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Carvacrol as an Antimicrobial Adjuvant in Complementary Therapy for Infectious Diseases: A Mini-Review

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Abstract

The rapid emergence of multidrug-resistant microorganisms has reduced the effectiveness of conventional antimicrobial therapy and intensified the search for alternative and complementary anti-infective strategies. Carvacrol, a naturally occurring phenolic monoterpenoid predominantly found in essential oils of *Origanum* and *Thymus* species, has attracted considerable attention because of its broad-spectrum antimicrobial and resistance-modifying properties. This mini-review summarizes the antimicrobial mechanisms of carvacrol and evaluates its potential as a complementary agent in infectious disease therapy. Carvacrol primarily targets the microbial cytoplasmic membrane, where its lipophilic nature facilitates membrane incorporation, perturbs lipid organization, increases permeability, and promotes leakage of ions and intracellular constituents. Its proton-exchange activity contributes to dissipation of the transmembrane pH gradient and proton motive force, resulting in impaired ATP generation and cellular homeostasis. In addition to direct antibacterial activity, carvacrol exhibits antibiofilm, antifungal, and antiviral properties through multiple mechanisms. Of particular therapeutic interest is its ability to enhance the activity of conventional antimicrobials. Experimental studies demonstrate synergistic or additive interactions with agents including polymyxin B, erythromycin, cefixime, ceftazidime, cefepime, and selected antifungal drugs, although outcomes vary according to the microorganism, antimicrobial, and experimental conditions. Carvacrol-rich essential oils have also demonstrated promising antimicrobial combinations, but their effects should be distinguished from those of purified carvacrol. Despite encouraging in vitro and preclinical evidence, limited pharmacokinetic information, formulation challenges, potential toxicity at therapeutic concentrations, and insufficient clinical validation currently restrict translation. Further standardized mechanistic, formulation, animal, and clinical studies are therefore required to establish carvacrol as a safe and effective antimicrobial adjuvant.

Keywords

Antimicrobial resistance, biofilm, carvacrol, combination therapy, essential oil

Introduction

Antimicrobial resistance (AMR) has emerged as one of the most consequential threats to global health, food security, and sustainable development. The progressive loss of antimicrobial efficacy compromises not only the treatment of infectious diseases but also medical interventions that depend on effective infection prevention and therapy, including surgery, organ transplantation, intensive care, and cancer chemotherapy. The global burden is already substantial: an estimated 4.71 million deaths were associated with bacterial AMR in 2021, including approximately 1.14 million deaths directly attributable to bacterial resistance. Earlier global estimates for 2019 attributed approximately 1.27 million deaths directly to bacterial AMR, confirming that resistance is an ongoing cause of considerable mortality rather than merely a future threat (GBD 2021 Antimicrobial Resistance Collaborators, 2024; Murray et al., 2022).

Recent surveillance further demonstrates the scale and continuing evolution of the problem. The World Health Organization (WHO) has reported that approximately one in six laboratory-confirmed bacterial infections worldwide in 2023 was resistant to antibiotic treatment. Between 2018 and 2023, resistance increased in more than 40% of monitored pathogen-antibiotic combinations, with particularly high burdens in the South-East Asia and Eastern Mediterranean regions (World Health Organization, 2025). Beyond mortality, AMR imposes substantial economic and health-system costs through prolonged illness, longer hospitalization, use of expensive second-line therapies, productivity losses, and disruption of food-producing systems.

The growing resistance of clinically important pathogens is especially concerning. The WHO Bacterial Priority Pathogens List 2024 identifies 15 families of antibiotic-resistant bacteria requiring prioritized research and development. Carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant and third-generation cephalosporin-resistant *Enterobacterales*, and rifampicin-resistant *Mycobacterium tuberculosis* are among the critical-priority threats, while methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Pseudomonas aeruginosa*, vancomycin-resistant *Enterococcus faecium*, and resistant *Salmonella*, *Shigella*, and *Neisseria gonorrhoeae* are included among high-priority pathogens (World Health Organization, 2024). These organisms employ multiple resistance mechanisms, including antimicrobial-inactivating enzymes, modification of drug targets, reduced membrane permeability, active efflux, biofilm formation, and acquisition of mobile resistance determinants.

The situation is further complicated by an inadequate antibacterial development pipeline. Although new antibacterial agents and non-traditional approaches are under development, only a limited proportion represent genuinely innovative therapies or provide activity against the most problematic critical-priority pathogens (World Health Organization, 2024). Consequently, strategies that preserve, restore, or potentiate the activity of existing antimicrobial drugs are becoming increasingly important alongside the discovery of entirely new antimicrobial classes.

One promising approach involves antimicrobial adjuvants, which may increase microbial susceptibility to conventional drugs by disrupting biofilms, altering membrane permeability, interfering with efflux, or modulating other resistance-associated processes. Plant-derived phytochemicals and essential-oil constituents have therefore received considerable attention because of their structural diversity and multitarget biological activities. Among these compounds, carvacrol (5-isopropyl-2-methylphenol), a phenolic monoterpenoid occurring predominantly in essential oils of *Origanum* and *Thymus* species, has emerged as a particularly promising antimicrobial candidate. Carvacrol demonstrates activity against Gram-positive and Gram-negative bacteria and also exhibits antibiofilm, antifungal, and antiviral properties (Marchese et al., 2018; Mączka et al., 2023; Sharifi Rad et al., 2018).

Unlike many conventional antibiotics that act predominantly on defined molecular targets, the antibacterial activity of carvacrol is strongly associated with membrane-centered and multitarget effects. Its hydrophobic character facilitates partitioning into microbial membranes, resulting in alterations in membrane organization and permeability, dissipation of electrochemical gradients, leakage of intracellular constituents, and disruption of cellular energy homeostasis (Ultee et al., 2002; Khan et al., 2017). Carvacrol may additionally influence efflux activity, biofilm development, and other physiological processes relevant to antimicrobial tolerance and resistance. These characteristics make carvacrol particularly interesting not only as an antimicrobial compound in its own right but also as a potential adjuvant capable of enhancing conventional antimicrobial therapy.

Experimental studies have demonstrated additive or synergistic interactions between carvacrol and several antimicrobial agents, including erythromycin, cefixime, polymyxin B, ceftazidime, cefepime, and selected antifungal drugs (Magi et al., 2015; Asadi et al., 2023; Cordeiro et al., 2020; de Souza et al., 2024). Particularly

relevant is its potential to enhance antimicrobial activity against resistant organisms such as MRSA and polymyxin-resistant *Klebsiella pneumoniae*. Nevertheless, outcomes vary according to the microorganism, antimicrobial agent, concentration, and experimental model, and evidence obtained using purified carvacrol must be distinguished from studies employing carvacrol-rich essential oils.

Therefore, this mini-review critically summarizes the antimicrobial properties of carvacrol, with particular emphasis on its membrane-associated mechanisms of action and its potential to complement conventional antimicrobial therapy. Special attention is given to experimentally demonstrated carvacrol-antimicrobial combinations, the relevance of these combinations against drug-resistant pathogens, and the distinction between purified carvacrol and carvacrol-rich essential-oil preparations. Current limitations, including formulation, bioavailability, toxicity, pharmacokinetic uncertainty, and the scarcity of clinical evidence, are also considered to identify major priorities for translating carvacrol from an experimentally promising phytochemical into a clinically useful antimicrobial adjuvant.

Chemical properties and natural sources of carvacrol

Carvacrol (5-isopropyl-2-methylphenol) is a lipophilic monoterpenoid phenol. Its aromatic ring and free phenolic hydroxyl group are central to its membrane-partitioning behavior and antimicrobial activity (Ultee et al., 2002; Marchese et al., 2018). It occurs prominently in essential oils from Lamiaceae plants, particularly *Origanum* and *Thymus* species, and is often present together with its positional isomer thymol (Kachur & Suntres, 2019; Mączka et al., 2023). Carvacrol is also reported in other aromatic plants, including *Trachyspermum ammi* (Khan et al., 2017). Its established use as a flavoring and food-related antimicrobial has encouraged investigation of pharmaceutical applications; however, food-use status should not be interpreted as evidence of safety or efficacy at therapeutic doses or by all routes of administration (Suntres et al., 2013).

Spectrum of antimicrobial activity and mechanisms

Carvacrol is active in vitro against numerous Gram-positive and Gram-negative bacteria, including *Escherichia coli, Staphylococcus aureus, Listeria monocytogenes, Salmonella enterica,* and *Streptococcus pyogenes*, although potency varies with strain, inoculum, growth state, medium, and formulation (Zhang et al., 2018; Wijesundara et al., 2021). Antifungal activity has also been reported, including activity against *Candida* species (Shaban et al., 2020). These observations support a broad antimicrobial spectrum, but direct comparison with clinical antibiotics requires caution because susceptibility methods, endpoints, and achievable drug exposures differ substantially.

The best-supported antibacterial mechanism of carvacrol is disruption of cytoplasmic-membrane function. In *Bacillus cereus*, carvacrol destabilized the membrane and was proposed to act as a proton exchanger, reducing the transmembrane pH gradient, collapsing the proton motive force, and depleting the cellular ATP pool (Ultee et al., 2002). Membrane perturbation can also increase permeability and promote leakage of ions and intracellular constituents. Carvacrol can modify efflux-associated phenotypes, although the magnitude of this effect depends on bacterial physiological state (Jánosity et al., 2023). In *Escherichia coli*, membrane depolarization and reactive oxygen species have also been implicated (Khan et al., 2017). These mechanisms are complementary rather than mutually exclusive and are likely to vary among organisms.

Taken together, the antiviral literature supports activity against selected viruses but does not yet justify describing carvacrol as a clinically validated broad-spectrum antiviral. Direct studies of purified carvacrol are particularly important because results obtained with *oregano* or *thyme* essential oils may reflect interactions among multiple constituents. This distinction is also essential when evaluating combination therapy

Combination therapy with carvacrol

Carvacrol has been investigated as an antimicrobial adjuvant because membrane perturbation and other pleiotropic effects may complement the targets of conventional drugs. Against *Staphylococcus aureus* and *Acinetobacter baumannii*, combinations of carvacrol or thymol with selected antibiotics have produced substantial reductions in inhibitory concentrations in vitro (Gan et al., 2025). In *Mycobacterium tuberculosis*, a systematic review identified preclinical evidence of synergistic activity between carvacrol and rifampicin, including membrane- and biofilm-associated models (Fermiano et al., 2024). These findings are promising, but most evidence remains preclinical and should not be interpreted as proof of clinical efficacy.

Multifunctional properties of carvacrol

Beyond direct antimicrobial effects, carvacrol has antioxidant and anti-inflammatory activities in experimental systems, including modulation of oxidative stress and inflammatory mediators (Imran et al., 2022; Suntres et al., 2013). These properties may be relevant to infection-associated tissue injury, but they should be considered supportive pharmacology rather than evidence of anti-infective efficacy. Carvacrol has also been investigated for other biological activities, including antitumor and antiparasitic effects; these topics fall outside the principal scope of this mini-review.

Limitations and translational considerations

Most evidence for carvacrol as an anti-infective agent derives from in-vitro experiments, essential-oil studies, or animal models. Concentrations effective in vitro may not be achievable safely at infected tissues, and carvacrol is poorly water soluble and volatile. Differences in formulation, purity, susceptibility methods, and synergy definitions also limit direct comparison among studies. Clinical translation will require standardized combination testing, pharmacokinetic and toxicological studies, optimized delivery systems, and well-designed in-vivo and clinical investigations.

Conclusion

Carvacrol is a membrane-active phenolic monoterpenoid with broad experimental antimicrobial activity and a growing body of evidence as an adjuvant to conventional anti-infective agents. The strongest mechanistic evidence supports membrane destabilization, dissipation of proton motive force, ion leakage, and ATP depletion. Combination effects are drug- and organism-specific: some are synergistic, whereas others are additive, and results obtained with carvacrol-rich essential oils must be distinguished from purified carvacrol. Current evidence supports further development of carvacrol-based adjunctive strategies, but not replacement of standard antimicrobial therapy.

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Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

Ethical approval was not required for this study, as it is a review article and did not involve animals or human participants,

Data Availability Statement

No new data generated in this study.

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Table 1. Studies on combinational therapy of carvacrol with antimicrobial agents

Antimicrobial agent / preparation	Target pathogen	Interaction / major outcome	Reference
Polymyxin B + carvacrol	*Klebsiella pneumoniae*	Synergistic; antibiofilm activity and improved in-vivo outcome	de Souza et al., 2024
Ceftazidime + carvacrol	*K. pneumoniae*	Additive antibacterial interaction	Cordeiro et al., 2020
Cefepime + carvacrol	*K. pneumoniae*	Additive antibacterial interaction	Cordeiro et al., 2020
Cefixime + carvacrol	*Escherichia coli*	Enhanced antibacterial and antibiofilm activity	Asadi et al., 2023
Erythromycin + carvacrol	*Group A Streptococcus*	Synergistic activity against erythromycin-resistant isolates	Magi et al., 2015
Rifampicin + carvacrol	*M. tuberculosis*	Preclinical synergy reported in membrane/biofilm models	Fermiano et al., 2024
Pristinamycin + carvacrol-rich Thymus EO*	*K. pneumoniae*	Synergistic interaction (whole essential oil)	Fadli et al., 2012
Fluconazole / amphotericin B / nystatin / caspofungin + carvacrol	*Candida auris*	Synergistic-to-additive effects depending on drug and isolate	Shaban et al., 2020
Antiretroviral therapy + carvacrol	*HIV-1*	Additive inhibition reported; carvacrol inhibits viral fusion	Mediouni et al., 2020

*Studies used carvacrol-rich essential oils or oregano essential oil rather than purified carvacrol