Origanum compactum Benth: A Review on Phytochemistry and Pharmacological Properties

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Abstract

Origanum compactum Benth (O. compactum) is an important aromatic and medicinal plant in Morocco. It is used as a culinary condiment and largely employed in popular medicine for the treatment of ailments. Several studies recently conducted have demonstrated that O. compactum possesses antimicrobial, antifungal, antioxidant, antibacterial, anti-mutagenic, cytotoxic, anticancer, and anti-corrosion activities. Phytochemical investigations of this genus have resulted in the extraction of a number of important bioactive compounds. This emphasizes the need for extensive study for reporting the additional information on mechanism of action of these effects.

Keywords: Essential oil; Extracts; Pharmacological properties; Origanum compactum

Introduction

Oregano is the common name for the aroma and taste that comes primarily from more than 60 species of plants used worldwide as a spice. The genus Origanum (Lamiaceae) includes 39 species widely distributed in the Mediterranean region [1]. These plants are perennial herbs spontaneously growing in calcareous substrates. Oregano characterize by the presence of glandular trichomes covering the aerial organs. The glandular trichoma secrete essential oils with a unique flavor, which is mainly due to its major compounds such as carvacrol, thymol and so on.

Lamiaceae family is represented in Morocco by 30 genera and 225 species (more than 90 are endemics). These species give a great ecological and economic interest. In effect, it offers many medicinal and aromatic plant species [2]. The genus Origanum is represented by five species (three are endemic), including O. compactum. Throughout Morocco, oregano, known locally as “Zaatar” and corresponding to the species O. compactum, is traditionally considered biggest species for health.

Many scientific studies have been conducted to examine and justify the practices associated with Zaatar. In effect, these studies have demonstrated that essential oils and extracts from this species have many biological activities as antimicrobial, antioxidant, cytotoxic, antitumoral, anti-corrosion, etc. This review details the morphology, distribution and systemic classification of O. compactum, its health beneficials, phytoconstituents of O. compactum and a detailed up-to-date literature survey of various research findings related to its ethnopharmacological property.

Classification, Description, Distribution and Traditional Use

Botanically known as O. compactum Benth. and commonly as Zaatar, is the sacred plant of Morocco and is also known by various names as Zaatar, Sahtar. The plant is known in English as Oregano. O. compactum is perhaps the most common and the most revered of all household plants in Morocco. This aromatic shrub belongs to the family Lamiaceae and genus of Origanum.

Kingdom: Plantae

Division: Magnoliophyta
Class: Magnoliopsida
Order: Lamiales
Family: Lamiaceae
Genus: Origanum
Species: Compactum
Binomial name: Origanum compactum

Description

O. compactum belongs to the compactum section where successive verticillasters are reconciled fake ears contracted terminal, short and globular (spicaste). It is a perennial, chamephyte generally pubescent, hairy stems, covered with long hair (3 mm) (Figure 1). The stem leaves are oval-ovoid, large, up to 35 mm, clearly stalked (2-8 mm). Hairless leaves, more than underside upper side margins hair long hair (3 mm). The inflorescences are in dense spikes and short, very purple, large flowers opposite (5-12 mm), sessile. The calyx is usually hairless, 3-4 mm long, 5 subequal triangular teeth (0.5-1 mm). The exote corolla covered with very fine hairs (<0.1 mm). The floral bracts are lanceolate ovales ovoides-not membranous, stiff, leathery, sessile, truncate base, 6-8 mm long, glabrous on 2 sides, with inconspicuous glands, higher margin (top edge) ciliote (eyelashes 0.2-0.5 mm). The floral bracts overlap each other from the base to the top of the ear and hide calices [3].

The principal morphological characteristic of this species is the presence of secretary organ (glandular and non glandular trichomes). This structure secretes essential oils with a unique flavor, which is...
mainly due to its major compounds such as carvacrol, thymol, and so on (Figure 2) [4,5].

Distribution

Biogeographically *O. compactum* is found in Morocco (grows in Rif, Tangier, Morocco central-northern, north western Morocco, west of southern Morocco, the Haouz, the Haut atlas and south of the Iberian Peninsula [6], South-West Spain and North Africa [7]. It is a perennial herb spontaneously growing in forests, calcareous substrates, bushes and rocky pastures of the plains and low mountains. Flowering occurs in May-July [2].

Traditional Application

Oregano has been used a long time by Morocco population for medicinal properties and food preparation purposes. This application is no wide because of its bitterness, despite the pleasant odor. The taste is very intense, quite unpleasant and strongly bitter, so its culinary application is limited to the region of origin, such as Morocco. It is mainly used as a culinary condiment and largely employed in popular medicine for the treatment of ailments such as dysentery, colitis, bronco-pulmonary, gastric acidity, and gastro-intestinal diseases [2,8,9]. *O. compactum* is also used as preservative for the melted butter (smen).

*Origanum compactum* essential oils composition

Essential oils are volatile compounds odorous found in aromatic plant [10]. The compound of essential oil are very complex and presents very promising biological agents and accepted by consumers and exploitation for potential multi-purpose use because of their relative safety [11].

This essential oil is stored in plants in special brittle secretory organ, such as glands for *O. compactum* [12]. The yield of essential oil of plants is generally depends on plant species, geographical distribution, storage organ, collection period and method of extraction. For example, the essential oil yields flower of *O. compactum* extracted by Elbably et al. [13] and Bouchra et al. [14] was respectively 2.10% and 5.4%. This difference in yield is attributed to geographical origin of plant collection.

Essential oils are hydrophobic and thus only slightly soluble in water. They are soluble in alcohol, non polar or weakly polar solvents, waxes and oils. Most essential oils are colorless or pale yellow, liquid and has lower density than water [15]. Essential oils are complex mixtures comprising many various compounds. Chemically they are derived from terpenes and their oxygenated compounds [15].

The chemical composition of the myrtle essential oil has been described by many authors [4,5,13,14,16-22]. Compounds that have been found in myrtle oils include *b*-Myrcene, *a*-Phellandrene, *a*-Terpinene, Limonene, 1,8-Cineole, *b*-Phellandrene, *g*-Terpinene, 3-Octanone, *p*-Cymene, Terpinolene, 1-Octen-3-ol, Trans-thuyanol, Camphre, Linalol, Cis-thuyanol, Terpinene-4-ol, *b*-Caryophyllene, Pulegone, *a*-Humulene, Neral, *a*-Terpineol, Bornol, *b*-Isaboldene, *d*-Cadinene, *g*-Cadinene, *p*-Cymene-8-ol, Piperitenone, Caryophyllene, oxide, Thymol and Carvacrol.

All these Oregano essential oil compounds may be classified into three main categories: terpenes (monoterpane hydrocarbons and sesquiterpene hydrocarbons), terpénoids (oxygenated monoterpenes and oxygenated sesquiterpenes) and phenylpropanoïdes, but also intohydrocarbons and oxygenated compounds. The main compounds found are carvacrol, thymol, *p*-mecyne, and *γ*-terpenine (Table 1).

Environmental factors were considered to play a key role in the chemical composition of oregano oil. The fragrance and chemical composition of essential oils can vary depend on the geo-climatic location and growing conditions, including concentration of nutrients, temperature, humidity, soil type, day length, climate, altitude, amount of available water, etc. The chemical composition also depends on season or vegetative period of plant [5].

According to these factors, plant biosynthetic pathways can change the relative proportion of the primary oil components. These variations in chemical composition led to the notion of chemotypes, which are generally defined as a distinct population within the same species that

<table>
<thead>
<tr>
<th>Sample</th>
<th>Carvacrol (%)</th>
<th>Thymol (%)</th>
<th>p-Cymene (%)</th>
<th>γ-Terpine (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morocco</td>
<td>3.8 to 71</td>
<td>0 to 43.4</td>
<td>10.7 to 25.4</td>
<td>-</td>
<td>[16]</td>
</tr>
<tr>
<td>Rabat Morocco</td>
<td>58.1</td>
<td>9.0</td>
<td>11.4</td>
<td>7.1</td>
<td>[14]</td>
</tr>
<tr>
<td>Balkans</td>
<td>73.98</td>
<td>3.74</td>
<td>3.18</td>
<td>3.38</td>
<td>[17]</td>
</tr>
<tr>
<td>Morocco</td>
<td>22</td>
<td>19</td>
<td>-</td>
<td>23</td>
<td>[18]</td>
</tr>
<tr>
<td>Rabat Morocco</td>
<td>30.53</td>
<td>27.50</td>
<td>7.89</td>
<td>18.20</td>
<td>[4]</td>
</tr>
<tr>
<td>Morocco</td>
<td>36.46</td>
<td>29.74</td>
<td>24.31</td>
<td>1.10</td>
<td>[13]</td>
</tr>
<tr>
<td>Taounat Morocco</td>
<td>43.97</td>
<td>11.56</td>
<td>17.87</td>
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<tr>
<td>Morocco</td>
<td>58.1</td>
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<td>11.4</td>
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<tr>
<td>Rabat</td>
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<td>Morocco</td>
<td>28.5</td>
<td>19</td>
<td>-</td>
<td>-</td>
<td>[22]</td>
</tr>
<tr>
<td>Morocco</td>
<td>31.22</td>
<td>22.67</td>
<td>13</td>
<td>18.6</td>
<td>[5]</td>
</tr>
</tbody>
</table>

**Table 1:** The main compounds of *O. compactum* essential oil (%).
produces different chemical profiles for a particular class of secondary metabolites [10].

Therefore, all these biotope factors, genetic and epigenetic, influence the biochemical synthesis of essential oils in a particular plant. Thus, the same species of plant can produce a similar essential oil, but with different chemical composition and therapeutic activities. As shown, there is considerable variability in the composition of myrtle essential oil depending on multiple biotope factors, but the most important constituents of myrtle oil are carvacrol, thymol, p-mecyne, γ-terpenine.

**Origanum compactum** extracts composition

A few studies aimed to investigate the chemical composition of *O. compactum* extracts; their profile constitutes polyphenolic compounds, which are grouped in three major chemical classes—phenolic acids, tannins and flavonoids. Extraction of dried and powdered aerial parts of *oregano* yielded thymohydroquinone, betulinic acid, α-amyrin, betulin, oleanolic acid, ursolic acid, aromadendrin, 21 α-hydroxyoleanolic acid, and 21 α-hydroxysauronic acid [22].

The chemical compositions of the aerial part of *O. compactum* has been evaluated by El Babil et al. [13]. The total amount of flavonoids, in oregano ethyl acetate extract, was the highest one (54.7 ± 1.8 g/kg equivalent quercetin), while the petroleum ether extract was the richest in polyphenols (707.8 ± 13.4 g/kg eq gallic acid). The anthocyanins (5.63 ± 0.19 mg eq cyaniding/kg) were present in higher amounts in the petroleum ether extract. Tannins were found in all extracts with an amount between 12.4 (ethanol extract) to 510.3 (petroleum ether extract) eq catechin (g/kg dry wt).

**Pharmacological Activities of Origanum compactum**

**Antibacterial effect**

The problems regarding application of conventional antibiotics, including antimicrobial resistance, environmental problems, cancerogeneity, side effects and high costs, have reinforced a tendency to replace synthetic antimicrobials with natural alternative agents [23]. Plant based products are among the alternative agents examined in order to replace conventional antibiotics. Accordingly, extensive research has been carried out in order to evaluate the antimicrobial effect of the essential oils and extracts which showed the ability to inhibit the growth of various pathogenic microorganisms [24].

The antibacterial properties of *O. compactum* essential oils and extracts against pathogenic bacteria were reported in many studies and obtained results are promising [19]. indicated antibacterial effect of Oregano flowers, leaves and stems essential oil against five of pathogenic bacteria of salmonella sp isolated from food borne.

Essential oil of *O. compactum* was tested against six Gram positive (*Staphylococcus aureus*, *Listeria monocytogenes* serovar 4b, *Listeria innocua* and *Enterococcus faecium*) and 4 Gram negative bacteria (*Escherichia coli* K12, *Escherichia coli* serovar O157:H7, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens* and *Bacillus subtilis*), and inhibited the growth of all tested bacteria MICs range from 0.0078 for *S. aureus* (MBLA) to over >1 ml/ml for *P. aeruginosa* [4].

**Mode of antibacterial action:** Different modes of action are involved in the antimicrobial activity of essential oils and extracts. Because of the variability of quantity and chemical profiles of the essential oil and extract components, it is likely that their antimicrobial activity is not due to a single mechanism. It is considered that these components have several sites of action at the cellular level. Generally, there are six possible mechanisms of antimicrobial action, which include: (1) disintegration of cytoplasmic membrane, (2) interaction with membrane proteins (ATPases and others), (3) disturbance of the outer membrane of gram negative bacteria with the release of lipopolysaccharides, (4) destabilization of the proton motive force with leakage of ions, (5) coagulation of the cell content, and (6) inhibition of enzymes synthesis.

The mechanism of antibacterial action seems to have a relationship with a great number of complex constituents in Eos and extracts instead of just specific bioactive metabolites, which may result in different action modes and difficult identification from molecular point of view [24,25].

Carvacrol (main compound of Origano oil) has been demonstrated able to destabilize the cytoplasmic membrane and acts as a proton exchanger, thereby reducing the pH gradient across the cytoplasmic membrane. The resulting collapse of the proton motive force and depletion of the ATP pool eventually lead to cell death [26].

*O. compactum* essential oil showed a strong antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. This activity may be associated with the presence of carvacrol and thymol, which is the major component of the oil. The mechanism of action is related with the capacity of *O. compactum* essential oil to induce leakage of intracellular K+ from cells, induce alterations of membrane potential and induce alterations in the bacterial membrane. These alterations led to the loss of membrane-selective permeability and thus the inhibition of respiratory activity, and also the loss of other essential enzymatic activities, all these changes led to cell death [27].

**Antibacterial action of carvacrol and thymol:** The compounds of phenolic structures, such as carvacrol and thymol presented as the main compounds (chemotypes) of OCEO, are highly active against several pathogenic bacteria. These compounds have been reported to be bacteriostatic or bactericidal agents, depending on the concentration used [28]. These compounds are highly active despite their relatively low capacity to dissolve in water [29-32]. In general, the EO having the most important antibacterial properties contain a high percentage of phenolic compounds such as carvacrol [34] and thymol [34-36].

Their mechanism of action is related to the capacity of these compounds in the disruption of the cell membrane, movement of protons, the flow of electrons, active transportation and the coagulation of the cell content [37,38].

Furthermore, carvacrol destabilizes the cytoplasmic membrane and also acts as a proton exchanger, thereby reducing the pH gradient across the cytoplasmic membrane. The collapse of the force protons movement and resulting depletion of ATP pool lead to cell death [39].

The importance of the presence of the hydroxyl group in the phenolic compounds such as carvacrol and thymol was confirmed [40,41]. The relative position of the hydroxyl group on the phenol ring does not appear to strongly influence the level of antibacterial activity. Indeed, the action of thymol against *Bacillus cereus*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* appears to be comparable to that of carvacrol [36,41]. However, in a study on the effects of carvacrol and thymol, it was shown that they act differently against Gram-positive and Gram-negative species [40].

Carvacrol and thymol are able to disintegrate the outer membrane of Gram negative bacteria, releasing lipopolysaccharides (LPS) and inducing the increase in the permeability of the cytoplasmic membrane toward ATP [36].
On other hand, studies of *B. cereus* showed that carvacrol interacts with the cell membrane, which it dissolves in the phospholipid bilayer and fit between the fatty acid chains [41]. This distortion of the physical structure lead to the expansion and destabilization of the membrane, increased membrane fluidity which and consequently increase the passive permeability [41].

**Antifungal activity**

The management of fungal infections possesses many problems, including a limited number of antifungal drugs, toxicity, and resistance to commonly used antifungal drugs, relapse of infections and the high costs. For that, it is very important and necessary to discover new antifungal agents to combat the strains expressing resistance to the available antifungal drugs. One of natural products used as therapeutic agent against fungi is Oregano, e.g., its essential oils and extracts. Considerable Oregano petroleum ether, hexane, chloroform and methanol extract activity were estimated by Fadel et al. against *penicillium digitatum* [42].

The petroleum ether extracts of *O. compactum* were highly active against the mycelial growth of *P. digitatum*. The effectiveness of petroleum ether extract might be due to its high levels of carvacrol, p-cymène, thymol and terpinene [14], the antifungal activity of carvacrol, the main compound of lamiaceae essential oil has been the subject of several studies [43].

The methanol 80% extracts of *O. compactum* aerial parts were also highly effective against *P. digitatum* mycelial growth. It was demonstrated that the mechanism of toxicity of total phenols against the fungi is based on the inactivation of the fungal enzymes which contain the SH group in their active sites classified the pure compounds according to their antifungal activity towards seven fungi, this activity decreases according to the type of chemical functions of compound: phenols>alcohols>aldehydes>acetones>ethers>hydrocarbures [14].

The antifungal activity of Oregano essential oil was tested against *Botrytis cinere* and the inhibition was IC$_{50}$=35.1 ppm). While the antifungal effect of carvacrol and thymol, the main compound of Oregano essential oil, was IC$_{50}$=18.6 ppm and IC$_{50}$=18.9 ppm against the same species respectively [14]. The Oregano antifungal effect may also be attributed to essential oil and phenolic compounds that are known to cause cell membranes damage, causing leakage of cellular materials and ultimately the microorganism death [44]. The antimicrobial, e.g., antifungal property of myrtle is suspected to be associated with their high contents of polyphenols and oxygenated monoterpenes.

**Antioxidant activity**

Antioxidants are compounds that react with free radicals, neutralizing them and thereby preventing or reducing their damaging effects in the human body [45]. Lipid oxidation is also responsible of deterioration of fats and oils resulting in change of color, flavor and nutritive value, while oxidative stress is involved in the pathogenesis of numerous diseases [46]. In order to prevent oxidation, the addition of either synthetic or natural antioxidants to fats, fatty foods and cosmetics is a common practice. Because of its carcinogenicity, synthetic antioxidants used in products for human application are being restricted, considerably increasing interest in antioxidants of natural origin [47].

Aromatic and medicinal plants, such as myrtle, are source of natural antioxidants because of the activity of secondary metabolites, such as phenylpropanoids and essential oils. Essential oils and extracts have been used for food preservation, pharmaceuticals, alternative medicine and natural therapies [24]. As demonstrated in several studies, the antioxidant activity of plant extracts is strongly related to phenolic content [48]. This activity is not a property of a single phenolic compound, but it is widely distributed among the phenolic phytochemical constituents. Particularly anthocyanins, flavonoids and phenolic acids seem to be responsible for the antioxidant capacity. Several methods are used to evaluate the antioxidant activity, and the obtained results depending on which method is used.

Several studies demonstrate the antioxidant activities of organic extracts and essential of *O. compactum*. In effect, Bouhid et al. have evaluated the antioxidant activity of Oregano essential oils by three main methods: reducing power, DPPH free radical scavenging assay and b-Carotene-linoleic acid assay. The results of this study revealed evidence that the essential oil of *O. compactum* possesses a good antioxidant effect with three assays used. This antioxidant capacity was depending on the oil concentration and was attributed to the phenolic compounds present in the oil [4]. On other hand, Elbabili et al. have evaluated the antioxidant activity of Oregano essential oil, Ethyl acetate, Petroleum ether, Ethanol extract and decoction using ABTS (acid 2,2’-azino-bis(3-ethylbenz-thiazoline-6-sulfonique) radical-scavenging assay and DPPH (1,1-diphényl-2-picrylhydrazil) free radical scavenging [13]. The results showed that the essential oil showed a higher antioxidant activity with an IC$_{50}$=2 ± 0.1 mg/L. Among the extracts, the aqueous extract had the highest antioxidant activity with an IC$_{50}$=4.8 ± 0.2 mg/L (DPPH assay). As demonstrated in several studies, the antioxidant capacity of plant extracts is strongly related to phenolic content [48].

The antioxidant activity of the phenolic compounds was attributed to its redox properties, which allow them to act as reducing agents, hydrogen donors, singlet oxygen quenchers and metal chelators [49]. Many in vitro studies indicate that phenolic compound like flavonoids and phenolic acid can have considerable antioxidant activity and this activity critically depends on the number and position of phenolic hydroxyls in the aromatic ring moieties [50].

Nowadays, the interest in naturally occurring antioxidants has considerably increased, because of their potential application in food, cosmetic and pharmaceutical products, in order to replace synthetic carcinogens, and thus restricted antioxidants [46]. In addition, oligomeric proanthocyanidins, which are mainly used in vascular diseases, have an ability to trap lipid peroxides and free radicals, as well as non-competitively inhibit xanthine oxidase, which is a major generator of free radical [51].

**Cytotoxicity**

Some studies have evaluated the cytotoxicity of Oregano extracts on human cell line. Elbabili et al. showed an activity against human breast cancer cells (MCF7) of the ethyl acetate extract (IC$_{50}$=30 mg/L) and ethanol extract (IC$_{50}$=56 mg/L). While, the petroleum ether extract and essential oil were inactive (IC$_{50}$= >100 (mg/L) [13]. Another study carried out by Chaouki et al. have shown that ethyl acetate extract of *O. compactum* had a cytotoxic effect on human breast tumor MCF-7 cells. In additionally, the same extract had a cytotoxic effect on human A549 lung cancer and SMMC-7721 hepatoma cell lines by a (IC$_{50}$=198 ± 12 μg/ml) and (IC$_{50}$=266 ± 14 μg/ml) [52].

**Anticancer activity**

Some studies recently conducted have demonstrated the antitumor activity of *O. compactum* against human cancer cell lines [52,53]. The
characterization of the mechanisms involved in this effect demonstrated that this extract was an apoptosis inducer in both cell lines tested. This apoptosis induction in A549 cells was directed by activation caspase signaling triggered via modulation of Bcl-2 family proteins [53].

The main compounds of O. compactum essential oil were studied for their anticancer investigation. Thymol was found to be associated with cell death of many types of cell line of melanoma [54,55], osteosarcoma [56], glioblastoma [57], breast cancer [13], leukemia [58], hepatoma, lung cancer and colon cancer [59].

This action was almost related with DNA strand breaks and cell cycle block in G0/G1 phase [58]. Carvacrol is an isomer of thymol and it is widely found in O. compactum essential oil. It shows also a similar activity than thymol against several cancers including liver, colon, and lung [59].

Anti-mutagenic activity

Carvacrol, the major component of oregano essential oil showed antimutagenic activity [60], which seems to be mainly linked to the induction of mitochondrial dysfunction [61].

Insecticidal activity

More recently, the essential oil of Oregano showed strong insecticidal activity against larvae of Spodoptera littoralis with an LD₅₀ ≤ 0.05 ml/larva [62].

Conclusion

O. compactum is used for various medicinal properties. The extract of the different parts of the plant shows various activities like antioxidant, antimicrobial, anticancer, insecticidal and anti-mutagenic activity. This review further highlights the discovered pharmacological effects and phytochemical details of O. compactum which provide way to further studies and research.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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