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OROBANCHACEAE PLANTS OF ISRAEL AND PALESTINE CHEMICAL AND MEDICINAL TREASURES

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Abstract: One of the most fascinating groups of plants in our area is the orobanchaceae. It is embodied by a few of plants, some of which have garnered considerable attention while others have been mostly disregarded. Very few people in the examined area actually make use of these plants for ethnobotanical purposes. Current understanding of these plants reveals a paucity of data on the chemical and therapeutic qualities of some, fascinating natural compounds extracted from others, and contradictory research trends in general. Despite the abundance of reviews devoted to this family, every single one is either missing key details or contains confusing language. Tables and figures will assist illustrate the known facts in this article, but the major focus will be on the areas that need thorough investigation. The discussion section will go more into the parasitic nature of these plants, and some

Keywords: Orobanchaceae; trixagol; iridoids; phenylethanoids; strigolactones; parasitic plants, medicinal activities,immunomodulation.

INTRODUCTION

There are over 20,600 species in the Orobanchaceae family, which is divided into 90 genera.1 The number of species in the reviewed area is a matter of disagreement among experts, with 17 species being represented.2 As an example, in 2014, G. Domina and A. Danin described a new species of Orobanche and gave it the name Orobanche cohenii.2 On the other hand, this species is not included among the 18 species on the website "Flora of Israel Online," which was created by Prof. A. Danin and still has his name on the homepage.3 It is worth noting that these plants were not used by ancient human communities.

Orobanchaceae plants are known for their parasitic nature, which has been the subject of much research. Numerous facets of this parasite were studied, including its chemical foundation and its genetic base.5 Parasitism in the Orobanche plant genus (Orobanchaceae family) may be induced, for instance, by the cyclohexene oxide-type sphaeropsidone (Figure 1).pests that attack a wide variety of crops, wreaking havoc on the vicia faba crop—a staple crop in Egypt and other Middle Eastern countries—and other Fabaceae plant varieties. Because of the parasitic plant's allelopathic effect, a biocontrol strategy based on powdered Euroca sativa seed was devised.8 One of the most researched members of this family, Cistanche tubulosa, had its parasitic nature investigated extensively, and the results showed how the parasite attaches itself to host plant roots. However, as we said before, all genera in this family are parasitic.

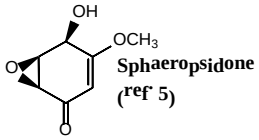

Figure 1. Sphaeropsidone, natural parasitism inducer of Orobancheplants

Orobanche plants are the most parasitic of the four species found in the area under consideration, and several efforts to manage them have been undertaken. In this debate, we will go further into this subject.

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Figure 2. *Bellardia trixago* (Orobanchaceae)

Lastly, the examined area is home to seventeen species belonging to the Orobanchaceae family. These species are listed in the following genera: 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

Cultures throughout the Middle East, and the reviewed area in particular, have paid little attention to the Orobanchaceae family of plants. In contrast to some countries in Europe or the Far East, only fragmentary evidence of these plants' ethnobotanical applications exists. We will not quote these findings here since these folks mostly utilised species that do not grow in Israel and Palestine. Despite this, we shall reference several works that discuss species native to this area, even if they were written about other parts of the globe. We summarised these reported uses in Table 1.

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 activatebrain function, promote memory andlengthen 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]

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Orobanche crenata	Italy. Food. Young shoots are preparedand consumed in various ways.[19]
Orobanche mutelii	Turkey. Harmful to melon crops.[20]

SELECTED PUBLISHED REVIEW ARTICLES:PRESENTATION AND DISCUSSION

There is a dearth of literature reviewing the medicinal, ethnobotanical, and chemical composition of plants belonging to the Orobanchaceae family, and even less reviewing their parasitic characteristics. Various plant genera, species, and even their natural products were evaluated, and we must say that some of them are of very good quality. Accordingly, an in-depth piece such as this one is required.

R. Shi and coworkers released a review paper not long ago.21 Among the many great things about this piece is

excellent images, tables, listing of traditional usage, citation of published findings from recent research, and a plethora of structures of natural compounds derived from Orobanche plants. The article's worldwide presentation of this genus's plants is another quality. However, it did reveal a few flaws, most notably in the list of references, which can be problematic for readers who are keen in delving further into the works referenced. One example is the work of "Han, 2017" which has been referenced at least 27 times. It is referenced as "Studies on the Chemical Composition, Content Determination and Antioxidant Activity of Orobanche Aegyptiaca Pers, Inner Mongolia. Med. Univ." in the article's references. I was unable to locate this work or any other references to it via an online search. However, as we said before, this assessment is among the greatest published works on this species because of its thoroughness. F. Scharenberg and C. Zidorn provided another excellent study about the Orobanche genus of natural goods.22 The essay delves further into these chemicals and their potential medical usefulness.

Compared to Orobanche, the Cistanche genus has an even higher coverage rate. Cistanches Herba is a Chinese traditional medicine formulation that includes five species of this genus. L-l. Wang and colleagues wrote a brief study regarding the composition and pharmacological activity of this formulation.23 This assessment is rather useful, even if only C. salsa and C. tubulosa grow in the evaluated location. A brief review paper about the same formulation was written by Z. Li and colleagues.24 Herba Cistanches, or Rou Cong-Rong in Chinese, was described along with its chemical make-up and therapeutic effects, as well as its long history of usage in traditional Chinese medicine, which dates back to 250 BC. In their most current review, H. Lei et al. discussed this concept.25 Compared to earlier review articles, it has two obvious benefits and is thorough. To start, it lists the plant species that were used to extract each natural substance. Second, this framework serves as a basis for the natural goods, which are organised in a generic way. A thorough understanding of the chemical make-up and therapeutic effects of this novel formulation is provided by the works of Y. Jiang and P-F. Tu, in addition to the three referenced review publications (refs. 23–25).26

However, not all evaluations of this formulation were broad in scope (see references 23–26), and some studies went into more detail about certain tasks. The neuropharmacological features of this formulation's many therapeutic effects were the subject of a high-quality review paper published by C. Gu et al.27 In their outstanding and all-encompassing review paper on this formulation, N. Wang and colleagues centred on its antiaging effects.28 Additional benefits of their study include demonstrating the structures of key active components, providing a variety of activities, and establishing links to traditional medicine.

There is a dearth of regional review publications focusing on individual species within the Orobanchaceae family. We have only examined Cistanche tubulosa and Orobanche crenata among these species. Many therapeutic actions of C. tubulosa were detailed in the essay by A. E. Al-Snafi, who reviewed the plant.29

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Traditional medicine and the structures of at least two main active natural product classes are absent from this otherwise excellent article, despite the fact that several

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.

	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]

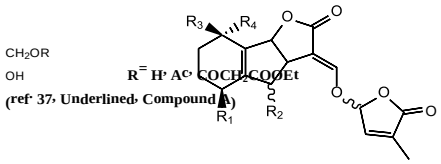
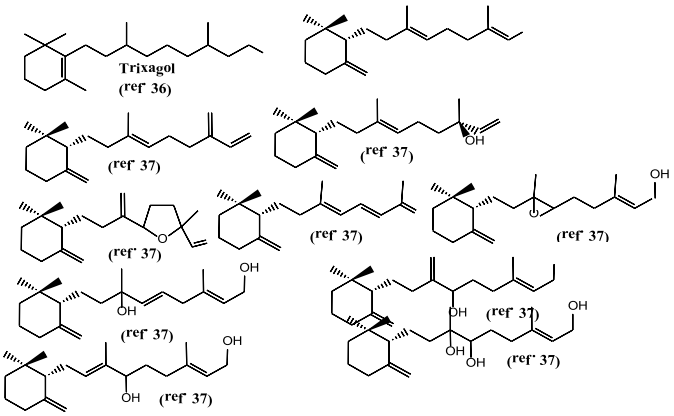


Figure 3. General structure of Striglactone (ref. 31)



MEDICINAL ACTIVITIES AND CHEMICAL COMPOSITION

An intriguing, though not well understood, finding emerged from a literature analysis of Orobanchaceae species native to the area under consideration. There is a dearth of research on many species, while others are highly under-researched, with many others going unnoticed entirely. Notably absent are the "classical" therapeutic qualities of this plant family that are often studied and documented for other plant families. No studies have shown the antidiabetic or associated effects of any of these herbs, for instance. The opposite is true; a fair number of articles have detailed the discovery and description of structurally intriguing natural compounds and brain-related processes. These results are summarised in the tables that follow, which are organised by species' names. It is evident that there are no published reports.

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.

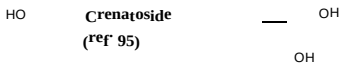


Figure 8. Crenatoside isolated from *Orobanche crenata*

Orobanche cumana* and *Orobanche hermonis

There are no publications relevant to this review article.

Orobanche lavandulacea

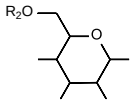
Whole plant was successively extracted with *n*-hexane, ethyl acetate, acetone, methanol and water. Essential oil was also prepared. All products were tested for general chemical composition and activity against B16F10 melanoma cancer cells.[94] Whole plant was successively extracted with *n*- hexane, ethyl acetate, acetone, methanol and water. Essential oil was also prepared. All products were tested for antioxidant activity (DPPH, FRAP, TEAC).[94] 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 *etal*. 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 Figure6).[108] The compound that they reported is shown in Figure 10.



group published an excellent review article about the activenatural products of *Cistanche tubulosa*.[110]

A detailed and relatively easy to perform synthesis oftrixagol (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 reportedits synthesis from another natural product present in theplant 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 studiesabout the medicinal/biological properties of *Orobanche*

In the reported synthesis, R_1=R_2=H, meaning that the aromatic ring is not substituted in positions 3, 4. Authors claim that (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 thisarticle).[118]

But not only sunflower is infected by *O. cumana*, wild plants of the same family (*Asteraceae*) are parasitized bythis plant, such as *Dittrichia viscosa* (False yellowhead), that grows in the Mediterranean basin. The host-parasiterelationship in this case was studied revealed that the host species produces a growth stimulant, Inuloxin E (Figure12).[119]

So, *Orobanche* plant species are real challenge. Manyefforts have been made to control them and the review article of S. Habimana is a good summary of these efforts ofdifferent 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 hiscolleagues presents the structures of the major compounds and the various methods that were developed for their isolation.[121]

CONCLUSIONS

Research on the Orobanchaceae family of plants in the Holy Land has been scant. The biological and therapeutic properties of the majority of these plants have remained undocumented. Parasites of these plants can be controlled if we learn more about the interactions between the parasites and the plants they inhabit. The species that were examined provide one-of-a-kind raw materials. Research into the medicinal applications of pure chemicals extracted from these rare plants is urgently needed because of the dearth of research into synthesising novel analogues and alterations utilising these plants' separated natural products.

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