; Parvu, 2006). The infusion from dried flower stalks was used against hemoptysis and chest pains (Butura, 1979). It was also used as a tonic, antipyretic and vulnerary, due to its cicatrizing properties (Grigorescu *et al*., 1986).

Chemical composition

The aerial parts contain phenolic compounds (chlorogenic, caffeic, rosmarinic and ellagic acids, quercetin, luteolin, apigenin, isoquercitrin, ursolic acid, umbelliferone), anthocyanins and anthocyanidins (peonidin 3-O-glucoside, malvidin, cyanidin, genistin) (Paun *et al*., 2016a; Paun *et al*., 2018).

Chlorogenic acid, p-coumaric acid derivatives, luteolin glucoside, luteolin-7-O-glucuronide, apigenin derivatives and phenylethanoid glycosides were identified in leaves (Sliumpaite *et al*., 2013).

The leaves and flowers contain low amounts of essential oil, the main constituents of the leaf essential oil being γ-muurolene, β-caryophyllene, benzaldehyde, phytol, allo-aromadendrene, δ-cadinol, β-bourbonene, while the main constituents of the flower oil were γ-muurolene, benzaldehyde, phytol, pimara-7,15-dien-3-one and germacrene (Dimitrova-Dyulgerova *et al*., 2015).

S. officinalis also contains betaine, iridoid glycosides, diterpene lactone, alkaloids and tannins (Ardelean & Mohan, 2008; Butura, 1979; Chevallier, 2016; Grigorescu *et al*., 1986; Gruenwald *et al*., 2000; Istudor, 2005; Parvu, 2006).

Pharmacological activities

S. officinalis polyphenolic-rich extract (from leaves and stems) exhibited *in vitro* antioxidant potential, and high *in vitro* and *in vivo* anti-inflammatory activity (Paun *et al*., 2018). The polyphenol-rich extract from the aerial parts also exhibited anti-diabetic potential, through the inhibition of α-amylase and α-glucosidase (Paun *et al*., 2016a).

The leaf extract also exhibited antioxidant activity, the most potent constituents being phenylethanoid glycosides and chlorogenic acid (Sliumpaite *et al*., 2013).

Leaf and flower extract exhibited *in vitro* antioxidant, moderate antimicrobial (against *Bacillus subtilis* and *Pseudomonas aeruginosa*) and moderate anti-inflammatory activities (Paun *et al*., 2017).

The active principles are thought to have tonic, astringent, anti-diarrhoeal, diuretic, antiseptic, antipyretic, cholagogue and vulnerary properties (Parvu, 2006).

Current uses

S. officinalis is used as fresh and dry herb, liquid extract and infusion (Duke *et al*., 2002; Gruenwald *et al*., 2000).

It is used internally for the treatment of gout, gallstones, kidney stones, pulmonary catarrh, asthma, diarrhoea, and to stimulate digestion (infusion of comminuted dried plant). Externally, it is used for the treatment of wounds and varicose ulcers (decoction from comminuted plant, as local washes) (Ardelean & Mohan, 2008; Oroian, 2011; Parvu, 2006). It is also used in dermal conditions, neuralgia, anxiety and neurotonic states (Duke *et al*., 2002; Istudor, 2005).

Precautions and adverse reactions
No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages (Gruenwald *et al*., 2000). The overdose may irritate the stomach (Duke *et al*., 2002). The use during pregnancy is not recommended (Chevallier, 2016).

Other warnings
Not to be confused with *Stachys alpina* (Gruenwald *et al*., 2000; Istudor, 2005).

Symphytum officinale L. (comfrey, „tătăneasă"), Boraginaceae family

Syn. *Symphytum consolida* Gueldenst. ex Ledeb. (Aprotosoaie & Stanescu, 2010; Istudor, 2005; Stanescu *et al*., 2014).
***Other common names*:** Ass Ear, Black Root, Boneset, Bruisewort, Consound, Gum Plant, Healing Herb, Knitback, Salsify, Slippery Root, Consolida, Boneset (Gruenwald *et al*., 2000), Knitbone (Chevallier, 2016; Gruenwald *et al*., 2000).
Officinal products: According to the European Medicine Agency (EMA), the officinal product is *Symphyti radix* represented by roots of *Symphytum officinale* L. (EMA/HMPC/572846/2009; EMA/HMPC/572844/2009). Literature also mentions the use of aerial parts (*Symphyti herba*) (Aprotosoaie & Stanescu, 2010; Stanescu *et al*., 2014), roots and leaves (*Symphyti radix et folium*) (Ardelean & Mohan, 2008; Gruenwald *et al*., 2000; Oroian, 2011), roots and flowers (*Symphyti radix et flores*) (Istudor, 2005). Literature also refers to the name *Consolidae radix* (Aprotosoaie & Stanescu, 2010; Butura, 1979; Hancianu *et al*., 2008; Muntean *et al*., 2007; Stanescu *et al*., 2014).

Botanical description
S. officinale is a perennial herbaceous plant. The rhizome is short and thick, branched, black, from which fleshy fusiform roots start. The roots are large (up to 30 cm long and 1-2.5 cm thick), branched, and black on the outside with a creamy white interior containing slimy mucilage. The aerial stem is 10-120 cm high, erect, in the upper part branched, winged-edged and covered with bristly hairs that cause itching when in contact with the skin. The leaves are alternate, decurrent, the lower ones are elliptical or ovate-lanceolate, acuminate, with winged petiole, canaliculate, the middle and upper ones are narrow-lanceolate, narrowed in a winged petiole, hairy, rough, with a prominent median rib. The flowers are mauve to violet or red-purplish arranged in 5-10 scorpioid, pedicellate cymes. The calyx is fused and has 5 tips. The corolla is also fused and is cylindrical-campanulate with a pentangular tube and 5-tipped border. The fruit consists of smooth, glossy nucules, grouped 4 in the persistent calyx (Aprotosoaie & Stanescu, 2010; Ardelean & Mohan, 2008; EMA/HMPC/572844/2009; Gruenwald *et al*., 2000; Hancianu *et al*., 2008; Istudor, 2005; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013; Stanescu *et al*., 2014; Stefan & Oprea, 2007). It blooms from May to August (Ardelean & Mohan, 2008; Istudor, 2005; Stanescu *et al*., 2014; Sarbu *et al.,* 2013; Stefan & Oprea, 2007).

Distribution and habitat: frequent through wet meadows, stream edge, wet grasslands, standing waters, meadows, ditches, from the plain to the lower mountain area (Aprotosoaie & Stanescu, 2010; Butura, 1979; Hancianu *et al*., 2008; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013; Stanescu *et al*., 2014; Stefan & Oprea, 2007). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011) and sporadically in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: roots, in autumn, when the allantoin levels are higher (Aprotosoaie & Stanescu, 2010; Chevallier, 2016; Istudor, 2005); leaves, during flowering stage (Parvu, 2006).

Traditional uses

According to the European Medicine Agency - Committee on Herbal Medicinal Products, the *S. officinalis* roots were traditionally used externally as a poultice or compress for blunt injuries, fractures, swollen bruises, boils, carbuncles, varicose ulcers and burns, and internally as tea or expressed juice, to soothe ulcers, hernias, colitis, and to stop internal bleeding (EMA/HMPC/572844/2009).

Traditionally, the comfrey root was used internally for gastritis, gastrointestinal ulcers, pleuritis, and as an anti-diarrhoeal agent; externally as a mouth wash and gargle for gum disease, pharyngitis, and strep throat, to promote the healing of bruises, sprains, fractures, broken bones, against insect bites, scars, skin inflammation, acne, and mastitis (Chevallier, 2016; Gruenwald *et al*., 2000). Traditional remedies include decoction from dried root/rhizome, liquid extract, ointment, infusion from dried leaves (Gruenwald *et al*., 2000).

In Romanian folk medicine, comfrey roots are used in the treatment of hyperacid ulcers and gastritis, respiratory diseases (cough of various etiologies, bronchitis) and rheumatism (Aprotosoaie & Stanescu, 2010; Hancianu *et al*., 2008; Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

It was also used in oral disorders (gingivitis, pharyngitis, periodontitis, toothache), laryngitis, tonsillitis, diabetes, diarrhoea, stroke, headache and rheumatism (Butura, 1979; Istudor, 2005; Stanescu *et al*., 2014). Externally, it was used in fractures and sprains (as poultices), and in postpartum pain (Parvu, 2006; Stanescu *et al*., 2014). It was also used in treating wounds, due to its hemostatic and cicatrizing effect (Muntean *et al*., 2007).

The roots were used as infusion, decoction (in water or milk), poultices, compresses, local frictions, tincture and soaked in honey (Butura, 1979; Parvu, 2006).

Chemical composition

S. officinale roots contain allantoin (0.6–4.7%), mucilage polysaccharides (29%), phenolic acids (rosmarinic, chlorogenic, caffeic, p-coumaric, α-hydroxy caffeic and hydroxybenzoic acids, salvianolic acid I, salvianolic acid A, B, C isomers), glycopeptides and aminoacids, proteins, triterpene saponins, tannins, carotenoids, coniferin, starch, gumiresins, phytosterols (β-sitosterol, sitosterol, stigmasterol), vitamins and mineral substances (Chevallier, 2016; EMA/HMPC/572844/2; Hancianu *et al*., 2008; Muntean *et al*., 2007; Salehi *et al*., 2019b; Stanescu *et al*., 2004b; Trifan *et al*., 2018; Vostinaru *et al*., 2018). Allantoin was also identified in seeds (Salehi *et al*., 2019b).

In herb, rosmarinic, chlorogenic, caffeic, p-coumaric and hydroxybenzoic acids were identified (Salehi *et al*., 2019b).

Pyrrolizidine alkaloids, such as intermedine and lycopsamine, are present in roots, stems and leaves. In addition, several other pyrrolizidine alkaloids were identified in roots, namely: echimidine, echimidine *N*-oxide, symviridine, symlandine, symphytine, symphytine *N*-oxide, intermedine *N*-oxide, acetyl intermedine, acetyl lycopsamine, lasiocarpine, uplandicine and uplandicine *N*-oxide (Aprotosoaie & Stanescu, 2010; Barnes *et al*., 2007; Chevallier, 2016; EMA/HMPC/572844/2; Gruenwald *et al*., 2000; Istudor, 2005; Oroian, 2011; Salehi *et al*., 2019b; Stanescu *et al*., 2014; Trifan *et al*., 2018).

Pharmacological activities

S. officinale roots and leaves exhibited antioxidant, antibacterial (against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli, Proteus vulgaris*), antifungal, anti-inflammatory, antinociceptive, hepatoprotective and wound healing activities, and benefic effects in the healing of fractured bones (Barnes *et al*., 2007; Chevallier, 2016; Duke *et al*., 2002; Gruenwald *et al*., 2000; Salehi *et al*., 2019b; Stanescu *et al*., 2004b; Trifan *et al*., 2018).

Randomized controlled trials have demonstrated the efficacy and safety of *S. officinale* topical preparations in the treatment of pain, inflammation and swelling of muscles and joints in degenerative arthritis, acute myalgia in the back, sprains, contusions and strains, also in children aged 3 or 4 and over (Staiger, 2012).

The topical use of root ointment and cream showed benefic effects in relieving pain and stiffness, and in improving physical functioning in patients with primary osteoarthritis of the knee (Masoudi & Saiedi, 2017a; Smith & Jacobson, 2011).

The oral administration of *S. officinale* extract (standardized in rosmarinic acid) showed anti-inflammatory (reducing significantly and dose-dependently the edema formation, superior to diclofenac) and analgesic effects (antinociceptive action, lower to diclofenac), that could be related to the ability of polyphenols to inhibit the synthesis and release of some pro-inflammatory mediators and cytokines, and also to the content in allantoin (Vostinaru *et al*., 2018).

The ethanol extract from comfrey roots exhibited a strong *in vitro* (non-cellular models) antioxidant potential (Trifan *et al*., 2018).

Allantoin stimulates the process of granulation and tissue repair, and by promoting the formation of callus, it stimulates the healing of fractured bones (Aprotosoaie & Stanescu, 2010; Hancianu *et al*., 2008; Istudor, 2005; Stanescu *et al*., 2014). Allantoin also exhibited anti-inflammatory and antitumor potential (Aprotosoaie & Stanescu, 2010; Hancianu *et al*., 2008; Muntean *et al*., 2007; Parvu, 2006; Stanescu *et al*., 2014).

Current uses

According to the European Medicine Agency - Committee on Herbal Medicinal Products, the pharmaceutical forms are represented by herbal preparations in semi-solid dosage forms for cutaneous use for the symptomatic relief of minor sprains and bruises (EMA/HMPC/572846/2009; EMA/HMPC/572844/2009).

The medicinal products marketed in the European Union include different liquid ethanol extracts from root, used as liquid, cream, ointment and poultice with topical

application in contusion, strain, sprain, bruises, joint and muscle pain, rheumatic pains, fractures, swellings and hematoma, phlebitis and local dermatitis, local skin inflammation (EMA/HMPC/572844/2009).

The German Commission E approved only the external use of comfrey roots (crushed root, extracts, the pressed juice of the fresh plant for semi-solid preparations and poultices) in case of bruising, pulled muscles and ligaments, sprains and blunt injuries (EMA/HMPC/572844/2009; Gruenwald *et al*., 2000).

On the pharmaceutical market there are a multitude of monocomponent or mixed preparations of comfrey extracts, most being in the form of creams, gels or ointments recommended against back pain, osteoarthritis of gonarthrosis, joint and muscle conditions, sprains and muscle fever (Stanescu *et al*., 2014).

According to a survey conducted in the UK, 75% of the interviewed herbalists (179 respondents out of 239) prescribed comfrey products for tendon, ligament or muscle problems, fractures, wounds, and perceived it to be most effective for fractures, tendon, ligament or muscle problems, post-surgery and wounds (Frost *et al*., 2014).

Externally, it is also used in vascular disorders (thrombophlebitis, phlebitis, hematomas, varicose ulcers), stomatitis, dental abscesses, hemorrhoids, varicose veins, psoriasis, as poultices, gargles, mouth washes or creams (Aprotosoaie & Stanescu, 2010; Ardelean & Mohan, 2008; Duke *et al*., 2002; Hancianu *et al*., 2008; Istudor, 2005; Parvu, 2006; Stanescu *et al*., 2014).

Extracts containing allantoin are part of cosmetics with a regenerative dermal effect (Hancianu *et al*., 2008; Muntean *et al*., 2007; Stanescu *et al*., 2014).

Precautions and adverse reactions

Not to be used in case of hypersensitivity to the active substance(s), not to be applied to broken or irritated skin, avoid contact with the eyes or mucous membranes. Due to the lack of sufficient data, the use during pregnancy and lactation is not recommended. The use in children and adolescents under 18 years of age has not been established (EMA/HMPC/572846/2009; Gruenwald *et al*., 2000; Istudor, 2005).

Animal studies suggest that pyrrolizidine alkaloids are hepatotoxic after oral administration (Barnes *et al*., 2007; Chevallier, 2016; EMA/HMPC/572846/2009; Oroian, 2011). The highest concentration of pyrrolizidine alkaloids is in the root, which should not be used internally, but the aerial parts of the plant are considered safe (Chevallier, 2016).

Pyrrolizidine alkaloids, present in higher amounts in *S. officinalis*, have mutagenic and teratogenic potential, thus the internal use of comfrey root extract is restricted in several countries, and the daily alkaloid quantity and the duration of treatment may be limited even in case of topical application. However, the penetration rate of lycopsamine (a pyrrolizidine alkaloid) through human epidermis was found to be low (Jedlinszki *et al*., 2017). Skin application is considered safe (Chevallier, 2016).

A study on 712 children confirmed an excellent benefit-to-risk ratio for the application of comfrey herb cream in the treatment of blunt traumas and sports injuries in children with intact and broken skin (Kucera *et al*., 2018).

In order to avoid the adverse reactions of pyrrolizidine alkaloids, some commercially available products include root extracts from which these compounds were removed

and others use the cultivar *Symphytum x uplandicum* var. *Harras* which does not produce these compounds (Stanescu *et al*., 2014).

Other warnings

According to the Complete German Commission E Monographs, the daily dose should not exceed more than 100 µg pyrrolizidine alkaloids with 1,2 unsaturated necine structure, including its *N*-oxides. The duration of treatment should not be longer than 4-6 weeks per year (Duke *et al*., 2002; EMA/HMPC/572844/2009).

Thymus glabrescens Willd. (thyme, „cimbrișor"), Lamiaceae family

Syn. *Thymus herbaceus* Klokov pro parte, *Thymus serpyllum* L. ssp. *serpyllum* var. *marschallianus s*ensu Boiss. pro parte (Doroftei *et al*., 2011).

Officinal products: According to the European Pharmacopoeia and the European Medicine Agency (EMA) (EMA/HMPC/342332/2013; EMA/HMPC/342334/2013; Eur. Ph. 8.0, 2013) the officinal product is the whole leaves and flowers separated from the previously dried stems of *Thymus vulgaris* L. or *Thymus zygis* L. or a mixture of both species. The European Pharmacopoeia also mentions the officinal product *Serpylli herba* (wild thyme) represented by the whole or cut, dried, flowering aerial parts of *Thymus serpyllum* L.s.l. (Eur. Ph. 8.0, 2013).

In the spontaneous flora of Romania, beside *Thymus vulgaris*, there are about 15 other species of *Thymus*, valuable as medicinal plants, such as *Thymus panonicus* All., *Thymus glabrescens* Willd., etc. (Stefan & Oprea, 2007). Literature also mentions the collective drug represented by the flowering aerial parts of the species *Thymus pulegioides*, *Thymus panonicus*, *Thymus austriacus*, *Thymus dacicus*, *Thymus marchalianus, Thymus glabrescens*, *Thymus austriacus,* from the spontaneous flora (Muntean *et al*., 2007; Stanescu *et al*., 2004b; Stanescu *et al*., 2014).

Botanical description

T. glabrescens is a perennial subshrub, 5-15 cm high. The stems are quadrangular, lignified at the base, pseudorepent, in the form of stolons, usually radiant, ending in inflorescences. The leaves are opposite, oval or elongated-elliptical, small, rigid, glabrous on both sides, with secretory trichomes. The inflorescences are contracted cymes, reunited in axillary whorls, globular or elongated, pink-purple in color. The calyx is obviously bilobed, with the upper lobe 3-toothed and the lower one bifid. The fruits are ellipsoidal tetra-achene, very small. The smell is characteristic (produces essential oil) and the taste is aromatic (Ardelean & Mohan, 2008; Muntean *et al*., 2007; Oniga, 2007; Oroian, 2011; Parvu, 2006; Sarbu *et al.,* 2013; Stanescu *et al*., 2014; Stanescu *et al*., 2014; Stefan & Oprea, 2007). It blooms from May to August (Sarbu *et al.,* 2013).

Distribution and habitat: frequent, in meadows, bushes, forest thickets, sands, grassy rocks, from the steppe area to the spruce floor (Sarbu *et al.,* 2013). In Dobrogea, *Thymus glabrescens* Willd. was reported in the Danube Delta area (Dunavat) (Doroftei *et al*., 2011) and in Macin Mountains (Suluc Mountain) (Andrei & Cristurean, 2006).

Also, *Thymus comptus* Friv. (*T. glaucus* Friv. ex Podp. - in Histria) and *Thymus zygioides* Griseb. (in Dolosman, including the Iancina Cape) were reported in the Danube Delta (Doroftei *et al*., 2011).

Harvesting period: aerial parts, during flowering stage (Chevallier, 2016; Oniga, 2007; Oroian, 2011; Parvu, 2006).

Traditional uses

There are limited data on the use of *T. glabrescens* in Romanian folk medicine, since traditionally a collective drug is used and known as thyme ("cimbrișor").

Traditionally, the infusions from thyme were used in colic, gastrointestinal disorders, urinary retention, chronic rhinitis, uterine contractions, bronchitis, cough, asthma, whooping cough, laryngitis, tracheitis, tuberculosis, headache, against intestinal worms, headaches, neuralgia, dizziness and nausea, but also to stimulate liver and kidney function. The plant was also used as steam inhalation against sore throat and chronic rhinitis (Butura, 1979; Parvu, 2006; Stanescu *et al*., 2014).

The decoction was used internally for the treatment of stomach diseases, intestinal gas, kidney diseases, migraines, asthenia, cough, to stimulate peripheral circulation and as a depurative, and externally as mouth wash against toothache, as compress to reduce eye soreness, as local baths for the treatment of skin wounds, ulcerations and rheumatism (Butura, 1979; Parvu, 2006).

Other ethnopharmacological data mention the use of the infusion from the aerial parts of thyme in anorexia, enterocolitis, bronchitis and cough (Tita *et al*., 2009).

Chemical composition

Several polyphenolic compounds were identified in *T. glabrescens* aerial parts, e.g. caffeic, chlorogenic, p-coumaric, ferulic and rosmarinic acids, catechin, epicatechin, eriodictyol, rutin, apigenin, apigenin-7-glucoside, naringenin, quercetin and dihydroquercetin (Boros *et al*., 2010).

The aerial parts also contain essential oil (0.73%), the main constituents being geraniol, neryl acetate, *β*-bisabolene, carvacrol, *trans*-β-caryophyllene, germacrene D, thymol (Ilić *et al*., 2017; Pavel *et al*., 2010; Salehi *et al*., 2019a).

The European Pharmacopoeia requires for *Serpylli herba* (wild thyme) minimum 3.0 mL/kg of essential oil (dried drug) (Eur. Ph. 8.0, 2013).

Pharmacological activities

The essential oil isolated from *T. glabrescens* aerial parts exhibited antibacterial (*Salmonella typhimurium*, *Pseudomonas aeruginosa, Proteus mirabilis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella enteritidis, Enterobacter aerogenes, Enterococcus faecalis, Bacillus cereus, Listeria monocytogenes*) and antifungal (*Candida albicans*) activities (Ilić *et al*., 2014; Ilić *et al*., 2017; Pavel *et al*., 2010).

Other *Thymus* species were reported to have appetizer, spasmolytic, diuretic, antilithiasis, emollient, antitussive, antibacterial, antifungal, anti-inflammatory, analgesic, carminative, stomachic, vulnerary, tonic, expectorant, diuretic, anticongestive and antiparasitic properties (Chevallier, 2016; Duke *et al*., 2002; Istudor, 2001; Tita *et al*., 2009).

Current uses
Thymus species are used internally in spastic/whooping cough, asthma (for their antispasmodic action), in respiratory tract inflammation, chronic rhinitis, kidney infections (due the antiseptic action), in digestive disorders (due to the stomachic, antispasmodic and cholagogue-choleretic action) (Ardelean & Mohan, 2008; Duke *et al*., 2002; Oniga, 2007; Oroian, 2011; Stanescu *et al*., 2004b).
Externally, they are used in wounds and skin ulcers, chronic rhinitis, rheumatism, abdominal, stomach and menstrual cramps (Ardelean & Mohan, 2008).
Thymus species are included in several tea formulas recommended for the conditions mentioned above, and are also used as tincture, liquid extract and isolated essential oil (Istudor, 2001; Muntean *et al*., 2007; Oniga, 2007; Parvu, 2006; Stanescu *et al*., 2014).
The essential oil is also used in neuro-psychic (asthenia, general fatigue, neurosis, neuralgia, sciatica, lumbago), respiratory (bronchitis, asthma, whooping cough), digestive (dyspepsia, flatulence, infectious enterocolitis), urogenital (cystitis, severe urinary tract infections), locomotor (arthritis, rheumatism) and dermal (infectious dermatitis, impetigo, abscesses, anthrax, superficial wounds) diseases (Istudor, 2001).
It is also used as infusion or syrup in the adjuvant treatment of flu and colds (Chevallier, 2016).

Precautions and adverse reactions
The prolonged use of the essential oil can cause skin irritation (Duke *et al*., 2002; Istudor, 2001; Oniga, 2007).

Typha latifolia L. (common cattail, „papură"), Typhaceae family

Syn. *Typha caspica* Pobed. (Doroftei *et al*., 2011).
Other common names: bullrush, reed mace (Gescher & Deters, 2011).

Officinal products: *Typha latifolia* is not an officinal product, but the literature mentions some traditional uses of the rhizomes (*Typhae rhizoma*) and inflorescences (*Typhae flos*) (Butura, 1979; Parvu, 2006).

Botanical description
T. latifolia is an herbaceous perennial plant, 1-3 m high, with a thick, gnarled and creeping rhizome, and a foliate stem. The leaves are linear, fleshy, 1-2 cm wide, most of them basal or near-basal, with a strongly sheathing base and an elongate, flattened, parallel-veined, flat, firm but spongy blade. The flowers are unisexual, very numerous, many or all of them axillary to short, bristle-like bracts, and are grouped in female and male spikes that are very dense, elongate-cylindrical. The male flowers have the androecium with staminal filaments 3 times longer than the anthers; the female flowers have an upper gynoecium, with the stigma black-brown, longer than the hairs in the upper part. The fruit is an achene (Gleason & Cronquist, 1991; Ciocarlan, 2009; Parvu, 2006; Sarbu *et al*., 2013). It blooms from June to August (Andrei & Cristurean, 2006; Parvu, 2006; Sarbu *et al*., 2013).

Distribution and habitat: frequent, in stagnant or slowly flowing waters, shallow waters and pond edges, reeds, swamps, from the steppe area to the beech floor (Andrei & Cristurean, 2006; Gescher & Deters, 2011; Parvu, 2006; Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (sporadically in the Macin Mountains National Park) (Andrei & Cristurean, 2006).
Harvesting period: rhizomes in autumn, towards the end of the vegetation season; the floral spikes (inflorescences) during flowering stage (Parvu, 2006).

Traditional uses

Literature data on the use of *T. latifolia* in the ethnomedicine are limited, but in antiquity this species was one of the most important vegetable, used by the indigenous peoples of North America (Moermann, 1998). It was a prominent diet component due to it's readably availability for the greater part of the year. Early in the spring its sprouts could be eaten like asparagus, in the late spring the flowers were boiled in water and eaten, and the pollen was used as an additive in other foods; in late summer, autumn and winter, the underground parts were used as a starch source (Liptay, 1989). Its nutritional value was also valued by the Chinese, Germans, Bosnians and the people of Sahara (Morton, 1975; Redzic, 2008). The first described use of cattail by Arabian doctors comes from the Middle Ages, but cattail pollen was used by man 4000 years ago (Gescher & Deters, 2011). The fruits (the achene and perigone hairs) were used in Northern America as wound dressing to absorb the sero-purulent discharges (Moermann, 1998). Medicinal use is also reported for roots and the sticky juice between young leaves (Carman, 2006). *Typhae pollen* (Pu Huang), consisting of the pollen of several species of *Typha* (e.g. *T. angustifolia*, *T. latifolia*, *T. angustata* and *T. orientalis*), is used as traditional Chinese folk remedy in dysmenorrhea, stranguria and injuries (Tao *et al.*, 2010).
In Romanian folk medicine, the rhizomes and flower spikes of *T. latifolia* have limited traditional uses in human and veterinary medicine. The rhizomes were used due to their tonic, astringent, antidiarrheal and calming properties. The floral spikes were presumed to have disinfectant and healing properties. Internally, the rhizomes were used as decoction in water and white wine (against diarrhoea and post-partum complaints) and alcohol macerate (against hernia); externally, the rhizome decoction was used as mouth wash in toothache (Butura, 1979; Parvu, 2006). The floral spikes were used externally as decoction in the treatment of the infected wounds (Butura, 1979).

Chemical composition

Literature data on the chemical composition of *T. latifolia* are limited, most studies focusing on the starch content and composition.
The nutritional value of the cattails is given by the high starch content of the rhizomes (Tursuna *et al*., 2011). However, the process of isolating the cattail rhizome starch, especially in the cell wall disintegration stage, is too difficult to recommend *T. latifolia* as an industrial source of starch (Kurzawska *et al*., 2014). Cattail starch containes 32% amylose. The dry mass of common cattail rhizomes consists of 60–70% starch in the winter; in the summer, its content is slightly lower. The other

morphological parts contain 10–15% starch (Biesboer, 1984; Kausch *et al*., 1981; Kurzawska *et al*., 2014).

In addition to starch, cattail rhizomes contain saccharides, such as glucose, galactose, xylose, mannose, glucuronic and galacturonic acids, arabinose, ribose, fucose, rhamnose and fructose (Gescher & Deters, 2011). Alkanolamines (Peru *et al*., 2004) and flavonol glucosides (Woo *et al*., 1983) were found in leaves. The stem is also rich in carbohydrates (Pollard, 1982). Carotenoid-like compounds and allelopathic sterols were also reported for *T. latifolia* plants (Della Greca *et al*., 1990a; Della Greca *et al*., 1990b), while lipids were identified in the pollen (Caffrey *et al*., 1987). *T. latifolia* reeds contain saponins, steroids, tannins, alkaloids and glycosides (Wangila, 2017).

Pharmacological activities

Literature data on the pharmacological activity of *T. latifolia* are limited.

The methanol extract from *T. latifolia* reeds exhibited *in vitro* antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* (Wangila, 2017). The fruit extracts showed *in vitro* wound healing properties, due to the strong stimulatory activity of the polysaccharides on keratinocytes proliferation and early differentiation (Gescher & Deters 2011).

The pollen of *Typha* species (containing sterols, terpenoids, flavones, cerebrosides and long-chain hydrocarbons) exhibited antiproliferative and immunosuppressive activities (Qin & Sun, 2005; Tao *et al*., 2010). *Typhae pollen* has also been found to have other benefic effects in improving the microcirculation, preventing and curing the coronary heart disease, hyperlipidemia and myocardial infarction (Qin & Sun, 2005).

Current uses

No data on the use of *T. latifolia* in the modern phytotherapy were found.

Precautions and adverse reactions

No available data.

Verbascum phlomoides L. (orange mullein, „coada vacii"), Scrophulariaceae family

Syn. *Thapsus phlomoides* (L.) Opiz. (Danihelka *et al*., 2012).

Other common names: common mullein, great mullein (Gruenwald *et al*., 2000), clasping mullein (Gleason & Cronquist, 1991).

Officinal products: According to the European Pharmacopoeia and the European Medicine Agency (EMA), the officinal product is *Verbasci flos*, represented by the dried flower, reduced to the corolla and the androecium, of *Verbascum thapsus* L., *V. densiflorum* Bertol. (*V. thapsiforme* Schrad), and *V. phlomoides* L. (EMA/HMPC/611531/2016; EMA/HMPC/611537/2016; Eur. Ph. 8.0, 2013). Since the corolla of *V. thapsus* is very small, in Europe the mullein flower originates mainly from cultivated plants of *V. densiflorum* and *V. phlomoides* (Willuhn, 2004).

Botanical description

V. phlomoides is a biennial herbaceous plant with a shallow taproot that produces a rosette in the first year and a tall flowering stem in the second year. The stem is 50-120 cm high. The leaves are alternate, oblong to lanceolate-ovate or ovate-oblanceolate, toothed, tomentaceous on both sides but only thinly so above, sessile, not decurrent or only very shortly so. The flowers are arranged in terminal spike-like racemes, in which one bract protects 2-9 flowers. The corolla is yellow-golden, 2.5-3.5 cm wide, with 5 petals united at the base. The androecium consists of 5 stamens, all with anthers, more or less dimorphic, the upper 3 filaments short, densely white-villous, with short anthers and the lower 2 filaments much longer, glabrous or nearly so, with linear anthers. The fruits are ovoid capsules, with 2 valves, and contain numerous small brown seeds (Ardelean & Mohan, 2008; Ciocarlan, 2009; Gleason & Cronquist, 1991; Muntean *et al*., 2007; Oroian, 2011; Parvu, 2006; Stefan & Oprea, 2007). It blooms from June to August (Sarbu *et al*., 2013; Stefan & Oprea, 2007).

Distribution and habitat: frequent, from the steppe to the beech floor, through meadows, sunny and dry shrubby areas (Ciocarlan, 2009; Sarbu *et al*., 2013). In Dobrogea, this species was reported in the Danube Delta area (Letea) (Ciocarlan, 2011; Doroftei *et al*., 2011) and in Macin Mountains (Andrei & Cristurean, 2006).

Harvesting period: during flowering stage (Oroian, 2011; Parvu, 2006).

Traditional uses

The European Medicines Agency - Committee on Herbal Medicinal Products mentions the traditional use of the comminuted herbal substance (as herbal tea for oral use) to relieve symptoms of sore throat associated with dry cough and cold (EMA/HMPC/611537/2016).

Traditionally, the ointments prepared from leaves were used as remedies for burns and earache (Haughton, 1978). Topically, the leaf poultice was used for its wound healing properties in wounds, ulcers, tumors and piles. A poultice made from the seeds and leaves was used to draw out splinters (Grieve, 1981). Flowers in olive oil were used as earache drops with strong antibacterial properties (Bown, 1995; Chevallier, 1996). The infusion was used internally in the treatment of a wide range of chest and abdominal complaints, including productive cough and diarrhoea (Bown, 1995; Chevallier, 1996; Murad *et al*., 2011). It was also used as a tobacco substitute (Wilhelm, 1974) and in rheumatic problems (Haughton, 1978).

In Romanian folk medicine, *Verbasci flos* was used internally as antirheumatic, diuretic, and in catarrhal-respiratory syndrome, cough and bronchitis; externally in dermatitis and eczema (Armatu *et al*., 2011; Lisovschi, 2004; Stanescu *et al*., 2004b). Traditionally, the infusion from the comminuted flowers (corolla and stamens) was used (Stanescu *et al*., 2020).

The infusion from the flowers was used against pulmonary diseases such as cough, asthma, tuberculosis and chest pains. The mullein root, boiled in wine, was taken against chest pains. The root, macerated in alcohol or boiled in water, was also used againts stomach ache. The leaf infusion was taken against stomach ache, and the flower infusion against sore throat. The decoction (as wash) and poultices were used against back pain. The leaves macerated in alcohol were taken against fever and icterus (Butura, 1979; Parvu, 2006). The flowers were also used to prepare an

ointment to massage the head/ scalp. The smashed leaves and flowers of *V. phlomoides* were macerated in alcohol and applied on boils (Lisovschi, 2004). *Verbasci flos* is used internally (as infusion or decoction) against acute laryngitis, bronchitis, cough, tracheitis, asthma, chest pain, bladder diseases. Externally, the leaf decoction was used against hemorrhoids and the root decoction to stimulate hair growth (Parvu, 2006).

Chemical composition

The characteristic chemical constituents of *Verbasci flos* are: polysaccharides (e.g. arabinogalactans, xyloglucan), iridoid glycosides (0.1-0.6% total amount, aucubin, catalpol, 6-xylosylaucubin, 6-xylosylcatalpol), iridoidester glycoside (6-(4"-p-coumaroyl)-xylosylaucubin, specioside), flavonoids (tamarixetin 7-rutinoside, tamarixetin 7-glucoside, apigenin and luteolin and their 7-glucosides, diosmin, chrysoeriol, eriodictyol, kaempferol, quercetin and rutin), phenolic acids (ferulic, caffeic and rosmarinic acids), triterpene saponins (verbascosaponin, verbascosaponin A and B, and desrhamnosyl verbascosaponin), phytosterols, fatty acids and phenylethanoid glycosides (verbascoside) (Armatu *et al*., 2011; EMA/HMPC/611531/2016; Grigore *et al*., 2013, Gvazava & Kikoladze, 2012; Klimek, 1996; Stanescu *et al*., 2004b; Stanescu *et al*., 2020; Tschesche *et al*., 1979). The leaves also contain triterpene saponins, e.g. verbascosaponins and verbascogenin (Klimek, 1996; Klimek *et al*., 2010; Stanescu *et al*., 2020; Willuhn, 2004).

Pharmacological activities

In vitro and *in vivo* studies highlighted for *Verbasci flos* extracts, fractions and isolated compounds the following biological activities: antibacterial, antiviral, antitumor, anti-inflammatory, hepatoprotective, analgesic and cardiovascular (Armatu *et al*., 2011; EMA/HMPC/611531/2016).

The phenolic compounds have antioxidant effect; the iridoid aucuboside has *in vivo* anti-inflammatory and hepatoprotective activities, *in vitro* antiviral action (against hepatitis B virus); verbascoside has *in vitro* and *in vivo* anti-inflammatory activity (Stanescu *et al*., 2020). *Verbasci flos* has demulcent (due to its content in mucilage), expectorant (due to the triterpene saponoids) and anti-inflammatory (due to iridoids and phenylethanoids) properties (Armatu *et al*., 2011; Parvu, 2006; Stanescu *et al*., 2020).

The flowers and leaves have analgesic, anti-inflammatory, antiseptic, spasmolytic, astringent, diuretic, emollient, expectorant and vulnerary properties (Debray, 1978; Grieve, 1981; Chiej, 1984; Hussain *et al.*, 2007).

Current uses

On the European market, several products with *Verbasci flos* are available, such as syrups (with fluid extract) and dried herbal substance (for herbal tea), recommended for the relief of sore throat accompanying the dry cough and cold (EMA/HMPC/611531/2016).

Precautions and adverse reactions

Not recommended in case of hypersensitivity to the active substance. Due to the lack of adequate data, the use in children under 12 years of age, and also during pregnancy and lactation is not recommended (EMA/HMPC/611531/2016; EMA/HMPC/611537/2016).

No known interactions of clinical relevance (Stanescu *et al*., 2020).

Other warnings
Buds and fallen flowers must not be harvested. The rough hairs may irritate the skin and the mucous membranes, thus it is not recommended to touch the eyes, nose and face during harvesting (Muntean *et al*., 2007).

Ziziphus jujuba Mill. (jujube, "măslin dobrogean"), Rhamnaceae family

Syn. *Rhamnus zizyphus* L., *Ziziphus mauritiana* Lam., *Ziziphus zizyphus* (L.) Meikle (Duke *et al*., 2002; Meikle, 1977; WHO, 2007).
Other common names: Chinese date, Chinese jujube, common jujube, da t'sao, annab, badari, ber, black date (WHO, 2007).

Officinal products: According to the World Health Organization (WHO), the officinal product is *Zizyphi fructus* represented by the dried ripe fruits of *Ziziphus jujuba* Mill. or *Ziziphus jujuba* var. *inermis* Rehd. (WHO, 2007). The Pharmacopoeia of People's Republic of China also mentions *Zizyphi semen* (PRC Ph., 2015).

Botanical description
Z. jujuba is a spiny, deciduous shrub or a small tree, up to 10 m high. At the base of the leaves it has spines, grouped in pairs, one straight, up to 2.5 cm long and one curved. The leaves are alternate, petiolate, oval-lanceolate, 2-7 cm long, 2.5-3.0 cm wide, with the apex slightly obtuse, base oblique, margin closely serrulate and 3 veins. The flowers are grouped seven to eight in each cluster (in an axillary cyme). The calyx has a cupuliform tube and five segments. The corolla has five yellow petals. The fruits are fleshy drupes, ovoid or oblong, 1.5-5.0 cm long, dark reddish brown when ripe. The stone is oblong and sharply pointed (Ciocarlan, 2009; Kariyone & Koiso, 1973; Keys, 1976; Sarbu *et al*., 2013; Savulescu, 1952; WHO, 2007). It blooms from April to May (Sarbu *et al*., 2013; Stefan & Oprea, 2007).
Distribution and habitat: in Romania, *Z. jujuba* is rarely found in the steppe region of Dobrogea, in dry stony places, calcareous rocks, in Constanta (Ostrov) and Tulcea (Mahmudia, Sfantu Gheorghe) counties (Ciocarlan, 2009; Sarbu *et al*., 2013; Stanica, 2019; Stefan & Oprea, 2007). It was reported in the Danube Delta area (Dolosman, including the Iancina Cape) (Doroftei *et al*., 2011).

Traditional uses
According to the World Health Organization, *Zizyphi fructus* was used traditionally as an antipyretic, diuretic, emmenagogue, expectorant, sedative and tonic, and in the treatment of asthma, bronchitis, diabetes, eye diseases, inflammatory skin conditions, liver disorders, scabies, ulcers and wounds (WHO, 2007).
In Oriental folk medicine, it was used as a tonic and antispastic, hypotensive, anti-nephritic, anticancer, antifungal, antibacterial, anti-ulcer, anti-inflammatory, cognitive, hypnotic-sedative, antioxidant, immunostimulant, antiallergenic and wound healing agent, to strengthen liver function (Chevallier, 2016; Damiano *et al*., 2017; Hovanet *et al*., 2016a). In Ayurvedic system of medicine, the fruits are traditionally used as

anthelmintic, hepatoprotective, antioxidant, antibacterial, anti-inflammatory agent and for their wound healing properties (Preet & Tomar, 2017). In Iranian folk medicine, the fruits are used as antitussive, laxative and hypotensive agent; the fruits and stem to treat digestive disorders (Hamedi *et al*., 2015).

Zizyphi spinosae semen, the dried seeds of *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou, is one of the most popular traditional Chinese herbal foods for the treatment of fright palpitations, insomnia and dreaminess (PRC Ph., 2015; Song *et al*., 2017; Charlot, 1990).

Data on the use of *Z. jujuba* in Romanian folk medicine are limited. The fruits are used in respiratory (cough, colds), hepatic, gastric (ulcer) and oral complaints (Istudor, 2005), and for its emollient properties (Stefan & Oprea, 2007).

Chemical composition

The fruit of *Z. jujuba* contain triterpene (e.g. betulinic, maslinic, alphitolic, oleanolic, 3-*O-trans-p*-coumaroyl-alphitolic and ursolic acids), triterpene saponins (jujuboside A and B, zizyphus saponins I, II and III, spinosin and swertisin), polysaccharides (zizyphus-arabinan), mucilage, flavonoids (catechin, epicatechin and rutin), phenolic acids (hydroxycinnamic, benzoic, chlorogenic and caffeic acids), cerebrosides, alkaloids, β-carotene, vitamins (A, B2 and C, α-tocopherol) and minerals (Chevallier, 2016; Cosmulescu *et al*., 2018; Hamedi *et al*., 2015; Ji *et al*., 2017; Istudor, 2005; Mitsuhashi *et al*., 2017; Preet & Tomar, 2017; Song *et al*., 2017; Tanideh *et al*., 2016; WHO, 2007). The fruits contain 20 times more vitamin C than citrus fruits (Chevallier, 2016). Polysaccharides are one of the most abundant components of the fruit (Ji *et al*., 2017).

In seeds, several triterpene oligoglycosides were identified, namely jujubosides A1 and C, and acetyljujuboside B (WHO, 2007). The seeds also contain phenolic compounds, e.g. catechin, epicatechin, magnoflorine, spinosin, vitexin, quercetin, kaempferol and ferulic acid, and fatty oil (Istudor, 2005; Moon *et al*., 2019).

The leaves contain flavonoids (catechin, gallocatechin, quercetin and kaempferol derivatives, spinosin A), triterpenes (alphitolic, maslinic, betulinic, oleanolic, ceanothic, epiceanothic and ceanothenic acids), triterpene saponins (jujubasaponin I-VI, zizyphus saponin I-III, ziziphin, jujuboside A1, B, B1, C and F, jujuboside II and III) and alkaloids (Damiano *et al*., 2017; Devi & Bora, 2017; Hovanet *et al*., 2016b; Masullo *et al*., 2019).

Pharmacological activities

Antiallergenic, anti-inflammatory, analgesic, anti-hyperglycemic, immunomodulatory, anti-platelet aggregation, antioxidant, antitumor and hepatoprotective activities, and gastrointestinal-protective effects were reported for *Z. jujuba* (Cosmulescu *et al*., 2018; Hovanet *et al*., 2016a; Ji *et al*., 2017; WHO, 2007).

An *in vitro* study highlighted the antihelmintic activity of *Z. jujuba* leaf extract (Preet & Tomar, 2017). Different extractive fractions obtained from leaves had insecticidal effects, affecting several developmental stages of *Aedes aegypti* (L.) (Devi & Bora, 2017). The leaf infusion exhibited *in vitro* antioxidant and antibiofilm activities against *Streptococcus mutans* (a causative agent of human dental caries), alphitolic acid being the main antibiofilm metabolite (Damiano *et al*., 2017). The topical application of an ointment with dry ethanol extract from leaves promoted the wound

healing in rat, in a manner similar with Cicatrizin (a known commercial ointment) (Hovanet *et al*., 2016b).

The hydroalcoholic extract from fruits showed *in vivo* (animal model) benefic effects in ulcerative colitis, mainly due to its antioxidant and anti-inflammatory action (Tanideh *et al*., 2016). The aqueous extract from *Z. jujuba* stem bark exhibited *in vivo* gastroprotective effects against hydrochloric acid/ethanol-induced gastric mucosal injury in rats (Hamedi *et al*., 2015).

Spinosin, a flavonoid isolated from the seeds of *Z. jujuba*, had anti-melanogenic effect in a human skin model, by suppressing αMSH- or UVB-induced melanogenesis (Moon *et al*., 2019).

It has been reported that *Zizyphi spinosae semen* displays anxiolytic (Han *et al*., 2009), hypnotic (Ma *et al*., 2008; Yi *et al*., 2007), memory modulating (Xie *et al*., 2014) and cardiotonic activities (Xie *et al*., 2012). Saponins are believed to be the main constituents responsible for its anxiolytic and sedative effects. Studies have demonstrated that jujuboside A is one key saponin in *Zizyphi spinosae semen* contributing to its sedative hypnotic effect (Ma *et al*., 2007; Yingjun *et al*., 2005; Cao *et al*., 2010).

Current uses

Z. jujuba is cultivated for thousands of years, about 700 cultivars being available in China. The fruits are consumed both fresh (immature) and dry (mature) (Chen *et al*., 2013). Although the plant contains potentially useful bioactive compounds, the research in this area is scarce and the pharmaceutical and nutraceutical companies neglected the use of this species in developing new products (Mahajan & Chopda, 2009). Some Pharmacopoeias and well established documents mention the use of the fruits to promote weight gain, improve muscular strength, as an immunostimulant and also in the treatment of insomnia (WHO, 2007).

Precautions and adverse reactions

The ethyl acetate extract of *Z. jujuba* bark was found to affect anti-steroidogenic activity and hence fertility in adult female mice, but the anti-fertility activity was found to be reversible in rat (Gupta *et al*., 2004).

Other warnings

Some drug interactions are possible in case of co-administration with drugs metabolized by CYP1A2, which may result in decreased concentrations of these drugs (Jing *et al*., 2015).

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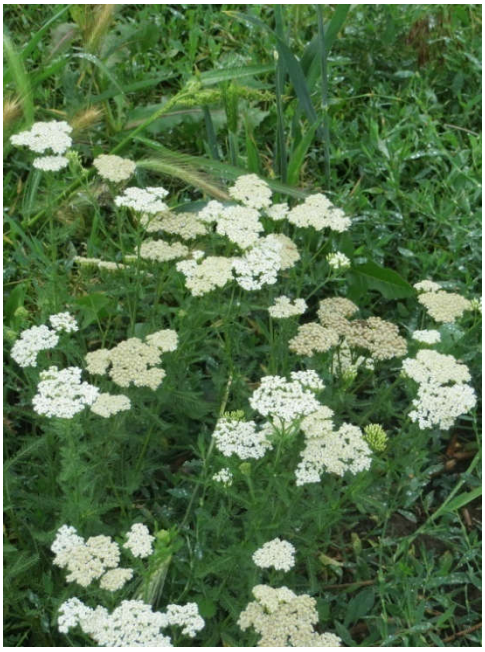
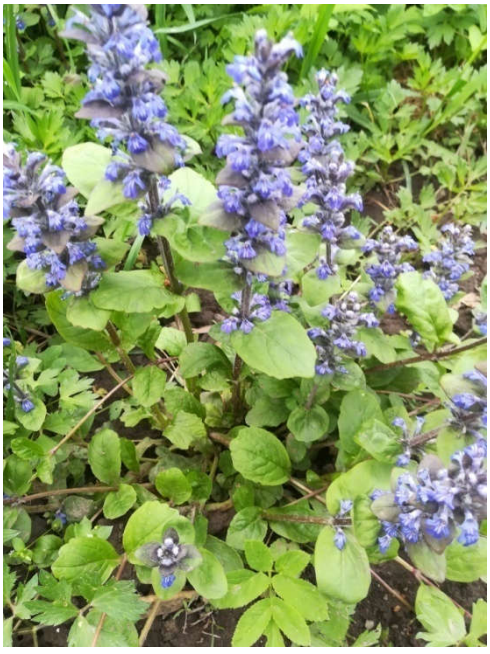
ANNEX – ORIGINAL PHOTOS OF THE SPECIES



Achillea sp.

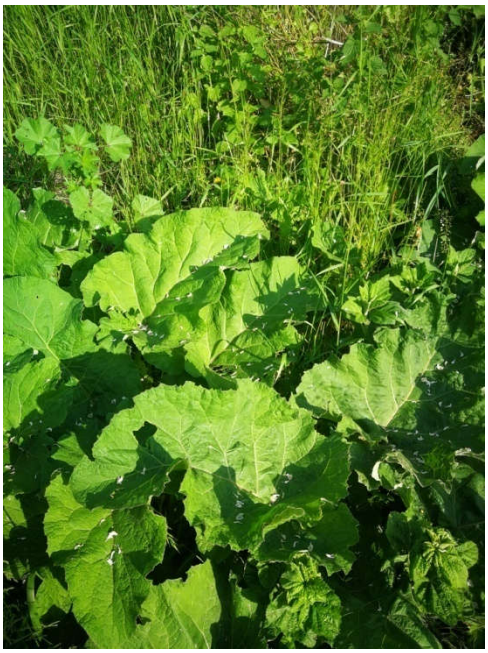
***Adonis vernalis* L.**

***Ajuga genevensis* L.**



***Ajuga reptans* L.**

***Althaea officinalis* L.**



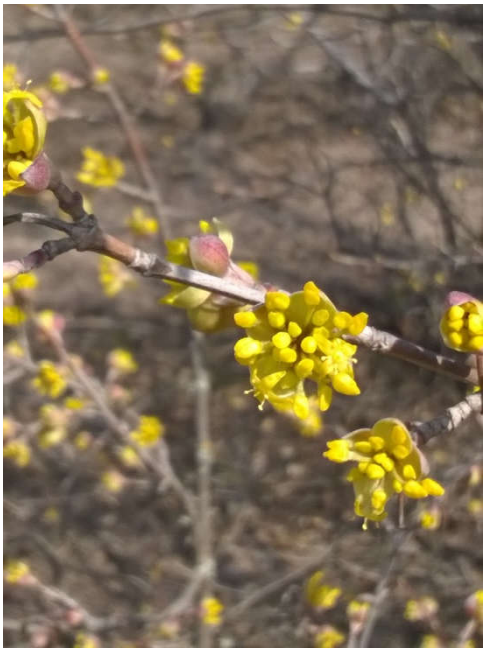
***Arctium lappa* L.**

***Artemisia absinthium* L.**

***Capsella bursa-pastoris* (L.) Medik.**

***Chelidonium majus* L.**

***Cichorium intybus* L.**



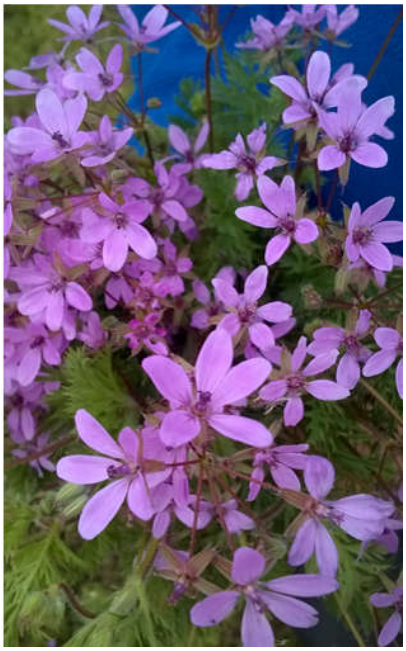
***Cornus mas* L.**

***Cotinus coggygria* Scop.**

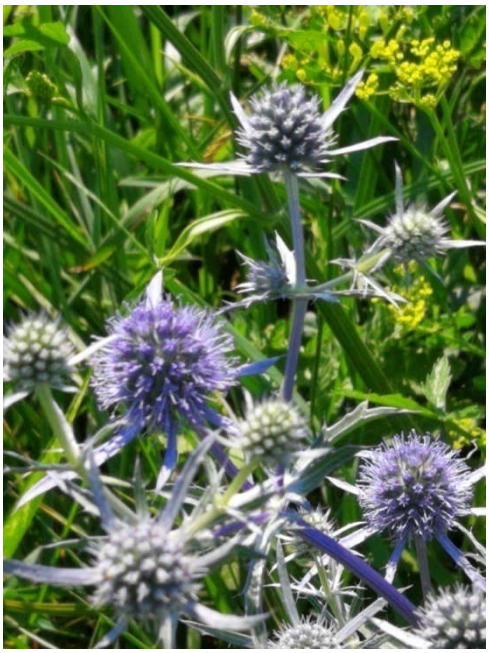
***Crataegus monogyna* Jacq.**

***Crataegus pentagyna* Willd.**

***Echium vulgare* L.**



***Erodium cicutarium* (L.) L'Hér.**



***Eryngium planum* L.**

Galium sp.

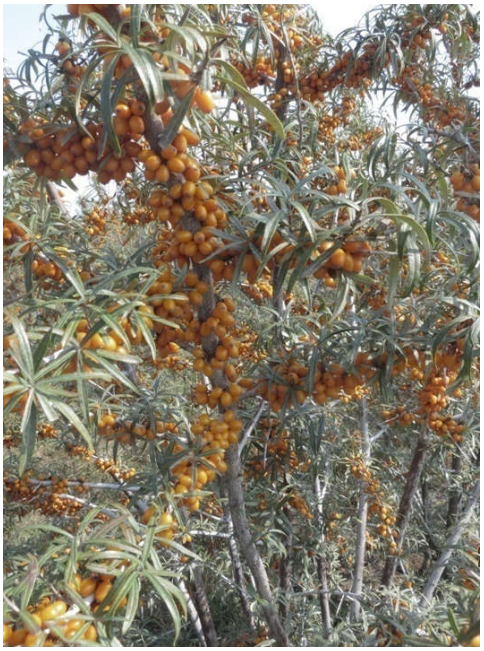
***Galium verum* L.**

***Geranium robertianum* L.**

***Glaucium flavum* Crantz**

***Helichrysum arenarium* (L.) Moench**

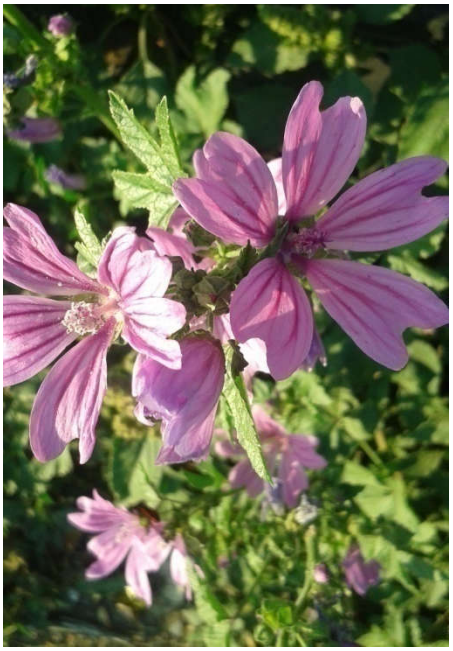
***Heracleum sphondylium* L.**



***Hippophaë rhamnoides* L.**

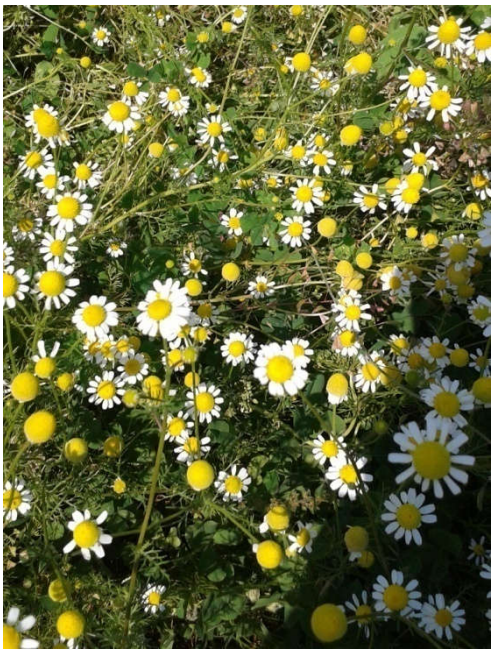
***Hypericum perforatum* L.**

***Inula helenium* L.**



***Malva neglecta* Wallr.**

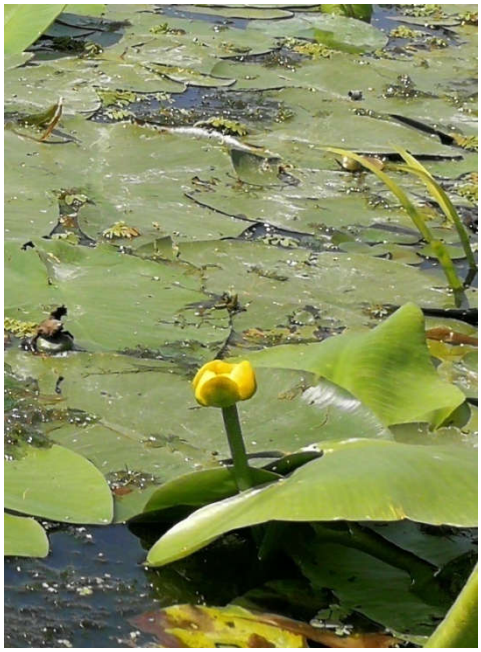
***Malva sylvestris* L.**



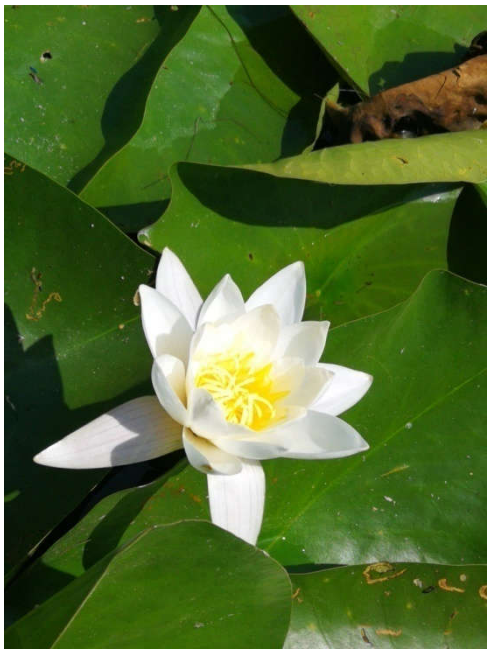
***Matricaria recutita* L.**

***Mentha aquatica* L.**

***Nigella arvensis* L.**



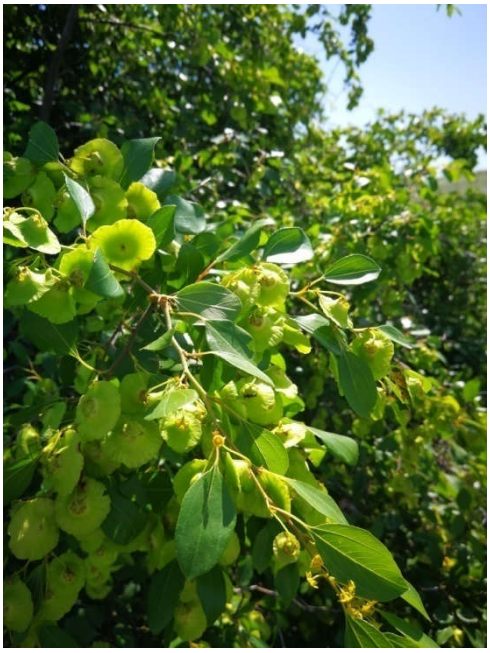
***Nuphar lutea* Sm.**



***Nymphaea alba* L.**

Ononis sp.

***Origanum vulgare* L.**



***Paliurus spina-christi* Mill.**

***Papaver rhoeas* L.**

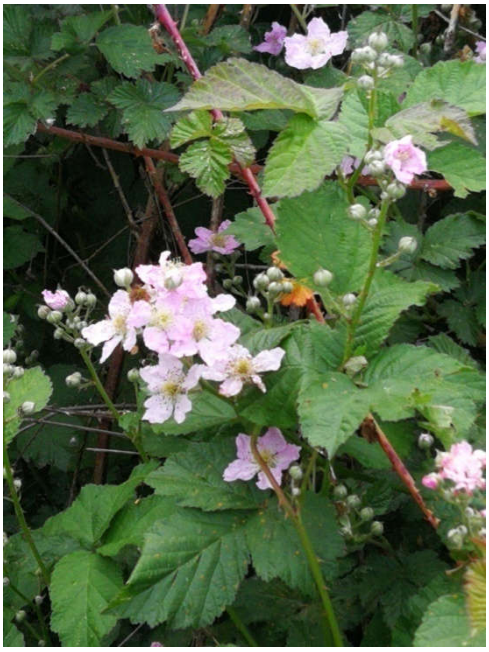
***Phragmites australis* (Cav.) Trin. ex. Steud.**

***Plantago lanceolata* L.**

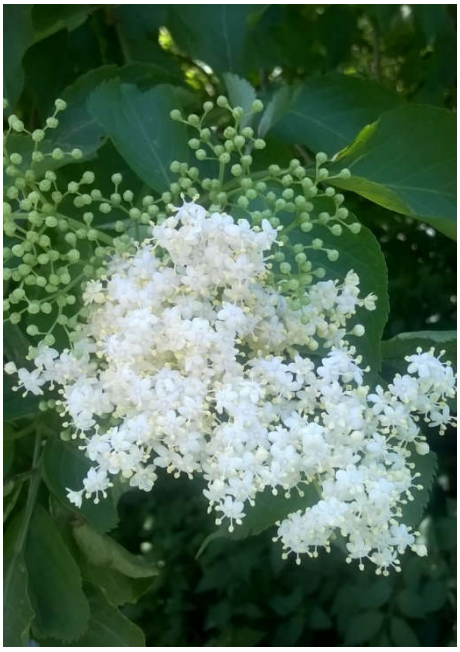
Potentilla sp.

***Prunus spinosa* L.**

***Rosa canina* L.**



***Rubus caesius* L.**

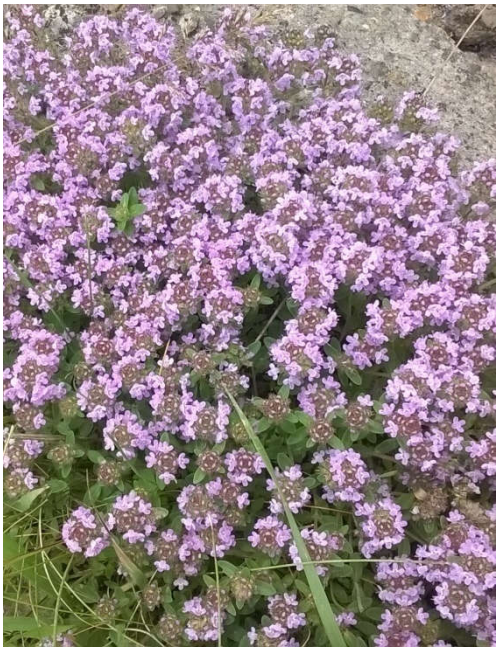


***Sambucus nigra* L.**

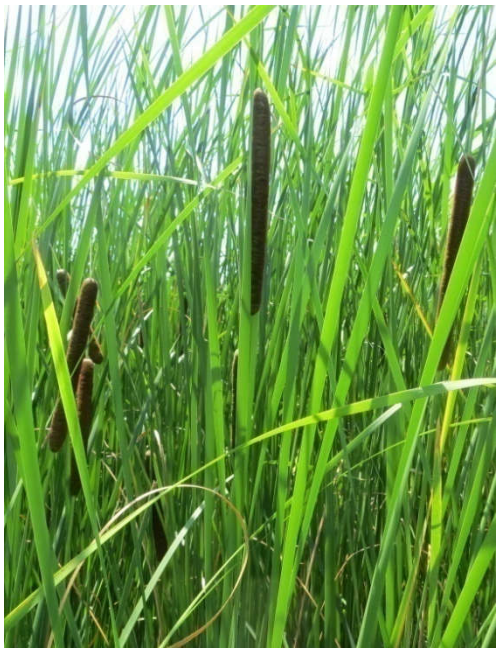
***Scirpoides holoschoenus* (L.) Soják**

***Stachys officinalis* (L.) Trevis.**

***Symphytum officinale* L.**



Thymus sp.



***Typha latifolia* L.**

Verbascum sp.

***Ziziphus jujuba* Mill.**

***Ziziphus jujuba* Mill.**