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An Updated Review of Research into Carvacrol and Its Biological Activities

Kemal Husnu Can Baser [1*], Ismail Celil Haskologlu [2] and Emine Erdag [3]

[1]*Department of Pharmacognosy, Faculty of Pharmacy, Near East University, Lefkoşa, Turkish Republic of Northern Cyprus*
[2]*Department of Pharmacology, Faculty of Pharmacy, Near East University, Lefkoşa, Turkish Republic of Northern Cyprus*
[3]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Near East University, Lefkoşa, Turkish Republic of Northern Cyprus*

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Abstract: Carvacrol, a monoterpenic phenol found abundantly in essential oils of *Origanum*, *Thymus*, *Satureja*, *Thymbra* and *Lippia* genera, is recognized for its extensive range of biological and pharmacological activities. This bioactive compound, primarily responsible for the health-promoting properties of oregano essential oil, exhibits diverse functionalities including antimicrobial, antitumor, antimutagenic, analgesic, anti-inflammatory, antioxidant, and neuroprotective effects. Its therapeutic applications extend to managing gastrointestinal ailments, reducing oxidative stress, and serving as an insecticidal agent. Furthermore, carvacrol has demonstrated potential as a feed additive and in honeybee breeding. Advances in encapsulation and nanotechnology have enhanced its stability and bioavailability, broadening its utility across food, pharmaceutical, and agricultural industries. This review synthesizes the evidence for carvacrol's biological activities and explores its possible *in vivo* mechanisms of action, emphasizing its promise as a natural therapeutic agent.

Keywords: Oregano; monoterpenic phenol; biological activity; carvacrol.

1. Introduction

Oregano oil, renowned for its therapeutic and culinary uses, has been an integral part of traditional medicine for centuries [1]. Carvacrol, a monoterpenic phenol, is the primary component responsible for the efficacy of the oil. It is found abundantly in various essential oils of *Origanum*, *Thymbra*, *Thymus*, and *Satureja* genera from the Lamiaceae family, as well as in the *Lippia* species from the Verbenaceae family. Its structural isomer, thymol, is also present, albeit in smaller quantities [2]. Among these, *Origanum* species account for the majority of oregano traded globally, highlighting their economic and botanical importance [3].

* Corresponding author: E-Mail: kemalhusnucan.baser@neu.edu.tr

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Additionally, the essential oil of *Plectranthus amboinicus (*Lour.) Spreng, a member of the Lamiaceae family, gained attention for its high carvacrol content, making it one of the few non-Thymus and non-Lippia plant species recognized for significant carvacrol presence

Carvacrol and thymol are biosynthesized from γ-terpinene via the intermediate *p*-cymene. In addition to these phenols, terpinen-4-ol, cumin alcohol, and *p*-cymen-8-ol can also be found in carvacrol-containing oils, as intermediate products of biosynthesis. These compounds not only contribute to the biological activity of oregano oil but also influence its distinct aroma and therapeutic potential [5].

The safety profile of carvacrol was a critical aspect of its growing acceptance in pharmacological and industrial applications. Compared to phenol, carvacrol and thymol exhibit significantly lower toxicity. This makes carvacrol a safer alternative for various applications, from biological agents to dietary supplements [6].

While previous reviews have extensively explored carvacrol's biological activities [7-18], the rapid growth of research in this field necessitates an updated perspective. Recent studies have uncovered novel mechanisms of action, emerging therapeutic applications, and innovative delivery systems, expanding our understanding of this versatile compound [19-20]. This review aims to summarize these advancements, bridging existing knowledge gaps and providing insights into the therapeutic potential and future directions of carvacrol research. A literature search was conducted ensuring a comprehensive and systematic analysis using databases such as Scopus, Web of Science, and Google Scholar. Studies published between 1995 and 2025 were included, focusing on carvacrol and carvacrol-containing essential oils. Inclusion criteria encompassed peer-reviewed articles, reviews, and experimental studies providing quantitative data on carvacrol's bioactivity, while exclusion criteria eliminated non-English articles and studies without full-text access.

2. Structural and Physical Properties of Monoterpenic Phenols

The biosynthetic origin of carvacrol and thymol differs from that of phenol. Carvacrol and thymol possess a monoterpenic framework, featuring an aromatic ring with methyl and isopropyl substituents positioned in a para configuration (1,4-positions) relative to each other [2, 5, 21].

Although carvacrol and thymol share structural similarities, the only difference lies in the position of the hydroxyl group. Structurally, phenol lacks the methyl and isopropyl substituents present in carvacrol and thymol (Figure 1). Phenol, carvacrol, and thymol exhibit distinct physical states and melting points. Phenol is crystalline with a melting point of 40–85°C, while carvacrol remains in liquid form under normal conditions, and thymol is also crystalline with a melting point of 50–51°C [5, 22].

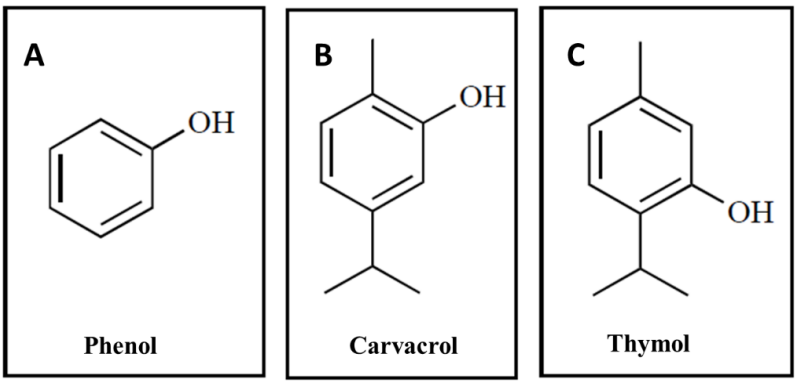

Figure 1. Phenol vs monoterpenic phenols

3. Biological Activities of Carvacrol

3.1. Antinociceptive Effects of Carvacrol

3.1.1. Pain-Relieving Mechanisms of Carvacrol

Carvacrol, a key component of essential oils derived from *Origanum onites* L., was demonstrated to exhibit significant analgesic properties. Comparative studies using the tail-flick test in mice showed that *O. onites* oil from the İzmir region (containing 67% carvacrol) produced a tail-flick latency of 8.60 ± 0.67 s at 0.33 mL/kg, which was statistically significant ($p < 0.005$) compared to the control (3.40 ± 0.87 s). This effect was comparable to fenoprofen (6.00 ± 0.65 s at 8 mg/kg) and morphine (16.00 ± 0.80 s at 2 mg/kg), confirming its notable analgesic activity primarily attributed to carvacrol [23]. Mechanistic studies have shown that carvacrol can reversibly modulate the activity of the rat sciatic nerve in a concentration-dependent way. Additionally, it reduces sodium ion currents through voltage-gated channels in dorsal root ganglion neurons, reaching an IC_{50} of 0.37 ± 0.05 mM at 0.6 mM, highlighting its potential as an anesthetic agent [24].

3.1.2. Synergistic Effects of Carvacrol with Other Natural Compounds

Further studies have explored the modulatory effects of carvacrol on the analgesic properties of other natural compounds. For instance, *p*-cymene, a monoterpene commonly found alongside carvacrol in plant species, has demonstrated significant antinociceptive effects in oncologic pain models. Preclinical investigations in male Swiss mice with S180 cell-induced hyperalgesia revealed that subcutaneous coadministration of carvacrol and *p*-cymene effectively decreased mechanical hyperalgesia, spontaneous nociception, and palpation-induced nociception. These effects were achieved without impacting tumor progression or neuromuscular function, and the underlying mechanisms were associated with the modulation of ascending and descending pain pathways and calcium channel activity [25].

3.1.3. Potential in Orofacial Pain Management

Carvacrol's potential in managing orofacial pain has also been extensively investigated. Preclinical murine models have demonstrated their anti-hypernociceptive and anti-inflammatory effects, suggesting their utility in alleviating conditions such as migraine-associated pain. Administered at doses of 25–50 mg/kg, carvacrol was shown to reverse thermal and mechanical allodynia, decrease head-scratching behavior, and mitigate light sensitivity in migraine models. These effects are likely mediated through its anti-inflammatory and antioxidant actions, targeting multiple mechanisms implicated in migraine pathology [26-28]. In addition, carvacrol demonstrated broad-spectrum analgesic activity in other orofacial pain models including formalin-, capsaicin-, and glutamate-induced pain [29].

3.1.4. Carvacrol and TRPV3-Associated Pathways

As an agonist of the Transient Receptor Potential Vanilloid (TRPV3) channel, carvacrol modulates thermosensation and pain perception by activating peripheral warm fibers. In human studies, carvacrol transiently induced irritation and self-desensitization while enhancing innocuous warmth perception, emphasizing its involvement in TRPV3-mediated mechanisms [30].

Carvacrol also plays a role in other TRPV3-associated pathways. In cardiomyocytes, TRPV3 activation by carvacrol exacerbates pathological hypertrophy through the calcineurin/NFATc3 signaling pathway, suggesting TRPV3 as a potential target for managing cardiac hypertrophy [31]. In skin keratinocytes, moderate TRPV3 activation promotes proliferation via Ca^{2+}-mediated TGFα/EGFR/PI3K/NF-κB signaling, though excessive activation induces cytotoxicity [32].

Additionally, carvacrol-induced TRPV3 activation enhances lipolysis in adipocytes *via* the NRF2/FSP1 axis, providing insights into its potential for addressing metabolic syndrome [33]. In the

gastrointestinal tract, TRPV3 activation in distal colon epithelial cells elevates intracellular Ca^{2+} levels and stimulates ATP release, implicating carvacrol in gut physiology and signaling [34].

3.1.5. Antioxidant and Analgesic Activities under Oxidative Stress

The analgesic potential of carvacrol particularly under oxidative stress conditions has also been studied across various experimental models. *In vitro* studies demonstrated carvacrol's potent antioxidant activity, including nitric oxide scavenging and lipid peroxidation inhibition. In murine models, carvacrol diminished the abdominal writhing ($p < 0.001$) without engaging opioid pathways. Additionally, carvacrol significantly alleviated capsaicin-induced (63.1–95.8%, $p < 0.001$) and glutamate-induced (46.4–97.9%, $p < 0.01$) nociception, while increasing latency at 100 mg/kg ($p < 0.05$), without impairing motor performance [35].

Derivatives of carvacrol, such as isopropoxy-carvacrol (IPC), exhibit enhanced antinociceptive and anti-inflammatory effects, reducing lipoperoxidation and nitric oxide levels, and further broadening its therapeutic scope [36].

3.1.6. Studies in Aquatic Models

A recent zebrafish larvae study confirmed carvacrol's ability to mitigate pain responses, showcasing its potential as an analgesic in aquatic models [37]. Collectively, these findings highlight carvacrol's diverse mechanisms of action and its promise as a multi-target analgesic agent.

3.2. Antiinflammatory Activities of Carvacrol

3.2.1. Antiinflammatory Mechanism of Action

Carvacrol has demonstrated significant anti-inflammatory properties through multiple mechanisms, including the inhibition of angiotensin-converting enzyme 2 (ACE2), lipoxygenase (LOX), and cyclooxygenase (COX) enzymes [38-41].

The molecular mechanisms underlying carvacrol's anti-inflammatory effects involve the inhibition of prostaglandin E_2 (PGE_2) production *via* COX-2, exhibiting potency comparable to standard inhibitors like indomethacin. In vitro COX-2 assay results showed that carvacrol inhibited PGE_2 production with an IC_{50} value of 0.8 μM, which is comparable to indomethacin (IC_{50} = 0.7 μM) and NS-398 (IC_{50} = 0.8 μM) [39]. Topical application of carvacrol (10 mg/ear) significantly reduced ear edema by 37.2% in a croton oil-induced inflammation model, whereas its structural isomer thymol exhibited an irritant response [40].

Furthermore, a study assessing carvacrol supplementation in an inflammatory model demonstrated a substantial reduction in pro-inflammatory cytokines, including TNF-α and IL-6 levels, alongside decreased oxidative stress markers, reinforcing its role in inflammation modulation [41].

3.2.2. Hybrid Compounds: Carvacrol-Ibuprofen Codrug

The identification of new anti-inflammatory drugs is critical in contemporary medicine. An innovative approach involves the synthesis of hybrid compounds that integrate natural and synthetic agents. An example is a codrug combining carvacrol (CDCC), with ibuprofen, a drug commonly known for its non-steroidal anti-inflammatory properties. Computational studies revealed that although CDCC has limited aqueous solubility ($LogP \geq 5.0$), it exhibits remarkable pharmacokinetic properties. *In vitro*, CDCC significantly reduced cytokine levels without cytotoxicity. Furthermore, CDCC showed an estimated LD_{50} of approximately 5000 mg/kg and significantly reduced leukocyte count and IL-1β levels *in vivo*, outperforming a physical mixture of carvacrol and ibuprofen at the same dose [42].

3.2.3. Role of Carvacrol in Inflammasome pathway

Carvacrol has also demonstrated protective effects in models of lipopolysaccharide (LPS)-induced septic cardiomyopathy. In H9c2 cardiomyoblast cells, it reduced reactive oxygen species production and mitigated pyroptosis by inhibiting the NLRP3 inflammasome. *In vivo*, carvacrol improved echocardiographic parameters, enhanced myocardial antioxidant levels, and decreased pro-inflammatory cytokines. Carvacrol also inhibited key proteins involved in the inflammasome pathway, such as NLRP3, ASC, caspase-1, and gasdermin-D, while modulating autophagy-related proteins, suggesting its potential to combat sepsis-related myocardial dysfunction [43].

3.2.4. Advanced Formulations of Carvacrol for Antiinflammatory Action

In recent research, advanced formulations such as niosomal gels were developed to enhance carvacrol's bioavailability and therapeutic efficacy. These multilamellar vesicles facilitated superior skin penetration and demonstrated improved drug release and antioxidant activity compared to conventional topical formulations, highlighting their potential for managing inflammatory conditions [44]. Similarly, carvacryl acetate, a derivative of carvacrol, exhibited enhanced anti-inflammatory activity when formulated as a nanoemulsion. This preparation displayed stable pharmacokinetics and significantly reduced IL-1β levels in an inflammation model, particularly via oral administration, without inducing toxicity [45].

3.2.5. Anti-inflammatory Effects in Preclinical Models

Carvacrol was observed in preclinical studies, where pretreatment significantly inhibited carrageenan- and TNF-α-induced hypernociception and edema. It also reduced nitrite production and TNF-α levels in pleural lavage, underscoring its potential in managing inflammatory diseases [27]. Co-administration with pioglitazone further demonstrated synergistic effects in reducing oxidative stress and systemic inflammation induced by paraquat exposure [46].

Additionally, *in vivo* studies utilizing a chorioallantoic membrane (CAM) assay revealed that *Origanum onites* L. essential oil, rich in carvacrol, significantly reduced inflammation-induced angiogenesis, with a reduction in neovascularization compared to control groups [47].

3.2.6. Application of Carvacrol in Rheumatoid Arthritis

Carvacrol has also been reported to show notable activity against arthritis when tested using Freund's adjuvant-induced arthritis model. In a rat model, oral administration of carvacrol (50 mg/kg) significantly reduced paw edema by 35.2% and hypernociceptive response by 42.1% ($p < 0.05$) compared to untreated arthritic controls. Additionally, myeloperoxidase activity, a key inflammatory marker, was suppressed by 24.8% ($p < 0.05$), highlighting its potential in managing rheumatoid arthritis [48].

3.3. Antioxidant Activities of Carvacrol

3.3.1. Carvacrol-Rich Essential Oils and Their Antioxidant Effects

The antioxidant properties of carvacrol were the subject of extensive research. Essential oils derived from *Thymbra capitata* (L.) Cav.* and *Origanum compactum* Benth., both rich in carvacrol, exhibit substantial antioxidant activity attributed to their phenolic composition, including thymol and γ-terpinene [49, 50]. Similarly, essential oils from *Thymus capitatus* (L.) Hoffmanns. & Link. cultivated in Tunisia, containing carvacrol concentrations of 62–83%, demonstrate robust antioxidant

* *Thymbra capitata* is synonymous with *Thymus capitatus*.

and antimicrobial effects against pathogens such as *Bacillus cereus, Salmonella sp*., and multi-resistant *Staphylococcus aureus* [51, 52].

The *Zataria multiflora* Boiss. essential oil, rich in carvacrol and p-cymene, was demonstrated to involve the reduction of nitric oxide levels and the neutralization of malondialdehyde due to its antioxidant properties [53]. Essential oils from *Origanum dubium* Boiss. further highlight carvacrol's potential by demonstrating strong superoxide anion scavenging abilities and lipoxygenase inhibition [54]. Hydrosols of *Syzygium aromaticum* (L.) Merr. & L.M. Perry and *Thymus vulgaris* L., rich in eugenol and carvacrol respectively, rank among the most effective natural antioxidants, although they exhibit limited activity against superoxide anions [55].

3.3.2. Carvacrol in Hepatic Protection as Natural Antioxidant

Beyond its role in essential oils, carvacrol effectively prevents lipid peroxidation and mitigates oxidative damage in hepatic cells, as demonstrated in models of diethylnitrosamine-induced hepatocellular carcinogenesis [56]. Additionally, carvacrol and thymoquinone from *Nigella sativa* L. seeds were identified as potent natural antioxidants with broad applications [57].

3.3.3. Machine Learning Insights into Antioxidant Activity

The individual contributions of essential oil components to antioxidant activity have also been evaluated in a recent study analyzing 61 commercial essential oils. Machine learning algorithms identified carvacrol, thymol, limonene, and linalool as significant contributors to antioxidant effects, with *Cananga odorata* (Lam.) Hook.f. & Thomson and *Cinnamomum verum* J.Presl oils demonstrating exceptional antioxidant activity [58]. Similarly, essential oil from *Monarda didyma* L., rich in carvacrol, thymol, and *p*-cymene, exhibited strong DPPH radical scavenging and anti-inflammatory effects through the modulation of IL-6 and miR-146a expression, indicating therapeutic potential [59].

3.3.4. Enhancing Antioxidant Stability in Food and Pharmaceuticals

Carvacrol’s antioxidant and antibacterial properties were highlighted in food preservation, particularly against spoilage bacteria like *Shewanella putrefaciens* [60]. Oregano essential oil, containing carvacrol and thymol, disrupts bacterial morphology, increases reactive oxygen species production, and reduces intracellular ATP levels in *Listeria monocytogenes*, showcasing its utility in food safety [61].

3.4. Antiprotozoal and Antimalarial Activities of Carvacrol

Carvacrol has demonstrated promising antiparasitic activity against *Leishmania* and *Trypanosoma* species. A recent study demonstrated the antiprotozoal activity of *Origanum onites* essential oil, attributing its significant in vitro efficacy against *Trypanosoma brucei rhodesiense* (IC_{50} = 0.18 μg/mL) to its carvacrol and thymol content, while its effects on *Leishmania donovani* and *Plasmodium falciparum* (IC_{50} = 17.8 and 7.9 μg/mL, respectively) were moderate [62]. The bioactivity of *O. onites* essential oil is influenced by extraction parameters, with extraction time significantly affecting its composition, as evidenced by carvacrol content peaking at 120 minutes (89–91%), which is crucial for optimizing its therapeutic potential [63].

Origanum compactum possesses an essential oil abundant in carvacrol, which has demonstrated significant antimalarial potential. Carvacrol emerged as the dominant compound (36.46%) in the leaf essential oil, followed by thymol and p-cymene. The extracts of *O. compactum* aerial parts, along with the essential oil, were assessed for antioxidant, antimalarial, and anticancer activities. Additionally, these extracts demonstrated cytotoxic effects. Importantly, the essential oil was classified as non-toxic, supporting its potential as a natural therapeutic agent [64].

3.5. Antimutagenic Activities of Carvacrol

Carvacrol, a major component of *Origanum* species, has demonstrated notable antimutagenic properties. The methanol extract of *Origanum vulgare* L. subsp. *vulgare* was evaluated using the Ames/Salmonella histidine reversion assay, incorporating *Salmonella typhimurium* tester strains TA1535 (base pair substitution mutations) and TA1538 (frameshift mutations). The extract was tested against direct-acting mutagens. The extract significantly reduced mutagenicity in TA1535 ($P < 0.05$), but no significant effect was identified in TA1538. In addition, moderate antimutagenic effects were observed in both strains, which may be attributed to the extract's antioxidant properties and its ability to alter lipid membranes and ion channel permeability [65].

Further insights into carvacrol's antimutagenic potential were obtained from studies on the essential oil of *Origanum compactum* [66, 67]. Using gas chromatography-mass spectrometry, carvacrol was identified as a key constituent. The mutagenic and antimutagenic potentials of the oil were illustrated. For this assessment, *Drosophila melanogaster* was utilized as the model organism. The oil showed no mutagenic effects under standard or high bioactivation conditions. When tested for antimutagenicity, it strongly inhibited mutagenicity induced by the indirect mutagen urethane (URE), particularly under high bioactivation conditions. However, its inhibition of methyl methanesulfonate-induced mutagenicity was mild. Fractionation of the essential oil identified seven fractions, two of which exhibited significant inhibition of URE-induced mutagenicity. Further analysis of these fractions, along with pure carvacrol and thymol, revealed that carvacrol was the principal active component, exerting antimutagenic effects comparable to the crude oil without evident synergistic contributions from other constituents [67].

3.6. Antiplatelet Activities of Carvacrol

Carvacrol has demonstrated significant antiplatelet activity, highlighting its potential therapeutic role in preventing thrombosis. The methanol-soluble fraction of black cumin oil, extracted from *Nigella sativa* seeds via cold-press methods, demonstrated significant suppression of platelet aggregation triggered by arachidonic acid as well as effects on blood coagulation. Using bioactivity-driven fractionation techniques, this methanol-soluble segment yielded thymol and carvacrol. These compounds exhibited strong inhibitory effects on platelet aggregation [68].

Subsequently, the antiplatelet effects of these compounds, along with eight structurally related analogs, were further evaluated. The results revealed that compounds containing aromatic hydroxyl and acetoxyl functional groups exhibited superior inhibitory activity compared to aspirin, a standard therapeutic agent for thrombosis. These findings underscore the potential of carvacrol and structurally related compounds as effective antiplatelet agents, warranting further investigation for their application in managing thrombotic disorders [68].

3.7. Antispasmodic Activities of Carvacrol

Carvacrol has demonstrated significant antispasmodic properties, as confirmed by numerous experimental studies [69-75].

3.7.1. Effects on Rat Ileum and Diarrhea Models

The essential oil of *Satureja montana* L., rich in carvacrol, has traditionally been used to alleviate gastrointestinal disorders such as spasms and diarrhea. Studies on isolated rat ileum tissues demonstrated its spasmolytic efficacy, showing the greatest activity against spontaneous contractions, followed by those induced by electrical field stimulation, KCl, and $CaCl_2$. Additionally, its essential oil exhibited antidiarrheal effects in castor oil-induced diarrhea models, potentially mediated by mechanisms involving Kv channel activation and Ca^{2+} channel inhibition [70].

Similarly, essential oil from *Origanum acutidens* (Hand.-Mazz.) letswaart, containing 65% carvacrol, displayed significant spasmolytic activity, completely inhibiting spontaneous contractions in isolated rat ileum at 0.1 mg/mL. The oil also demonstrated strong antioxidant and antimicrobial

activities, further emphasizing its therapeutic potential [71]. Comparative studies on essential oils from two Mexican oreganos, *Poliomintha longiflora* A. Gray and *Lippia graveolens* Kunth, revealed carvacrol's role in selectively inhibiting carbachol-induced contractions in guinea pig ileum, supporting its spasmolytic effects [72].

3.7.2. Effects on Smooth Muscle Models

In aquaculture, carvacrol showed promise in managing bacterial infections caused by *Edwardsiella piscicida*. Carvacrol was reported to reduce biofilm formation, virulence gene expression, and cytotoxicity while improving survival rates in infected zebrafish. These findings highlight carvacrol's potential for controlling zoonotic pathogens while exhibiting antispasmodic properties in smooth muscle models [73].

3.7.3. Mechanistic Insights: Calcium Channel Modulation

Studies on *Origanum compactum* essential oil further confirmed carvacrol's spasmolytic activity, showing inhibition of muscle contractions induced by acetylcholine, histamine, serotonin, and $BaCl_2$. The oil modulated calcium signaling by reducing intracellular and extracellular calcium availability, inhibiting stored calcium release, and blocking extracellular calcium influx, ultimately relaxing smooth muscle cells [74].

3.8. Anxiolytic Activities of Carvacrol

Carvacrol has shown promising anxiolytic-like effects in preclinical studies, particularly when evaluated in established behavioral models of anxiety [75, 76].

In a recent study, carvacrol was orally given to male mice, and the applied concentrations were 12.5, 25, and 50 mg/kg. Carvacrol significantly increased anxiolytic-associated behaviors in the elevated plus maze (EPM) test without impairing spontaneous motor activity. Importantly, the anxiolytic effects observed in the EPM were reversible with flumazenil (a GABA receptor antagonist), suggesting the involvement of GABAergic pathways. As a result, carvacrol did not affect the onset of sleep or duration in barbiturate-induced sleeping time tests, indicating its anxiolytic effects are independent of sedative properties [75].

In addition, the anxiolytic properties of carvacryl acetate, which is derived from carvacrol, were investigated. Behavioral studies demonstrated that carvacryl acetate induces pronounced anxiolytic-like effects. These effects were likely mediated through GABAergic pathways, and carvacryl acetate exhibited no psychomotor side effects [76].

3.9. Bronchodilatory Activities of Carvacrol

Carvacrol has demonstrated significant bronchodilatory effects, as evidenced by its ability to relax precontracted tracheal chains in guinea pig models. In a previous study, three experimental groups were analyzed: non-incubated tissues, tissues incubated with propranolol (a beta-blocker), and tissues incubated with chlorpheniramine (an H1 receptor antagonist). Carvacrol exhibited potent relaxant effects across all groups, significantly outperforming ethanol and theophylline, a standard bronchodilator ($p < 0.05$ to $p < 0.001$). Notably, its mechanism of action was independent of beta2-adrenergic stimulation, H1 histamine receptor inhibition, or muscarinic receptor blockade, as evidenced by similar efficacy in the presence of these inhibitors. The observed relaxation effects were dose-dependent, further underscoring carvacrol's potential as a bronchodilator [77].

Further investigations explored the bronchodilatory components of *Carum copticum* L. essential oil, focusing on its anticholinergic, H1 histamine inhibitory, and xanthine-like activities. Fractionated components of the essential oil were tested on guinea pig tracheal chains, under similar experimental conditions. Essential oil fractions 2 and 3 showed notable relaxant effects dependent on concentration, comparable to theophylline, particularly in the methacholine-precontracted tissues ($p < 0.05$ to $p < 0.002$). Carvacrol, identified as a key component of Fraction 2, demonstrated relaxant activity similar

to theophylline, with greater efficacy than ethanol. These findings highlight that the primary bronchodilatory effects of *Carum copticum* essential oil are attributed to carvacrol, providing additional but lesser contributions [78].

3.10. Cardiovascular Benefits of Carvacrol

Among the pathological processes driving cardiovascular disease (CVD) progression, inflammation, and apoptosis are pivotal, particularly the loss of cardiomyocytes. In this context, natural terpenophenolic compounds, including carvacrol, have shown potential in mitigating inflammation and apoptosis, positioning them as promising nutraceutical candidates for alleviating CVD-related complications [79].

3.10.1. Vascular Regeneration and Endothelial Protection

Carvacrol exhibits diverse biological activities, including potent antioxidant, antihypertensive, and cardioprotective effects. Its role in vascular regeneration was explored in hypertensive models, where carvacrol improved endothelial repair and endothelial progenitor cell (EPC) functionality in spontaneously hypertensive rats (SHR). When administered, carvacrol enhanced EPC migration, colony formation, and nitric oxide synthase activity, while reducing reactive oxygen species and cellular senescence. Moreover, it decreased vascular ROS levels and upregulated endothelial markers such as CD31 and CD34, suggesting its efficacy in mitigating endothelial dysfunction [80].

3.10.2. TRPV3 Activation and Vasodilation in Cardiovascular Health

The cardioprotective effects of the Mediterranean diet, rich in oregano—were partially attributed to carvacrol's ability to activate TRVP3 cation channels. Research has demonstrated that carvacrol activates TRPV3 channels in the endothelium, inducing calcium influx and smooth muscle hyperpolarization, which results in vasodilation. This process is inhibited by TRPV blockers, such as ruthenium red, underscoring the role of TRPV3 activation in arterial relaxation and its contribution to the cardiovascular benefits associated with the Mediterranean diet [81].

3.10.3. Role of Carvacrol in Cardiac Hypertrophy and Hypertension

In the context of cardiac hypertrophy, carvacrol has demonstrated anti-apoptotic properties. Studies in rats subjected to aortic banding showed that carvacrol reduced average blood pressure and the proportion of heart weight to body weight. It also modulated apoptosis-related genes by the inhibition of pro-apoptotic factors (Bad, Bax) and the promotion of anti-apoptotic factors (Bcl-2, Bcl-xL), thereby protecting cardiomyocytes from programmed cell death [82].

Regarding hypertension, carvacrol was shown to induce vasodilation via TRPA1 channels. Studies identified carvacrol as a TRPA1 agonist, with antagonism of TRPA1 significantly reducing its vasodilatory effects. Molecular docking and in silico analyses have further proposed novel TRPA1 activators based on carvacrol's structure, presenting promising avenues for developing antihypertensive therapies [83].

3.11. Food Additive and Food Preservation Activities of Carvacrol

3.11.1. Interaction of Carvacrol with Food Matrix Components

Carvacrol has garnered significant attention for its antimicrobial properties, particularly in food preservation. The interaction between food matrix components and essential oil components can significantly influence their efficacy [84-89].

A study revealed that substances like bovine serum albumin and carbohydrates significantly interfere with or completely inhibit the antimicrobial activity of essential oil components, including

vanillin. However, compounds such as carvacrol showed greater effectiveness in overcoming these inhibitory effects when D-lactose was involved [84].

3.11.2. Antimicrobial Effects Against Foodborne Pathogens

Addressing foodborne pathogens such as *Campylobacter jejuni*, a leading cause of bacterial foodborne illness, carvacrol has shown potent antimicrobial activity. In combination with peroxyacetic acid, carvacrol effectively reduced *Campylobacter* counts on poultry products. Peroxyacetic acid alone achieved reductions of up to 3.3 log units on chicken skin, while modest effects were observed on chicken fillets when used in combination. These results highlight the suitability of carvacrol as a natural antimicrobial agent in poultry processing, especially for surface treatments [85].

3.11.3. Carvacrol in Postharvest Disease Management

The antifungal efficacy of carvacrol was demonstrated in studies on *Botrytis cinerea*, the pathogen responsible for gray mold in cherry tomatoes. Essential oils from *Origanum vulgare*, rich in carvacrol and thymol, significantly inhibited mycelial growth and spore germination. Vapor contact tests showed that the essential oil at 250 mg/L reduced decay by 96.39%, with complete inhibition of gray mold achieved at 125 mg/L concentrations of thymol and carvacrol. These results suggest the potential of *O. vulgare* essential oil as an eco-friendly, botanical fungicide for postharvest disease management [86].

3.11.4. Carvacrol-Fortified Coatings for Poultry Preservation

In poultry preservation, coatings fortified with carvacrol have shown promise in controlling *C. jejuni*. Gum Arabic and chitosan coatings containing carvacrol reduced *C. jejuni* counts by up to 3.0 $\log_{10}$ CFU during refrigerated storage. Furthermore, these coatings modulated the expression of virulence and survival genes in *C. jejuni* while maintaining the sensory qualities of chicken wingettes. This highlights the efficacy of carvacrol as a natural intervention to enhance food safety [87].

3.11.5. Bioactive Films and Packaging Innovations

Bioactive films incorporating carvacrol have emerged as innovative solutions in food packaging. Films made from polylactic acid and chitosan, enhanced with carvacrol and other natural extracts, demonstrated robust antimicrobial properties against pathogens like *Listeria monocytogenes* and *Salmonella spp*. These materials extended the shelf-life of meat products, making them suitable for refrigerated storage [88, 89].

3.12. Role of Carvacrol in Erectile Dysfunction

Carvacrol was evaluated for its therapeutic potential in managing erectile dysfunction (ED) associated with aging, employing an aging model induced by D-(+)-galactose. The study involved five groups of male rats, including control and treatment groups receiving carvacrol or sildenafil. Findings revealed that carvacrol alleviated ED by mitigating excessive contractility, enhancing endothelial performance, and preserving the structural integrity of erectile tissues, highlighting its protective effects on cavernous endothelial health. Carvacrol also preserved the structural integrity of erectile tissues and decreased cellular senescence, likely through its antioxidative mechanisms. These findings highlight carvacrol's promise as an innovative therapeutic option for treating age-related erectile dysfunction [90].

Further insights into the potential mechanisms of natural compounds, including carvacrol, in treating sexual dysfunction were provided through integrative pharmacological analyses. A study investigating the Yougui pill combined with the Buzhong Yiqi decoction identified active components and their therapeutic targets via pharmacokinetic screening. Functional analyses involving pathway mapping, biological process categorization, and interaction network construction revealed a

pharmacological network consisting of 89 nodes and 176 connections. Among these, 12 herbal medicines (*e.g.*, orange peel, licorice, and ginseng), nine bioactive compounds (*e.g.*, carvacrol, quercetin, and stigmasterol), and 62 target proteins were identified. Six key pathways were identified, encompassing mechanisms related to signal transduction, cyclic nucleotide signaling, and receptor-ligand interactions involved in neural activity. These pathways suggest that the active components modulate critical cellular processes to exert therapeutic effects on sexual dysfunction, further supporting the therapeutic potential of carvacrol [91].

3.13. Anticancer Activities of Carvacrol

3.13.1. Chemopreventive Potential of Carvacrol in Detoxification Pathways

Carvacrol, has demonstrated promising anticancer properties in various studies. The essential oil of *Thymus pulegioides* L., containing carvacrol (17.9%) and thymol (4.4%), has shown chemopreventive potential by modulating phase II detoxification enzymes. These findings indicate the potential utility of *Thymus*-derived compounds in cancer prevention and treatment strategies [92].

3.13.2. Carvacrol Formulations against Multiple Myeloma

Carvacrol-loaded nanocomposites of selenium/chitosan/polyethylene glycol (SCP-Car-NCs) exhibited significant cytotoxic effects against multiple myeloma (MM) U266 cells. These nanocomposites diminished cell proliferation, increased the accumulation of oxidative radicals, and initiated apoprosis through the Bax/caspase pathway. These results highlight SCP-Car-NCs as a promising therapeutic option for managing multiple myeloma [93].

3.13.3. TRPV3 Activation and Dual Role in Breast Cancer Progression

Carvacrol's role as a TRPV3 channel agonist in breast cancer was explored. Increased levels of TRPV3 expression were detected in breast cancer tissues as well as in associated cell lines. Silencing TRPV3 using siRNA significantly inhibited MCF-7 cell migration and proliferation, induced apoptosis, and reduced intracellular calcium levels ($[Ca^{2+}]i$). In contrast, activating TRPV3 with carvacrol led to enhanced migration and proliferation while suppressing apoptosis. Mechanistic studies revealed that carvacrol-induced TRPV3 activation elevated the phosphorylation of EGFR and AKT, pathways known to drive cancer progression. These effects were reversed by co-treatment with EGFR (Erlotinib) and PI3K (LY294002) inhibitors, which mitigated carvacrol-induced cell migration and proliferation while promoting apoptosis. This underscores the dual role of carvacrol in modulating cancer pathways through TRPV3 activation, presenting both therapeutic potential and mechanistic insights into breast cancer progression [94].

3.13.4. Anti-Angiogenic and Pro-Apoptotic Effects of Carvacrol

In angiogenesis studies, *Origanum onites* L. essential oil, rich in carvacrol, demonstrated anti-proliferative and pro-apoptotic effects in transformed fibroblasts and endothelial cells. These effects included inhibition of tube formation and cell migration *in vitro*, suggesting its potential for anti-cancer therapies [95].

A recent study investigated the cytotoxic and pro-apoptotic effects of *Origanum dubium* Boiss. essential oil, which contains carvacrol as its major constituent (88.3%), on human mesenchymal stem cells (hMSC-telo1) and their tumorigenic counterparts. The study demonstrated that carvacrol exerted cytotoxic effects on tumorigenic hMSC-telo1 cells at all tested concentrations. In addition, the carvacrol-rich essential oil of *Thymus capitatus* (L.) Hoffm. & Link selectively spared normal hMSC-telo1 cells while inducing cytotoxicity in tumorigenic cells at a concentration of 0.005 v/v %. Apoptotic cell death was confirmed via TUNEL assay, which revealed DNA fragmentation in response to carvacrol exposure. These findings indicate that carvacrol induces apoptosis in cancerous

mesenchymal cells, suggesting a potential anti-angiogenic and pro-apoptotic role in cancer therapy [96].

3.14. Nematicidal Activities of Carvacrol

3.14.1. Carvacrol as a Plant-Derived Nematicidal Agent

Plant-parasitic nematodes, particularly those belonging to the *Meloidogyne* genus, pose a significant threat to agriculture, causing considerable economic losses. Conventional nematode control methods often rely on chemical fumigants, which are associated with environmental and health risks. As a result, alternative strategies leveraging plant-derived bioactive compounds have garnered interest. Essential oils from genera such as *Thymus*, *Mentha*, *Ocimum*, *Artemisia*, and *Cymbopogon* are known for their nematicidal properties. As one of the major components, carvacrol, in combination with other compounds such as geraniol and eugenol, exhibits synergistic nematicidal activity. Notably, carvacrol demonstrated an LC_{50} value of 14.2 μg/mL after 24 h of treatment against *Meloidogyne incognita* J2 larvae, resulting in an 82% mortality rate [97].

3.14.2. Essential Oils and Synthetic Derivatives in Nematode Control

The nematicidal potential of *Thymus linearis* Benth. essential oil, rich in thymol (50.62%) and carvacrol (13.23%), was extensively studied. These compounds effectively inhibited the hatching of *Meloidogyne javanica* eggs, while also exhibiting strong antioxidant properties, comparable to standard antioxidants like trolox. Such dual functionality highlights the potential of *T. linearis* essential oil as an eco-friendly nematicidal and antioxidant agent [98].

Synthetic derivatives of phenolic compounds, including hydroxylated and prenylated acetophenones and chalcones, as well as carvacrol and thymol, have also shown potent nematicidal effects. Hydroxylated derivatives demonstrated significant efficacy in inhibiting nematode egg hatching, offering valuable insights into the structural determinants of nematicidal activity and paving the way for designing new phenolic-based agents for nematode control [99].

3.14.3. Carvacrol in Integrated Pest Management

Within sustainable pest control strategies, entomopathogenic nematodes (EPNs) and plant-derived terpenes such as carvacrol, thymol, geraniol, and eugenol play complementary roles. Carvacrol was identified as the most potent nematicidal agent among the tested terpenes, with *Heterorhabditis bacteriophora* being the most susceptible species. Importantly, exposure to sublethal doses of terpenes did not diminish the virulence of EPNs, underscoring the potential of incorporating terpenes into pest control strategies without compromising EPN efficacy. Field studies are necessary to validate the compatibility of terpenes and EPNs under practical agricultural conditions [100].

3.14.4. Animal Health Benefits and Gastrointestinal Nematode Control

Plant-based feed supplements containing carvacrol and limonene have shown promise in improving animal health and reducing gastrointestinal nematode burdens. In studies involving lactating ewes and lambs, dietary supplementation with these compounds improved metabolic parameters, such as reducing beta-hydroxybutyrate, triglycerides, and fructosamine levels. While gastrointestinal nematode egg counts were reduced, additional studies are necessary to elucidate the precise pathways underlying these antiparasitic effects [101].

3.14.5. Toxicity Assessments and Environmental Applications of Carvacrol

The safety of carvacrol and thymol was assessed in toxicity studies to ensure their viability for agricultural applications. Acute and repeated oral toxicity studies in rats revealed no significant toxicological effects at lower dose levels, with the threshold for no observed adverse effects exceeding

250 mg/kg/day. However, higher concentrations led to pulmonary changes, suggesting the importance of dose optimization for safe use [102].

In addition to mammalian toxicity studies, the impact of carvacrol on non-target organisms has been investigated. Research on zebrafish (*Danio rerio*) embryos demonstrated that carvacrol and its derivative, acetylcarvacrol, exhibited dose-dependent toxicity. The concentrations below 50 μM did not induce observable developmental abnormalities or acute lethality, suggesting a potential safety margin for controlled applications in aquatic environments [103]. Furthermore, the 1:1 combination of carvacrol and thymol exhibited high acaricidal activity against *Varroa destructor*. In the same study, a safety assessment revealed that these compounds did not have any adverse effects on the learning and memory abilities of honeybees (*Apis mellifera*) [104].

Beyond agricultural applications, carvacrol has shown potential in environmental remediation. Plant-derived terpenes, including carvacrol and thymol, were utilized in liquid-liquid extraction systems to remove persistent contaminants such as azole fungicides from aqueous environments. Eutectic solvent formulations, particularly those based on carvacrol-octanoic acid combinations, demonstrated efficacy as green alternatives for addressing water pollution, further emphasizing the versatility of carvacrol in sustainable applications [105].

3.15. Neurological Activities of Carvacrol

Carvacrol has exhibited notable neuroprotective effects in experimental models of cognitive impairment and neurodegenerative diseases [106-115].

3.15.1. Effects of Carvacrol on Memory Deficits

In studies involving amyloid-beta (Aβ) and scopolamine-induced memory deficits, carvacrol (0.5–2 mg/kg) and thymol significantly improved cognitive function in rats. These effects were attributed to their anticholinesterase, antioxidant, and anti-inflammatory properties. The essential oil derived from *Thymus numidicus* Poiret leaves, characterized by high thymol (42.1%) and carvacrol (22.1%) content, displayed potent acetylcholinesterase inhibitory activity (IC_{50}: 158.94 μg/mL) and robust free radical scavenging capabilities, reinforcing its applicability in managing neurodegenerative disorders [106].

3.15.2. Neuroprotective Effects in Aging and Postmenopausal Models

Carvacrol has also demonstrated efficacy in improving cognitive functions in aged and stress-induced animal models. In aged rats, carvacrol (15–30 mg/kg) enhanced learning and memory performance, likely through its antioxidative effects, including reductions in malondialdehyde levels and elevations in thiol group concentrations in the hippocampus and cortex [107]. In ovariectomized hypertensive rats, carvacrol reduced amyloid-beta deposition and neuroinflammation, suggesting its protective role against memory deficits in postmenopausal women [108].

3.15.3. Potential Role of Carvacrol in Neurological Diseases

Neurological conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD) are heavily influenced by oxidative stress and inflammation [109, 110]. Carvacrol has demonstrated the ability to modulate these processes by reducing reactive oxygen species production and decreasing proinflammatory cytokine levels. It also prevents dopaminergic neuronal loss in PD models and enhances cognitive and motor functions, highlighting its promise as a therapeutic candidate for neurodegenerative conditions [111].

3.15.4. Carvacrol in Stress-Induced and Environmental Neurotoxicity Models

Additionally, carvacrol has shown protective effects in acute and chronic stress-induced memory impairment models. Extracts of *Satureja montana*, containing carvacrol as a key component, improved cognition and novel object recognition in rats subjected to chronic unpredictable mild stress. Furthermore, carvacrol mitigated oxidative stress and systemic inflammation induced by paraquat exposure, demonstrating its potential to counteract the neurotoxic effects of environmental toxins [112, 113].

3.15.5. Potential Role of Carvacrol in Myelin Regeneration and Multiple Sclerosis

Recent studies emphasize carvacrol's role as a potential treatment for supporting myelin regeneration and reducing neuroinflammation [113-115]. Carvacrol was shown to exert significant therapeutic benefits in autoimmune encephalomyelitis-induced Lewis rats. In these studies, carvacrol treatment effectively reduced clinical scores, indicative of diminished disease severity. The treatment inhibited pro-inflammatory mediators which are key contributors to the neuroinflammatory environment in MS. Simultaneously, carvacrol enhanced the expression of genes associated with myelin formation [115].

Histopathological analyses corroborated these molecular findings, revealing a marked decrease in inflammatory cell infiltration within the spinal cord in treated animals. These results suggest that carvacrol not only mitigates neuroinflammation but also actively promotes remyelination, addressing a key pathological feature of multiple sclerosis [115].

3.16. Hepatoprotective Activities of Carvacrol

Carvacrol was widely investigated for its hepatoprotective effects, particularly in models of liver fibrosis and oxidative stress [116-119].

3.16.1. Carvacrol and Liver Fibrosis

In a study examining its effects on alcoholic liver fibrosis, carvacrol demonstrated enhanced efficacy when combined with cilostazol. This combination significantly mitigated liver fibrosis, with results surpassing those observed with carvacrol alone. Silymarin, a well-known anti-fibrotic agent, served as a reference, further highlighting the potential of carvacrol-based interventions in liver disease management [116].

3.16.2. Genotoxicity Assessment of Carvacrol in Hepatocytes

Carvacrol’s antioxidative potential has also been confirmed in studies assessing DNA damage in hepatocytes. It significantly reduced oxidative DNA damage without exhibiting genotoxic activity, reinforcing its safety and utility as a hepatoprotective compound [117].

3.16.3. Hepatoprotective Effects of Infection Models

In infection-induced liver damage models, carvacrol displayed dual antimicrobial and hepatoprotective effects. For example, in a model of *Staphylococcus aureus*-induced liver injury, carvacrol reduced pro-inflammatory cytokine levels, malondialdehyde, and liver enzymes (ALT and AST) while preserving hepatic glutathione (tGSH) levels. Although its antibacterial efficacy was less pronounced compared to cefazolin, carvacrol provided superior protection against oxidative stress and histopathological liver damage, making it a promising candidate for managing infection-associated liver injury [118].

3.16.4. Carvacrol in Metabolic Liver Disorders

The hepatoprotective and anti-steatohepatitic effects of carvacrol were further supported by studies on extracts of *Thymbra spicata* L. rich in carvacrol (44.13%). Both diethyl ether and aqueous extracts from this plant led to a notable decline in plasma cholesterol and triglyceride levels, while simultaneously enhancing high-density lipoprotein levels, superoxide dismutase activity, and glutathione content in mice consuming a fat-enriched diet. Histopathological analysis of liver tissues revealed improved hepatic conditions in the diethyl ether extract-treated group, demonstrating carvacrol's role in mitigating hypercholesterolemia and hepatic steatosis [119].

3.17. Gastrointestinal Activities of Carvacrol

Carvacrol, a prominent component of *Satureja montana* and *Origanum onites*, has demonstrated antibacterial and gastroprotective properties, making it a promising agent for gastrointestinal therapies [120, 121].

3.17.1. Traditional and Experimental Uses in Gastrointestinal Disorders

The aqueous distillate of *O. onites*, with carvacrol as a major component, has traditional uses in ethnomedicine, particularly for gastrointestinal ailments. Experimental studies using isolated rat fundus, duodenum, and ileum revealed dose-dependent inhibition of acetylcholine-induced contractions by the distillate [121].

3.17.2. Gastroprotective Effects of Carvacrol and Mechanisms of Action

In rodent models, carvacrol exhibited strong gastroprotective properties against gastric damage caused by various agents, including ethanol, acidic ethanol solutions, ischemia-reperfusion injury, and NSAID exposure. These effects were mediated through mechanisms involving the activation of endogenous prostaglandins, nitric oxide synthase, ATP-sensitive potassium (K-ATP) channels, and enhanced mucus production. Additionally, carvacrol showed antioxidant properties, further contributing to its gastroprotective profile. In pylorus-ligated rats, carvacrol significantly increased gastric secretion and mucus production, emphasizing its therapeutic potential in protecting gastric mucosa [122].

3.17.3. Carvacrol in Smooth Muscle Relaxation and Ion Channel Modulation

The mechanism by which carvacrol exerts smooth muscle relaxation was elucidated in studies using isolated rat duodenum. Carvacrol induced dose-dependent relaxation through the activation of specific potassium ion channels, including barium chloride-sensitive Kir2.1 and Kir3.1 channels, as well as tetraethylammonium-sensitive Kv7.4 and Kv7.5 channels. This effect was abolished by the combined use of barium chloride and tetraethylammonium but was unaffected by glibenclamide, ruthenium red, or nitroarginine, delineating its precise mechanism of action. These findings suggest carvacrol's potential as a therapeutic agent for gastrointestinal smooth muscle disorders [123].

3.18. Insecticidal, Larvicidal, and Acaricidal Activities of Carvacrol

3.18.1. Insecticidal Activities

Monoterpenes, due to their biodegradability, safety, and efficacy, are emerging as promising alternatives to synthetic pesticides. Among these, carvacrol has demonstrated significant insecticidal and larvicidal properties against various pest species. A study evaluating 42 monoterpenes for their termiticidal activity against *Reticulitermes chinensis* identified oxygenated monoterpenes, such as carvacrol and (+)-pulegone, as the most effective, with LC_{50} values of 0.007 μL/L and 0.003 μL/L, respectively. This highlights their potential as natural termiticides [124].

Recent investigations have provided the broad-spectrum insecticidal potential of carvacrol across various pest species, highlighting its diverse mechanisms of action [125-128]. Research on *Solenopsis spp*. (imported fire ants) showed that carvacrol exhibited strong repellent activity as an eco-friendly pest control agent. Carvacrol was reported to surpass thymol in efficacy across different *Solenopsis* species (*S. invicta, S. richteri*) and their hybrid forms, achieving the lowest effective doses of 0.98 µg/g, 7.80 µg/g, and 0.98 µg/g, respectively [127]. Additionally, structural modifications of carvacrol and thymol have been explored to enhance their insecticidal properties, with certain derivatives demonstrating superior toxicity through interactions with insect odorant-binding proteins and acetylcholinesterase enzymes, leading to increased mortality rates [128]. These findings collectively underscore carvacrol's versatile insecticidal mechanisms, ranging from microbiome disruption and neurotoxicity to repellent effects.

3.18.2. Larvicidal Activities

A recent investigation examined the larvicidal potential of *Thymus vulgaris* essential oil, which contains a high concentration of carvacrol, against *Alphitobius diaperinus* larvae. At a 2% concentration, carvacrol achieved 97.5% mortality in young larvae, surpassing thymol and thyme oil in efficacy, demonstrating its strong larvicidal potential [129]. Furthermore, studies on *Lymantria dispar* larvae have demonstrated that carvacrol disrupts the gut bacterial structure, affecting detoxification metabolism and leading to increased mortality rates at concentrations above 1.120 mg/mL, making it a promising natural alternative [130].

In another study, plant-derived essential oils from *Thymbra spicata* subsp. *spicata*, *Rosmarinus officinalis* L., *Foeniculum vulgare* Mill., and *Laurus nobilis* L. were evaluated for their activities against pests. Thyme oil, with carvacrol as its principal component (70.9%), exhibited the highest insecticidal efficacy, achieving complete adult mortality at a concentration of 5 µg/mL air. These findings underscore the potential of carvacrol-rich oils in agricultural pest management, especially against cotton whitefly [131].

In veterinary applications, *Thymus vulgaris*, *Origanum vulgare*, and *Illicium verum* Hook. f. were tested for the larvicidal activity of their essential oils against third-instar larvae of *Cochliomyia hominivorax*, a critical ectoparasite in livestock. Among its components, carvacrol displayed significant efficacy with an LC_{50} value of 931.1 µg/cm², highlighting its suitability for developing ectoparasiticides in livestock management [132].

Carvacrol has demonstrated significant larvicidal toxicity against multiple mosquito species. Studies have reported its effectiveness in targeting *Anopheles mosquitoes, including A. stephensi* and *A. subpictus, as well as Culex species*, where notable toxicity was observed. *The* LC_{50} values varied within the range of 21.15 to 27.95 µg/mL, indicating its potential as a natural larvicide against vectors of malaria, filariasis, and Japanese encephalitis [133].

Additionally, a study focusing on *Culex pipiens* biotype molestus demonstrated that short-term exposure to sublethal concentrations of carvacrol-rich oregano essential oil and pure carvacrol resulted in acute larval mortality, delayed development, morphological abnormalities, and reduced adult emergence. These findings suggest that carvacrol and its derivatives could serve as effective, environmentally friendly larvicides at doses lower than acute lethal levels [134].

Furthermore, field assessments of carvacrol-rich essential oils have shown promising results. Emulsified formulations exhibited significant larvicidal activity, with an LC_{90} of 58.747 mg/L, and repellent properties achieving up to 86% efficacy on the first day of application. These characteristics position carvacrol-rich essential oils as viable candidates for mosquito control measures [135].

3.18.3. Acaricidal Activities

Carvacrol exhibits strong acaricidal activity against *Rhipicephalus* ticks, effectively inducing high mortality rates in both larvae and adults, with enhanced potency observed in optimized formulations and synergistic combinations [136-139].

Carvacrol's acaricidal potential was further evaluated in combination with synthetic agents against *Rhipicephalus sanguineus*, a common tick species. While carvacrol or eugenol combined with

fipronil demonstrated antagonistic effects, the combination of carvacrol and eugenol exhibited synergistic activity, achieving 80–100% mortality across all tick life stages. This synergism highlights the feasibility of integrating natural and synthetic compounds to enhance acaricidal efficacy [136].

In another study, carvacrol-loaded invasomes (CLI) were reported to enhance carvacrol's acaricidal activity against *Rhipicephalus annulatus* and *Rhipicephalus sanguineus*. The study demonstrated that CLI (5%) achieved 100% mortality in adult *Rhipicephalus annulatus* with a lower LC_{50} (2.60%) compared to pure carvacrol (4.30%). Chromatographic analyses revealed that CLI had 3.86 times higher permeability than pure carvacrol, indicating superior penetration and bioavailability. Furthermore, carvacrol inhibited acetylcholinesterase activity, disrupting tick neural function, which supports its mechanism of acaricidal action [137].

A study by Costa *et al*. examined the repellent and acaricidal properties of carvacrol against *Amblyomma sculptum* and *Rhipicephalus sanguineus sensu lato* nymphs. Their study demonstrated that encapsulated carvacrol formulations enhanced acaricidal efficiency and prolonged repellent effects. Encapsulation also improved stability and controlled release, making carvacrol a promising candidate for long-term tick control in livestock management [138].

Recently, Rodrigues *et al*. explored the synergistic and antagonistic interactions of carvacrol with other essential oil compounds, including thymol and eugenol, against *Rhipicephalus microplus*. The study highlighted that carvacrol exhibited strong acaricidal activity, but its efficacy varied depending on solvent choice and formulation strategies. Notably, the combination with glycerol and vaseline resulted in strong synergistic effects, whereas Tween 80® and ethanol led to antagonism, reducing acaricidal effectiveness. These results emphasize the necessity of optimized formulation strategies for maximizing carvacrol's acaricidal potential [139].

3.19. Role of Carvacrol as Feed Additive

3.19.1. Carvacrol for Pest Control in Poultry Farming

Carvacrol has garnered attention for its potential role as a natural feed additive, offering both pest control and health benefits in livestock management. Carvacrol-enriched starch granules have demonstrated efficacy in controlling *Alphitobius diaperinus* (lesser mealworm), a common pest in poultry farming. Simulated trials involving a mixture of 10% carvacrol-enriched granules and straw pellets (40:60 ratio) resulted in complete mortality of larvae and adults within 3–4 days. Importantly, this treatment had no detrimental effects on broiler growth, although a slight increase in feed conversion rates and marginally reduced body weight were observed. This approach underscores the potential of integrating carvacrol as a natural pest control agent in poultry operations [140].

3.19.2. Growth-Inhibitory Effects in Poultry

Origanum vulgare L.subsp. *hirtum* (Link) Ietswaart (Greek oregano) characterized by its essential oil with a high proportion of carvacrol, also exhibited strong larvicidal activity against *A. diaperinus*. At a 1% concentration, the essential oil effectively reduced larval body weight gain and inhibited the growth of pathogenic microorganisms, such as *Candida albicans* and certain bacterial species. Its use aligns with European Union regulations promoting natural alternatives to antibiotics in livestock farming, highlighting its potential to improve farm hygiene while controlling pests [141].

3.19.3. Carvacrol in Gut and Immune Development

Carvacrol's application in *in ovo* delivery offers innovative avenues for enhancing early immune modulation and gut development in broilers. Administering carvacrol into the yolk or amniotic fluid on embryonic day 17.5 improved gut and immune system maturation without compromising hatchability. When combined with polysorbate 80 as a surfactant, carvacrol was efficiently delivered to embryonic tissues, maintaining bioavailability during the peri-hatching phase. This method presents an opportunity to optimize broiler health from the earliest stages of development [142, 143].

3.19.4. Effects of Carvacrol on Meat Quality in Ruminants

In ruminants, dietary supplementation with a blend of cinnamaldehyde and carvacrol has shown promise in enhancing growth performance and meat quality. A study on lambs supplemented with 120 mg/kg of essential oils revealed a reduction in acetate-to-propionate ratios and volatile fatty acid concentrations in the rumen. This modulation of rumen biohydrogenation resulted in increased accumulation of polyunsaturated fatty acids in meat, improving its nutritional quality while supporting lamb growth. These findings highlight carvacrol's potential in promoting sustainable livestock production [144].

3.20. Antiviral Activities of Carvacrol

3.20.1. Carvacrol Against Respiratory Viruses

Carvacrol has shown antiviral potential, particularly against coronaviruses (CoVs) and other pathogens. Beta CoVs may lead to severe respiratory symptoms, as evidenced during the COVID-19 pandemic [145, 146]. Plant-derived compounds from the Lamiaceae family, such as thymol and carvacrol, found in *Thymus vulgaris* and *Zataria multiflora*, have demonstrated anti-inflammatory and antiviral properties. These compounds suppress pro-inflammatory mediators while promoting the production of IFN-γ, an essential mediator of anti-inflammatory responses. Molecular docking studies further support their potential to inhibit viral entry by interacting with viral proteins, underscoring their promise for managing CoV-induced lung disorders [147].

3.20.2. Carvacrol Against Tulane Virus

Immobilizing carvacrol onto silica microparticles (SiO_2-EOCs) was shown to significantly reduce viral infectivity, particularly against the Tulane virus (TuV). Reductions were observed for carvacrol, attributed to its ability to disrupt the viral capsid, as confirmed by RT-qPCR and RNase treatment. These findings suggest that SiO_2-EOCs could meet stringent water disinfection standards and offer innovative antiviral strategies [148].

3.20.3. Carvacrol Against Herpes Simplex Viruses

Supercritical CO_2 extracts of *Thymus* species have also been explored for their potential antiviral effects, with specific activity against herpes simplex viruses. *Thymus zygis* extracts exhibited the most potent antiviral effects, especially during the viral adsorption phase. The efficacy was linked to the high concentrations of carvacrol, thymol, and borneol, highlighting the utility of supercritical extraction techniques in isolating bioactive antiviral compounds [149].

3.20.4. Specific Role of Carvacrol Against SARS-CoV-2

Thyme oil vapor with a high concentration of carvacrol has demonstrated remarkable virucidal activity against SARS-CoV-2. Exposure to thyme oil vapor resulted in a >99.99% reduction in airborne viral particles within 60 minutes, suggesting its potential as a natural air disinfectant for public health applications, particularly in shared or high-risk environments [150].

3.20.5. Carvacrol in Plant Virus Management

In agricultural contexts, molecular docking studies on *Acinetobacter baumannii* coat proteins revealed that carvacrol, along with eucalyptol and eugenol, exhibits high binding affinities. These findings open avenues for leveraging carvacrol in plant virus management strategies, presenting a dual benefit of antiviral activity in human health and agriculture [151].

3.21. Antimicrobial Activities of Carvacrol

3.21.1. Synergistic Effects of Carvacrol with Antibiotics

Carvacrol has demonstrated significant antimicrobial properties, both independently and in combination with other agents, across various applications. Containing abundant amounts of carvacrol and thymol, the essential oil extracted from *Satureja montana* exhibited enhanced antimicrobial effects when combined with gentamicin. This combination effectively reduced biofilm formation in *Escherichia coli*, *Staphylococcus aureus*, and *Listeria monocytogenes*. Scanning electron microscopy confirmed morphological alterations in bacterial cells, suggesting its potential use in combined therapies for clinical and agricultural applications [152].

Carvacrol also displayed potent antimicrobial activity against multidrug-resistant pathogens, including *Acinetobacter baumannii*. Its synergistic effects with ciprofloxacin significantly inhibited bacterial growth, providing a promising strategy against resistant strains [153].

3.21.2. Carvacrol in Biofilm Control and Surface Sanitization

Alcohol-based sanitizers fortified with carvacrol showed efficacy comparable to standard formulations, with a 45% isopropanol solution containing 1-5% carvacrol achieving inhibition rates similar to 70% alcohol, presenting a cost-efficient alternative for disinfection [154].

Biofilm-associated bacterial resistance remains a major challenge in healthcare, agriculture, and food safety. Essential oils containing carvacrol, thymol, and eugenol have shown efficacy in disrupting biofilms and reducing bacterial viability [155-159]. For example, treatments incorporating carvacrol successfully controlled biofilm formation on industrial surfaces, such as stainless steel, and exhibited significant activity against biofilm-forming *Salmonella serovars*. Furthermore, combinations of carvacrol with compounds like 2-aminobenzimidazole demonstrated potent antibiofilm properties, highlighting their potential for diverse applications [160, 161].

3.21.3. Applications in Food Safety and Agricultural Disease Control

Carvacrol's antimicrobial potential extends to food safety, where it was shown to inhibit resistant strains of *Staphylococcus aureus* obtained from uncooked poultry products. In comparison, hydroquinone exhibited superior antibacterial activity, offering alternative strategies for combating foodborne pathogens [162].

Nanoemulsions containing *Zataria multiflora* essential oil disrupted biofilm formation in *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *S. aureus*, further underscoring its clinical potential [163].

In agriculture, carvacrol was utilized to manage plant diseases and pests. For example, carvacrol-rich *Lippia graveolens* essential oil exhibited antimicrobial and plant defense-eliciting properties against bacterial canker in kiwifruit [105]. Additionally, thymol-carvacrol mixtures have demonstrated effective larvicidal and ovicidal activity against *Culex pipiens*, indicating their potential as botanical insecticides [164].

3.21.4. Carvacrol Combinations against Multi-Drug Resistant Infections

Carvacrol was shown to enhance the efficacy of antibiotics like imipenem against antibiotic-resistant bacterial strains including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Similarly, essential oils from *Origanum compactum* and *Origanum elongatum* (Bonnet) Emb. & Maire containing carvacrol and thymol, demonstrated synergistic effects with ciprofloxacin and ceftriaxone, suggesting their role as antibiotic potentiators [165,166].

3.21.5. Carvacrol in Aquaculture and Veterinary Applications

In aquaculture, dietary oregano leaves enriched with carvacrol enhanced disease resistance in Nile tilapia, reducing susceptibility to *Streptococcus* infections [167, 168]. Efforts to stabilize and enhance the efficacy of carvacrol have included synthesizing derivatives like carvacryl benzoate, which exhibited superior antimicrobial and insecticidal activity compared to the parent compound [169].

3.21.6. Carvacrol as an Antifungal Agent

Fungal infections, particularly those caused by biofilm-forming pathogens, pose significant global health challenges, especially with the increasing emergence of antifungal resistance driven by environmental contamination with antifungal agents. Carvacrol has demonstrated potent antifungal activity, providing a promising alternative to conventional treatments.

Recent advancements in nanotechnology have facilitated the development of carvacrol-based therapeutics, such as gelatin nanoemulsions. These nanoemulsions effectively penetrated *Candida albicans* biofilms, selectively eliminating fungal cells without harming fibroblasts in co-culture models. Additionally, they exhibited biodegradability in the presence of physiological biomolecules, reducing their environmental impact and ecotoxicity, thus offering a sustainable solution for drug-resistant fungal infections [170].

Carvacrol's antifungal efficacy extends across multiple *Candida* species. Its structurally related phenolic compounds, such as thymol and isoeugenol, further exhibit significant antifungal potential. These compounds disrupt fungal cell walls and membranes, alter vacuole integrity, and inhibit biofilm formation. Moreover, carvacrol induces oxidative stress by modulating genes involved in cell wall and membrane biosynthesis, demonstrating a multifaceted mechanism of action against fungal pathogens [171, 172].

Another study on *Candida albicans* demonstrated that a gelatin-based nanoemulsion formulation combining terbinafine and carvacrol enhanced biofilm inhibition fourfold compared to terbinafine alone. This combination not only improved biofilm penetration but also prevented fungal resistance development over successive passages [173]. Similarly, a comparative analysis by Park *et al*. revealed that carvacrol-based nanoemulsions had superior antibiofilm activity compared to traditional formulations, as evidenced by a greater reduction in viable biofilm-associated fungal cells [174].

In immunosuppressed rat models of vaginal candidiasis, carvacrol exhibited superior efficacy compared to eugenol, significantly reducing fungal burdens and eradicating *C. albicans* infections. Histological analysis confirmed the absence of fungal organisms in treated tissues, positioning carvacrol as a promising alternative to conventional antifungal agents like nystatin [175, 176].

Liposomal preparations incorporating oregano oil, rich in carvacrol, have also been developed for targeted delivery in vaginal infections, effectively releasing active antifungal agents with minimal toxicity [176].

In food safety, carvacrol's antifungal and antioxidant properties were applied to enhance the stability and longevity of perishable items by inhibiting fungal growth and mycotoxin production, emphasizing its potential in food preservation and packaging [177].

Carvacrol was effectively utilized in combination therapies to enhance antifungal efficacy. For instance, the synergistic action of carvacrol and itraconazole successfully cleared *C. albicans* infections in the visceral organs of mice, underscoring its potential to complement existing antifungal regimens [178].

In addition to *Candida albicans*, carvacrol and carvacrol-rich essential oils have demonstrated significant antifungal activity against *Candida auris*, a multidrug-resistant fungal pathogen. For instance, a study reported that carvacrol effectively inhibited the growth and survival of *C. auris*, with minimum inhibitory concentration values ranging from 125 to 500 μg/mL. Furthermore, carvacrol was found to induce oxidative stress in *C. auris* by increasing lipid peroxidation levels and significantly altering the gene expression and activity of key antioxidant enzymes [179].

Another investigation involving *C. auris* highlighted that carvacrol exert antifungal effects by disrupting fungal cell membrane integrity. The phenolic -OH group in these compounds facilitates proton exchange, leading to membrane damage and ionic imbalance, ultimately compromising fungal

viability [180]. Additionally, carvacrol has been shown to exhibit both antifungal and antivirulence activities, with enhanced efficacy when used in combination with conventional antifungal agents [181].

3.21.7. Carvacrol in Biofilm-Associated Infections of Oral Cavity

Zinc oxide nanoparticles (ZnO NPs) combined with *Urtica dioica* extracts, enriched with carvacrol, demonstrated efficacy against fungal and bacterial pathogens. Biodegradable carvacrol-containing nanoemulsions also showed promise in treating biofilm-associated infections in the oral cavity, effectively diffusing through biofilms and exhibiting high biocompatibility with oral tissues [182, 183].

3.21.8. Carvacrol as a Quorum Sensing Inhibitor

Carvacrol was identified as a potent natural compound capable of interfering with quorum sensing (QS) mechanisms, thereby disrupting bacterial communication and the regulation of virulence factors. Several studies have demonstrated that carvacrol inhibits QS by impairing the synthesis and perception of autoinducer molecules, leading to the suppression of biofilm formation, attenuation of virulence traits, and potential reversal of antibiotic resistance in pathogenic bacteria [184-187].

A recent study reported the role of carvacrol in inhibiting *Listeria monocytogenes* biofilms under different acidic conditions and food matrices. The results demonstrated that nano-encapsulated carvacrol effectively reduced biofilm levels in both standard culture media and food substrates, with greater reductions observed in the mutant strains, suggesting enhanced vulnerability due to quorum sensing impairment. These findings indicate that carvacrol not only exerts direct antimicrobial effects but also targets QS-regulated biofilm formation [186].

The anti-QS properties of carvacrol were further investigated to suppress QS-regulated gene expression in *Pseudomonas aeruginosa.* The findings demonstrated that carvacrol significantly downregulated the expression of the *lasI* gene, which is crucial for biofilm formation. Similarly, the study by Morgaan *et al*. revealed that carvacrol significantly downregulated the expression of the *luxS* gene, a key regulator in the autoinducer-2 (AI-2) quorum sensing system. This inhibition led to a reduction in biofilm formation and motility [187].

3.22. Carvacrol's Role in Combating Honey Bee Pathogens

Honey bee health is essential for ecosystem stability and agricultural productivity; however, diseases such as American Foulbrood (AFB) and European Foulbrood (EFB) present major challenges to apiculture. Previous research has demonstrated the promising effects of carvacrol, as a plant-based agent in managing these diseases [188].

Essential oils derived from *Origanum onites*, rich in carvacrol, demonstrated strong antimicrobial activity against both *Paenibacillus larvae* and *Melissococcus plutonius*. These findings suggest that carvacrol and *O. onites* essential oil may serve as eco-friendly alternatives to synthetic antibiotics, reducing reliance on chemical treatments that can lead to resistance or residue accumulation in bee products. The use of carvacrol as a natural agent for foulbrood disease management aligns with growing efforts to develop sustainable strategies for protecting honey bee populations and maintaining hive health [188].

3.23. Anti-Corrosion Properties of Carvacrol

3.23.1. Carvacrol in Anti-Corrosion Coatings

The application of natural compounds in anticorrosion technology has attracted considerable interest because of their eco-friendly and multifunctional characteristics. Carvacrol has demonstrated considerable potential as an anti-corrosion agent, particularly in coatings designed for harsh environments [189-191].

A study on coaxial electrospun coatings incorporating carvacrol showcased its dual antibacterial and anticorrosion functionalities. The core-shell structure, developed using carvacrol within the core and pullulan and ethyl cellulose as the shell layer, was confirmed through transmission electron microscopy. The coating exhibited a uniform, smooth surface morphology, and enhanced hydrophobicity without fractures. Ethylcellulose, a biopolymer with excellent mechanical strength and biodegradability, contributed significantly to resistance against microbially induced corrosion. Electrochemical impedance spectroscopy revealed improved corrosion resistance in bacterial solutions, while antibacterial assays demonstrated carvacrol's effectiveness in disrupting bacterial cell membranes. These findings highlight the potential of carvacrol-based nanofiber coatings for protecting materials in marine environments [189].

3.23.2. Essential Oils Containing Carvacrol as Corrosion Inhibitors

Essential oils rich in carvacrol, such as those derived from *Thymus vulgaris*, have also shown promise in anti-corrosion applications. Electrochemical studies confirmed the essential oil's role as a protective agent against corrosion in carbon steel when exposed to 1 M HCl, demonstrating an inhibition rate of 94.4% at 303 K and 400 ppm. Surface morphology analyses further validated its protective effects on steel surfaces [190].

The mechanistic understanding of carvacrol's anticorrosion properties was further enhanced by computational studies. Density functional tight-binding (DFTB) simulations evaluated the adsorption of carvacrol and thymol on the α-Fe(110) surface, revealing insights into their structural and electronic interactions with metal surfaces. These simulations highlighted the ability of these monoterpenes to modify the electronic properties of the metal surface, thereby mitigating corrosion. Such findings underscore the potential of natural organic compounds like carvacrol as sustainable and efficient corrosion inhibitors [191].

3.24. Anti-Cholinesterase Activities of Carvacrol

3.24.1. Acetylcholinesterase Inhibitory Activities of Carvacrol

Carvacrol has demonstrated notable acetylcholinesterase (AChE) inhibitory activities, making it a potential candidate for the therapy of neurodegenerative disorders. Studies evaluating the therapeutic properties of essential oils derived from various *Satureja* and *Origanum* species revealed that these oils exhibited over 80% inhibition of AChE and tyrosinase enzymes. Interestingly, the synergistic interactions within the essential oil matrix contributed to this potent bioactivity, as the major constituents, including carvacrol and thymol, were less effective when tested individually [192].

Furthermore, biochemical analysis of *Origanum compactum* essential oils from various geographical regions found carvacrol as one of the most important key constituents. These oils demonstrated robust inhibition of AChE, tyrosinase, and α-glucosidase, with inhibition rates ranging from 79.90% to 94.01% [193].

3.24.2. Butyrylcholinesterase Inhibitory Activities of Carvacrol

The essential oil from *Thymus numidicus* Poiret, an aromatic species native to Algeria, further highlighted the AChE inhibitory potential of carvacrol. The essential oil rich in carvacrol showed strong inhibitory effects on AChE and butyrylcholinesterase (BChE) [194].

Similar findings were reported for *Ammoides verticillata* extracts, which contained carvacrol as the dominant essential oil component. The essential oil exhibited moderate AChE and BChE inhibitory activity, whereas the ethanolic extract showed strong antioxidant and antihemolytic properties but lacked cholinesterase inhibition [194].

3.25. Anticonvulsant Activities of Carvacrol

3.25.1. Maximal Electroshock-Induced Seizure Model

The anticonvulsant properties of *Thymus vulgaris* essential oil rich in carvacrol, were investigated in several studies, highlighting their potential in seizure management [195-197].

The anticonvulsant potential was evaluated using the maximal electroshock-induced seizure model in mice. The essential oil provided partial seizure protection, with efficacy rates of 50% and 62.5% when administered 15 and 30 minutes before testing. Among the isolated compounds, borneol, thymol, and eugenol demonstrated the most robust anticonvulsant effects. Importantly, the essential oil and its constituents showed no acute toxicity in central nervous system evaluations, supporting their potential for safe therapeutic use in managing seizures [195].

3.25.2. Pentylenetetrazole-Induced Seizure Model

Carvacrol has displayed significant anticonvulsant activity through its interaction with key neuronal ion channels and receptors. These mechanisms likely reduce neuronal hyperexcitability by modulating ionic fluxes. In animal models, including penicillin-induced epileptiform activity and pentylenetetrazole (PTZ)-induced seizures in rats, prolonged the latency to myoclonic jerks and decreased spike frequency and amplitude at certain doses. However, its efficacy in acute seizure models appeared limited, potentially due to restricted penetration to epileptic foci. These findings underscore the need for further research in chronic epilepsy models to better understand carvacrol's pharmacokinetics and molecular targets [196].

3.26. Antifeedant Activities of Carvacrol

3.26.1. Carvacrol as a Natural Rodent Repellent

Carvacrol has shown remarkable antifeedant properties, positioning it as a promising natural agent for rodent-repellent applications. In studies evaluating its efficacy, carvacrol demonstrated strong deterrent effects against gnawing behavior in rodents, underscoring its potential to mitigate damage caused by these pests. This bioactivity aligns with the growing demand for eco-friendly and sustainable rodent control measures, offering an alternative to conventional chemical repellents. The effectiveness of carvacrol in this context highlights its utility in integrated pest management strategies, contributing to environmentally safe approaches for preventing rodent-related damage across various sectors [198].

3.26.2. Carvacrol-Rich Essential Oils in Pest Management

The essential oils of *Origanum compactum*, *Thymus capitatus*, against *Tribolium castaneum* were assessed for their repellent, antifeedant, and contact toxicity properties. The multifaceted effects observed were largely attributed to the high carvacrol content in these oils (90% in *O. compactum* and 78% in *T. capitatus*), demonstrating the potential of carvacrol-rich essential oils as natural alternatives for pest management [199].

3.26.3. Carvacrol in Wood Preservation and Termite Control

The efficacy of carvacrol as a key ingredient in natural bio-preservatives was examined in a study aimed at wood preservation. Several bioactive compounds, including carvacrol, rosifoliol, cubebolo, citronellol, and neoisopulegol, were identified for their notable bioactivity. The extracts exhibited significant antitermitic, repellent, and feeding inhibition effects in bioassays. These findings suggest that extracts from *Palaquium gutta* and *Pongamia pinnata* have substantial potential as natural bio-preservatives for the wood industry [200].

3.27. Effects of Carvacrol on Bone Defects

Bone defects resulting from trauma or aging pose significant clinical challenges, often requiring advanced therapeutic strategies such as bone tissue engineering. Carvacrol has garnered attention for its potential applications in this area [201-203].

3.27.1. Role of Carvacrol in Bone Regeneration

One promising approach involves three-dimensional printed silica-doped tricalcium phosphate (SiO_2-TCP) scaffolds functionalized with carvacrol-loaded lipid nanoparticles (CA-LNPs). These nanoparticles demonstrated an impressive entrapment efficiency of ~97%, a small average size (129 nm), and a zeta potential of -16 mV. CA-LNPs exhibited sustained release over 35 days, significantly enhancing antibacterial efficacy, with over 90% reduction in *Staphylococcus aureus* and *Pseudomonas aeruginosa* growth. Furthermore, these scaffolds doubled osteoblast viability and reduced osteosarcoma cell viability three-fold, highlighting their dual role in promoting bone regeneration and combating infections [201].

Another innovative strategy combined carvacrol with curcumin in dual-drug delivery systems encapsulated into 3D-printed calcium phosphate (CaP) scaffolds. Carvacrol-curcumin nanoparticles (CC-NPs), synthesized via melt emulsification, showed pH-sensitive release profiles, with enhanced drug release under acidic conditions (pH 5.0). At this pH, carvacrol, and curcumin release reached nearly 100% and 53%, respectively, compared to lower release rates at physiological pH (7.4). These CC-NPs promoted osteoblast growth by 1.4-fold and effectively suppressed osteosarcoma cell proliferation by 2.9-fold while achieving 98% antibacterial efficacy against *S. aureus* and *P. aeruginosa*. This approach underscores the potential of dual-drug systems to enhance therapeutic outcomes in bone regeneration and infection control [202].

3.27.2. *Effects of Carvacrol in Infected Bone Fractures*

Another study explored calcium phosphate cements (CPCs) loaded with carvacrol for treating infected bone fractures. Traditional CPCs often lack sufficient antimicrobial properties and carry an increased risk of contamination during manual mixing. Carvacrol-loaded, premixed, two-paste CPCs addressed these limitations, demonstrating excellent biocompatibility, osteogenic capacity, and broad-spectrum antimicrobial efficacy, including against drug-resistant bacteria. In vivo studies further confirmed their remarkable ability to combat infection while promoting bone healing, making carvacrol-loaded CPCs a promising candidate for managing infected bone defects [203].

3.28. Antitussive Activities of Carvacrol

The antitussive properties of thyme species, particularly *Thymus vulgaris* and *Thymus serpyllum*, were extensively studied due to their thymol and carvacrol content, highlighting their ability to alleviate cough and respiratory discomfort. Thymol and carvacrol demonstrated potent tracheal relaxant properties when administered in sufficient doses. The pharmacological analysis confirmed their significant contribution to the antitussive effects [204].

3.29. Herbicidal Properties of Carvacrol

3.29.1. Carvacrol-Rich Essential Oils as Natural Herbicides

The application of carvacrol-containing essential oils as natural herbicides has garnered attention due to their phytotoxic carvacrol content and their potential as eco-friendly alternatives to synthetic herbicides. Research on essential oils from *Origanum syriacum*, *Micromeria fruticosa*, and *Cymbopogon citratus*, all of which are rich in carvacrol, showed significant inhibitory effects on seed germination. At concentrations between 20 and 80 ppm, these oils strongly suppressed the germination of species such as wheat (*Triticum aestivum*). Furthermore, mixing the oils with the upper soil layer

(0.5 cm) inhibited the germination of wheat and *Amaranthus* seeds, with the degree of inhibition influenced by soil type. These findings indicate that carvacrol-rich essential oils could potentially be applied as natural herbicides in agricultural practices [205].

3.29.2. Allelopathic Effects of Carvacrol

A study exploring the allelopathic effects of aqueous extracts from black cumin roots and shoots highlighted their inhibitory impact on the germination and early growth of charlock mustard (*Sinapis arvensis* L.) and wheat. The black cumin extracts contain bioactive compounds terpenoids (e.g., carvacrol, thymol, p-cymene), increased levels of hydrogen peroxide, lipid peroxides, and proline levels while diminishing germination efficiency. These results indicated that black cumin extract might serve as a natural herbicide and be integrated into crop rotation strategies to control charlock mustard and minimize reliance on chemical herbicides [206].

3.29.3. Herbicidal Potential of Mediterranean Thymus Species

Further investigation into the herbicidal properties of essential oils from Mediterranean Thymus species has revealed significant phytotoxic potential. The ecotype Fasano and cultivar Varico 3 of *Thymus vulgaris* were found to be rich in carvacrol. These oils investigated potent germination-inhibiting effects on *Lolium perenne* and *Amaranthus retroflexus*. At higher concentrations (1000 μL/100 mL), complete inhibition of early-stage plant development was observed, with the *T. vulgaris* ecotype Fasano oil demonstrating the highest herbicidal efficacy. These results underscore the potential of *Thymus* species essential oils as bioherbicides [207].

3.30. The Role of Carvacrol in Dentistry

The therapeutic potential of carvacrol in dentistry is increasingly evident due to its antimicrobial, anti-inflammatory, and osteogenic properties. Research highlights its applicability in managing precancerous conditions, dental caries, and implant-related complications, as well as promoting oral and bone health [208-211].

3.30.1. The Role of Carvacrol in Oral Submucous Fibrosis Treatment

A precancerous condition, oral submucous fibrosis (OSF), is primarily linked to areca nut consumption, characterized by buccal mucosal fibroblast (BMF) transformation into myofibroblasts, exacerbated by pyroptosis mediated by inflammasomes. A recent study targeted the long non-coding RNA (lncRNA) PVT1, a key regulator in OSF, using carvacrol. Treatment with carvacrol reduced PVT1 expression, which in turn decreased pyroptosis markers and myofibroblast activation. This process involved the modulation of PVT1 as a sponge for microRNA (miR)-20a, highlighting carvacrol's ability to influence the PVT1/miR-20a pathway. These findings present carvacrol as a potential natural therapeutic agent for OSF management, addressing both inflammatory and fibrotic pathways [208].

3.30.2. Anti-Caries Effects of Carvacrol

Dental caries, primarily caused by *Streptococcus mutans*, result from the formation of acidogenic and biofilm-forming bacteria in the oral cavity. Essential oils derived from *Origanum vulgare* L., rich in carvacrol, have shown significant antibacterial effects against *S. mutans*. These essential oils reduce acid production, bacterial hydrophobicity, and biofilm formation, with molecular studies revealing the downregulation of key virulence genes (*e.g.*, gtfB/C/D, spaP, gbpB, vicR, relA). Docking studies confirmed carvacrol's direct interaction with virulence proteins, contributing to its efficacy. Importantly, no cytotoxic effects were observed in human keratinocyte cells treated with these oils, suggesting their safety and potential as natural caries-preventive agents [209].

Furthermore, another study investigated the impact of adding carvacrol-rich essential oil to various herbal toothpastes and observed a significant increase in antibacterial activity. The combination of herbal toothpastes with *Origanum dubium* oil doubled their efficacy against *S. mutans*, as evidenced by an increase in inhibition zone diameters from 12 mm to 23 mm. These findings further highlight carvacrol's potential as a natural antimicrobial agent for oral health applications, particularly in the development of herbal dentifrices with enhanced anti-caries properties [210].

3.30.3. Carvacrol in Dental Implant Coatings and Bone Healing

Carvacrol's role in bone healing and infection prevention was explored in implantology. Plasma-sprayed hydroxyapatite (HA) coatings on Ti6Al4V implants were combined with carvacrol, whose release was modulated by polycaprolactone (PCL) and polyethylene glycol (PEG) polymers. The release was pH-sensitive, with a faster release under acidic conditions mimicking postsurgical environments and extended release (up to 50 days) with polymer coatings. Carvacrol inhibited *Staphylococcus epidermidis* growth, reduced osteoclast activity, and minimized bone resorption. These findings position carvacrol as a promising agent for enhancing the osteointegration of dental implants while preventing infections [211].

3.30.4. Metal-Organic Frameworks for Carvacrol Delivery in Dentistry

Metal-organic frameworks (MOFs), particularly UiO-66 (zirconium-based), were utilized to enhance the solubility and stability of carvacrol. UiO-66 demonstrated high loading capacities (~79.6%) and sustained release of carvacrol over 72 hours. In vitro, these MOFs exhibited robust antifungal and antibacterial activity. In *vivo* studies revealed reductions in inflammation and enhanced bone healing, facilitated by cytokine regulation (e.g., TNF-α, IL-6, IL-10). These multifunctional properties highlight the potential of carvacrol-loaded MOFs as innovative solutions for managing oral infections and supporting bone regeneration in dentistry [212].

3.31. The Role of Carvacrol in Diabetes

3.31.1. Carvacrol in Protecting Testicular Function and Male Fertility in Diabetes

Diabetes mellitus (DM) significantly impacts male fertility by disrupting spermatogenesis, testicular structure, and hormonal balance. A study investigated the antidiabetic and testicular protective effects of carvacrol in diabetic male Wistar rats. Four groups were studied: healthy controls, untreated diabetic controls, carvacrol-treated diabetic rats (75 mg/kg orally), and carvacrol-treated non-diabetic rats. Following an 8-week treatment duration, diabetic rats that received no intervention showed a notable decline in germ and Sertoli cell counts, accompanied by disrupted insulin levels. In contrast, carvacrol-treated diabetic rats demonstrated preserved testicular cell populations and significantly improved hormonal levels. Molecular analyses revealed that carvacrol promoted key genes and proteins associated with spermatogenesis. These findings highlight carvacrol's potential to counteract DM-induced testicular damage by enhancing hormonal balance and modulating critical pathways in spermatogenesis [213].

3.31.2. Carvacrol's Neuroprotective Effects in Diabetic Neuropathy

Neuropathy is a major and progressive complication of DM. It is mainly triggered by oxidative stress and metabolic dysregulation. The neuroprotective effects of carvacrol were evaluated in an alloxan-induced diabetic neuropathy model. Diabetes was induced in Wistar rats using alloxan (120 mg/kg intraperitoneally). In this model, a blood glucose threshold of 250 mg/dL was used to define diabetes in the experimental animals. Three groups were studied: healthy controls, alloxan-induced diabetic rats, and diabetic rats treated with carvacrol (50 mg/kg intraperitoneally), with treatment administered daily for three months [213].

Carvacrol demonstrated significant anti-hyperglycemic properties, reducing blood glucose levels and alleviating neuropathic pain in diabetic rats. Oxidative stress markers indicated that carvacrol maintained the oxidant/antioxidant balance by inhibiting excessive reactive oxygen species production. Behavioral assessments, including pain threshold tests, showed marked improvement in neuropathic pain symptoms among carvacrol-treated diabetic rats [214].

3.32. DNA-Protective Activities of Carvacrol

The cytotoxicity, genotoxicity, and DNA-protective effects of carvacrol, thymol, and eucalyptol were assessed in human leukemic K562 cells and hepatoma HepG2 cells using the trypan blue exclusion method and comet assay. While eucalyptol displayed negligible DNA-protective or antioxidant effects, both carvacrol and thymol significantly mitigated hydrogen peroxide (H_2O_2)-induced DNA damage in K562 cells. This effect is attributed to carvacrol's ability to neutralize reactive oxygen species [215].

Further investigations explored the antioxidant, iron-chelating, and DNA-protective properties of carvacrol and other essential oil components, including thymol, eugenol, borneol, and intact *Rosmarinus officinalis* oil (RO). Carvacrol, thymol, and eugenol exhibited strong antioxidant activity across multiple assays, correlating with their DNA-protective effects against H_2O_2-induced damage in HepG2 cells. Interestingly, borneol and RO demonstrated significant DNA protection despite exhibiting negligible antioxidant activity. Specifically, borneol safeguarded HepG2 DNA and plasmid DNA from Fe^{2+}-induced damage, indicating a distinct mechanism of action independent of ROS scavenging. These findings suggest that carvacrol and related compounds may employ multiple pathways to confer DNA protection, including direct interactions with DNA or modulation of cellular repair mechanisms [216].

3.33. Role of Carvacrol in Renal Damage Repair

A study was conducted to examine carvacrol's protective effects against kidney damage caused by methotrexate (MTX), with various experiments evaluating its antioxidant and histological properties. Rats were utilized in the experiment, including a control group, a group receiving MTX alone, and a group administered both MTX and carvacrol. It was observed that carvacrol treatment effectively improved total antioxidant status, demonstrating its antioxidant capabilities in mitigating MTX-induced oxidative damage. The results indicated that carvacrol could potentially play a preventive action in mitigating MTX-induced nephrotoxicity, warranting further research to confirm its clinical applicability [217].

3.34. Antihypercholesterolemic Activities of Carvacrol

Thymbra spicata, a species within the Lamiaceae family, has recently garnered attention for its potential therapeutic effects, largely attributed to its high carvacrol content. In a study, extracts rich in carvacrol (44.13% of its composition) derived from *Thymbra spicata* var. *spicata* were investigated for their antihypercholesterolemic, antioxidant, and anti-steatohepatitic properties in a mouse model with a lipid-enriched diet. The mice consuming this regimen exhibited elevated levels of plasma total cholesterol and enzymatic antioxidants. These findings suggested that the extract rich in carvacrol, contributed to cholesterol reduction, oxidative stress mitigation, and liver protection, offering a scientific explanation for their traditional use in ethnomedicine [119].

In another study, diets supplemented with carvacrol were shown to substantially reduce cholesterol levels in cockerels. These isoprenoid compounds demonstrated showed no impact on the activity of cytosolic prenyl alcohol dehydrogenase. However, supplementation led to a more than twofold increase in microsomal geranyl pyrophosphate pyrophosphatase activity. This enzyme activation may contribute to the production of cholesterol [218].

3.35. Role of Carvacrol in Aquaculture

3.35.1. Health and Growth Performance Benefits of Carvacrol in Fish Diets

The incorporation of natural compounds such as thymol and carvacrol into aquaculture practices has attracted considerable interest due to their ability to promote fish health, reduce stress, and prevent disease outbreaks. These compounds, primarily derived from essential oils, exhibit a range of biological activities that may address key challenges in aquaculture systems.

A study evaluating the supplementation of thymol and carvacrol in tambaqui (*Colossoma macropomum*) revealed their effects on physiological health indicators and growth performance. Over 60 days, five feed concentrations of thymol: carvacrol were tested, with hematological, biochemical, immunological, zootechnical, parasitic load, and bacteriosis resistance parameters assessed at 30 and 60 days [219].

3.35.2. Carvacrol-Rich Essential Oils as Anesthetics in Aquaculture

Carvacrol-rich oregano essential oil was explored as an anesthetic for Nile tilapia (*Oreochromis niloticus)* during handling processes such as transportation and vaccination. Compared to clove oil, oregano essential oil was tested at concentrations ranging from 20–100 mg/L, while clove oil was administered at 50 mg/L. The study identified 60 mg/L as the optimal oregano oil concentration for effective anesthesia, with opercular beat rates comparable between oregano and clove oils [220].

Post-anesthetic stress was assessed by measuring glucose and plasma cortisol levels at intervals of 0, 2, 6, 12, and 24 hours. Glucose levels spiked immediately after anesthesia in all groups, significantly higher than basal levels in control fish (39.33 mg/dL, $p < 0.05$). Cortisol levels in the clove oil group peaked at 12 hours (17.91 ± 4.21 ng/mL) due to a secondary stress response but declined by 24 hours in both oregano and clove essential oil-treated groups to levels below the control group. As a result, oregano essential oil effectively minimized stress and mortality associated with handling in aquaculture systems, presenting an effective substitute for conventional anesthetics [220].

4. Clinical Trial Studies of Carvacrol

4.1. Randomized Controlled Trials of Carvacrol in Asthmatic Patients

Asthma, a prevalent chronic inflammatory airway disease, is characterized by respiratory symptoms such as wheezing, coughing, and breathlessness. Carvacrol, found in various aromatic plants, has demonstrated significant potential in alleviating asthma symptoms [221-223].

A clinical trial reported that patients who received carvacrol showed notable improvements in pulmonary function tests, including forced expiratory volume in one second (FEV_1) and peak expiratory flow rate, compared to the placebo group. Additionally, inflammatory biomarkers such as serum IL-4 and eosinophil count were significantly reduced, indicating a potential immunomodulatory role of carvacrol in asthma management [221].

In a randomized, double-blind, placebo-controlled Phase II clinical trial, asthmatic patients who received 1.2 mg/kg/day of carvacrol for two months showed significant improvements in pulmonary function tests and a notable reduction in C-reactive protein levels [222]. Similarly, in another trial, 40 moderate to severe asthmatic patients treated with carvacrol showed marked decreases in C-reactive protein levels and overall leukocyte count. Pulmonary function improved, correlating with reduced airway inflammation and respiratory symptoms [223]. These findings underscored carvacrol's potential for asthma management.

4.2. Clinical Trial of Carvacrol in Sulfur Mustard-Induced Lung Injury

Sulfur mustard (SM) exposure leads to chronic pulmonary conditions, often characterized by persistent inflammation and impaired lung function. A clinical trial involving 20 SM-exposed patients assessed carvacrol's effects on inflammatory cytokines. Over two months, patients treated with

carvacrol resulted in increased levels of anti-inflammatory cytokines. The maximum mid-expiratory flow and maximum expiratory flow of patients significantly improved, demonstrating carvacrol's role in mitigating SM-induced pulmonary damage [224].

5. Nanotechnology Studies Involving Carvacrol

5.1. Biodegradable Magnesium Alloys with Carvacrol-Loaded Hydrogel Coatings

Biodegradable magnesium alloys (MgAs) are considered promising candidates for use in orthopedic implants because of their superior biocompatibility and favorable mechanical properties. Nonetheless, their use in biomedical applications is restricted by issues like insufficient corrosion resistance, vulnerability to microbial contamination, and mechanical mismatches with human tissue. To overcome these limitations, advanced surface modifications were developed. For example, micro/nanocomposite structures integrating pH-responsive hydrogel micropatterns and inorganic nanomaterials were fabricated on MgA surfaces to enhance biological activity. In such an approach, MgO films were applied via micro-arc oxidation, followed by the growth of hydroxyapatite nanorods (HANRs) using a microwave-assisted hydrothermal method.

Subsequently, pH-responsive hydrogel micropatterns, loaded with the antimicrobial agent carvacrol, were constructed on the HANRs through UV-initiated polymerization of 2-hydroxyethyl methacrylate and 2,2-dimethylacryloyloxy-1-ethoxypropane. This strategy significantly improved the hydrophilicity, biocompatibility, and antimicrobial performance of the MgA surface. The hydrogel micropatterns released carvacrol via ketone bond cleavage at a pH of around 5.0, greatly enhancing its antimicrobial activity. Compared to unmodified MgA, the treated samples exhibited a decrease in corrosion current density. Furthermore, the antibacterial performance demonstrated 96% and 89% effectiveness against *Staphylococcus aureus* and *Escherichia coli*, respectively, showcasing long-term stability and effectiveness [225].

5.2. Carvacrol-Enhanced Polylactic Acid (PLA) Composites

Carvacrol was integrated into poly(lactic acid) (PLA) matrices, combined with cellulose nanocrystals and zinc oxide (CNC-ZnO), to develop antimicrobial composite films, particularly for food packaging applications. Using a straightforward solution casting technique, PLA-based films displayed superior mechanical attributes, UV-blocking properties, and antibacterial effectiveness. Films incorporating 20% carvacrol and 3 wt% CNC-ZnO exhibited improved mechanical properties with bacteriostatic activity against different bacterial strains. These films also extended the shelf life of strawberries, underscoring their potential in sustainable food packaging applications [226].

5.3. Hybrid Nanocomposites for Green Antibacterial Materials

Additionally, hybrid nanocomposites of carvacrol and natural attapulgite were developed using mechanical milling. The substitution of attapulgite’s zeolitic water with carvacrol molecules resulted in stable hybrids with rapid-release properties. The strong antibacterial effects against *S. aureus* and *E. coli* highlighted their potential as green antibacterial materials for replacing synthetic antibiotics in animal feed [227].

5.4. Nanoencapsulation Strategies for Stability and Controlled Release

Nanotechnology has further advanced carvacrol's applications by addressing challenges related to its volatility and strong aroma. Nanoencapsulation strategies, such as the formation of sodium casein/hydroxypropyl-beta-cyclodextrin nanoemulsions, have improved the stability and controlled release of carvacrol. These nanoemulsions demonstrated lower MIC and minimum bactericidal concentration (MBC) values against *Bacillus cereus* compared to free carvacrol, along with better antimicrobial performance in dairy products [228].

Similarly, gelatin/chitosan nanofiber membranes containing carvacrol and cetyltrimethylammonium bromide (CTAB) showed enhanced antibacterial and antioxidant properties, significantly extending the shelf life of strawberries and chilies [229].

5.5. Postharvest Preservation with Carvacrol-Based Nanoemulsions

In postharvest preservation, chitosan-essential oil nanoemulsions with carvacrol were applied to fruits such as guava and mango, reducing weight loss, delaying pericarp browning, and maintaining firmness and phenolic content during storage. This strategy demonstrates the potential of carvacrol-based nanoemulsions in maintaining postharvest quality and extending shelf life [230, 231].

5.6. Beta-Cyclodextrin Complexes for Food Preservation

Carvacrol has also been incorporated into beta-cyclodextrin (beta-CD) inclusion complexes to enhance its stability and controlled release. These complexes, optimized for specific ratios, demonstrated selective antibacterial and antifungal properties against *Bacillus cereus* and *Geotrichum candidum*. Molecular modeling studies revealed that thymol and carvacrol form thermodynamically stable complexes within beta-CD cavities, enabling their use in food preservation applications [232].

5.7. Antimicrobial Thin Films Using Halloysite Nanotubes

In food packaging, antimicrobial thin films were developed using halloysite nanotubes (HNTs) for the encapsulation and sustained release of carvacrol. Layer-by-layer assembly on polyethylene surfaces created films with significant antimicrobial effects, reducing bacterial contamination on chicken meat surfaces and showcasing antibiofilm activity [233].

6. Conclusions

This review provides a comprehensive overview of the diverse applications of carvacrol. The extensive biological activities of carvacrol, coupled with its relative safety and natural origin, underscore its promise as a multifunctional therapeutic and industrial agent. Despite the substantial body of evidence supporting its efficacy, further research is warranted to explore its full mechanistic pathways, optimize its formulations for targeted applications, and assess its long-term safety and efficacy in clinical and industrial settings. This review is expected to encourage further scientific investigations into the potential of carvacrol across multiple disciplines.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

ORCID
Kemal Husnu Can Baser: 0000-0003-2710-0231
Ismail Celil Haskologlu: 0009-0003-3961-5918
Emine Erdag: 0000-0002-1431-935X

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