I J C R M

International Journal of Contemporary Research In Multidisciplinary

Research Article

Essential Oils and Phytoconstituents as Novel Antimicrobial Strategies against Drug-Resistant Pathogens

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DOI: https://doi.org/10.5281/zenodo.19558910

Abstract

Multidrug resistance (MDR) represents a significant global challenge in the treatment of acute and chronic microbial infections. The overuse and misuse of antibiotics have been major contributors to the rising prevalence of resistant pathogens, leading to reduced effectiveness of conventional antimicrobial agents. Consequently, there is an urgent need to explore novel and effective therapeutic alternatives. Plant-derived phytocompounds and essential oils have emerged as promising antimicrobial agents owing to their broad-spectrum activity against clinically relevant pathogens. This review critically evaluates the role of plant extracts, phytochemicals and essential oils against a wide range of drug-resistant microorganisms, with particular emphasis on their mechanisms of action, synergistic interactions with conventional antibiotics and emerging delivery strategies designed to enhance bioavailability. Overall, these natural compounds demonstrate considerable potential as adjuncts or alternatives in combating antimicrobial resistance; however, further standardisation and well-designed clinical studies are required to support their widespread clinical application.

Manuscript Information

- **ISSN No:** 2583-7397
- **Received:** 10-03-2026
- **Accepted:** 08-04-2026
- **Published:** 13-04-2026
- **IJCRM:**5(2); 2026: 606-616
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- **Plagiarism Checked:** Yes
- **Peer Review Process:** Yes

How to Cite this Article

Khushbu C, Thapa S, Yadav J S. Essential Oils and Phytoconstituents as Novel Antimicrobial Strategies against Drug-Resistant Pathogens. Int J Contemp Res Multidiscip. 2026;5(2): 606-616.

Access this Article Online

www.multiarticlesjournal.com

KEYWORDS: Multiple Drug Resistance, Essential Oils, Phytoconstituents, Antimicrobial Activity, Antibiotic Synergy, Drug-Resistant Pathogens.

INTRODUCTION

The global public health threat posed by antimicrobial resistance (AMR), through high levels of resistance found in pathogenic microorganisms, is of great concern, given that many of these widely available and commonly used antibiotics are not able to be successfully used in clinical practice due to the inability of the antibiotic to kill the bacteria. The major contributor to this occurrence is the inappropriate and/or excessive use of antibiotics, emphasising the urgent need to develop new, effective, and sustainable antimicrobial treatments [1].

Medicinal plants and their secondary metabolites have always provided great sources of therapeutic agents. Among these agents, there has been much attention focused on essential oils because of their chemical diversity and great range of biological activities. Plants synthesise many secondary metabolites such as terpenes, phenolics and flavonoids, which play an important role in the plant's natural defence from microbial invasion [2].

Essential oils (EO) are natural, complex, volatile compounds and are found in all plant organs. It consists of 2-3 main components at high concentrations & other trace components. For example, Origanum compactum consists of 30% carvacrol, 27% thymol & other constituents. The chemical & biological properties of essential oils differ in different plant molecules, and it also depends on the method of extraction used. EOs & some of their constituents are very effective against a wide variety of pathogens (fungi, bacteria, viruses, protozoa, etc.), i.e., “broad-spectrum effect”, as well as they also show biological activities like antioxidant, analgesic, anti-inflammatory, etc. Also, using essential oils in antimicrobial formulations has been trending to replace synthetic chemical preservatives [3].

Synthetic chemicals & their use have been limited as being an environmental hazard, showing carcinogenic as well as toxic side effects & adverse drug reactions. This makes the use of essential oils as an infection combating tool, a more effective, economical& promising approach [4].

Essential Oils

As a natural defence against microbes and pests, plants produce a wide range of secondary metabolites that act as attractants for colour, scent, and pollinators. Essential oils, also referred to as volatile oils, are byproducts of aromatic plants' secondary metabolism. Essential oils are typically generated by steam distillation or mechanical expression, while simple plant extracts typically utilise extraction with a solvent such as acetone, ethanol, or hexane [5]. During distillation, the water vapour and condensate are separated via gravity, with only a very small amount of volatile liquid left, which is the essential oil.

Therefore, essential oils are very concentrated, based purely on the extraction process used. According to the National Cancer Institute, oils produced through chemical solvent extraction are not considered true essential oils as the solvent residue may alter the purity and scent of the oil [6]. The constituents consist of two chemically similar groups known as terpenes and aromatic compounds. This is a blend of multiple constituents in which two or three major components are more abundant (20-70%) than trace components [7]. For example, the main component of clove (Syzygium aromaticum) essential oil is eugenol (68.52%) and -caryophyllene is a trace component.

(1.85%) [8]. Examples of important components in essential oils include terpinen-4-ol (30.41%) from marjoram (Origanum majorana L.) essential oil, thymol (57.7%) from Thymus vulgaris essential oil, bicyclogermacrene (26.1%) and -caryophyllene (24.4%) from Lantana camara L. essential oil, -thujone (41.48%) from Salvia officinalis L. essential oil, and -(-)-bisabolol (63%) from Eremanthus erytropappus essential oil [9-13].

Various EOs possess various activities such as anti-inflammatory, antiviral, Antimicrobial, and anticytotoxic activities. In many of the studies analysed, only the primary Constituents of some essential oils, like carvacrol, eugenol, and thymol, were assessed [14, 15]. There have been various studies that report these constituents showed significant antimicrobial effects when tested alone [13-16]. It has also been stated that the function of the primary components is regulated by other minor molecules that help to potentiate the

synergistic effect. Indeed, the idea is more meaningful and rational to study the whole essential oil than its components, as to whether or not the concept of synergism actually exists between components in essential oils [17].

Table 1: Essential oils and phytoconstituents and their antibacterial activity against human pathogens.

Essential oils	Part used	Major chemical compounds	Inhibited microorganisms	Reference
Achillea clavennae	Leaves and Flowers	Camphor,myrcene, 1,8-cineole,linalool Geranyl acetate	*Klebsiella pneumonia, Streptococcus pneumonia, Haemophilus influenzae*	[65]
Achillea ligustica	Aerial parts	Viridiflorol,terpinen-4-ol	*Streptococcus mutans*	[31]
Artemisia cana	Aerial parts	Santolina triene,alpha-pinene, camphene	*E.coli, S.aureus, S.epidermidis*	[66]
Artemisia dracunculus	Aerial parts	Methychavicol, methyl eugenol, terpinolene Beta-phellandrene	*E.coli, S.aureus, S.epidermidis, Brochothrix thermosphacta,*	[66]
Achillea fragrantissima	Aerial parts	Yomogi alcohol, 1,8-cineole, Artemisia alcohol, Thujone	*Staphylococcus aureus, Staphylococcus epidermidis, E.coli*	[67]
Aretmisia frigida	Aerial parts	1,8-cineole,methylchavicol, camphor	*Escherichia coli, S.aureus, S.epidermidis*	[66]
Copaifera officinalis	Essential oil	Beta-Caryophyllene, beta-bisabolene, germacrene B, Alpha-copaene, germacrene D	*S.aures, E.coli*	[1]
Cymbopogon citratus	Fruit	Ethanolic compounds	*Enterobacteriaceae, S.aureus*	[46]
Cuminum cyminum	Leaves	Gamma-terpin-7-al, Gamma-terpinene, Beta-pinene, Cuminaldehyde	*S.typhimurium, E.coli*	[68]
Cyper longus	Arial part	Beta-Himachalene, Alpha-humulene, Gamma-himachalene	*S.aureus, L.monocytogenes* *E. faecium* *S. Enteritidis, E.coli*	[69]
Daucus littoralis	Leaves, stems, Roots, fruits, flower	Germacrene D, Acorenone B	*S. aureus, E. coli*	[70]
Euphrasia rostkoviana	Essential oils	n-Hexadecanoic acid, thymol, myristic acid, linalool	*E. faecalis, E.coli, K.pneumoniae, S.aureus P.aeruginosa*	[71]
Eugenia caryophyllata	Flower buds	Phenylpropanoids such as carvacrol, Thymol, eugenol, Cinnamaldehyde	*Staphylococcus epidermidis*	[72]
Laurus nobilis	Arial part	Eucalyptol (1,8- cineole), Linalool	*Mycobacterium smegmatis, E.coli*	[73]
Fortunella margarita	Leaves	Gurjunene, Eudesmol, Muurolene	*B.subtilis, S.aureus, S.faecalis, E.coli, K.pneumonia*	[74]
Lavandula x Intermedia “Provence” (blue lavandin) (a cross between L. Angustifolia, *L.latifolia*	Arial part	Camphor, Eucalyptol(1,8-Cineole, linalool, beta- pinene, Alpha-pinene	*Mycobacterium Smegmatis, E.coli*	[73]
Lippia sidoides	Leaves	Thymol and Carvacrol	*S. mutans, S.sanguis, S.mitis*	[75]
Melaleuca Alternifolia (Tea tree oil)	Essential oil	Terpinen-4-ol, 1,8-cineole, Terpinolene	*E.coli, S.aureus, S.epidermidis, E.faecalis, P.aeruginosa M.avium*	[19]
Nigella sativa	Seeds	Thymoquinone, p-cymene, alpha- thujone, thymohydroquinone	*S.aureus, B.cereus, E.coli, P.aeruginosa*	[76]
Ocimum gratissimum	Leaves	Eugenol, methyl eugenol, camphor, Cis-ocimene, Trans-ocimene,	*S.aureus, Bacillus spp. E.coli, S.typhi, P.aeruginosa, E.cloacae*	[33]
Petroselinum sativum	Leaves, stems	Myristicin, apiol, 1,2,3,4- tetramethoxy-5-(2-Propenyl)- benzene	*B.thermosphacta, E.coli, L.innocua, S.typhimurium, S. putrefaciens*	[77]
Pimpinella anisum	Seed	Trans-anethole	*S.typhimurium, E.coli*	[78]
Ocimum kilimandsharicum	Flowers and leaves	Eugenol, borneol, Linalool, methyl eugenol	*B.subtilis, S.aureus, E.coli, Klebsiella spp., Micrococcus spp Salmonella spp*	
Piper nigrum	Essential oil	Limonene, sabinene, myrcene, Para-cymene, Linalool, Terpinolene, safrole	*S.aureus, E.coli*	[1]
Satureja hortensis	Arial part	Carvacrol, thymol, and gamma-terpinene	*C.botulinum, C.perfringens*	[80]
Origanum vulgare	Leaves, Arial part	Carvacrol, thymol, Trans-sabinene Hydrate, borneol, Terpinen-4-ol, Linalool	*Clostridium Botulinum, C. perfringens, L. monocytogenes, E. coli, S.choleraesuis, S.typhimurium, Shigella sonnei.*	
Satureja cuneifolia	Aerial parts	Carvacrol and p-cymene	*E.coli, Campylobacter Jejuni, S. sonnei, S. aureus, S.aureus, S. enteritidis*	[32]
Thymus mastichina	Leaves, stems	m-thymol, carvacrol, trans-caryophyllene	*B.thermosphacta, E.coli, l.innocua, L.monocytogenes P.putida, P. putida, S. putrefaciens*	[77]

Activity of Essential Oils

However, even with recent progress in the area, comparatively very little is known concerning the mechanism(s) of action of many EO components, particularly the terpenoids. This is despite their common use with both economic (e.g. food preservation) and health (e.g. anti-infective and other pharmacological) benefits. This uncertainty is primarily due to the complexity of the volatile oils, which are usually made up of tens of different components. In addition, EO components are typically absent from traditional conceptualisations of interactions because EO components are classically viewed as hydrophobic, volatile molecules existing at room temperature (i.e. plant oils, some extracts, and isolates) rather than mesoscale structured systems, which states specifically may engage interactions associated with actions of other molecules. Moreover, these hydrophobic molecules may specifically engage a few select protein targets at high specificity when interfacing with an aqueous medium *in vivo* in an attempt to mediate desired phenolic or antiseptic actions [3].

Antimicrobial Activity

The antibacterial properties of essential oils (EOs) have been recognised and employed for several centuries, primarily due to their potential impact on specific microbial infections. Their efficacy has become more critical as microbes continue to develop resistance to antibiotics. There is ample evidence to suggest that essential oils possess significant activity against a broad spectrum of pathogens, including fungi, viruses, and bacteria. Some essential oils eliminated all tested samples of a particular bacterium, while a considerable fraction of samples displayed antibacterial activity against different species of microbes. This broad effectiveness is significant compared to many antibiotics, which typically combat either Gram-positive or Gram-negative bacteria, but not both [18]. Countless EOs have the ability to compromise bacterial cell membranes, resulting in cell leakage and ultimately death. For example, tea tree oil and eucalyptus oil have been shown to disrupt the bacterial cell wall. As another example, oil extracted from Melaleuca Alternafolia is effective against multiple antibiotic-resistant bacteria. There has also been evidence that extracts of Lamiaceae spp have even greater efficacy as antimicrobials than some pharmaceuticals [19].

Anti-Inflammatory Effects

EOs yield the best results in the treatment of acute and chronic skin conditions. In particular, psoriasis, neurodermatitis, and atopic eczema all show beneficial outcomes with the external application of creams or oils that contain essential oils. Essential oils can even have an immunosuppressive effect; for instance, one study demonstrated strong inhibition of T-lymphocyte proliferation with certain essential oils. Thus, caution should be taken when using these oils when some immunostimulation is desired, such as during recovery from fatigue, convalescence, or in the elderly. More recent clinical research suggested a role for tea tree oil in the prevention of recurrent colds [20]. Inhalation of EOs is often used in aromatherapy and has a whole series of suggestive names: epigenetic, psychophysiological neuroneuroendocrinology, psychoimmunoendocrinology, neuroendocrinoimmunology, and neuroendocrinoimmunomodulation all describe the effects of EOs through the sense of smell. Treating infections with essential oils can be considered a type of aromatherapy. The most considerable effect of EOs on inflammation is inhibition through the activities of COX (cyclooxygenase-1 and 2) and LOX (lipoxygenase) [21].

Antibacterial Actions of Essential Oils

Currently, there are numerous antibiotics available to treat different bacterial pathogens. Nevertheless, increasing multidrug resistance has exacerbated the severity of diseases caused by bacterial pathogens. Moreover, low immunity in host cells, as well as bacteria's ability to develop biofilm-associated drug resistance, has increased the number of life-threatening bacterial infections in humans [22]. As a result, bacterial infection continues to be one of the leading causes of human mortality, even today. Additionally, the higher dosage use of several antibacterial agents may induce toxicity in humans or animals. For this reason, some research has targeted alternative new key molecules against bacterial strains [23]. In this regard, essential oils of plants and their major chemical constituents can be potential candidates for antibacterial agents. Various types of essential oils and their major chemical constituents from several MAPs have been shown to have varying degrees of bacterial inhibitory potential. (TABLE 1) The effectiveness of essential oils varies depending on the type of essential oil and also the bacterial structure (Gram-positive and Gram-negative). For example, sandalwood and vetiver demonstrated greater inhibitory activity against Gram-positive bacteria, but they did not inhibit Gram-negative bacterial strains [24, 22]. Essential oils of cinnamon, clove, pimento, thyme, oregano, and rosemary had significant antibacterial activity against Salmonella typhi, Staphylococcus aureus, and Pseudomonas aeruginosa [25]. Clove oil was the most effective of all essential oils evaluated. The antimicrobial activity was correlated to the presence of the primary constituents carvacrol, thymol, cinnamic aldehyde, eugenol, and p-cymene. Similarly, carvacrol, eugenol, and thymol from MAPs inhibited food-borne pathogens such as Escherichia coli, Salmonella typhimurium, Listeria monocytogenes, and Vibrio vulnificus [26]. The compounds of benzoic acids, benzaldehydes, and cinnamic acid have shown up to 50% inhibition on Listeria monocytogenes under anaerobic conditions [27]. Santoyo *et al.* [28] reported that oregano oil possessed antibacterial activity against Bacillus subtilis, S. aureus, E. coli, and Pseudomonas aeruginosa. The MBC values were between 0.75 and 2.25 mg/mL, with carvacrol being the most effective compound with MBC values between 0.75 and 1.53 mg/mL, and linalool showing activity with MBC values between 1.04 and 1.75 mg/mL. Like oregano oil, the essential oil of oregano demonstrated activity against E. coli and Providencia stuartii [29]. The essential oils of Thuja spp. (T. plicata and T. occidentalis) inhibited the growth of K. pneumoniae, E. coli, P. aeruginosa, and S. aureus [30]. Achillea ligustica, a medicinal plant that includes terpinen-4-ol, β-pinene, 1,8-cineole, and linalool, exhibited effective inhibitory action against S. mutans with a minimum inhibitory concentration (MIC) from 155 to 625 µg/mL in this study [31]. Satureja cuneifolia essential oil also inhibited many foodborne and spoilage bacterial pathogens with a MIC, relative to those pathogens, ranging from 600-1400 µg/mL [32]. Coriandrum sativum essential oil was also capable of inhibiting many bacterial pathogens, with the best results against Bacillus cereus and Escherichia coli; the MIC for Gram-positive bacteria was recorded at 108 mg/mL and for Gram-negative bacteria, ranging from 130 to 217 mg/mL [33]. Furthermore, thyme and mint leaf-derived essential oils had antibacterial activity against S. aureus, S. typhimurium, Vibrio parahaemolyticus, L. monocytogenes, E. coli, C. botulinum, C. perfringens, Shigella sonnei, Sarcina lutea, and Micrococcus flavus [34, 35]. The Gram-negative strains displayed more sensitivity towards the thyme oil with an MIC from 0.33 to 2.67 mg/mL [35].

Antiviral Actions of Essential Oils

Plant-sourced items and bioactive pure substances may be a novel source of antiviral medicine, as natural products inherently have high chemical diversity. Viral diseases continue to represent a significant issue for human health around the world. To date, there are only a limited number of medicines that target many of these viruses, which highlights the need to explore new antiviral lead molecules. Overall, based on what we saw after surveying the literature, it appears that many essential oils are virucidal (potentially TARGET viruses that cause disease and there is some evidence that essential oils possess some antiviral properties against both DNA [VIRUSES] and RNA[VIRUSES](herpes simplex virus type 1 (HSV 1), herpes simplex virus type 2 (HSV 2), dengue virus type 2, Junin virus, influenza virus adenovirus type 3, poliovirus, and coxsackievirus B1 [36, 37, 22, 38, 39]. The antiviral properties of the main MAPs' essential oils and constituent oils are shown in the detailed Table 3. Oregano and clove essential oils have also been found to have strong antiviral activity against several nonenveloped RNA and DNA viruses, which include adenovirus type 3, poliovirus, and coxsackievirus B1 [38, 39]. Various essential oils have been reported to suppress the ability of the HSV-1 virus to replicate under *in vitro* experimental conditions [40–41]. HSV-1 causes the common viral infections of herpetic keratitis and herpetic encephalitis in humans, in addition to mucocutaneous herpes infections and neonatal herpes. Some studies have evaluated the essential oils of Artemisia arborescens, Glechon spathulata, and Glechon marifolia and showed that all three suppressed HSV-1 considerably [42, 43]. Major constituent essential oils of Melissa officinalis, citral and citronellal could inhibit HSV-2 replication [36, 38, 41]. Moreover, the antiherpes activities of Australian tea tree oil, eucalyptus oil, and thyme oil have also been reported [42, 40–43]. The major chemical constituent α-caryophyllene, which is found in the essential oils of many medicinal plants, is considered the best antiviral [40].

Antifungal Effects of Essential Oils

Essential oils and compounds within essential oils have yielded antifungal activity against many fungal pathogens. Table 2 lists essential oils, including chemical constituents, their antifungal activity against human pathogens, and studies related to the oils. Plant extracts obtained from many essential oils, such as basil, citrus, fennel, lemongrass, oregano, rosemary, and thyme, have exhibited substantial antifungal activity against many fungal pathogens [8]. Arora and Kaur [44] investigated the antimicrobial activity of essential oils that they extracted from spices on fungal pathogens. They observed that garlic and clove essential oils inhibited the growth of Candida acutus, C. albicans, C.apicola, C. catenulata, C. inconspicua, C. tropicalis, Rhodotorula rubra, Saccharomyces cerevisiae, and Trigonopsis variabilis. In addition, Grohs and Kunz [45] studied mixtures of ground spices and demonstrated antifungal activity against C. lipolytica. As stated in the report of Ultee and Smid [46], oregano and thyme essential oils had some of the highest antifungal activity against fungal pathogens when considering the phenolic compounds (carvacrol and thymol) as the main constituents of oregano and thyme essential oils, which ultimately disrupt the fungal cell membrane.

Mechanism of Antimicrobial Action of Essential oils against Human pathogens

MAPs contain various types of chemical constituents that possess antimicrobial activity, which are produced to protect against microbial pathogens. The antimicrobial activity of essential oils primarily depends on the chemical constituents and the amount of the major individual components present (47). These chemical constituents are produced via several molecular interactions that occur under specific biotic/abiotic stress conditions (47, 48). Each chemical constituent likely has a different mode of action against microbes. Overall, the mode of action for the antibacterial activity is likely mediated by a series of biochemical reactions in the bacterial cell that are dependent on the chemical constituents present in the essential oil (47,49). In addition, an essential oil's antibacterial activity is also likely to differ due to differing bacterial architecture, such as Gram-negative and Gram-positive bacteria, due to differences in cell membrane structure and composition (24, 22).

Action at the Cellular level

Examining the mechanisms of action of essential oils (EOs) at the cellular level provides insights into the complex ways in which these natural products act at the cellular level and their medicinal effects. An important objective is to shift our inquiry from the evaluation of microorganisms to considering their role in their host and how their efficacy may be enhanced through their appropriate environment. Of note, attention should be given to our commensal organisms in our body, and most importantly, our immune system that benefits from microbial detoxification and hormonal support, as well as consideration of how cultivated specific microbiota may benefit the host [50, 51]. This scheme is relatively straightforward and clear to visualise, as EOs represent the concentrated essence of the plant's own chemical defences, being quite capable of functioning effectively to disrupt the crucial actions of the two main cellular actions of pathogens. The acknowledged oil resistance of numerous microbial pathogens and various ways that cells can provide resistance to the bactericidal potential of EOs have been the main focus of many authors in recent years. The prevalent and resistant phenotype of cutaneous and systemic fungal pathogens likely relates to the pace-making skills dependent on growth rate and slow, but sustainable, overall improvement in quality. There is a constant flow of endo-metabolites, but the comparatively narrow pool of toxic exo-metabolites, represented virtually entirely by EOs, are only experienced by the organisms that can eliminate the smallest (and thus) the most numerous microbes denying catabolism, while postponing the moment that used-up, hesitant, and recalcitrant cells can monopolize the substrate supply and receive the approval signal [52].

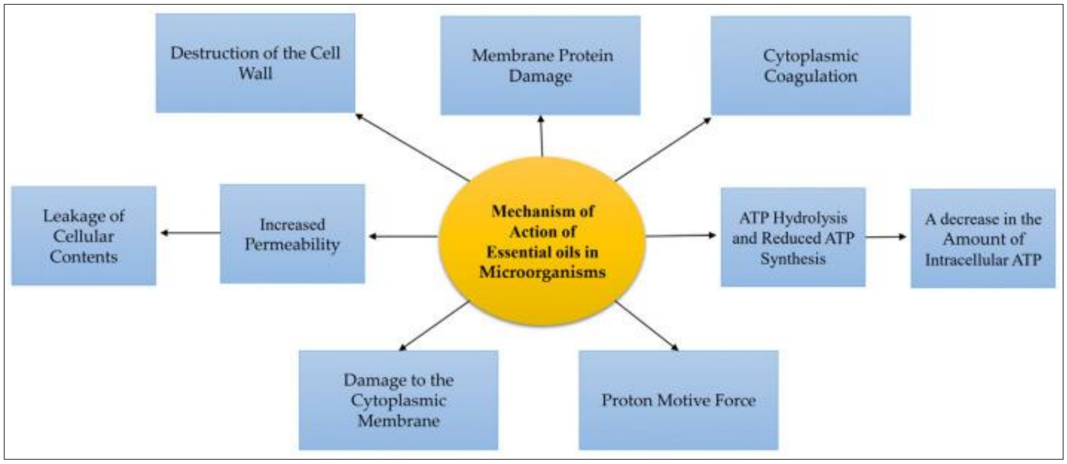

Fig 1: Various types of mechanisms of activities of Essential oils

Action against Bacterial Pathogens

Different mechanisms of antibacterial actions of essential oils have been proposed. Essential oils mainly disrupt the cellular architecture, leading to integrity failure of the membrane and increased permeability that affects many cell activities, including energy production (membrane-coupled), membrane transport, and other metabolic regulatory functions. Through rupture of the cell membrane by essential oils, the process may interfere with a variety of different important processes, such as energy conversion processes, nutrient processing, the production of structural macromolecules, and the excretion of growth regulators [53]. Essential oils may affect processes taking place in both the external envelope of the cell and processes occurring in the cytoplasm [47, 22]. Essential oils are lipophilic compounds that easily pass through bacterial cell membranes. Essential oils from different MAPs can increase permeability of bacterial cell membranes, leading to the leaking of cellular recompounds and loss of ions [53, 22, 54].

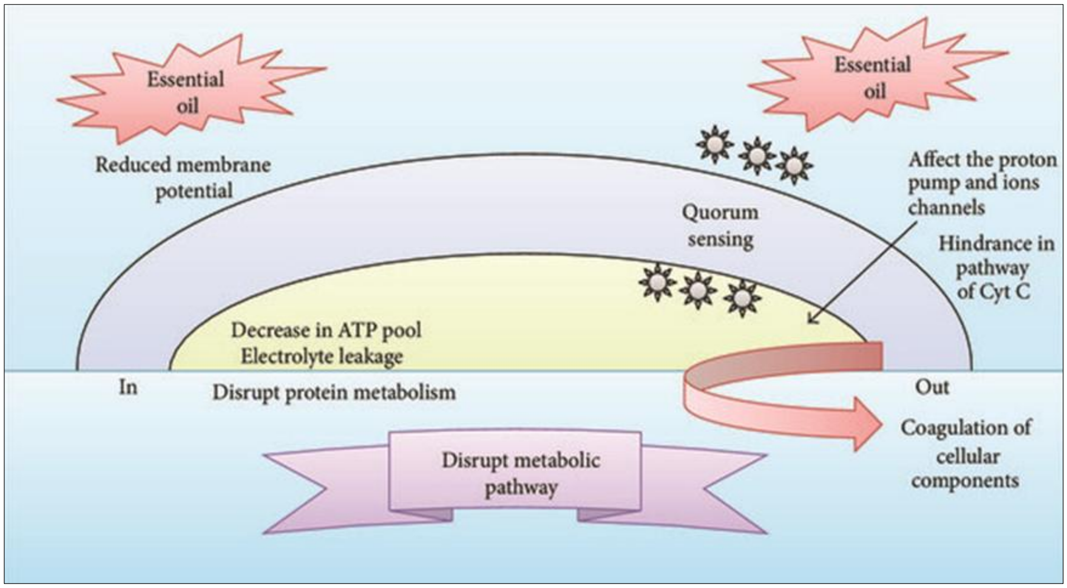

Fig 2: Antimicrobial mechanisms of essential oils in microbes

Action against fungal pathogens

The antifungal activities of essential oils are very similar to those of previously discussed antibacterial modes of action. Generally, the application of essential oils results in coagulation of cellular components due to irreversible damage to the cell membrane. For example, in yeast cells, essential oils induce a membrane potential across the cell membrane and hinder the production of ATP, which then compromises their cellular membrane integrity [55]. The essential oils are able to penetrate the fungal cell walls and disrupt the cytoplasmic membranes through the permeabilisation method, leading to the disintegration of any mitochondrial membranes. The means of electrodynamic alteration to the flow of electrons in the ETS pathway may also damage the lipids, proteins, and nucleic acids of the cell infected by fungal pathogen exposure [56]. The essential oils are also able to affect ion channels, such as Ca2+ and proton pumps, and ATP pools to cause depolarisation of the mitochondrial membranes, and thereby decrease the membrane potential. Accordingly, the result of heightening membrane fluidity may then result in electrolyte leakage and inhibit cytochrome C pathways, protein metabolism, and cytosolic ion concentrations, such as calcium. Thus, the permeabilisation of inner or outer mitochondrial membranes may induce cell apoptosis or necrosis and kill the cells.

Combination of Antibiotics and Essential Oils

In combination therapy, synergy occurs when the combined impact of the two drugs exceeds the sum of their separate effects. An additive effect occurs when the combined effect is equal to the sum of the separate effects. Indifference occurs when there is no interaction. Antagonism occurs when the combined effect is less than that of the two components individually. Reversal of resistance occurs in cases of synergy. An example of strategies used is to screen against β-lactamase producers by mechanism-based inhibition of the active-site serine hydrolases for compounds that can antagonise the antibiotic-destroying hydrolases. For example, the result of this was the use of clavulanic acid (sulbactam or tazobactam) from a streptomycete in combination with amoxicillin [57]. Unfortunately, the victory against bacterial resistance was short-lived; the frequent use of clavulanic acid has led to the emergence of resistant variants just like its own antibiotic forefathers [58]. The use of conventional antimicrobial agents in combination with essential oils represents a new approach, and some examples are presented (Table 2). Essential oils have been reported to act as synergistic enhancers, meaning they may not show any significant inhibition effects individually, but there is an additional combination effect when they are used in conjunction with the standard drugs, producing enhanced antimicrobial activity [59]. Synergistic activity from using essential oils is shown to decrease the minimum effective dose of antibiotics to treat infections, which has the added benefit of reducing antibiotic-related adverse effects. More importantly, the associations of antibiotics and essential oils in targeting resistant bacteria may have different mechanisms of action, resulting in new options to mitigate the effects of microbial resistance. The combination of essential oils in preventing bacterial resistance is viewed as a more promising approach, as essential oils will usually have a multi-component nature, unlike many of the conventional antimicrobials that only have a single-target action site [5].

Table 2: List of essential oils/antibiotics combinations showing combinatory effects against microorganisms.

Pair combinations	Microorganisms	Methods	Interaction	References
Eremanthus erythropappus/ ampicillin	*S. aureus*	Time-kill assay	Synergistic	[60]
Citrus limon/amikacin Cinnamomum zeylanicum/amikacin	*Acinetobacter spp*	Broth microdilution Checkerboard Assay	Synergistic	[61]
Pelargonium graveolens/ norfloxacin	*S. aureus, B. cereus*	Agar dilution checkerboard assay	Synergistic	[15]
Lantana montevidensis/amino glycosides	*E.coli*	Broth microdilution Checkerboard Assay	Synergistic	[62]
Zataria multiflora/ vancomycin	*S. aureus* (MRSA and MSSA)	Broth microdilution Checkerboard Assay	Synergistic	[63]
Croton zehntneri/ gentamicin	*S.aureus, P.aeruginosa*	Disk diffusion test	-	[60]
Rosmarinus officinalis/ ciprofloxacin	*K.pneumoniae*	Broth microdilution Checkerboard Assay	Synergistic	[64]
Aniba rosaeodora/gentamicin Pelargonium graveolens/gentamicin	*Bacillus cereus, Bacillus subtilis, S.aureus, E.coli, Acinetobacter baumannii*	Broth microdilution Checkerboard Assay	Synergistic	[15]

CONCLUSION

The accelerating emergence of antibiotic resistance highlights the urgent need to preserve a healthy human-associated microbial ecosystem and to better understand the evolutionary trajectories of pathogenic microorganisms. Essential oils (EOs), with their broad antimicrobial spectrum and capacity to disrupt cell membranes, alter metabolic pathways, and interfere with enzyme kinetics, have emerged as promising adjuncts or alternatives to conventional antibiotics. Their potential to enhance antibiotic efficacy presents a compelling path toward reversing or mitigating resistance.

Despite encouraging *in vitro* evidence, significant challenges remain before essential oils can be translated into clinically viable therapies. Issues of chemical stability, selectivity, bioavailability, and possible herb-drug interactions must be rigorously evaluated. Moreover, standardised dosing regimens, optimal EO–antibiotic ratios, and a clearer understanding of molecular mechanisms are essential to ensure reproducibility and therapeutic reliability. Many current studies lack detailed chemical characterisation and mechanistic insights, limiting their translational value.

Advances in high-throughput screening, analytical chemistry, and modern drug-discovery platforms present new opportunities to accelerate progress in this field. As biopharmaceutical industries increasingly seek eco-friendly and effective antimicrobial agents, essential oils derived from medicinal and aromatic plants (MAPs) may represent a new era of phytopharmaceuticals. With continued mechanistic research and well-designed clinical trials, essential oils hold strong potential to evolve from traditional remedies into widely accepted therapeutic agents capable of addressing microbial infections in the modern medical landscape.

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