



## Review Article

# Phytochemistry, Toxicology, and Pharmacological Properties of *Origanum elongatum*

Balahbib Abdelaali <sup>1</sup>, Naoual El Menyiy <sup>2</sup>, Nasreddine El Omari <sup>3</sup>, Taoufiq Benali,<sup>4</sup>  
Fatima-Ezzahrae Guaouguaou,<sup>5</sup> Najoua Salhi,<sup>6</sup> Hanae Naceiri Mrabti <sup>6</sup>  
and Abdelhakim Bouyahya <sup>7</sup>

<sup>1</sup>Laboratory of Biodiversity, Ecology and Genome, Mohammed V University in Rabat, Rabat, Morocco

<sup>2</sup>Laboratory of Physiology, Pharmacology and Environmental Health, University Sidi Mohamed Ben Abdellah, Fez, Morocco

<sup>3</sup>Laboratory of Histology, Embryology, and Cytogenetic, Mohammed V University in Rabat, Rabat, Morocco

<sup>4</sup>Environment and Health Team, Polydisciplinary Faculty of Safi, Cadi Ayyad University, Marrakech, Morocco

<sup>5</sup>Mohammed V University in Rabat, LPCMIO, Materials Science Center (MSC), Ecole Normale Supérieure, Rabat, Morocco

<sup>6</sup>Laboratory of Pharmacology and Toxicology, Faculty of Medicine and Pharmacy, Mohammed V University in Rabat, BP 6203, Rabat, Morocco

<sup>7</sup>Laboratory of Human Pathologies Biology, Department of Biology, Mohammed V University in Rabat, Rabat, Morocco

Correspondence should be addressed to Abdelhakim Bouyahya; bouyahya-90@hotmail.fr

Received 11 October 2020; Revised 20 April 2021; Accepted 7 June 2021; Published 17 June 2021

Academic Editor: Roberto K. N. Cuman

Copyright © 2021 Balahbib Abdelaali et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Origanum elongatum* L. is an endemic aromatic and medicinal plant. This work reports previous studies on *O. elongatum* concerning its taxonomy, botanical description, geographical distribution, bioactive compounds, toxicology, and biological effects. Chemical analyses showed that *O. elongatum* contains different chemical compounds, in particular volatile compounds. Pharmacological investigations showed that volatile compounds and extracts from *O. elongatum* exhibit different pharmacological properties, such as antibacterial, antifungal, antiviral, antioxidant, vasodilator, corrosion inhibitor, and hepatoprotective effects. Moreover, toxicological reports revealed the safety of this species. The pharmacological effects of *O. elongatum* could be correlated with the main compounds, which exhibit different pharmacological properties with numerous mechanism insights.

## 1. Introduction

*Origanum elongatum* (Bonnet) Emberger et Maire is an endemic aromatic and medicinal species of Morocco. It is a medicinal plant of the Lamiaceae family, a perennial herb of the *Origanum* genus. It is distributed in the wild species and is limited to the northeast (NE) of Morocco and extends from the Middle Atlas to the Rif Mountains ranges, mainly at high altitude on the mountains (the mountain of Tazekka and the mountain of Bouyahlane).

Phytochemical investigations showed that *O. elongatum* contains several classes of bioactive compounds, including terpenoids, flavonoids, oxygenated compounds, hydrocarbon compounds, and phenolic compounds [1–8]. The main

volatile compounds of this species are carvacrol, thymol, linalool, and limonene. Chemical analysis showed that the chemical composition is different between several published studies depending on the plant part and the collection site.

Pharmacological reports showed that extracts and essential oils (EOs) of *O. elongatum* exhibited various biological activities such as antibacterial [3, 4, 6, 9–11], antifungal [3, 12], antiparasitic [5, 13–16], antiviral [6], antioxidant [1], vasodilator [10, 17], corrosion inhibitor [18], and hepatoprotective effects [19]. These biological effects are certainly due to the chemical composition of *O. elongatum*, in particular the main compounds such as carvacrol, linalool, and thymol. Indeed, literature reports revealed that these compounds possess several pharmacological effects.

Moreover, the toxicological investigations showed that *O. elongatum* caused a slight change in behavior with loss of appetite and temporary sedation without any change in pathophysiological and neurological activity and LD<sub>50</sub> was greater than 3000 mg/kg [19].

This review is designed to explore all previous studies on *O. elongatum* L. in terms of taxonomy, botanical description, geographic distribution, ethnobotanical prospecting, and toxicology and all the investigations on the biological activities of the different parts of this plant, and we will summarize the list of all phytochemicals isolated and identified from the extracts or EOs of this plant. This work aims to provide a scientific basis for further studies and the development of medicinal agents from *O. elongatum*.

## 2. Research Methodology

The collection of data about *Origanum elongatum* concerned its botanical description, taxonomy, destruction, phytochemistry, and biological properties. Numerous databases such as Google Scholar, Web of Science, Scopus, ScienceDirect, SpringerLink, Wiley Online, SciFinder, and PubMed were consulted to collect publications about *O. elongatum*. The collected data have covered all years. The collected articles were organized in tables, analyzed, and highlighted in this review according to each field. The chemical compounds of *O. elongatum* were PubChem database and their chemical structures were drawn using ChemDraw Pro 8.0 software.

## 3. Results and Discussion

**3.1. Botanical Description.** *Origanum elongatum* (Bonnet) Emberger et Maire is an endemic species of Morocco. It is a woody perennial, which stems up to 90 cm. Its stems are erect, light or dark brown (purplish) and at the bases hirsute (hairs *c.* 1.5 mm long), otherwise, glabrous, and often glaucous leaves. Branches of the first order are present, in the upper 1/3–1/2 of the stems, up to 15 pairs per stem, 4 cm long; branches of the second order sometimes present; those of the third order seldom so. All branches entirely or for the greater part consist of spikes. Leaves up to 30 pairs per stem are shortly petiolate in the lower part to sessile in the upper part (petioles up to 5 mm long), ovate or oval, margins entire, tops obtuse, 10 mm long, 8 mm wide, somewhat leathery, light green or purplish, often glaucous, glabrescent (pilose to glabrous; hairs *c.* 1.2 mm long), sessile glands up to 1600 per cm<sup>2</sup>. Spikes are very loose and tenuous, 40 mm long, *c.* 3 mm wide. Bracts are 10 pairs per spike, ± lanceolate, tops acute, 3 mm long, 1 mm wide, glabrous or pilosellous, green, often glaucous. Flowers are sessile. Calyxes are 3.5 mm long, outside glabrous or pilosellous; teeth 1 mm long. Corollas are 6 mm long, pink, outside pilosellous; upper lips divided, for *c.* 1/5, into 2, *c.* 0.3 mm long lobes; lower lips divided, for *c.* 3/5, into 3, somewhat unequal, 1 mm long lobes. Staminal filaments are up to 2 and 3.5 mm long. Styles are up to 8 mm long [20].

**3.2. Taxonomy and Geographic Distribution.** *Origanum* is derived from two Greek words, “oros” which means mountain and “ganos” which means shine; this word would mean “ornament of the mountains” [21]. The appearance of the French term was in the 13th century, European (*Origanum* sp.) and Mexican (*Lippia* sp.) “oregano.” The name “Oregano” is commonly used around the world to define a spicy aroma and flavor [22].

The genus *Origanum* belongs to the Lamiaceae family and the Nepetoideae subfamily. The taxonomic point of view was completely revised by Dr. JH Ietswaart in 1980 [20]. In this work, Ietswaart divided the genus into 3 groups, 10 sections, grouping in total 38 species (one with 6 subspecies and another with 3 varieties), and 17 hybrids. This classification was based on the morphological characters of the plant (length of the stem, number of branches, and shape of the leaves) [20].

The flora of Morocco includes five taxa of *Origanum*, of which two (*O. compactum* and *O. vulgare* subsp. *virens*) are considered to be Ibero-Moroccan taxa and the other three taxa (*O. elongatum*, *O. grosii*, and *O. fontqueri*) are endemic in Morocco [2]. Due to their very similar morphologies, these three Moroccan steno-endemics are subject to taxonomic confusion. According to some databases [23], *O. grosii* and *O. × fontqueri* are considered to be synonyms of *O. elongatum*. However, Ietswaart [20] described *O. grosii* and *O. elongatum* as two different *Origanum* species according to their morphological characters, the length of the stems, ears, and leaves of *O. Elongatum* being larger than those of *O. Grosii*, but with *O. grosii* having a longer and wider bract than *O. elongatum*, while the hybrid, *O. × fontqueri*, is not described in the Ietswaart classification [20]. On the other hand, *O. elongatum* and *O. grosii* show obvious morphological differences from *O. compactum* (section *Prolaticorolla* Ietsw.) and from *O. vulgare* subsp. *virens* (section *Origanum* L.).

*Origanum elongatum* (Bonnet) Emb. & Maire belongs to the *Elongatispica* section (Section 7) of group C [20]. It is recognized in Morocco by its common Arabic name “Zaatar.” The geographical distribution of the wild species is limited to the NE of Morocco and extends from the Middle Atlas to the Rif Mountains ranges, mainly at high altitude on the mountains (the mountain of Tazekka and the mountain of Bouyablane) [20].

**3.3. Ecological Factors.** The wild species of *O. elongatum* grows at altitudes between 400 and 1500 m [24]; it abounds in open forests, rockeries, and mountain matorrals, on siliceous substrates and deep and well-drained soils. It is characterized by a fairly significant bioclimatic plasticity ranging from semiarid to per humid. The most favorable vegetation stages for this species are the thermo-Mediterranean and the meso-Mediterranean [25]. These oregano flowers from June to October [20] are known for their white inflorescence attached to vertical stems [24]. The abundance of their inflorescences, their lightness, and the sequence of flowering provide an ornamental interest to this species [20]. *O. elongatum* grows readily in temperate continental

climates and grows rapidly, but with limited development in size. However, harvesting is possible in the first year but with a low yield of dry matter [7]. The germination of *O. elongatum* seeds is extremely affected by abiotic factors, such as temperature, salinity stress, and pH. Thus, a temperature of 20°C, a pH of 6, and a salinity of 1 g/L constitute the optimal conditions for germination of this species [26].

**3.4. Phytochemistry.** The phytochemical analysis of *O. elongatum* extracts and EOs revealed the presence of a set of compounds, which are summarized in Table 1. Terpenoids were among the chemical classes dominating in *O. elongatum* EOs (Figure 1).

The methanol extract and the ethyl acetate extract from the leaves of *O. elongatum* are rich in phenolic compounds. The total phenol content of these extracts is  $153.22 \pm 2.67$  mg GAE/g of methanol extract and  $130 \pm 3.0567$  mg GAE/g of ethyl acetate extract. However, the flavonoid content is  $4.83 \pm 0.72$  mgEQ/g of ethyl acetate extract and  $5.02 \pm 0.26$  mgEQ/g of methanol extract [17].

The analysis by gas chromatography of *O. elongatum* EO from Morocco shows that it consists of 11 compounds, of which 3 are in the majority; carvacrol (60.42%), *p*-cymene (13.9%), and  $\gamma$ -terpinene (9.4%) [1].

In the same country (Morocco), 28 compounds were identified in *O. elongatum* EO, including carvacrol, thymol, and *p*-cymene, constituting the majority compounds. Additionally, limonene, thymoquinone, and thymohydroquinone have been reported in some EOs [2].

The main compounds identified in *O. elongatum* EO are carvacrol (63.06%),  $\gamma$ -terpinene (15.99%), *p*-cymene (9.51%), and other compounds, with appreciable percentages such as  $\alpha$ -phellandrene, caryophyllene, and  $\alpha$ -pinene [3].

On the other hand, a previous study [4] showed that the chemical profile of *O. elongatum* EO shows the predominance of oxygenated compounds (65.14%), followed by hydrocarbon compounds (28.02%), knowing that thymol is the major compound with 63.44%. These results confirm the findings of [5], which showed that the main constituents found in the aerial parts of *O. elongatum* EO are carvacrol (67.34%),  $\gamma$ -terpinene (3.29%), *p*-cymene (3.62%), and thymol (1.79%). However, in 2013, Moussaoui et al. [6] showed that the main constituents identified in the *O. elongatum* EO are carvacrol (40.12%), thymol (14.24%), *p*-cymene (16.19%), and  $\gamma$ -terpinene (13.48%).

Chromatographic analysis of the seeds of *O. elongatum* EO revealed the richness of the chemical composition predominated by carvacrol with a percentage of 79.2%, followed by  $\gamma$ -terpinene (3.7%), *p*-cymene (5.2%), and linalool (2.4%) [7, 8].

**3.5. Pharmacological Studies.** EOs and extracts from *O. elongatum* showed different pharmacological properties such as antibacterial, antiparasitic, anticancer, and antioxidant effects (Figure 2). In the following part, all of these biological activities will be discussed.

**3.6. Antibacterial Activity.** Several studies showed the antibacterial efficacy of different EOs or extracts from different

*O. elongatum* parts [3, 4, 6, 9–11]. Table 2 summarizes all the studies evaluating the antimicrobial activity of *O. elongatum* extracts and EOs.

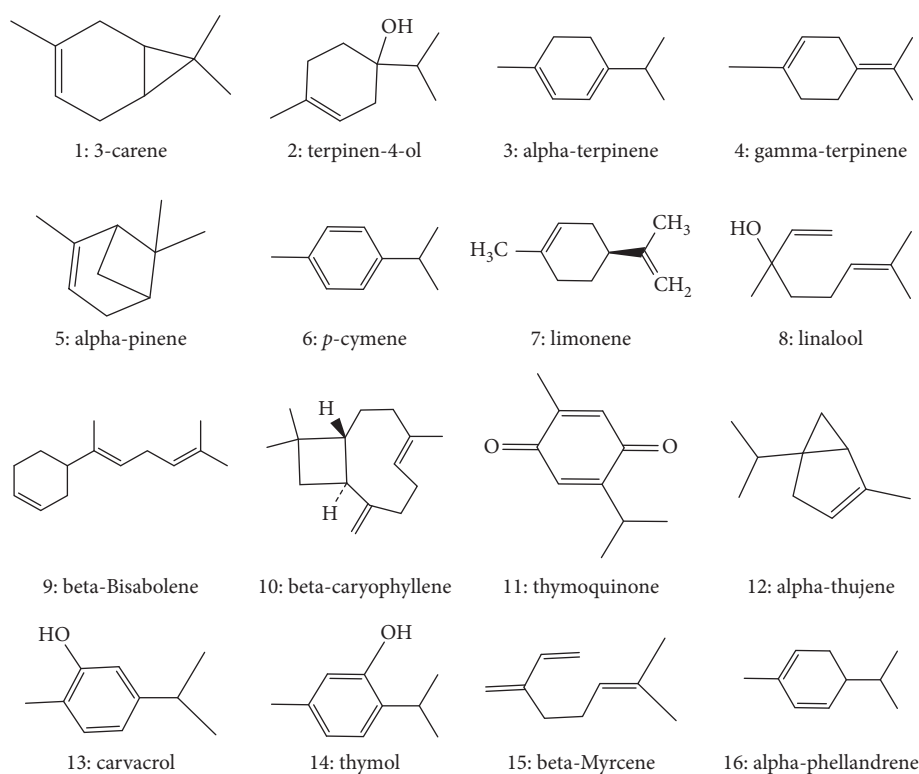
Bouharb et al. [9] evaluated *in vitro* the antibacterial activity of two extracts (aqueous and ethanolic) of *O. elongatum* leaves, from the Zerhoun region (central Morocco), on the growth of six strains of *Pseudomonas aeruginosa* (P, P3, P65, P381, P2, and P5), using the agar diffusion method and the broth macrodilution method of the active extract. The screening test revealed that *O. elongatum* aqueous extract was more active than the ethanolic extract, with zones of inhibition ranging from 9.33 to 11.83 and 8.33 to 11 mm, respectively. Douhri et al. [19] also studied the antibacterial activity *in vitro* of ethanolic extracts of *O. elongatum* leaves. The results showed a very important antimicrobial effect against *Escherichia coli* ( $30.33 \pm 2.51$  mm). Moreover, El Harsal and colleagues evaluated the antimicrobial activity of the volatile fractions extracted from the hydrosol (DVF) and of EOs from *O. elongatum* aerial parts growing in northern Morocco against four bacterial strains; *E. coli* ATCC 25922, *E. coli* K12, *S. aureus* ATCC 25923, and *B. subtilis* DCM 6633. They found that the antibacterial effect of DVF was significantly higher than that of total EO. The DVF was active against all the studied bacteria; the strongest effect was observed on *B. subtilis* DCM 6633 with a large inhibition zone ( $41.0 \pm 2.6$  mm). Also, the total EO of *O. elongatum* was highly active against *S. aureus* ATCC 25923, *B. subtilis* DCM 6633, and *E. coli* ATCC 25922, with inhibition zones ranging from 21.3 to 24.6 mm, while a moderate effect was observed against *E. coli* K12 [4].

In another study, the *O. elongatum* EO extracted from flowering tops and that extracted from leaves were tested against five microorganisms (*Salmonella* S64, *Salmonella* CECT 915, *Listeria monocytogenes* CECT4031, *L. monocytogenes* L23, and *E. coli* O157:H7 CECT4267), using the disk-diffusion assay and the microtitration assays. Additionally, the EOs showed the highest activities against the microorganisms tested, in particular against *Salmonella* and *L. monocytogenes* with zones of inhibition varying between  $21.67 \pm 0.58$  mm and  $34.33 \pm 4.04$  mm. The moderate activity was recorded against *E. coli*, with zones of inhibition from  $14.33 \pm 2.52$  to  $19.67 \pm 1.15$  mm [6]. Furthermore, a concentration of 0.06% of *O. elongatum* EO, extracted from flowering tops, showed a significant increase in the growth of total mesophilic aerobic flora (FMAT) [10]. In addition, the antibacterial activity of the *O. elongatum* EO (aerial part flowering) was tested against *Staphylococcus aureus*, *P. aeruginosa*, and *E. coli*. Therefore, an important inhibitory activity against all the strains tested was observed, with an inhibition diameter between 9.33 and 35.67 mm and high efficacy against *E. coli* and *S. aureus* [3].

**3.7. Antifungal Activity.** *O. elongatum* is one of the plants with antifungal properties [3, 12]. Indeed, several studies have evaluated these properties in *O. elongatum* EOs (Table 3). The antifungal activity of the essential oil of

TABLE 1: Chemical composition of extracts and essential oils of *O. elongatum*.

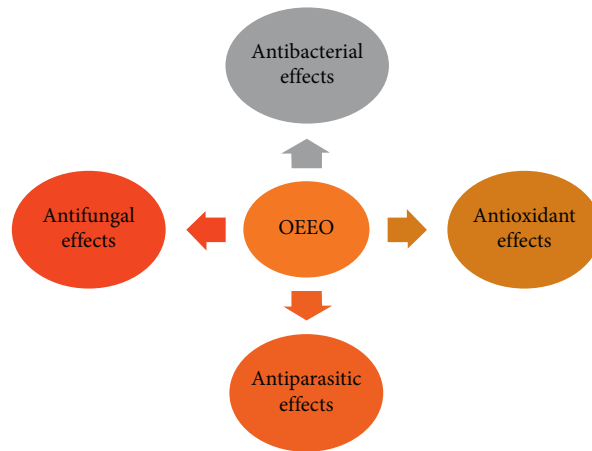
Country	Part	Extracts/essential oils	Compounds groups	Compounds	References
Morocco	Leaves	Ethyl acetate and methanol extracts	Total polyphenols Flavonoids	— —	[17]
Morocco	Leaves and flowering tops	Essential oil	Terpenoids	$\alpha$ -Thujene, $\beta$ -myrcene, <i>p</i> -cymene, $\gamma$ -terpinene, linalool, terpinene-4-ol, thymol, carvacrol, $\beta$ -caryophyllene, $\beta$ -bisabolene, and caryophyllene oxide	[1]
Morocco	Aerial parts	Essential oil	Terpenoids	Carvacrol, thymol, <i>p</i> -cymene, $\alpha$ -terpinene, limonene, thymoquinone, and thymohydroquinone	[2]
Morocco	Aerial parts	Essential oil	Terpenoids	Carvacrol, $\gamma$ -terpinene, <i>p</i> -cymene, $\alpha$ -phellandrene, caryophyllene, 3-carene, and $\alpha$ -pinene	[3]
Morocco	Aerial parts	Essential oil	Terpenoids	Thymol, $\gamma$ -terpinene, and <i>p</i> -cymene	[4]
Morocco	Aerial parts	Essential oil	Terpenoids	Carvacrol, thymol, $\gamma$ -terpinene, and <i>p</i> -cymene	[5]
Morocco	Leaves and flowering tops	Essential oil	Terpenoids	Carvacrol, thymol, $\gamma$ -terpinene, and <i>p</i> -cymene	[6]
Morocco	Seeds	Essential oil	Terpenoids	Carvacrol, thymol, $\gamma$ -terpinene, <i>p</i> -cymene, and linalool	[8]
Morocco	Seeds	Essential oil	Terpenoids	Carvacrol, <i>p</i> -cymene, $\gamma$ -terpinene, and linalool	[7]

FIGURE 1: Chemical structures of terpenoids identified in *O. elongatum* EOs.

*O. elongatum* aerial parts was tested and evaluated by the microdilution method against three strains of fungi: *Candida*, *Aspergillus*, and *Rhizopus* [12]. Therefore, all *Candida* strains showed marked sensitivity to the essential oil. The *Rhizopus* strain was less sensitive, whereas for *Aspergillus*, this oil showed an effect only on tree strains. In another study, the antifungal activity of *O. elongatum* EO was evaluated by the agar plug diffusion method, which

consequently showed promising results against *Aspergillus brasiliensis* (no measurable zone of inhibition) and *Candida albicans* ( $33.67 \pm 0.33$  mm) [3].

**3.8. Antiparasitic Activity.** Many species of the genus *Origanum* have shown antiparasitic activities [13–15]. Moreover, the antiparasitic effect of *O. elongatum* was

FIGURE 2: Pharmacological properties of *O. elongatum*.TABLE 2: Antibacterial effects of *O. elongatum*.

Use part	Extracts	Used method	Tested strains	Key results	References	
Leaves	Ethanollic extract	Method of diffusion in solid medium Macromethod of dilution in liquid medium	P	—	[1]	
			P3	$\Phi = 10 \pm 0.8$ mm		
			P65	$\Phi = 11 \pm 0.8$ mm		
			P381	$\Phi = 8.5 \pm 0.4$ mm		
			P2	$\Phi = 9 \pm 0.8$ mm		
Leaves	Aqueous extract		P5	$\Phi = 8.33 \pm 0.8$ mm	[1]	
			P	$\Phi = 11.66 \pm 0.47$ mm		
			P3	$\Phi = 11 \pm 0.95$ mm		
			P65	$\Phi = 11.83 \pm 0.23$ mm		
			P381	$\Phi = 9.33 \pm 1.24$ mm		
Leaves	Aqueous extract		P2	$\Phi = 10 \pm 0$ mm	[1]	
			P5	$\Phi = 9.5 \pm 0.4$ mm		
			<i>Staphylococcus aureus</i>	$\Phi = 35.67 \pm 0.66$ mm MIC = 0.03% MMC = 0.13%		[3]
			<i>Escherichia coli</i>	$\Phi = 26.33 \pm 1.66$ mm MIC = 0.03% MMC = 0.03%		
			<i>Pseudomonas aeruginosa</i>	$\Phi = 9.33 \pm 0.66$ mm MIC = 0.5% MMC = 0.5%		
Leaves	Ethanollic extract	Agar-well diffusion assay	<i>Escherichia coli</i>	$\Phi = 30.33 \pm 2.51$ mm	[11]	
Leaves	Essential oil	Disk-diffusion assay Microtitration method	<i>Salmonella</i> CECT 915	$\Phi = 34.33 \pm 4.04$ mm MIC = 0.0625% MBC = 0.0625%	[6]	
			<i>Salmonella</i> S64	$\Phi = 28.17 \pm 1.61$ mm MIC = 0.0625% MBC = 0.125%		
			<i>E. coli</i> O157 : H7 CECT4267	$\Phi = 19.67 \pm 1.15$ mm MIC = 0.25% MBC = 0.5%		
			<i>L. monocytogenes</i> CECT4031	$\Phi = 34.00 \pm 0.00$ mm MIC = 0.125% MBC = 0.0625%		
			<i>L. monocytogenes</i> L23	$\Phi = 31.00 \pm 3.46$ mm MIC = 0.5% MBC = 0.5%		

TABLE 2: Continued.

Use part	Extracts	Used method	Tested strains	Key results	References
Flowering tops	Essential oil	Disk-diffusion assay Microtitration method	<i>Salmonella</i> CECT 915	$\Phi = 31.50 \pm 2.78$ mm MIC = 0.0625 MBC = 0.125%	[6]
			<i>Salmonella</i> S64	$\Phi = 28.17 \pm 1.61$ mm MIC = 0.0625% MBC = 0.125%	
			<i>E. coli</i> O157:H7 CECT4267	$\Phi = 18.00 \pm 0.00$ mm MIC = 0.25% MBC = 0.5%	
			<i>L. monocytogenes</i> CECT4031	$\Phi = 29.00 \pm 1.73$ mm MIC = 0.125% MBC = 0.25%	
			<i>L. monocytogenes</i> L23	$\Phi = 31.00 \pm 3.46$ mm MIC = 0.5% MBC = 0.5%	
Flowering tops	Essential oil		Total mesophilic aerobic flora (FMAT)	Significant effect on microbial growth	[10]
Aerial parts	Essential oil	Agar-well diffusion method Microdilution assay	<i>E. coli</i> ATCC 25922	$\Phi = 21.33 \pm 0.57$ mm MIC = 0.5% MBC < 1%	[4]
			<i>E. coli</i> K12	$\Phi = 16.00 \pm 1.00$ mm MIC = 0.25% MBC = 0.5%	
			<i>B. subtilis</i> DCM 6633	$\Phi = 24.66 \pm 1.52$ mm MIC = 0.5% MBC = 0.5%	
			<i>S. aureus</i> ATCC 25923	$\Phi = 27.00 \pm 1.73$ mm MIC = 0.125% MBC = 0.125%	
Aerial parts	Dissolved volatile fraction	Agar-well diffusion method Microdilution assay	<i>E. coli</i> ATCC 25922	$\Phi = 28.33 \pm 0.57$ mm MIC = 0.125% MBC = 0.25%	[4]
			<i>E. coli</i> K12	$\Phi = 17.00 \pm 1.73$ mm MIC = 0.125% MBC = 0.125%	
			<i>B. subtilis</i> DCM 6633	$\Phi = 41.00 \pm 2.64$ mm MIC = 0.0625% MBC = 0.0625%	
			<i>S. aureus</i> ATCC 25923	$\Phi = 30.00 \pm 2.00$ mm MIC = 0.0312% MBC = 0.0312%	

TABLE 3: Antifungal activity of *O. elongatum*.

Use part	Extracts	Used method	Tested strains	Key results	References
Aerial parts	Essential oil	Agar plug diffusion method	<i>Candida albicans</i> <i>Aspergillus brasiliensis</i>	$\Phi = 33.67 \pm 0.33$ mm No measurable zone of inhibition	[3]
Aerial parts	Essential oil	Microdilution method	<i>Candida</i> <i>Aspergillus</i> <i>Rhizopus</i>	Sensitive to the essential oil Susceptible to the oil Moderately susceptible to the oil	[12]

reported by several investigators (Table 4) [5, 16]. In 2017, Ramzi and collaborators [5] tested the acaricidal activity of the EOs of *O. elongatum* leaves on the *Varroa* mite. Therefore, these plant-derived EOs showed certain effectiveness against *Varroa*. Besides, the antiparasitic effect of *O. elongatum* EO was evaluated in experimental animals (female Wistar rats) infected with 6 *Anisakis*

larvae using the gastric catheter method [16]. This technique was also used to administer *O. elongatum* (46.9 mg/0.5 mL of olive oil). Consequently, an EO activity against larva L3 of *Anisakis pegreffii* was observed; moreover, significant alterations of the esophageal region and the cuticle were detected in a large number of recovered larvae.

TABLE 4: Other activities of *O. elongatum*.

Activities	Use part	Extracts	Experimental approach	Key results	References
Antiviral	Leaves	Essential oil	Cytopathogenic murine norovirus (MNV-1) RAW 264.7 cells	0.37 log <sub>10</sub> TCID <sub>50</sub> /ml reductions	[6]
	Flowering tops	Essential oil	Cytopathogenic murine norovirus (MNV-1) RAW 264.7 cells	0.75 log <sub>10</sub> TCID <sub>50</sub> /ml reductions	[6]
Antiparasitic	Leaves	Essential oil	Colonies of <i>Apis mellifera</i> bees Efficacy against <i>Varroa</i> mite in beehives	Significant increase in mite drop All <i>Varroa</i> mites died	[5]
	Leaves	Essential oil	Larva L3 of <i>Anisakis pegreffii</i> isolated from the host <i>Scomber japonicas</i> and <i>Trachurus trachurus</i> Female Wistar rats infected with 6 <i>Anisakis</i> larvae by gastric catheter Administration of <i>O. elongatum</i> (46.9 mg/0.5 mL of olive oil)	Significant larvicidal activity Significant alterations in the esophageal region and cuticle detected in a large number of recovered larvae	[16]
Antioxidant	Leaves	Essential oil	EC <sub>50</sub> = 1.20 g of extract/g DPPH		[1]
Vasodilatory activity	Leaves	Methanol extract	Perfusion pressure (PP) of the mesenteric bed of the rat Synthesis inhibitor endothelial vasodilators factors Vasoconstrictor $\alpha$ -mimetic: phenylephrine (PHE) Difference between the blood pressure before injection and blood pressure after injection	Vasodilatory activity (PP = 50 mmHg)	[17]
Vasodilatory activity	Leaves	Ethyl acetate extract	Perfusion pressure (PP) of the mesenteric bed of the rat Synthesis inhibitor endothelial vasodilators factors Vasoconstrictor $\alpha$ -mimetic: phenylephrine (PHE) Difference between the blood pressure before injection and blood pressure after injection	Vasodilatory activity (PP = 20 mmHg)	[17]
Effect on pomegranate juice quality	Flowering tops	Essential oil	pH variation Determination of total sugars Growth of natural flora in the pomegranate juice	Improved the juice conservation process while preserving the nutritional and organoleptic qualities	[10]
Corrosion inhibition	Leaves and flowers	Methanol/chloroform extract	Corrosion current density (j <sub>corr</sub> ) Electrochemical measurements Electrochemical impedance spectroscopy (EIS) Mass loss method Adsorption isotherms	Corrosion potential (e <sub>corr</sub> ) decreased from -399.446 mV/ESC to -365.607 mV/ESC Significant decrease in corrosion current (j <sub>corr</sub> ) Increased the charge transfer resistance (R <sub>ct</sub> ) with increased OEE concentration Ability of OEE to act as a protective layer against corrosion on mild steel	[18]
Hepatoprotective effect against carbon tetrachloride (CCl <sub>4</sub> )	Leaves	Methanol extract	Single-dose intraperitoneal injection of carbon tetrachloride (CCl <sub>4</sub> ) (0.6 ml/kg) induced hepatotoxicity in rats Rats treated orally by gavage four doses of 250, 500, 1000, and 2000 mg/kg body weight	Significant ( $P < 0.0001$ ) decrease in serum aminotransferase levels and canalicular enzyme ALP reduced the architectural destruction cells	[19]

**3.9. Antiviral Activity.** The *O. elongatum* EOs, cultivated in northern Morocco, were studied for the inactivation of Murine norovirus (MNV-1) (Table 4), which is a human norovirus surrogate. Interestingly, the EOs from leaves and flowering tops showed antiviral activities of 0.87-0.50  $\log_{10}$ TCID<sub>50</sub>/mL reduction and 0.75  $\log_{10}$ TCID<sub>50</sub>/mL reduction, respectively [6].

**3.10. Other Biological Activities.** Besides the antiparasitic and antiviral activities, the antioxidant effect of endemic *O. elongatum* was examined in the Rif in northern of Morocco (Table 4) [1, 17]. The authors evaluated the vasodilator activity of *O. elongatum* leaves, extracted by methanol and ethyl acetate on a Wistar rat mesenteric vascular bed precontracted with norepinephrine. Measurement of the perfusion pressure of the rat mesenteric bed revealed that the methanolic extracts (PP = 50 mmHg) gave more active substances than the leaves of *O. elongatum* extracted in ethyl acetate (PP = 20 mmHg) [17]. Furthermore, the food conservation aspect of flowering tops of the studied plant on fresh pomegranate juice was demonstrated [10]. The findings demonstrated that the EOs combined with heat reduce the growth of natural flora presented in the pomegranate juice and thus improve the juice conservation process, while nutritional and organoleptic qualities were also preserved. Moreover, the impact against corrosion inhibition of *O. elongatum* leaves and flowers, using a mixture of methanol/chloroform, was deeply elaborated by applying the electrochemical impedance spectroscopy (EIS), mass loss method, and adsorption isotherms method [18]. According to their electrochemical parameters measurement, it was shown that the use of extracts decreased the corrosion potential ( $E_{corr}$ ), which ranged from  $-399.446$  mV/ESC to  $-365.607$  mV/ESC. A similar decrease was observed with corrosion current ( $j_{corr}$ ). Nonetheless, a significant increase of charge transfer resistance ( $R_{ct}$ ) was noted, with the increase of the OEE concentration (the ability of layer protection from corrosion on the mild steel) [18]. Another important impact of *O. elongatum* was surveyed by Douhri et al. [19].

Scientists have shown the hepatoprotective effect of methanolic leaf extracts of this species at different doses against the toxicity induced by carbon tetrachloride (CCl<sub>4</sub>) in rats. The biochemical examination of serum hepatic biomarkers showed a significant decrease in serum aminotransferase levels, the canalicular enzyme, and alkaline phosphatase and reduction in the destruction of hepatic cell architecture at the dose of 2000 mg/kg/d [19].

**3.11. Toxicology.** *O. elongatum* is an aromatic plant well known for its flavor and widely consumed in Morocco as a condiment and food preservative [24]. From a toxicological point of view, only one study investigated the toxicological properties of *O. elongatum* extract by evaluating acute oral toxicity [19]. The results showed a slight change in behavior with loss of appetite and temporary sedation without any change in pathophysiological and neurological activity with an LD<sub>50</sub> greater than 3000 mg/kg. Jenner et al. [27] also

reported the same signs in rats when testing carvacrol, the major component of *O. elongatum*, in an acute oral toxicity test. The LD<sub>50</sub> in this test was 810 mg/kg, suggesting that carvacrol is the active ingredient responsible for the behavioral change caused by this plant [27].

#### 4. Biological Mechanism Insights into *O. elongatum* Main Compounds

The potent anti-inflammatory activity of the extracts encouraged the authors to isolate the main compounds (thymol, carvacrol, limonene,  $\alpha$ -pinene, and linalool), which might be responsible for the anti-inflammatory effect. The reported studies showed that thymol inhibits inducible lymphocyte proliferation [28], reduces edema and leukocyte influx to injured areas [29], and induces membrane stabilization (84.11%) in human red blood cell membrane stabilization assay [30]. Moreover, this molecule had inhibitory effects on various inflammatory mediators such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and TNF- $\beta$  [31]. It also decreased c-Fos, NFAT-1, and NFAT-2 expression, with inhibition of inducible phospho-SAPK/JNK and phospho-STAT3 levels [32]. Molecular investigations showed that thymol also inhibits TLR4 upregulation and suppresses IKK,  $\text{I}\kappa\text{B}\alpha$ , and p65 phosphorylation [33]. Additionally, carvacrol has also shown an anti-inflammatory effect [34]. This compound was reported to be able to inhibit the production of PGE2 (inflammatory mediator catalyzed by COX1) and suppress COX-2 promoter activity by activating PPAR $\alpha$  and PPAR $\gamma$ . It also reduced the expression of LPS-induced COX-2 mRNA and protein, suggesting that the action of carvacrol on COX-2 is mediated through its agonistic effect on PPAR $\gamma$  [35]. Moreover, Yoon et al. [36] showed that limonene decreased the production of proinflammatory cytokines and inflammatory mediators in macrophages by the inhibition of LPS-induced NO and PGE2, which decreased iNOS and COX-2 expression [36]. This monoterpene also exhibited an anti-inflammatory effect *via* the inhibition of some signaling pathways leading to the inflammatory process in leukemia (HL-60) cell lines, such as ROS, monocyte chemoattractant protein-1 (MCP-1), NF- $\kappa$ B, and p38 mitogen-activated protein kinase (MAPK) [37]. On the other hand,  $\alpha$ -pinene exhibited potent activity in the inflammatory process and neuropathic pain [38]. It inhibited ear edema at 0.15 h (120–135% vs. 175%), paw edema at 12 h (146  $\pm$  6%), and a decrease in COX-2 (115  $\pm$  74% vs. 202  $\pm$  20%) [39] and reduced the level of IL-6 in the hippocampus, cortex, and striatum [40]. In addition, linalool is another monoterpene, which also exhibited an anti-inflammatory effect. This compound significantly reduced hypersensitivity and paw edema at doses of 50 and 200 mg/kg of carrageenan-induced edema model in rats [41, 42].

Several studies showed the antidiabetic effect of different compounds identified in *O. elongatum*. The authors showed that carvacrol exhibits antidiabetic effects via several mechanisms such as reduction in blood glucose and insulin levels, decrease in (HOMA-IR) index, and decrease in the expressions of the mRNA of gluconeogenic genes, PEPCK, and G6Pase [43]. Additionally, carvacrol may also decrease



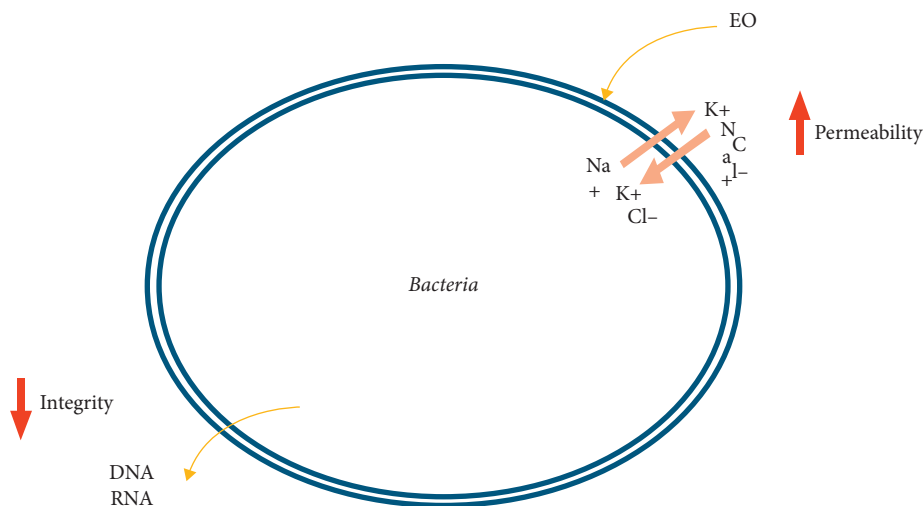


FIGURE 3: Antibacterial action of *O. elongatum* bioactive compounds.

glucose levels by lowering HbA<sub>1c</sub>, G6Pase, and FBPase activities. It also promoted the activities of glucokinase and glucose-6-phosphate dehydrogenase in the liver and protected pancreatic islets [44]. This monoterpene inhibited the activity of  $\alpha$ -amylase ( $IC_{50} = 152.3 \pm 1.21 \mu\text{g mL}^{-1}$ ),  $\alpha$ -glucosidase ( $IC_{50} = 94.02 \pm 0.78 \mu\text{g mL}^{-1}$ ) [45], and  $\beta$ -galactosidase [46]. On the other hand, limonene ameliorates glucose homeostasis by increasing hepatic glycogen with a decrease in plasma glucose and HbA<sub>1c</sub> levels and suppresses the activities of gluconeogenic enzymes (G6Pase and FBPase) [47]. Moreover, it ameliorates the reduction of FBG level and glucose tolerance along with the activation of PPAR $\alpha$  signaling [48]. In addition, using two different cell lines, C2C12 skeletal muscle cells [49] and 3T3-L1 preadipocytes [50], limonene has been shown to improve glucose absorption by increasing phosphorylation of activated protein kinase B (Akt) and promoting p38 mitogen-activated protein kinase (p38MAPK) [50].

Furthermore, linalool also showed an antidiabetic effect [51, 52]. This compound was reported to be able to decrease blood glucose, HbA<sub>1c</sub>, fructosamine, IL-6 and TNF- $\alpha$ , and area under the curve of ( $AUC_{\text{glucose}}$ ) glucose value and increase insulin level [52]. On the other hand, thymol was also able to treat hyperglycemia by normalizing blood sugar, plasma insulin, HbA<sub>1c</sub>, and insulin resistance index [53]. Rhayour et al. [54] investigated the expression levels of genes involved in insulin transcription in STZ-induced diabetic rats and reported an increase in expression of the *Mafa* and *Pdx1* genes.

The major compounds of this plant are limonene, linalool, carvacrol, and thymol. In fact, these molecules have shown in some studies a significant antibacterial power [55–57]. Rhayour et al. [58] examined the mechanism of action of thymol on bacteria *E. coli* and *Bacillus subtilis* as the model of Gram-positive and Gram-negative bacteria. This action was demonstrated by the release of absorbent substances at 260 nm. This release of substances associated with rapid bacterial mortality could be the consequence of lesions on the envelopes induced by antibacterial agents (Figure 3).

Another study [59] showed that carvacrol affects cell membranes of bacteria by changing the composition of fatty acids, which subsequently affects the fluidity and permeability of the membrane. On the other hand, several studies have indicated that linalool alters normal cell morphology, destroys the cell wall and cell membrane, inhibits the growth of *P. aeruginosa*, and even leads to its death [60]. However, the mechanism of action of limonene against cytoplasmic membranes of microorganisms results in a loss of membrane integrity (Figure 3), inhibition of respiratory enzymes, and dissipation of the proton motive force [61].

Numerous studies have been published on the anticancer activity of the main compounds of oregano EOs such as limonene, carvacrol, and thymol [62–64]. Islam et al. [63] determined that the mechanism of action of thymol in a cancer cell caused severe DNA damage through several mechanisms (e.g., ROS induction and subsequent increase in oxidative stress and/or mitochondrial dysfunction or nuclear factor of activated T-cells (NFAT-2) pathway), which eventually upregulates Bax/Bcl-2 protein expression and results in the cytochrome- (cyto-) c release from the mitochondria (intrinsic pathway). In another work, carvacrol treatment induced cell apoptosis, possibly through the activation of the mitochondrial apoptotic, MAPK, and PI3K/Akt signaling pathways. Taken together, our results indicate that carvacrol might be a promising natural product in the management of colon cancer [65].

## 5. Conclusion

Morocco is a country rich in plant resources with a specific diversity of medicinal plants used in the treatment and prevention of several illnesses. This study provides evidence that the Moroccan *O. elongatum* L. species possesses active principles that exhibit marked therapeutic effects confirming and justifying the popular uses of these plants to treat certain diseases as antibacterial, antifungal, antiviral, antioxidant, vasodilator, corrosion inhibitor, and hepatoprotective agents. The current study represents useful documentation

that can provide sufficient support for clinical trials of *O. elongatum* L. Although preliminary studies have confirmed their therapeutic effect, further investigations should be carried out, in particular, to ensure the safety of the treatment.

## Data Availability

The data used to support the findings of this study are included within the article.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Abdelaali Balahbib and Abdelhakim Bouyahya contributed equally to this work.

## References

- [1] H. Oualili, R. Nmila, and F. Chibi, "Chemical composition and antioxidant activity of *Origanum elongatum* essential oil," *Pharmacognosy Research*, vol. 11, no. 3, p. 283, 2019.
- [2] M. Bakha, C. Al Faiz, M. Daoud et al., "Genome size and chromosome number for six taxa of *Origanum* genus from Morocco," *Botany Letters*, vol. 164, no. 4, pp. 361–370, 2017.
- [3] S. Boukhira, F. Boustia, S. Moularat, A. Abdellaoui, Z. B. Ouaritini, and D. Boustia, "Evaluation of the preservative properties of *origanum elongatum* essential oil in a topically applied formulation under a challenge test," *Phytothérapie*, vol. 18, no. 2, pp. 92–98, 2018.
- [4] A. El Harsal, A. Ibn Mansour, N. Skali Senhaji et al., "Influence of extraction time on the yield, chemical composition, and antibacterial activity of the essential oil from *origanum elongatum* (E. & M.) harvested at Northern Morocco," *Journal of Essential Oil Bearing Plants*, vol. 21, no. 6, pp. 1460–1474, 2018.
- [5] H. Ramzi, M. R. Ismaili, M. Aberchane, and S. Zaanoun, "Chemical characterization and acaricidal activity of *Thymus satureioides* C. & B. and *Origanum elongatum* E. & M. (Lamiaceae) essential oils against *Varroa destructor* Anderson & Trueman (Acari: Varroidae)," *Industrial Crops and Products*, vol. 108, pp. 201–207, 2017.
- [6] N. Moussaoui, G. Sanchez, and E. O. Khay, "Antibacterial and antiviral activities of essential oils of northern moroccan plants," *British Biotechnology Journal*, vol. 3, no. 3, pp. 318–331, 2013.
- [7] G. Figuéredo, P. Cabassu, J.-C. Chalchat, and B. Pasquier, "Studies of mediterranean oregano populations. vi: chemical composition of essential oils of *origanum elongatum* memberger et maire from Morocco," *Journal of Essential Oil Research*, vol. 18, no. 3, pp. 278–280, 2006.
- [8] G. Figueredo, "Etude chimique et statistique de la composition d'huiles essentielles d'origans (Lamiaceae) cultivés issus de graines d'origine méditerranéenne," Université Blaise Pascal-Clermont-Ferrand II, Clermont-Ferrand, France, Theses, 2007.
- [9] H. Bouharb, K. El Badaoui, T. Zair, J. El amri, S. Chakir, and T. Alaoui, "Sélection de quelques plantes médicinales du Zerhoun (Maroc centrale) pour l'activité antibactérienne contre *Pseudomonas aeruginosa*," *Journal of Applied Biosciences*, vol. 78, pp. 6685–6693, 2014.
- [10] N. E. Moussaoui, E. O. Khay, N. Amajoud et al., "Effect of *Origanum elongatum* essential oil and heating on pomegranate juice quality," *International Journal of Current Microbiology and Applied Sciences*, vol. 5, no. 4, pp. 1–8, 2016.
- [11] H. Douhri, I. Raissouni, N. Amajoud et al., "Antibacterial effect of ethanolic extracts of Moroccan plant against *Escherichia coli*," *Journal of Materials and Environmental Sciences*, vol. 8, no. 12, pp. 4408–4414, 2017.
- [12] A. Amakran, M. Hamoudane, and B. Ramdan, "Antifungal activity of the essential oil of *origanum elongatum* on candida, aspergillus and rhizopus species," *Journal de Mycologie Medicale*, vol. 2, no. 24, p. e78, 2014.
- [13] S. Coskun, O. Girisgin, M. Kürkcüoğlu et al., "Acaricidal efficacy of *Origanum onites* L. essential oil against *Rhipicephalus turanicus* (Ixodidae)," *Parasitology Research*, vol. 103, no. 2, pp. 259–261, 2008.
- [14] S. Degerli, B. Tepe, A. Celiksoz, S. Berk, and E. Malatyali, "In vitro amoebicidal activity of *Origanum syriacum* and *Origanum laevigatum* on *Acanthamoeba castellanii* cysts and trophozoites," *Experimental Parasitology*, vol. 131, no. 1, pp. 20–24, 2012.
- [15] M. Machado, A. M. Dinis, L. Salgueiro, C. Cavaleiro, J. B. A. Custódio, and M. d. C. Sousa, "Anti-Giardia activity of phenolic-rich essential oils: effects of *Thymbra capitata*, *Origanum virens*, *Thymus zygis* subsp. *sylvestris*, and *Lippia graveolens* on trophozoites growth, viability, adherence, and ultrastructure," *Parasitology Research*, vol. 106, no. 5, pp. 1205–1215, 2010.
- [16] N. Abattouy, A. Valero López, and M. C. Romero, "Actividad IN VIVO del aceite esencial de *Origanum elongatum* frente a larvas L3 de *Anisakis pegreffii*," *IN VIVO Activity of Essential Oil Origanum Elongatum Against Larva L3 of Anisakis Pegreffii*, vol. 51, pp. 107–111, 2010.
- [17] K. E. Yousfi, H. Greche, H. Misbahi, and R. B. Cheikh, "Phytochemical evaluation and vasodilatory activity of *O. elongatum*, *C. salviifolius* and *C. laurifolius*," *Moroccan Journal of Chemistry*, vol. 8, no. 1, pp. 226–234, 2020.
- [18] H. El Attari, K. Chefira, and H. Rchid, "Corrosion inhibition study of the *origanum elongatum* extract: electrochemical, gravimetric and adsorption isotherms studies in 0.5 m sulfuric acid," *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, vol. 10, no. 1, 2019.
- [19] B. Douhri, M. Idaomar, N. S. Senhaji, A. Ennabili, and J. Abrini, "Hepatoprotective effect of *origanum elongatum* against Carbon Tetrachloride (CCl<sub>4</sub>) induced toxicity in rats," *European Journal of Medicinal Plants*, vol. 4, no. 1, pp. 14–28, 2014.
- [20] J. H. Ietswaart and V. Else, *A Taxonomic Revision of the Genus Origanum (Labiatae)*, The Hague: Leiden University Press, The Hague, The Netherlands, 1980.
- [21] S. E. Kintzios, "Oregano," in *In Handbook of Herbs and Spices*, K. V. Peter, Ed., pp. 417–436, Woodhead Publishing, Sawston, UK, 2nd edition, 2012.
- [22] X. Simonnet, M. Quennoz, D. Bellenot, and B. Pasquier, "Evaluation agronomique et chimique de différentes espèces d'origan," *Revue suisse de viticulture, arboriculture et horticulture*, vol. 43, no. 6, pp. 344–349, 2011.
- [23] Euro+MedPlantBase, "The information resource for euro-mediterranean plant diversity," 2006, <http://ww2.bgbm.org/EuroPlusMed/query.asp>.
- [24] E. Christaki, E. Bonos, I. Giannenas, and P. Florou-Paneri, "Aromatic plants as a source of bioactive compounds," *Agriculture*, vol. 2, no. 3, pp. 228–243, 2012.

- [25] A. Benabid, "Flore et ecosystemes du Maroc: evaluation et preservation de la biodiversite," 2000.
- [26] O. Belmehdi, A. El Harsal, M. Benmoussi, Y. Laghmouchi, N. Skali Senhaji, and J. Abrini, "Effect of light, temperature, salt stress and pH on seed germination of medicinal plant *Origanum elongatum* (Bonnet) Emb. & Maire," *Biocatalysis and Agricultural Biotechnology*, vol. 16, pp. 126–131, 2018.
- [27] P. M. Jenner, E. C. Hagan, J. M. Taylor, E. L. Cook, and O. G. Fitzhugh, "Food flavourings and compounds of related structure I. acute oral toxicity," *Food and Cosmetics Toxicology*, vol. 2, pp. 327–343, 1964.
- [28] Z. Amirghofran, R. Hashemzadeh, K. Javidnia, H. Golmoghaddam, and A. Esmailbeig, "In vitro immunomodulatory effects of extracts from three plants of the Labiataefamily and isolation of the active compound(s)," *Journal of Immunotoxicology*, vol. 8, no. 4, pp. 265–273, 2011.
- [29] M. E. Pascual, K. Slowing, E. Carretero, D. Sánchez Mata, and A. Villar, "Lippia: traditional uses, chemistry and pharmacology: a review," *Journal of Ethnopharmacology*, vol. 76, no. 3, pp. 201–214, 2001.
- [30] J. Sheorain, M. Mehra, R. Thakur, S. Grewal, and S. Kumari, "In vitro anti-inflammatory and antioxidant potential of thymol loaded bipolymeric (tragacanth gum/chitosan) nanocarrier," *International Journal of Biological Macromolecules*, vol. 125, pp. 1069–1074, 2019.
- [31] Y.-M. Yu, T.-Y. Chao, W.-C. Chang, M. J. Chang, and M.-F. Lee, "Thymol reduces oxidative stress, aortic intimal thickening, and inflammation-related gene expression in hyperlipidemic rabbits," *Journal of Food and Drug Analysis*, vol. 24, no. 3, pp. 556–563, 2016.
- [32] N. Gholijani, M. Gharagozloo, S. Farjadian, and Z. Amirghofran, "Modulatory effects of thymol and carvacrol on inflammatory transcription factors in lipopolysaccharide-treated macrophages," *Journal of Immunotoxicology*, vol. 13, no. 2, pp. 157–164, 2016.
- [33] Q. Wang, F. Cheng, Y. Xu et al., "Thymol alleviates lipopolysaccharide-stimulated inflammatory response via downregulation of RhoA-mediated NF- $\kappa$ B signalling pathway in human peritoneal mesothelial cells," *European Journal of Pharmacology*, vol. 833, pp. 210–220, 2018.
- [34] P. Landa, L. Kokoska, M. Pribylova, T. Vanek, and P. Marsik, "In vitro anti-inflammatory activity of carvacrol: inhibitory effect on COX-2 catalyzed prostaglandin E2 biosynthesis," *Archives of Pharmacol Research*, vol. 32, no. 1, pp. 75–78, 2009.
- [35] M. Hotta, R. Nakata, M. Katsukawa, K. Hori, S. Takahashi, and H. Inoue, "Carvacrol, a component of thyme oil, activates PPAR $\alpha$  and  $\gamma$  and suppresses COX-2 expression," *Journal of Lipid Research*, vol. 51, no. 1, pp. 132–139, 2010.
- [36] W.-J. Yoon, N. H. Lee, and C.-G. Hyun, "Limonene suppresses lipopolysaccharide-induced production of nitric oxide, prostaglandin E2, and pro-inflammatory cytokines in RAW 264.7 macrophages," *Journal of Oleo Science*, vol. 59, no. 8, pp. 415–421, 2010.
- [37] D. A. Wiseman, S. R. Werner, and P. L. Crowell, "Cell cycle arrest by the isoprenoids perillyl alcohol, geraniol, and farnesol is mediated by p21cip1 and p27kip1 in human pancreatic adenocarcinoma cells," *Journal of Pharmacology and Experimental Therapeutics*, vol. 320, no. 3, pp. 1163–1170, 2007.
- [38] N. Quintão, G. da Silva, C. Antonialli, L. Rocha, V. Filho, and J. Ciccio, "Chemical composition and evaluation of the anti-hypernociceptive effect of the essential oil extracted from the leaves of *ugni myricoides* on inflammatory and neuropathic models of pain in mice," *Planta Medica*, vol. 76, no. 13, pp. 1411–1418, 2010.
- [39] X.-J. Li, Y.-J. Yang, Y.-S. Li, W. K. Zhang, and H.-B. Tang, " $\alpha$ -Pinene, linalool, and 1-octanol contribute to the topical anti-inflammatory and analgesic activities of frankincense by inhibiting COX-2," *Journal of Ethnopharmacology*, vol. 179, pp. 22–26, 2016.
- [40] M. Khoshnazar, M. R. Bigdeli, S. Parvardeh, and R. Pouriran, "Attenuating effect of  $\alpha$ -pinene on neurobehavioural deficit, oxidative damage and inflammatory response following focal ischaemic stroke in rat," *Journal of Pharmacy and Pharmacology*, vol. 71, no. 11, pp. 1725–1733, 2019.
- [41] P. A. Batista, M. F. de Paula Werner, E. C. Oliveira et al., "The antinociceptive effect of (-)-linalool in models of chronic inflammatory and neuropathic hypersensitivity in mice," *The Journal of Pain*, vol. 11, no. 11, pp. 1222–1229, 2010.
- [42] A. T. Peana, P. S. D'Aquila, F. Panin, G. Serra, P. Pippia, and M. D. L. Moretti, "Anti-inflammatory activity of linalool and linalyl acetate constituents of essential oils," *Phytomedicine*, vol. 9, no. 8, pp. 721–726, 2002.
- [43] K. G. Woon, J. H. Kyung, K. Do Yeon, and C. S. Hyun, "Beneficial effects of carvacrol on insulin resistance in high fat diet-induced diabetic mice," in *Proceedings of the Fall General Meeting and Academic Conference 2013*, p. 281, San Francisco, CA, USA, October 2013.
- [44] M. Ezhumalai, T. Radhiga, and K. V. Pugalendi, "Anti-hyperglycemic effect of carvacrol in combination with rosiglitazone in high-fat diet-induced type 2 diabetic C57BL/6J mice," *Molecular and Cellular Biochemistry*, vol. 385, no. 1–2, pp. 23–31, 2014.
- [45] S. Govindaraju and P. I. Arulselvi, "Characterization of coleus aromaticus essential oil and its major constituent carvacrol for in vitro antidiabetic and antiproliferative activities," *Journal of Herbs, Spices & Medicinal Plants*, vol. 24, no. 1, pp. 37–51, 2018.
- [46] J. Wang, X. Hu, W. Ai et al., "Phytol increases adipocyte number and glucose tolerance through activation of PI3K/Akt signaling pathway in mice fed high-fat and high-fructose diet," *Biochemical and Biophysical Research Communications*, vol. 489, no. 4, pp. 432–438, 2017.
- [47] R. Murali and R. Saravanan, "Antidiabetic effect of d-limonene, a monoterpene in streptozotocin-induced diabetic rats," *Biomedicine & Preventive Nutrition*, vol. 2, no. 4, pp. 269–275, 2012.
- [48] L. Jing, Y. Zhang, S. Fan et al., "Preventive and ameliorating effects of citrus d-limonene on dyslipidemia and hyperglycemia in mice with high-fat diet-induced obesity," *European Journal of Pharmacology*, vol. 715, no. 1–3, pp. 46–55, 2013.
- [49] I. Soundharrajan, D. H. Kim, S. Srisesharam, P. Kuppasamy, R. Sivanesan, and K. C. Choi, "Limonene promotes osteoblast differentiation and 2-deoxy- d -glucose uptake through p38MAPK and Akt signaling pathways in C2C12 skeletal muscle cells," *Phytomedicine*, vol. 45, pp. 41–48, 2018.
- [50] I. Soundharrajan, D. H. Kim, S. Srisesharam, P. Kuppasamy, and K. C. Choi, "R-limonene enhances differentiation and 2-Deoxy-D-Glucose uptake in 3t3-l1 preadipocytes by activating the akt signaling pathway," *Evidence-Based Complementary and Alternative Medicine*, vol. 2018, pp. 1–10, 2018.
- [51] T. A. More, B. R. Kulkarni, M. L. Nalawade, and A. U. Arvindekar, "Antidiabetic activity of linalool and limonene in streptozotocin- induced diabetic rat: a combinatorial therapy approach," *International Journal of Pharmacy and Pharmaceutical Sciences*, vol. 6, no. 8, p. 6, 2014.
- [52] B. Deepa and C. V. Anuradha, "Linalool, a plant derived monoterpene alcohol, rescues kidney from diabetes-induced

- nephropathic changes via blood glucose reduction,” *Diabetologia Croatica*, vol. 17, 2011.
- [53] S. Saravanan and L. Pari, “Role of thymol on hyperglycemia and hyperlipidemia in high fat diet-induced type 2 diabetic C57BL/6J mice,” *European Journal of Pharmacology*, vol. 761, pp. 279–287, 2015.
- [54] A. Saadat Brujeni, “Thymol effect on the expression of Mafa and Pdx1 genes in streptozotocin-induced diabetic rats,” *Razi Journal of Medical Sciences*, vol. 26, no. 10, 2019.
- [55] K. Hąc-Wydro, M. Flasiński, and K. Romańczuk, “Essential oils as food eco-preservatives: model system studies on the effect of temperature on limonene antibacterial activity,” *Food Chemistry*, vol. 235, pp. 127–135, 2017.
- [56] W. Churklam, S. Chaturongakul, B. Ngamwongsatit, and R. Aunpad, “The mechanisms of action of carvacrol and its synergism with nisin against *Listeria monocytogenes* on sliced bologna sausage,” *Food Control*, vol. 108, Article ID 106864, 2020.
- [57] A. Duarte, Â. Luís, M. Oleastro, and F. C. Domingues, “Antioxidant properties of coriander essential oil and linalool and their potential to control *Campylobacter* spp.,” *Food Control*, vol. 61, pp. 115–122, 2016.
- [58] K. Rhayour, T. Bouchikhi, A. Tantaoui-Elaraki, K. Sendide, and A. Remmal, “The mechanism of bactericidal action of oregano and clove essential oils and of their phenolic major components *onescherichia coli* and *bacillus subtilis*,” *Journal of Essential Oil Research*, vol. 15, no. 4, pp. 286–292, 2003.
- [59] M. K. Swamy, M. S. Akhtar, and U. R. Sinniah, “Antimicrobial properties of plant essential oils against human pathogens and their mode of action: an updated review,” *Evidence-based Complementary and Alternative Medicine*, vol. 2016, Article ID 3012462, 2016.
- [60] X. Liu, J. Cai, H. Chen et al., “Antibacterial activity and mechanism of linalool against *Pseudomonas aeruginosa*,” *Microbial Pathogenesis*, vol. 141, Article ID 103980, 2020.
- [61] Z. Zhang, F. Vriesekoop, Q. Yuan, and H. Liang, “Effects of nisin on the antimicrobial activity of d-limonene and its nanoemulsion,” *Food Chemistry*, vol. 150, pp. 307–312, 2014.
- [62] J. Baranauskaite, A. Kubiliene, M. Marksa et al., “The influence of different oregano species on the antioxidant activity determined using HPLC postcolumn DPPH method and anticancer activity of carvacrol and rosmarinic acid,” *BioMed Research International*, vol. 2017, Article ID 1681392, 2017.
- [63] M. T. Islam, A. B. R. Khalipha, R. Bagchi et al., “Anticancer activity of thymol: a literature-based review and docking study with Emphasis on its anticancer mechanisms,” *IUBMB Life*, vol. 71, no. 1, pp. 9–19, 2019.
- [64] K. C. Sekhar, A. Rajanikanth, M. N. Bobby, and J. R. Kanala, “A review on anticancer potential of natural drugs: hispolon and limonene,” *International Journal of Current Microbiology and Applied Sciences*, vol. 7, no. 11, pp. 3253–3263, 2018.
- [65] K. Fan, X. Li, Y. Cao et al., “Carvacrol inhibits proliferation and induces apoptosis in human colon cancer cells,” *Anti-Cancer Drugs*, vol. 26, no. 8, pp. 813–823, 2015.