CISTACEAE PLANTS OF ISRAEL AND PALESTINE. UNDER-INVESTIGATED FAMILY WITH GREAT POTENTIAL

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Cistaceae plant family is one of the most under-investigated families in our region. Few plants of this family were reasonably studied, but most of them were either totally "ignored" or very limitedly published. Those that were studied reveal the richness in special natural products that have unique structures with special sub-units. Even traditional medicines worldwide made very little use of these plants, compared with other plant families that grow in Israel and Palestine. In this short review article, we will present some ethnomedicinal uses of this family's plants, along with a comprehensive literature survey of medicinal, biological and other activities published by modern research. The presentation will include tables and figures for the convenience of readers. The discussion section will focus on some of the studies about chemistry and the biochemistry of the special natural products of this family and the importance of accurate scientific reporting. To the best of our knowledge, a review article about this plant family of our region was never published and it will be a significant contribution since very few review articles about this family were published hitherto. Conclusions and future research recommendations are presented for the benefit of interested scholars.

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INTRODUCTION

Cistaceae is a medium-size plant family, where it consists of eight genera that include about 180 species.[1] In the reviewed region of Israel and Palestine, this family is represented by four genera and 16 species.[2] It is very important to mention here that *Cistus incanus* is not discussed in this review article since its position as separate species (not a subspecies or hybrid of *C. creticus*) is still debated. While references 1 and 2 completely overlook it, A. Carni and his colleagues consider it an independent species,[3] and M. Rizzotto indicate "the taxonomic difficulties concerning *C. incanus* L.".[4]

Figure 1. Cistus creticus

Archeological investigations showed that seeds of different *Helianthemum* species were used and stored by humans in Turkey during the Neolithic period (10000-4500 BC).[5] *Cistus* species were used by some ancient cultures of Eurasia for medicinal purposes and preparation of fermented beverages.[6]

Finally, the species of the *Cistaceae* plant family that grow in the reviewed area are *Cistus creticus*, *C. salviifolius*, *Fumana arabica*, *F. thymifolia*, *Helianthemum aegyptiacum*, *H. kahiricum*, *H. ledifolium*, *H. lippii*, *H. salicifolium*, *H. sancti-antonii*, *H. sessiliflorum*, *H. stipulatum*, *H. syriacum*, *H. ventosum*, *H. vesicarium* and *Tuberaria guttata*.

ETHNOBOTANICAL USES OF *CISTACEAE* FAMILY

In the past, human societies were very selective in their ethnobotanical uses of the *Cistaceae* family's plants. As far as we could find in our literature survey, only 6 species out of 16 are reported for traditional uses. It is possible and even likely that some of the species that are not reported as part of the ethnobotanical heritage were practically in use, but these uses are not documented and published yet. One of the major reasons that give validity to our hypothesis about undocumented traditional uses of at least some of these plants is that they are very common. For example, *Helianthemum aegyptiacum* (common name: Egyptian Sun-rose) is very widespread within its natural habitat, that is, the Mediterranean basin and the Middle east. It is also unmistakable flowering in shape and yellow color. This plant grows all over the reviewed region, except in the very dry and arid areas, and it can be easily found even in some parts of the desert.

A summary of the published literature about the traditional uses of these plants is presented in **Table 1**.

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

Species	Region, uses, methods, references
Cistus creticus	Turkey. Flowers are used as colorants.[7] Italy. Used for treating animal wounds (antiseptic) and foot rot. Fresh leaves or fruits decoction are used. For humans, it is used as revulsive, antidermatosic and tonic.[8] Turkey, Morocco. Leaves decoction (or mixed with honey) to treat diabetes.[9-11] Turkey. Leaves and branches are used after crushing or as infusion, to treat abdominal pain, diabetes and as hemostatic.[12] Morocco. Decoction, infusion or powder, are prepared from all parts of the plant, and they are used to treat respiratory, digestive, skeleton, circulatory and urinary disorders.[13] Turkey. Crushed leaves are used to treat cuts.[14] Morocco. Leaves decoction or consumed fresh, to treat diabetes.[15,16]
C. salviifolius	Turkey. Leaves and branches are used after crushing or as infusion, to treat diabetes and as hemostatic.[12] Morocco. Decoction, infusion or powder, are prepared from leaves, stems or seeds, and they are used to treat respiratory and digestive disorders.[13] Turkey. Crushed leaves are used to treat cuts.[14] Morocco. Leaves decoction or consumed fresh, to treat diabetes.[15,16]
H. kahiricum	Algeria. Leaves decoction is used to treat diabetes.[17]
H. lippii	Algeria. Leaves decoction is used to treat diabetes.[17] Saudi Arabia. Roots decoction is used to treat colic problems in camels.[18] Sahara Desert. Food for camels.[19] Algerian Sahara. Leaves powder or compress is used to treat wounds and skin diseases.[20]
H. salicifolium	Turkey. The presence of this plant indicates presence of edible mushrooms.[21]
H. syriacum	Spain. Infusion (with coffee or tea, or as substitute of both) of aerial parts ameliorates digestive pain and acts as febrifuge.[22-24]

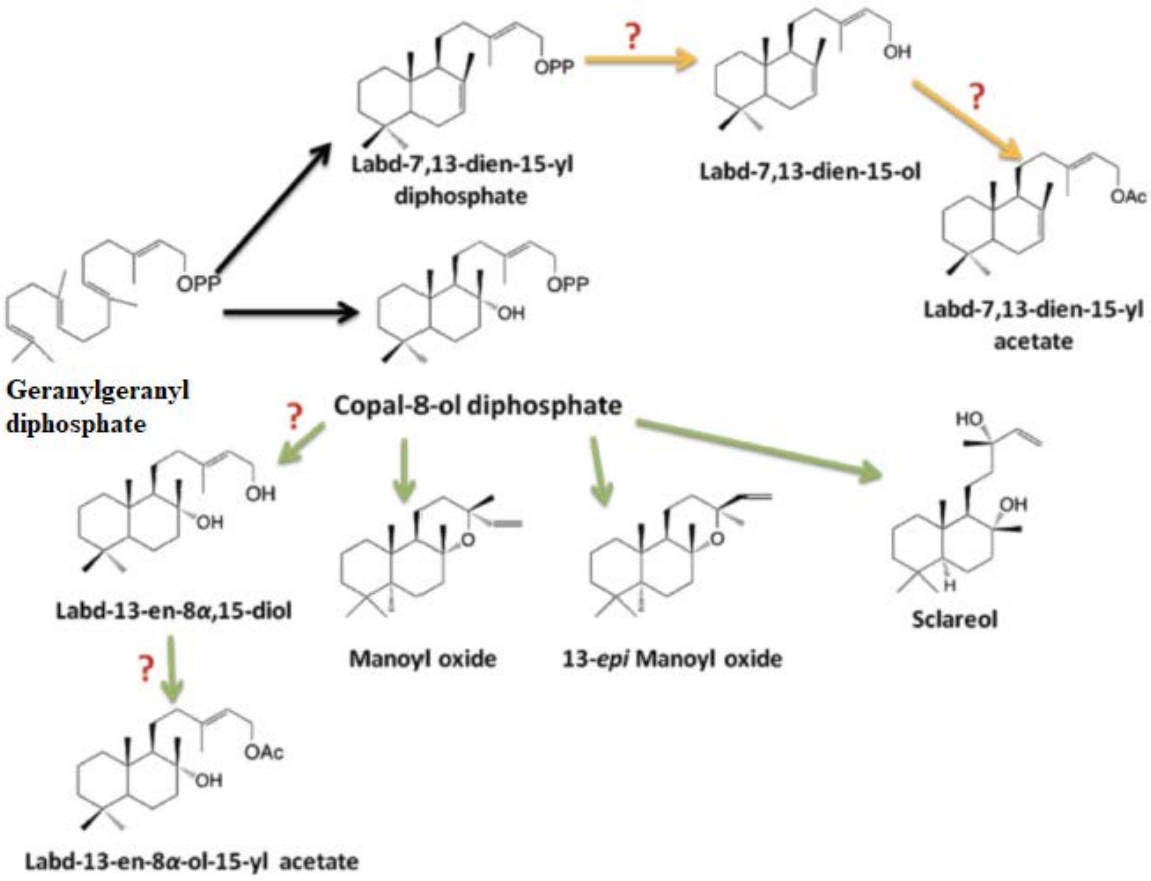

Figure 2. Proposed pathway of labdane-type diterpenes[25]

REVIEW ARTICLES ABOUT *THE CISTACEAE* PLANT FAMILY

Compared with other plant families represented in our region, *Cistaceae* was very limitedly reviewed so far. We found only four review articles that directly discuss this family.

D. Papaefthimiou and her colleagues published a comprehensive review article about the genus of *Cistus*.[25] They extensively review the botanical aspects of this genus, chemical compositions and pharmacological activities. But the major focus of this publication is to present a possible pathway of the biosynthesis of labdane-type diterpenes predominant in *Cistus creticus* resin. We present the proposed scheme of D. Papaefthimiou and her colleagues in **Figure 2**, and we will elaborate on this topic in the **Discussion** section. The only weakness is that other than the compounds presented in this scheme, they mention many active and unique natural products of this family, but they do not present their structures.

A minireview of the same genus, *Cistus*, was published by A. Stepien and her colleagues.[26] This article has an additional weakness to the one in reference 25: the biological properties of these plants are not categorized or presented separately, and so, it is not easy to find a specific property. A. Stepien published a year before a very short review about the cytotoxic and anticancer activities of the *Cistus* genus.[27] The article includes wonderful photos of *C. criticus*, but its informative value is very limited since it is written as a bulk text and active natural products and their structures are missing. Moreover, its title is weakly phrased "Cytotoxic and anticancer activity of the *Cistus* species of herbal plants".

B. Z. Awen and his colleagues published an outstanding and very comprehensive review article about the laboratory synthesis of labdane diterpenoids.[28] In addition to being superbly written 43 pages, it includes no less than 51 schemes. And despite being 12 years old, it is the best review of this topic so far.

BIOLOGICAL, CHEMICAL AND OTHER PROPERTIES OF *CISTACEAE* PLANTS

Cistus creticus

See Table 2.

Table 2. Biological, medicinal and other properties of *Cistus creticus*

Activity/Property	Major Findings/Reference
Antibacterial, antifungal	Leaves essential oil (of two different subspecies) was prepared and had strong activity against several bacteria species. It was analyzed and major components found were manoyl oxide and 13-epi-manoyl oxide (Figure 3).[29,37] Aerial parts were separately extracted with *n*-hexane, ethyl acetate and water. All extracts and essential oil (composition is provided) were active against *Borrelia burgdorferi*.[30] Aerial parts were extracted with acidic methanol to obtain phenolics (composition is listed) rich extract, which had strong activity against *Candida* species.[31] Aerial parts were extracted with diethyl ether and extract was analyzed for its components. These were tested for anti-borrelia activity and epi-manoyloxide and carvacrol were found most active.[32] Leaves were successively extracted with ethanol, dichloromethane and *n*-hexane. Extracts found active against several bacteria species.[33] Leaves were hydro-distilled for essential oil, and it was found active against several bacteria species. Its composition is provided.[34] Five labdane-type were isolated from the plant resin (ladano), and they had activity against several bacteria species. Two of these compounds were new. One of them is shown in Figure 3.[35] Natural compounds (6) isolated from the same resin, by the same research group and their new semisynthetic derivatives (11, two of them are shown in Figure 3) were found active against 9 bacteria species.[36] Leaves and fruits were extracted with water and fractionized with organic solvents. Extracts and fractions had weak activity against several bacteria species.[43] Whole plant chloroform extract had activity against various fungi species.[44] Essential oil was obtained from aerial parts and it had strong activity against several bacteria species. A very detailed composition is presebted.[45] Aerial parts were extracted with water and extract was active against several bacteria species. It was also analyzed by HPLC and its composition is provided.[46]
Anticancer and related activities	Known natural products that were isolated according to ref. 36,37 were found active against two different human cancer cell lines.[38] Shoots and roots were separately extracted with ethanol and extracts were tested against several human cancer cell lines. Only shoots extract was active. Partial HPLC analysis of extracts is presented.[39] Known labdane-type diterpenes were isolated from leaves and they had activity human leukemic cell lines.[40] Aerial parts were extracted with water and extract had antiproliferative activity (MTT).[46]
Antidiabetic	Aerial parts aqueous extract had α-glucosidase inhibition activity.[41]

Antioxidant, anti-inflammatory	Leaves were successively extracted with ethanol, dichloromethane and *n*-hexane. Extracts were tested for their antioxidant (DPPH) and metal chelating (Fe^{+2}) activities.[33] Leaves were hydro-distilled for essential oil, and its antioxidant activity (DPPH, FRAP) was tested.[34] Known labdane-type diterpenes were isolated from leaves and they had anti-inflammatory activity (skin barrier disruption model) in rats.[40] Aerial parts aqueous extract had antioxidant (ABTS, CUPRAC) activity.[41] Aerial parts were extracted with water and extract had antioxidant activity (FRAP).[46] Aerial parts were separately extracted with water and 80 % aqueous methanol. Both extracts had notable antioxidant capacity (DPPH).[47] Flowers essential oil was prepared and analyzed (detailed composition is listed), and its antioxidant capacity was tested (DPPH, ABTS).[48]
Blood system related activities	Aerial parts aqueous extract had antithrombotic and antiatherogenic activities.[41]
Antileishmanial	Compounds described in ref. 36 had antileishmanial activity.[42]
Nutrition	Aerial parts aqueous extract improved nutritional pasta qualities.[41]
Chemical composition	In addition to the mentioned, the following publications reported isolation and characterization of new natural products. Structures of selected compounds are presented in Figure 3.[49-53] It is important to indicate that authors of ref. 52 carried out a total synthesis of the natural product in order to find its exact stereochemistry, which was incorrectly reported in previous publications. This publication reported general chemical composition and did not present novel natural products, but its importance comes from the fact that it reported comprehensive metal content.[54] This publication did not report new compounds as well, but it presents the development of a new method for the simultaneous determination of selected flavonoids from different *Cistus* species by HPLC-PDA.[55]

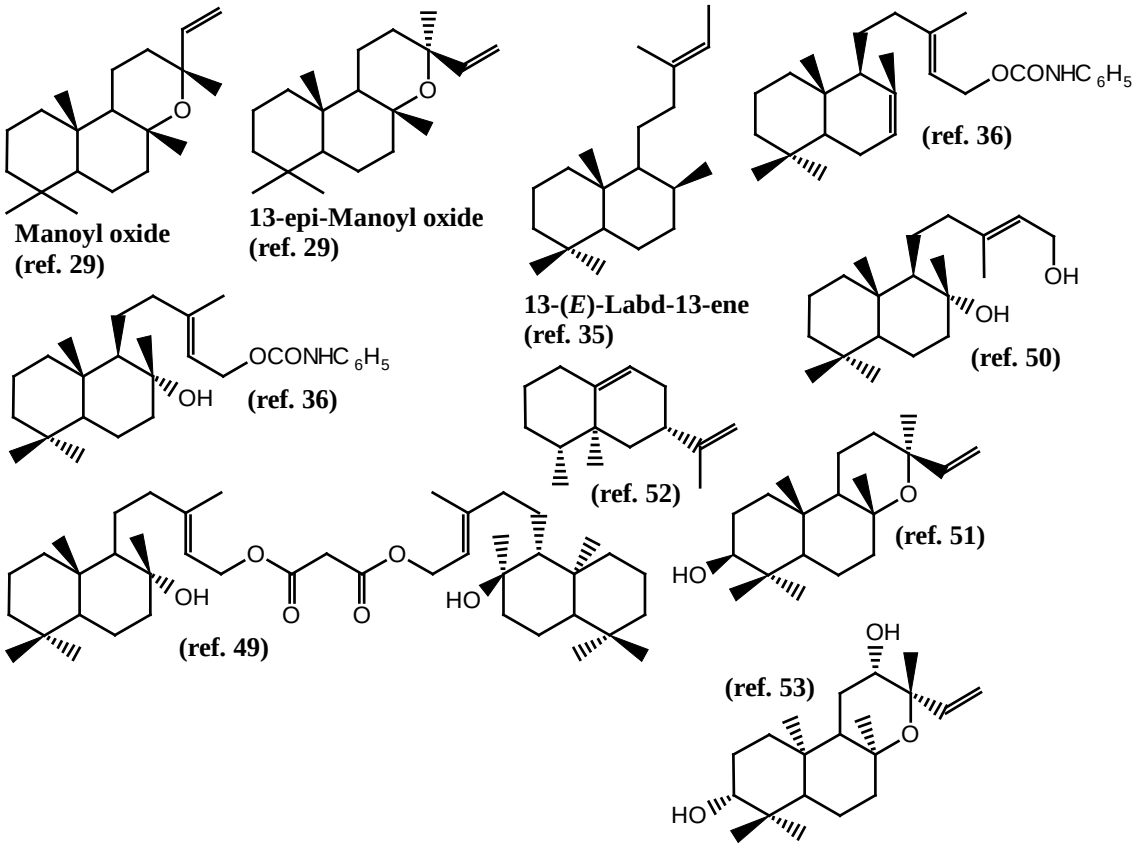

Figure 3. Active natural products isolated from *Cistus creticus*

Cistus salviifolius or salvifolius

See Table 3.

Fumana arabica.

No publications were relevant to this review article.

Fumana thymifolia

The aqueous extract had activity against Herpes simplex virus type-1 (HSV-1).[77] Essential oil of aerial parts was obtained and analyzed by GC-MS. A detailed composition is listed. New compounds were not reported.[78]

Helianthemum aegyptiacum

No publications were relevant to this review article.

Helianthemum kahiricum

n-Butanol extract of aerial parts had activity against 6 bacteria species.[79] Aerial parts were extracted with methanol and the antioxidant capacity of this extract was determined by the DPPH method. In addition, this extract had antiulcer (ethanol-induced) activity in rats.[80] Essential oil of aerial parts was obtained and analyzed by GC-MS. A detailed (known) compound list is presented.[81]

Helianthemum ledifolium

Aerial parts were extracted with 80 % aqueous methanol, and the extract had xanthine oxidase inhibition activity.[82]

Helianthemum lippii

See Table 4.

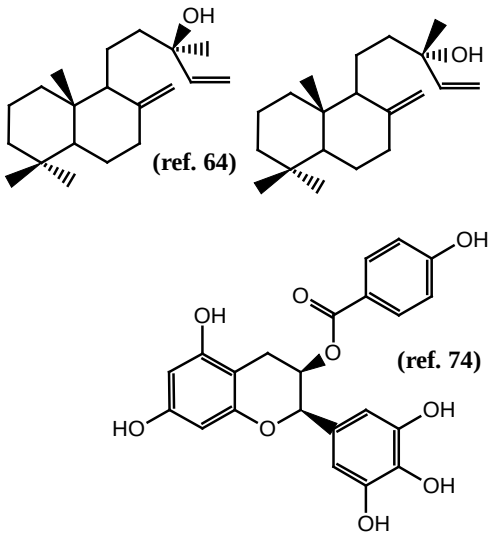

Figure 4. Active natural products isolated from *Cistus salviifolius*

Table 3. Biological, medicinal and other properties of *Cistus salviifolius*

Activity/Property	Major Findings/Reference
Analgesic	Aqueous extract of aerial parts was prepared and tested for analgesic activity in rats by two methods: acetic acid-induced writhing test and tail immersion test.[56]
Antibacterial, antifungal, antiviral	Leaves and fruits were extracted with water and fractionized with organic solvents. Extracts and fractions had weak activity against several bacteria species.[43] Whole plant chloroform extract had activity against various fungi species.[44] Essential oil was obtained from aerial parts and it had strong activity against several bacteria species. A very detailed composition is presebted.[45] Aerial parts were extracted with water and extract was active against several bacteria species. It was also analyzed by HPLC and its composition is provided.[46] Leaves and flowers were separately extracted with ethanol and each extract was tested against several species of bacteria and fungi. Leaves extract was more potent.[57] Aerial parts ethanolic extract was active against food bacteria.[58] Essential oil was extracted from aerial parts and it had strong activity against several bacteria species. In addition, composition of this EO is presented, and the effect of drying period of the plant material on EO yield is investigated.[59] Aerial parts ethanolic extract had activity against influenza virus.[62] Leaves were separately extracted with water and methanol. Both extracts had activity against several bacteria species that are involved in dermatitis.[63] Essential oil of aerial parts was obtained from different populations of the plant, and the effect of locality on the yields and compositions of the different oils was studied. A detailed composition is listed. The oils had strong activity against some bacteria species. New compounds were isolated and characterized. Two enantiomers are shown in Figure 4.[64]
Anticancer	Aerial parts were extracted with water and extract had antiproliferative activity (MTT).[46] Leaves and flowers were separately extracted with 80 % aqueous methanol. Both extracts had activity against OVCAR and MCF-7 cancer cells.[61]
Antidiabetic	Aerial parts were extracted with 80 % aqueous methanol, and extract had α-amylase and α-glucosidase inhibitory activity.[60]

Antioxidant, anti-inflammatory	Aerial parts were extracted with water and extract had antioxidant activity (FRAP).[46] Aerial parts were separately extracted with water and 80 % aqueous methanol. Both extracts had notable antioxidant capacity (DPPH).[47] Flowers essential oil was prepared and analyzed (detailed composition is listed), and its antioxidant capacity was tested (DPPH, ABTS).[48] Aqueous extract of aerial parts was prepared and tested for anti-inflammatory activity (carrageenan-induced) in rats.[56] Aerial parts were extracted with 80 % aqueous methanol, and extract was tested for antioxidant (DPPH, ABTS, FRAP) capacity.[60] Leaves and flowers were separately extracted with 80 % aqueous methanol. Both extracts 5-LOX inhibition (anti-inflammatory) activity, and their antioxidant capacity was measured with three methods (DPPH, ABTS, FRAP).[61]
Cardiovascular system	Leaves were extracted with *n*-hexane, ethyl acetate and methanol, by ultrasound assisted apparatus. Methanolic extract had highest vasodilatory activity.[65]
Antidiarrheal, intestine relaxant	Aqueous extract of stems and leaves had activity against castor oil-induced diarrhea in female rats.[66] Aqueous extract of stems and leaves had relaxant activity in contracted jejunum of rats and rabbits.[67]
Enzyme inhibition	Leaves and flowers were separately extracted with 80 % aqueous methanol. Both extracts inhibited xanthine oxidase, superoxide dismutase, acetylcholinesterase.[61]
Antiparasitic	Aerial parts methanolic extract had antileishmanial activity.[68]
Metals related activities	Plant revealed high capacity of metal ions (As^{+3}, Cu^{+2}, Zn^{+2}) from mine soils.[69] Exposure to As^{+3} did not affect the biological functioning on the plant that showed high tolerance to this toxic metal.[70] Plant showed high capacity of phytoremediation for Zn^{+2}, Pb^{+2} and Cd^{+2}.[71]
Toxicity	Sheep grazing on the plant showed signs of neurotoxicity and were treated with sulbutiamine.[72] Plant caused toxicity in grazing cattle.[73]
Chemical composition	Five new phenolics were isolated and characterized by A. Danne *et al*. One of them is shown in Figure 4.[74] These publications did not report new compounds, but they have special interest. Development of new method for the simultaneous determination of different selected natural product families from different *Cistus* species.[55,75] First isolation of some structurally interesting, known, active natural products from *Cistus* species.[76]

Table 4. Biological, medicinal and other properties of *Helianthemum lippii*

Activity/Property	**Major Findings/Reference**
Analgesic	Whole plant was separately extracted with petroleum ether, chloroform and methanol. All extracts had activity in hot plate test in mice.[83]
Antibacterial	Aerial parts were separately extracted with ethyl acetate and methanol. Both extracts were active against *Acanthamoeba castellanii*, but ethyl acetate extract was more potent.[84] Aerial parts were successively extracted with petroleum ether, chloroform or methanol. All extracts had activity against 3 bacteria species.[85] Aerial parts from three different growth stages of the plant were extracted with methanol. All extracts had activity against 4 bacteria species.[86]
Anticancer	Aerial parts were separately extracted with petroleum ether, chloroform or methanol. All extracts had cytotoxic activity in MTT assay.[87]
Antidiabetic	Aerial parts aqueous extract had α-amylase inhibition activity.[88] Aerial parts were extracted with 80 % aqueous methanol and fractionized with ethyl acetate. Fraction had α-glucosidase inhibition activity.[89]
Antioxidant, anti-inflammatory	Whole plant was separately extracted with petroleum ether, chloroform and methanol. All extracts had activity against carrageenan-induced paw edema in mice.[83] Aerial parts were successively extracted with petroleum ether, chloroform or methanol. All extracts had activity against carrageenan-induced paw edema (mice), and their antioxidant capacities were determined (DPPH).[85] Aerial parts from three different growth stages of the plant were extracted with methanol. The antioxidant capacities of all extracts were tested with three methods.[86]

Antiulcer, muscle relaxation	Aerial parts were successively extracted with petroleum ether, chloroform or methanol. All extracts had activity against ethanol-induced ulcer in mice.[85] Aerial parts were extracted with 80 % aqueous methanol and fractionized with water and four organic solvents. All fractions had relaxant activity of smooth muscle of the rat distal colon.[90]
Chemical composition	This publication did not report new compounds, but it presents very detailed composition of the essential oil of aerial parts, as well as comprehensive nutritional values.[91]

Helianthemum salicifolium

No publications were relevant to this review article.

Helianthemum sancti-antonii

No publications were relevant to this review article.

Helianthemum sessiliflorum

Aerial parts were extracted with *n*-butanol. This extract had activity against three bacteria species and its antioxidant capacity was determined by the DPPH test. Known phenolics were isolated.[92] In addition to 19 known compounds, a new lignan was isolated from the aerial parts ethyl acetate extract[93] **(Figure 5**).

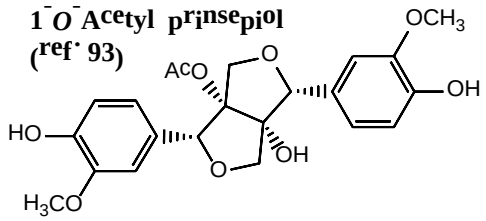

Figure 5. 1-*O*-Acetyl prinsepiol isolated from *Helianthemum sessiliflorum*

Helianthemum stipulatum

No publications were relevant to this review article.

Helianthemum syriacum

Leaves were extracted with 80 % aqueous methanol, with 1 % formic acid, to obtain the phenolic-rich extract. This extract's antioxidant capacity was determined by two methods (DPPH, ABTS), and it had very weak activity against 5 bacteria species.[94]

Helianthemum ventosum

No publications were relevant to this review article.

Helianthemum vesicarium

No publications were relevant to this review article.

Tuberaria guttata

No publications were relevant to this review article.

DISCUSSION

The general view that rises from the previous sections can be described as a massive lack of published studies about the biological and medicinal properties of the *Cistaceae* plant family in the reviewed region, Israel and Palestine. While very few plants were relatively investigated, most of them are completely unknown in terms of these properties.

Despite the fact that the *Cistus* genus is represented only by two plants in the reviewed region, most of the publications that we cited discussed these two species, especially *cistus criticus*, But before discussing some other interesting publications about this plant, it is worthy of mentioning some interesting publications about products of these plant. For example, H. Maruyama *et al*. published an outstanding work about bee pollen ethanolic extract's anti-inflammatory activity.[95] Pollen was used by the insects was produced by various *Cistus* species in Spain, and researchers treated it in the same manner as plant parts. Paw edema inflammation was induced in rats with carrageenan, and the extract showed high activity against it. Moreover, the extract was analyzed and five known active phenolics were identified (NMR).

As we mentioned earlier, the biosynthesis of the labdane-type natural products in this family's plats drew major interest among researchers (see the review article of D. Papaefthimiou and her colleagues, ref. 25). V. Falara from the same group conducted a genetic study that concluded that copal-8-ol diphosphate synthase has a key role in the production of pharmacologically active, oxygen-containing labdane-type (such as manoyl oxide, see **Figure 3**) diterpenes in *Cistus creticus*.[96] The substrate, copal-8-ol diphosphate, is shown in **Figure 2**. This publication includes very important figures and structures.

Each plant's chemical composition can provide very important and biologically active natural products for direct use of the plant or the compounds and prepare modifications and derivatives for drug discovery. But this composition is directly influenced by various factors, such as the growing locality of the plant. On this basis, C. Demetzos and his colleagues carried out an interesting study, where the isolated essential oil (aerial parts) from *C. creticus* grow in 25 different locations in Crete, Greece.[97] In addition to slight differences in EO yields, differences in the chemical composition were found between all 25 samples, and thus, this data can provide a method for plant authentication. A

similar study was performed by P. M. Mastino and her colleagues for the same species, but in seven plant populations in Sardinia, Italy.[98] C. Demetzos and his colleagues were among the first groups to study this plant, and one of their early works that did not report new compounds, reported interesting phenolics such as astragalin.[99]

While searching for publications to be used in writing a review article, one must examine literature very carefully, even when a certain article is published in the well-known journal. Mistakes occur sometimes, but in rare cases, there are very inaccurate presentations. For example, N. S. Christodoulakis and his colleagues published an interesting article about the leaf structure of *C. creticus*.[100] In the introduction, they wrote: "*C. creticus* has been investigated for the physiology of its leaves (16), its uses in traditional folk medicine, and the antimicrobial, antioxidant, antitumor, antinociceptive, analgesic effects of its leaf extracts (4,15,25) as well as their antiproliferative effect on human prostate cells (37). Extracts and purified substances from *C. creticus* tested showed selective activities against the influenza virus due to the bioactive secondary metabolites they contain, including flavonoids, aromatic compounds, phenolics, and tannins (6,19). The latter have been investigated separately, and *C. creticus* is considered, among phenolic accumulating plants, as the one with the most extensive accumulation of phenolic compounds in its leaves (4)". And since the cited references can be used for this review article, we decided to follow them.

The work of E. Barrajon-Catalan and his colleague cited as reference 4, studied antioxidant, anticancer and antimicrobial activities of *C. ladanifer* and *C. populifolius*, and does not even mention *C. creticus*.[101] Cited reference 15 published by A. I. de Andres *et al*. presents effects of extract of *C. populifolius* on the central nervous system, and again, *C. creticus* is not mentioned.[102] The article of E. Kupeli and E. Yesilada, cited as reference 25 reports flavonoids with anti-inflammatory and antinociceptive activity from *C. laurifolius* not *C. creticus*.[103] Cited reference 37 can be accepted if we consider *C. incanus* as a hybrid of *C. creticus*, and *C. monspeliensis* is also studied in this research for anticancer activity.[104] But as we mentioned in the introduction, some botanical resources do not consider *C. incanus* as hybrid or subspecies of *C. creticus*, but a hybrid of *C. albidus* and *C. crispus*.[105]

In addition to the influence of locality, which we discussed above and will be mentioned again, processing and storage of plant material can have notable effects on its contents, and consequently, its biological properties. A. E. Stepien and her colleagues reported the effect of drying methods on energy consumption (for drying of *C. creticus leaves*), total phenolic content, color change and antioxidant capacity (DPPH, ABTS) of leaves extract.[106] They conclude that the best conditions are drying at 40°C or vacuum-microwave drying at 240 W.

In a similar, compound-targeted and very recent study, N. Matlok (who participated in the previously cited research) and her colleagues tested the drying conditions on the content of specific phenolics in *C. creticus* dried matter.[107] They concluded that the optimum conditions are drying 50°C with (not or) vacuum-microwave drying at 240 W. An even more focused study was published by M. Ammendola and his colleagues. They studied the effect of sterilization on anticancer compounds isolated from *Cistus* plants dried matter.[108] .

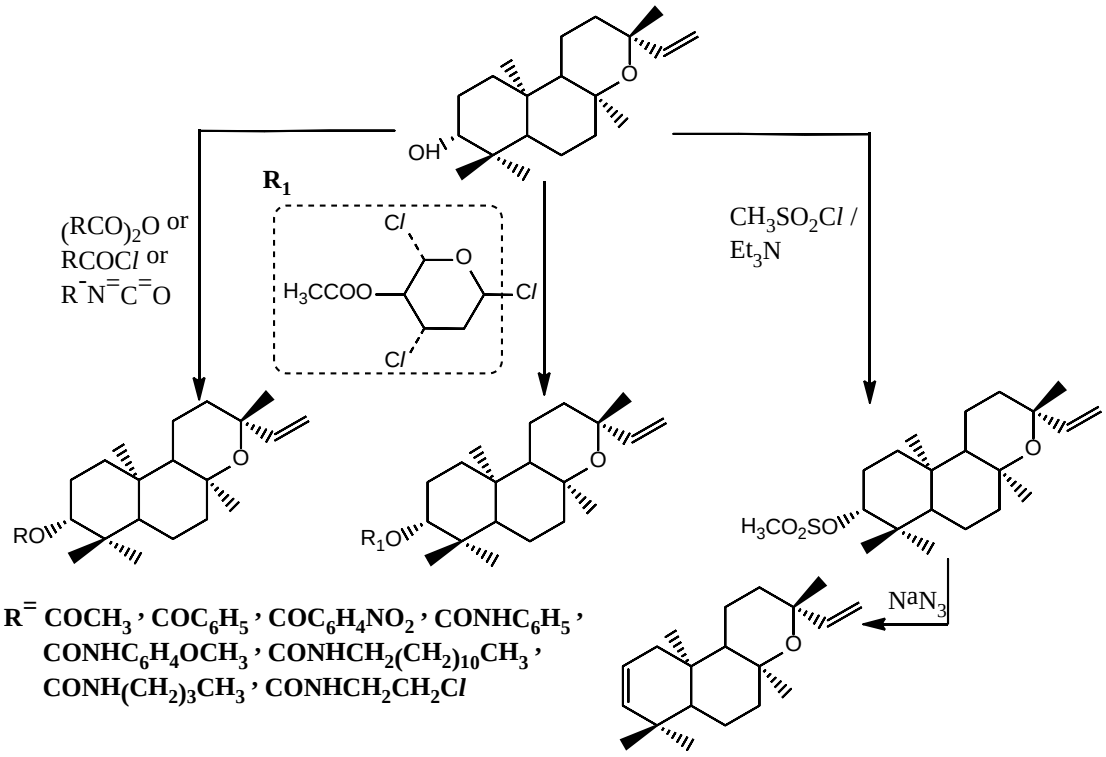

Figure 6. Manoyl oxide synthetic derivatives[112]

This work has special importance for manufacturing natural products in the form of commercial drugs, whether encapsulated or not. Finally, we will present two works for this subject where the chemical composition of different *Cistus* species and subspecies was tested and found to be the "fingerprint" of each plant. First, the research of S. Moosmag and his colleagues that distinguished these plants from each other by identification of their metabolites using NMR spectroscopy.[109] Second, P. M. Mastino and her colleagues, who used the composition of essential oil of *C. creticus* as an indication to plants localities (ref. 98), used the same method to distinguish different *Cistus* species from each other.[110]

Searching literature of laboratory attempts to preparing labdane-type natural products did not result in many findings, even though these compounds are notably active. We mentioned earlier two publications concerning the biosynthesis of these compounds (ref. 25 and 96). In this sense, C. Ignea and her colleagues' work has special importance: they developed a method for the synthesis of these natural products and their analogs by biosynthesis in genetically modified yeast.[111] And to the best of our knowledge, the only pure synthesis of these compounds was published by E. Kalpoutzakis and his colleagues.[112] The general scope of their synthesis is shown in **Figure 6**

CONCLUSIONS AND FUTURE VISION

1) The plants of the *Cistaceae* family are very under-studied and published.

2) The ethnobotanical uses of these plants are partly documented and there is a need for a comprehensive review and reporting of these uses.

3) It is highly important to cite references in a completely accurate way.

4) Organic and bioengineered synthesis of natural products of this family are way under reasonable, and they must be thoroughly performed.

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