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Harnessing Monoterpenes and Monoterpenoids as Weapons against Antimicrobial Resistance

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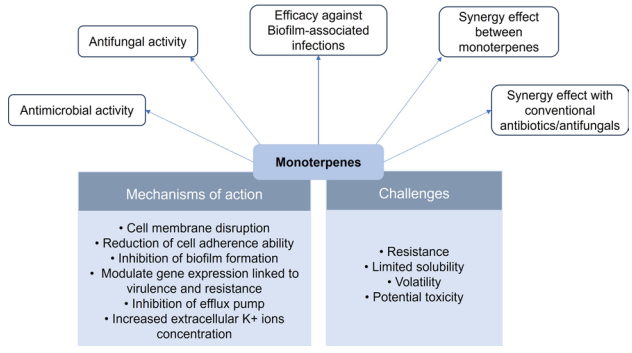
Abstract

Antimicrobial resistance (AMR) poses a formidable challenge in global healthcare, driving the exploration of natural products for novel antimicrobials. Among these, essential oils (EOs) derived from medicinal plants are rich sources of diverse bioactive compounds. Monoterpenes and monoterpenoids, critical constituents of EOs, have emerged as promising agents in combating multidrug-resistant (MDR) pathogens. This review analyzed recent literature on the efficacy of monoterpenes against AMR, highlighting their broad-spectrum activity and potential as alternative therapeutic options for MDR infections. Mechanistic insights reveal their ability to disrupt cell membranes, inhibit biofilm formation, and modulate gene expression linked to virulence and resistance, thereby reducing microbial viability through alterations in membrane potential, enzymatic activity, and genetic regulation. Synergistic interactions between monoterpenes and conventional antibiotics are also elucidated. Innovative approaches in monoterpene research are explored, although challenges such as resistance, limited solubility, volatility, and potential toxicity are acknowledged, emphasizing the need for advanced formulation strategies and interdisciplinary research.



The synergy observed with conventional antibiotics, coupled with their ability to target specific microbial resistance mechanisms, underscores the potential of monoterpenes in combating antibiotic-resistant infections. Future investigations should prioritize optimizing monoterpenes' therapeutic properties and assessing their safety profiles to fully exploit their potential in addressing AMR.

K e y w o r d s: antimicrobial resistance, monoterpenes, essential oils, multidrug resistance

Introduction

Antimicrobial resistance (AMR) presents a critical challenge in global healthcare, with over two million cases and 23,000 deaths annually in the United States due to antibiotic-resistant infections (Prestinaci et al. 2015). Similarly, Europe reports around 400,000 infections and 25,000 deaths from multidrug-resistant (MDR) bacteria annually. The World Health Organization notes a concerning stagnation in developing

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new antimicrobials, with only 12 antibiotics approved since 2017, most of which are from existing classes with known resistance mechanisms. This has fueled the search for alternative therapies with broader-spectrum activity (Corona-Gómez et al. 2022).

Natural products offer a promising avenue for the discovery of novel antimicrobials, with plants providing a rich source of structurally diverse bioactive compounds. Essential oils (EOs) from medicinal plants are a promising source of novel antimicrobials (Khan et al. 2020). These oils have demonstrated effectiveness against a wide range of pathogens, including *Pseudomonas aeruginosa*, *Pseudomonas putida*, and *Staphylococcus aureus*; they have shown potential in eradicating biofilms, which are crucial for treating persistent infections (Kavanaugh and Ribbeck 2012; Aggarwal et al. 2000). EOs contain volatile compounds such as terpenes and terpenoids, identified as potent antimicrobial agents against bacteria, fungi, and viruses (Barbosa et al. 2020).

Monoterpenes and monoterpenoids, significant components of EOs, exhibit antimicrobial, anti-inflammatory, antioxidant, and anticancer properties (Zielińska-Błajet and Feder-Kubis 2020). Many studies have highlighted their potential in antimicrobial drug development, with results delving into the composition and effectiveness of EOs, revealing their potency against a spectrum of pathogens (Mahizan et al. 2019; Moo et al. 2020; 2021; Yang et al. 2021a; 2021b). For instance, the EO from *Rosmarinus officinalis* exhibited a rich composition, including α-pinene, camphene, β-pinene, myrcene, 1,8-cineole, camphor, β-*trans*-terpineol, myrtenol, and α-terpineol, showcasing robust antimicrobial activity against Gram-positive bacteria such as *S. aureus*, *Micrococcus luteus*, and *Bacillus cereus*, along with effectiveness against Gram-negative bacteria and fungal strains (Chraibi et al. 2020). Similarly, *Asteriscus graveolens* EO, characterized by compounds such as α-thujone (17.92%), carvacrol (14.14%), *p*-cineole (13.83%), and camphor (12.71%), presents a rich monoterpene profile with significant antimicrobial potential (Aljeldah 2022).

Considering these significant findings, this review aims to synthesize recent literature on the effectiveness of monoterpenes in combating AMR and to explore their broad-spectrum activity and potential as alternative therapeutic agents against MDR pathogens.

Exploring the antimicrobial potential of monoterpenes

Exploring the antimicrobial potential of monoterpenes presents a promising avenue in combating microbial infections amidst the escalating threat of AMR. Fig. 1 illustrates the chemical structures of the monoterpenes discussed throughout this review. These structures were sourced from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). These compounds demonstrate broad-spectrum antimicrobial activity against bacteria and fungi. Studies have highlighted their efficacy against both Gram-positive and Gram-negative bacteria, including drug-resistant strains like methicillin-resistant *S. aureus* (MRSA) and MDR *Escherichia coli*. Furthermore, monoterpenes exhibit significant antifungal activity against common pathogens such as *Candida* species. Table I depicts monoterpenes' reported mechanism of action, while Fig. 2 visually represents these mechanisms targeting MDR bacteria.

Antibacterial activity. Sim et al. (2019) reported the antimicrobial efficacy of oregano oil, carvacrol, thyme oil, and thymol against bacterial isolates from dogs with otitis externa, showing MIC_{90} values ranging from 200 to 2,292 μg/ml for various MDR strains, including methicillin-resistant *Staphylococcus pseudintermedius* and *P. aeruginosa*. Carvacrol was notably effective, with an MIC_{90} of 146 μg/ml against *S. pseudintermedius*. Similarly, Sharma et al. (2023) found that thymol and eugenol had MICs of 125–250 μg/ml and 500–1,000 μg/ml against *S. aureus*, respectively.

Muniz et al. (2021) highlighted the potential of synthetic and natural eugenol derivatives to inhibit the NorA efflux pump in *S. aureus*, with their studies suggesting mechanisms involving hydrogen bonds and hydrophobic interactions. The findings suggest that eugenol holds promise for development in antibacterial drug formulations; mainly targeting strains carrying the NorA efflux pump. Additionally, Buru et al. (2022) demonstrated that eugenol exposure leads to downregulated *luxS* expression in MRSA, potentially enhancing biofilm production and secondary metabolite biosynthesis through the upregulation of the *argC* gene, indicating potential targets for antibacterial development against drug-resistant strains.

Kwiatkowski et al. (2020) evaluated the antimicrobial efficacy of 1,8-cineole and linalyl acetate against *S. aureus*, with MIC values ranging from 28,800–57,600 μg/ml and 28,200–112,600 μg/ml, respectively. Caballero Gómez et al. (2022) studied various compounds including cinnamaldehyde, thymol, carvacrol, limonene, and geraniol against *Enterococcus*, *Pseudomonas*, and *Staphylococcus* strains, finding cinnamaldehyde the most effective with MICs of 10 to 50 μg/ml. Carvacrol and thymol demonstrated increased MIC_{90} values of 292–400 μg/ml against β-hemolytic *Streptococcus* compared to staphylococcal isolates (146–200 μg/ml) (Sim et al. 2019). Thymol showed the highest MIC_{90} (800 μg/ml) against *P. aeruginosa*, and displayed comparable activity against *Proteus mirabilis* at MIC_{90} 200–292 μg/ml. Additionally, de Souza et al. (2021)

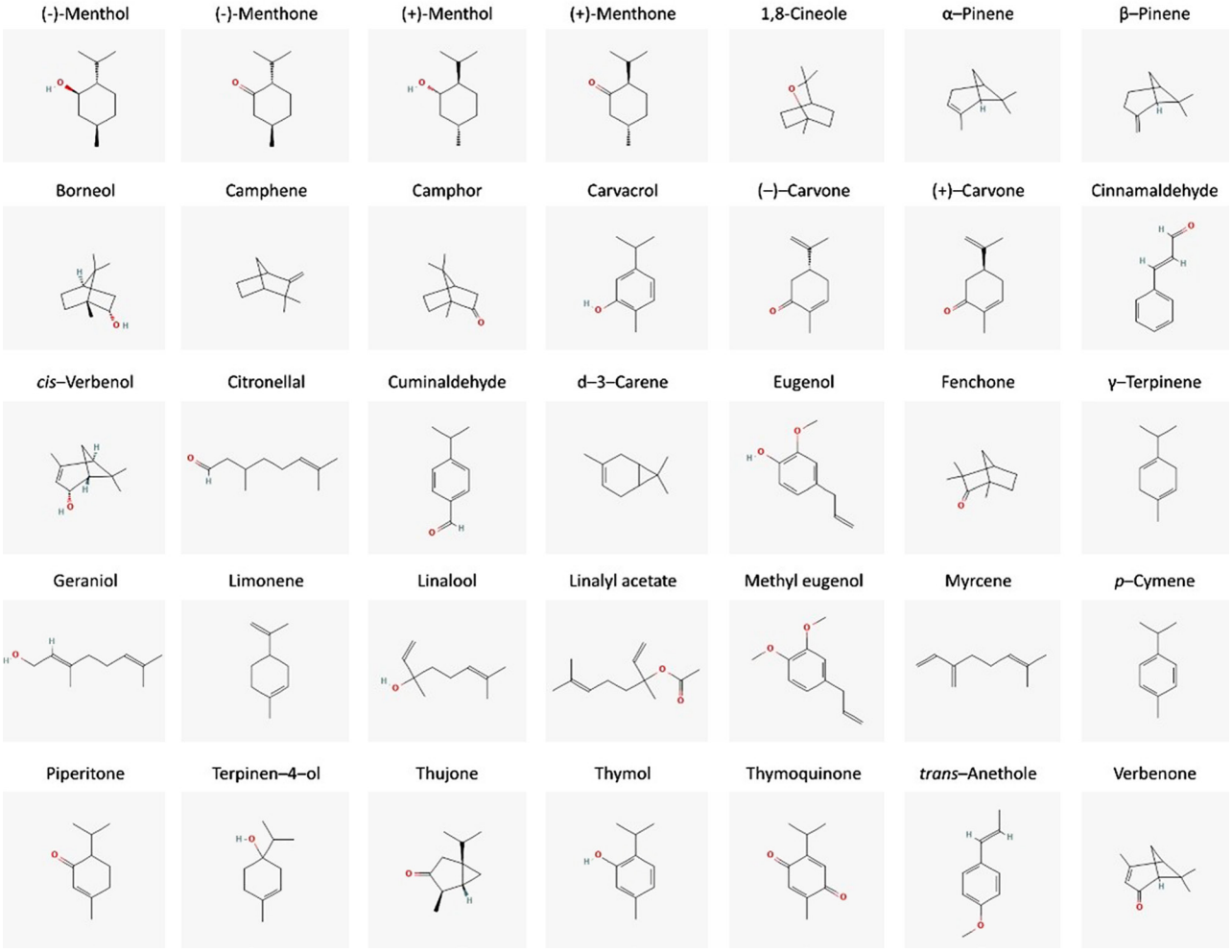

Fig. 1. Chemical structures of monoterpenes discussed in this review, sourced from the PubChem database.

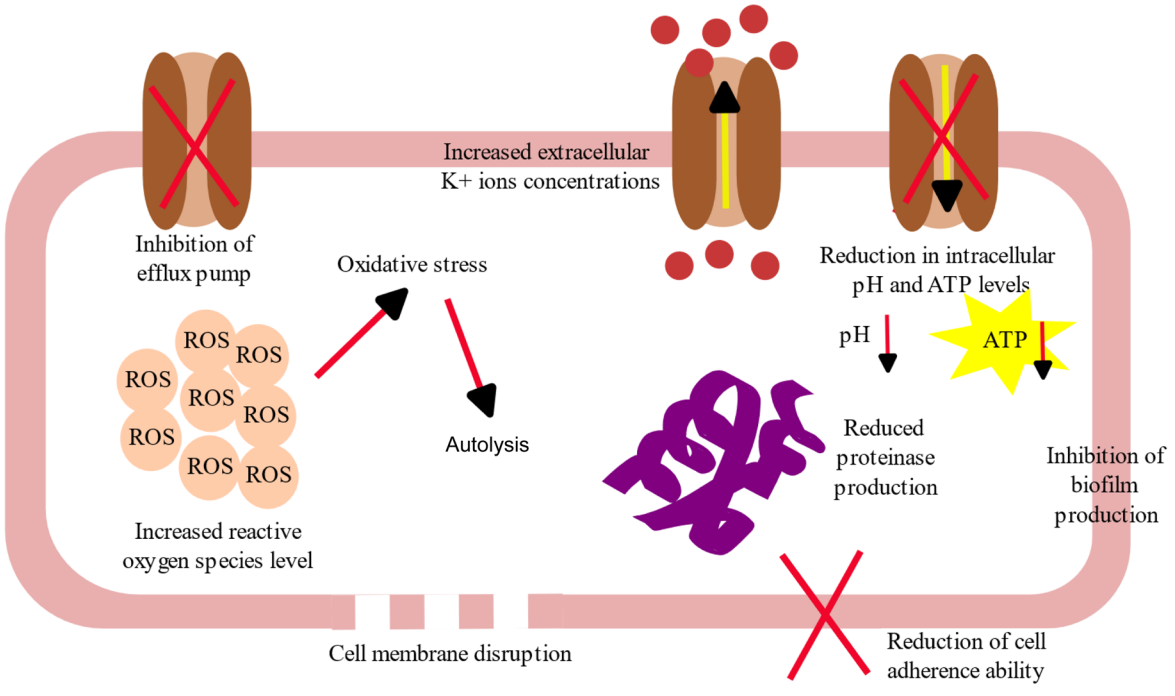

Fig. 2. A schematic representation of mechanisms of action of monoterpenes targeting MDR bacteria. The diagram was created using Inkscape 1.3.2.

Table I
Mechanism of action of monoterpenes against tested pathogens.

Chemical compounds	Tested pathogen	Mechanisms of action	References
Eugenol	*Staphylococcus aureus*	• Inhibition of efflux pump	Macêdo et al. 2022
Eugenol	*Staphylococcus aureus*	• Inhibition of *norA* efflux pump	Muniz et al. 2021
Eugenol α-Bromo-*trans*-cinnamaldehyde	*Staphylococcus aureus*	• Gene expression reduction linked to intracellular adhesion	Mastoor et al. 2022
Eugenol	Methicillin-resistant *Staphylococcus aureus*	• Downregulation of *luxS* gene • Inhibition of biofilm production • Enhancement of secondary metabolites • Upregulation of *argC* protein	Buru et al. 2022
Eugenol	Methicillin-resistant *Staphylococcus aureus*	• Downregulation of biofilm-related genes (*sarA*, *icaA*, *icaD*) • Reduction of polysaccharide accumulation and cell adhesion	El-Far et al. 2021
Carvacrol	*Staphylococcus aureus* *Pseudomonas fluorescens*	• Targeted extracellular polymeric substances • Disruption of biofilm structures	Wang et al. 2020b.
Eugenol Geraniol	*Acinetobacter baumannii*	• Reduction in exopolysaccharide production • Disruption and inhibition of biofilm • Downregulation of *csuE* gene	Choudhary et al. 2022
p-Cymene	*Campylobacter jejuni*	• Inhibition of efflux pump	Šimunović et al. 2020
Carvacrol	*Pseudomonas aeruginosa* *Enterococcus faecalis*	• Cell membrane destruction • Leakage of the intercellular pool • Anti-biofilm properties • Increased extracellular K^+ ions concentrations	Mechmechani et al. 2022
Carvacrol Thymol	*Salmonella* Thyphimurium	• Anti-inflammatory effects • Anti-oxidant properties • Enhanced epithelial barrier integrity • Reduction of bacterial translocation • Improved transepithelial electrical resistance • Inhibited bacterial growth	Giovagnoni et al. 2020
Eugenol	Extended-spectrum β-lactamases-quinolone-resistant strains of *Klebsiella pneumoniae*	• Induced shrinkage of cell surfaces • Diminished cytoplasm • Triggered cellular stress and autolysis	Dhara and Tripathi 2020
Eugenol	Carbapenem-resistant *Klebsiella pneumoniae* (CRKP)	• Disruption of cell membrane • Reduction in intracellular pH and ATP levels • Cell membrane hyperpolarization • Downregulation of biofilm-related genes (*pgaA*, *luxS*, *wbbM*, *wzm*) • Upregulation of *mrkA* gene	Qian et al. 2020
Carvacrol	Extended-spectrum beta-lactamases *Escherichia coli*	• Disintegration of bacterial cell membranes • Elevation of reactive oxygen species levels • Protected macrophage cells from bacterial invasion • Increased the release of K^+ ions, ATP, and cellular DNA • Anti-biofilm properties	Khan et al. 2020
Carvacrol Thymol Eugenol Methyl eugenol	*Candida albicans*	• Reduced proteinase production	Shaban et al. 2020
Carvacrol Thymol Eugenol Methyl eugenol	*Candida auris*	• Reduced proteinase production and host cell adherence	Shaban et al. 2020
Carvacrol	*Candida auris*	• Induced oxidative stress • Increased CAT, SOD and GPx enzyme activity • Decreased GR and GST enzyme activity • Caused membrane disintegration	Ismail et al. 2022

reported that carvacrol showed inhibitory effects against carbapenem and polymyxin-resistant *Klebsiella pneumoniae*, with MICs of 130–260 μg/ml. In murine models, carvacrol treatment significantly improved survival and reduced bacterial counts in infections, indicating its potential for modulating host immune responses and reducing infection severity compared to polymyxin B treatment.

Owen et al. (2019) highlighted carvacrol's potent antimicrobial properties, exhibiting the lowest MICs (0.99–15.81 mM) across various microorganisms and bactericidal effects. Although ineffective against carbapenem-resistant *E. coli* and *P. aeruginosa*, carvacrol showed no significant cross-resistance with antibiotics, positioning it as a promising candidate against AMR. Linalool exhibited higher activity against antibiotic-sensitive *P. aeruginosa* (MIC 228.20 mM) than resistant strains (MIC 912.90 mM), while cuminaldehyde showed higher activity against antibiotic-sensitive *E. coli* (MIC 2.10 mM) compared to resistant strains (MIC 8.40 mM). Moreover, cuminaldehyde displayed better efficacy against vancomycin-susceptible *enterococci* (VSE) (MIC 134.41 mM) than resistant strains (MIC 537.65 mM).

Šimunović et al. (2020) further demonstrated that monoterpenes such as carvacrol, thymol, and thymoquinone possess significant antimicrobial activity, each with MICs of 31.25 μg/ml, while *p*-cymene and γ-terpinene showed reduced efficacy with MICs of 1,000 μg/ml. Notably, *p*-cymene also inhibited efflux pumps in *C. jejuni* while carvacrol displayed a weaker effect. Rossi et al. (2021) reported that thymol, carvacrol, eugenol, geraniol, and cinnamaldehyde effectively inhibited two *Vibrio* species, *Vibrio anguillarum*, and *Vibrio harveyi*, with MICs ranging from 0.94–7.5 mM, whereas eucalyptol, linalool, menthol, α-pinene, and limonene showed no activity at the tested concentrations.

Giovagnoni et al. (2020) investigated thymol and carvacrol's protective effects against *Salmonella* Typhimurium, revealing a dual mechanism of action with MICs of 1.87 mM. These compounds enhanced epithelial barrier integrity while directly inhibiting *Salmonella* growth and modulating virulent genes. Noumi et al. (2023) explored limonene's antimicrobial properties, demonstrating inhibition of bacterial growth and biofilm formation at a MIC of 48 μg/ml, surpassing the efficacy of the whole *Anethum graveolens* EO. Limonene also showed anti-adhesion activity and inhibited violacein production, highlighting its potential for targeted interventions.

Antifungal activity. Stringaro et al. (2022) explored the antimicrobial effects of *Oregano vulgare* EO (OVEO) against *Candida* species, finding variable sensitivity across strains, with *C. albicans* being less sensitive than *Candida glabrata*, *Candida tropicalis*, and *Candida krusei*. Carvacrol showed superior antimicrobial activity compared to OVEO and thymol, with MIC values of 97.5–195 μg/ml and 195–390 μg/ml for thymol, respectively. Larvae viability studies using *Galleria mellonella* revealed that OVEO slightly reduced survival rates by about 30% in *C. albicans*. Post-infection treatment with OVEO, carvacrol, or thymol generally improved survival, notably with carvacrol treatment increasing survival by 100% in *C. albicans*, while thymol and OVEO showed lesser improvement.

Sousa Silveira et al. (2020) demonstrated the antibacterial efficacy of thymol and carvacrol against *S. aureus*, with MIC values of 72 and 256 μg/ml, respectively. Shaban et al. (2020) reported that carvacrol was more effective against *Candida auris* than thymol, with MICs of 125 μg/ml and 312 μg/ml, respectively. The study also noted that carvacrol inhibited *C. auris* adherence to host cells and reduced proteinase production in *C. auris* and *C. albicans*, even at sub-inhibitory concentrations.

Touil et al. (2020) explored carvacrol and cuminaldehyde against amphotericin B-resistant *C. albicans*, individually and in combination, in single- or mixed-infections. They found variable inhibitory effects on *C. albicans* yeast formation compared to hyphae development, with carvacrol exhibiting MIC values ranging from 250–1,000 μg/ml and cuminaldehyde from 2000–4000 μg/ml), varying among *Candida* isolates. Carvacrol showed greater efficacy than cuminaldehyde, particularly against *C. albicans* isolates. Both compounds exhibited inhibitory effects against bacteria co-isolated with *C. albicans*, with MIC values of 1,000 μg/ml for carvacrol and 1,000–4,000 μg/ml for cuminaldehyde. These results highlight the potential of carvacrol and cuminaldehyde, alone or in combination, in combating AMR in *C. albicans* infections.

In assays against *C. albicans*, different cell forms, such as hyphal or yeast are influenced by environmental conditions such as pH, temperature, and nutrient availability. The studies reviewed here primarily focused on the hyphal form of *C. albicans*, which is the infectious form, with the exception of Sharifzadeh et al. (2019), Iraji et al. (2020), and Stringaro et al. (2022). Table II summarizes research on monoterpenes, detailing their minimum inhibitory concentration (MIC) against Gram-positive, Gram-negative, and fungal pathogens.

Antiviral activity. Panagiotopoulos et al. (2021) found that *p*-cymene binds to the nuclear localization signal of SARS-CoV-2, impairing its nuclear translocation and viral replication, achieving up to 90% inhibition in Vero cells at non-toxic concentrations (0.0125 to 200 μg/ml). Similar effects were observed against influenza H1N1, where *p*-cymene at 20 μg/ml reduced virus protein expression and impaired nuclear translocation. These findings propose *p*-cymene as a potential antiviral agent, either as a standalone treatment or as an adjuvant in treating COVID-19 and other RNA virus infections.

Table II
Comprehensive summary of MIC values of monoterpenes against AMR pathogens, grouped as Gram-positive, Gram-negative, and fungal pathogens.

Tested pathogens	Chemical compounds	MIC/Sensitivity	References
Gram-positive bacteria			
Bacillus subtilis	Limonene	0.048 μg/ml	Noumi et al. 2023
Listeria monocytogenes	Limonene	0.048 μg/ml	Noumi et al. 2023
Enterococcus sp.	Thymol Carvacrol Geraniol Limonene Eugenol Cinnamaldehyde	200–450 μg/ml 100–450 μg/ml 100–350 μg/ml 100–450 μg/ml 200–450 μg/ml 10–50 μg/ml	Caballero Gómez et al. 2022
Vancomycin-sensitive *Enterococcus* (VSE)	Carvacrol Cuminaldehyde Linalool *p*-Cymene γ-Terpinene	593.37 μg/ml 19919562 μg/ml 35199850 μg/ml 8599475.4 μg/ml 17060082.9 μg/ml	Owen et al. 2019
Vancomycin-resistant *Enterococcus* (VRE)	Carvacrol Cuminaldehyde Linalool *p*-Cymene γ-Terpinene	593369 μg/ml 79679730 μg/ml 8799962.5 μg/ml 8599475.4 μg/ml 17060082.9 μg/ml	Owen et al. 2019
Staphylococcus sp.	Thymol Carvacrol Geraniol Limonene Eugenol Cinnamaldehyde	200–400 μg/ml 200–400 μg/ml 100–400 μg/ml 100–400 μg/ml 300–400 μg/ml 10–50 μg/ml	Caballero Gómez et al. 2022
Staphylococcus aureus	Thymol Carvacrol Limonene α-Pinene β-Pinene *p*-Cymene 1,8-Cineole Limonene Fenchone Linalool Camphor *cis*-Verbenol Borneol Terpinen-4-ol Verbenone Carvone Eugenol Linalyl acetate *trans*-Anethole Menthone	72–800 μg/ml 256–3200 μg/ml 0.048 μg/ml 11.88 μg/ml 10.13 μg/ml 10.25 μg/ml 5.63–115100 μg/ml 2.63 μg/ml 4.25 μg/ml 2.88–6800 μg/ml 7.63 μg/ml 2.38 μg/ml 3.75 μg/ml 3.13 μg/ml 5.88 μg/ml 11.38 μg/ml 24–11100 μg/ml 46900 μg/ml 494000 μg/ml 27900 μg/ml	Kwiatkowski et al. 2020; Sayout et al. 2020; Sousa Silveira et al. 2020; Macêdo et al. 2022; Noumi et al. 2023; Sharma et al. 2023
Methicillin-susceptible *Staphylococcus aureus*	Carvacrol Cuminaldehyde Linalool *p*-Cymene γ-Terpinene	297435.6 μg/ml 4979520 μg/ml 17599925 μg/ml 1075102.2 μg/ml 8529360.3 μg/ml	Owen et al. 2019
Methicillin-resistant *Staphylococcus aureus*	Carvacrol Cuminaldehyde Linalool *p*-Cymene γ-Terpinene	148717.8 μg/ml 9960522 μg/ml 8799962.5 μg/ml 2150204.4 μg/ml 17060082.9 μg/ml	Owen et al. 2019

Table II.
Continued

Tested pathogens	Chemical compounds	MIC/Sensitivity	References
Gram-positive bacteria			
Mupirocin-susceptible *Staphylococcus aureus*	1,8-cineole Eugenol Carvacrol Linalool (−)-Menthone Linalyl acetate *trans*-Anethole	307000 µg/ml 2080 µg/ml 950 µg/ml 6800 µg/ml 27910 µg/ml 450500 µg/ml 494000 µg/ml	Kwiatkowski et al. 2019
Mupirocin-resistant *Staphylococcus aureus*	1,8-cineole Eugenol Carvacrol Linalool (−)-Menthone Linalyl acetate *trans*-Anethole	57560 µg/ml 8340 µg/ml 480 µg/ml 2830 µg/ml 6980 µg/ml 450500 µg/ml 494000 µg/ml	Kwiatkowski et al. 2019
Staphylococcus pseudintermedius	Thymol Carvacrol	100–200 µg/ml 146–292 µg/ml	Sim et al. 2019
β-haemolytic *Streptococcus* spp.	Thymol Carvacrol	200–400 µg/ml 146–292 µg/ml	Sim et al. 2019
Streptococcus suis	Cinnamaldehyde Carvacrol Thymol	156.25–312.5 µg/ml 156.25 µg/ml 156.25 µg/ml	de Aguiar et al. 2019
Gram-negative bacteria			
Acinetobacter baumannii	α-Pinene Camphene β-Pinene d-3-Carene *p*-Cymene 1,8-Cineole Limonene γ-Terpinene Fenchone Linalool Camphor *cis*-Verbenol Borneol Terpinen-4-ol Verbenone Carvone	11.88 µg/ml 20.00 µg/ml 13.50 µg/ml 7.88 µg/ml 5.13 µg/ml 5.63 µg/ml 5.25 µg/ml 4.88 µg/ml 1.06 µg/ml 1.44 µg/ml 10.17 µg/ml 9.50 µg/ml 0.94 µg/ml 0.78 µg/ml 4.70 µg/ml 7.58 µg/ml	Sayout et al. 2020
Campylobacter jejuni	Thymol Carvacrol Thymoquinone *p*-Cymene γ-Terpinene	31.25 µg/ml 31.25 µg/ml 31.25 µg/ml 1000 µg/ml 1000 µg/ml	Šimunović et al. 2020
Enterobacter aerogenes	β-Pinene 1,8-Cineole Limonene γ–Terpinene Fenchone Linalool Camphor *cis*-Verbenol Borneol Verbenone Carvone	20.25 µg/ml 2.81 µg/ml 1.31 µg/ml 4.88 µg/ml 2.13 µg/ml 1.44 µg/ml 15.25 µg/ml 2.38 µg/ml 0.94 µg/ml 2.94 µg/ml 5.69 µg/ml	Sayout et al. 2020

Table II
Continued

Tested pathogens	Chemical compounds	MIC/Sensitivity	References
Gram-negative bacteria			
Enterobacter cloacae	α-Pinene β-Pinene Myrcene d-3-Carene *p*-Cymene 1,8-Cineole Limonene γ-Terpinene Fenchone Linalool Camphor *cis*-Verbenol Borneol Terpinen-4-ol Verbenone Carvone	11.88 µg/ml 5.06 µg/ml 7.75 µg/ml 7.88 µg/ml 4.10 µg/ml 5.63 µg/ml 2.63 µg/ml 6.50 µg/ml 1.70 µg/ml 1.92 µg/ml 6.10 µg/ml 3.17 µg/ml 1.50 µg/ml 3.13 µg/ml 3.36 µg/ml 9.10 µg/ml	Sayout et al. 2020
Ciprofloxacin-resistant *Escherichia coli*	Carvacrol Cuminaldehyde Linalool *p*-Cymene γ-Terpinene	297435.6 µg/ml 1244880 µg/ml 8799962.5 µg/ml 1075102.2 µg/ml 34120165.8 µg/ml	Owen et al. 2019
Escherichia coli	Carvacrol Cuminaldehyde Linalool *p*-Cymene γ-Terpinene Limonene α-Pinene Camphene β-Pinene Myrcene d-3-Carene *p*-Cymene 1,8-Cineole Limonene γ-Terpinene Fenchone Linalool Camphor *cis*-Verbenol Borneol Terpinen-4-ol Verbenone Carvone	297435.6 µg/ml 311220 µg/ml 8799962.5 µg/ml 2150204.4 µg/ml 34120165.8 µg/ml 0.048 µg/ml 11.88 µg/ml 15.00 µg/ml 5.06 µg/ml 1.94 µg/ml 7.88 µg/ml 2.56 µg/ml 2.81 µg/ml 2.63 µg/ml 4.88 µg/ml 4.25 µg/ml 2.88 µg/ml 7.63 µg/ml 4.75 µg/ml 3.75 µg/ml 3.13 µg/ml 5.88 µg/ml 11.38 µg/ml	Owen et al. 2019; Sayout et al. 2020; Noumi et al. 2023
Klebsiella oxytoca	β-Pinene 1,8-Cineole Limonene γ-Terpinene Fenchone Linalool Camphor *cis*-Verbenol Borneol Terpinen-4-ol Verbenone Carvone	13.50 µg/ml 5.63 µg/ml 2.63 µg/ml 4.88 µg/ml 2.13 µg/ml 1.44 µg/ml 10.17 µg/ml 3.17 µg/ml 2.5 µg/ml 6.25 µg/ml 5.88 µg/ml 11.38 µg/ml	Sayout et al. 2020

Table II
Continued

Tested pathogens	Chemical compounds	MIC/Sensitivity	References
Gram-negative bacteria			
Klebsiella pneumoniae	Thymol Carvacrol Geraniol α-Pinene Camphene β-Pinene Myrcene d-3-Carene *p*-Cymene 1,8-Cineole Limonene γ-Terpinene Fenchone Linalool Camphor *cis*-Verbenol Borneol Terpinen-4-ol Verbenone Carvone	780 μg/ml 130–1910 μg/ml 1740 μg/ml 23.75 μg/ml 30.00 μg/ml 10.13 μg/ml 15.50 μg/ml 7.88 μg/ml 10.25 μg/ml 11.25 μg/ml 2.63 μg/ml 4.88 μg/ml 2.13 μg/ml 3.83 μg/ml 5.08 μg/ml 2.38 μg/ml 0.47 μg/ml 1.56 μg/ml 3.36 μg/ml 15.17 μg/ml	Sayout et al. 2020; de Souza et al. 2021; Kwiatkowski et al. 2022
Malassezia pachydermatis	Thymol Carvacrol Cinnamaldehyde	10–800 μg/ml 10–585 μg/ml 2.5–640 μg/ml	Schlemmer et al. 2019; Sim et al. 2019
Salmonella enterica	Limonene	0.048 μg/ml	Noumi et al. 2023
Salmonella spp.	β-Pinene 1,8-Cineole Limonene γ-Terpinene Fenchone Linalool Camphor *cis*-Verbenol Terpinen-4-ol Verbenone Carvone	8.10 μg/ml 7.50 μg/ml 2.63 μg/ml 6.50 μg/ml 1.70 μg/ml 2.88 μg/ml 6.10 μg/ml 1.90 μg/ml 3.13 μg/ml 3.92 μg/ml 22.75 μg/ml	Sayout et al. 2020
Shigella flexeneri	Limonene	0.048 μg/ml	Noumi et al. 2023
Proteus mirabilis	Thymol Carvacrol	200 μg/ml 146–292 μg/ml	Sim et al. 2019
Pseudomonas sp.	Thymol Carvacrol Geraniol Limonene Eugenol Cinnamaldehyde	100–300 μg/ml 100–400 μg/ml 100–400 μg/ml 100–300 μg/ml 300–400 μg/ml 10–50 μg/ml	Caballero Gómez et al. 2022
Ciprofloxacin-resistant *Pseudomonas aeruginosa*	Carvacrol Cuminaldehyde Linalool *p*-Cymene γ-Terpinene	4749956.4 μg/ml 39840606 μg/ml 140799400 μg/ml 8599475.4 μg/ml 34120165.8 μg/ml	Owen et al. 2019
Pseudomonas aeruginosa	Thymol Carvacrol Cuminaldehyde Linalool *p*-Cymene γ-Terpinene Limonene β-Pinene	400–800 μg/ml 585–1120 μg/ml 39839124 μg/ml 35199850 μg/ml 8599475.4 μg/ml 68240331.6 μg/ml 0.048 μg/ml 10.13 μg/ml	Owen et al. 2019; Sim et al. 2019; Noumi et al. 2023

Table II
Continued

Tested pathogens	Chemical compounds	MIC/Sensitivity	References
Gram-negative bacteria			
Pseudomonas aeruginosa	Limonene Fenchone Linalool Camphor *cis*-Verbenol Borneol Terpinen-4-ol Verbenone Carvone	2.63 µg/ml 1.70 µg/ml 1.92 µg/ml 6.10 µg/ml 1.58 µg/ml 1.88 µg/ml 3.13 µg/ml 4.70 µg/ml 9.10 µg/ml	Owen et al. 2019; Sim et al. 2019; Noumi et al. 2023
Vibrio vulnificus	Limonene	0.048 µg/ml	Noumi et al. 2023
Vibrio anguillarum	Thymol Carvacrol Eugenol Geraniol Cinnamaldehyde	282413.6 µg/ml 282413.6 µg/ml 308696 µg/ml 1156875 µg/ml 555750 µg/ml	Rossi et al. 2021
Vibrio harveyi	Thymol Carvacrol Eugenol Geraniol Cinnamaldehyde	141206.8 µg/ml 141206.8 µg/ml 308696 µg/ml 1156875 µg/ml 278616 µg/ml	Rossi et al. 2021
Fungal pathogens			
Candida albicans	Thymol Carvacrol Eugenol Methyl eugenol (+)-α-Pinene (−)-α-Pinene β-Pinene (+)-Limonene (−)-Limonene (+)-Menthone (−)-Menthone Thujone Piperitone (+)-Carvone (−)-Carvone Camphor (+)-Citronellol (−)-Citronellol (+)-Menthol (−)-Menthol	195–625 µg/ml 43.75–250 µg/ml 500–2000 µg/ml 1250 µg/ml 51767.4–1716498 µg/ml 858249–54927936 µg/ml 213881.1–13731984 µg/ml 8173.8–6865992 µg/ml 8173.8–13731984 µg/ml 3578600–6787000 µg/ml 1789300–28628800 µg/ml 459734.6–7355753.6 µg/ml 239762.25–3732679.6 µg/ml 473193–3785544 µg/ml 473193–3785544 µg/ml 494747.5–3957980 µg/ml 49360–1665900 µg/ml 49360–1665900 µg/ml 221889.2–7125456 µg/ml 221889.2–7125456 µg/ml	Sharifzadeh et al. 2019; Iraji et al. 2020; Shaban et al. 2020; Stringaro et al. 2022; Biernasiuk et al. 2022
Candida auris	Carvacrol Thymol Eugenol Methyl eugenol	125 µg/ml 312 µg/ml 625 µg/ml 1250 µg/ml	Shaban et al. 2020
Candida dubliniensis	(+)-α-Pinene (−)-α-Pinene β-Pinene (+)-Limonene (−)-Limonene (+)-Menthone (−)-Menthone Thujone Piperitone (+)-Carvone (−)-Carvone Camphor (+)-Citronellol (−)-Citronellol (+)-Menthol (−)-Menthol	103534.8–1716498 µg/ml 858249–27463968 µg/ml 103534.8–6865992 µg/ml 12260.7–3432996 µg/ml 12260.7–1716498 µg/ml 223662.5–6787000 µg/ml 894650–14314400 µg/ml 919469.2–7355753.6 µg/ml 112650.2–3732679.6 µg/ml 114167.2–1892772 µg/ml 114167.2–1892772 µg/ml 246612.6–1978990 µg/ml 24680–208237.5 µg/ml 24680–208237.5 µg/ml 53128.4–3562728 µg/ml 53128.4–3562728 µg/ml	Iraji et al. 2020

Table II
Continued

Tested pathogens	Chemical compounds	MIC/Sensitivity	References
Fungal pathogens			
Candida glabrata	Thymol Carvacrol Eugenol (+)-α-Pinene (−)-α-Pinene β-Pinene (+)-Limonene (−)-Limonene (+)-Menthone (−)-Menthone Thujone Piperitone (+)-Carvone (−)-Carvone Camphor (+)-Citronellol (−)-Citronellol (+)-Menthol (−)-Menthol	390 µg/ml 62.50–195 µg/ml 1000–2000 µg/ml 51767.4–1716498 µg/ml 858249–54927936 µg/ml 103534.8–1716498 µg/ml 50405.1–3432996 µg/ml 50405.1–3432996 µg/ml 447325–7157200 µg/ml 1789300–14314400 µg/ml 1838938.4–14711507.2 µg/ml 232911.9–3732679.6 µg/ml 114167.2–3785544 µg/ml 114167.2–3785544 µg/ml 59369.7–989495 µg/ml 49360–208237.5 µg/ml 49360–208237.5 µg/ml 26564.2–445341 µg/ml 26564.2–445341 µg/ml	Sharifzadeh et al. 2019; Iraji et al. 2020; Biernasiuk et al. 2022; Stringaro et al. 2022
Candida krusei	Thymol Carvacrol Eugenol (+)-α-Pinene (−)-α-Pinene β-Pinene (+)-Limonene (-)-Limonene (+)-Menthone (−)-Menthone Thujone Piperitone (+)-Carvone (−)-Carvone Camphor (+)-Citronellol (−)-Citronellol (+)-Menthol (−)-Menthol	390 µg/ml 87.50–125 µg/ml 250–1000 µg/ml 51767.4–858249 µg/ml 858249–1716498 µg/ml 103534.8–429124.5 µg/ml 8173.8–6865992 µg/ml 8173.8–429124.5 µg/ml 447325–3578600 µg/ml 3578600–7157200 µg/ml 919469.2–7355753.6 µg/ml 112650.2–933169.9 µg/ml 114167.2–1892772 µg/ml 114167.2–1892772 µg/ml 246612.6–3957980 µg/ml 100262.5–832950 µg/ml 100262.5–1665900 µg/ml 100006.4–445341 µg/ml 53128.4–445341 µg/ml	Sharifzadeh et al. 2019; Iraji et al. 2020; Biernasiuk et al. 2022; Stringaro et al. 2022
Candida parapsilosis	Eugenol (+)-α-Pinene (−)-α-Pinene β-Pinene (+)-Limonene (−)-Limonene (+)-Menthone (−)-Menthone Thujone Piperitone (+)-Carvone (−)-Carvone Camphor (+)-Citronellol (−)-Citronellol (+)-Menthol (−)-Menthol	500–100 µg/ml 51767.4–429124.5 µg/ml 429124.5–1716498 µg/ml 213881.1–431849.1 µg/ml 50405.1–429124.5 µg/ml 50405.1–213881.1 µg/ml 107975–1789300 µg/ml 894650–14314400 µg/ml 3677876.8–14711507.2 µg/ml 479524.5–3732679.6 µg/ml 473193–7571088 µg/ml 473193–7571088 µg/ml 59369.7–1978990 µg/ml 49360–416475 µg/ml 49360–416475 µg/ml 53128.4–890682 µg/ml 53128.4–445341 µg/ml	Iraji et al. 2020; Biernasiuk et al. 2022

Table II. Continued

Tested pathogens	Chemical compounds	MIC/Sensitivity	References
	Fungal pathogens		
Candida tropicalis	Thymol	390 μg/ml	Iraji et al. 2020; Stringaro et al. 2022
	Carvacrol	97.5 μg/ml	
	(+)-α-Pinene	429124.5–1716498 μg/ml	
	(−)-α-Pinene	6865992–27463968 μg/ml	
	β-Pinene	103534.8–3432996 μg/ml	
	(+)-Limonene	213881.1–3432996 μg/ml	
	(−)-Limonene	213881.1–1716498 μg/ml	
	(+)-Menthone	447325–1789300 μg/ml	
	(-)-Menthone	1789300–14314400 μg/ml	
	Thujone	919469.2–7355753.6 μg/ml	
	Piperitone	112650.2–3732679.6 μg/ml	
	(+)-Carvone	114167.2–1892772 μg/ml	
	(−)-Carvone	114167.2–1892772 μg/ml	
	Camphor	246612.6–989495 μg/ml	
	(+)-Citronellol	24680–100262.5 μg/ml	
	(−)-Citronellol	24680–100262.5 μg/ml	
	(+)-Menthol	100006.4–445341 μg/ml	
	(−)-Menthol	100006.4–445341 μg/ml	

Recently, Wang et al. (2024) identified 100 μM eugenol as optimal concentration for inhibiting Singapore grouper iridovirus (SGIV) infection by reducing mRNA expression and protein synthesis. Eugenol's mechanism involves inhibiting the MAPK signaling pathway, reducing inflammatory factor expression (IL-1β, IL-6, TNF-α), and upregulating interferon-related genes while reducing oxidative stress by suppressing intracellular reactive oxygen species.

Wang et al. (2020a) demonstrated that HSV-2 infection reduced intracellular protein ubiquitination, a process reversed by carvacrol, suggesting its role in modulating the ubiquitin-proteasome system. Carvacrol inhibited HSV-2 replication, lowering virus titers, and reducing the virus release rate to 33.67% at 1 mmol/l. It downregulated the expression of key HSV-2 replication proteins (ICP4, ICP27, VP16, gB, UL30), and induced increase in TNF-α and reduced RIP3 and MLKL protein expressions via the RIP3-mediated necrosis pathway. These findings suggest that carvacrol exerts its antiviral activity by interfering with the replication process of HSV-2, making it a potential therapeutic agent against HSV-2 infections.

Similarly, Mediouni et al. (2020) found that carvacrol and thymol disrupted the cholesterol content of the viral envelope membrane, blocking HIV-1 entry into target cells without affecting other stages of the viral life cycle. Carvacrol exhibited significant antiviral potency with an IC50 of 16 μM, while thymol displayed a slightly higher IC50 of 25.2 μM. Pretreatment of HIV with carvacrol reduced viral infectivity by 60.6%, underscoring its effectiveness in altering viral particles. Testing against viruses using the CCR5 coreceptor further demonstrated that carvacrol and thymol inhibited HIV replication without affecting cell viability or receptor endocytosis.

Kumar et al. (2021) demonstrated that thymoquinone (TQ) inhibited Chikungunya virus (CHIKV) replication with an EC50 value of 4.478 μM. A plaque reduction assay revealed that TQ significantly reduced CHIKV titer in a dose-dependent manner, with over 90% reduction observed at 20 μM concentration. Additionally, immunofluorescence assays showed reduced expression of CHIKV glycoprotein in cells treated with 10 μM TQ, indicating lower viral load. Time-of-addition and time-of-elimination studies confirmed TQ's inhibitory action in the late stages of the CHIKV life cycle (8–12 hours post-infection). These findings underscore TQ's significant antiviral activity by disrupting CHIKV replication at both molecular and cellular levels.

Synergy effect of monoterpene against AMR

The synergistic potential of antibacterial agents can enhance effectiveness when combined, addressing AMR challenges by overcoming single-drug therapy limitations. Combining agents with varied mechanisms can target a broader range of pathogens and minimize resistance. Research into synergistic antibiotic combinations offers hope for more effective treatments against AMR (Al-Marzooq et al. 2022; 2023; Daoud et al. 2023).

Combining multiple monoterpenes to combat AMR. Šimunović et al. (2020) demonstrated promising synergistic effects in various monoterpenes such as carvacrol, thymol, and thymoquinone combinations. Combinations like carvacrol + thymoquinone (fractional inhibitory concentration indices (FICI) 0.5),

carvacrol + thymol (FICI 0.2), and thymol + thymoquinone (FICI 0.3) showed robust synergistic activities. All other tested combinations exhibited additive effects without any antagonistic effects observed. Similarly, Touil et al. (2020) observed promising synergistic effects of carvacrol and cuminaldehyde against *C. albicans* and co-isolated bacteria. The combination significantly reduced MIC values to 60–250 μg/ml for carvacrol and 500–2,000 μg/ml for cuminaldehyde, showing synergistic interactions (FICI values ranged 0.36–0.5) for 12 strains of *C. albicans* and indifferent interactions (FICI values between 0.62–1.0) for four *Candida* strains.

Combining monoterpenes with conventional antibiotics/antifungals to combat AMR. Owen et al. (2020) investigated the synergy between vancomycin and monoterpenes, particularly carvacrol and cuminaldehyde, against VSE and VRE. Significant synergy was found in binary combinations of vancomycin with carvacrol or linalool against VSE, with a substantial four to eight-fold reduction in vancomycin's MIC. The combination of carvacrol and cuminaldehyde with vancomycin showed bactericidal activity against VSE, resulting in a 5.87 $\log_{10}$ reduction, indicating strong synergy, while ternary combinations of two monoterpenes with vancomycin demonstrated significant reductions in MIC (1,024-fold) against VRE.

Kwiatkowski et al. (2019) identified carvacrol as highly potent against MRSA strains, with 1,8-cineole exhibiting synergy when combined with mupirocin against mupirocin-susceptible (FICI 0.44) and mupirocin low-level resistant strains (FICI 0.28), while (−)-menthone showing synergistic activity against mupirocin-susceptible MRSA strains (FICI 0.38). Additionally, Kwiatkowski et al. (2020) explored the synergistic potential of 1,8-cineole and linalyl acetate with conventional antibiotics against MRSA strains, revealing synergistic effects of 1,8-cineole with penicillin G (FICI 0.1) and additive activities of linalyl acetate in combination with methicillin and penicillin G at FICI 0.4 and FICI 0.6, respectively against all MRSA isolates, highlighting the versatility of these combinations.

AMR, especially carbapenem resistance in bacteria like *K. pneumoniae*, presents a formidable treatment challenge (Köse 2022). Köse (2022) investigated combining carvacrol with meropenem against carbapenem-resistant *Klebsiella pneumoniae* (CRKP) strains. Their findings revealed synergy between carvacrol and meropenem against 8 of 25 CRKP strains, confirmed by checkerboard assays (FICI = 0.5) and time-kill assays. This combination induced significant membrane damage to CRKP cells, as shown by live-dead tests and spectrophotometric measurements. Sousa Silveira et al. (2020) demonstrated a notable decrease in tetracycline MIC against *S. aureus*, from 114–101 μg/ml, when combined with thymol. Although thymol and carvacrol exhibited antibiotic activity, they did not act as efflux pump inhibitors (EPIs), suggesting alternative mechanisms for overcoming resistance apart from the TetK efflux pump.

Dhara and Tripathi (2020) investigated the effects of eugenol on extended-spectrum-β-lactamase producing quinolone resistant (ESBL-QR) strains of *E. coli* and *K. pneumoniae*, revealing distinct responses in cellular morphology. ESBL-QR *K. pneumoniae* exhibited cellular stress and autolysis upon eugenol treatment, accentuated when combined with cefotaxime/ciprofloxacin, indicating synergistic interactions. The combination therapy also suppressed the expression of the *acrB* and beta-lactamase genes (bla_{TEM} and $bla_{\text{CTX-M}}$) in *K. pneumoniae*, suggesting a multifaceted approach to combating AMR.

Aleksic Sabo et al. (2021) demonstrated the potent antimicrobial activity of carvacrol, thymol, and eugenol, against *Acinetobacter baumannii*, comparable to antibiotics, particularly when combined with ciprofloxacin (FICI range 0.25–0.32). Binary combinations of gentamicin with carvacrol or thymol showed additive effects, while combinations with ciprofloxacin displayed synergy against both reference and MDR strains.

The study by Shaban et al. (2020) underscores carvacrol's potent antifungal properties with a median MIC of 125 μg/ml, revealing synergistic and additive effects when combined with established antifungal agents like fluconazole, amphotericin B, nystatin, and caspofungin. Notably, carvacrol not only reduced the MIC values of these drugs but also inhibited critical virulence factors of *C. auris* by reducing its adherence and proteinase production. Sharifzadeh et al. (2019) demonstrated synergistic potential between carvacrol and voriconazole against *Candida* species, minimizing the risk of side effects from high drug concentrations. The reported FICI values against all tested *C. albicans* isolates were at FICI 0.370–0.853 and *C. glabrata* at FICI 0.412–0.625. Sharifzadeh and Shokri (2021) further confirmed synergy between eugenol and voriconazole against *C. tropicalis* and *C. krusei* isolates at FICI 0.25–0.88 and 0.19–0.63, respectively. Schlemmer et al. (2019) explored synergistic interactions of monoterpenes with antifungal agents, revealing primary synergies in combinations like carvacrol + nystatin, thymol + nystatin, and carvacrol + miconazole at a rate of 80%. Some combinations showed indifference such as thymol + terbinafine and cinnamaldehyde + terbinafine, while antagonistic effects were observed in carvacrol + ketoconazole, thymol + ketoconazole, and cinnamaldehyde + ketoconazole, emphasizing the need for careful combination selection for effective antifungal strategies.

Biernasiuk et al. (2022) revealed significant synergistic effects when cinnamaldehyde and eugenol were

combined with cetylpyridinium chloride against *Candida* spp. strains, resulting in a notable reduction in MICs by 4–8 fold and 2–4 fold, respectively, across various strains. Similar synergistic outcomes were observed with chlorhexidine at FICI 0.375–0.5 for all strains except *Candida parapsilosis* (addition at FICI 0.562). These compounds act by binding to ergosterol in the fungal membrane, increasing ion permeability and leading to cell death, offering potential for topical antifungal preparations.

Efficacy of monoterpenes against biofilm-associated infections

Recent studies revealed the potent efficacy of monoterpenes and monoterpenoids against biofilms, complex bacterial communities resistant to conventional antibiotics. El-Far et al. (2021) demonstrated that eugenol effectively eradicated established MRSA biofilms at MIC or 2 × MIC concentrations compared to controls. Post-treatment gene expression analysis showed significant downregulation of biofilm-related genes (*sarA*, *icaA*, *icaD*), leading to reduced polysaccharide accumulation and cell adhesion within the biofilms *in vitro*.

Mastoor et al. (2022) explored the molecular mechanisms of natural compounds like eugenol and α-bromo-*trans*-cinnamaldehyde against *S. aureus* biofilms, noting significant reductions in gene expression related to intracellular adhesion, suggesting a strategy to disrupt biofilm formation early on. Swetha et al. (2020) demonstrated the synergistic antimicrobial interaction of carvacrol and thymol against biofilms of *C. albicans* and *Staphylococcus epidermidis*. This combination hindered biofilm formation and delayed growth upon short-term exposure, potentially reducing dosing frequency and resistance development. Carvacrol's efficacy extends beyond single-species infections; Wang et al. (2020b) found it to exhibit stronger activity against *S. aureus* compared to *Pseudomonas fluorescens*, attributed to its reactivity with membrane proteins. Carvacrol targeted extracellular polymeric substances, disrupting biofilm structures in a concentration-dependent manner.

Qian et al. (2020) investigated eugenol's mechanism against CRKP biofilms, revealing potent antimicrobial activity with MIC values of 200 μg/ml. They found that eugenol damages the CRKP cell membrane, leading to biofilm cell death. Insights into its mechanism include a reduction in intracellular pH, ATP levels, and cell membrane hyperpolarization, indicating intracellular component leakage and the organelle dysfunction. Additionally, eugenol downregulated biofilm-related genes (*pgaA*, *luxS*, *wbbM*, and *wzm*) while upregulating *mrkA*, hindered biofilm development.

Choudhary et al. (2022) demonstrated eugenol and geraniol's efficacy against *A. baumannii* isolates. Time-kill assays showed decreased growth at MIC levels, with reduced exopolysaccharide production indicating biofilm disruption. The binding of eugenol and geraniol to the adhesion tip of the *csuE* pilus suggested disruption of mature biofilms, confirmed by scanning electron microscopy images. They showed the penetration of the biofilm matrix and cell membrane dissolution, with downregulation of the *csuE* gene, further supporting inhibition of biofilm formation. These findings underscore the multifaceted approach of monoterpenes, particularly eugenol, in combatting AMR by disrupting biofilms.

In a study by Jafri et al. (2019), eugenol showed notable activity against *C. albicans* and *Streptococcus mutans*, with planktonic MICs of 200 μg/ml, demonstrating efficacy against both planktonic and sessile growth modes. This study highlighted eugenol's advantage over antibiotics like fluconozole, azithromycin, and chlorhexidine digluconate, which exhibited increased resistance levels in the latter mode. Marini et al. (2019) investigated carvacrol's efficacy against *Mycobacterium* biofilms, including *Mycobacterium abscessus* and *Mycobacterium fortuitum*, notorious for their antibiotic resistance. Carvacrol inhibited biofilm formation and disrupted pre-formed biofilms, even at sub-MIC concentrations, indicating its potential against established infections. These findings collectively emphasize the promising role of monoterpenes and monoterpenoids in combating biofilm-associated infections, suggesting new avenues for antimicrobial research and clinical applications.

Innovative approach of using monoterpenes and monoterpenoids

Recent studies utilizing monoterpenes and monoterpenoids have shown promise across various sectors, including food preservation, wound healing, and medical devices. In the food industry, Abdelhamid and Yousef (2021) demonstrated that incorporating carvacrol and thymol into food-grade milk powder reduced desiccation resistance in *Salmonella enterica* and increased lethality during milk dehydration, enhancing safety in low-water activity foods. Similarly, Flores et al. (2021) showed that carvacrol-enriched edible films improved mechanical and optical properties, enhancing water vapor barrier capability and potentially extending food shelf life.

In nanotherapeutics, Oz et al. (2021) developed carvacrol-loaded nanoemulsions for combating bacterial biofilms, noted for their stability and selective biofilm eradication with minimal impact on mammalian cells. This platform could deliver multiple EOs,

increasing antimicrobial efficacy. Li et al. (2021) and Mir et al. (2019) further advanced nanoemulsion and nanoparticle delivery systems. Li et al. (2021) reported broad-spectrum antimicrobial activity with gelatin, riboflavin, and carvacrol against biofilms, contributing to wound infection management and accelerated closure in a murine model. Mir et al. (2019) enhanced skin retention of carvacrol using poly(ε-caprolactone), targeting skin infections and showing potential against MRSA. These innovations indicate significant strides in applying monoterpenes and monoterpenoids for clinical and commercial uses.

Eugenol has demonstrated promise in food packaging through a novel multilayer structure with electrospun eugenol on a biopolymer base, offering significant antibacterial activity against *S. aureus* and *E. coli*, and improved barrier properties against water and aroma vapors (Figueroa-Lopez et al. 2020). These structures could effectively reduce food-borne bacteria while preserving food's organoleptic qualities. In veterinary medicine, geraniol offers a potential non-antibiotic treatment for bovine mastitis, showing equivalent therapeutic effects without impacting gut microbiota or leaving drug residues in milk, suggesting a sustainable approach to managing mastitis in dairy cattle (Guo et al. 2023).

Additionally, eugenol-coated silicone segments have shown effectiveness in reducing biofilm-associated bacterial counts and preventing bacterial adhesion in catheter-associated urinary tract infections (CAUTIs), presenting a novel anti-virulence strategy for long-term protection against *P. aeruginosa*-induced CAUTIs (Rathinam et al. 2021).

Challenges and future prospects

Monoterpenes and monoterpenoids, known for their antimicrobial efficacy, are confronting emerging resistance mechanisms. Pesingi et al. (2019) highlighted the MexAB-OprM efflux pump's role in carvacrol resistance in *P. aeruginosa*, with the inactivation of the *mexA* gene substantially reducing carvacrol's MIC value. The combination of carvacrol and efflux pump inhibitor exhibited synergistic effects, suggesting a potential avenue for combating resistance. Kwiatkowski et al. (2022) demonstrated carvacrol's remarkable antibacterial potency against uropathogenic *K. pneumoniae* strains producing New Delhi metallo-β-lactamase-1 carbapenemase, particularly effective against biofilm formation, crucial in chronic infections. However, concerns about resistance development persist, as shown by Berdejo et al. (2020), indicating the adaptability of *S. enterica* subsp. *enterica* serovar Typhimurium LT2 to carvacrol through gradual MIC values increases.

Utilizing monoterpenes and monoterpenoids as antimicrobial agents presents challenges that require effective solutions. The challenges of resistance call for concerted effects to optimize the therapeutic potential of monoterpenes and monoterpenoids. Limited water solubility affects bioavailability, requiring formulation strategies or chemical modifications. Volatility and instability pose formulation and storage challenges, while potential toxicity demands careful consideration. Variability in antimicrobial activity and the risk of resistance highlights the need for mechanistic research. Interdisciplinary efforts in pharmacology, formulation science, and microbiology can lead to novel antimicrobial agents with improved efficacy, safety, and clinical utility, aiding in the fight against AMR.

Conclusion

In conclusion, this review highlights the substantial potential of monoterpenes and monoterpenoids as antimicrobial agents against MDR pathogens. They effectively combat biofilms, target virulence factors, and show synergy with conventional antibiotics. Challenges such as limited solubility, volatility, and toxicity need to be addressed through innovative formulations and interdisciplinary research. Despite these obstacles, these natural compounds offer promising avenues for developing effective treatments against AMR, emphasizing their importance in the fight against MDR bacterial infections.

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The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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