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Oliveria decumbens, a Long-Neglected Plant with Promising Phytochemical and Biological Properties

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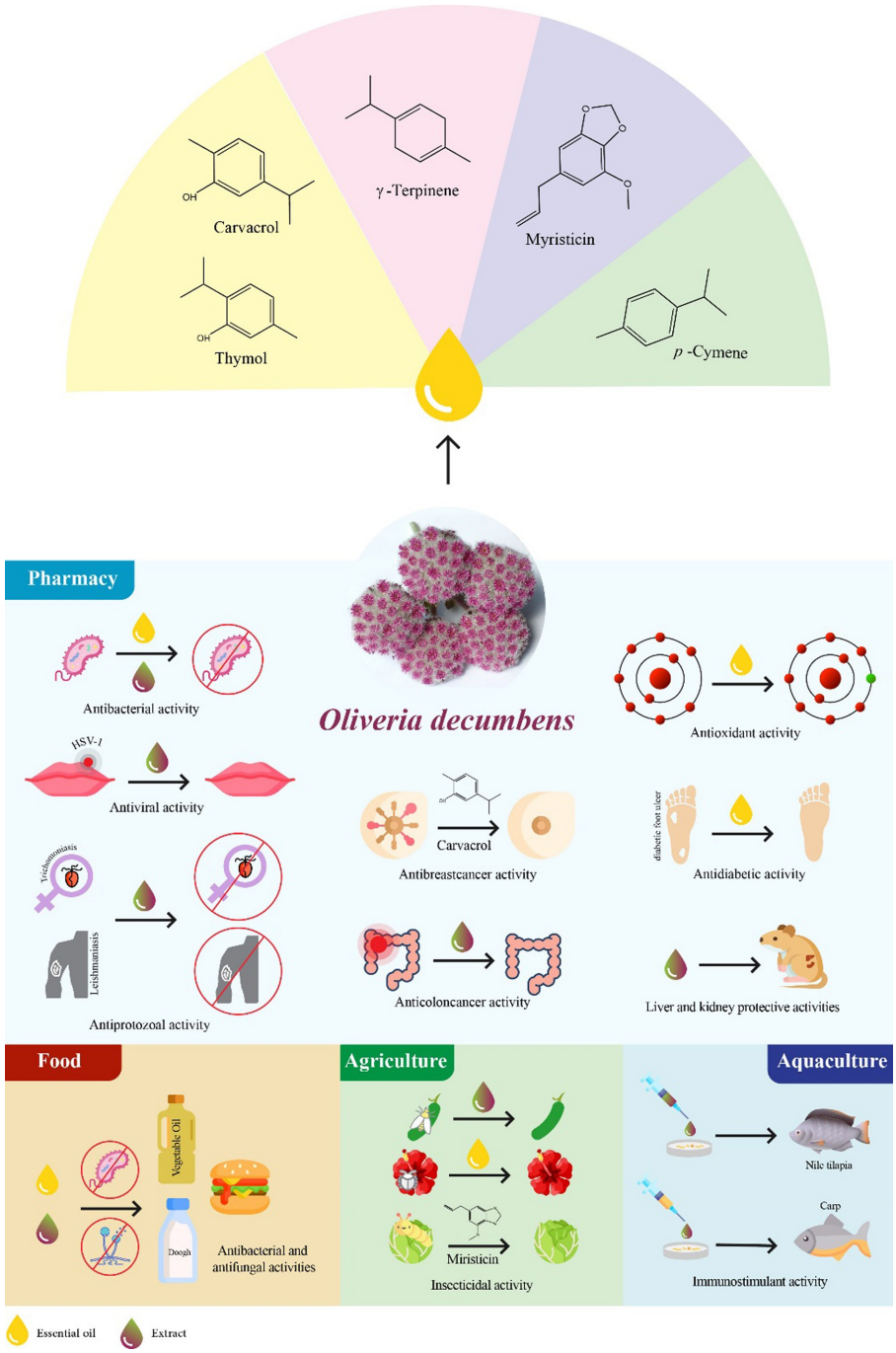

Oliveria decumbens is a folkloric medicinal plant belonging to the Apiaceae family, traditionally utilized to treat various diseases like gastrointestinal disorders, fever, and wounds. This review aims to provide a comprehensive overview of the plant's phytochemical composition and biological properties, with potential implications for various industries and avenues of further research. The data presented here has been compiled through searches utilizing the keyword *"Oliveria"* across scientific databases such as PubMed, Web of Science, Scopus, ScienceDirect, and SciFinder. Carvacrol and thymol have been identified as the primary volatile constituents, though the complete profile of the plant extract remains to be fully elucidated. Notably, *Oliveria decumbens* essential oil exhibits significant antibacterial, antifungal, antioxidant, and anticancer properties. Additionally, the plant extract demonstrates promising antiprotozoal, antiviral, hepatoprotective, and immunostimulant effects, although these findings are primarily derived from preliminary studies. While *in vitro* and *in vivo* investigations have validated some traditional uses of *O. decumbens*, further pre-clinical testing is warranted to ascertain both efficacy and safety profiles. Moreover, the identification of specific components within the plant extract is crucial for a more comprehensive understanding of the mechanisms of action underlying its therapeutic properties within the realm of phytomedicine.

1. Introduction

The Apiaceae family is one of the largest essential oil-bearing families in medicinal plants. It possesses 446 genera and 3820 species which are mostly aromatic and some of them have been used for therapeutic purposes.[1] *Oliveria decumbens* is an annual, herbaceous and native plant which is growing in Iran, Syria, Iraq, and southeastern of Anatolia. Its distribution has been restricted in some subtropical regions of western and southwestern of Iran including Ilam, Kermanshah, Kohgiluyeh and Boyer-ahmad and Fars provinces, with local names "Denak", "Den" or "Moshkorak".[2] The plant has hollow and branched stem with ramified leaves and white, pink-purple and pink florets in umbel inflorescence (Figure 1).[2]

O. decumbens has been accessed for the treatment of various diseases since ancient time. A number of studies have reported its usage as traditional medicine by local people. It has been widely used to treat gastrointestinal disorders in Iran and usually prescribed as a decoction to cure disorders such as indigestion, abdominal pain and bloating, gastritis, stomach pain, reflux, nausea, diarrhea, postpartum complications and heart pain by local people of west and south regions of Iran.[3–7] Moreover, it is reported that herbal preparation of its aerial parts acts as hepatoprotective and liver and heart tonic agent and possesses febrifuge effect to cure different diseases.[6] The traditional application of the decoction has also documented to relieve thirst in children.[6,8] *O. decumbens* has also been recognized as an effective remedy against inflammation and cancer symptom in Persian traditional medicine.[9] The effect of its aerial parts on the healing of wound has further been recorded.[10,11] Besides its medicinal applications, *O. decumbens* has extensively been consumed as flavoring agents in Persian foods.[6]

Considering the emergence of microbial resistance of human, plant pathogens, and food spoilage, natural resources have always been considered as a global demand for substitution of the chemical drugs, pesticides (in crops protection), and food preservations, due to their fewer side effects and diverse structures leading to production of novel compounds in the pharmaceutical, agricultural and food industries. For this reason, the potential investigation of the plant active ingredients especially its essential oil (EO) has been of great interest to researchers in diverse fields, aiming of using natural resources instead of chemicals to improve the society health biocontrol and reduce losses of agricultural products (pre- and post- harvest) and improve the shelf life of food products (as preservatives).

Several studies have been conducted in recent years in the field of identifying EO components and different aspects of the biological properties of *O. decumbens*. In general, oxygenated monoterpenes have been identified as the main volatile chemical class of the EO. However, the non-volatile components are still unknown, the EO, isolated constituents (thymol, carvacrol, γ-terpinene, *p*-cymene) and extracts have been subjected to assess biological potencies performed on preclinical *(in vitro* and *in vivo)* settings.

This review comprehensively described the secondary metabolites and the EO effects as antimicrobial (antibacterial, antifungal, antiviral, antiprotozoal), antioxidant, anticancer, antidiabetic, liver and kidney protective, immune-stimulant, and insecticidal agents based on the existing data for the first time. The reports were collected using scientific databases including

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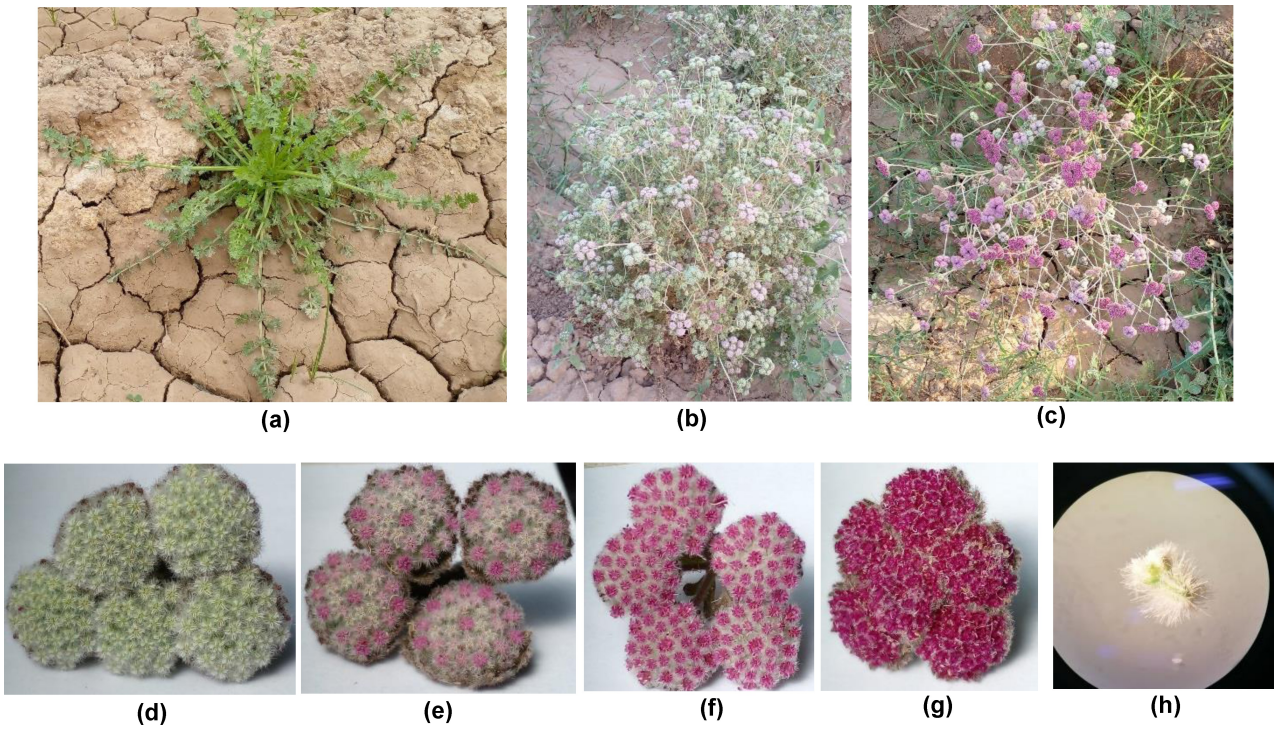

Figure 1. whole plant of *Oliveria decumbens* in vegetative (a) and flowering stages (b,c). (d-g) flower colour during development stages, (h) seed.

Anahita Boveiri Dehsheikh studied PhD in Physiology of Medicinal Plants at the Shahid Chamran University of Ahvaz, discussed a thesis about the feasibility study for domestication of Oliveria decumbens and evaluation of its phytochemical properties. She is author or co-author of six articles about medicinal plants and natural products.

Mohammad Mahmoodi Sourestani completed his studies in PhD Physiology of Medicinal and Aromatic Plants in 2010 at the Tarbiat Modares University of Tehran. He is currently working as Associate Professor at the Shahid Chamran University of Ahvaz (2010-present) and interested in the optimization of the extraction, separation, and analysis methods of natural products.

Naeimeh Enayatizamir undertake, PhD in Fertility Management and Soil Biotechnology-graduated from the Tehran University. She is an Associate Professor since 2009 at the Shahid Chamran University of Ahvaz and held the courses in Soil Biology.

Mehdi Safdarian received his PhD degree in Pharmaceutical Nanotechnology from the Ahvaz Jundishapur University of Medical Sciences in 2016. He is an Assistant Professor at the Ahvaz Jundishapur University of Medical Sciences (2017-present) and works in the Nanotechnology Research Center. His interests include Surface Modified Magnetic Nanoparticles, Liquid and Gas Chromatography, Separation, Design and Construction of New Analytical Device and Molecularly Imprinted Polymers.

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PubMed, Web of Science, and SciFinder using the keyword "*Oliveria*" (last research: 07.01.2024).

2. Phytoconstituents

Aerial parts, inflorescence, and flower of *O. decumbens* at different growth stages were subjected to analyze the EOs' content and composition. All studies were conducted on the populations grown in Iran, whilst the highest and lowest content of the EO extracted by hydrodistillation were detected at full flowering (8.1%) and vegetative stages (0.37%), respectively. The chemical structures of the major EO components are illustrated in Figure 2. The certain compounds that have been identified were α-thujene (**1**), α-pinene (**2**), β-pinene (**3**), camphene (**4**), sabinene (**5**), myrcene (**6**), δ-3-carene (**7**), α-phellandrene (**8**), β-phellandrene (**9**), α-terpinene (**10**), γ-terpinene (**11**), *p*-cymene (**12**), limonene (**13**), terpinolene (**14**), 1,8-cineole (**15**), linalool (**16**), terpinene-4-ol (**17**), α-terpineol (**18**), thymol (**19**), carvacrol (**20**), myristicin (**21**), elemicin (**22**), and spathulenol (**23**). According to the Tables 1 and S1 (supplementary material), majority of the EO compounds were classified into monoterpene hydrocarbons; however, oxygenated monoterpenes have a larger proportion of EO. Thymol (**19**), carvacrol (**20**), γ-terpinene (**11**), *p*-cymene (**12**) and myristicin (**21**) were frequently detected as abundant constituents of its oil. Taking into account that profile of the *O. decumbens* extract is unknown, few studies have been aimed to determination of the total phenol and flavonoid contents, showing that the plant extracts harvested at the flowering stage contain higher phenol and flavonoid content than those harvested at the seed set stage.[12] (Table S2).

3. Biological Activities

O. decumbens is target of different of biological and pharmacological investigations and the most studies have focused on the antibacterial, antifungal, antiviral, antiprotozoal, antioxidant, anticancer, antidiabetic, liver and kidney protective, immunostimulant, as well as insecticidal properties. The EO and its phytochemicals, including thymol, carvacrol, γ-terpinene, and *p*-cymene have received the greater biological studies than extract and its compounds. The EO of *O. decumbens* aerial parts exhibited higher biological activities compared to other parts of the plant due to the higher level of bioactive compounds. To date, scientific evidence supports the antibacterial effects against *Acinetobacter baumannii*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Helicobacter pylori*, *Escherichia coli*, *Bacillus subtilis*, *Xanthomonas citri*, *Klebsiella pneumonia*[3,16,17,28–31] and antifungal efficacy against *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans*, *Kluyveromyces marxianus*, *Alternaria alternata*, *Alternaria solani*, and *Penicillium digitatum*.[3,14,23,30–33] Also, it has also been reported the high antioxidant property of EO against free radicals[12,19,21,34,35] and its remarkable anticancer effect against breast and colorectal cancer (MCF-7, MDA-MB-231, 4T1, HT-29 cell lines).[22,36–38] In addition, the EO showed high antidiabetic properties and insecticidal effects against *Trichoplusia ni*, *Bemisia tabaci*, and *Phenacoccus solenopsis*.[16,39,40] The antiviral, antiprotozoal, liver and kidney protective and immuno-stimulant properties of *O. decumbens* EO have not been studied yet, and the preliminary studies of these properties have only focused on the extract, which requires further exhaustive investigations. A summary of the biological activity assessments performed on *O. decumbens* active substances have been represented in Table S3.

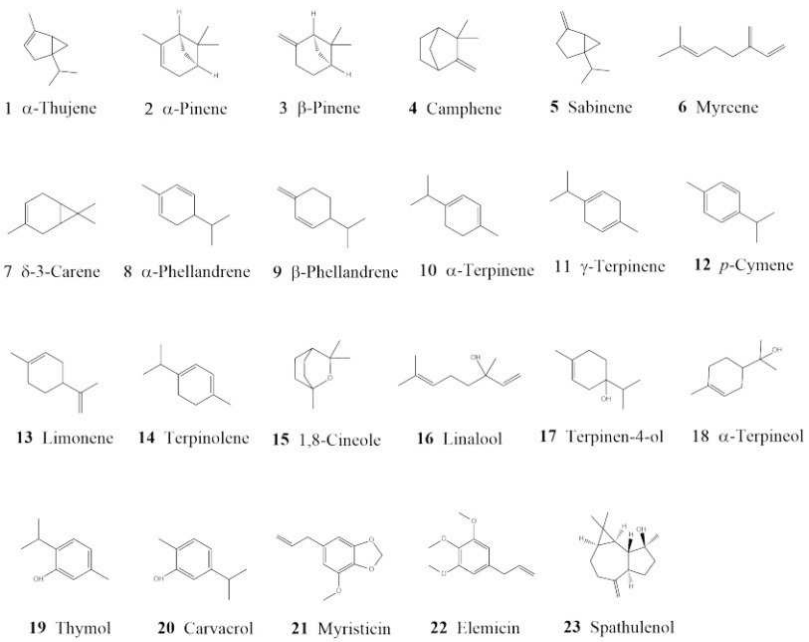

Figure 2. The chemical structure of most common major compounds of *Oliveria decumbens* essential oil reported in scientific literatures.

Table 1. The most common compounds of *Oliveria decumbens* essential oil reported in scientific literature.

Compounds	Chemical classes	Formula	Content (%)	Reference
α-Thujene	MH	C10H16	0.04–0.80	[13, 14]
α-Pinene	MH	C10H16	0.06–3.53	[15, 16]
Camphene	MH	C10H16	0.01–0.40	[13, 17]
Sabinene	MH	C10H16	0.01–1.90	[13, 18]
β-Pinene	MH	C10H16	1.51–3.31	[19]
Myrcene	MH	C10H16	0.07–3.60	[20]
α-Phellandrene	MH	C10H16	0.01–0.13	[5, 21]
δ-3-Carene	MH	C10H16	0.02–0.07	[13, 22]
α-Terpinene	MH	C10H16	0.07–3.20	[20, 23]
p-Cymene	MH	C10H14	0.63–22.07	[21, 22]
β-Phellandrene	MH	C10H16	0.02–2.70	[13]
Limonene	MH	C10H16	0.63–5.50	[12, 24]
γ-Terpinene	MH	C10H16	0.90–28.80	[24]
Terpinolene	MH	C10H16	0.04–0.5	[20]
1,8-Cineole	MO	C10H18O	0.06–1.83	[24, 25]
Linalool	MO	C10H18O	0.03–0.15	[24, 26]
Terpinene-4-ol	MO	C10H18O	0.11–0.23	[12, 14]
α-Terpineol	MO	C10H18O	0.02–0.10	[12, 24]
Carvacrol	MO	C10H14O	8.80–51.80	[24]
Thymol	MO	C10H14O	2.46–50.10	[4, 17]
Myristicin	PP	C11H12O3	0.05–21.68	[4, 27]
Elemicin	PP	C12H16O3	0.03–9.94	[14, 26]
Spathulenol	SO	C15H24O	0.02–20.9	[14]

[MH] monoterpene hydrocarbons. [MO] oxygenated monoterpene. [PP] phenylpropene. [SO] oxygenated sesquiterpene.

3.1. Antibacterial Activity

The antimicrobial resistance against different type of pathogens like bacteria is one of the serious global challenges and concerns in the fields of medicine, agriculture, and food production. Numerous losses caused by microbial activity have increased efforts to find new antimicrobial agents with more efficacy and low side effects in recent years.

The antibacterial potential of *O. decumbens* 's active ingredients has been evaluated in several researches focused on the fields of medicine and food industry. The general details of antibacterial studies were presented in Table S3. For instance, Mahboubi et al.[17] by applying disc diffusion (DD) assay elaborated the EO effect on growth of *Acinetobacter baumannii*, as a red alert pathogen due to its resistance against extensive antibiotics, besides as an important bacterium causing nosocomial infections. The results showed that the EO significantly reduced growth of clinical isolates *A. baumannii*, whereas the lowest bacterial infection was observed in application of EO (2 μL) with a 28.8 mm inhibitory zone diameter.

The antibacterial property of different concentrations of EO was experimented against clinical and standard strains of Gram-positive bacteria *Staphylococcus epidermidis* and *Streptococcus pyogenes* and Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*, via DD, microbroth dilution (MbD) and PP (pour plate) assays.[28] The results indicated the clinical strains were more resistant than standard ones in all concentrations. Moreover, the gram-positive bacteria were most susceptible to the EO compared to the Gram-negative bacteria. Furthermore, the EO exhibited high antibacterial potency against both standard strains *S. epidermidis* and *S. pyogenes* with an MIC value of 1 mg/mL and the lowest MBC of EO was detected against *S. pyogenes* with an MBC value of 1 mg/mL.

In a similar study, it was experimented that the EO (30 μL/disc) had a remarkable antibacterial potential against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus cereus* with an IZD (inhibition zone diameter) of 80, 60, and 40 mm compared to the gentamicin, with an IZD of 28, 35 and 28 mm, respectively, whilst lowest MIC value of the EO was recorded towards *Pseudomonas aeruginosa* with 23.1 μg/mL.[3]

Eftekhari et al.[16] evaluated the antibacterial activity of the EO and commercial isolated thymol (**19**) against *Helicobacter pylori*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Escherichia coli* utilizing DD and agar dilution (AD) methods. The results demonstrated that the EO was more active against *H. pylori* with a MIC value of 20.4 μg/mL than amoxicillin and thymol (**19**) with values 50 and 150 μg/mL, respectively. Also, the largest zone of inhibition against *S. aureus*, *S. epidermidis*, and *E. coli* was observed at concentration of 20.4 μg/mL of EO, with an IZD of 20, 15 and 14 mm, respectively.

The plant EOs of different populations were previously subjected to MbD assay in order to investigate the antibacterial potential against an extensive range of human and plant pathogenic bacteria *Staphylococcus aureus*, *Bacillus subtilis*, *Clavibacter michiganensis*, *Curtobacterium flaccumfaciens*, *Xanthomonas citri*, *Agrobacterium tumefaciens*, and *Escherichia coli*.[29]

Consequently, the Nourabad Mamasani population with an MBC value of 2 mg/mL and the Dehdasht population oil with MBC values of 4 and 2 mg/mL were more potent against *X. citri and E. coli* compared to chloramphenicol (positive control), possessing an MBC value of 5 mg/mL, respectively. Moreover, the EO of Nourabad Mamasani population was a stronger inhibitor than chloramphenicol (with MIC values of 0.0625 mg/mL vs. 0.8 mg/mL) against *B. subtilis*.

Similarly, the antibacterial effect of the aerial parts EO was investigated against a variety of bacteria employing DD and MbD methods. The highest activity was recorded against *Klebsiella pneumonia* with 30 mm of IZD and 0.0625 μL/mL values of MIC and MBC.[30]

Several studies have evaluated the effectiveness the *O. decumbens* active substances as a food product preservative against most common bacterial food poisoning such as *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*

(Table S3). The EO was assessed *in vitro* and in a food model system for 28 days of storage to determine its effect on the health and safety of 'doogh', a fermented dairy drink against *Staphylococcus aureus* and *Escherichia coli*, by.[31] Results of the DD and MbD assays revealed that EO effectively inhibited both bacteria, while *S. aureus* was more susceptible than *E. coli* (with 9.72 mm of IZD and an MBC of 6.25 μg/mL against *S. aureus* and 8.73 mm of IZD and an MBC of 12.50 μg mL against *E. coli*). It was concluded that although the samples of 'doogh' fortified with EO possessed longer storage time against *S. aureus* compared with *E. coli* (5.28 days vs. 4.72 days at a 28-day bacterial incubation period), in general, the potential of using EO as a natural 'doogh' preservative was proven with the higher durability of the samples fortified with EO compared with control.

In a similar study, the potency of the EO as a natural source of preservative in controlling pathogenic spoilage growth of hamburger was studied against *Staphylococcus aureus* and *Escherichia coli*, using DD and well dilution (WD) methods in vitro and food model system.[27] Overall, the EO had more inhibitory potency against *S. aureus* than *E. coli*. The most potential of the oil was observed at 2.5 μL/mL against both bacteria in DD and WD assays; however, amoxicillin and tetracycline antibiotics were more effective. This study was followed by evaluating the total bacterial contamination of samples during the storage period. The results showed that the samples treated with 1.25 μL/g of EO had greatly lower contamination in comparison with the control group after 60 days (4 log CFU/g vs. 95 log CFU/g against *S. aureus* and 45 log CFU/g vs. 210 log CFU/g against *E. coli*).

More recently, the preservative effect of *O. decumbens* EO against several food pathogens of vegetable oil was evaluated by antimicrobial effectiveness test (DD and MbD) against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[32] The EO significantly reduced growth of *S. aureus* with 51.7 mm of IZD, 0.25 μg/mL value of MIC, 0.5 μg/mL value of MLC (minimal lethal concentration), and *E. coli* contaminations (IZD: 38.0 mm, MIC: 0.25 μg/mL MLC: 0.5 μg/mL); however, it showed weaker effect against *P. aeruginosa* (IZD: 10.8 mm, MIC and MLC: 4 μg/mL). The lowest bacterial colony formation ($\leq$0.1 log CFU/mL) was observed in samples treated with 1 and 0.5% v/v of the concentration of EO after 28 days. The antibacterial activity of *O. decumbens* EO in combination of *Pelargonium graveolens* oil in ratio of 0.5:0.5 possessed enough efficacies as natural preservative in vegetable oil.

So far, only one study has focused on the antibacterial activity of the *O. decumbens* extract. The DD and MbD assays were utilized to evaluate antibacterial effects of the methanolic and ethanolic extracts of aerial parts at different concentrations against a panel of 19 microorganisms including the clinical Gram-positive and Gram-negative bacteria.[41] The ethanolic extracts exhibited higher efficacy in growth inhibition compared to the methanolic ones. Among them, the largest inhibitory zone, with a diameter of 19 mm against *Staphylococcus aureus*, was observed at maximum concentration of ethanolic extract (400 mg/mL). No significant difference was detected between the MIC values of ethanolic and methanolic extracts against *S. aureus*, while the ethanolic extract was shown to be stronger than methanolic ones with MBC and MIC values of 20 and 10 mg/mL against *Streptococcus pyogenes*, respectively.

According to the high level of thymol and carvacrol compounds in the conducted studies, the antibacterial property of the *O. decumbens* EO can be related to the high amount these constituents and their mechanism of action. Thymol and carvacrol are hydrophobic oxygenated monoterpenes that disrupt the integrity of bacterial cell membranes.[42,43] They increase the fluidity and permeability of the cell membrane by altering the components and arrangement of the fatty acids and destroys the phospholipid bilayer membrane and thereby lead to the leakage and loss of ATP and ions.[42] Also, it has been proved the effect of carvacrol on inhibition of protein required for bacterial mobility, called 'flagellin'.[44] Also, the higher resistance of gram-negative bacteria compared to gram-positive bacteria can be related to hydrophilic nature of their cell walls and the presence of lipopolysaccharides (important components their outer membrane), which limits the penetration and accumulation of EOs in their cell membranes.[45] Besides, due to the few studies on the antibacterial activity of the *O. decumbens* extract and the lack of information on its profile, in-depth evaluations should be carried out on the antibacterial potential of its, focusing on identifying the compounds responsible for such activities.

3.2. Antifungal Activity

There are few studies on the antifungal effect of the EO, whereas no research has been performed on the fungicidal potency of extract (Table S3). Numerous food and agricultural products are being frequently spoiled and poisoned in many countries. The variety of these fungi has been the target of fungicidal tests of the *O. decumbens* EO in recent experimentations. *Aspergillus niger* and *Candida albicans* are the most common food's fungal contaminations; indeed, their presence and growth lead to severe health issues associated with the production of mycotoxins.

Amin et al.[3] investigated the antifungal potential of the EO against *A. niger* and *C. albicans* using DD test. The EO (30 μl/disc) significantly inhibited growth of both fungi, with an IZD of 80 and 60 mm of the oil against *A. niger* and *C. albicans*, respectively, whilst the standard drug, nystatin (25 μg/ disc), was less active (with an IZD of 36 and 40 mm of oil against *A. niger* and *C. albicans*, respectively). Remarkably, its high potency has further been confirmed against the mentioned fungi by Hajimehdipoor et al..[4]

Mahboubi et al.[32] evaluated the fungicidal activity of *O. decumbens* EO against *A. niger* and *C. albicans* in vegetable oil (edible oil). It was found the minimal fungal contamination in vegetable oil containing the combination of the *O. decumbens* and *Pelargonium graveolens* EOs at 0.5:0.5 ratio, with $\leq$0.1 L CFU/mL of both *A. niger* and *C. albicans*.

Rhodotorula glutinis, *Kluyveromyces marxianus*, and *Penicillium digitatum* are also considered as common food spoilage

fungi that lead to unpleasant smell and appearance. The antifungal efficacy of the EO was assessed towards these fungi to preserve 'doogh'. The highest potency of the oil was recorded against *K. marxianus* (IZD: 9.46 mm, MIC: 3.13 μg/mL) by Zolfaghari and Ansari;[31] in addition, the 'doogh' samples treated with the EO for a longer time had a longer shelf life.

In a similar study, the preservative effect of the EO in order to increase the health and shelf life of hamburger was evaluated.[27] The lowest mold and yeast contaminations (1.70 log CFU/g) was observed in the sample treated with the highest concentration of EO (at 1.25 μL/g); furthermore, the longer treatment period of the sample with the EO significantly reduced the contamination.

The results of MbD assay against *Alternaria alternata*, *Fusarium solani*, and *Aspergillus niger*, as plant pathogenic fungi causing leaf blight and root and fruit rotting, respectively, revealed that *A. alternaria* was most susceptible (MIC: 16 mg/mL) and *F. solani* and *A. niger* were found to be resistant to the EO (MIC: 64 mg/mL against both fungi).[33]

In another investigation, the EOs obtained from hydrodistillation (HD) and microwave-assisted hydrodistilation (MAHD) methods was compared to determine the antifungal effect against a variety of fungi responsible for large crop losses including *Trichoderma harzianum*, *Byssochlamys spectabilis*, *Paecilomyces variotii*, *Penicillium chrysogenum*, *Aspergillus oryzae*, and *Aspergillus niger*, via AD and PP tests.[13] There was no significant difference between the antifungal potential of the EO obtained by both methods. *P. variotii* was the most sensitive among tested fungi and greatly controlled by the EO (99% of growth inhibitory), while the antifungal drug, amphotericin B, had 100% of growth inhibitory.

Similarly, Bahraminejad et al.[23] evaluated the antifungal efficacy of the EO against *Alternaria solani* (the most important pathogenic fungus of tomato, potato, and eggplant) by AD assay. Results showed that the growth of fungus was completely inhibited, with 100% of growth inhibitory, and the highest MGI (mycelial growth inhibition), with 100% value was recorded at 0.25 μL/mL.

In another study, the investigation of plant protection property of the EO against *A. niger*, *Aspergillus flavus*, and *C. albicans* demonstrated a higher potency (IZD: 45.3, 27.3 and 32 mm, respectively), compared to amphotericin B (positive control), with 10, 8 and 17 mm of IZD, respectively.[30] In this study, the lowest MIC and MFC of the EO were recorded against both *A. niger* and *A. flavus*.

Moreover, the potency of the EO in inhibition of growth of *Penicillium digitatum* causing decays of vegetables and fruits particularly citrus during storage of postharvest chain was measured by DD test.[14] The growth inhibitory increased at high concentrations and on the first day of the treatment; subsequently, the highest inhibitory was observed at $\geq$0.50 μL/mL of the EO.

Therefore, the antifungal effects of the *O. decumbens* EO can be due to the presence of high amounts of oxygenated monoterpenes such as thymol and carvacrol and their effects on the destruction of the fungal cell wall and disrupting the integrity of its membrane through damage to lipids. It is also recommended to evaluate the impact of the extract on the control of fungal pathogens.

3.3. Antiviral Activity

Few studies have been carried out on the antiviral effect of the *O. decumbens* extracts, besides there is no data available on antiviral property of its EO (Table S3). Dashtimakan et al.[46] assessed inhibitory effect of the flower methanolic extract (80%) at different concentration (31.25, 62.5, 125, 250, 500, and 1000 μg/mL) on Vero cells (kidney cells of African green monkey) infected with virus herpes simplex virus 1 (HSV-1) before and after treatment via an MTT test. The results revealed that the extract possessed a moderate potency and the highest inhibitory effect (43.75%) was found in HSV-1-inoculated Vero cells treated with a concentration of 1000 μg/mL of extract before infecting the target cell. However, both the pretreatment target cell and treatment infected target cell with the extract (1000 μg/mL) possessed weak antiviral efficiency with 35.94 and 21.88%, respectively.

Since the research on the antiviral property of the *O. decumbens* extract is limited and its profile is still unknown, the investigation of the antiviral effect of the extract needs a deeper study targeting the discovery of its antifungal phytochemicals. In addition, the evaluation of the effect of essential oil on pathogenic viruses has been neglected and needs to be studied.

3.4. Antiprotozoal Activity

Leishmaniasis is a chronic disease caused by the genus *Leishmania* of protozoans transmitted by sandflies and appeared with three main clinical manifestations of cutaneous, mucocutaneous, and visceral leishmaniasis.[47] Moreover, *Trichomonas vaginalis*, a flagellated protozoan triggers genitourinary system disease called trichomoniasis.[48] The therapeutic effect of *O. decumbens* has been assessed for the treatment of leishmaniasis and trichomoniasis diseases.

The leaf ethanolic extract of *O. decumbens* was subjected to MTT assay aiming to evaluate antiprotozoal activity against human *Leishmania* species after 24, 48, and 72 h.[49] The results were promising and the highest activity of the leaf extract was obtained after 72 h with IC_{50} values of 0.85 and 0.23 μg/mL against *Leishmania major* and *Leishmania infantum*, respectively, compared to the glucantime (drug used to treat leishmaniasis) as positive control with IC_{50} values of 40.2 and 18.5 μg/mL, respectively (Table S3).

Similar results were detected for inhibitory potency of the extract after 12 and 48 h against *L. major* (IC_{50}: 2.3 and 2.7 μg/mL, respectively) and *L. infantum* (IC_{50}: 7.1 and 1.13 μg/mL, respectively), while the glucantime had weaker effect, with IC_{50} values of 104.4 and 61.4 μg/mL against *L. major* after 24 and 48 h, respectively, and IC_{50} values of 99.7 and 45.6 μg/mL against *L. infantum*, respectively.

In another study, Fakhrieh-Kashan et al.[50] have discussed the antiprotozoal potential of the different concentration of ethanolic extract of the aerial parts against *Trichomonas vaginalis* protozoan after 12, 24 and 48 h of the treatment. The lowest number of protozoa was recorded in the concentration of 400 μg/mL of the ethanolic extract, with values of 5.6×10^4, 7×10^4, and 0 after 12, 24, and 48 h, respectively. Therefore, it is premature to judge the antiprotozoal activity of *O. decumbens* extract without further evidence and requires in-depth study. Also, the investigation of the antiparasitic effect of the EO is recommended due to the high content of oxygenated monoterpenes and may have interesting results.

3.5. Antioxidant Activity

Several studies were conducted to experiment the radical scavenging power of the *O. decumbens* EO. Saidi[51] evaluated the antioxidant capacity of the aerial parts EO by different methods and populations. TEAC (trolox equivalent antioxidant capacity), FRAP (ferric reducing antioxidant power), and DPPH assays were utilized to analyze the antioxidant activities. The EO was found to be potent, with values of 2.5 mmol TE (trolox equivalent)/μL of EO, 75.6% hydrogen donation, and 6.2 mmol Fe^{+2}/μL of EO.

In another study, the antioxidant capacity of the aerial parts EO obtained from different *O. decumbens* populations was measured using a DPPH (2, 2-diphenyl-1-picrylhydrazyl) test.[19] The highest scavenging potential of DPPH radicals was recorded in Behbahan populations (at 400 μL), with a value of 97% (Table S3).

Moreover, the DPPH radical inhibitory activity of the aerial parts EO extracted by HD and MAHD methods demonstrated that the EO gained by MAHD was more potent with an IC_{50} value of 0.142 mg/mL, compared to HD, with an IC_{50} value of 0.146 mg/mL.[13] Similarly, results of a study on the antiradical potential EO obtained by HD and ultrasonic pre-treatment prior to hydrodistillation (US-HD) methods evaluated by DPPH assay showed that the EO gained by US-HD was stronger, with an IC_{50} value of 29.61 μg/mL vs. 141.11 μg/mL in HD.[37]

Jamali et al.[21] investigated the free radical inhibitory of the EO and thymol (19), carvacrol (20), *p*-cymene (12), and γ-terpinene (11) using DPPH, ABTS (2, 2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid), and SOX (superoxide ion) tests. In DPPH, ABTS and SOX tests, the EO exhibited higher scavenging capacity (IC_{50}: 53, 36.7 and 89 μg/mL of DPPH, ABTS SOX inhibitory, respectively) than apocynin and L-NAME (L-Nitro-arginine methyl ester), with IC_{50} values of 88.6, 59.7 and 123.7 μg/mL in DPPH, ABTS and SOX inhibitory, respectively; however, it was weaker than gallic acid (IC_{50}: 39 and 26.6 μg/mL in DPPH and ABTS inhibitory, respectively). Among the components of the oil, *p*-cymene (12) and γ-terpinene (11) showed no activity, whereas thymol (19) and carvacrol (20) moderately inhibited the DPPH and ABTS radicals. Also, the authors compared the radical scavenging power of different concentrations of the EO and thymol (19), carvacrol, *p*-cymene (12), and γ-terpinene (11) in scavenging of ROS (reactive oxygen species), and NO (nitric oxide) production of the LPS-stimulated macrophages. The results demonstrated that the EO was stronger at both concentrations of 5 and 10 μg/mL in ROS inhibitory (IC_{50}: 14.3 and 9.7 μg/mL, respectively) and the concentrations of 10 μg/mL of EO had higher antioxidant activity (with IC_{50} values of 14.7 μg/mL in NOP inhibitory) than L-NAME (at 1.3 μg/mL with IC_{50} values of 21 μg/mL in NOP inhibitory). Besides, carvacrol (20) and thymol (19) possessed more activity at 10 μg/mL in all tests.

Esmaeili et al.[12] previously assessed the antioxidant capacity of the flower and seed EO, whereas the results showed that the flower EO was stronger inhibitor of DPPH radical, with an IC_{50} value of 86.1 μg/mL, compared to seed EO, with an IC_{50} value of 98.5 μg/mL. The investigation of the macrophage cells treated by different concentrations of the EO exhibited that the highest concentration (3000 ng/mL) remarkably reduced $DCFH_2$-DA (2′,7′-dichlorodihydrofluorescein diacetate), NO, and TBARS (thiobarbituric acid reactive substances) radicals, with values of 872 fluorescence intensity, 15 nM and 0.28 nM, respectively.[52]

Furthermore, the radical scavenging of the aerial parts EO obtained by HD and the oil extract in inhibition of glucose oxidation (GO), lipid peroxidation (LP), protein peroxidation, and glycation reactions caused by active radicals (PRP and PRG) in diabetic cells was assessed by Siahbalaei et al. and Siahbalaei and Kavoosi.[34,35] Consequently, the EO and the oil extracted by solvent exhibited antiradical potential in suppression of GO, LP, PRP and PRG, whereas the positive controls (EDTA at 1 mM, BHT at 10 mg/mL, and aminoguanidine at 10 mg/mL) indicated higher inhibitory effect.

Only one study elaborated the antioxidant activity of *O. decumbens* stem extract, demonstrating that the ethanolic extract (96%) ($IC_{50} > 200$ μg/mL) was weaker than quercetin as the positive control utilized (IC_{50}: 26.51 μg/mL).[53]

Hence, the antiradical property of the essential oil can be related to the high content of oxygenated monoterpenes and the presence of the hydroxyl group in their structure, which allows them to act as hydrogen donors and singlet oxygen quenchers. It is also suggested to further study the antioxidant potential of extracts of other plant organs, in particular flowers, focusing on the discovery of bioactive compounds. Also, some extraction methods, such as MAHD and US-HD, have a higher antioxidant effect due to better efficiency in tearing cells compared with conventional method HD and increasing the amount of extraction of the effective anti-radical substance.

3.6. Anticancer Activities

The treatment of breast and colon cancer was the most important subject studied to measure the anticancer effect of *O. decumbens* active ingredients. By applying an MTT assay, the EO at the different doses were analyzed to assess apoptotic activity in L929 (mouse normal fibroblasts cell line), MCF-7 and MDA-MB-231 cell lines (as two model of breast cancer) in monolayers (2D) and spheroids (3D) cell cultures.[36] The highest growth inhibitory effect on MCF-7 and MDA-MB-231 cells was recorded in 200 μg/mL of EO (Table S3). Moreover, the EO

remarkably inhibited growth of MCF-7 and MDA-MB-231 cells with values of 108 and 97% in 2D cell culture, respectively, compared to L929. In comparison the EO with thymol (**19**), carvacrol (**20**) and *p*-cymene (**12**) as main components of oil, the lowest growth was observed in all MCF-7 and MDA-MB-231 cells treated by EO. Thymol (**19**) and carvacrol (**20**) were the most active apoptotic components of oil in growth inhibitory of MCF-7 cell with 92 and 90%, respectively, and weakest agent was *p*-cymene (**12**) with 45 and 44% in MCF-7 in 2D cell culture, respectively. In 3D cell culture, no significant growth inhibitory effect was observed in the MCF-7 and MDA-MB-231 cell lines.

In an *in vivo* experiment, the anti-breast cancer potential of EO was investigated after administrating as simultaneously injection of oil with exposure to the 4T1 cell lines tumor of rat and intraperitoneal injection of oil (every 2 days for 2 weeks), during exposure to these cells.[22] The results showed that the rats treated with simultaneously injection of oil with exposure to the 4T1cells possessed higher weight and volume with values 0.83 g and 750 mm^3, respectively, compared to those received intraperitoneal injection of oil, with a weight of 0.38 g and a volume of 250 mm^3.

Mollaei et al.[37] have evaluated the cytotoxicity effect of EOs yielded by the conventional hydrodistillation (HD) and ultrasonic pre-treatment prior to hydrodistillation (US-HD) on MCF-7 and normal HFF2 cells via an MTT assay. The EO obtained by US-HD was more effective on MCF-7 cells with an IC_{50} value of 5.52 μg/mL, compared to HD method (IC_{50}: 6.19 μg/mL).

In a similar study, the cytotoxicity activity of aerial parts EO and thymol (**19**) and carvacrol (**20**) against MCF-7 cells was compared with etoposide as chemotherapy drug used in the management and treatment of various cancers, by using an MTT assay.[16] The cytotoxicity potential of EO and thymol (**19**) and carvacrol (**20**) were promising. Carvacrol (**20**) was found to be the most cytotoxic compound with an IC_{50} value (0.019 μg/mL) of one thousandth of etoposide (16.082 μg/mL) against MCF-7 cells.

In another study, the anticancer activity of flower extract against HT-29 colorectal cancer cell line has been evaluated by utilizing an MTT assay.[38] The ethanolic extract (80%) of flower possessed a good anticancer potency with an IC_{50} value of 14.39 μg/mL.

Cytotoxic activity of essential oils containing oxygenated monoterpene compounds such as thymol and carvacrol has been reported through reducing the proliferation of cancer cells and arresting different phases of the cell cycle.[54,55] Therefore, it seems that the anticancer effect of the *O. decumbens* EO is related to the presence of these compounds. The high anticancer effect of the essential oil obtained by US-HD method can be attributed to its higher efficiency in destroying the cell wall and extracting the active substances, however, the effect of different extraction methods on the anticancer property of the EO needs further study. The cytotoxic property of the extract is promising and indicates that the anticancer effect of the *O. decumbens* is not limited to EO compounds, however, further research on the anticancer activity of the extract is recommended for further validation.

3.7. Antidiabetic Activity

Few studies have been conducted on the antidiabetic potency of *O. decumbens* under *in vitro* and *in vivo* conditions (Table S3). The EO obtained by hydrodistillation method and the oil extract were evaluated to determinate antidiabetic effect, using a-amyalse and glucosidase enzymes inhibition assays.[34,35] The oil extracted by solvent greatly inhibited α-amyalse enzymes, with an IC_{50} value of 141 μg/mL, compared to EO obtained hydrodistillation method, with an IC_{50} value of 223 μg/mL; however, acarbose (antidiabetic drug, 10 μg/mL) was more effective (with an IC_{50} value of 126 μg/mL). No significant difference was observed in the glucosidase enzymes inhibition of the samples treated with essential oil and the oil extracted by solvent (IC_{50}: 220 and 223 μg/mL, respectively), and the acarbose was stronger (IC_{50}: 139 μg/mL).

Yarizade et al.[56] have evaluated *in vitro* antiglycation activity of different extracts of aerial parts (aqueous, ethanolic, methanolic and ethanol-methanolic extracts) by BSA-fluorescent assay. The results showed that ethanolic and methanolic extracs had higher efficiency of AGEs (advanced glycation end products) formation inhibition, with a 59 and 58% of AGEs inhibitory, respectively, compared to aqueous and ethanol-methanolic extracts (with a 44 and 31% of AGEs inhibitory, respectively).

In another study, the effect of aerial parts EO on the healing of diabetic food ulcer was tested by Mahboubi et al..[57] It was found that the EO significantly reduced the size of the diabetic food ulcer on the 8th day compared to normal saline (0.17 vs. 0.39 cm).

Therefore, it seems that the antidiabetic property of the *O. decumbens* EO is due to the effect of thymol and carvacrol as antioxidant compounds, on reducing PRG (protein glycation) and GO (glucose oxidation), as well as the competitive and non-competitive inhibition strategies of these compounds in preventing the activity of α-amyalse and glucosidase enzymes.[34] Also, considering the wound healing and anti-inflammatory activities of thymol, the anti-ulcerogenic effect of the *O. decumbens* EO may be due to the presence of this compound.[58] Besides, although the extract showed good antidiabetic potential, further and in-depth studies should be carried out to confirm findings and determine which compounds plays this important role.

3.8. Liver and Kidney Protective Activities

In an in vivo experiment, the hepatoprotective effect of the flower hydro-ethanolic extract was assessed on serum enzymes level of adult male of Wistar rats.[59] Based on the results administering 500 mg/kg of the extract receiving 2 mg/kg of cadmium significantly reduced the serum level of the alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) enzymes with values of 84.5, 312.5 and 619 u/L, respectively (Table S3). Furthermore, Rahimi Kazerooni et al.[60] assessed the kidney protective activity of the extract at different doses, reporting the hydro-ethanolic extract

increased body weight of the rats with 500 mg/kg administration. Moreover, the level of creatinine, blood urea nitrogen, and uric acid were also reduced in rats receiving 2 mg/kg of cadmium by the same dose of hydro-ethanolic extract. Hence, the bioassay guided isolation of the extract in future research to determine its compounds that have liver and kidney protective effects can help to replace drugs and supplements based natural origin.

3.9. Immuno-Stimulant Activity

Immuno-stimulant activity and tonic effects of the *O. decumbens* active ingredients were evaluated in aquaculture to increase health level of fishes. The effect of different doses of the aerial parts EO and extract on the health status of Nile tilapia fish (*O. niloticus*), as the second major aquaculture species in the world, was investigated in an animal experiment by Jalali et al..[61] Overall, the results revealed that the administration of ethanolic extract at a dose of 0.01 % in the diet improved body weight, special growth rate, and total protein content with values of 139.88 %, 4.35 %, and 3.8 g/dL, respectively, whereas the dose of 0.1 % was more effective on respiratory burst activity and lysozyme activity with 0.89 % and 0.79 U/m, respectively (Table S3). Despite the fluctuation in albumin, globulin, triglyceride, cholesterol aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase enzymes levels of Nile tilapia, use of the EO and extract in diet had no negative or significant effects.

In another study, Alishahi et al.[62] evaluated the variation of lysozyme activity (LA), number of the alive bacteria (NAB), and antibody (AB) level after administration of the EO and extract in diet of vaccinated and non-vaccinated carps (*C. carpio*). The extract had higher immune-stimulant activity than the EO and improved LA, NAB, and AB levels in both vaccinated carps that received the supplemented diet with the extract (with values of 225 U/mL, 150, and 4 Log_2 1, respectively), and non-vaccinated carps (with values of 200 U/mL, 130, and 0.8 Log_2 1, respectively). Therefore, the immune system booster property of the *O. decumbens* extract is probably due to the presence of antioxidant compounds and additional research is needed to validate and identify compounds that that are responsible for this property. It is also suggested to study the effect of *O. decumbens* EO on stimulating the immune system.

3.10. Insecticidal Activity

So far, the insecticidal potential of *O. decumbens* has been experimented in controlling some agricultural pests such as *Trichoplusia ni*, *Bemisia tabaci*, and *Phenacoccus solenopsis*, which cause high economic losses to cabbage, cucumber and Chinese hibiscus, respectively. By topical and fumigation applications test, the insecticidal activity of the EO and thymaol (**19**), carvacrol (**20**), miristicin, and *p*-cymene (**12**) as the main plant volatile constituents were investigated towards *Trichoplusia ni* (known as cabbage looper larva).[16] Topical administration of the EO, thymaol (**19**), and carvacrol (**20**) demonstrated a moderate potency in killing larvae with lethal dose of larval by 50 % (LD_{50}) of 52.1, 50.1, and 68.8 μg/mL larvas, respectively (Table S3). Although the artificial mixture of the main constituents used as positive control, was stronger with an LD_{50} value of 30.8 μg/mL larva, the insecticidal effect of myristicin was promising with a value of 32.7 μg/mL larva. On the other hand, the most insecticidal agent against *Trichoplusia ni* in fumigation test was *p*-cymene (**12**) with LD_{50} of 97.9 μg/mL larva. However, the positive control (artificial mixture of main constituents) possessed higher potency with an LD_{50} value 78.8 μg/mL larva. Moreover, the EO indicated higher insecticidal effect with less inhibitory of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) enzymes (with IC_{50} values of 0.117 μg/mL and >0.5 μg/mL, respectively), whereas, tacrine (centrally acting acetylcholinesterase inhibitor, as positive control) suppressed the AChE and BuChE enzymes with values of IC_{50} 0.0095 and 0.0020 μg/mL, respectively.

Mollaei et al.[37] compared the insecticidal effects of two extraction methods hydrodistillation (HD) and ultrasonic pretreatment prior to hydrodistillation (US-HD) against *Trichoplusia ni* (cabbage looper), while they reported that the EO obtained from US-HD method was stronger, with LD_{50} value of 32.69 μg/larva in comparison with the HD method with LD_{50} value of 63.21 μg/larva.

In another work, insecticidal potential of the ethanolic extract at doses of 250, 500, and 1000 mg/L against *Bemisia tabaci* (important pest causing cucumber losses) was determined by Moghadam et al..[39] The highest extract dose (1000 mg/L) was recorded to possess the maximum insecticide efficiency with a value of 80 % that was more than acetamiprid at same concentration, with a value of 75 %, utilized as the positive control.

Roozdar et al.[40] have also evaluated the toxicity effect of different concentration of the EO extracted from mixture of flower and seed on first instar nymph and adult's insect of *Phenacoccus solenopsis* (a pest that causes dry branches and severe damages Chinese hibiscus. Interestingly, the EO exhibited higher toxicity potency against both first instar nymph and adults insect (LC_{50} and LC_{90} values of 49.77 ppm and 137.81 ppm, respectively, for first instar nymph and LC_{50} and LC_{90} values of 195.92 ppm and 362.55 ppm, respectively, in adult insect), compared to Dayabon (10 %), as positive control with (LC_{50} and LC_{90} values of 4256.10 ppm and 6566.26 ppm, respectively, for first instar nymph and LC_{50} and LC_{90} values of 6177.85 ppm and 9683.0 ppm, respectively, in adult insect). In contrast, it was found that the insecticidal effect of EO was weaker than the efficacy of another positive control, acetamiprid (20 %) with LC_{50} and LC_{90} values of 16.45 ppm and 91.51 ppm, respectively, for first instar nymph and LC_{50} and LC_{90} values of 62.28 ppm and 171.05 ppm, respectively, in adult insect. On the other hand, the potency of the EO against first instar nymph and adult insect of *P. solenopsis* in intervals of 1, 3, 7, and 14 days after spraying showed the highest insecticidal efficiency of EO (250 mg/L) was in the first day after treatment (91.92 % and for both first instar nymph and adult insect) that was weaker than acetamiprid in same concentration (with

values of 94.50 and 93.21% for first instar nymph and adult insect, respectively) and stronger than 5000 mg/L of dayabon (with values of 90.62 and 89.98% for first instar nymph and adult insect, respectively), as positive controls.

Hence, it seems that the inhibitory effect of AChE and BuChE enzymes is one of the important mechanisms in the insecticidal activity of the *O. decumbens* EO, which can be related to the high contribution of thymol and carvacrol compounds. The anti-AChE activity of thymol and carvacrol compounds have also been reported in previous researches.[63,64] The positive effect of US-HD method on the insecticidal property of the EO can be attributed to its higher efficiency in extracting active compounds, however, it is necessary to further investigate the efficiency of different extraction methods on the insecticidal activity needs further investigation. However, further research provides more evidence to confirm these findings. On the other hand, accepting the insecticidal property of the *O. decumbens* extract also requires further investigations and isolation of compounds with pesticide potential.

4. Summary and Outlook

Oliveria decumbens from the Apiaceae family, mainly grown in Iran, Syria, Turkey and Iraq, has been extensively consumed in traditional medicine and prescribed to treat gastrointestinal disorders, fever, abdominal pain and bloating, and wounds. This herb is often used as infused and decoction in ancient medicine. The EO predominantly contains oxygenated monoterpenes highlighting remarkable contents of thymol (**19**) and carvacrol (**20**). Other characterized EO constituents have been reported as γ-terpinene (**11**), *p*-cymene (**12**), and myristicin (**21**). Despite the comprehensive investigations carried out on the EO components, the extract profile is yet unknown. The biological activities were mainly studied *in vitro* and *in vivo* focusing on antimicrobial (antibacterial, antifungal, antiviral, antiprotozoal), antioxidant, anticancer, antidiabetic, liver and kidney protective, immune-stimulant, and insecticidal activities. In summary, despite few researches, the *O. decumbens* EO have shown efficacy in controlling food spoilage bacteria and fungi and can be considered as an herbal-based food preservative. Due to the insufficient information regarding the antibacterial and antifungal effects of the extract, there is also an interesting research topic in evaluating its antimicrobial potential in food industry. The antibacterial, antifungal, and insecticidal properties of the EO against pests and plant diseases showed its capacity to be used as a plant protective and natural pesticide and insecticide in agricultural aspect. Due to few studies carried out on the plant extracts it is difficult to judge its effectiveness; indeed, the reported beneficial health effects of the *O. decumbens* extract particularly its significant and promising strengthening potency in aquatic animals' immune system can be confirmed via complementary assessment in vitro and in vivo.

Likewise, due to the anticancer, antidiabetic, and antioxidant properties of the EO and the antiviral, antiprozoa and liver and kidney protection effects of the extract and the oil recorded in various studies, the active ingredients of *O. decumbens* possess notable therapeutic and preventive capacities. Moreover, further research on the EO potential for the treatment of viral and protozoan diseases should be considered. It is also suggested to study the phytotoxic (herbicidal) effect of active ingredients of *O. decumbens*, especially EO. The chemical profile of the *O. decumbens* extracts is neglected, thus investigation of them through bioassay guided isolation and identification of bioactive constituents can be informative and provide valuable information to be considered for further phytopharmaceutical purposes. Although so far by performing different animal studies some of the traditional applications have been validated; however, the clinical trials are required to determine the efficacy and safety for supporting the rationale for using folk remedies.

Supporting Information

The authors have cited additional references within the Supporting Information.[65–75] Further details are represented in Tables S1, S2 and S3.

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Conflict of Interests

The authors declare no conflict of interest.

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