Pharmacological activities and medicinal properties of endemic Moroccan medicinal plant *Origanum compactum* (Benth) and their main compounds

Abdelhakim Bouyahya1,2†, Fatima-Ezzahrae Guaouguaou1, Nadia Dakka1, Youssef Bakri1

1Laboratory of Human Pathologies Biology, Department of Biology, Faculty of Sciences, and Genomic Center of Human Pathologies, Mohammed V University, Rabat, Morocco
2Biology and Health Laboratory, Department of Biology, Faculty of Science, Abdelmalek Essaadi University, Tetouan, Morocco

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ABSTRACT

Oregano (*Origanum compactum* Benth. (*O. compactum*), Lamiaceae) is an endemic Moroccan medicinal herb. It is used traditionally to fight against several disorders such as diarrhea, urethritis, hypertension, diabetes, and inflammation. A large number of components have been identified and isolated from the essential oil of this plant. Carvacrol, thymol, p-cymene and γ-Terpinene are among the more compounds presented in *O. compactum* essential oil and considered to be the main biologically active components. Numerous experimental studies showed that *O. compactum* organic extracts, essentials oil and its major compounds possess a broader spectrum of pharmacological and therapeutic activities such as antibacterial, antifungal, antioxidants, and anticancer activity. The present review attempts to give an overview of pharmacological studies of *O. compactum* and its major compounds.

1. Introduction

The man was always depending on the nature to live and survive. He had used products from different sources to fight against illnesses. Among these sources, we found aromatic and medicinal plants which have been used since ancient times for centuries as remedies for human diseases because of their vast biosynthetic capacity[1]. They are rich in a wide variety of secondary metabolites such as tannins, terpenoids, alkaloids and flavonoids with known therapeutic properties[2]. Actually, there are a growing number of studies for the biological effects of active compounds produced by medicinal plants during secondary metabolism.

The biosynthesis of secondary metabolites of medicinal plants is depending on geographical location, climate and environmental conditions in which a medicinal plant is growing[3,4]. The change of these parameters can totally induce gene expression and subsequently change metabolites compounds. Morocco, by its Mediterranean climate, is rich in vegetation including a spectrum of medicinal and aromatic plants.

Among the most medicinal plant mostly found in Morocco, we find oregano (*Origanum compactum* Benth. (*O. compactum*)). Oregano is an endemic Moroccan medicinal plant which has widely been used by Moroccan population for its culinary and medicinal properties since antiquity[5,6]. Today, several studies have been conducted through Morocco areas for screening of pharmacological properties of *O. compactum* essential oils and extracts[7-12]. Therefore, this review presents an overview of the results found about phytochemical and pharmacological applications of *O. compactum* and its major compounds.

2. Overview on *O. compactum*

*O. compactum* (Figure 1) belongs to the family Lamiaceae and genus *Origanum* which is divided into 38 species, 6 subspecies and 18 hybrids that are mostly distributed in North Africa and Eurasia[13,14]. It is known in English as oregano and in Morocco it is known by its various vernaculars names such as “Zaatar” and “Sahtar” depending of areas. It is a perennial plant (chamaephyte) and has generally pubescent stems and covered with hairs. Oregano leaves are hairy especially in its lower faces and hair margins of long hairs. The inflorescences are dense spikes and short, very purple, large flowers and considered to be the main biologically active compounds. Numerous experimental studies showed that *O. compactum* organic extracts, essentials oil and its major compounds possess a broader spectrum of pharmacological and therapeutic activities such as antibacterial, antifungal, antioxidants, and anticancer activity. The present review attempts to give an overview of pharmacological studies of *O. compactum* and its major compounds.
to the top of the ear and hide chalices[16]. The principal morphological characteristic of this species is the presence of secretary organ which synthesis and secretes essential oils.

Figure 1. *O. compactum* collected from different geographical location at different pheno logical stages. 1 and 2: Vegetative stage; 3 and 4: Flowering stage; 5 and 6: Post-flowering stage.

Oregano with compact flowers is an endemic species from Morocco and Southern Spain (Southern Andalusia). In Morocco, *O. compactum* grows in the Rif, Tangerois, Central Northern Morocco, North-western Morocco, South-western Morocco, Haus, the High Atlas and the south of the Iberian Peninsula [Spain][3]. It grows naturally on dry rocky terrain (Figure 1), and sometimes grows between trees and shrubs and flowers from June to August. It is widespread in forests, plain and low mountains, rather limestone, on well-drained soil, up to 700 m above sea level. It is found in semi-arid and subhumid bioclimatic areas and with warm and fresh bioclimatic variants on floors of thermomediterranean and mesomediterranean vegetation[17].

3. Ethnomedical uses of *O. compactum*

Traditional herbal medicine is a discipline that studies the relationships that link humans to so-called medicinal plants. In the countries of the whole world and elsewhere in Morocco, this dictatorship has been widely applied since antiquity. Thanks to its rich Mediterranean climate, which offers an important plant biodiversity, Morocco has always used medicinal plants to treat certain pathologies. Indeed, several medicinal plants are constituted a therapeutic source for the Moroccan population. By the most widely used medicinal plants in Morocco, *O. compactum* is found at the most of these species. It is a plant considered a real drug in Morocco and it is applied against several pathologies with a spectrum of use which varies between the regions regarding to the pathologies, the parts used and the mode of preparation (Table 1). The aerial parts of this plant have been used for a long time against lung and gastrointestinal infections. The aerial part is used in Morocco in decoction or infusion as spasmyloytic and sedative in the region of Ksar Kbir[28] and Zaër[26]. Leaves and stems are used in infusion and decoction against pathologies of the digestive system, cardiac diseases and sometimes against diabetes[20,21]. It is also used against constipation and bile acid pathologies as well as for increased appetite[24]. *O. compactum* leaves have been found various applications across Moroccan regions. They are prepared in decoction and/or infusion and administered orally against several pathologies such as diabetes[5,6,18], inflammation[19], hypertension[5,6], against pyelonephritis and cystitis[23], stomachic, febrifuge, against cooling and respiratory diseases[22].

4. Chemical compounds of *O. compactum*

4.1. Phenolic compounds

Polyphenolic compounds such as tannins, flavonoids, lignans and others phenylpropanoids derivates are biosynthesized from phenylalalnine or tyrosine pathways by medicinal and aromatic plants[30,31]. Their phenol group gives them several biological properties such as antioxidant[32-35], anticancer[36], antimicrobial[37].

| Region | Part used | Mode of preparation | Traditional use | References |
|--------|-----------|---------------------|-----------------|------------|
| South-east Morocco (Tafilalet) | Leaves | nd | Diabetes | [18] |
| Fez-Boulemane, Meknes-Tafilalet, Marrakech-Tensift-El Haouz and Tanger-Tetouan region (Morocco) | Leaves | Infusion | Inflammation | [19] |
| Taounate province (Northern Morocco) | Leaves and stem | Infusion | Heart and intestinal pains | [20] |
| Oriental Morocco | Leaves and stem | Decoction, infusion and poudre | Pathologies of the digestive system, cold problems and diabetes | [21] |
| Oriental Morocco | Leaves | nd | Diabetes and hypertension | [5] |
| North centre region of Morocco (Fez-Boulemane) | Leaves | nd | Diabetes and hypertension | [6] |
| Haut Atlas oriental (Haute Moulaya) (Morocco) | Leaves | Decoction | Stomachic, febrifuge, against cooling and respiratory diseases | [22] |
| City of Tan-Tan (Sahara Moroccan) | Leaves | Infusion | Urolithiasis | [23] |
| Province of Settat (Morocco) | Leaves and stem | Infusion | Aerophagia, colitis, cellulites, constipation, painful periods and to increase appetite | [24] |
| City of Khenifra (Morocco) | Leaves and stem | Decoction | Bronchopulmonary, mouth, gastrointestinal and biliary disorders | [24] |
| Region of Zaïr (Morocco) | Aerial part | Infusion or decoction | Against cooling and diarreha disorders | [25] |
| North west of Morocco | Leaves and inflorescence | Infusion or decoction | Digestive and bronchial disorders | [26] |
| Ksar Lakbir district (North west of Morocco) | Aerial part | Infusion | Hypertension and diabetes | [27] |
| Ouazzane (North west of Morocco) | Flowering top | Decoction | Against stomach disorders and febrifuge | [29] |

nd: Not determined.
41 and litholytic activity[42,43]. A few studies have been investigating the chemical composition of *O. compactum* essential oils. Then, phenolic compounds have not yet been determined exactly. El Babili et al. have determined the total phenols, flavonoids, tannins and anthocyanins of *O. compactum* ethyl acetate, petroleum ether, ethanol and decoction extracts[44]. The petroleum ether extract possesses the highest level of polyphenols (707.8 ± 13.4 mg equivalent gallic acid), tannins (510.3 ± 13.7 mg equivalents catechin), and anthocyanins (5.63 ± 0.19 mg equivalent cyanidin) than others extracts. While, ethyl acetate and decoction extracts have possessed the most flavonoids content at (54.7 ± 1.8) and (52.9 ± 1.6) mg equivalent quercetin, respectively. In other early study, researchers have found the present of the phenols, flavans, flavonoids, leucoanthocyanins, saponins sterols and terpenoids[45]. Some chemical molecules have been identified from *O. compactum* extracts, including thymohydroquinone, betulinic acid, β-amyrin, betulin, oleanolic acid, ursolic acid, aromadendrin, 21 α-hydroxyoleanolic acid and 21 α-hydroxyursolic acid[46].

### 4.2. Essential oils

From a biological point of view, essential oils are substances obtained from a plant material by extraction procedures such as steam distillation, hydro-distillation, dry distillation and mechanical extraction from the epicarp of certain plants such as citrus. From the biochemical point of view, essential oils are complex mixtures of natural compounds with various organic structures (except the fatty substances contained in vegetable oils)[47]. The word oil is attributed to its hydrophobic character and to its solubilizing properties in fats, whereas the essential word reflects the distinctive odor emitted by the producing plant.

Essential oils are biometabolized by so-called aromatic plants as secondary metabolites and usually have the characteristic odor of the producing plant. The chemical composition of an essential oil is formed essentially of terpenic compounds and their oxygenated derivatives[38]. Essential oils possesses numerous pharmacological properties such as antibacterial, antitumor, antioxidant, antifungal and anti-inflammatory[47-49].

*O. compactum* has a special structure which synthesizes and secretes essential oils. The yield of this oil is depending on part of plant used, the area of collection and method of extraction used. Several studies have been focused on the chemical composition of *O. compactum* essential oil[3,4,50]. This oil is rich in terpenic and phenolic compounds such as α-thujene, myrcene, α-terpinene, p-cymene, γ-terpinene, cis-sabinene hydrate, linalool, α-terpinol, carvaeryl methyl oxide, thymol, carvacrol, and (E)-β-caryophyllene[4,44].

There are four main compounds presents in *O. compactum* essential oils, viz. carvacrol, thymol, p-cymene and γ-terpinene. The content of these molecules in oregano oil is varied depending on the area of collection, phonological stage of plant and storage condition of oils. Table 2 summarizes fluctuations of percentage content of each of these molecules in oregano oil through Morocco regions[3,4]. It is seen clearly that carvacrol and thymol always present with high proportion, while γ-terpinene and p-cymene present with low proportion.

#### 5. Pharmacological properties

*In vitro* studies on revealed that the extracts, essential oils and their derivatives extracted from *O. compactum* showed several biological activities such as antibacterial, antioxidant, antitumor and antifungal. These activities are due the presence of bioactive components such as phenolic and terpenic group.

#### 5.1. Antibacterial properties

Antibiotics have been a revolution in medicine since their first appeared. However, the co-evolution of the microorganisms on the one hand and the misuse of these antibiotics on the other hand were led to the appearance of resistant or even multiresistant forms against these antibiotics[38]. Natural products from medicinal plants have been able to overcome the challenge of antibiotics[32,36,40,41]. *O. compactum* has proved its candidacy in the inhibition of bacteria pathogenic strains including those which resist to antibiotics[50]. Several accumulative studies (Table 3) have revealed the antibacterial activity of *O. compactum* extracts and essential oils[8,10,50,56,61,62]. Indeed, essential oils inhibited the growth of Gram-negative bacteria

### Table 2: Main chemical compounds of *O. compactum* essential oils.

| Sample                  | Carvacrol (≥ %) | Thymol (≥ %) | p-cymene (≥ %) | γ-terpinene (≥ %) | References |
|-------------------------|----------------|--------------|----------------|------------------|------------|
| Morocco                 | 3.80–71.00     | 0.00–43.40   | 10.70–25.40    | –                | [51]       |
| Rabat Morocco           | 58.10          | 9.00         | 11.40          | 7.10             | [52]       |
| Morocco                 | 22.00          | 19.00        | –              | 23.00            | [53]       |
| Tetouan Morocco         | 30.53          | 27.50        | 7.89           | 18.20            | [50]       |
| Morocco                 | 36.46          | 29.74        | 24.31          | 1.10             | [44]       |
| Taounat Morocco         | 43.97          | 11.56        | 17.87          | 8.43             | [8]        |
| Taounate region (Morocco) | 47.85       | 15.75        | 8.44           | 17.25            | [10]       |
| Larache                 | 42.90          | 4.80         | 14.80          | 22.60            | [54]       |
| Tetouan Morocco         | 29.70          | 2.20         | 11.50          | 30.10            |            |
| Tetouan Morocco         | 6.70           | 28.30        | 11.60          | 26.70            |            |
| Morocco                 | 31.22          | 22.67        | 12.99          | 18.60            | [3]        |
| Tetouan Morocco         | 68.992         | 18.671       | 2.531          | 3.979            | [9]        |
| nd                      | 41.80          | 16.20        | 11.40          | 16.60            | [55]       |
| Pronarôm International (Ghislenhgien, Belgium) | 22.00 | 19.36 | 13.26 | 22.90 | [52] |
| Pronarôm International (Ghislenhgien, Belgium) | 46.88 | 15.26 | 13.10 | 11.61 | [7] |
| Pranarôm International (Ghislenhgien, Belgium) | 46.37 | 13.70 | 13.33 | - | [56] |
| Ouazzane (North-West Morocco) | 37.70 | 17.70 | 12.10 | - | [57] |
| Morocco                 | 49.52          | 1.57         | 21.22          | 14.21            | [58]       |
| Morocco                 | 55.90          | 0.20         | 8.60           | 15.10            | [59]       |
| Al Hoceima (Northern Morocco) | 59.10     | 9.10         | 11.70          | 1.10             | [45]       |
| nd                      | 20 ≥ % ≤ 40    | 15 ≥ % ≤ 30  | 10 ≥ % ≤ 25   | 4 ≥ % ≤ 25.5    | [60]       |

nd: Not determined.
Table 3
Pharmacological properties of *O. compactum*.

| Biological Activity | Part used | Type of extract | Main compound | Used method | Tested organism | Effects | References |
|---------------------|-----------|-----------------|---------------|-------------|----------------|---------|------------|
| Antibacterial       | Aerial part | EO               | nd            | Inhibition of bacteria strains in Baby-leaf salad Broth dilution method | *E. coli* O157:H7 | 0.5 log reductions after 5 days of storage of baby-leaf salads treated with 10% EO | 7 |
| Flowering tops      | EO        | Carvacrol Thymol γ-Terpinene p-Cymene | | | *P. aeruginosa* ATCC 27853 | MIC = 1% (v/v) | 61 |
| Flowering tops      | EO        | Carvacrol Thymol γ-Terpinene p-Cymene | | | *S. aureus* ATCC 29213 | MIC = 0.031% (v/v) | |
| Flowering plant     | EO        | Carvacrol Thymol γ-Terpinene p-Cymene | | Well diffusion and broth dilution methods | *S. aureus* MBLA | Ø = 27 mm | 50 |
| Leaves and stems    | EO        | Carvacrol Thymol γ-Terpinene p-Cymene | | Agar disc diffusion and microdilution method | *S. aureus* CECT 976 | Ø = 12 mm | |
|                     |           |                  |               |              | *S. aureus* CECT 794 | Ø = 10 mm | |
|                     |           |                  |               |              | *B. subtilis* DCM 6633 | Ø = 25 mm | |
|                     |           |                  |               |              | *Enterococcus faecium* CECT 410 | Ø = 25 mm | |
|                     |           |                  |               |              | *E. coli* K12 MBLA | Ø = 20 mm | |
|                     |           |                  |               |              | *E. coli* serovar O157:H7 CECT 4076 | Ø = 20 mm | |
|                     |           |                  |               |              | *Proteus mirabilis* IH | Ø = 32 mm | |
|                     |           |                  |               |              | *Listeria innocua* CECT 4030 | Ø = 32 mm | |
|                     |           |                  |               |              | *L. monocytogenes* serovar 4b CECT 4032 | Ø = 15.5 mm | |
|                     |           |                  |               |              | *Pseudomonas fluorescens* CECT 378 | Ø = 5 mm | |
|                     |           |                  |               |              | *P. aeruginosa* IH | Ø = 1% | |
|                     |           |                  |               |              | *P. aeruginosa* CECT 110T | Ø = 2 mm | |
|                     |           |                  |               |              | *P. aeruginosa* CECT 118 | Ø = 1 mm | |
|                     |           |                  |               |              | *Salmonella typhimurium* ATCC 14028 | Ø = 16.6 ± 0.3 mm | |
|                     |           |                  |               |              | *Salmonella typhimurium* S0584 | Ø = 24.5 ± 0.3 mm | |
|                     |           |                  |               |              | *E. coli* O157:H7 ATCC 35150 | Ø = 15.4 ± 0.2 mm | |
|                     |           |                  |               |              | *E. coli* O157:H7 S0575 | Ø = 17.5 ± 0.3 mm | |

(continued on next page)
| Biological Activity | Part used | Type of extract | Main compound | Used method | Tested organism | Effects | References |
|---------------------|-----------|----------------|---------------|-------------|----------------|---------|------------|
| Aerial part | EO | Carvacrol Thymol γ-Terpinene p-Cymene | | Disk diffusion and broth dilution methods | Staphylococcus pyogenes | Ø = 12 mm MIC = 0.75% (v/v) | [55] |
| | | | | | E. coli | EO at 0.03% or 0.06% showed an inhibitory activity against E. coli O157:H7, E. coli ATCC 25922 and E. coli cocktail during storage at 25 °C and at 7 °C in casings | [62] |
| | Leaves | EO | Carvacrol Thymol γ-Terpinene p-Cymene | | | | |
| | | | | Disc diffusion method | Salmonella spp. 1 | Ø = 30 mm MIC = 0.3125% (v/v) MBC = 0.3125% (v/v) | [8] |
| | | | | Micro broth dilution method | Salmonella spp. 2 | Ø = 30 mm MIC = 0.3125% (v/v) MBC = 0.625% (v/v) | |
| | | | | | Salmonella spp. 3 | Ø = 30 mm MIC = 0.625% (v/v) MBC = 0.625% (v/v) | |
| | | | | | Salmonella spp. 4 | Ø = 32.5 ± 2.12 mm MIC = 0.3125% (v/v) MBC = 0.3125% (v/v) | |
| | | | | | Salmonella spp. 5 | Ø = 34.5 ± 2.12 mm MIC = 0.3125% (v/v) MBC = 0.3125% (v/v) | |
| Aerial parts | EO | Carvacrol Thymol p-Cymene | | Agar disc diffusion method | S. aureus | Ø = 46.66 ± 2.88 mm MIC = 0.125% (v/v) MBC = 0.125% (v/v) | [10] |
| | | | | Microdilution method | B. subtilis | Ø = 41.66 ± 2.88 mm MIC = 0.031% (v/v) MBC = 0.062% (v/v) | |
| | | | | | E. coli | Ø = 34.33 ± 8.32 mm MIC = 0.062% (v/v) MBC = 0.125% (v/v) | |
| | | | | | P. aeruginosa | Ø = 9.00 ± 1.00 mm MIC > 4% (v/v) MBC > 4% (v/v) | |
| Methanol extract | nd | Agar well diffusion assay | E. coli K12 | | | Ø = 8.00 ± 2.4 mm | [33] |
| | | | S. aureus | | | Ø = 14.00 ± 0.75 mm | |
| | | | L. monocytogenes | | | Ø = 26.00 ± 2.00 mm | |
| | | | P. aeruginosa | | | | |
| Ethanol extract | nd | Agar well diffusion assay | E. coli K12 | | | Ø = 8.00 ± 2.40 mm | |
| | | | S. aureus | | | Ø = 14.00 ± 0.75 mm | |
| | | | L. monocytogenes | | | Ø = 26.00 ± 2.00 mm | |
| | | | P. aeruginosa | | | na | |
| n-Hexane extract | nd | Agar well diffusion assay | E. coli K12 | | | Ø = 8.00 ± 2.40 mm | |
| | | | S. aureus | | | Ø = 14.00 ± 0.75 mm | |
| | | | L. monocytogenes | | | Ø = 26.00 ± 2.00 mm | |
| | | | P. aeruginosa | | | na | |
| Ethyl acetate | nd | Agar well diffusion assay | E. coli K12 | | | Ø = 8.00 ± 2.40 mm | |
| | | | S. aureus | | | Ø = 14.00 ± 0.75 mm | |
| | | | L. monocytogenes | | | Ø = 26.00 ± 2.00 mm | |
| | | | P. aeruginosa | | | NA | |
| Antioxidant | Leaves | EO | nd | ABTS assay | | IC₅₀ = 2.0 ± 0.1 µg/mL | [44] |
| | | | DPPH assay | | IC₅₀ = 60.1 ± 3.3 µg/mL | |
| | | | | | IC₅₀ = 7.2 ± 0.3 µg/mL | |
| | | | Ethyl acetate extract | ABTS assay | | IC₅₀ = 33.9 ± 0.8 µg/mL | |
| | | | Petroleum ether extract | DPPH assay | | IC₅₀ = 17.4 ± 0.8 µg/mL | |
| | | | Ethanol extract | ABTS assay | | IC₅₀ = 99.5 ± 2.5 µg/mL | |
| | | | Decoction | DPPH assay | | IC₅₀ = 9.6 ± 0.3 µg/mL | |
| | | | | | IC₅₀ = 9.9 ± 0.3 µg/mL | |
| | | | | | IC₅₀ = 4.8 ± 0.2 µg/mL | |
| | | | | | IC₅₀ = 137.60 ± 14.26 µg/mL | [9] |
| Biological Activity | Part used               | Type of extract | Main compound | Used method                          | Tested organism                  | Effects                          | References |
|---------------------|-------------------------|-----------------|---------------|--------------------------------------|----------------------------------|----------------------------------|------------|
|                     | Flowers, leaves and stems | EO              | Carvacrol     | β-Carotene linoleic acid assay        | Human breast cancer cells        | IC₅₀ = 100 µg/mL                 | [44]       |
|                     |                         | Thymol          | p-Cymene      | DPPH assay                           | MCF7                            | IC₅₀ = 30 µg/mL                  |            |
|                     |                         | β-Carotene      | linoleic acid | TBARS assay                          |                                  |                                 |            |
|                     | Methanol extract        | nd              | DPPH assay    | IC₅₀ = 48.34 µg/mL                   |                                  |                                 | [34]       |
|                     | Ethanol extract         | n-Hexane extract| DPPH assay    | IC₅₀ = 74.25 µg/mL                   |                                  |                                 |            |
|                     | Ethyl acetate extract   | nd              | DPPH assay    | IC₅₀ = 39.83 µg/mL                   |                                  |                                 |            |
|                     |                        | nd              | DPPH assay    | IC₅₀ = 137.35 µg/mL                  |                                  |                                 |            |
| Antitumor           | Aerial part             | Ethyl acetate   | extracts      | MTT assay                            | A549 lung cancer                 | IC₅₀ = 198 ± 12 µg/mL            | [63]       |
|                     |                        | nd              | MT assy       | SMMC-7721 hepatoma cells             |                                 |                                 |            |
|                     | Methanol                | nd              | MT assay      | IC₅₀ = 275.05 ± 14.00 µg/mL          |                                 |                                 | [64]       |
|                     |                        | nd              | MTT assay     | IC₅₀ = 274.01 ± 16.00 µg/mL          |                                 |                                 |            |
| Antifungal          | Aerial aprt             | EO              | p-Cymene      | Incorporation in a solid medium assay | Botrytis cinerea                 | IC₅₀ = 35.1 ppm                  | [52]       |
|                     |                        | γ-Terpinene     | Carvacrol     | Penicillium digitatum                | P. falciparum                    | IC₅₀ = 34 µg/mL                  | [44]       |
|                     |                        | Thymol          | p-Cymene      | At 2000 ppm, inhibition = 83%        |                                 |                                 | [65]       |
|                     |                        | nd              | Incorporation in a solid medium assay| P. falciparum                    | IC₅₀ = 33 µg/mL                  |                                 |            |
|                     |                        | nd              | At 2000 ppm, inhibition = 35.3%       | P. falciparum                    | IC₅₀ > 100 µg/mL                 |                                 |            |
|                     |                        | nd              | At 2000 ppm, inhibition = 29.4%       | P. falciparum                    | IC₅₀ > 100 µg/mL                 |                                 |            |
|                     |                        | nd              | At 2000 ppm, inhibition = 45.9%       | P. falciparum                    | IC₅₀ = 90 µg/mL                  |                                 |            |
| Antimalaria         | Leaves                  | EO              | (3H)-hypoxanthine | P. falciparum | IC₅₀ = 34 µg/mL                  |                                 | [44]       |
|                     |                        | nd              | Incorporation in a solid medium assay | Drosophila melanogaster | na                               |                                 |            |
|                     | Ethyl acetate extract   | nd              | (3H)-hypoxanthine | P. falciparum | IC₅₀ = 33 µg/mL                  |                                 |            |
|                     | Petroleum ether extract | nd              | (3H)-hypoxanthine | P. falciparum | IC₅₀ > 100 µg/mL                 |                                 |            |
|                     | Ethanol extract         | nd              | (3H)-hypoxanthine | P. falciparum | IC₅₀ > 100 µg/mL                 |                                 |            |
|                     | Decoction               | nd              | (3H)-hypoxanthine | P. falciparum | IC₅₀ = 90 µg/mL                  |                                 |            |
| Mutagenic           | Flowering tops          | EO              | Carvacrol     | Somatic mutation and recombination test (SMART) | Drosophila melanogaster | na                               | [65]       |
|                     |                        | Thymol          | p-Cymene      | Drosophila melanogaster              | Strong inhibitory effect against URE-induced mutagenicity | [65]       |
|                     |                        | γ-Terpinene     | Carvacrol     |                                 | Weak inhibitory effect on the mutagenicity induced by MMS was observed | [65]       |
|                     |                        | p-Cymene        |                         |                                 |                                 |                                 |            |
|                     | Antimutagenic           | Flowering tops  | EO              | Somatic mutation and recombination test (SMART) by indirect-acting mutagen urethane (URE) and direct-acting mutagen methyl methanesulfonate (MMS) | Drosophila melanogaster | Strong inhibitory effect against URE-induced mutagenicity | [65]       |
|                     |                        | Ethyl acetate   | Hexane         |                                 | Weak inhibitory effect on the mutagenicity induced by MMS was observed | [65]       |
|                     |                        | Chloroform      | Methanol       |                                 |                                 |                                 |            |
|                     | Anticorrosion activity  | Aerial part     | EO              | Potentiodynamic polarization and electrochemical impedance spectroscopy assay | nd                               | A promising inhibitory corrosion | [52]       |
and Gram-positive bacteria at low concentrations with a MIC of 0.0078% (v/v) against S. aureus[50]. Mechanisms of action of this oil were investigated against S. aureus and P. aeruginosa using flow cytometry and scanning electron microscopy[61]. In addition to leakage in ions transport, the oil has induced morphological and structural deformations leading to cell death[61]. In another study, the O. compactum essential oil extracted from the aerial part is shown efficacy in the inhibition of Staphylococcus pyogenes at a concentration of MIC = 0.75% (v/v)[58]. Salmonella species was also inhibited by O. compactum essential oil extracted from aerial part[8]. In addition to this bacteriostatic action, this oil has a bactericidal action against Salmonella at low concentration which suggests this application against diseases and food deterioration caused by Salmonella species.

Organic extracts from O. compactum have also showed significant antibacterial effect. Indeed, Bouyahya et al.[34] have tested the antibacterial activity of the methanol, ethanol, ethyl acetate and n-hexane extracts of flowering tops against for pathogenic strains (E. coli, S. aureus, L. monocytogenes and P. aeruginosa). All extracts showed important bacterial tested with some variability, and these results are not correlated with the amount of phenolic and flavonoid contents of extracts which indicate the presence of specific bioactive molecules that inhibit bacterial growth. Interesting in this results, n-hexane extract showed significant zone diameter especially against P. aeruginosa (Ø = 9.0 ± 1.5 mm); species revealed multi-resistance against antibiotics[34].

5.2. Antioxidant properties

Oxidative stress is defined as disequilibrium in the transfer of electrons in living systems. This stress is mainly due to the free radicals resulting from incomplete oxidation reactions of oxygen (reactive oxygen species) or of nitrogen (reactive nitrogen species) [69]. In homeostasis situation, oxygen reactive intermediates are eliminated by enzymatic catalytic (glutathione peroxidase, superoxide dismutase and catalase) and non-enzymatic systems (vitamins, carotenoids, polyphenols and flavonoids)[70].

Oxidative stress is now considered a major challenge, and its elimination takes an importance for human health. It has become an etiological factor for much serious pathology such as cancer, cardiovascular diseases and neurodegenerative pathologies[71,72]. Synthetic antioxidants have revealed side effects that exceed their actual pharmacological effects, hence natural products are considered as important antioxidants. In this way, medicinal plants are promising sources[48,73]. Essential oils and extracts of O. compactum have shown their ability in reducing free radicals[9,44,50,74] (Table 3). O. compactum essential oil was tested by Boughid et al. and showed its ability to reduce the DPPH radical, iron and β-carotene in a dose-dependent manner and significantly with standard antioxidants[50]. This oil was also tested for its antioxidant effects using DPPH and ABTS methods and showed the IC50 values respectively at IC50 = 2.0 ± 0.1 µg/mL and IC50 = 60.1 ± 3.3 µg/mL[44]. Whereas Amakran et al.[9] found an IC50 = 137.60 ± 14.26 µg/mL. The difference between the results obtained is due to the difference in the chemical composition[9]. Petroleum ether, ethanol and ethyl acetate extracts of O. compactum are also shown to be antioxidants at significant concentrations compared to standard antioxidants[44].

5.3. Anticancer properties

Cancer is a complex disease of various etiologic and multiple risk factors. It can be generated by genetic, epigenetic, nutritional,
environmental and physiological perturbations[75-77]. Cancer presents several pathologies that are distinguished from one to another according to the cellular tropism. The fight against this disease is controversial by the development of the resistance of the tumor cells against the chemotherapy (multi-drug resistance) and by the difficulty related to the application of other treatments. Medicinal plants have found their contributions in the development of anticancer drugs[16,34,49]. O. compactum has been tested by some studies and showed cytotoxic effects against some tumor cell lines[44,63,64] (Table 3). The essential oil, decoction, ethanol, ethyl acetate and petroleum ether extracts of O. compactum were all able to inhibit the breast cancer line MCF-7[44]. Using the (3H)-hypoxanthin incorporation assay, authors proved the cytotoxicity of O. compactum decoction extract and essential oil against MCF-7 cell line at an IC50 > 100 µg/mL. While, the IC50 of petroleum ether, ethanol and ethyl acetate were respectively IC50 = 70, IC50 = 56, IC50 = 30 µg/mL. On the other hand, the ethyl acetate extract of the aerial part tested against the same tumor line (MCF7) using the MTT assay showed an IC50 = 275.05 ± 14.00 µg/mL[64]. The antitumor activity in vitro of plants extracts is depending in fact on several parameters such as the part of the plant used and the method used. The ethyl acetate extract of the aerial part from O. compactum is tested by Chaouki et al.[63] against two human tumor lines (A549 lung cancer tumor line and a SMMC-7721 hepatic tumor cell line). The cytotoxicity obtained for the two lines A549 and SMMC-7721 is respectively IC50 = 198 ± 12 and IC50 = 266 ± 14 µg/mL[63]. Cytotoxic effect of ethyl acetate extract is mainly dedicated to apoptosis which has been shown by fragmentation of genomic DNA in two tested cell lines. The induction of apoptosis pathway is related to the modulation of some Bcl-2 family genes[63].

5.4. Mutagenic and anti-mutagenic activity

Today it is widely known that cancer is linked essentially to mutagens and carcinogens. Among the most promising strategies to fight this disease is chemoprevention against mutagens and carcinogens. Several factors have been demonstrated in the last years as antimutagenic and anticarcinogenic which suppress and/or prevent carcinogenesis[78]. It has been accepted that plants and their products represent one of the sources possessing potential chemoprotective properties. Indeed, several secondary metabolites from medicinal plants are shown chemoprotective[79-82]. O. compactum essential oil and their major compounds are shown to be effective for their mutagenic and antimutagenic effects using the somatic mutation and recombination assay. Mutagenic induction was made by direct acting (urethane) and indirect (methyl methanesulfonate) mutagen. The essential oil showed a significantly strong ability to inhibit Urathane-induced mutagenesis, while the inhibition of methyl-methanesulfonate-induced mutagenesis was moderate. On the other hand, the use of the oil itself did not produce mutagenic effects. The bioguided fraction of O. compactum oil has identified and isolated two phenolic molecules, namely thymol and carvacrol. The antimutagenic action of the carvacrol was simultaneously effective in relation to the action of the oil, which suggested that the inhibition of the urethane by the carvacrol is responsible of the chemoprotective action of O. compactum essential oil[66,68].

5.5. Antifungal activity

In recent years, opportunistic fungal infections have greatly increased in patients because of the increasing population with HIV infection, cancer patients and organ or bone marrow transplant patients[69]. On the other hand, the conventional treatments for systemic mycoses have some limitations which are due to the restricted access of the population to essential medicines, the poor efficiency of the existing medicine, the high toxicity and high cost of existing medicine, and infective recidivism due to fungistatic effects[83]. Among fungal pathogen strains, we found B. cinerea. It is a ubiquitous pathogen fungal, which causes severe damage in fruits, vegetables and ornamental crops in pre- and post-harvest[84]. The frequent applications of the most effective fungicides resulted in the selection and predominance of the pathogen resistant strains showed that B. cinerea develops resistance against specific fungicides such as benzimidazoles, dicarboximides and diethofuncarband[85]. Medicinal plants have been shown as a potential source against fungal strains[86,87].

The essential oils and extracts of O. compactum have been tested for its antifungal effects (Table 1). The anti-fungal effect of four organic extracts (petroleum ether, methanol, hexane and chloroform) is evaluated against Penicillium digitatum by Fadel et al.[88]. Petroleum ether extract inhibited 83% of the fungal strain at a concentration of 2000 ppm, while the inhibition percentage of chloroform, hexane and methanol extracts at the same concentration were respectively 29.4%, 35.3% and 45.9%(88). The essential oil has been tested against B. cinerea and is shown to be an important inhibition at low concentration IC50 = 35.1 ppm). This activity is attributed to the richness of the oil tested in phenolic compounds such as carvacrol and thymol[52].

5.6. Antimalarial activity

Malaria is one of the dangerous diseases in the world. Malaria is an infectious disease with periodic fever caused by the parasite Plasmodium and transmitted by certain kind of mosquitoes called Anopheles. Malaria can infect humans, birds, monkeys and other primates, reptiles and rodents. Symptoms of malaria include fever, chills, sweating and may be accompanied by other symptoms such as headache, nausea and vomiting. The human body is the nest for Plasmodium to breed (asexual cycle). Meanwhile, the Anopheles mosquito is a vector or definitive nest. There are many synthetic drugs as malaria treatment or as an antimalarial, for example, mefloquine. It is inhibiting lactate dehydrogenase that serves to compete with NADH as a cofactor on NADH binding site of the enzyme. Inhibitory lactate dehydrogenase of cofactor enzyme causes an inactive function of energy production in Plasmodium body[89]. Plasmodium has developed resistance against chemical drugs, so it is necessary to seek natural compounds from medicinal plants against this strains. In this ways, medicinal plants play a
key role[90,91]. The antimalaria activity is evaluated against *P. falciparum* using the cytotoxicity test based on the incorporation of (3H)-hypoxanthine. Petroleum ether and ethanol extracts showed low activity with inhibition concentration 50 which exceeded 100 µg/mL (IC_{50} > 100 µg/mL). While water decoction, ethyl acetate extract and essential oil gave respectively an IC_{50} = 90, IC_{50} = 33 and IC_{50} = 34 µg/mL[44].

5.7. Others biological activity of *O. compactum*

The essential oils and extracts of *O. compactum* have shown others biological activities[45,51,66,67]. The insecticidal activity of essential oils against *Spodoptera littoralis* has been reported, which induced insecticidal activity at a lethal dose 50 (LD_{50} = 0.041 mL/larva)[66]. Essential oils are also reported as antispasmodic[51]. On the other hand, ethyl acetate extract has shown a cercaricide effect against *Schistosoma haematobium*[45]. In addition, organic extracts (petroleum ether, methanol, hexane, ethyl acetate and dichloromethane) have tested for their molluscicidal activity against *Bulinus truncatus*. Ethyl acetate extracts were the most active against these two strains was respectively MIC = 1 and MIC = 1.2 mM[95]. The antibacterial activity of thymol against *S. typhimurium* and *E. coli* has inhibited when it was combined with *β*-cyclodextrin[115]. The *p*-cymene to inhibit the growth of *Shigella sonnei* and *Shigella flexneri*[113]. The *γ*-terpinene inhibited *Salmonella* and *E. coli*[117]. The *γ*-terpinene has an inhibitory activity against *Shigella sonnei* and *Shigella flexneri*[113].

6. Pharmacological properties of main compounds *O. compactum*

6.1. Thymol

Thymol or 2-isopropyl-5-methylphenol is a monoterpenes that present in essential oil of *O. compactum* and other aromatic plants such as thyme. Its synthesis is derivatives from cymene and isomerization of carvacrol[92]. Thymol possesses several biological effects such as antibacterial, antioxidant, antitumor, anti-inflammatory and antifungal activities[93,94]. The antibacterial effects of thymol have been evaluated by several studies[95-100] against *E. coli* and *S. typhimurium* and the MIC values against these two strains was respectively MIC = 1 and MIC = 1.2 mM[95]. The antibacterial activity of thymol against *S. typhimurium* has been also studied by Palaniappan and Holley[97] and Chauhan and Kang[98], and the MIC values were respectively MIC = 2.5 mM and MIC = 750 mM. The antifungal activity of thymol has also been investigated by some works[101-104]. In some cases, this compound has inhibited *Candida tropicalis* at very low concentrations: MIC = 39 µg/mL[101], MIC = 0.12% (v/v)[102] and MIC = 350 µg/mL[103]. The anti-inflammatory and cicatrizating effects of thymol have also proved using rodents as a model study[105].

6.2. Carvacrol

The 5-isopropyl-2-methylphenol or carvacrol is present in oregano essential oils such *O. compactum* and *Origanum vulgare*. Biochemically, the carvacrol is an isomer of thymol and its derivate is also from cymene. The yield of thymol and carvacrol is depending on the isomerization that is affected by ecological habitat of the plant[4]. Carvacrol possesses numerous pharmacological properties such as antioxidant, antimicrobial, antifungal and antitumor activities[106-109]. The antibacterial activity of carvacrol has been studied by Xu *et al.* against *E. coli* and the result showed an inhibition growth of this strain at 200 µg/mL[108]. The mechanism associating with this inhibition is related to a decreasing of membrane potential of *E. coli*. The carvacrol has also shown an antifungal effect against *Candida albicans* on in immunosuppressed rats[106]. On the other hand, Yanishlieva *et al.* have proved the antioxidant activity of carvacrol[109]. This activity was related the capacity of carvacrol to prevent lipid oxidation. In another study, Koparal *et al.* have tested and showed the antitumor potency of carvacrol against lung cancer by inhibiting cell growth in A549 cell line[107].

6.3. *p*-Cymene

The *p*-cymene is an alkyl-substituted aromatic hydrocarbon found in essential oils of several aromatic plants such as *O. compactum*. This molecule is a precursor of carvacrol in oregano essential oils, but it is also found in other aromatic plants essential oils such as oregano and thyme[110,111]. The *p*-cymene is a hydrophobic molecule that contains the benzene ring substituted by the methyl group such as isopropyl. It can be isomerized into two isomers forms depending on the geometric substitution; the Ortho-substitution gives the *α*-cymene, while the meta-substitution gives the *m*-cymene[112]. The *p*-cymene has shown several pharmacological properties such as antimicrobial, antioxidant and anti-inflammatory effects[113-115]. The *p*-cymene was effective for its antioxidant property by decreasing the lipid peroxidation and nitrite content by increasing in the SOD and catalase activity[114], while the anti-inflammatory activity of *p*-cymene was important when it was combined with *β*-cycloexetride[115]. The *p*-cymene has an inhibitory activity against *Shigella sonnei* and *Shigella flexneri*[113].

6.4. *γ*-Terpinene

The *γ*-terpinene is hydrocarbon that has a similar structure to *α*-phellandrene[116]. It is found in *O. compactum* essential oils as well as in other aromatic plants essential oils such as thyme. This compound possesses a range of pharmacological properties such as antibacterial, antioxidant, antifungal, anti-inflammatory and antitumor[117]. The *γ*-terpinene possesses some biological properties such as antioxidant and antioxidant activities. Indeed, Li and Liu[118] have shown the antioxidant potency of *γ*-terpinene. These effects were related to the protection of methyl linolenate, DNA and erythrocyte oxidation. On the other hand, Oyedemi *et al.* have shown the capacity of *γ*-terpinene to inhibit the growth of *L. monocytogenes* (MIC = 0.50%), *Streptococcus pyogenes* (MIC = 0.50%), *Proteus vulgaris* (MIC = 0.75%) and *E. coli* (MIC = 0.50%)[119]. The inhibition of bacterial growth was associated with cell lysis induced by the leakage of protein and lipid. In another study, Li *et al.* have shown that the *γ*-terpinene inhibited *Salmonella enteritidis* at MIC = MBC = 3.125%, while, these values were higher
than 50% against *S. aureus* and *E. coli*[20].

### 7. Conclusion

*O. compactum* has been used as traditional medicine in Morocco. Several parts of this species have been used in the treatment and prevention of several illnesses such as diarrhea, inflammation, and intestinal disorders. Phenols such as carvacrol and thymol are the main bioactive compounds in the essential oils of this plant. While, chemical molecules of organic extracts have poorly studied. The extracts, essential oils and their derivates have been found to possess several biological properties such as anticancer, antimicrobial and antioxidant effects. This review has presented a comprehensive overview on the phytochemistry and pharmacological applications of *O. compactum* and its main compounds. Some of oregano essential oil molecules (carvacrol, thymol, p-cymene and γ-terpinene) have found several applications in modern medicine. However, more bioactive molecules in oregano oils and extracts should be identified using bioguided isolation assays. In addition, clinical evaluation of the possible toxicity related these isolated compounds needs to be assessed for finding their application as biotherapeutical medicine.

### Conflict of interest statement

We declare that we have no conflict of interest.

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