Journal of Medicinal and Chemical Sciences 6 (2023) 112-120

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Review Article

Three Little-known Medicinal Plants Growing in the State National Natural Park "Tarbagatai" (Republic of Kazakhstan): Their Ethnobotany, Phytochemistry, and Pharmacology

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ARTICLE INFO

Article history

Receive: 2022-05-20
Received in revised: 2022-06-20
Accepted: 2022-07-25
Manuscript ID: JMCS-2206-1534
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Mohammad Mansoob Khan

DOI:10.26655/JMCHEMSCI.2023.1.14

KEYWORDS

Corydalis
Malus
Daphne
Chemical composition
Medicinal plants

ABSTRACT

The review article presents the results of studying plants growing on the territory of the State National Natural Park Tarbagatai, on the basis of which it will be possible to develop new medicines. In recent years, the popularity of herbal medicine, despite a great success in the creation of chemical drugs, has been growing. Interest in natural healing substances and drugs created on their basis is increasing due to both the unique properties of herbal remedies and rapidly developing research technologies in biology, medicine, and the production of drugs. The analysis and structuring of literature sources contain some information about herbal medicines, such as Corydalis ledebouriana Kar. et Kir., Malus sieversii, and Daphne altaica Pall. were carried out. They were grown in Asian countries, mainly in China and Kazakhstan. Many Corydalis species are rich in alkaloids that have a positive effect on the central nervous, digestive, cardiovascular, and pituitary-adrenal systems. Malus sieversii has a high antioxidant activity, it can inhibit cancer cell proliferation, reduce lipid oxidation, and lower cholesterol levels according to in vitro studies of animals, which may explain their roles in reducing the risk of chronic diseases. Daphne have a wide range of pharmacological activity, including anticancer, anti-inflammatory, anti-HIV, hypocholesterolemic, neurotrophic, anti-fertile, skin irritant, nematocidal activity, and pesticide activity. Phytopreparations have some advantages such as low toxicity with sufficiently high efficiency, a wide range of therapeutic action, complex organ protective effect, harmonizing effect on all organs and systems of the body, the minimum number of side effects, relative cheapness compared to synthetic drugs, and the possibility of cooking at home. Phytotherapy has some applications such as primary and secondary preventions of various diseases, health improvement, and rehabilitation of the general population under the influence of negative environmental factors, as a means of increasing the adaptive reserves of a healthy body in sports medicine.

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GRAPHICAL ABSTRACT

Introduction

Official medicine increasingly recognizes the overall potential and gives a priority to medicinal plants in the treatment of many diseases. Many years of experience in studying medicinal plants have indicated that their extracts have a low toxicity and exhibit the necessary medicinal properties, and a variety of biologically active substances provide a wide range of pharmacological effects for herbal preparations. In this regard, the search for new types of medicinal plant raw materials is a very urgent task. There are more than 1400 species of wild medicinal plants in Kazakhstan, of which only 230 species are used in official medicine [1]. The list of officially recognized medicinal plant species in Kazakhstan, represented by 260 species, includes, along with wild plants, also cultivated plants on the territory of the republic [2]. Kazakhstan's Altai has 783 species of medicinal plants from 99 families, of which 87 species are pharmacopoeial in Kazakhstan, the remaining species are used to varying degrees in folk medicine [3].

Medicinal plants such as *Corydalis ledebouriana* Kar. et Kir., *Malus sieversii,* and *Daphne altaica* Pall. which are grown in the Tarbagatai State National Natural Park, the main purpose of which is to preserve the biological and landscape diversity of flora [4].

For thousands of years, traditional medical systems in Asian nations, particularly China, have used *Corydalis*, *Malus sieversii,* and *Daphne* as analgesics, anti-cancer, anti-inflammatory, antioxidants, and laxatives. These plants are also biological sources of various pharmaceutically active components like alkaloids, polyphenols, phytosterols, and diterpenoids [5- 7].

Botanical description

Corydalis ledebouriana Kar. et Kir. are perennial herbaceous plants up to 25 cm tall, with a tuber found in the Dzungarian Alatau, Tarbagatai, Tien Shan. It was estimated that about 428 species of the genus *Corydalis* are distributed all over the world, and 4 species of *Corydalis* are grown in Kazakhstan (*Corydalis glaucescens* Regel, *Corydalis ledebouriana* Kar. et Kir., *Corydalis sewerzowii* Regel, and *Corydalis sibirica* (L.fil.)) [1]. The tuber is rounded, deep in the ground, and becomes hollow with aging. The leaves, in number 2, are opposite, twice, or thrice triple-dissected. The flowers are pale pink, collected on loose racemes. The fruit is a broad-lanceolate or pointed elliptical capsule. The seeds are black, and shiny with a very faint dot pattern. *Corydalis ledebouriana* Kar. et Kir. grows from the belt of semi-savannas and shiblyak to the highlands, on open fine-grained slopes, in rose gardens, and barley fields [8, 9, 10].

Three species of wild apple trees grow in the Republic of Kazakhstan, but the predominant species is *Malus sieversii* (Ledeb.) M. Roem. As a result of a ten-year study of wild apples in the mountain systems of Kazakhstan, conducted by A.D. Dzhangaliev, a high polymorphism of *M. sieversii* in size, shape, color, taste of fruits,

ripening time, and many other valuable features were revealed. Field evaluation of samples collected during several joint Kazakh–American expeditions revealed similarities in fruit quality between some forms of *M. sieversii* and varieties of *M. domestica*. Molecular markers for comparative DNA analysis revealed a close similarity between Kazakh apples and cultivated apples. Thus, the hypothesis that the wild apple tree of Kazakhstan is the ancestor of the most modern varieties of this important crop that is confirmed [11,18].

Malus sieversii is a tree 2-10 (14) m tall, with a gray-brown or dark gray trunk, and a wide crown. The size of its leaves is large, about 6-11 cm long, 3-5 cm wide, from short elliptical to oblong, more or less wedge-shaped, less often rounded at the base, usually sharply slimy, whole at the base, and otherwise rough and shallow toothed leaves. Petioles are relatively short or rather long, 1.2-3.5 cm thick, inflorescences 3-5-flowered, flowers are large, 3.5-6 cm in diameter, with long, serrated-villous pedicels. The fruits of the apple tree are quite large 3-4 cm in diameter, mostly spherical or flattened-spherical, less often slightly elongated, often angular or ribbed from the sides, yellow, and often partially anthocyanin in color, with blooms in April-May [12].

Daphne altaica is a deciduous shrub, 0.4-0.8 m tall, erect. The bark is brown, and becomes dark gray; the branches are elongated, first pubescent, and then glabrous. The leaves are alternate; the petiole is absent or almost absent, the leaf blade is oblong-elliptic or elliptic-lanceolate, 2.5-6 × 0.7-1.5 cm, membranous, abaxially glaucous, and both surfaces are glabrous, the base is wedge-shaped, the edge is sometimes slightly curved, the apex is blunt or sharp, short-pointed; veins 5-7 pairs. Inflorescences are apical, 3-7-flowered; bracts are absent. The pedicel is absent or almost absent. The calyx is white; the tube is cylindrical, 10-12 mm long, thin, and rarely pubescent on the outside; 4 lobes, narrowly ovate or broadly elliptical, 6-8 × 4-5 mm, blunt at the apex and apical. The disk is small. The drupe is purplish-black, ovate, 5-7 mm. Blooms in May-June and bears fruit in July-September [13].

Use in traditional medicine and pharmacological action

Corydalis in folk medicine, tea from aboveground parts is used as a hypnotic, soothing, also for trembling limbs, hypertension, obesity, mental, and gynecological diseases. Externally, a decoction of the herb is used for bruises, eczema, and purulent wounds. A decoction of tubers is used as an anthelmintic. *Corydalis ledebouriana* Kar. et Kir. is used for tick-borne encephalitis. In Tibetan medicine, various types of tufts are used to treat fevers, hepatitis, gastritis, cholecystitis, and hypertension [10].

Many *Corydalis* species are rich in alkaloids that have a positive effect on the central nervous, digestive, cardiovascular, and pituitary-adrenal systems. They are prescribed for colds, hypertension, hepatitis, bleeding, edema, gastritis, cardiovascular and cerebrovascular diseases, and neurological disorders, as well as in dentistry for periodontal diseases, stomatitis, inflammation of the mucous membrane of the oral cavity, middle ear, with long-term non-healing wounds, ulcers, and infected burn wounds [9,14].

Corydalis ledebouriana Kar. et Kir. is used in the treatment of cerebral palsy, myopathy, muscular dystrophy, neuritis, arachnoiditis, gynecological diseases, eczema, dermatoses, ulcers, and sinusitis [9].

Apples are recognized as healthy and epidemiological studies have linked their consumption with a reduction in the risk of certain types of cancer, cardiovascular diseases, asthma, and diabetes. It has also been experimentally proven that apples have a high antioxidant activity, inhibit the proliferation of cancer cells, reduce lipid oxidation, and lower cholesterol levels.

Malus sieversii is used for food and as a medicinal plant. In ancient medicine, it was believed that eating apples is useful for palpitations, shortness of breath, poor appetite, and strengthens the entrance to the stomach. If a sour apple is smeared with dough, baked on ashes, and eaten, it will help with bloody diarrhea and tuberculosis. Apple blossom jam helps with the weakness of the heart, brain, and strengthens the flesh. In

scientific medicine, it has been determined that frequent consumption of apples significantly reduces the incidence of cardiovascular diseases. Apples also remove salts of heavy metals lead, cobalt, nickel, and radioactive elements from the body [15].

Several species of the plant genus *Daphne* have been used as traditional medicines for the treatment of cancer, inflammation, and rheumatism in Asia, North Africa, and Europe, and some of these plants have also been considered potent poisons. With the help of a significant number of modern pharmacological and chemical studies, it has been demonstrated that diterpenoids from the genus *Daphne* have a wide range of pharmacological activity, including anticancer, anti-inflammatory, anti-HIV, hypocholesterolemic, neurotrophic, anti-fertile, skin irritant, nematocidal activity, and pesticide activity. Among these types of biological activity, the greatest attention is paid to antitumors, since there is still a need for both effective and safe antitumor drugs with a new structure [16].

Table 1: Chemical composition of *Corydalis ledebouriana* Kar. et Kir

No.	Name	Pharmacological activity	Reference
1	protopine	— anti-inflammatory — antiplatelet — anticancer — analgesic — vasodilator — anticholinesterase — anti-addictive — anticonvulsant — anti-pathogenic — antioxidant — hepatoprotective — neuroprotective — cytotoxic — anti-proliferative effect	[19-21]
2	dl-raddeanine	—	[22,23]
3	ledeboridine	—	[22,23]
4	corledine	—	[23,24]
5	ledeborine	—	[23,25]
6	bulbocapnine	— inhibitory effect	[26,27]
7	d-isocorydine	— analgesic — sedative effect	
8	protocine	—	
9	allocryptopine	—	[19,26,27]
10	cryptopine	—	
11	corydaline	—	
12	tetrahydropalmatine	— hypnotic — analgesic effect	
13	dihydrochelerythrine	—	
14	dihydrosanguinarine	—	[26]
15	oxosanguinarine	—	
16	lederine	—	[28]
17	ledecorine	—	[29,23]
18	sanguinarine	— inhibitory effect	[20,27,30]
19	oxysanquinarine	—	[19]
20	dihydroxysanguinarine	—	
21	*l*-cavidine	—	[30]
22	*d*-tetrahydrocorysamine	—	

The chemical composition of plants growing in the Tarbagatai National Nature Park has not been studied enough. Studies have shown that all types of crested contain various, extremely valuable spirobenzylisoquinoline alkaloids. *Corydalis* species are rich in alkaloids with acetylcholinesterase inhibition, antiproliferative activity, antiviral activity, and antiplasmodial activity [8], and also contain coumarins, flavonoids, steroids, organic acids, and other chemical components. Chemical constituents of important medicinal species of *Corydalis* have been reported since 1962. A total of 381 alkaloids were listed, including 117 quaternary isoquinoline types, 60 benzophenanthridine types, 37 aporphine types, 10 protopine types, 59 phthalide isoquinoline types, 52 simple isoquinoline types, 25 lignin amides, and 21 other alkaloids [9]. Some alkaloids isolated in their pure form turned out to be biologically active substances and were proposed as new effective medicines. 0.533-1.74% of alkaloids were found in tubers of *Corydalis ledebouriana* Kar. et Kir., of which 22 were identified (protopine, sanguinarine, cryptopine, allocryptopine, ledeborine, ledecorine, lederine, ledeboridine, cavidine, etc.). Salts contain tufted roots Mg, Na, K, and P [10, 17].

The Sievers apple tree has an analgesic effect, the pharmaceutical activity of medicinal plant raw material is determined by the chemical composition. Depending on the types of apples, their chemical composition can vary greatly, and there are also slight differences in chemicals during fruit ripening. Apples contain substances such as quercetin, catechin, chloridzine, chlorogenic acid, polysaccharides (pectin), triterpenoids (triterpenic acid, ursolic acid, 2-hydroxy ursane, 3, 2-hydroxy ursane-28-oic acid, oleanolic acid, 2- hydroxy oceanol, betulinic acid, 3-O-p-coumaryl, 3-O-p-coumaryl), phytosterols (sitosterol and daucosterol), polyphenols (phenolic acids, dihydrochalcones, and flavonoids) and other components such as protein [31], vitamins (A, C, and E), *β*-carotene, metals, and essential trace elements (iron, magnesium, calcium, zinc, manganese, sulfur, copper, and potassium) that a person needs [32]. Apple fruit has high antioxidant activity, can inhibit cancer cell proliferation, reduce lipid oxidation, and lower cholesterol levels according to in vitro studies of animals, which may explain their role in reducing the risk of chronic diseases (Tables 1, 2)[33].

Table 2: Chemical composition of *Malus sieversii*

No.	Name	Pharmaceutical activity	Reference
1	Polyphenols	— antioxidant activity — hepatoprotective activity — inhibit hepatic steatosis — reduce inflammation — reduce antibacterial glycemia — anticancer activity — lower blood pressure — insulin resistance — inhibit atherosclerosis — cardioprotective effect	[34]
2	Pectin	— anticancer — reduces the level of cholesterol in the blood — inhibits fat absorption	[35]
3	Phytosterols	— anti-inflammatory properties — anti-asthma properties — expectorant action — inhibits the synthesis and absorption of cholesterol — antioxidant properties	[36]
4	Pentacyclic triterpenes	— cytotoxicity — anticancer — anabolic action	[37]

Plants of the genus *Daphne* from the family *Thymelaeaceae* contain abundant natural diterpenoids having a 5, 7, and 6-tricyclic ring system and usually with an orthoester group. To date, a total of 135 diterpenoids have been isolated from species of the genus *Daphne,* which can be divided into three main types according to the pattern of substitution of the A ring and oxygen-containing functions in the B ring [38]. 11 chemical compounds were found in the stem bark of *Daphne altaica* Pall, of all the isolated compounds, compounds 1-7 and 9-11 were initially detected in *Daphne altaica*. Previously, only compound 8 (as indicated in Table 3) was reported in the literature [39]. Cytotoxicity against some tumor cell lines has been described for compounds 3, 4, 6, 8, 9, and 10 (Table 3). Thus, it can be assumed that the isolated compounds may be of great importance for the anti-proliferative activity of *D. Altaica* [40].

Table 3: Chemical composition of Daphne altaica

No.	Name	Pharmaceutical activity	Reference
1	*p*-Hydroxybenzoic acid	— antimicrobial agent — anti-algae agent — anti-mutagenic agent — nemacid agent — antiviral agent — anti-atherogenic agent — anti-inflammatory agent — hypoglycemic agent — antioxidant agent	[40,41]
2	Daphnetin	— antithrombotic agent — anti-inflammatory agent — antioxidant action — treatment of blood clotting disorders — treatments for rheumatoid arthritis — reduces fever	[40,42]
3	Genkwanol A	—	[40]
4	Luteolin	—	[40]
5	Physcion	— Laxative — hepatoprotective — anti-inflammatory agent — antimicrobial — anti-proliferative	[40,43]
6	Luteoloside	— antimicrobial — anti-cancer	[40,44]
7	Daphnetin-7-*O*-*β*-*D*-glucoside	— anti-proliferative action	[42,45]
8	Daphnoretin	— antiviral activity	[40,46]
9	Demethyldaphnoretin-7-*O*-*β*-*D*-glucopyranoside	— anti-proliferative action	[40,45]
10	Syringin	— removal of free radicals — protection against damage to neurons — inhibition of apoptosis — anti-diabetic effect — anti-inflammatory potential — anti-nociceptive action — anti-allergic effect	[40,47]
11	Oleodaphnone	—	[40]

Conclusion

The results of the literature review showed that endemic medicinal plant raw materials growing on the territory of the Tarbagatai National State Park are little studied. The chemical composition that determines the pharmacological activity of

medicinal plant materials is not well understood. In *Corydalis ledebouriana* Kar. et Kir. 22 individual substances were obtained, of which only a few were found to have pharmaceutical activity since the rest were not completely understood. In addition, the literature analysis revealed that there are no studies on the isolation of individual substances from *Malus sieversii*. *Daphne* species are a source of several classes of valuable phytochemicals such as coumarins, flavonoids, lignans, steroids, and various classes of terpenes. The phytochemical diversity of this genus is demonstrated by over 350 secondary metabolites isolated from various species. Therefore, species belonging to the genus *Daphne* can be considered an important source of synthesis of new drugs. There are no publications in international databases. Thus, further studies of endemic plants growing in the territories of Kazakhstan are needed.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the article, and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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HOW TO CITE THIS ARTICLE

Baltabay Bekbolat Saparbayuly, Abilkassymova Alima Maratkyzy, Majitova Mariyam Akhiyatkyzy, Satmbekova Dinara Kanatovna, Datkhayev Ubaidilla Makhambetovich, Sarsenova Lazzat Kadyrgaliyevna. Three Little-known Medicinal Plants Growing in the State National Natural Park "Tarbagatai" (Republic of Kazakhstan): Their Ethnobotany, Phytochemistry, and Pharmacology. *J. Med. Chem. Sci.*, 2023, 6(1) 112-120
https://doi.org/10.26655/JMCHEMSCI.2023.1.14
URL: http://www.jmchemsci.com/article_154599.html