Biomedical Effects of Oregano

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The term oregano refers to a group of several plant genera, including Thymbra, Thymus, Coridothymus, Satureja, and Origanum, containing a high amount of the phytochemicals carvacrol and thymol in their essential oils.

Keywords: Phytonutrients ; Phytochemicals ; Oregano ; Lipinski's rule of 5 ; Veber's rules ; Ghose filter ; Anticancer ; Antioxidant ; Antimicrobial ; Anti-inflammatory ; Immunomodulatory

1. Botanical Description

The genus *Origanum* consists of 43 species. *Origanum vulgare (O. vulgare)*, commonly named "oregano", is the name of the aromatic plant used as a condiment herb in Mediterranean cuisine [1][2][3]. *O. vulgare* size is usually 20–80 cm; its 1–4 cm leaves are dark green, with 2-mm bell-shaped calyx purple flowers arranged in erect spikes [4][5][6]. Like other aromatic plants, the oregano plant produces essential oils as secondary metabolites in response to various infectious agents, UV light, and even oxidative stress. Oregano essential oils (OEOs) are usually extracted from the plant leaves and flowering tops. OEOs are famous for their medicinal value and are traditionally used in Turkey to cure diseases such as cough, chronic cold, wounds, gastrointestinal disorders, and skin problems in humans and domestic animals [7].

2. Phytochemicals

The main bioactive compounds present in the OEOs are the aromatic oxygenated monoterpene thymol (5-methyl-2-(1-methylethyl) phenol) and its constitutive isomer carvacrol (5-isopropyl-2-methylphenol, 2-p-cymenol). The ratio of thymol/carvacrol varies according to the oregano plant's geographical location [8]. Both compounds are lipophilic, volatile, highly soluble in ethanol, and possess low densities [7][9][10][11]. Other bioactive oregano phytochemicals include o-cymene (2-Isopropyltoluene), apigenin (4′,5,7-trihydroxyflavone), and luteolin (7,3′,4′,5-tetrahydroxyflavone) [12][13]. Due to their low general toxicities, the two main chemicals of *O. vulgare*, thymol and carvacrol, have been approved as food additives by the Food and Drug Administration (FDA) [14].

3. Biomedical Effects

3.1. Anticancer

The antiproliferative/anticancer properties of oregano have been documented in vitro and animal models for cancers. A recent study by Spyridopoulou et al. showed that OEO exerts dose-dependent cytotoxicity against breast cancer (MCF-7), colon cancer cells (HT-29), melanoma (A375), and hepatocellular carcinoma (HepG2) cells, with respective IC_{50} values of 0.35, 0.35, 8.90, and 10.0 mg/mL. The authors also showed that the treatment of HT-29 cells with 50 mg/mL of OEO correlated with an attenuated migration and an induced apoptosis-related morphological change in HT-29 cells. Furthermore, the oral administration of OEO for 13 days (0.370 g/kg b.w/day) proved to inhibit the growth of CT26 colon tumors in vivo in BALB/c mice [15]. Another study by Coccimiglio reports that an ethanolic leaf extract of *O. vulgare* promotes the death of A549 human lung carcinoma in a dose-dependent manner (IC_{50} = 14.0 µg/mL) [16]. The antiproliferative properties of oregano are believed to be mediated by thymol and carvacrol, which possess antioxidant characteristics while being non-mutagenic to cells [16][17][18]. The anticancer properties of thymol were evidenced in in vitro and in vivo models for colorectal cancers [19][20]. One astonishing property of carvacrol is its potential to specifically target cancer cells while being less toxic to normal cells [21]. Furthermore, carvacrol seems to exert a modulatory effect on the toxicity of cisplatin in vitro, a property that could be exploited for reducing the side-effects associated with classical cisplatin-based antitumor treatments [18].

3.2. Antioxidant

An in vitro study by Gavaric et al. showed that OEO possessed a robust antioxidant activity (IC_{50} = 0.2 µg/mL). While thymol and carvacrol were the components accounting for the antioxidant properties of oregano, the antioxidant activities of the two compounds were much inferior to the one observed for the whole extract with (IC_{50} = 70–80 mg/mL for thymol and carvacrol). The authors concluded that thymol, carvacrol, and other extract phytocompounds acted in synergy to promote the scavenging of free radicals [22]. According to a study conducted on the human colon carcinoma intestinal Caco-2 cell line, thymol, carvacrol, and their mixture seem to exhibit double-edged anti- or pro-oxidant effects, depending on the concentration at which they are administered (pro-oxidants at sub-cytotoxic concentrations vs. antioxidants at higher concentrations) [23].

3.3. Antimicrobial

3.3.1. Antiviral

An in vitro study conducted on simian Vero cell line CCL-81 showed that thymol, carvacrol, and p-cymene (all major components of oregano oils) possess antiviral properties against the human herpes simplex virus type 1 with respective IC_{50} values of 0.002%, 0.037%, and >0.1%. The antiviral properties of the three compounds are believed to be correlated to their ability to interfere with the viral membrane fusion mechanism during the adsorption phase of the virus [24]. Furthermore, an in vitro study by Sánchez and Aznar have reported a dose-dependent titer inhibition of the feline calicivirus and the murine norovirus by thymol, in the 1–2% (v:v) range concentrations [25].

3.3.2. Antibacterial

Thymol and carvacrol have been shown to exert antibacterial activities against Gram-positive and Gram-negative bacteria [26]. In studies using thymol concentrations ranging from 26.5–52.9 mg/cm^2 showed potent inhibitory activity against the *S. aureus*, *B. subtilis*, *E. coli*, and *Salmonella enteritidis* [27]. Studies performed by Du et al. showed the following results: strong antibacterial activity of the OEOs, thymol, and carvacrol against *E. coli*, *C. perfringens*, and Salmonella strains. They also performed in vivo studies in 448 male broiler chicks by oral gavage using OEO. They found that OEO alleviated intestinal lesions and decreased *E. coli* populations [28]. In another study, oregano oil showed great antibacterial activity against the following multidrug-resistant bacteria: three *Acinetobacter baumannii*, three *Pseudomonas aeruginosa*, and four methicillin-resistant *Staphylococcus aureus* with inhibitory concentrations ranging from 0.08–0.64 mg/mL [29]. Another in vitro study showed that the use of OEO and carvacrol could curve Group A *streptococci* erythromycin-resistant bacterial infections [30].

3.3.3. Antifungal

The in vitro antifungal properties of OEO, thymol, and carvacrol in the 40–350 mg/mL ranges have been reported in several studies against plant pathogenic fungi *Colletotrichum acutatum* and *Botryodiplodia theobromae* [31]; *Penicillium digitatum* and *Penicillium italicum* [32]; food-relevant fungi *Cladosporium* spp. and *Aspergillus* spp. [33]; longan pathogens, *Lasiodiplodia* spp., *Phomopsis* spp., *Pestalotiopsis* spp. and *Geotrichum candidum* [34]; and against *Fusarium verticillioides* and *Rhizopus stolonifera* [35]. Furthermore, an in vivo study conducted in *Caenorhabditis elegans* suggests that thymol possesses antifungal activity against *Candida albicans*, the most prevalent cause of fungal infections in humans [36].

3.4. Anti-inflammatory

OEOs possess a strong anti-inflammatory activity, a property that is proposed to be mediated by its main active compounds: thymol and carvacrol. The impact of the OEOs on 14 protein biomarkers was closely related to the inflammatory response. The results show dose-dependent inhibition of the expression of all the proinflammatory and remodeling biomarkers studied: monocyte chemoattractant protein 1 (MCP-1), vascular cell adhesion molecule 1 (VCAM-1), intracellular cell adhesion molecule 1 (ICAM-1), interferon gamma-induced protein 10 (IP-10), interferon-inducible T-cell alpha chemoattractant (I-TAC), monokine induced by gamma interferon, collagen I, collagen III, epidermal growth factor receptor (EGFR), matrix metalloproteinase 1 (MMP-1), plasminogen activator inhibitor 1 (PAI-1), tissue inhibitor of metalloproteinase (TIMP) 1 and 2, and macrophage colony-stimulating factor (M-CSF) [37]. The anti-inflammatory activity of thymol was also reported in vivo in BALB/c mice affected by LPS-induced endometritis [38].

3.5. Immunomodulatory

Recent investigations cited in previous sections have demonstrated that oregano has potent antioxidant, antimicrobial, and anti-inflammatory properties, leading to an improved immune response. Oregano's immunomodulatory activity can be

attributed to thymol by its ability to modify the secretion of cytokines, probably through the regulation of NF-κB, but also through the MAPK signaling pathway, or through their ability to affect the cellular expression of iNOS and the secretion of prostaglandins [39]. De Santis et al. studied the immunomodulatory effects of several 50% (*v*/*v*) hydroalcoholic *O. vulgare* extracts on human-derived dendritic cells type-1 and type-2 macrophages infected with *M. bovis* Bacille Calmette–Guérin. The authors showed that the hydroalcoholic extract stimulated the anti-mycobacterial innate immunity and limited the inflammatory response in all the tested cell types [40]. On the contrary, Gholijani et al. showed that intraperitoneal injections of 80 mg/kg of thymol or carvacrol in BALB/c mice trigger an immunosuppressive response, a property that could be exploited for treating autoimmune diseases [41].

3.6. Predicted gastrointestinal absorption (GIA)

The physicochemical properties for the main five most bioactive phytochemicals in oregano (carvacrol, thymol, o-cymene, apigenin, and luteolin) were calculated based on the combination of Lipinski's, Ghose's, and Veber's rules (L-Ro5, GF, VR). The range of pharmacokinetics data for the molecules are summarized as follow: molecular weight (160-500 Da); hydrogen bond donors ≤5; hydrogen bond acceptors ≤10; molar refractivity (40-130); lipophilicity (LogP) (-0.4–5.6); rotatable bonds ≤ 10: polar surface area <140; the total number of atoms (20-70); lipophilicity considering ionizable groups at pH 7.4 (LogD) [42],[43],[44],[45]. 40 % of the oregano's bioactive phytochemicals (apigenin and luteolin) comply with all of the "drug-likeness" rules. The remaining 60% (carvacrol, thymol, and o-cymene) violate the GF of MW = 160 – 480 Da rule. Accordingly, oregano, carvacrol, thymol, and o-cymene are predicted to have the lowest GIA.

4. Contraindications

As detailed in this entry, *O. vulgare* offers a wide range of medicinal benefits. In addition, Schönknecht et al. concluded that including primrose and thymol in combination with conventional therapy could alleviate cough and dyspnea in upper respiratory tract infections [46]. However, in a study of several decades ago, thymol and carvacrol have been shown to induce dose-dependent structural chromosomal aberrations in *Rattus norvegicus*, when consumed at doses over 40 mg/kg, despite being non-toxic at low to moderate doses [47]. Although all the studies mentioned here cited oregano, more robust studies are needed to have a profound evaluation of its efficacy.

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