OROBANCHACEAE PLANTS OF ISRAEL AND PALESTINE. CHEMICAL AND MEDICINAL TREASURES

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Orobanchaceae plant family is one of the most interesting plant families in our region. It is represented by small number of plants and some of them attracted major interest while others have been almost completely neglected. Even the ethnobotanical uses of these plants in the reviewed region are very limited. The present day knowledge about these plants indicates contradicting research tendencies, interesting natural products that were isolated from some of these plants, along with massive lack of information about the chemical and medicinal properties of others. Many review articles were published about this family, but each one of them lacks some essential information or includes ambiguities. This article will present the known information in helpful tables and figures, but will mainly emphasize the areas where intensive research efforts are needed. In the discussion section, the parasitic nature of these plants will be elaborated, and some synthetic and biosynthetic paths will be introduced.

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INTRODUCTION

Orobanchaceae plant family includes around 2060 species, classified in 90 genera.[1] In the reviewed region, it is represented by 17 species, and this number is debated among scholars.[2] For example, G. Domina and A. Danin have defined a new species in 2014, and they named it *Orobanche cohenii*.[2] But searching the website "Flora of Israel Online", that was established by Prof. A. Danin himself and still has his name on homepage, shows that this species is not included in the 18 species presented there.[3] Interestingly, ancient human societies did not utilize these plants for their needs.

The major botanical property of *Orobanchaceae* plants is their parasitic nature, which was very extensively studied. Many aspects of this parasitism were investigated, such as the genetics of this property,[4] and the chemical basis of it.[5] For example, the cyclohexene oxide-type sphaeropsidone (Figure 1), induces parasitism of *Orobanche* plants, which is a genus in the *Orobanchaceae* family.

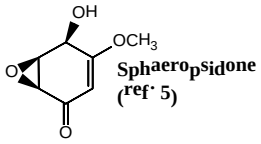

Figure 1. Sphaeropsidone, natural parasitism inducer of Orobanche plants

Among the four genera that are represented in the reviewed region, *Orobanche* plants are the most parasitic, and many attempts were made to control them. An extensive presentation of this topic will be introduced in the discussion section, but we will indicate here some of these publications. *Orobanche crenata* and *Orobanche aegyptiaca* are among the most harmful species of this genus, and a method of controlling them (Imazapic, $C_{14}H_{17}N_3O_3$) in parsley crops was reported.[6] Another study that investigated the mechanism of parasitic activity of *O. aegyptiaca*, revealed the involvement of horizontal genes transfer.[7] *O. crenata* is harmful to many crops, especially *Fabaceae* plants, and so, it causes many agricultural damages to *Vicia faba* production, which is a major food source in the Middle East, particularly in Egypt. So, a method of biocontrol of this parasitic plant was developed based on the allelopathic property of *Euroca sativa* seed powder.[8] But as we mentioned above, all genera of this plant family are parasitic, and a notable study of this property of one of the most studied plants of this family, *Cistanche tubulosa*, was performed and it revealed the mechanism that this parasite attaches itself to the roots of host plants.[9]

Figure 2. *Bellardia trixago* (Orobanchaceae)

Finally, in the reviewed region, the *Orobanchaceae* plant family is represented by four genera that include 17 species namely *Bellardia trixago*, *Cistanche fissa*, *Cistanche salsa*,

Cistanche tubulosa, *Odontites aucheri*, *Orobanche aegyptiaca*, *Orobanche cernua*, *Orobanche crenata*, *Orobanche cumana*, *Orobanche hermonis*, *Orobanche lavandulacea*, *Orobanche mutelii*, *Orobanche palaestina*, *Orobanche pubescens*, *Orobanche schultzii*, *Parentucellia flaviflora* and *Parentucellia viscosa*.

ETHNOBOTANICAL USES

Generally, cultures of the Middle East and particularly these of reviewed region, have almost ignored the *Orobanchaceae* plant family. There is very partial documentation of ethnobotanical uses of these plants, contrary to some nations in the Far East or Europe. But these peoples mostly used species that do not grow in Israel and Palestine, so we will not cite these reports here. And yet, some of the literature that we will cite about the species that grow here, were published about other regions in the world. In Table 1, we summarized these published uses.

Table 1. Ethnomedicinal and ethnobotanical uses of *Orobanchaceae* plants

Species	Region, uses, methods, references
Bellardia trixago	Spain. Flowers are sucked as food.[10]
Cistanche salsa	Korea. As part of a traditional formulation named PJBH, to activate brain function, promote memory and lengthen life span.[11]
Cistanche tubulosa	Pakistan. Whole plant powder used against diarrhea,[12] blood purifier, epistasis, cough, fever, bleeding nose, laxative, digestive, remove the pain of stomach, flavoring agent in pot herbs,[13,14] aprodisiac.[15] India. Fertility of males and females, jaundice, whooping cough, stomach aches, diabetes.[16] Ethiopia. Whole plant powder with butter to treat burns.[17]
Orobanche aegyptiaca	Nepal. Seeds are used as toys.[18]
Orobanche crenata	Italy. Food. Young shoots are prepared and consumed in various ways.[19]
Orobanche mutelii	Turkey. Harmful to melon crops.[20]

SELECTED PUBLISHED REVIEW ARTICLES: PRESENTATION AND DISCUSSION

Aside from very few review articles about the parasitic properties of the entire *Orobanchaceae* plant family, there are no reviews about its medicinal, ethnobotanical and chemical composition of the plants. Different genera, species or even natural products contained in the plants, were reviewed, and in our humble opinion, some of them have high quality. So, the need for a comprehensive article like this one is felt.

The most recent review article was published by R. Shi and her colleagues.[21] This article is outstanding in terms of the very good photos, tables, listing of traditional uses of the plants, citation of modern research published results and numerous structures of natural products that were isolated from the plants of the genus of *Orobanche*. Another strength that this article is its global presentation of the plants of this genus. But it showed some shortcomings also, especially in the cited literature, particularly if an interested reader is interested to follow, and learn more about some presented woek. For example, the work of "Han, 2017" has been cited no less than 27 times. When reading the references part of the article, it is cited as "Studies on the Chemical Composition, Content Determination and Antioxidant Activity of *Orobanche Aegyptiaca* Pers, Inner. Mongolia. Med. Univ.". Searching the internet for this work or any other citations of it, did not lead to a single result. But as we mentioned earlier, this review is one of the best published about this genus, due to its comprehensiveness. Another outstanding review about the genus of *Orobanche* natural products was published by F. Scharenberg and C. Zidorn.[22] It is a vast article that focuses on these compounds and some of their medicinal activities.

The genus of *Cistanche* was even more covered than *Orobanche*. L-l. Wang and her colleagues published a short review about the composition and the pharmacological activities of the Chinese traditional medicine formulation named Cistanches Herba, which contains five species of this genus.[23] Despite the fact that only two of them grow in the reviewed region (*C. salsa* and *C. tubulosa*), this review is highly informative. Z. Li and his colleagues published a short review article about the same formulation.[24] They name it Herba Cistanches (Rou Cong-Rong, in Chinese), and they presented its ancient use in traditional Chinese medicine, that go back to 250 BC, its composition and medicinal activities. The most recent review article about this formulation was published by H. Lei *et al*.[25] It is comprehensive, with two clear advantages over previous review articles. First, it indicates the plant species from which each natural product was isolated. Secondly, the natural products are arranged in general structure that presents each one of them as a derivative of this structure. Along with the three cited review articles (ref. 23-25), the publication of Y. Jiang and P-F. Tu, give a comprehensive view of the chemical composition and the medicinal activities of this unique formulation.[26]

But this formulation was reviewed not just in general scope as in references 23-26, but some reviews elaborated on some specific activities. An excellent review article of this type was published by C. Gu *et al*. that presented various medicinal activities of this formulation but focused on neuropharmacological aspects.[27] N. Wang and her colleagues focused on antiaging activity in their excellent, comprehensive review article about this formulation.[28] Their review has more advantages which are, linking to traditional medicine, presenting various activities and showing the structures of major active ingredients.

Review articles about single species of the *Orobanchaceae* plant family, in our region, are very limited. Among these species, only *Cistanche tubulosa* and *Orobanche crenata* have been reviewed. *C. tubulosa* was reviewed by A. E. Al-Snafi, and the article presents many medicinal activities that this plant showed.[29] This good article lacks two topics: traditional medicine and structures of at least major active natural products, even though some

of them are indicated. C. Genovese and his colleagues reviewed the chemical composition and the biological activities of *O. crenata*.[30] This very good review is very informative, with excellent tables and figures but lacks introduction to use in traditional medicine.

Finally, R. Halouzka and his colleagues summarized in a very useful review article the analytical methods of isolation and quantification of strigolactones (see general structure in Figure 3).[31] These natural products are found in *Orobanche* and *Striga* genera, but the second one is not represented in the reviewed region and not included in this article.

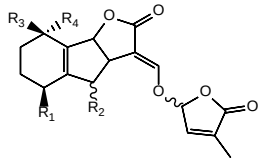

Figure 3. General structure of Striglactone (ref. 31)

MEDICINAL ACTIVITIES AND CHEMICAL COMPOSITION

Scanning the published literature about the plants of *Orobanchaceae* family that grow in the reviewed region, revealed an interesting but not completely understood result. Few species are extensively studied, others are very limitedly studied and many have been completely ignored. Moreover, some "classical" medicinal properties that are usually tested and published for other plant families, are not mentioned at all. For example, there are no publications that report antidiabetic or related activities, for any of these plants. On the contrary, there is relatively considerable amount of publications that reported isolation and characterization of structurally interesting natural products and of brain related activities.

Summary of these findings are shown in the following tables, that appear according to alphabetical order of the names of the species. An absence of published reports has been clearly indicated.

Bellardia trixago

Table 2. Biological, medicinal and other properties of *Bellardia trixago*

Activity/Property	Major Findings/Reference
Antifungal	Resin of the plant was analyzed, and 8 known flavonoids were identified. Some of these compounds were methylated and found active against the fungus *Cladosporium herbarum*.[32]
Insecticidal	Essential oil of whole plant was prepared and analyzed by GC-MS. A detailed list of compounds is presented. New natural products are not reported, but this EO showed antifeedant activity against *Spodoptera littoralis*.[33] Aerial parts were extracted with dichloromethane and extract showed weak antifeedant activity against *Spodoptera litura*. Extract was analyzed and detailed list of (known) compounds and structures are provided.[34]
Chemical composition	Isolation and characterization of new compounds have been reported. The structures of most of them are shown in Figure 4.[35,36] Malonate ester of compound A in Figure 4.[37] Isolation of known, active, interesting natural products found in this plant has been reported.[38,39]

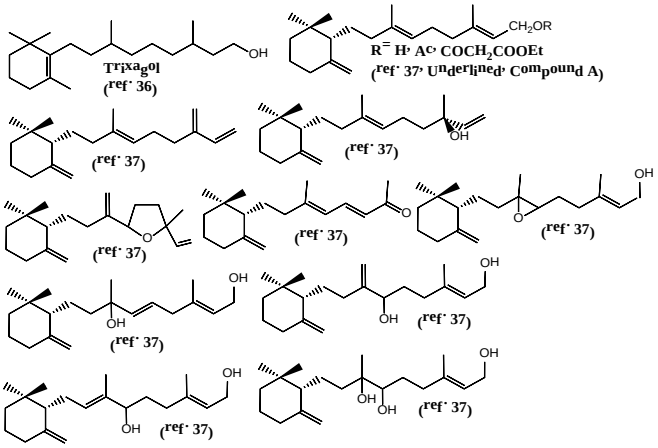

Figure 4. New compounds isolated from *Bellardia trixago*

Cistanche fissa.

There are no publications relevant to this review article.

Cistanche salsa

Table 3. Biological, medicinal and other properties of *Cistanche salsa*

Activity/Property	Major Findings/Reference
Analgesic	Stems were extracted with 80% aqueous ethanol, assisted with microwave radiation. Extract showed antinociceptive activity in mice, that was tested with three methods.[40]
Anticancer and related activities	Whole plant was extracted with 50 % aqueous ethanol, and this extract showed anti-proliferative activity against prostate cancer cells in rats.[41]
Bones related activities	Whole plant was extracted with methanol and extract was fractionized by several organic solvents, yielding and new compound [*R*-HDOA, see Chemical composition below]. This compound showed anti-osteoporotic activity in mice.[42]
Brain related activities	Phenylethanoid glycoside-rich extracts were prepared by extracting different parts of the plant with organic solvents.

	These extracts showed activity against neurotoxicity of MPTP in mice.[43-46] *Echinacoside* (phenylethanoid glycoside) was isolated from stem methanolic extract, and it alleviated hypobaric hypoxia-induced memory impairment in mice.[47]
Hepatoprotection	Phenylethanoid-rich (mainly *Echinacoside*) stem methanolic extract showed protective activity against ethanol-induced hepatotoxicity in mice.[48]
Enzyme inhibition	Whole plant was extracted with methanol and extract was chromatographed obtaining five new compounds (see Chemical composition below). These compounds inhibited the production of NO that was induced by LPS.[49]
Immune system related activities	Three studies that were published in the same year by the same research group, reporting immunomodulatory and immunostimulant effect of extracts of the plant.[50-52]
Chemical composition	*R*-HDOA (Figure 5) was isolated and its structure was confirmed by spectroscopic analyses and by laboratory synthesis of it.[42] Five new phenylpropanoid-substituted diglycosides were isolated (Figure 5).[49] Six new *Salsasides* were isolated from the stems of the plant. Their structures are presented in the review article that we cited earlier (ref. 25).[53] This publication did not report new compounds, but it is interesting since it presents the HPLC method of isolation of active glycosides of this plant.[54]

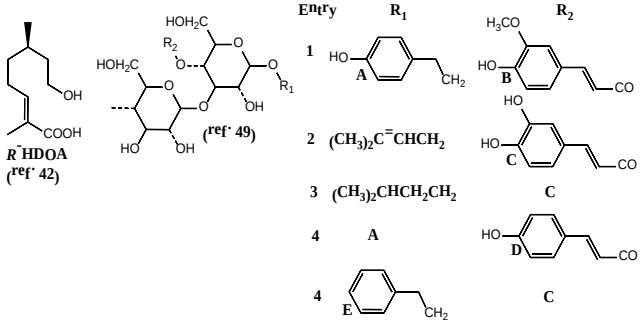

Figure 5. New compounds isolated from *Cistanche salsa*

Cistanche tubulosa

Table 4. Biological, medicinal and other properties of *Cistanche tubulosa*

Activity/Property	**Major Findings/Reference**
Anticancer and related activities	Commercial mixture of phenylethanoids that was isolated from the plant, showed activity against B16-F10 cancer cells.[55] Whole plant aqueous extract showed activity against human colon cancer cells.[56] Commercial mixture of phenylethanoids that was isolated from the plant, showed activity against H22 hepatocellular carcinoma cells.[57]
Antidiabetic, anti-hyperlipidemic	Stem ethanolic extract showed antidiabetic and hypolipidemic activities in db/db mice model.[58] Roots were extracted with 70 % aqueous ethanol and extract was hypocholesterolemic in mice.[61]
Antioxidant, anti-inflammatory	Commercial Echinacoside (Figure 6), a major compound in the extracts of the plant, and various extracts, showed antioxidant (DPPH, trolox) and anti-inflammatory activity in STZ-nicotineamide-induced diabetic rats[59] Ultrasonic-assisted extraction of aerial parts yielded new polysaccharide (rhamnose, mannose, glucose, and galactose), which showed *in vitro* antioxidant activity.[60]
Bone, muscle, eye, growth and hair related activities	Commercial echinacoside and acteoside (Figure 6) showed anti-osteoporotic activity in rat model.[62] Commercial extract (no other details) showed novel eye protection against blue light emission, that was confirmed by 6 methods, *in vitro* and *in vivo*.[63] Stems were extracted with 30 % aqueous ethanol and this extract enhanced muscles activity, in forced immobilized rats.[64] Commercial mixed extract of the plant with *Laminaria japonica*, was orally (pills) administered to healthy female human who suffered hair loss and unhealthy scalp. This supplementation improved both conditions.[65] Stems aqueous extract was chromatographed to obtain nearly pure echinacoside, with small amount of acteoside and tubuloside A (Figure 6). This powder was fed to rats and it stimulated growth hormone, suggesting antiaging activity.[66]
Brain related activities	Commercial echinacoside and acteoside showed anti-Alzheimer activity in rat model.[62] Patented phenylethanoid glycosides pills produced from plant extract found efficient for treating moderate Alzheimer disease (AD).[67] Phenylethanoid glycosides-rich stem aqueous extract was showed anti-Alzheimer disease-like activity in rat model, and slowed memory loss and improved other brain functions.[68] Stem aqueous extract that contained mainly echinacoside, acteoside and isoacteoside (Figure 6), inhibited aggregation of amyloid-β in AD-like model in rats.[69] A decoction was prepared from Herb *Cistanche*, a traditional Chinese medicine, which is a mixture of *C. tubulosa* and *C. deserticola* (not included in this review). This decoction was rich with phenylethanoid glycosides, and it was supplied to rats that were exposed to

	several stress methods. The decoction showed antidepressant and cognitive improvement activities.[70] Aqueous extract of Herb *Cistanche* that contained mainly *C. tubulosa*, was supplied to rats that were subjected to various depression inducers. The extract showed clear antidepressant activity, confirmed by behavioral and brain chemical tests.[71,72] Plant nano-powder was orally supplied to rats that were exposed to various stress methods. Results showed antidepressant and neuroprotective (dopaminergic neurons) activities.[73]
Cardiovascular system related activities	Echinacoside and acteoside that were extracted with water from the stems of the plant, showed blood glucose lowering and hypotensive effect *in vitro*.[74]
Hepatoprotection	Methanolic extract from fresh stems have hepatoprotective effects against D-galactosamine/lipopolysaccharide (LPS)-induced liver injury in mice. The extract was rich with phenylethanoid glycosides and their acetyls.[75] Roots were extracted with 70 % aqueous ethanol, to obtain phenylethanoid glycosides-rich extract. It showed activity against hepatic fibrosis in rats.[76]
Nutrition, toxicity	The group that published Ref. 68 tested the safety of their capsules (Memoregain®) and found it safe.[77]
Reproductive system, sex	Commercial Echinacoside, and various extracts, showed steroidogenisis in STZ-nicotineamide-induced diabetic rats[59] Stems were extracted with 70 % aqueous ethanol and this extract enhanced sex hormone levels in rats.[78]
Chemical composition	Four new tubulosides were isolated and characterized. One of them, tubuloside A is shown in Figure 6.[79] New iridoid glycosides, kankanosides A-D, kankanol and kankanoside E (Figure 6) were isolated from the methanolic extract of dried stems.[80] Interesting studies of chemical composition and methods for their determination have been reported though no new compounds were detected.[81-84]

Odontites aucheri

There are no publications relevant to this review article.

Orobanche aegyptiaca

Whole plant aqueous extract showed hypotensive activity.[85]

Orobanche cernua

A new phenylethanoid, 3'-O-methyl isocrenatoside, was isolated from fresh whole plant and characterized (Figure 7). This compound, along with other two known compounds were active against human lung cancer cell lines.[86] Stems of the plant were extracted with 70 % aqueous ethanol and this extract showed strong antioxidant activity (DPPH),[87] and their ethanolic extract showed protective effect against UVB-induced human skin photoaging.[88]

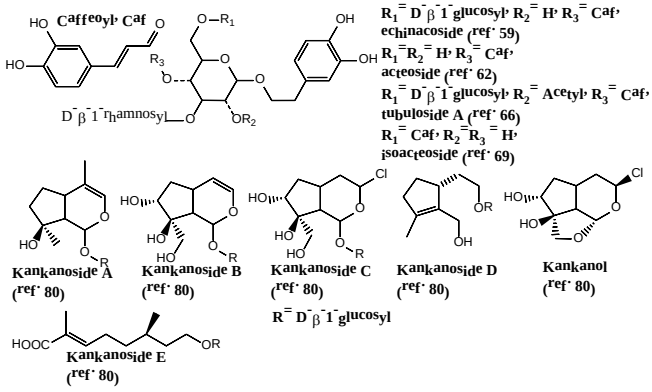

Figure 6. New compounds isolated from *Cistanche tubulosa*

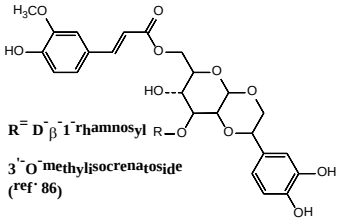

Figure 7. 3'-Omethyl isocrenatoside isolated from *Orobanche cernua*

Orobanche crenata

Table 5. Biological, medicinal and other properties of *Orobanche crenata*

Activity/Property	Major Findings/Reference
Analgesic	Whole plant was successively extracted with chloroform and 70 % aqueous methanol, and the organic solvent was removed. The water solution was fractionized with ethyl acetate and chloroform. The ethyl acetate fraction showed analgesic activity in hot plate method in mice.[89]
Antibacterial, antifungal	Acetone extract of leaves showed activity against several bacteria and fungi species.[90] Aerial parts were separately extracted with methanol and water. Both extracts showed antioxidant activity (DPPH, ABTS).[91] Leaves were extracted with 80 % aqueous methanol and extract was fractionized to obtain phenolics-rich fraction. This fraction showed activity against 8 fungi species.[93]
Anticancer	Methanolic extract of the plant (parts not indicated) was prepared and showed activity against several cancer cell lines.[92] Whole plant was successively

	extracted with *n*-hexane, ethyl acetate, acetone, methanol and water. Essential oil was also prepared. All products were tested for general chemical composition and activity against B16F10 melanoma cancer cells.[94]
Antioxidant	Acetone extract of leaves showed antioxidant activity (DPPH).[90] Aerial parts were separately extracted with methanol and water. Both extracts were tested against 18 bacteria species. Methanolic extract was active in 17 cases, but aqueous extract was not.[91] Methanolic extract of the plant (parts not indicated) was prepared and antioxidant activity (FRAP, DPPH) was tested.[92] Whole plant was successively extracted with *n*-hexane, ethyl acetate, acetone, methanol and water. Essential oil was also prepared. All products were tested for antioxidant activity (DPPH, FRAP, TEAC).[94]
Antispasmodic, muscles related activities	Whole plant ethyl acetate fraction (see analgesic) showed smooth muscles relaxation effect and antispasmodic activity in mice.[89]
Diuretic	Whole plant ethyl acetate fraction (see analgesic) showed diuretic activity in mice.[89]
Hypotensive	Whole plant ethyl acetate fraction (see analgesic) showed hypotensive activity in mice.[89]
Chemical composition	Crenatoside was isolated and characterized from aerial parts of the plant (Figure 8).[95]

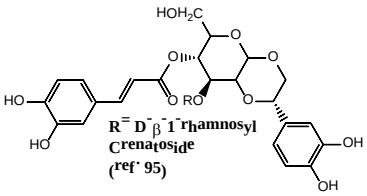

Figure 8. Crenatoside isolated from *Orobanche crenata*

Orobanche cumana* and *Orobanche hermonis

There are no publications relevant to this review article.

Orobanche lavandulacea

Whole plant was successively extracted with *n*-hexane, ethyl acetate, acetone, methanol and water. Essential oil was also prepared. All products were tested for general chemical composition and activity against B16F10 melanoma cancer cells.[94]Whole plant was successively extracted with *n*-hexane, ethyl acetate, acetone, methanol and water. Essential oil was also prepared. All products were tested for antioxidant activity (DPPH, FRAP, TEAC).[94]

Orobanche mutelii, Orobanche palaestina, Orobanche pubescens, Orobanche schultzii*, and *Parentucellia flaviflora

There are no publications relevant to this review article.

Parentucellia viscosa

Aerial parts were extracted with dichloromethane and extract showed notable antifeedant activity against *Spodoptera litura*. Extract was analyzed and detailed list of (known) compounds and structures are provided.[34]

General chemical composition and analysis of polar compounds in the plant, in order to compare with other plants of the *Orobanchaceae* family. New compounds are not reported, but the study confirmed the presence of known active compounds found in other plants of this family.[96] Other authors found a new compound, gardoside methyl ester (Figure 9).[97]

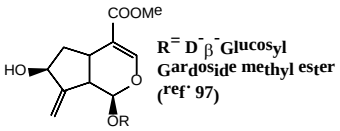

Figure 9. Gardoside methyl ester isolated from *Parentucellia viscosa*

DISCUSSION

The previous section of "Medicinal activities and chemical composition" reveals a dismal picture about the medicinal and chemical research of the *Orobanchaceae* family in the reviewed region of Israel and Palestine. A minority of them was sufficiently studied and published, while the majority was not. Nine species out of 17 have no medicinal activities-type articles and their chemical composition is unknown. Some other species were very limitedly studied.

Although the *Cistanche* genus is represented by 3 species and the *Orobanche* genus by 10, the number of publications about *Cistanche* is way higher, and they are much more frequent. This is due to the massive use of *Cistanche* plants in East Asian traditional medicines, and especially, the successful medicinal formulation "*Cistanches* Herba" in Chinese traditional medicine. So, the interest of East Asian researchers in the species *Cistanche tubulosa* yielded many important publications (see previous section and discussion below).

One of the major research finding was that of the active natural products in the *Cistanche* plants and study the various conditions of growth or cultivation that affect the qualities and the quantities of these compounds in the plants. In this regard, Y. Wang *et al*. published one of the most comprehensive works.[98] Geographically, they sampled plants from all over the world but mainly focused on China and Mongolia. They tested the presence and concentrations of seven phenylethanoid glycosides and found several conditions that affect these compounds.

Even though *Cistanche salsa* was moderately studied for medicinal activities, its chemical composition drew major interest of researchers. On this basis, many works about its cultivation conditions were published, such as the study of X. Sun *et al*.[99] In addition, J-Y. Liu *et al*. developed a method to increase the production of phenylethanoid glycosides (echinacoside, acteoside, 2′-acetylacteoside) by feeding the plants with precursors such as tyrosine, phenylalanine, caffeic acid and cucumber juice.[100] J. Chen *et al*. reported that cultivation of the plant under administration of hydrogen peroxide, upregulated the genes responsible for the production of these important natural products, and their biosynthesis was enhanced.[101]

As we mentioned above, *Cistanche tubulosa* was and still extensively investigated, since it is an important ingredient of "*Cistanches* Herba". An early, interesting botanical study of this plant was published by T. S. Rangan and N. S. Rangaswamy, focusing on the parasitic nature of this species, and biochemical parasite-host relationship.[102] T. Deyama *et al*. published an outstanding work of isolation of phenylethanoid glycosides from this plant, and a comprehensive spectroscopic identification of them. Moreover, their major biological activities are presented.[103] S-Y. Zhao *et al*. reported that microwave processing of the plant increased the production of acteoside.[104] They report that this treatment activates β-glucosidase that hydrolyses echinacoside to acteoside, and for this purpose, several β-glucosidases were tested. C. Xei *et al*. developed a very efficient method (high-speed counter-current chromatography) for isolation of echinacoside and acteoside from this plant.[105] Y. Li *et al*. developed a unique method using ultraperformance liquid chromatography-quadrupole time-of-flight mass spectrometry to identify echinacoside metabolites, produced by human intestinal bacteria.[106] Q. Cui *et al*. reported the development of very similar method to identify metabolites of echinacoside and acteoside in rat plasma, bile, urine and feces.[107]

Attempts to achieve an increase in the amount of the important phenylethanoids found in *Cistanche tubulosa*, were not limited to growing the plant under various conditions, which promoted their production. G. Guchhait and A. K. Misra reported a short synthesis of the trisaccharide major unit in these compounds (see Figure 6).[108] The compound that they reported is shown in Figure 10.

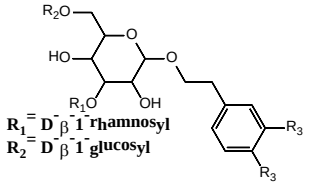

Figure 10. Trisaccharide prepared by Guchhait & Misra (ref. 108)

In the reported synthesis, R_1=R_2=H, meaning that the aromatic ring is not substituted in positions 3, 4. Authors claim that they prepared the core trisaccharide of Kankanoside F. But in this compound, which was first isolated by M. Yoshikawa and his colleagues, the aromatic ring is doubly hydroxylated (R_3=OH).[109] Additional synthetic steps are needed to hydroxylate the aromatic ring. M. Yoshikawa and his colleagues report that these compounds (the isolated kankanosides F and G) have vasorelaxant activity. Finally, in this regard, this research group published an excellent review article about the active natural products of *Cistanche tubulosa*.[110]

A detailed and relatively easy to perform synthesis of trixagol (Figure 4) found in *Bellardia trixago* was published by R. J. Armstrong and Larry Weiler.[111] A. F. Barrero and his colleagues published a unique report on the use of this plant for the synthesis of enantiospecific odorant products.[112] For example, the important natural product dihydro-γ-ionone is present only in small amounts in *Bellardia trixago* and other plants. So, this group reported its synthesis from another natural product present in the plant in larger concentration. The synthesis is shown in Figure 11.

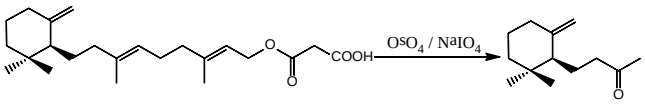

Figure 11. Synthesis of dihydro-γ-ionone.

Relying on the success previous synthesis (60 % isolated yield) of dihydro-γ-ionone, this group used that compound to prepare other natural products present in small quantities in the same plant, such as Siccanochromene F.[113] Finally, a comprehensive work of the synthesis and use of this compound and its closely related structures, was published by A. Barakat and his colleagues.[114]

Among the plants of the *Orobanchaceae* family, species of the *Orobanche* genus are more parasitic than other genera, and among these, *O. crenata* is the most aggressive.[115] The research of this species is ranging between two contradictions: on one hand, attempts to use it as food and utilize its medicinal properties (Table 5), and on the other hand, efforts to understand its parasitic mechanism, and develop methods to control it.

Strigolactones (Figure 3) are produced by different host plants and they play major role of growth stimulation of *O. crenata*. On this basis, I. Trabelsi and her colleagues published their research about various factors that affect the production of strigolactones, and consequently, possible methods to control *O. crenata*.[116] R. Matusova and her colleagues investigated the biosynthetic paths of strigolactones, and discovered the involvement of carotenoids as starting materials.[117]

As we mentioned earlier, there are no published studies about the medicinal/biological properties of *Orobanche cumana*. But as a harmful weed, many researches were published. One of them studied the effect of Heliolactone (Figure 12), a growth stimulant produced by sunflower (*Helianthus annuus*) on the parasitic activity of *O. crenata* and *O. cumana* (and other plants that are not included in this article).[118]

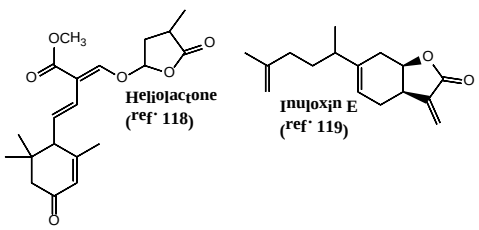

Figure 12. Growth stimulants of *Orobanche* plants

But not only sunflower is infected by *O. cumana*, wild plants of the same family (*Asteraceae*) are parasitized by this plant, such as *Dittrichia viscosa* (False yellowhead), that grows in the Mediterranean basin. The host-parasite relationship in this case was studied revealed that the host species produces a growth stimulant, Inuloxin E (Figure 12).[119]

So, *Orobanche* plant species are real challenge. Many efforts have been made to control them and the review article of S. Habimana is a good summary of these efforts of different types.[120] But they are also a very rich source of active natural products, that have unique structures with useful sub-units for organic synthesis. For this reason, many analytical methods were developed for their isolation and quantification. The review article of S. V. Luca and his colleagues presents the structures of the major compounds and the various methods that were developed for their isolation.[121]

CONCLUSIONS

Generally, plants of the *Orobanchaceae* family in Israel and Palestine, were very limitedly studied. The medicinal and biological activities of most of these plants have never been published. These plants have parasitic activity and understanding these parasite-host relationships might result in controlling these parasites. The species that were studied are sources of unique natural products.

There is a great lack of using the isolated natural products of these plants for synthesis of new analogues and modifications, thus it is a real need to investigate the medical uses of pure compounds isolated from these unique plants.

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