

Review

# A Review on *Cistus* sp.: Phytochemical and Antimicrobial Activities

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**Abstract:** Resistance to drugs is reaching alarming levels and is placing human health at risk. With the lack of new antimicrobials drugs, infectious diseases are becoming harder to treat. Hence, there is an increasing awareness of active phytochemicals with therapeutic functions. The tremendous research interest on the *Cistus* L. genus includes numerous plants used in traditional medicine by people living around the Mediterranean Sea, also resulted in some interesting discoveries and written literature. This review aimed at gathering scientific literature about *Cistus* species, describing phytochemical profiles and the various pharmacological activities. We also extensively reviewed the antimicrobial activities, including antiviral, antiparasitic, antifungal, and antibacterial potentials of Essential Oils (EO), raw extracts as well as isolated compounds. Mechanisms of action along with methods used are also investigated in this review. Considering the findings of the *Cistus* species extracts, this genus offers an adequate reserve of active phytochemicals since many have been used to create drugs. Therefore, this review work can serve society by providing a global view on *Cistus* L. sp. regarding pharmacological potentials and their chemical profiles.

**Keywords:** *Cistus* sp.; phytochemicals; microorganisms; antimicrobials; multidrug resistance



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## 1. Introduction

Nature is the source of natural remedies widely used by 80% of the world population [1]. In North America, Europe, and other developed regions, over 50% of the population has used traditional medicine at least once [2].

The World Health Organization (WHO) has a keen interest in documenting medicinal plants used by indigenous people from different parts of the world [3,4]. The use of plant derivatives as medicinal treatments gained popularity in the late 1990s [5].

Plants are a biologically and chemically diverse resource. The total plant species estimated on planet Earth is about 25,000 to 500,000 [6], and more than 10% of them are used for therapeutic purposes [7]. Around 71% of drugs have directly or indirectly been derived from natural products [8].

The extraordinary advantages of bioactive molecules as a source of biotherapeutics are beyond question [9,10]. Studies have identified more than 5000 individual phytochemicals, and this number is continuously increasing due to the introduction of new and efficient isolation and characterization techniques [11–14].

Most of the studies showed that many herbs are rich in phenols, flavonoids, tannins, vitamins, and many more phytochemicals [9,10,15,16]. Moreover, researchers in the last few years have shown an increasing interest in these compounds [13,14]. Plant-derived products have potential against illnesses with no or few secondary effects when compared to synthetic ones [9,16–18].

The screening of phytochemical composition in medicinal and aromatic plants plays a significant role in many areas, such as the human diet, animal feed, pharmaceuticals, fragrances, and cosmetics, etc. [19–22].

The Mediterranean basin, one of the hot spot biodiversity in the world [23,24], is rich in vegetation, including medicinal plants [25–27]. One example is *Cistus* L. sp., which was intensively studied in terms of medicinal properties along with its chemical composition. In this sense, this work was conducted to gather data on *Cistus* L. regarding antimicrobial potential and chemical profiles.

## 2. Genus's Presentation

*Cistus* plants are the dominant shrubs in the Mediterranean region. Most species have a widespread distribution but there are a few narrow endemics among the family *Cistaceae* L. known as rockrose [28,29]. This family comprises several perennial medicinal plants [30], with eight genera, including the *Cistus* genus [31].

The genus *Cistus* is relatively tiny and complex because of the polymorphism and the hybridization between related species [32]. It contains about 21 species after several taxonomic re-evaluations based on molecular analysis of phylogeny [33,34].

### 2.1. Botanical Presentation

The genus is composed of pioneer species [35]. The straight branches can range from 50 to 100 cm in height. On the branches, corrugated leaves grow entangled and straightforward [36]. Plants of the genus are cross-pollinated between species. Their big visible flowers are hermaphroditic, actinomorphic, and hypogynous, with three of five sepals opposite the petals [6,29,37,38]. Petal color ranges from white to purple/dark pink depending on the subgenus, with a conspicuous dark red spot at the base of each petal present in a few species [31], which makes it a common ornamental plant [39]. Besides, they have viscid stems and leaves that produce a fragrant oleoresin [40]. Most family members are very fragrant and sweet-smelling, much appreciated in the perfume industry [41].

### 2.2. Cultural Characteristics

*Cistus* species are frequent, particularly in mountainous regions with acidic and basic soils [33]. Environmental specificity referring to substrate confers additional value to acidophilous and basophils species as predictable indicators of woodland disturbances [33]. As well as an adaptation to resist summer droughts, this genus adapts well to frequent disturbance events such as poor soils, fire-degraded soils, and grazing that destroy large forest areas [42]. These species are well known for producing large quantities of seeds that resist fires and rapidly populate in the following season [32,43–45].

The germination is influenced by insect pollination, attracted by the odors released by the monoterpenes produced by the flowers [35,36].

Adding the ability of *Cistus* species to colonize degraded areas, these shrubs inhibit the growth of other plants by restricting their aerial growth or by inhibiting germination of other species due to its phytotoxicity over other plants and soil [39,46–48].

### 2.3. Chemical Analysis

The *Cistus* species are rich in polyphenolic compounds (the main components are polyphenolic compounds, commonly known as catechins). This characteristic makes these plants able to withstand extreme conditions. The metabolism of polyphenols protects the plants against different stresses, whether biotic or abiotic [49]. This abiotic protection is

due to polyphenols that can reduce nitrogen's mobility in the soil and then allow these shrubs to grow in nitrogen-deficient soils [50].

Chemical analysis of different *Cistus* species' tissues showed different chemical classes, including diterpenes, which are usually detected in *Cistus monspeliensis* L. and *Cistus libanotis* L. [51]. These plants are also recognized to contain multiple compounds from different chemical classes such as flavonoids, coumarins, terpene derivatives, hydrocarbons [45,52]. Many studies have reported on the phytochemicals in extracts of different *Cistus* species from several regions. The first study on the *Cistus* genus, published by R. Hegnauer, determined the constitution of diterpenes in the aerial parts of *C. monspeliensis* [53]. A few years later, this genus started to interest researchers. JDP Teresa focused studies on the aerial parts of *Cistus laurifolius* L. growing in Spain, from which new terpenes were isolated: salmantic acid and its methyl ester, salmantidiol [54], also the labdane-type diterpene 6 $\beta$ ,8-dihydroxy-ent-13E-labden-15-oic acid (laurifolic acid) [55]. Studies continued from 1990 to 2000, focusing on diterpenes by studying others species, especially *Cistus creticus* subsp. *creticus* L. from Greece, from which several labdane-type diterpenes were identified [56–60]. The Essential Oil (EO) of *Cistus* species is widely studied, especially *Cistus creticus* L., *Cistus ladaniferus* L., and *C. monspeliensis*. Manoyl oxide isomers and 13-epi-manoyl oxide were the most reported diterpenes in *C. monspeliensis* [61–63] as well as sesquiterpene oxygenated ( $\alpha$ -cadinol as the main compound) isolated in France from leaves [64]. *C. monspeliensis* is also known to have a high content of terpenoids. Aerial parts of *C. ladaniferus* are another example of the richness in terpenoids (oxygenated sesquiterpenes and monoterpene hydrocarbons) among them, viridiflorol,  $\alpha$ -pinene, ledol, bornyl acetate [63,65–67]. A chemoprofile of *C. creticus* was highly variable due to the variance of subsp., geographic regions, and then pedoclimatic conditions due to seasonal variations. Three classes were identified: phenylpropanoids (carvacrol [68–70]), carbonylic compounds (norisoprenoids representing by vitispirane I [68]), and terpenes. The latter were the most reported in this species's oil, especially diterpene in *C. creticus* subsp. *creticus*. The most reported diterpene were manoyl oxide, 13-epi-manoyl oxide, drimane-7,9(11)-diene, and labdane skeletons [59,68–71], and sesquiterpene ( $\alpha$ -cadinene,  $\delta$ -cadinene) which are predominant in *Cistus creticus* subsp. *Eriocephalus* Viv. [70]. *Cistus albidus* L. was also studied for its EO composition. Conversely, in this EO diterpenes and monoterpenes were absent. Sesquiterpene derivatives were dominant with high content, the main components being  $\alpha$ -zingiberene,  $\alpha$ -curcumene, (E)- $\beta$ -caryophyllene,  $\alpha$ -cadinol,  $\alpha$ -bisabolol,  $\delta$ -cadinene, and germacrene D [72–74]. A study carried out on 15 types of *Cistus salviifolius* L. from the Crete island showed 167 compounds dominated with high percentages of sesquiterpenes (Camphor and viridiflorol as main compounds) [75]. Another study on the EO composition of 5 *Cistus* species, including *salviifolius*, showed 89 components dominated by sesquiterpenes (oxygenated ones were higher than hydrocarbons represented especially by germacrene D as a leading compound, this latter was absent in EO from Crete island). Diterpenes were also present among the EO of *C. libanotis* and *Cistus villosus* L. from Tunisia, 56 and 54 elements were isolated respectively, monoterpenes hydrocarbons characterized the first species. However, the second major class of compounds was carbonylic compounds (undecan-2-one and hexahydrofarnesylacetone were the most abundant) and hydrocarbon (heptacosane and nonacosane as principal ones) [62].

Also known as *C. creticus* and *C. villosus*. Several investigations focused on aqueous and semi-organic extracts from *Cistus incanus* L., marketed as herbal infusions and dietary supplements. Viapiana's team analyzed by HPLC the phenolic profile of hydromethanolic and aqueous extracts of different commercial samples from different regions. The results proved that all samples were rich in phenolic acids and flavonoids, gallic acid, rutin, and the most abundant of them in all samples is isoquercetin. However, there are differences in the content of the other compounds identified depending on the extraction solvent (chlorogenic acid, ferulic acid syringic acid were not found in aqueous extracts of *C. incanus*) in addition to the growing conditions, tissue maturity, and post-harvest treatment [31]. As it is now

recognized, the preparation method, the temperature used, duration, and the type of water strongly influence phenolic compounds during cooking.

Riehle has proven a significant decrease of different groups of phenolic compounds and flavonoids when brewing the commercially available *C. incanus* infusions with different water used at various conditions [76]. The profile of phenolic compounds from *C. incanus* pollen was different between nonhydrolyzed and hydrolyzed. Although the in vivo data about the metabolism of various food sources of phenolic compounds isolated after feeding are contradictory and rare, it is essential to consider data on these compounds and the changes they may undergo once in the human body [77].

The study of the two Tunisian and Italian teams represented by Marcello Nicoletti and Mariem Ben Jemia, focusing on terpenes, phenols, and glycosides of raw methanolic extract of *C. monspeliensis*, showed that diterpenes were evident and polyphenols were present in different concentrations. Flavonoids were also reported with isolation of new phenylglucoside, 1-(3,5-dihydroxy-2-methylphenyl)ethanone-5-O- $\beta$ -D-glucopyranoside, named monspelioid, which was identified for the first time from the genus *Cistus* [70].

Ben Jemia identified 36 compounds from hexane extracts of *C. monspeliensis* leaves as a part of the investigation on Tunisian medicinal plants. Top-class was represented by fatty acids and a good amount of hydrocarbons; Vitamin E was also present [41]. The teams have also studied *C. libanotis*, a complete analysis of the hexane extracts from leaves, and showed 47 constituents. Flavonoids were dominant, followed by fatty acids, monoterpene hydrocarbons, hydrocarbons, oxygenated monoterpenes, diterpenes, sesquiterpenes, oxygenated sesquiterpenes, which were present in a small amount [41]. In contrast, when they focused only on terpenes and phenols constituents, they reported the evidence of diterpenes and flavonoids in methanol extracts [78]. According to the same papers, these diterpenes were rarely reported in *C. villosus*, dominated by hydrocarbons and Vitamin E and some tannins [69,71].

The first investigation on ethanolic extracts of *C. laurifolius* aerial parts from Spain concluded the isolation of a new diterpene called laurifolic and identification of five glucosides ( $\beta$ -D-glucopyranosiloxyethane, 4- $\beta$ -D-glucopyranosiloxyacetophenone, reseoide, 1,3-dihydroxy-5- $\beta$ -D-glucopyranosiloxybenzene, 1-O-methyl-epi-inositol) [55]. Between 2007 and 2012, Erdem Yesilada published two papers about organic extracts of *C. laurifolius* leaves from Turkey, which reported three flavonoids (3-O-/methylquercetin, 3,7-O-dimethylquercetin, and 3,7-O-dimethylkaempferol) [73,74]. Considering the wide use of the *C. laurifolius* by the Turkish population, studies on its chemical composition continue. In 2013, another paper was published and reported comparing the chemical profile of aqueous and ethanolic leaves extracts. Results showed higher phenolic contents in ethanolic extract rather than the aqueous one. Flavonoids, chlorogenic acid, gallic and ellagic acid were the most phenolic compounds in *C. laurifolius* ethanol extract [79]. The aerial parts of *C. creticus* from the Island of Crete were analyzed by IR, CID-MS, NMR, DEPT. Nine labdane-type diterpenes were found [53]. In 2012, sonication testing was analyzed by GC/FID, and GC/MS concluded the identification of 24 compounds, also dominated by labdane-type diterpenes [51]. To find a correlation between the activities and biomolecules, a team of Micol was carried out on the composition of different extracts of 4 *Cistus* species abundant in Spanish semi-arid regions. The semiquantitative analysis by RRLC-ESI-TOF-MS of the composition of *Cistus clusii* Dunal, *C. albidus*, *C. ladaniferus*, and *C. salviifolius* did not reveal a significant difference between the four *Cistus* extracts. The presence of phenylpropanoid compounds (phenolic acids, flavonoids, and tannins derivatives) in all species should be mentioned; the proportions were varied. Cyclohexane carboxylic acids, gallic acid, glycosylated quercetin, and myricetin were especially abundant in the *C. clusii*, *C. albidus*, *C. salviifolius* extracts. In contrast, labdanoic acid, betuloside, apigenin, kaempferol, and galloylated flavanols were more abundant in those extracts of *C. ladaniferus* and *C. clusii* [80].

### 3. Biological Potent of *Cistus* Species

All *Cistus* species produce several compounds with pharmacological properties. The international literature has reported the biological activities of *Cistus* species, which are widely known in folk and traditional medicine around the Mediterranean basin.

#### 3.1. *C. ladaniferus* L.

Extracts from *C. ladaniferus* showed to have an antiaggregant effect by inhibiting the thrombin [81]. Also, an antispasmodic action confirms its traditional use for treating intestinal aches [82]. An evaluation of aqueous extracts against glycemic and lipidemic status in diabetic rats showed a significant reduction in blood glucose levels (similar to those obtained with glibenclamide) and the total cholesterol triglycerides in plasma [83]. A reduction of systemic blood pressure in two animal models of hypertension, and then it has antihypertensive properties [84]. Analgesic and anti-inflammatory purposes were also detected in this species [85]. Two papers have focused on antioxidant activity and revealed excellent effectiveness against peroxy radicals [41,55]. Aqueous extracts of *C. ladaniferus* also have anticarcinogenic compounds, which have cytotoxicity against pancreatic cancer cell lines M220, breast cancer cells MCF7/HER2, and JIMT-1 [86]. The first report about the toxicity of *C. ladaniferus* was published by El Kabbaoui using male and female mice, reported that a dose of 3 and 5 g/kg produced a 10% to 30% mortality rate (acute toxicity test) [87].

#### 3.2. *C. monspeliensis* L.

Considerable research on pharmacological proprieties of *C. monspeliensis* has been done. One of the first examples of cytotoxic activity of extracts and compounds of this species was studied by Dimas and his colleagues. They have demonstrated the inhibition of myricetin isolated from the hexane aerial parts extract against nine human leukemic cell lines. They also showed that acetylation of this compound enhances the growth inhibition, decreasing from IC<sub>50</sub> 50.1 µM to 38.3 µM. It should be noticed that any paymasters' modification will modify the results [88]. Demetzos showed that a diterpene isolated from hexane extract from leaves of *C. monspeliensis* does not present any cytotoxic or cytostatic activity against any of the nine cell lines tested [89]. On the other hand, Ben Jemia demonstrated that hexane extract from *C. monspeliensis* leaves was rich with many compounds, especially fatty acids, hydrocarbons, and Vitamin E. The compounds showed significant cytotoxicity against human breast cancer cells with IC<sub>50</sub> 52.44 mg/mL (better than reference drug IC<sub>50</sub> 142.36 mg/mL) [41]. Nevertheless, the main limitation of those investigations is the absence of toxicity determination of those extracts. Based on this observation, Vitali studied the acute toxicity using *Artemia salina* L., and cytotoxicity on normal human prostate cells, of lyophilized aqueous extract from aerials parts of *C. monspeliensis*. They observed that the toxicity increase after 24 h with a concentration of 5 mg/mL, but the exposure for 48 h to the extract displayed significant growth inhibition from the concentration of 0.1 mg/mL [29]. Demetzos investigated the in vivo anti-inflammatory activity of the cis-clerodane type Diterpene isolated from hexane extract on the back of hairless mice. The topical application did not seem to have any outcome to the skin barrier repair. Compared to Sayah, who found that aerial parts aqueous extract has a potent effect against carrageenan and analgesic reaction at a dose of 500 mg/Kg body weight [85,89]. This effect may be due to the richness of polyphenolic compounds in the aqueous extract and the lack of epoxide structure in the cis-clerodane molecule. Other researchers reported that methanolic or ethanolic extracts of *C. monspeliensis* are rich in polyphenolic compounds related to antioxidant activity because they can chelate transition metals and prevent them from participating in metal-catalyzed initiation and hydroperoxide decomposition reactions [78,90].

EO's use as a food supplement for neuroprotective proprieties has also been investigated by M.R. Loizzo, aiming acetylcholinesterase (AChE) butyrylcholinesterase (BChE) enzyme. EO of *C. monspeliensis* does not have any activity against AChE and a slight BChE inhibitory. This observation could be due to the limited amount of compounds that belong

to monoterpenes with AChE inhibitory potent such as  $\alpha$ -pinene,  $\beta$ -pinene, and  $\alpha$ -terpinene. On the other hand, plenty of diterpenes was responsible for the highest lipid peroxidation inhibition [62]. Using in vitro model, Sayah demonstrated the strong effect of aqueous and hydro-methanolic extracts to inhibit  $\alpha$ -glucosidase and  $\alpha$ -amylase activity (enzymes responsible for the degradation of oligosaccharides into glucose and then increase his level in blood). This inhibition could then be essential in managing blood glucose levels in diabetic patients and preventing type 2 diabetes. The same researchers also established the correlation between total phenolic content, enzyme inhibition, and different antioxidant activities (DPPH, ABTS, FRAP) [91].

### 3.3. *C. salviifolius* L.

Numerous studies have been conducted to evaluate biologicals proprieties of *C. salviifolius* compounds. Oxidative stress is an essential factor included in chronic and degenerative diseases and is targeted by researchers. Studies on different extracts of *C. salviifolius* showed an interesting source of natural antioxidants. A study was done by Fadi Qa'dan using Fremy's salt assay to demonstrate the ability of a purified proanthocyanidin from three fractions to reduce free radicals [92]. Additionally, S.K. El Euch aimed to compare methanolic extract from leaves and flower buds, targeting different antioxidant activity tests (DPPH, ABTS, FRAP), enzyme inhibition (xanthine-oxidase XOD, superoxide dismutase SOD, and AChE), anti-inflammatory and cytotoxic activities. In general, the results revealed that extract's organ origin influenced considerably chemical composition and then biological activities. The highest antioxidant and cytotoxic amounts were observed in flower buds extract, rich with phenolic and flavonoid compounds. On the other hand, leaves extract was rich with tannin compounds and had an inhibitory potent against XOD, SOD, AChE, and anti-inflammatory activity [93]. Another study with aqueous and hydromethanolic aerial parts of Moroccan *C. salviifolius* by K. Sayah also showed a significant phenolic and flavonoid content and effective antioxidant activities. Still, if IC<sub>50</sub> values of each test were compared, we will find a difference that may be explained by many parameters such as geographical area, organ origin, extraction methods, Etc. Extracts used in this study also exhibited a strong inhibitory toward  $\alpha$ -amylase and  $\alpha$ -glucosidase, influencing glucose blood levels [91]. To our best knowledge, the survey carried by M.R. Loizzo is the only in literature focused on the antioxidant activity of *C. salviifolius* EO. EO was able to scavenger DPPH and ABTS radicals to reduce antioxidant compounds on ferric tripyridyltriazine (FRAP assay) and inhibit lipid peroxidation ( $\beta$ -carotene), also inhibit AChE and BChE. IC<sub>50</sub> values reported in this study are much lower compared to those noted with organic extracts. This difference may be attributable to the proportion of different chemical compounds present because EO is a complex mixture of several molecules which can act in synergy or by one or two main components. However, this supports EO's practical use as a food additive and herbal tea because compounds lipophilic could be delivered by the bloodstream to the brain, an area affected by oxidative damage [62].

Considering the importance of developing pharmaceutical products with lesser side effects for inflammation and pain treatments. The current study proposed by [94] reports the anti-inflammatory and analgesic potent of Moroccan *C. salviifolius* aqueous extracts, an important reduction of inducing paw edema (97.57%), and significant inhibition of writhes for a dose of 500 mg/Kg of body weight. In a recent paper published by I. Chiochio, the authors demonstrated for the first time the skin protection effect of *C. salviifolius* hydro-methanolic extracts [95]. Trials aimed to test the *in vitro* inhibition of two enzymes which are cosmetic targets (tyrosinase and elastase), showed the inhibition of 51% against elastase and 61% against tyrosinase at a concentration of 50  $\mu$ g/mL. Also, a correlation was established between inhibition enzymatic potency and the total phenolic and flavonoids content.

### 3.4. *C. albidus* L.

Ethnopharmacological data revealed the use of *C. albidus* flowering top in decoction against respiratory disorders by the North-West of Morocco population [96]. In this regard, a study was carried to support the traditional pharmacopeia in Morocco. A high value of total phenolic content and total flavonoid content was registered from ethanolic extract (TPC  $112.48 \pm 1.78$  mg GAE/g extract; TFC  $24.55 \pm 0.58$  mg QE/g extract). Those compounds are secondary metabolites that could act as antibacterial responsible for respiratory infections [90].

### 3.5. *Cistus heterophyllus* subsp. *Carthaginensis* (Pau)

The influence of environmental conditions in the production of phenolic compounds is a fact. A study carried on how the medium composition affects both the performance and the antioxidant capacity of *C. heterophyllus* shoots cultured in vitro. The finding suggested modulation of parameters suited by physical state and chemical composition. Still, a correlation between phenolic compound levels and the antioxidant capacity (evaluated by DPPH assay) in shoots extracts showed the prominent role of defense against oxidative stress [97].

### 3.6. *C. clussii* Dunal

In contrast, a study carried out with *C. clussi* on the role of a secondary metabolic pathway in responses to stress such as summer drought, reported the increased syntheses of many phenolic compounds and the maximum efficiency of photosystem II. The induced drought may be due to the compound's action to protect the plant from oxidative damage [98].

### 3.7. *Cistus populifolius* L.

The *C. populifolius* aqueous extract from Spain have demonstrated for the first time a high polyphenol (especially ellagitannins) content and high antioxidant capacity observed in many analysis, data reported in this study suggests the use of this species in the food industry and biological systems [86].

### 3.8. *Cistus crispus* L.

Mainly *C. crispus* was studied by A. Bouyahya's team. It is used as a poultice applied against wounds [96]. It is well known that secondary metabolites are infused by the solvent used for the extraction, thus affecting biological activities. *C. crispus* methanolic extract showed a higher TPC and TFC, which are the most widely used phenolic substances [99]. Based on our knowledge, there is only one report discussing the ability of *C. crispus* n-hexane extract to act against tumor cells (embryonal rhabdomyosarcoma cancerous) without affecting normal cells (high selectivity indexes) and remarkable IC<sub>50</sub> value. This finding is interesting, while the absence of correlation between antioxidant and antiproliferative activities supports other targets of phenolic compounds on cancer cell lines [100].

### 3.9. *Cistus libanotis* L. and *Cistus villosus* L.

Similar to the previous investigation on the *Cistus* genus, *C. libanotis*, and *C. villosus*, we report the leading presence of flavonoid compounds with other phenolic substances in hexane extract without any antiproliferative potent against three different cell lines [41]. However, the same species' methanolic extracts also have a significant amount of phenolic, flavonoid, and tannins content. That could prevent the participation of ions in metal-catalyzed initiation and hydroperoxide decomposition reaction. Indeed, this mechanism has been reported to escape oxidative stress, thus prevent many chronic diseases [78]. Moreover, the EO from Italian *C. libanotis* had a fraction composed mainly of Monoterpene hydrocarbons, with the most significant antioxidant potent studied by DPPH, ABTS, FRAP,

$\beta$ -carotene bleaching test, AChE, and BChE. Except for *C. villosus*, which does not have a FRAP activity and low ABTS inhibition [62].

### 3.10. *Cistus creticus* L.

Investigation on biological activities of *C. creticus* has started since 1994. Many compounds have been isolated from resin and hexane extract, especially labdane type-diterpenes, which exhibited interesting cytostatic and cytotoxic effects against variable human leukemic cell lines with a promising IC<sub>50</sub> suggesting an induction of apoptosis via p-53i independent pathway [89,97,101]. Further in vivo use is hindered by their water-insolubility. To overcome that, liposome formulation was used to encapsulate two compounds and compare their activity against human cancer cell lines with the free compounds. It has been proven that encapsulation may have several advantages, but it is also important to signal that it may modify the efficacy (not the same IC<sub>50</sub>) [102]. Some of those labdane types were also evaluated for their anti-inflammatory activity in vivo on the back of hairless mice. Still, one of the tested compounds has shown a significant contribution to the skin barrier repair compared to the control, which may be due to the lack of the tested molecule's epoxide structure [89].

Research on biotechnology to produce secondary metabolites has received particular interest. Marijana has successfully established in vitro culture of the shoots and roots of *C. creticus*, which presented a similarity in secondary metabolites with those found in the native plant, which offers an excellent opportunity for further commercial use while respecting the ecosystem [103].

The south-Moroccan population has reported leaf decoction in the traditional treatment of diabetes [104]. It has also recently been declared that it had a positive influence on the foraging field containing *C. creticus* on the quality of goat milk [105].

Known as *C. incanus*, Italy's aqueous extract has shown to act as spasmolytic on intestinal and vascular smooth muscle. Its action is concentration-dependently and reversible inhibitory. This finding supports local folk medicine's beneficial effect on diarrhea and digestive disorders [106]. As known, compounds belonging to labdane-type diterpenes were subject to much research and demonstrated their cytostatic and cytotoxic ability. A study aimed to prepare liposomes and incorporate sclareol has shown a notable reduction in human cancer tumor growth rate than free sclareol [107].

On the other hand, underlining men's life quality impairs because of benign prostatic hypertrophy. The aqueous extract has been active in suppressing the growth of human epithelial prostate cells. This might be used for treatment since they do not reveal significant toxicity [29]. A polyphenol-rich extract from herb *C. incanus* has increased intracellular oxidative stress in Chinese hamster pulmonary fibroblast cells cultured [108].

Indeed, many mechanisms were suggested, such as regulation-free radical processes as a signal of the transduction pathway or the pro-oxidant activity of polyphenols and their ability to inhibit and reduce the P-gp protein efflux. An evaluation of oxidant/antioxidant status, estrogenic/anti-estrogenic activity, and gene expression profile in mice fed with *Cistus incanus* reach bee pollen, revealed a very noticeable health-protective potential and antioxidant activity [77]. Considering the important use of those antioxidants in the human diet, attention has been paid to herbal infusion, which promoted a high content of phenolic substances and strong antioxidant potent.

### 3.11. *Cistus laurifolius* L.

*C. laurifolius* is mainly known in Turkish folk medicine to treat various types of pain and disorders. As a part of evaluating this traditional use, numerous studies have been conducted. It has been demonstrated in vivo by many modules the anti-inflammatory effect of leaves extracts against multiple molecules, which play a crucial role in inflammatory and immune response such as IL-1, TNF- $\alpha$ , prostaglandins by inducing inflammation in mice. The results were interesting. Extracts and molecules isolated could exert a strong antinociceptive and anti-inflammatory potent without causing any apparent acute

toxicity or damage [109–111]. The chloroform extract could also exert an analgesic effect by inhibiting tail-flick response rapidly compared with morphine [112]. Another striking point was the *in vivo* antioxidant activity of extract and compounds isolation, observing possible liver damage and acute toxicity. The potent studied was more than ascorbic acid [113,114]. Whereas the burden of diabetes and its complications increases, specific attention is given to the utilization of tea leaves from *C. laurifolius* to explore its potential effect as antidiabetic. It is a possible influence on platelet aggregation and blood coagulation. Results indicated that this species might also benefit diabetic patients [79,115].

Upon reviewing the literature on the *Cistus* genus, it is found that numerous studies have been carried out on multiple features, uses, and valuable activities which we have mentioned above. To our best knowledge, the first review about the *Cistus* genus has been published by Papaefthimiou. It has summarized an overview of the main *Cistus* species present in the Mediterranean basin [116]. More recently, Stepień also has published a review paper about the biological properties of *Cistus* species [117]. Both teams have highlighted mainly the studies showing promising potential on numerous biological applications without showing value details.

As known multidrug-resistant microorganisms have become increasingly problematic, new drugs are essential to tackle this ever-increasing problem. This document's quest was to summarize and update recent scientific investigations to determine anti-infective activities separately (antiviral, antiparasitic, antifungal, antibacterial, and antibiofilm). Also classified antibacterial potency on three levels: a—Effect of EO, b—Effect of isolated compounds, and c—Effect of crude extracts.

#### 4. Antiviral Activity of *Cistus* Extracts

Viral infections are life-threatening diseases because of their rapid outbreak. Among the most aggressive viral infections are Ebola, AIDS, influenza, and SARS. For instance, influenza is responsible for over 3 million new severe disease cases and 300,000–500,000 deaths yearly [118]. Alarming, the number of patients diagnosed with viral infections is increasing every year. For example, the covid-19 pandemic alone infected about 141 M people and caused 3.1 M deaths (WHO 21/04/2021). Treatment of viral diseases is a great challenge even today because of the virus's adaptation, the emergence of resistant viral pathogens, new viral strains, the high cost and side effects of medicine, and host resistance antiviral drugs [119].

Herbal drugs have gained much importance due to their easy adaptability, low cost, and fewer side reactions on patients [120]. Most studies related to traditional *Cistus* species' uses have been carried out in Greece and Turkey.

Three *Cistus* have been reportedly studied for their *in vitro* and *in vivo* activity against viral pathogens. Different locations, parts of the plant, and solvents have been used to prepare extracts against H7N7, H1N1, H5N1, HIV, Ebola virus, HSV-1, PI-3, and dengue virus (Table 1).

Dr Pandalis developed a selective extract CYSTUS052 from a distinct variety of *C. incanus*, with a content of more than 26% of polyphenol. This variety is the main ingredient for several products (Cream, tea, syrup, bio pastilles, decoction, salve, food supplements). This extract has demonstrated the greatest antiviral action against influenza A (H7N7) in *in vitro* (90% inhibition) but also in *in vivo* model (mice treated with aerosols of *Cistus* extract were protected from infection). All experiments concluded on the safety of extracts without toxicity or adverse effects on systemic immune response neither epithelial bronchioles cells, suggesting a direct interaction of polymeric polyphenols with viruses before infection leading to the prevention of absorption in the cells [121]. Ehrhardt et al. attempted to demonstrate anti-influenza activity against other subtype strains (H1N1, H7N7, H5N1). Overall results showed the extract's ability to reduce the progeny virus titers of different strains with a dose-dependent response [122]. Following safety analysis, the extract did not show any harmful effect on cells. Moreover, confirmation of the previous hypothesis (reduction of the progeny virus titers) was demonstrated using several experiments to indicate that components of the CYSTUS052 extract can directly be interfering with viral

HA to block binding to cellular receptors with an unspecific physical mode of antiviral action (using HRV14 as an example). The model proposed overcame resistance problems by mutations of amino-acid residues.

Since the first International Conference on Traditional Medicine and AIDS was held in Dakar in 1999, highlighting the considerable support of medicinal plants among HIV-infected individuals, HIV/AIDS was selected as a priority for future research and development in the area of medicinal plants. The Canadian AIDS Treatment Information Exchange (CATIE) has prepared a list of medicinal plants showing potential beneficial effects for HIV-infected individuals “Decade for the Development of African Traditional Medicine” (2000). In this interest and based on antiviral potent demonstrated by CYSTUS052, Rebenburg showed the inhibitory potent of aqueous extracts and the polyphenol-enriched fraction of *C. incanus* against clinical isolation of HIV with multidrug resistance profile, moreover, the potency of these extracts against emerging viruses such Ebola virus and Marburg virus. The inhibition percentages were more than 80% and an EC<sub>50</sub> ranging from 5.40 to 15.06 µg/mL. These results have led to further investigation of the mode of action using different systems (EASY-HIT, TOA, GFP-labelled HIV-1 particles) and the observation demonstrating that *C. incanus* blocks viral particles’ attachment to which inhibit viral entry into host cells. In addition, it blocks gp-120 envelope protein in HIV-1 and envelopes glycoproteins of Ebola and Marburg viruses, which prevent these viral proteins from mediating infection. Even after long-term *C. incanus* treatment (168 days), viruses did not show any resistance. This is presumably attributed to the combination of actives molecules in the extracts compared to treatment with a single-compound antiretroviral drug.

Although these findings were under cell culture conditions and did not identify the individual antiviral agents, it is still believed to have a therapeutic application after extensive investigations, mainly as topical microbicides to prevent STD [123]. Based on the utilization of oleoresin of *C. incanus* as the main ingredient of “Aliptamuscata” by doctors during epidemics of the medieval period for prevention [124] and to ensure a much investigation of *C. incanus* antiviral potency, Kuchta has explored the raw extract and fractions of labdanum resin against the dengue virus, leading to severe forms of the disease. Unfortunately, it had a strong cytotoxic effect. Simultaneously, two subfractions of dichloromethane fraction showed the intense anti-dengue activity of 100% with non-toxic concentration (31.25 µg/mL). The chemical composition revealed epi-manoyloxide, 3-hydroxy-manoyloxide, manoyloxide, 3-acetoxy-manoyloxide [125]. The authors have highlighted an interesting point in this study: why water-soluble polyphenols had the greatest antiviral potency? In contrast, in this case, the water-soluble fraction has enhanced viral proliferation, which may be because the aqueous fraction was previously washed with a solvent much more polar.

An initial finding of antiviral potent of *C. laurifolius* in leaves was reported against HSV-1 and PI-3. No % of inhibition was written. However, the maximum non-toxic concentration measured revealed that hexane fraction had significant activity against PI-3, like the reference drug oseltamivir (32 µg/mL). On the other hand, HSV-1 was less sensitive, with the maximum cytopathogenic effect of 16–32 µg/mL. It is still an interesting finding through the insufficient data since HSV infections are usually severe problems among immunocompromised individuals [126].

**Table 1.** Antiviral potent of *Cistus* extracts.

<i>Cistus</i> Species	Collection Area	Part of Plant	Type of Extract	Viruses	Technique	Concentration $\mu\text{g/mL}$	% of Inhibition	Mechanism	References
<i>C. incanus</i> <i>PANDALIS</i>	Northern Greece	ND	CYSTUS052 solved in sterile PBS and sterile H <sub>2</sub> O	H7N7	Cell culture and mouse infection model	10,000	90%	Binding with virus and prevent adsorption to cells	[121]
<i>C. incanus</i> <i>PANDALIS</i>	Northern Greece	ND	CYSTUS052 solved in sterile PBS	H1N1 H7N7 H5N1	Cell culture and plaque titration of progeny virus	50	Maximum reduction in the order of two logs	Interaction of CYSTUS052 components with viral protein surface and block binding to cellular receptors	[122]
<i>C. incanus</i> CYSTUS052 <sup>®</sup> and Cystus <sup>®</sup>	Northern Greece Germany	ND	Aqueous extract and Polyphenol-enriched fraction	HIV Ebola virus Marburg virus	Cell culture and EASY-HIT technology for identification of HIV inhibitors	100	More than 80%	Blocking the viral gp120-mediated binding of virus protein to heparin and prevent primary attachment to host cells	[123]
<i>C. laurifolius</i>	Kurtboğazi, Ankara, Turkey	Leaves	Ethanollic Extract and its fractions	HSV-1 PI-3	Cell culture and Maximum cytopathogenic effect.	512	Not determined most activity with hexane (32 $\mu\text{g/mL}$ MNTC)	ND	[126]
<i>C. creticus</i>	Northern Crete	Labdanum resin	Diethyl ether and its fractions	Dengue virus	Cell culture and MTT-test	31.25	100%	Based on literature: neuraminidase inhabiting and blocking viral proteins to prevent infection of host cells	[125]

ND: Not determined; H7N7: Avian influenza virus A/FPV/Bratislava/79; H1N1: Human influenza virus A/Puerto Rico/8/34; H5N1: Human influenza isolate A/Thailand/1(KAN-1)/2004; HIV: Human immunodeficiency virus; HSV-1: Human alphaherpesvirus 1; PI-3:Parainfluenza type 3.

## 5. Antiparasitic Activity of *Cistus* Extracts

Each year diseases caused by parasites lead to hundreds of millions of infected people, particularly in tropical and subtropical regions, resulting in one million deaths [127]. At first report about the potential of *Cistus* against parasites, Fokialakis have demonstrated the significant antileishmanial activity of raw extract of *C. monspeliensis* and *C. creticus* [128,129]. Also, the authors tested pure and semisynthetic compounds from the same species against *L. donovani* promastigote (causative agent of visceral leishmaniasis). Obviously, among the eight natural compounds from *C. monspeliensis*, 18-acetoxy-cis-clerod-3-en-15-ol was the most active with an IC<sub>50</sub> value of 3.3 µg/mL, while *C. creticus* compounds were less sensitive ent-3b-acetoxy-13-epi-manoyl oxide active with an IC<sub>50</sub> value of 17 µg/mL. As far as we could observe, semisynthetic derivatives showed variable responses, ranging from inactivated to more active than the parent compound. As it is commonly acknowledged that the fundamental concepts of activity are about selective toxicity against the target without any toxicity to the host cell, none of all compounds tested in this study was cytotoxic to mammalian cells up to the highest concentration of 47.6 µg/mL.

A recent report by Bouyahya on macerated extracts from *C. crispus* leaves against three *Leishmania* species tests at the promastigote stage have demonstrated that among the solvent used, methanol and ethanol, n-hexane showed the best anti-promastigote activity regarding *L. major*, *L. tropica*, and *L. infantum*. Moreover, *L. Infantum* was the most sensitive IC<sub>50</sub> 47.29 µg/mL. Also, it should not be forgotten that all results obtained with *C. crispus* extracts were lower than the control used (Glucantime<sup>®</sup> IC<sub>50</sub> > 500 µg/mL) [130]. However, no toxicity tests were performed. Unfortunately, there is a high probability that the products that have been classified as active against a particular parasite in vitro are likely to be known toxins to host cells (Table 2).

**Table 2.** Antiparasitic potent of *Cistus* extracts.

<i>Cistus</i> Species	Collection Area	Part of Plant	Type of Extract	Parasite	Technique	Concentration µg/mL	IC <sub>50</sub> µg/mL	Mechanism	References
<i>C. monspeliensis</i> <i>C. creticus</i>	Greece	Aerial parts Resin	Pure compounds from Dichloromethane extracts and semisynthetic derivatives	<i>L. donovani</i>	In vitro culture of promastigote and Alamar blue assay	1.6–8–40	From 3.5 to 37	ND	[129]
<i>C. crispus</i>	Ouezzane, Morocco	Leaves	Methanolic, Ethanolic and n-hexane extracts	<i>L. major</i> <i>L. tropica</i> <i>L. infantum</i>	MTT assay	ND	n-hexane against <i>L. major</i> = 47.29	ND	[130]

ND: Not determined; *L.*: *Leishmania*.

The in vivo screen should assess activity against an intracellular stage of parasite development to be genuinely representative for an antiparasitic product suitable for development. Nevertheless, no screening system is perfect because of the lack of correlation between tests in vitro and in vivo in all areas of drug discovery. We cannot emulate the complex situation in vivo.

## 6. Antifungal Activity of *Cistus* Extracts

Even though fungi were the first source of antibacterial agents, they are also responsible for fruits and vegetable diseases, like humans affecting the quality of life, causing pain, discomfort, and psychological symptoms. This concern is more severe with the increase of the resistance phenomena.

In search for antifungal drugs in the *Cistus* genus, rockrose is also known as *C. creticus* = *C. villosus* = *C. incanus*, was widely investigated. First, by Demetzos et al., in both reports about EO's composition and its effect against *C. albicans* which had almost the same effect [69,70]. Comparative MIC analyses of Moroccan and Turkish rockrose against *C. glabrata* and *C. albicans* show respectively significant MIC values with methanol extract from Moroccan species 0.19–6.25 mg/mL and 8–32 mg/mL with aqueous extract from Turkish samples. Interestingly the bio-guided extraction (fractionation with increasing polarity solvent) of Bouamama allowed a better activity localization. Butanol fraction

and remaining aqueous layer were more active than the raw extract. It also should be noticed that *C. glabrata* was the most sensitive while *C. krusei* was the most resistant to extracts [31,131]. However, the highest anti-candida activity was reported with phenolic extract of *C. ladaniferus*. MIC was lower 0.05 mg/mL for *C. albicans*, *C. glabrata*, and *C. parapsilosis* [132]. This extract was mainly made of phenolic compounds, which might explain its activity.

Meanwhile, it has been established that EO, aqueous and organic extracts of rockrose are also active against *Aspergillus* species [131,133,134]. Hydro-methanolic extract of *C. incanus* showed a pretty interesting finding against *A. parasiticus* since, at a concentration of 0.2 mg/mL, it inhibited the growth in a percentage of 46% and also inhibited the production of Aflatoxin B1 from 72.5% to 90.1% [30]. It is such an outstanding finding considering Aflatoxin's risk and damage to crops and to human health, which is supposed to use these extracts as natural products for biological control. Other studies indicate the potential of extracts derived from rockrose in protection against post-harvest diseases. Ameziane reported activity against *P. digitatum*, *P. italicum*, *G. candidum* with mycelial growth inhibition ranging from 27% to 79% using methanol extract. However, they did not test it in vivo against fruits. At the same time, more recently, Talbi demonstrated the tremendous antifungal potential against *G. candidum*. The extract has inhibited mycelial growth and germination spores at 100%. It has decreased the incidence and severity of sour rote disease respectively to 40% and 32% compared with a control group without causing any phytotoxic effect [135,136].

Karim did similar investigations to demonstrate the effectiveness of eight *Cistus* varying types of extracts. Obviously, for anti-*G. citri-aurantii*, water was the best extraction solvent, followed by methanol and chloroform. In both studies at a concentration of 5 mg/mL aqueous and methanolic, extracts of *C. creticus*, *C. albidus*, *C. laurifolius*, *C. monspeliensis*, *C. crispus*, *C. salviifolius*, and *C. populifolius* exhibited a total inhibition of arthrospore germination. However, among all extracts, aqueous ones of *C. salviifolius* and *C. monspeliensis* have strongly inhibited the fungi with MIC values low than 0.625 mg/mL.

In comparison, methanolic extracts of the same species had a MIC of 5 mg/mL. Indeed Karim has also uncovered the significant activity of all tested plant extracts to reduce disease incidence and severity [137,138].

To the best of our knowledge, little is shown about post-harvest citrus fungal pathogens. These studies have pointed out that *Cistus* extracts will widen the list of allelopathic plants to *G. citri-aurantii* growth.

A recent Moroccan report about the ethanolic extract from rockrose against *P. expansum* and *P. digitatum*: the research was done using agar dilution, and the results revealed the sensitivity of *P. digitatum* MIC 1 mg/mL while *P. expansum* was more resistant with MIC of more than 10 mg/mL. Also, the same study has evaluated the effect against unusual fungi such as *C. versicolor*, *G. trabeum*, *P. placenta*, and *C. puteana*, which is known to be wood decomposition. Most of them presenting a resistance against ethanolic extract. However, they were more sensitive against EO [134].

According to studies published about EO of *C. ladaniferus*, firstly, Mrabet have highlighted its activity against various fungi, in which *M. racemosus*, a polluting fungus, was the most sensitive to the EO. The activity observed may be due to the presence of sesquiterpenes compounds [139]. Years later, Upadhyay has published a detailed report about the potent inhibition of the tested EO against *A. flavus* (MIC 0.6 µL/mL). Its capacity to suppress Aflatoxin B1 production suggests a mode of action based on inhibition of ergosterol biosynthesis (basic sterol of the fungal cell membrane) and enhancement of ions leakage from fungal cells, which leads to fungal growth inhibition. Also, the reduction of methylglyoxal, thus the removal of Aflatoxin B1 biosynthesis. It is also shown that EO was mainly composed of  $\alpha$ -asarone, known for its antimicrobial quality but also its toxicity. However, the phytotoxicity investigation has proved EO's safety for seeds used [140]. Tables 3 and 4 summarize the work done on the fungi.

Table 3. Antifungal potent of *Cistus* extracts.

<i>Cistus</i> Species	Collection Area	Part of Plant	Type of Extract	Fungi	MIC µg/mL	MGI %	References
<i>C. creticus</i>	Greece	Leaves	EO	<i>C. albicans</i>	MID (1/250)	ND	[69]
<i>C. criticus</i> subsp. <i>eriocephalus</i>	Kandanos Chania, Greece	Aerial parts	EO	<i>C. albicans</i>	MID (<1/200)	ND	[70]
<i>C. criticus</i> subsp. <i>creticus</i>					MID (<1/250)		
<i>C. ladaniferus</i>	ND	ND	Essential Oil; Concrete; Absolute and Resinoid	<i>A. niger</i> <i>B. cinerea</i> <i>M. racemosus</i> <i>V. albo-atrum</i>	4000 to 10,000 ppm of EO	99.4% ( <i>M. racemosus</i> )	[139]
<i>C. villosus</i>	Ourika, Morocco	Leaves	Methanolic extracts and their fractions	<i>A. fumigatus</i>	100,000 to 200,000	ND	[131]
<i>C. monspeliensis</i>				<i>C. albicans</i>	1560 to 200,000		
				<i>C. krusei</i>	6250 to >200,000		
				<i>C. glabrata</i>	190 to 390		
				<i>A. fumigatus</i>	25,000 to 200,000		
				<i>C. albicans</i>	25,000 to 200,000		
				<i>C. krusei</i>	12,500 to 100,000		
				<i>C. glabrata</i>	1560 to 3125		
			Plant powders			100%	
						100%	
						100%	
<i>C. villosus</i>	Agadir, Morocco	Leaves+stem	EO	<i>P. digitatum</i> <i>P. italicum</i> <i>G. candidum</i>	ND	37%	[135]
			Methanolic			30%	
						18%	
			Chloroformic			77%	
						17%	
						79%	
						27%	
						27%	
						21%	
<i>C. villosus</i>	Agadir, Morocco	Leaves and stem	Aqueous	<i>G. candidum</i>	156	100%	[136]
<i>C. ladanifer</i>	Montesinho, Portugal	Leaves	Phenolic extract	<i>C. albicans</i>	<50	ND	[132]
				<i>C. tropicalis</i>	625		
				<i>C. glabrata</i>	<50		
				<i>C. parapsilosis</i>	<50		

Table 3. Cont.

Cistus Species	Collection Area	Part of Plant	Type of Extract	Fungi	MIC µg/mL	MGI %	References
<i>C. incanus</i>	Greece	ND	Hydro-methanolic	<i>A. parasiticus</i> <i>A. carbonarius</i>	ND	45.91% 30.65%	[133]
<i>C. incanus</i>	Turkey	Unknown	Aqueous	<i>C. albicans</i> <i>C. glabrata</i>	32,000 8000	ND	[31]
<i>C. albidus</i>	Morocco	Aerial parts	Aqueous	<i>Geotrichumcitri-aurantii</i>	>10,000	>80%	[137]
<i>C. creticus</i>		Aerial parts			1250	100%	
<i>C. laurifolius</i>		Aerial parts			<625	100%	
<i>C. salviifolius</i>		Aerial parts			<625	ND	
<i>C. monspeliensis</i>		Aerial parts			<625	100%	
<i>C. ladanifer</i>		Aerial parts			<625	100%	
<i>C. crispus</i>		Aerial parts			>10,000	100%	
<i>C. populifolius</i>		Leaves			<625	100%	
<i>C. creticus</i>	Tafraout, Morocco	Leaves	EO	<i>C. versicolor</i> <i>G. trabeum</i> <i>C. puteana</i> <i>P. placenta</i> <i>P. digitatum</i> <i>P. expansum</i> <i>A. niger</i>	1/64 1/250 1/1000 1/2000 1/100 1/32 1/100 >10,000 1000 >10,000 1000 1000 >10,000 >10,000	ND	[134]
<i>C. salviifolius</i> <i>C. monspeliensis</i>	Jendouba, Tunisia	Leaves	Ethanol Hexane Water	<i>C. albicans</i> <i>A. niger</i>	ND	6300–12,500 3100–12,500	[141]

ND: Not determined; *C. albicans*: *Candida albicans*; *A. niger*: *Aspergillus niger*; *B. cinerea*: *Botrytis cinerea*; *M. racemosus*: *Mucor racemosus*; *Verticillium albo-atrum*; *A. fumigatus*: *Aspergillus fumigatus*; *C. krusei*: *Candida krusei*; *C. glabrata*: *Candida glabrata*; *P. digitatum*: *Penicillium digitatum*; *P. italicum*: *Penicillium italicum*; *G. candidum*: *Geotrichum candidum*; *C. tropicalis*: *Candida tropicalis*; *C. parapsilosis*: *Candida parapsilosis*; *A. parasiticus*: *Aspergillus parasiticus*; *A. carbonarius*: *Aspergillus carbonarius*; *C. versicolor*: *Coriolus versicolor*; *G. trabeum*: *Gloeophyllum trabeum*; *C. puteana*: *Coniophora puteana*; *P. placenta*: *Poria placenta*; *P. digitatum*: *Penicillium digitatum*; *P. expansum*: *Penicillium expansum*.

Table 4. Antifungal and antiaflatoxigenic potent of *Cistus* extracts.

<i>Cistus</i> Species	Collection Area	Part of Plant	Type of Extract	Fungi	Fungi Secondary Metabolites	MIC $\mu\text{L}/\text{mL}$	Finding	Mode of Action	References
<i>C. incanus</i>	North Greece	ND	Hydro-methanolic	<i>Aspergillus parasiticus</i>	Aflatoxin B1	ND	Both mediums (macadamia, YES) inoculated in the presence of <i>C. incanus</i> extract showed potent inhibition of AFB1 production ranging from 72.5% to 90.1%	ND	[30]
<i>C. ladanifer</i>	ND	ND	Essential Oil	<i>Aspergillus flavus</i> AF-M-K5	Aflatoxin B1	0.6	The EO was found to have an intense antifungal activity, with fungistatic action (MFC 3.0 $\mu\text{L}/\text{mL}$ ). Moreover, it caused absolute suppression of AFB1 at 0.5 $\mu\text{L}/\text{mL}$ , without any phytotoxicity against tested seeds	Inhibition of ergosterol biosynthesis and enhancement of ions leakage from fungal cells leads to fungal growth inhibition -Antiaflatoxigenic potential can be attributed to the reduction of methylglyoxal which represses the expression of <i>aflR</i>	[140]

## 7. Antibacterial Activity of *Cistus* Extracts

Following the worldwide epidemiology of bacterial infections, antibiotic resistance has become a global pandemic and one of the most considerable worldwide anxieties. The spread of MDR, XDR, and PDR bacteria suggests that in 2050 the leading cause of death will be antibiotic resistance. World Bank has indicated that the number of deaths will rise to 10 million every year if no action is taken.

The development of new molecules of antibiotics is crucial mainly for the treatment of Gram-negative infections such as EPC (Enterobacterales Producing Carbapenemases), ABIR (*Acinetobacter baumannii* Imipenem Resistant), and PAIR (*Pseudomonas aeruginosa* Imipenem Resistant). Also, considering all data about these concerns, to date, several plants have been identified from ethnobotanical information as having valuable properties. Most research into these effects on bacterial infections has been undertaken using EO, aqueous, or organic extracts from purified compounds. Here we analyze the studies about *Cistus* antibacterial impact by type of extract. First EO followed by isolated compounds and then raw extracts.

### 7.1. Antibacterial Effect of EO

Plant EO can be extracted from leaves, fruits, stems, and roots. *Cistus* EO has shown having a broad antimicrobial spectrum, being antifungal and antibacterial, as demonstrated by Demetzos et al. in its three reports with *C. creticus* for the first time. EO from leaves and aerial parts shows a similar profile. Their compounds, mainly diterpenes especially manoyl oxide isomers, inhibit the in vitro growth of *S. aureus*, *S. epidermidis*, and *B. subtilis* even at high dilution (1/2000). Simultaneously, Gram-negative strains represented by *E. coli* and *P. aeruginosa* were more resistant to EO's action [69,70].

Nevertheless, the oil from *C. creticus* resin Ladano tested against three *Staphylococcus* species shows similar activity with MIC value of 2 mg/mL, which was estimated high according to authors compared to the better action of the isolated compound Ent-3 $\beta$ -hydroxy-13-epi-manoyl oxide MIC = 0.1 mg/mL. The first time this diterpene was reported in the literature, resin EO was most known for its richness with sesquiterpene [142]. These two-chemical structures (Labdane-type diterpenes and sesquiterpenes) might be called phytoalexin. *Cistus* plants produce those compounds in response to infections with fungi, bacteria, viruses, and parasites, explaining their effectiveness against microbial strains on in vitro tests.

Following experimental research for antistaphylococcal activity, Guinoiseau [143] demonstrated the potential of *C. ladaniferus* EO and its efficacy against tested strain, ranging from 0.012 mg/mL for acetate fraction to 0.8 mg/mL for EO in coordination with the inhibition zones. These concentrations were much efficient than those reported with *C. creticus* EO [142]. Authors have suggested and attempted to introduce these extracts at their MIC and measure the reduction in the number of CFU/mL over 7 h. Results show that alcohol fraction led to 99.9% inhibition in less than one hour; furthermore, they act without cell lysis or drastic cell wall damage. Indeed, the low density of plant oils and their rapid diffusion across cell membranes due to their hydrophobicity might support the non-specific inhibition by disturbing ATPase efficiency or the proton motor force, thus blocking the cell division [143]. This propriety might also offer an alternative delivery route, including transcutaneous delivery after scarification or patch application for burns or skin infections. Even though a screening on agar-diffusion, the available evidence of the effectiveness of *C. ladaniferus* EO against Gram-positive strains could not be excluded. It has been reported by Viera [144] that this EO has strongly inhibited a Methicillin-resistant *S. aureus* but also *S. pneumoniae*. Moreover, these activities include inhibition of *E. coli* ESBL producer, which more sensitive (20 mm) than the *E. coli* ATCC 25922 (10 mm). However, a recent study aimed with several EOs *C. ladaniferus* EO inhibited *S. aureus* with a high MIC (0.4 mg/mL). These observations raise several questions of parameters influencing activity, which need further research. The phytochemical data indicate the high content in  $\alpha$ -pinene, camphene, fenchone, bornyl acetate, and viridiflorol [143,144]. Despite this,

a study carried out the same EO against several strains, including both references and clinical isolates of Gram-negative and positive, did not show any activity except for *L. monocytogenes* whose diameter of zone inhibition was 19 mm [145]. This may eventually be due to the low volume deposited per disc (3  $\mu$ L) (Table 5).

**Table 5.** Antibacterial potential of the essential oils of *Cistus*.

<i>Cistus</i> Species	Collection Area	Part of Plant	Type of Extract	Tested Bacteria	DZI (mm)	MID	References
<i>C. creticus</i>	Greece	Leaves	EO	<i>S. aureus</i> <i>S. epidermidis</i> <i>E. coli</i> <i>P. aeruginosa</i> <i>B. subtilis</i> <i>M. luteus</i>	ND	1/2000 1/500 <1/125 <1/400 1/2000 1/500	[69]
<i>C. creticus</i>	Kandanos, Chania, Greece	Aerial parts	EO	<i>B. subtilis</i> <i>S. aureus</i> <i>S. epidermidis</i> <i>P. aeruginosa</i> <i>E. coli</i>	ND	<1/2000 1/2000 1/500 <1/400 <1/125	[70]
<i>C. creticus</i>	Greece	Resin Ladano	EO	<i>S. aureus</i> <i>S. epidermidis</i> <i>S. hominis</i>	ND	2000 $\mu$ g/mL	[142]
<i>C. ladaniferus</i>	Corsica, France	Aerial parts	EO	<i>S. aureus</i>	52	800 $\mu$ g/mL	[143]
			Hydrocarbonated fraction		6.70	50,000 $\mu$ g/mL	
			Oxygenated fraction		35	100 $\mu$ g/mL	
			Acetate fraction		30	12.5 $\mu$ g/mL	
			Alcohol fraction		50	1500 $\mu$ g/mL	
<i>C. ladaniferus</i>	Alentejo, Portugal	Leaves	EO	<i>S. aureus</i> <i>B. subtilis</i> <i>S. pneumoniae</i> <i>E. coli</i> <i>P. aeruginosa</i> MRSA <i>E. coli</i> ESBL	11 11 38 10 9 23 20	ND	[144]
<i>C. ladaniferus</i>	Unknown	Leaves and branches	EO	<i>S. aureus</i>	ND	400	[146]

MID: Maximum Inhibitory Dilution; ND: Not determined; *S. aureus*: *Staphylococcus aureus*; *S. epidermidis*: *Staphylococcus epidermidis*; *E. coli*: *Escherichia coli*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *B. subtilis*: *Bacillus subtilis*; *M. luteus*: *Micrococcus luteus*; *S. hominis*: *Staphylococcus hominis*; *S. pneumoniae*: *Streptococcus pneumoniae*; MRSA: Methicillin-resistant *Staphylococcus aureus*; *E. coli* ESBL: *Escherichia coli* Extended Spectrum  $\beta$ -lactamases.

## 7.2. Antibacterial Effect of Isolated Compounds

However, little work has been carried out using purified compounds. Several isolated compounds from *Cistus* species have definite activity in laboratory trials. In addition to *C. creticus*, in which Demetzos [142] have provided action against *Staphylococcus*, the team's investigation continued to isolate other compounds that have antibacterial activity. Years later, they report a novel clerodane diterpene called (+)-19-acetoxy-cis-clerodan-3-ene-15-oic acid from *C. monspeliensis* leaves extract tested toward Gram-positive and Gram-negative models. The results showed that the smaller concentration of 0.031 mg/mL used induced inhibition of all *Staphylococcus* growths at this concentration, no inhibition of Gram-negative. When the concentration increases, the compound had a MIC of 0.499 mg/mL against *E. coli*, *K. pneumoniae*, *P. aeruginosa* [147]. Recently, a work published by M6ricz [148] was undertaken to investigate and identify antibacterial components from several *C. incanus* herbal tea. Experiments focused on multi-step extraction to select a fraction that contains flavonoid aglycone.

Additionally, the antibacterial profile of reported components (Apigenin, Kaempferide, Cis-tiliroside/trans-tiliroside, p-coumaric acid-conjugated tiliroside) against *B. subtilis* and *A. fischeri*. The determination was done using a simple, rapid, and inexpensive method, namely thin-layer chromatography-direct bioautography (TLC-DB). The bioautograms discovered were corresponding to the total inhibition of both strains. Furthermore, this

study has shown the ineffectiveness of the raw extract in comparison to the isolated fraction. Indeed, the authors have highlighted the side effect of the usual fractionation protocols whose formation of artifacts may be present. It is generally well known that artifacts lead to loss of activity, the formation of active compounds from inactivating ones, Right away toxic compounds, and the difficulty of reproducing an extraction or purification method. These products and their published activity are recorded in Table 6.

**Table 6.** Antibacterial potent of isolated compounds of *Cistus*.

Cistus Species	Collection Area	Part of Plant	Isolated Compounds	Tested Bacteria	MIC (µg/mL)	References
<i>C. creticus</i>	Greece	Resin Ladano	<i>Ent-3β-hydroxy-13-epi-manoyl oxide</i>	<i>S. aureus</i> <i>S. epidermidis</i> <i>S. hominis</i>	100 100 100	[142]
<i>C. monspeliensis</i>	ND	Leaves	<i>(+)-19-acetoxy-cis-clerodan-3-ene-15-oic acid</i>	<i>S. aureus</i> <i>S. epidermidis</i> <i>S. hominis</i> <i>K. pneumoniae</i> <i>E. coli</i> <i>P. aeruginosa</i>	31 31 31 499.4 499.4 499.4	[147]
<i>C. incanus</i> *	Turkey	Aerial parts	Apigenin Kaempferide <i>Cis-tiliroside/trans-tiliroside</i> <i>p-coumaric acid-conjugated tiliroside</i>	<i>B. subtilis</i> <i>A. fischeri</i>	ND	[148]

ND: Not determined; MIC: Minimum Inhibitory Concentration; *S. aureus*: *Staphylococcus aureus*; *S. epidermidis*: *Staphylococcus epidermidis*; *S. hominis*: *Staphylococcus hominis*; *K. pneumoniae*: *Klebsiellapneumoniae*; *E. coli*: *Escherichia coli*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *B. subtilis*: *Bacillus subtilis*; *A. fischeri*: *Aliivibrio fischeri*; \*: The antibacterial assay in this study was performed using Thin-layer chromatography-direct bioautography.

### 7.3. Antibacterial Effect of Crude Extracts

Nevertheless, raw extracts and liquid-liquid fractions were widely used to explore the antibacterial potential. *S. aureus* and *E. coli* were the most studied strains in all cases. Among the *Cistus* extracts investigated, ethanolic and its fractions from *C. laurifolius* exhibited the best inhibition activity against *S. aureus* (MIC = 0.064 mg/mL) and *E. coli* (MIC = 0.032 mg/mL) [126] in comparison with other species [31,86,99]. A quiet observation about the activity of *C. monspeliensis* in two studies revealed a difference in MIC while it was about the same strain and same solvent (methanol). Bouamama [131] reports a MIC value of 25 mg/mL while Ben Sassi [149] have found 0.312 mg/mL. However, none of the extracts in this study could inhibit *E. coli*, reinforcing the suggestion about a difference in regions' chemotype.

Suppose carrying out a comparison of other species from each Gram class to attempt an extrapolation of activity observed with *E. coli* and *S. aureus*, and considering the risk in which such species *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *E. hireae*, and *L. monocytogenes* may be incriminated (food safety issues, nosocomially acquired infections...). Data analysis of the subsequent studies [86,143,149–151] showed that we could not cluster inhibition activity following bacterial species or *Cistus* species. The same extract might exert a different effect on strains from the same Gram class, even from the same genus. For example, raw extract of *C. monspeliensis* demonstrated a significant inhibition against *P. aeruginosa* (MIC = 0.625 mg/mL) while it did not affect *K. pneumoniae* [149], which was sensitive to ethanolic extract from *C. laurifolius* (MIC = 0.032 mg/mL) [126]. However, if taken independently, *L. monocytogenes* was more sensitive to ethanolic extract from *C. salviifolius* (MIC = 0.515 mg/mL) [152] than ethanolic extract from *C. crispus* (MIC = 8 mg/mL) [99]. Based on these observations and the chemical class differences in each solvent used for extraction, the report of Ustun [126] raises several questions about how a strain presents the same sensitivity profile against all extracts tested (MIC of *A. baumannii* 0.032 with hexane, chloroform, butanol, ethanol and remaining aqueous extracts).

On the other hand, few studies were done with clinical isolates and resistant strains. According to Ben Sassi [149], none of the tested extracts was active against isolated bacteria (*E. coli*, *K. pneumoniae*, *E. cloaceae*, *S. marcescens*, *A. hydrophila*, *S. aureus*) except for *S. epidermidis* and *S. saprophyticus*. Viapiana [31] have reported the activity of aqueous extract

of *C. incanus* against MRSE (MIC 1 mg/mL) and MRSA (MIC 0.5 mg/mL). Furthermore, this is the only work done against *H. pylori* and *S. pyogenes*. This might be due to difficulty maintaining cultures. However, MICs reports were moderate (64 and 8 mg/mL for *H. pylori* and *S. pyogenes*, respectively). Nevertheless, there is great hope with this species since *C. incanus* is widely used as herbal tea.

A short communication published in Natural Product Research reports the potential of ethanolic extract of *C. ladaniferus* against several strains. Clinical samples of *H. pylori* were more sensitive than reference strain. Also *B. cereus* was inhibited at 0.625 mg/mL [153]. Ahlem [154] and Mahmoudi have demonstrated the overall activity of leaves ethanolic extract from *C. monspeliensis* compared to *C. salviifolius*. However, the patterns of inhibition varied.

It is not entirely clear why phytochemists and microbiologists have not further researched mycobacteria, even if WHO reports a total of 1.5 million people died from tuberculosis in 2018. Pharmaceutical companies are spending many resources searching for new agents. To our best knowledge, the only report about the antimycobacterial effect with *Cistus* extracts is from *C. albidus*, *C. salviifolius*, and *C. monspeliensis* by the Iraqi team. Results show complete inhibition of these species against atypical mycobacteria and *M. bovis*. Even the lack of details and referenced methods to study the activity against this particular strain gives us hope that further research may eventually lead to potential agents [155,156].

The very nature of the disease being studied may play a significant role in whether effective natural products will be identified for its treatment. Interestingly, patients reported that the ingestion of tea infusion and aqueous dry extract in the capsule from *C. creticus* had improved their clinical conditions related to Lyme borreliosis disease. Hence, it was confirmed first by Hutschenreuther [68] whose total stagnation of *B. burgdorferi s.s* in vitro growth at 0.2% concentration of EO. EO was dominated by labdane-type manoyloxides and carvacrol, while none of the polar extracts has exhibited activity against tested strain. Years later, Rauwald [157] aimed to clarify the anti-Borrelia active component already reported. Bioassay-guided procedure on Crete *C. creticus* led to the confirmation and isolation of carvacrol and four manoyloxide, in which epi-manoyloxide was the strongest antispirochaetal whose effect was equal to amoxicillin (Table 7).

A minimal number of studies carried out the anti-adhesive activity of *Cistus* extracts (Table 8). To reinforce the use of *C. incanus* herbal tea (from Dr. Pandalis) as an appropriate alternative available in everyday life and verify its possible exploitation in dentistry as well. The study of Hanning [158] showed that the impact of *cistus*-tea on initial oral biofilm using a model. Indeed, the fluorescence microscopy showed a pronounced reduction of initial bacterial colonization due to rinses with *cistus*-tea. Furthermore, another report in the same field has demonstrated the potential of ethanolic extract from *C. ladaniferus* against *P. aeruginosa* marine bacterium, which accelerates the corrosion of 304 L Stainless Steel. The HPLC-Q-TFO-MS analysis revealed many phenolics compounds, which show antibacterial effects and corrosion inhibition [159].



Table 7. Cont.

<i>Cistus</i> Species	Collection Area	Part of Plant	Solvent Used	Sensitive Bacteria	DZI (mm)	MIC (µg/mL)	References						
<i>C. ladaniferus</i>	Spain	Unknown	Water Hydroalcohol	<i>S. aureus</i> <i>E. coli</i>	ND	MIC <sub>50</sub> 144–569 113–612	[151]						
<i>C. albidus</i>						60–292 233–336							
<i>C. salviifolius</i>						45–52 221–289							
<i>C. clusii</i>						91–392 116–1064							
<i>C. monspeliensis</i>	Ouezzane, Morocco	Leaves	Ethanol	<i>E. coli</i> K12 <i>S. aureus</i>	9 16	ND	[90]						
<i>C. albidus</i>		Aerial parts			9 17								
<i>C. crispus</i>	Ouezzane, Morocco	Leaves	Ethanol <i>n</i> -butanol Methanol– Ethyl acetate (fraction)	<i>E. coli</i> K12 <i>S. aureus</i> <i>L. monocytogenes</i> <i>P. aeruginosa</i>	<8–14 15–29 21–31 <8–13	>8000 1000–3000 1000–8000 1000–>8000	[99]						
<i>C. crispus</i>						Turkey		Unknown	Water	<i>S. aureus</i> MRSA <i>S. epidermidis</i> MRSE <i>S. pyogenes</i> β <i>E. hirae</i> <i>B. subtilis</i> <i>E. coli</i> <i>P. aeruginosa</i> <i>H. pylori</i>	ND	500 500 1000 1000 8000 16,000 8000 8000 8000 64,000	[31]

Table 7. Cont.

<i>Cistus</i> Species	Collection Area	Part of Plant	Solvent Used	Sensitive Bacteria	DZI (mm)	MIC (µg/mL)	References
<i>C. laurifolius</i>	Ankara, Turkey	Leaves	Ethanol <i>n</i> -hexane Dichloromethane Butanol	<i>E.coli</i>	ND	32	[126]
				<i>P. aeruginosa</i>		64	
				<i>P. mirabilis</i>		32	
				<i>K. pneumonia</i>		32	
				<i>A. baumannii</i>		32	
				<i>S. aureus</i>		64	
				<i>E. faecalis</i>		64	
<i>C. monspeliensis</i>		Leaves	Methanol	<i>E. coli</i>	13	64	[160]
				<i>E. aerogenes</i>	11	68	
				<i>K. pneumoniae</i>	8	71	
				<i>P. stuartii</i>	10	75	
				<i>P. aeruginosa</i>	9	65	
<i>C. ladaniferus</i>	Taza, Morocco	Leaves	Ethanol	<i>P. aeruginosa</i>	ND	2500	[159]
<i>C. salviifolius</i>	Sidi Mechreg, Tunisia	Leaves and Flowers	Ethanol	<i>E. coli</i> <i>P. aeruginosa</i> <i>S. typhimurium</i>	22–24	12,500	[154]
					23–26	12,500	
					21–25	12,500	
					22–25	1562–3125	
					23–24	12,500	
					20–25	1562–12,500	
<i>C. monspeliensis</i>				<i>S. aureus</i> <i>B. subtilis</i> <i>L. monocytogenes</i>	11–22	12,500	
					15–25	12,500	
					15–24	12,500	
					15–25	1562	
					15–24	12,500	
					15–22	1562–3125	
<i>C. salviifolius</i>	Jendouba, Tunisia	Leaves	Ethanol Hexane Water	<i>E. coli</i>	18	12,500	[141]
				<i>S. typhimurium</i>	20	25,000	
				<i>P. aeruginosa</i>	10	3100	
				<i>S. aureus</i>	17	12,500	
				<i>E. faecalis</i>	13	6300	

Table 7. Cont.

<i>Cistus</i> Species	Collection Area	Part of Plant	Solvent Used	Sensitive Bacteria	DZI (mm)	MIC (µg/mL)	References
<i>C. monspeliensis</i>					14	6300	
					17	12,500	
					10	6300	
					17	12,500	
					16	12,500	

ND: Not determined; DZI: Diameter of Zone Inhibition; MIC: Minimum Inhibitory Concentration; *S. aureus*: *Staphylococcus aureus*; *B. subtilis*: *Bacillus subtilis*; *B. cereus*: *Bacillus cereus*; *E. coli*: *Escherichia coli*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *E. hirae*: *Enterococcus hirae*; *M. aurum A<sup>+</sup>*: *Mycobacterium aurum A<sup>+</sup>*; *M. smegmatis MC<sup>2</sup>*: *Mycobacterium smegmatis MC<sup>2</sup>*; *M. bovis*: *Mycobacterium bovis*; *M. vaccae*: *Mycobacterium vaccae*; *S. epidermidis*: *Staphylococcus epidermidis*; *S. saprophyticus*: *Staphylococcus saprophyticus*; *E. faecalis*: *Enterococcus faecalis*; *L. monocytogenes*: *Listeria monocytogenes*; MRSA: Methicillin-resistant *Staphylococcus aureus*; MRSE: Methicillin-resistant *Staphylococcus epidermidis*; *S. pyogenes* β: *Streptococcus pyogenes*; *E. hirae*: *Enterococcus hirae*; *H. pylori*: *Helicobacter pylori*; *P. mirabilis*: *Proteus mirabilis*; *K. pneumoniae*: *Klebsiella pneumoniae*; *A. baumannii*: *Acinetobacter baumannii*; *E. aerogenes*: *Enterobacter aerogenes*; *P. stuartii*: *Providencia stuartii*; *S. typhimurium*: *Salmonella typhimurium*.

Table 8. Antibiofilm potent of *Cistus* extract.

<i>Cistus</i> Species	Collection Area	Part of Plant	Solvent Used	Bacteria Used	Surface Used	Finding	References
<i>C. incanus</i> Dr. Pandalis	Northern Greece	Unknown	Water	Oral bacteria	Cylindrical enamel slabs	Rinses with <i>cistus</i> -tea rich with polyphenols have reduced initial bacterial colonization (visualized by microscopic fluorescence method) on enamel in situ. Also, enzymes present in the pellicle were conserved and not affected by compounds present in the extract.	[158]
<i>C. ladaniferus</i>	Taza, Morocco	Leaves	Ethanol	<i>P. aeruginosa</i>	304 L SS coupons	<i>P. aeruginosa</i> accelerates the corrosion rate, while the compounds present in ethanolic extract demonstrate a dual effect: damage in the morphology of bacterial cell membrane and adsorption on a surface. That changes physicochemical properties and led to the formation of the non-conducting protective layer, which inhibited the 304 L SS coupon surface's biocorrosion.	[159]

*P. aeruginosa*: *Pseudomonas aeruginosa*.

## 8. Conclusions

*Cistus* is a Mediterranean native genus of shrubs belonging to the family *Cistaceae*. Species of this genus can grow during hot summers and after wildfires. *Cistus* species are most widespread in the Mediterranean region, whilst some of them are endemic. *Cistus* plants can grow under slightly different environmental conditions. Most species are very fragrant and sweet-smelling. Studies have reported that *Cistus* species are rich in polyphenolic compounds. Meanwhile, *C. incanus* and *C. albidus* are rich in flavonoids. *C. ladaniferus*, *C. salvifolius*, *C. laurifolius*, *C. monspeliensis*, and *C. libanotis* are mainly enriched in ellagitannins and flavonoids. Terpenes were identified in *C. ladaniferus* and *C. laurifolius*. Diterpenes were reported in *C. monspeliensis*, *C. libanotis*, *C. villosus*, and *C. creticus*. While sesquiterpenes were detected in *C. albidus* and *C. salvifolius*.

*Cistus* species have long been used as remedies in traditional folk medicines of different populations around the world. The crude extracts and EO of these herbs have been effective against inflammation, wound and skin disease, various microbial infections, diabetes, pain, arterial hypertension. *Cistus* EO is approved by the Food & Drug Administration (FDA) as a food additive and flavoring agent. Due to the increasing interest in natural products and the benefits of *Cistus* species, EO, labdanum, bee pollen, and tea are owning a significant mark in herbal products. It was reported that *C. monspeliensis* has the function of promoting energy metabolism pathways in human intestinal epithelial cells. Extracts from *C. incanus* are used as a dietary supplement to prevent chronic diseases due to their higher and diverse phenolic compounds. These characteristics can be much appreciable for being exploited in the food industry.

Previous summarized works in this review have indicated and confirmed the broad biological potentials of *Cistus* plant extracts. In *in vivo* model, *Cistus* showed anti-influenza, analgesic, anti-inflammatory, and spasmolytic potentials. In the *in vitro* model, *Cistus* showed promising effects against HIV, Ebola, Marburg virus, and clinical bacteria.

We can confirm that *Cistus* can constitute a great source of drug discovery. However, besides all the beneficial attributes of this plant as well investigated above, it is essential to highlight some limitations. Some species belonging to *Cistus* can exhibit *in vivo* toxic effects. Moreover, extracts from some *Cistus* species were reported to be active *in vitro* only.

The present review sheds light on the antimicrobial activity of *Cistus* sp. In this sense, we can conclude that this genus has great potential to serve society as it provides promising chemicals to fight such infections.

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