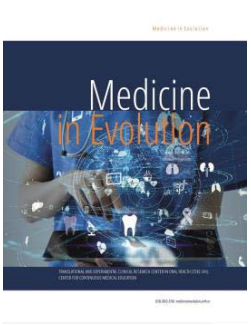
Carvacrol, a Promising Anti-inflammatory, Anti-bacterial and Antioxidant Agent, in Periodontal Disease Therapy



Potra-Cicalău G. I.[1], Ciavoi G.[1], Todor L.[1], Lile I.[2], Marian D.[2], Berari A.[2], Pasca C.[2], Stana O. L.[2]

[1]*Department of Dental Medicine, Faculty of Medicine and Pharmacy, University of Oradea, Romania*
[2]*Department of Dentistry, Faculty of Dental Medicine, "Vasile Goldis" Western University of Arad, Romania*

Correspondence to:
Name: Ciavoi Gabriela
Address: Department of Dental Medicine, Faculty of Medicine and Pharmacy, University of Oradea, Romania, December 1st Square no. 10, 410068, Oradea, Bihor Conty, Romania
Phone: +40 729099622
E-mail address: gabrielaciavoi@yahoo.com

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Abstract

Aim and objectives: This research aims to provide a summary of the therapeutic benefits of carvacrol in cases of periodontitis. We focused on the anti-inflammatory, antibacterial, and antioxidant properties of this natural extract, which may help in the treatment of periodontal disease.

Material and methods: Plant extracts are getting increasingly popular due to their anti-inflammatory, anti-bacterial and antioxidant properties, as well as their ability to alter inflammatory response.

Results and discussions: An intriguing possibility for treatment of periodontal disease is the effectiveness of carvacrol against gram-negative microorganisms.

Conclusions: Carvacrol is a promising anti-inflammatory, antibacterial, and antioxidant agent in the treatment of periodontal disease, based on the provided data.

Keywords: Carvacrol, periodontitis, anti-inflammatory, antioxidant, antimicrobial

INTRODUCTION

Herbal extracts have been used for medicinal purposes since antiquity. Researchers are currently interested in a growing number of natural chemicals, essential oils and vegetable extracts due to their characteristics and benefits for human health [1]. One of these compounds, carvacrol, has been found in high amounts in essential oils and has been shown to have a variety of bioactivities in cells and animals [2].

Carvacrol is a phenolic monoterpenoid produced by a variety of plants, the most well-known of which is *Origanum vulgare* (Greek oregano), *Thymus vulgaris* (thyme), *Origanum majorana* (marjoram), *Satureja hortensis* (summer thyme) and *Satureja montana* (winter thyme) are among the plants that produce it [3]. Carvacrol has long been known to be a component of oregano essential oil and it is one of the most studied [4]. Anti-inflammatory, anti-bacterial and antioxidant activities are acquired by carvacrol 5, 6]. Carvacrol also contains analgesic [7], antifungal, anti-diabetic, cardioprotective [8], anti-hepatotoxic [9], anticancer [10], antimutagenic [11] and antiparasitic [12] pharmacological activities. The chemical structure and characteristics of carvacrol are illustrated in Figure 1.

Periodontal disease is a collection of chronic, inflammatory and microbial-induced diseases that typically present as gingivitis and chronic periodontitis. Both kinds of periodontal disease are caused by bacteria, gram-negative anaerobes being the most common periodontal pathogens [13, 14]. This infection, commonly known as periodontitis, is an oral infection characterized by irreversible deterioration of the tooth-supporting structures. Periodontal disease is a public health issue since it is a pathology that connects other illnesses [15]. Periodontitis, particularly its mild and moderate forms, is extremely common in adult-aged populations all over the world, with prevalence rates of approximately 50% [16], while its severe form becomes more common in the third and fourth decades of life, with global prevalence rates of around 10% [17].

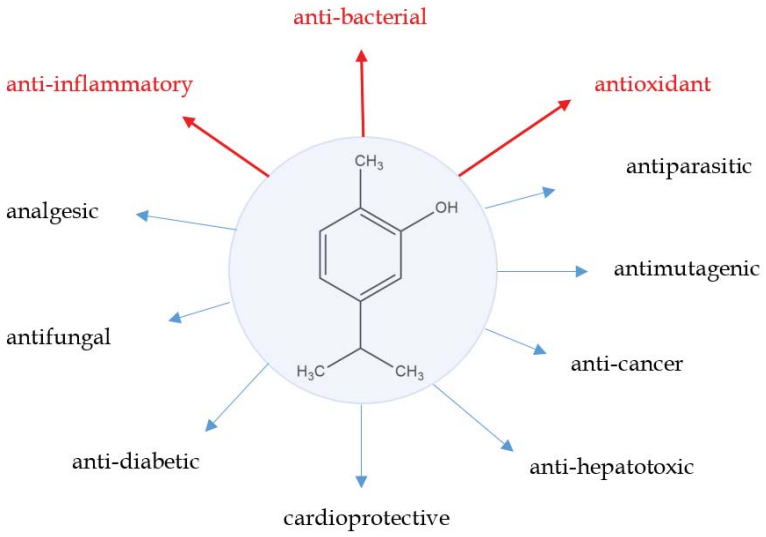

Figure 1. Chemical structure of carvacrol and pharmacological activities [5-12, 18]

Aim and objectives

The purpose of this paper is to present an overview of therapeutic effects of carvacrol in periodontitis. We will focus on the anti-inflammatory, anti-bacterial and antioxidant qualities of this essential oil, which could support periodontal disease treatment.

MATERIAL AND METHODS

In order to conduct this review, we searched the PubMed and Google Scholar databases using the following keywords: periodontal disease, carvacrol, anti-inflammatory, anti-bacterial and antioxidant. Articles that addressed periodontal disease *in vitro* or *in vivo* using carvacrol and for which we had access to the complete text met the inclusion criteria. The exclusion criteria were represented by articles to which we had access only to the abstract. Following the removal of inappropriate and duplicate articles, our analysis contained 64 bibliographic references.

RESULTS AND DISCUSSIONS

Periodontal therapy's main goal is to lessen the infectious and inflammatory threat while also halting tissue deterioration. Removal of pathogenic biofilms and reduction of inflammation can stop periodontal tissue degradation. Nevertheless, depending on the kind of tissue defects, systemic health state and age, only a limited regrowth of lost tissues occurs [19]. To eliminate the microbial load on the periodontium, one of the most prevalent approaches is mechanical treatment and periodontal surgery. However, because periodontal disease is immunogenetically regulated and hence necessitates adjuvant therapy, this method is not always optimal [20]. Researchers are motivated to identify new treatment plans for the prevention and treatment of marginal periodontitis due to an increase in the frequency of the disease, growing resistance of gram-negative bacteria to ordinary antibiotics and even their side effects [21].

As a result, the creation of new herbal medicine formulas containing bioactive molecules would be advantageous not only for less invasive, uncomplicated and predictable therapy, but also for the prevention of marginal periodontitis. Natural remedies are made out of plant extracts that are thought to have therapeutic effects. Due to the complex action of the extracts, little side effects and inexpensive cost compared to manufactured medications, phytotherapy is gaining popularity. At the same time, because contemporary drugs might cause antibiotic resistance, herbal remedies are a viable alternative in the treatment of a variety of body and oral disorders [22].

Because of their anti-inflammatory and anti-bacterial characteristics, as well as their role in modifying the inflammatory response, plant extracts are becoming increasingly popular [23]. More and more plant extracts have been studied in terms of their effect on the bacterial flora of periodontal disease in recent years [24-27]. One of this natural extracts that has been demonstrated to reduce the symptoms of periodontal disease is carvacrol.

Carvacrol, which is efficient against bacteria linked to caries, has been shown to be a possible therapeutic agent in periodontal disease in a fascinating study [28]. Carvacrol improves experimentally generated periodontitis in rats, according to an *in vivo* research that used radiographic examinations to study the effect of intragastric administration of carvacrol on alveolar bone resorption. In small doses, carvacrol is safe and effective in the treatment of periodontal disease. According to the findings, carvacrol preserves gingival tissue in rats with periodontal disease, which are mediated through carvacrol's inhibitory action on inflammation and periodontal tissue deterioration. Carvacrol also suppresses the inflammatory response and matrix metalloproteinase-9 (MMP-9) expression [29]. Integrated into herbal periodontal gels, essential oil with carvacrol was utilized in other research to treat experimentally generated periodontitis in rats and it was found that local application of carvacrol reduced alveolar bone resorption [30, 31]. These findings in the literature urge us to investigate the possible advantages of carvacrol in periodontal disease in greater depth.

a. Anti-inflammatory properties of carvacrol on periodontitis

Inflammatory cytokine levels, inducible nitric oxide synthase (iNOS) expression and cyclooxygenase-2 (COX-2) expression have all been demonstrated to be inhibited by carvacrol [32]. Carvacrol suppresses neutrophil elastase production as well as the synthesis of prostaglandins E2 (PGE2), prostaglandins F1 and prostaglandins F2, according to other studies [32-34].

Xiao et al. (2018) found that carvacrol not only inhibited the production of nitric oxide (NO) and PGE2 generated by interleukin-1 (IL-1), but it also suppressed the expression of iNOS, COX-2 and matrix metalloproteinases (MMPs) in chondrocytes through decreasing the nuclear factor-kappa B (NF-κB) signaling pathway [35]. In an *in vivo* animal investigation, da Silva Lima et al. (2013) found that administering carvacrol in doses of 50-100 mg/kg has anti-inflammatory effects, reduces inflammatory edema in rats paws and lowers IL-1 and PGE2. At the same time, they showed that a dose of 100 mg/kg lowers COX-2 and IL-1 messenger ribonucleic acid expression in mice. Carvacrol boosted the levels of interleukin-10 (IL-10) and anti-inflammatory cytokines, indicating that this natural extract has a protective impact [33]. Tabibzadeh Dezfuli et al. (2017) also found that once-daily oral administration of carvacrol lowers the levels of IL-1, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) in mice with streptozotocin-induced diabetes [36]. On the other hand, contrary results were obtained, stating that carvacrol has a favorable effect in lowering IL-1, interleukin-4 (IL-4) and interleukin-8 (IL-8), but not IL-6 and TNF-α, most likely due to the approach utilized in the research by Carvalho et al. (2012, 2020) [37, 38].

Carvacrol anti-inflammatory activity could be attributed to inhibition of one or both cyclooxygenase (COX) enzymes, as evidenced by other studies which demonstrate that carvacrol inhibits both cyclooxygenase-1 (COX-1) and COX-2 [7, 32]. Another study found that carvacrol inhibits inflammatory edema and leukocyte migration, indicating that it has anti-inflammatory properties [37]. Carvacrol in thyme oil inhibits LPS-induced production of COX-2 mRNA and protein, possibly suppressing inflammation [34, 39]. Tsai et. al (2011) found that *Thymus vulgaris* essential oil contains 2.03% cavracrol and has significant anti-inflammatory action [39].

Using carvacrol, which has the characteristics of particular anti-anaerobic bacteria, anti-inflammation, and immunomodulation, Hu et al. (2023) created the first near-infrared (NIR) light-responsive nanodrug delivery system. By remodeling the classic inflammatory immunity pathways, such as the MAPK, interleukin-17 (IL-17) and tumor necrosis factor (TNF) signaling pathways, the plant-based monomer in conjunction with the in situ light-sensitive nano-drug delivery system developed by these authors, restores immunity and speeds up periodontal restoration. This combination potentially offers a non-invasive treatment option for periodontal disease [40].

b. Anti-bacterial activity of carvacrol on periodontitis

Carvacrol works on microbial cells and damages bacterial membranes structurally and functionally [12]. Carvacrol is one of the few components of essential oils that may breakdown the outer membrane of gram-negative bacteria, allowing lipopolysaccharides (LPS) to be released [41, 42]. Monoterpenes with anti-bacterial qualities, like carvacrol and thymol, are found in the essential oils and other extracts made from different sections of the aromatic *Verbenaceae* shrub *Lippia sidoides* [43-45].

Maquera–Huacho et al. (2018) investigated the anti-bacterial capabilities of carvacrol and terpinen-4-ol against *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, as well as the cytotoxic effect on fibroblasts. For *Porphyromonas gingivalis* the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of carvacrol were 0.007%, respectively 0.002% for *Fusobacterium nucleatum*. Carvacrol had anti-biofilm activity and its cytotoxicity was comparable to that of chlorhexidine [46].

Gandova et al. (2023) evaluated the anti-bacterial efficacy of carvacrol against seven pathogenic and conditionally damaging microorganisms. Gram-positive or gram-negative microorganisms such as *Salmonella enterica* subsp. *Enterica serovar Abony*, *Bacillus subtilis*, *Staphylococcus aureus*, *Listeria monocytogenes* and *Escherichia coli* had inhibitory zone diameters measured between 3.9 and 4.9 mm [47]. Additionally, it has been discovered that carvacrol possesses anti-bacterial properties against *Salmonella spp.*, *Enterococcus sp.*, *Shigella*, *Pseudomonas aeruginosa*, *Salmonella spp.* and *Escherichia coli* [48].

Wang et al. (2016) investigated the anti-bacterial properties of the phenolic components of oregano essential oil against oral pathogens. Hinokitiol, carvacrol, thymol and menthol were the components studied. The MIC and MBC of these components were determined, resulting in carvacrol having MIC 200-400 g/mL and MBC 200-600 g/mL against *Aggregatibacter actinomycetemcomitans, Streptococcus Mutans*, *Methicillin-resistant Staphylococcus aureus* and *Escherichia Coli* [49].

Miladi et al. (2017) investigated the anti-bacterial and antibiofilm properties of five essential oils: eugenol, carvacrol, thymol, p-cymene, and γ-terpinene. The oils were studied either alone or in combination with tetracycline, and the results showed that the essential oils had a selective antimicrobial activity when used alone, and that they had a synergistic effect when used in combination with tetracycline, reducing oral bacteria at a rate of two to eight times when used in that manner. Notably, essential oils provided either alone or in conjunction with tetracycline shown significant antibiofilm activity. This adds carvacrol to the group of natural compounds capable of altering bacterial resistance and eliminating bacterial biofilm [50].

When compared to synthetic medicines, the anti-bacterial activity values for *Thymus zygis* and *Origanum compactum* essential oils demonstrated a potent antimicrobial action [51]. Carvacrol and thymol are two herbal substances contained in this essential oils with significant broad-spectrum anti-bacterial activity. It has been demonstrated that nanoparticles encapsulated in carvacrol and thymol are more soluble and have stronger anti-bacterial properties [52].

As a result, the researchers discovered that carvacrol exhibits anti-bacterial action against periodontal biofilm [46]. Drug resistance can be decreased and therapeutic efficacy increased when carvacrol and antibiotics are used together. Carvacrol is safe and has little cytotoxicity even at high concentrations [53]. Despite the lack of information regarding carvacrol's metabolism in humans, the molecule is thought to be safe [54].

c. Antioxidant effects of carvacrol on periodontitis

Essential oils have strong biological and pharmacological properties, which makes them very interesting. Chroho et al. (2024) studied essential oils isolated from *Thymus zygis* and *Origanum compactum*. These essential oils contain carvacrol and thymol, which exhibited a significant antioxidant activity, according to the tests [51]. The essential oil of *Thymus vulgaris* has antioxidant action because it contains high levels of carvacrol and thymol, natural chemicals with increased antioxidant activity [39, 55]. Using the oxygen radical absorbance capacity (ORAC) method as reported in a study, the antioxidant effect of carvacrol was found to be 1687.0 ± 102.90 μmol TE/mL [47].

Pathologies produced by reactive oxygen species (ROS) imposed by free radicals are referred to as oxidative stress. The imbalance between oxidants and antioxidants in favor of oxidants, with damaging and pathogenetic potential, is termed as oxidative stress. Oxidative stress can occur intracellularly or extracellularly, depending on its severity. Intracellular oxidative stress can result in cell necrosis or more or less pronounced cell disorganization, with catastrophic consequences in the case of a cell that is unable to replicate. Extracellular oxidative stress can also be harmful to cells. Free radicals are molecules formed from incompletely oxidized chemicals that have experienced partial combustion and include

oxygen groups in their structure that can initiate aggressive oxidation events on the surface of cell membranes or even inside cells [56].

Rapid metabolism attracts more free radicals, resulting in an imbalance between ROS formation and antioxidant defenses. These free radical species cause oxidative damage to lipids, proteins and nucleic acids in diverse tissues [57]. Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) are the first line of defense antioxidants [58].

Carvacrol has significant antioxidant effects and can prevent and suppress a variety of diseases [59]. Chronic stress can cause cytotoxicity and oxidative stress is a significant factor that may be involved [57]. Carvacrol inhibits lipid peroxidation by increasing the activity of SOD, GPx, glutathione reductase (GR) and CAT. Free radicals such as peroxyl radicals, superoxide radicals, hydrogen peroxide and NO are effectively eliminated by carvacrol [60, 61].

Treatment with carvacrol raises glutathione (GSH) levels considerably. Carvacrol ability to maintain GSH levels is mostly owing to its radical elimination actions, which remove ROS. In cell cultures and animals, carvacrol has been found to boost antioxidant capacity [62]. Oregano extract has been shown to have a preventive effect against free radical activity, preventing tissue damage caused by prolonged stress [1].

Carvacrol has antioxidant properties *in vitro* and *in vivo*, which are attributable to the existence of the hydroxyl group (–OH) which is linked to the aromatic ring [63, 64]. Another study, conducted by Samarghandian et al. (2016) found that carvacrol reduces oxidative damage to the brain, liver and kidneys, making it a promising novel pharmacological agent for treating oxidative stress [1]. In a study by Tabibzadeh Dezfuli et al. (2017) it was discovered that giving diabetic rats 15 mg/kg body carvacrol per day reduced malondialdehyde (MDA) levels and increased CAT, SOD and GPx activity compared to rats who did not receive the extract, implying that carvacrol has antioxidant properties [36]. Per se, treatment with carvacrol has been shown to reduce the negative effects of chronic stress.

CONCLUSIONS

Based on the above-mentioned, carvacrol is a promising anti-inflammatory, anti-bacterial and antioxidant agent in periodontal disease therapy.

We can conclude that carvacrol is a viable perspective in the treatment of periodontal disease and due to its qualities it could be an excellent excipient in various topical preparations or per os treatments, in order to lessen the impact of periodontitis on the mouth and the rest of the body. However, more clinical trials are needed before a definite treatment plan can be implemented in the dentist office.

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