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Carvacrol as a Potential Modulator of TGF-β Expression in Periodontitis: A Narrative Review

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ABSTRACT

Periodontitis is a chronic inflammatory disease driven by polymicrobial infection and an imbalance between subgingival microbiota and the host inflammatory response, leading to progressive destruction of the periodontal ligament and alveolar bone. Carvacrol, a phenolic monoterpene found in oregano and thyme, demonstrates antimicrobial and anti-inflammatory properties relevant to periodontal pathogens. Transforming growth factor-beta (TGF-β) plays a dual, context-dependent role in periodontal tissue, supporting early anti-inflammatory responses and matrix repair but promoting fibrosis and periodontal ligament stem cell senescence when its activity is sustained. Carvacrol and TGF-β have largely been studied independently, and direct evidence linking the two in periodontitis remains limited. This review summarises current knowledge on carvacrol's chemical properties, molecular mechanisms of anti-inflammatory action, effects on periodontal-related cytokines including TGF-β, and available preclinical evidence. Carvacrol suppresses inflammation by inhibiting NF-κB and MAPK/ERK signalling, reducing IL-1β, TNF-α, and IL-6, and increasing IL-10. Its effects on TGF-β are context-dependent, increasing expression in an autoimmune CNS model but decreasing it in a murine asthma model; the only study demonstrating direct TGF-β1 modulation was conducted in renal epithelial cells rather than periodontal tissue. Preclinical evidence supports carvacrol's antimicrobial and anti-inflammatory effects in periodontal disease, but its influence on TGF-β signalling in periodontal tissue remains unexplored. Further studies using periodontal cell and animal models are needed to clarify this relationship.

Keywords: carvacrol; TGF-β; periodontitis; NF-κB; periodontal ligament; anti-inflammatory; tissue repair

INTRODUCTION

Periodontitis ranks among the most prevalent chronic inflammatory diseases worldwide. In 2019, severe periodontal disease affected an estimated 18.8% of individuals aged 15 years and older, corresponding to over 1 billion cases globally [1]. In Indonesia, a national health survey reported a periodontitis prevalence of 71.4%, with chronic periodontitis being the most common form, affecting approximately 50% of the adult population [2]. This disease is characterised by inflammation of the periodontal soft tissues and progressive destruction of the periodontal ligament and alveolar bone, which provide structural support to teeth [3, 4].

Periodontitis is driven by polymicrobial infection, primarily driven by an imbalance between subgingival microbiota and the host inflammatory response, while factors such as smoking, diabetes, and genetic predisposition further modulate disease severity [5, 6]. In addition to local tissue destruction, periodontitis is linked to systemic conditions, including cardiovascular diseases, diabetes, and respiratory diseases, which underscores its broader clinical relevance [7]. The persistent inflammatory response characteristic of periodontitis emphasises the need for therapeutic strategies that target both inflammation control and periodontal tissue regeneration.

The multifactorial and inflammatory nature of periodontitis has stimulated research into bioactive compounds with anti-inflammatory and antimicrobial properties. Carvacrol, a phenolic monoterpene found in the essential oils of aromatic plants such as oregano and thyme, has attracted considerable attention due to its established antimicrobial and anti-inflammatory effects [8, 9]. Experimental studies demonstrate that carvacrol modulates inflammatory responses by increasing production of the anti-inflammatory cytokine interleukin-10 and reducing levels of inflammatory mediators [10]. Carvacrol has also shown anti-inflammatory effects in cardiomyocytes exposed to lipopolysaccharide from Porphyromonas gingivalis, a major periodontal pathogen. In these studies, carvacrol reduced the expression of TLR4, NF-κB, NALP3, and IL-1β, as well as decreased reactive oxygen species production, indicating its potential to suppress inflammatory signalling induced by periodontal pathogen-derived stimuli [11]. These findings justify further investigation of carvacrol as a bioactive compound for modulating inflammatory processes in periodontitis.

Controlling periodontal inflammation alone does not ensure complete tissue recovery, as effective healing requires coordinated regulation of extracellular matrix formation and tissue repair processes [12]. Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that plays a central role in immune regulation, extracellular matrix turnover, and tissue repair. In periodontitis, altered TGF-β signalling is associated with inflammatory responses and structural changes in periodontal tissues [13]. A systematic review identified TGF-β1 as the most extensively studied isoform in periodontitis, underscoring the complex involvement of TGF-β signalling in disease pathogenesis and progression [14]. In addition to its immunomodulatory functions, TGF-β is essential for extracellular matrix deposition and remodelling during tissue repair [15]. Experimental evidence supports the role of TGF-β1 in tissue repair; in vitro studies with human periodontal ligament cells have demonstrated that TGF-β1 enhances collagen production and the expression of periodontal ligament-related genes, with ACTA2 implicated in TGF-β1-induced Smad2/3 phosphorylation [16]. Preclinical and animal studies further confirm the importance of TGF-β signalling in wound healing and tissue remodelling [15].

The anti-inflammatory effects of carvacrol and the regulatory functions of TGF-β in periodontal inflammation and tissue repair indicate a potential biological relationship between these factors. However, most existing research has examined carvacrol and TGF-β independently, and direct evidence linking carvacrol to TGF-β modulation in periodontitis remains limited.

This review synthesises current evidence on carvacrol as a potential modulator of TGF-β expression in periodontitis. It examines carvacrol's sources and chemical properties, molecular mechanisms of anti-inflammatory action, effects on periodontal-related cytokines including TGF-β, relevant preclinical findings, and identifies research gaps in its therapeutic application.

SOURCES AND CHEMICAL CHARACTERISTICS OF CARVACROL

Carvacrol (2-methyl-5-(1-methylethyl) phenol) is a naturally occurring phenolic monoterpenoid predominantly present in the essential oils of various aromatic plant species, particularly those within the Lamiaceae family [14]. It is a principal bioactive constituent in Origanum vulgare (oregano), Thymus species (thyme), Satureja (savoury), Lippia graveolens, Lavandula multifida, and Nigella sativa [17, 18]. Carvacrol concentrations vary considerably among these sources; for example, Origanum vulgare essential oil may contain carvacrol as the predominant compound at concentrations up to 85.78% [19]. In Origanum vulgare, carvacrol synthesis and accumulation are tissue-dependent, with key biosynthetic genes showing specific expression patterns in structures such as peltate glandular trichomes [20]. Furthermore, carvacrol concentration and presence can differ not only between genera and species but also within species due to intraspecific chemical polymorphism [17, 21].

Carvacrol's chemical structure is fundamental to its classification and biological activity. Carvacrol is a monoterpenoid phenol derived from p-cymene, with the molecular formula $C_{10}H_{14}O$ and a molecular weight of 150.22 g/mol [18, 22]. Its structure consists of a benzene ring substituted with a hydroxyl (-OH) group at position 1, a methyl ($-CH_3$) group at position 2, and an isopropyl group ($-CH(CH_3)_2$) at position 5 [22]. Carvacrol is a structural isomer of thymol; the methyl and isopropyl substituents occupy different positions in the two compounds, with thymol featuring the hydroxyl at position 1, the isopropyl at position 2, and the methyl at position 5. Although both are phenolic monoterpenoids, recent structural analyses indicate substantial differences in their liquid-state organisation. Carvacrol remains liquid at room temperature and tends to orient its aromatic rings perpendicularly, forming O–H···π hydrogen bonding interactions. In contrast, thymol displays a more heterogeneous organisation, with both parallel and antiparallel ring orientations and a greater tendency to form hydroxyl-hydroxyl hydrogen bonds [23].

Several physicochemical properties of carvacrol are pertinent to its biological activities. The phenolic hydroxyl group imparts amphiphilicity, enabling interactions with both polar and non-polar environments [18, 22]. Carvacrol is a small, lipophilic molecule with an XLogP3 value of approximately 3.1, reflecting moderate-to-high lipophilicity [22]. Additional characterisation indicates a surface tension of 53.11 to 60.38 mN/m and a density ranging from 0.978 to 0.99 g/cm^3 between 30 and 80°C [24], both relevant to its biological effects.

Carvacrol concentration in essential oils varies widely and depends on plant chemotype, geographical origin, environmental conditions, and extraction method [21, 25, 26]. Even within a single species, distinct chemotypes can yield substantially different carvacrol levels, and factors such as soil composition, climate, and growth stage additionally affect their accumulation [21, 26]. This variation underscores the need to standardise plant source and extraction methods for research or therapeutic use.

A complete understanding of these chemical characteristics and the factors affecting carvacrol concentration provides a basis for assessing its biological properties, which are examined in the following sections.

MOLECULAR MECHANISM OF THE ANTI-INFLAMMATORY ACTION OF CARVACROL

Carvacrol modulates several inflammatory signalling pathways relevant to periodontal tissue, including NF-κB, MAPK/ERK, and JAK/STAT. Each pathway contributes to distinct downstream effects on pro- and anti-inflammatory mediators, as summarised in Table 1.

TABLE 1: Signalling Pathways Modulated by Carvacrol in Anti-Inflammatory Action.

Signaling Pathway	Effect of Carvacrol on the Pathway	Biological Meaning	Source
NF-κB	↓ Activity (Inhibited)	Blocks NF-κB translocation to the nucleus. As a result, inflammatory genes (IL-1β, COX-2, TNF-α) are reduced.	[10, 11, 27]
MAPK (ERK1/2)	↓ Activity (Inhibited)	Suppresses ERK/MAPK signalling pathway, reducing inflammatory responses and oxidative stress in various inflammatory models.	[27–29]
JAK/STAT	↓ Activity (Indirect evidence)	Carvacrol reduces IL-6 and IFN-γ levels (cytokines that signal through STAT), though direct JAK inhibition is not yet proven.	[30]

Carvacrol inhibits NF-κB activation by blocking p65 subunit translocation from the cytoplasm to the nucleus, thereby suppressing NF-κB-dependent transcription. Somensi et al. first demonstrated this mechanism in LPS-stimulated RAW 264.7 macrophages, where carvacrol inhibited both basal and LPS-induced NF-κB transactivation [27]. Researchers have validated the downstream effects of NF-κB inhibition in various models. In a CFA-induced paw inflammation model, carvacrol (50 and 100 mg/kg, i.p.) significantly reduced IL-1β and PGE2 levels, decreased COX-2 and IL-1β mRNA expression, and increased both IL-10 levels and IL-10 mRNA expression. Importantly, carvacrol did not reduce TNF-α levels, and its anti-edematogenic effect was absent in IL-10 knockout mice, indicating that IL-10 is essential for its anti-inflammatory action [10].

Similarly, comparable NF-κB suppression has been reported in HL-1 cardiomyocytes exposed to P. gingivalis LPS [11]. Furthermore, nanoemulsified carvacrol (200 mg/kg, oral) significantly reduced IL-1β levels in inflamed paw tissue, demonstrating efficacy similar to dexamethasone. In contrast, free carvacrol administered at the same dose and route did not exhibit anti-inflammatory activity [29]. This NF-κB-focused mechanism may be particularly relevant to periodontitis, as the TLR4/MyD88-driven pathway upregulates RANKL and promotes osteoclastogenesis, causing periodontal tissue destruction [31]. Thus, carvacrol's inhibition of NF-κB suggests a plausible, although not yet directly demonstrated, mechanism for controlling periodontal bone resorption.

Carvacrol also modulates the mitogen-activated protein kinase (MAPK) pathway, specifically the extracellular signal-regulated kinase (ERK1/2) branch. Carvacrol inhibits ERK1/2 phosphorylation induced by LPS. Somensi et al. first demonstrated this mechanism in LPS-stimulated RAW 264.7 macrophages, where carvacrol suppressed ERK1/2 activation in parallel with its effects on NF-κB [27]. Carvacrol has also modulated ERK signalling in other inflammatory contexts; carvacrol and its nanoemulsion formulation suppress inflammation by modulating the ERK pathway [29]. Furthermore, in a mouse model of cisplatin-induced acute kidney injury, carvacrol treatment markedly reduced phosphorylated ERK expression and decreased the phospho-ERK-to-total ERK ratio, indicating suppression of ERK1/2 activation [28]. The MAPK/ERK pathway operates downstream of the same TLR-mediated signalling cascade implicated in periodontal tissue destruction [31]. This inhibition of ERK1/2 activation in non-periodontal models indirectly supports carvacrol's potential to interfere with periodontal inflammatory signalling. However, direct evidence in periodontal tissue is limited.

Carvacrol has also been reported to reduce IFN-γ and IL-6 production by MOG-stimulated splenocytes in an experimental autoimmune encephalomyelitis (EAE) model [30]. Both IFN-γ and IL-6 are cytokines that signal through the JAK/STAT pathway; IFN-γ.

activates STAT1 via JAK1/JAK2, while IL-6 activates STAT3 via JAK1/JAK2/TYK2 [32, 33]. Although Mahmoodi et al. did not directly assess JAK or STAT phosphorylation, the documented decrease in these cytokines indicates that carvacrol may indirectly modulate JAK/STAT signalling.

Collectively, these pathways converge to regulate cytokines that are essential for periodontal tissue homeostasis, such as TGF-β. TGF-β's dual role in periodontal inflammation and tissue repair warrants further investigation.

THE BIOLOGICAL ROLE OF TGF- β IN PERIODONTAL TISSUE

Anti-inflammatory cytokines that downregulate periodontal inflammation include IL-4, IL-10, and TGF-β, whereas pro-inflammatory mediators such as TNF, IL-1β, IL-6, IL-8, and IL-17 amplify periodontal tissue inflammation [34]. Transforming growth factor-beta (TGF-β) is a multifunctional cytokine with a central role in immune regulation, extracellular matrix (ECM) turnover, and tissue repair. In periodontal tissues, TGF-β is produced by several cell types, including gingival fibroblasts, periodontal ligament (PDL) cells, osteoblasts, and infiltrating immune cells. The TGF-β family consists of three mammalian isoforms: TGF-β1, TGF-β2, and TGF-β3. Among these, TGF-β1 is the most extensively studied in periodontitis [14].

TGF-β signalling is initiated when the cytokine binds to the type II receptor, which then recruits and phosphorylates the type I receptor. This process leads to SMAD2/3 phosphorylation and subsequent nuclear translocation to regulate target gene transcription. In addition to the canonical SMAD pathway, TGF-β activates non-canonical pathways such as MAPK/ERK, PI3K/AKT, and JNK [15]. Clinically, elevated TGF-β expression in gingival tissue and gingival crevicular fluid of periodontitis correlates with disease severity and decreases following non-surgical therapy, supporting its potential as a biomarker for treatment response [14].

In periodontitis, the role of TGF-β is complex and situation-dependent. TGF-β suppresses the activation of pro-inflammatory immune cells, including macrophages and T cells, and reduces the production of pro-inflammatory cytokines such as IL-1β and TNF-α [14]. Furthermore, TGF-β stimulates fibroblasts and PDL cells to synthesise collagen type I, fibronectin, and proteoglycans, which play essential roles in periodontal tissue regeneration and wound healing [15, 16].

TGF-β negatively regulates the early differentiation of PDL cells into hard tissue-forming cells, such as osteoblasts and cementoblasts, by competing with BMP-2 signalling. Inhibition of TGF-β enhances BMP-2-dependent calcification and accelerates the expression of ossification genes, including ALP, Runx2, and Osterix, during early differentiation. However, TGF-β is required for collagen synthesis at later stages, reflecting its dual function [35]. In contrast, excessive or prolonged TGF-β signalling results in abnormal ECM deposition and gingival fibrosis and induces senescence of PDL stem cells through increased ROS production, ultimately impairing tissue regeneration [14, 36]. This double role emphasises the requirement for precise regulation of TGF-β signalling to maintain periodontal homeostasis and supports its potential as a therapeutic target in periodontal disease [14, 35, 36].

EFFECTS OF CARVACROL ON PERIODONTAL-RELATED CYTOKINES, INCLUDING TGF-β

Given carvacrol's inhibitory effects on NF-κB and MAPK signalling described earlier, and the dual, context-dependent role of TGF-β outlined above, this section analyses how carvacrol may specifically influence TGF-β expression and other periodontal-related cytokines.

In HL-1 cardiomyocytes exposed to P. gingivalis LPS, carvacrol reduced TLR4, NF-κB, NALP3, IL-1β, and ROS production, demonstrating its ability to suppress inflammation induced by periodontal pathogens [11]. In non-periodontal models, carvacrol exhibited context-dependent effects on TGF-β: it increased TGF-β expression in an experimental autoimmune encephalomyelitis (EAE) model [30], but decreased TGF-β gene expression in a murine asthma model, accompanied by reduced IL-4 and IL-17 and increased IFN-γ and FOXP3 [37]. These results suggest that carvacrol's modulation of TGF-β is influenced by the specific inflammatory environment.

In human kidney-2 (HK-2) cells, carvacrol ameliorated TGF-β1-induced extracellular matrix deposition and reduced epithelial-mesenchymal transition through regulation of the PI3K/AKT pathway. Although this investigation was conducted in renal epithelial cells rather than periodontal tissues, it remains the only study to date directly demonstrating that carvacrol can modulate TGF-β1 signalling at the molecular level, thereby providing indirect evidence for its possible relevance to periodontal tissue [38]. Additionally, carvacrol exhibits antimicrobial activity against oral pathogens, including P. gingivalis, F. nucleatum, A. actinomycetemcomitans, and S. mutans, through disrupting bacterial cell membranes, inhibiting biofilm formation, and interfering with quorum sensing [8, 39].

A review of carvacrol's anti-inflammatory, antioxidant, antimicrobial, and anti-osteoclastic properties reported reductions in IL-1β, IL-6, TNF-α, and PGE2, as well as increased IL-10 across several models. However, this review did not specifically address carvacrol's modulation of TGF-β in periodontal models, leaving this an area that needs further investigation [9]. Supporting evidence from a non-periodontal oral tissue model demonstrated that propolis extract suppressed NF-κB while concurrently increasing TGF-β1 expression in odontoblast-like cells [40]. While this finding pertains to pulp rather than periodontal tissue, it

suggests a potential NF-κB–TGF-β crosstalk mechanism that carvacrol may also influence during periodontal inflammation. Although molecular and cytokine-level findings show several mechanisms by which carvacrol may regulate TGF-β, their significance for periodontal disease requires validation by tissue- and animal-level studies, as discussed in the following section.

PRECLINICAL EVIDENCE

Preclinical studies indicate that carvacrol holds therapeutic potential for periodontitis, although the current evidence base remains limited. Most available data derive from investigations of carvacrol's antimicrobial, anti-inflammatory, and antioxidant properties in diverse disease models, with relatively few studies directly testing its effects in periodontal disease models [9]. Carvacrol has exhibited antibacterial activity against oral pathogens commonly implicated in periodontitis, such as Porphyromonas gingivalis, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, and Streptococcus mutans [8]. The antibacterial mechanisms of carvacrol include disruption of bacterial cell membranes, inhibition of biofilm formation, and interference with quorum sensing [8, 39].

A recent review summarised the anti-inflammatory, antioxidant, antimicrobial, and anti-osteoclastic properties of carvacrol and magnolol in the context of periodontal disease and diabetes. The review reported that intragastric administration of carvacrol reduced alveolar bone resorption, inflammatory response, and MMP-9 expression in rat models of periodontitis. Additionally, topical application of carvacrol gel inhibited alveolar bone resorption and decreased periodontal bacterial load in similar animal models. However, the molecular mechanisms underlying the effects of gel formulation remain insufficiently characterised. *In vitro*, studies have demonstrated that carvacrol inhibits RANKL-induced osteoclast formation and induces apoptosis in mature osteoclasts, suggesting a potential mechanism for preventing alveolar bone resorption [9]. In periodontal ligament cell models, inhibition of TGF-β signalling with a TGF-β receptor kinase inhibitor (SB431542) enhanced BMP-2-dependent calcification and accelerated ossification gene expression, suggesting that modulation of TGF-β signalling may promote periodontal tissue regeneration. These data provide a rationale for further investigation of compounds capable of modulating TGF-β signalling in periodontal tissues [35].

Despite these promising results, direct evidence of carvacrol's effects on TGF-β signalling in periodontal tissues is currently lacking. The only study demonstrating carvacrol-mediated modulation of TGF-β1 signalling was performed in a non-periodontal model using HK-2 renal cells [38]. No investigations have specifically addressed whether carvacrol influences TGF-β expression or signalling in gingival fibroblasts, periodontal ligament cells, or animal models of periodontitis [9]. Consequently, although preclinical data support the antimicrobial, anti-inflammatory, and anti-osteoclastic properties of carvacrol, additional studies are required to determine its capacity to modulate TGF-β signalling in periodontal disease [9, 35, 38].

CONCLUSIONS

Carvacrol demonstrates well-established anti-inflammatory and antimicrobial effects relevant to periodontal disease, as indicated by decreased pro-inflammatory cytokines, increased interleukin-10 (IL-10), and direct antibacterial activity against key periodontal pathogens. However, the specific relationship between carvacrol and transforming growth factor-beta (TGF-β) expression in periodontal tissue remains insufficiently characterised. TGF-β exhibits a dual, context-dependent role in periodontal tissue, promoting early anti-inflammatory responses and matrix repair, but causing fibrosis and periodontal ligament stem cell senescence when its expression is sustained. Therefore, the impact of carvacrol on TGF-β should be interpreted in relation to the cellular and pathological context, rather than as a simple increase or decrease in expression.

Current evidence directly linking carvacrol to TGF-β modulation is limited to a few non-periodontal models, such as an autoimmune central nervous system condition (experimental autoimmune encephalomyelitis), a murine asthma model, and renal epithelial cells. None of these models precisely represent the periodontal microenvironment. Direct investigations of carvacrol-induced changes in TGF-β expression in gingival fibroblasts, periodontal ligament cells, or animal models of periodontitis are currently lacking. Future research needs to prioritise direct evaluation of carvacrol's effects on TGF-β expression and signalling using periodontal cell models and in vivo periodontitis models. Improved understanding of this relationship may facilitate the development of carvacrol as a targeted adjunct in periodontal therapy.

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