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Essential Oils: Chemical Composition and Diverse Biological Activities : A Comprehensive Review

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Abstract

Essential oils (EOs) are complex mixtures of volatile compounds, primarily terpenoids and phenolic constituents, derived from plants. They have been widely studied for their diverse biological activities, including antibacterial, antifungal, antiviral, anticancer, and anti-inflammatory effects, among others. These bioactivities are attributed to the unique chemical composition of EOs, which enables multi-targeted modes of action such as disruption of microbial cell membranes, inhibition of spore germination, and modulation of inflammatory pathways. Their potential as alternatives to conventional antimicrobial therapies has gained attention, particularly in addressing antimicrobial resistance. Additionally, EOs exhibit significant antioxidant and antimicrobial properties, contributing to food preservation by preventing spoilage and extending shelf life. In agriculture, their roles in pest management and plant growth regulation highlight their sustainable applications. In conclusion, EOs present a promising avenue for sustainable applications in healthcare, food preservation, and agriculture, though further research is necessary to overcome challenges related to their variability and clinical validation.

Keywords

essential oils, chemical composition, biological activities, antimicrobial resistance, food preservation, therapeutic applications

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Introduction

Essential oils (EOs) have long been acknowledged for their diverse biological activities. Among these secondary plant metabolites, many exhibit notable antimicrobial properties, leading to their historical use as antiseptics and preservatives in food.[1] The significance of EOs extends back to ancient civilizations, including Egypt, Greece, and China, where their aromatic and volatile qualities were integral to cultural and medicinal practices. Over the centuries, the application of EOs has significantly evolved, shaped by advancements in our understanding of their therapeutic benefits and improvements in extraction techniques.[2,3]

EOs are identified as containing a wide array of bioactive compounds, including terpenes-such as monoterpenes, sesquiterpenes, and diterpenes-as well as phenolics and aldehydes, each of which plays a vital role in mediating their therapeutic effects. These components are known for their extensive biological activities, including but not limited to antimicrobial, anti-inflammatory, antioxidant, antifungal, antiviral, and anticancer properties.[4,5]

The antimicrobial properties of EOs have been extensively studied, with numerous investigations highlighting their effectiveness against a wide range of pathogenic microorganisms.[6] This growing body of evidence has spurred interest in the use of EOs as natural alternatives or complements to synthetic antibiotics, especially in the face of increasing antibiotic resistance. EOs also exhibit anti-inflammatory and antioxidant activities, along with the ability to influence the central nervous system.[7–9] These properties have opened new pathways for the application of EOs in the management and treatment of chronic diseases, including diabetes,[10] and cancer.[11] Their potential to modulate immune responses and control oxidative stress has positioned EOs as promising candidates in the development of innovative therapeutic strategies.

EOs are being explored for their potential roles in non-medicinal fields. In agriculture, EOs are being investigated as natural pesticides and growth enhancers, offering a more sustainable and environmentally friendly alternative to conventional chemical pesticides. Their ability to deter pests, enhance plant growth, and improve crop yields makes them a valuable tool in sustainable farming practices.[12,13] Additionally, EOs are being studied for their role in food preservation, where their antimicrobial properties can help extend the shelf life of perishable goods.[14] This has significant implications for reducing food waste and improving food safety, particularly in regions

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where access to refrigeration and other preservation technologies is limited. Despite these advancements, challenges remain regarding EOs stability, bioavailability, and mechanisms of action. This review aimed to offer an in-depth examination of the biological activities of EOs and their applications, emphasizing their potential to tackle current challenges and enhance multiple disciplines.

Research Methodology

Inspired by the PRISMA guidelines, the research methodology employed in this study was initiated with a systematically formulated search strategy. To ensure thorough coverage, a set of specific keywords was selected, including essential oils, essential oil chemistry, antimicrobial, antibacterial, antifungal, antiviral, antiparasitic, antioxidant, cancer, tumor/tumour, anti-inflammatory, anti-diabetic, insecticidal, larvicidal, central nervous system, mechanisms of action, and the application of EOs in food products. Subsequently, a comprehensive research was conducted across multiple academic databases, including PubMed, ScienceDirect, Web of Science, and MDPI, to gather relevant literature. The Research was confined to experimental studies published in English.[15]

Chemistry of Essential Oils

Essential oils (EOs) are volatile, hydrophobic liquids extracted from various plant parts, known for their strong aroma and similar chemical compositions when sourced from the same species.[1,3] EOs are generally colorless but may appear in a range of colors, including green, orange, or blue due to the presence of pigments or other compounds, depending on the plant source and extraction conditions.[16]

The production and characteristics of EOs are influenced by factors like plant organ, harvest stage, and climate.[2] EOs are abundant in families like Zingiberaceae and Lamiaceae and are derived from about 17,500 known plant species.[17–19] Their full bioactivities are not completely understood, but they are significant for their pharmacological potential and natural preservative properties.[4] EOs play crucial ecological roles, including plant-animal interactions and pollinator attraction.[20] They are vital in various industries, such as agriculture, cosmetics, food technology, perfumery, pharmaceuticals, and aromatherapy, due to their antimicrobial and preservative properties.[6]

The components of EOs originate from distinct primary metabolic precursors and are synthesized through various biosynthetic pathways. They are generally divided into two principal groups : terpenoids, which constitute the majority, and non-terpenoids, mainly phenylpropanoids. These compounds are hydrocarbons and their oxygenated derivatives, appearing in numerous chemical forms such as aldehydes, ketones, alcohols, oxides, esters, amines, amides, phenols, nitrogen and sulfur compounds, and heterocycles (Figure 1).[5]

Terpenes

Terpenes (C_5H_8) are a diverse class of plant secondary metabolites characterized by their unique structure, composed of isoprene units. These compounds are synthesized within plant cells primarily through the mevalonic acid pathway, a process crucial for the production of various essential biomolecules.[21]

Terpenoids, often referred to as the oxygenated derivatives of terpenes, are formed through various biochemical modifications, including rearrangement, oxidation, and other functional group transformations. These processes yield a multitude of compounds such as acids, alcohols, esters, and ketones, each contributing uniquely to the biological and ecological functions of plants.[20] The diversity of terpenoids highlights their significance in both plant biology and human applications, ranging from pharmaceuticals to flavors and fragrances.

EOs are rich in terpenoids and are primarily composed of hemiterpenoids, monoterpenoids, and sesquiterpenoids (Figure 2). These volatile compounds impart distinctive aromas and flavors to plants, making them invaluable in the culinary, cosmetic, and medicinal industries. EOs consist of a complex mixture of various terpenes, including mono-, sesqui-, and diterpene hydrocarbons, along with their oxygenated derivatives such as alcohols, aldehydes, and esters.[22,23] The classification of terpenes is based on the number of carbon atoms and the arrangement of isoprene units. Monoterpenes, consisting of ten carbon atoms (C_{10}), are the simplest and most common form, followed by sesquiterpenes (C_{15}), diterpenes (C_{20}), and triterpenes (C_{30}). While higher terpenes such as tetraterpenes (C_{40}) and their oxygenated counterparts are less common, they play essential roles in plant coloration and photosynthesis.[24]

Monoterpenes

Monoterpenes ($C_{10}H_{16}$) are a class of terpenes formed by the head-to-tail linkage of two isoprene units, resulting in a structure with ten carbon atoms (C_{10}). These low molecular weight compounds are a fundamental component of many EOs and contribute significantly to the characteristic aromas and flavors of various plants. They include compounds such as limonene, found in citrus fruits, and pinene, present in pine resin. In some EOs, They can comprise over 90% of the total composition, highlighting their importance in defining the scent profiles of numerous botanical species. These compounds are not only crucial for the characteristic aromas but also contribute to the potential therapeutic effects associated with various EOs (Figure 3).[25]

The structural diversity of monoterpenes is reflected in their classification into over 30 basic skeletons, each offering distinct chemical and functional properties. These skeletons are further divided into three main subgroups based on their molecular configurations : acyclic, monocyclic, and bicyclic monoterpenes.[25,26]

Sesquiterpenes

Sesquiterpenes ($C_{15}H_{24}$) are a major class of terpenes found abundantly in EOs, distinguished by their relatively lower

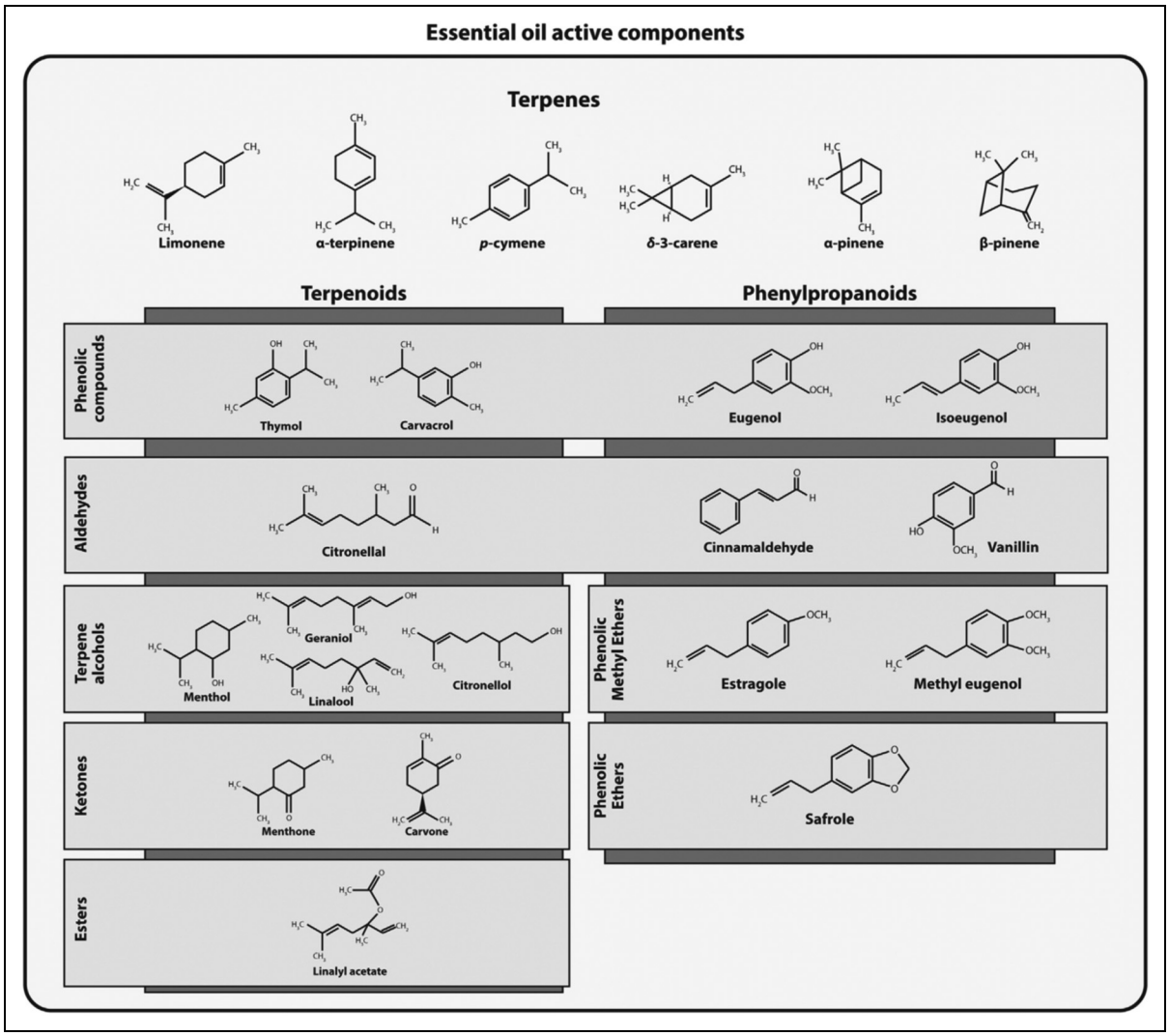

Figure 1. Chemical structure and function of some of the most common EO active components.

volatility compared to monoterpenes. These compounds are formed through the combination of three isoprene units, resulting in a structure with fifteen carbon atoms (C_{15}). The additional isoprene unit allows for an even greater structural diversity than monoterpenes, enabling sesquiterpenes to exist in various forms, including linear, monocyclic, bicyclic, and tricyclic structures.

Sesquiterpenes are naturally occurring in a wide range of organisms, including insects and higher plants, and they represent the most diverse group of terpenoids. This diversity is achieved through several processes, such as chain extension, multiple cyclizations, and a variety of biochemical modifications, including rearrangement and oxidation. These modifications result in a broad spectrum of structures and functionalities, contributing to the complexity and versatility of sesquiterpenes.[25,27] Like monoterpenes, sesquiterpenes can exist as simple hydrocarbons or include various oxygen functionalities, such as carboxylic acids, lactones, alcohols, aldehydes, ketones, and epoxides, each contributing to unique chemical properties and biological activities. Notable examples include humulene, found in hops, and farnesene, present in various plant EOs. These sesquiterpenes exhibit a range of biological effects, with humulene being recognized for its anti-inflammatory properties and farnesene for its role in plant defense mechanisms. Their diverse structures and functionalities underscore the complexity of sesquiterpenes in nature (Figure 4).

Diterpenes

Diterpenes ($C_{20}H_{32}$) are a class of terpenes renowned for their chemical and structural complexity. Characterized by a C20 skeleton, these compounds are primarily found in plant resins and are occasionally produced as byproducts during the extraction of EOs. Unlike monoterpenes and sesquiterpenes, diterpenes have a higher molecular weight, which contributes to their lower volatility and makes them less prevalent in EOs (Figure 5).

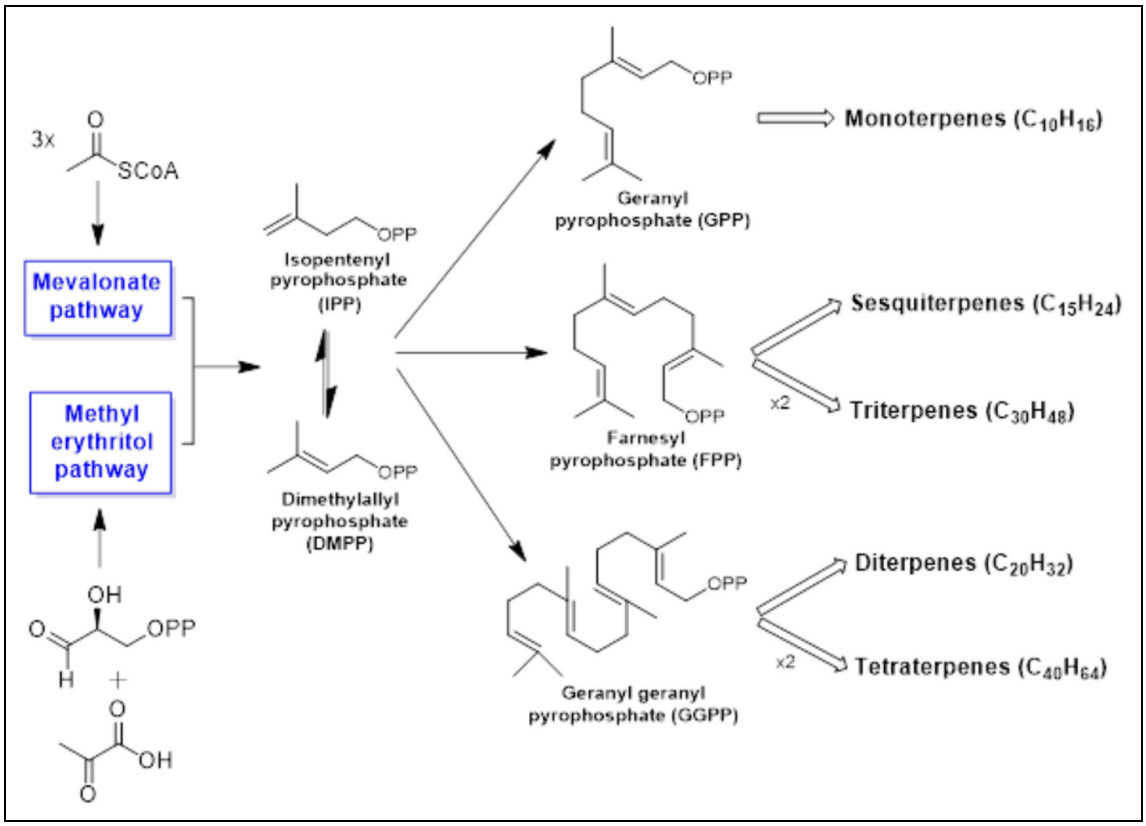

Figure 2. General scheme for the biosynthesis of terpenoids.

In EOs, an example of a diterpene is manool, which is commonly found in coniferous tree oils such as those from cypress and fir. Another example is sclareol, present in clary sage (*Salvia sclarea*) EO, known for its fragrance and antimicrobial properties. Due to their high molecular weight and low volatility, isolating these diterpenes from EOs using traditional distillation methods, like steam distillation, can be difficult. Instead, methods such as solvent extraction or CO_2 supercritical extraction are often more effective in isolating these less volatile compounds.[28]

Biological Activities of Essential Oils

Antioxidative Activities of Essential Oils

EOs with antioxidant properties have garnered significant attention, particularly in the fields of food science and medicine. The modern GC-MS system can detect thousands of constituents in these EOs, allowing for a comprehensive analysis of their diverse and intricate chemical profiles. Among these components, those exhibiting antioxidant activity are of particular interest. They represent a crucial portion of these mixtures and are frequently highlighted as promising sources for the discovery and development of new bioactive compounds with potential applications in medicine, pharmaceuticals, cosmetics, and other areas.[29]

Understanding the efficacy and mechanism of action of each constituent within an EO is important for predicting the overall antioxidant activity of the EO (Figure 6). From a chemical perspective, antioxidant activity refers to the ability of a compound, even when present in small amounts, to protect materials prone to oxidation, such as polyunsaturated lipids, from undergoing oxidative processes.[24] Oxidation is primarily driven by a radical-chain reaction, where oxygen is incorporated into organic molecules, resulting in the formation of hydroperoxides, epoxides, and other oxygen-containing derivatives. This process is known as peroxidation.[30] In the peroxidation process, alkylperoxyl radicals (ROO●) are the primary radicals involved in carrying out the chain reaction. Other short-lived radicals, such as hydroxyl radicals (HO●) generated through the Fenton reaction, can also play roles in initiating and propagating the reaction. The effectiveness of an antioxidant is closely linked to its capacity to neutralize ROO● radicals.[30]

In silico methods, alongside traditional *in vitro* approaches, have been employed to evaluate the antioxidant properties and safety of EOs and bioactive compounds. Karakoti et al.[31] highlighted the potential of three *Vitex* species (*V. agnus-castus*, *V. negundo*, and *V. trifolia*) as natural phytotoxic agents and antioxidants, indicating their broader applications in traditional medicine beyond crop protection. Additionally, Minchán-Herrera et al.[32] suggested that volatile components of *Valeriana pilosa* might contribute to its antioxidant effects by acting as potential

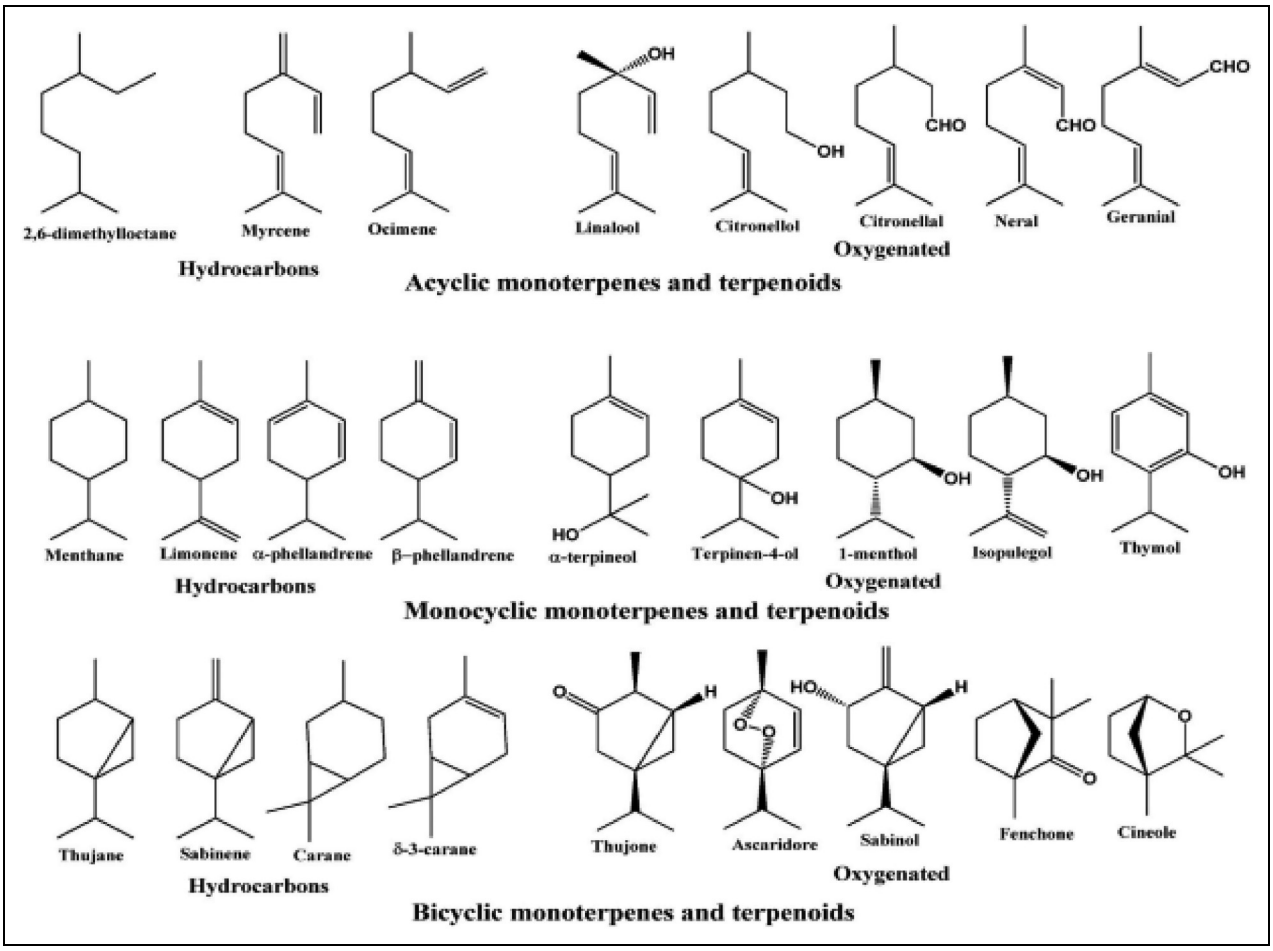

Figure 3. Some of the monoterpene and monoterpenoid constituents of EOs.

inhibitors of the CYP2C9 gene and xanthine oxidase. In their study, Herrera-Calderon et al.[33] identified two unique oxygenated terpenes, α-bisabolol and an unknown compound with the formula $C_{22}H_{42}O_4$, in the EO of *Allium sativum* cultivated in Peru. These compounds were associated with the EO high antioxidant activity. In silico studies on nicotinamide adenine dinucleotide phosphate oxidase demonstrated that α-bisabolol had the highest docking score and excellent stability. Additionally, ADMET predictions indicated that all garlic components are safe for oral and topical administration without causing toxicity. Shah et al.[34] were the first to explore the pharmacological activities of *Scutellaria edelbergii* EOs. They identified methyl 7-abieten-18-oate as a key bioactive constituent with potential antioxidant, pain-relieving, and anti-inflammatory properties. This compound also shows promise as a candidate for antimicrobial use. Computational studies confirmed its anti-inflammatory effect by inhibiting cyclooxygenase-2 enzyme activity, and ADMET properties indicate that it is suitable for further clinical investigation. Mohamed et al.[35] conducted *in vitro* and *in vivo* studies on *Artemisia judaica* L. and *A. visnaga* L. EOs, as well as *Heracleum persicum* oil nanoemulsion. Their research on *A. judaica* L. highlighted its antioxidant properties, attributed to high levels of oxygenated monoterpenes and cinnamate derivatives, and its therapeutic potential for treating skin wounds. Kamal et al.[36] examined *A. visnaga* L. chemical composition and antioxidant capabilities. While in vitro results showed low antioxidant potential, *in vivo* studies on *Swiss albino* mice demonstrated that *A. visnaga* L. EO supplementation significantly improved antioxidant capacity by increasing catalase, superoxide dismutase, and plasma glutathione peroxidase activities, and reducing 3,4-methylenedioxyamphetamine (MDA) levels. Cascaes et al.[37] provided new insights into the antioxidant activity, chemical composition, and preliminary toxicity of EOs from Brazilian Amazonian species *Duguetia* and *Xylopia* (Annonaceae). They found that while the EO from *D. riparia* was low in toxicity, EOs from *D. echinophora*, *X.* frutescens, and *X. emarginata* exhibited significant toxicity. *X. frutescens* and *X. emarginata* EOs showed the strongest antioxidant activity against DPPH and ABTS radicals, with their primary components likely responsible for this effect, though minor constituents also play a role. De Moraes et al.[38] studied EOs from *Myrcia sylvatica* and *Myrciaria floribunda*. Their results indicated that *M. floribunda* EO was moderately toxic, whereas *M. sylvatica* EO was highly toxic. *M. floribunda* EO was more effective at

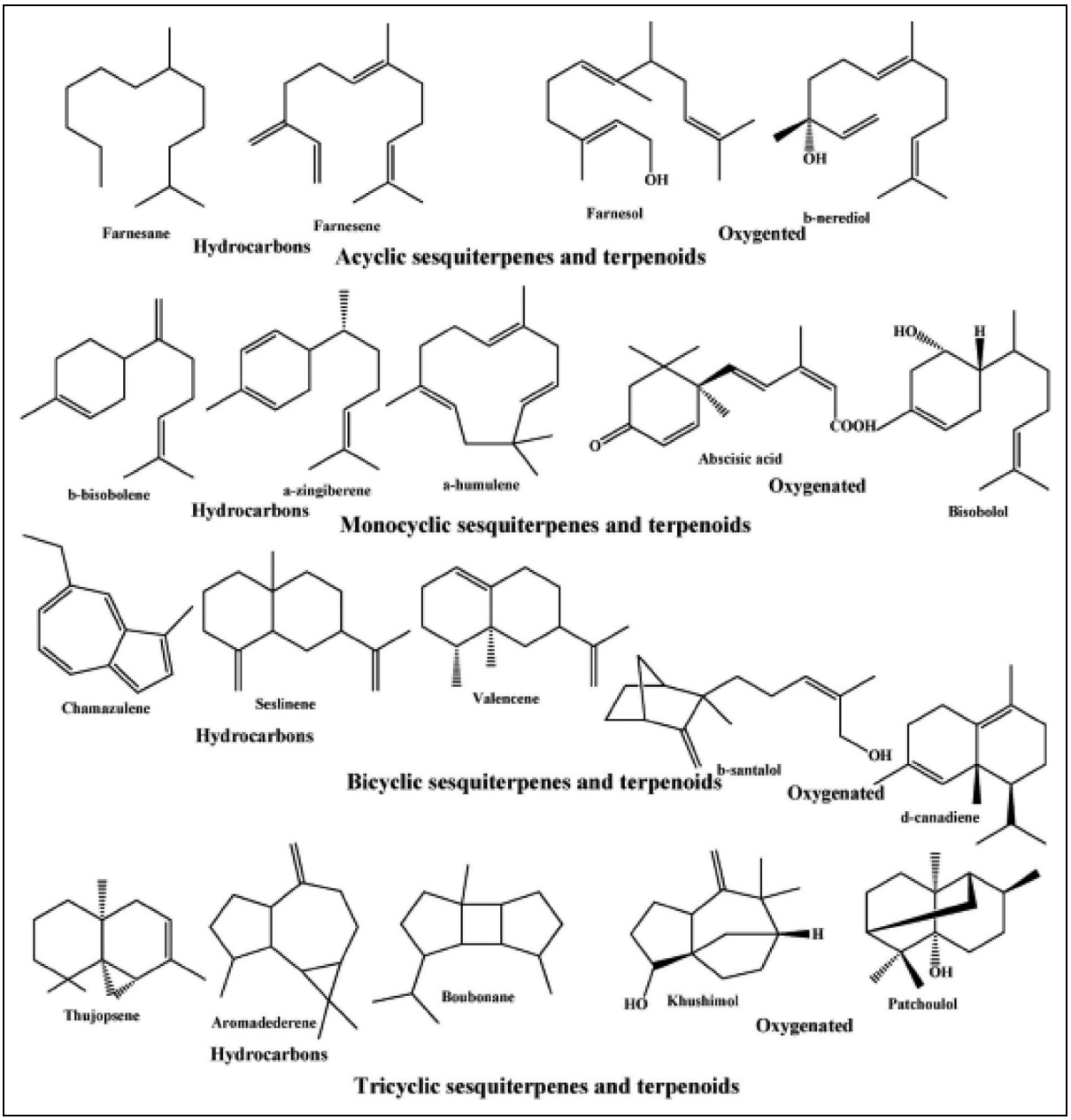

Figure 4. Some of the sesquiterpenes and sesquiterpenoid constituents of EOs.

blocking DPPH radicals. Da Costa et al.[39] presented the first study on *Croton campinarensis*, revealing its EO had a high concentration of sesquiterpene hydrocarbons and significant DPPH radical suppression. Sharma et al.[40] showed that *Embelia ribes* may prove to be an efficient medicinal tool in the treatment of many illnesses, due to the abundance and variety of bioactive compounds that demonstrate antioxidant, wound-healing, anti-diabetic, antiviral, antibacterial, antifungal, anti-obesity, cardioprotective, and antifertility action, among other interesting pharmacological properties, such as those related to diseases of the central nervous system. Manzur et al.[41] evaluated the antioxidant and antipathogenic properties of the commercial EOs from orange—*Citrus sinensis* (L.) Osbeck—and concluded that these oils may serve as natural and secure substitutes to increase the period of validity of foods by preventing contamination and oxidation with pathogens that ruin food. Additionally, sweet orange EOs may offer an inventive dual strategy for food conservation.

Antimicrobial Activity

EOs have been used in various industries, including pharmaceuticals, nutraceuticals, cosmetics, perfumes, agronomy, and sanitation, due to their antimicrobial properties. With the rise

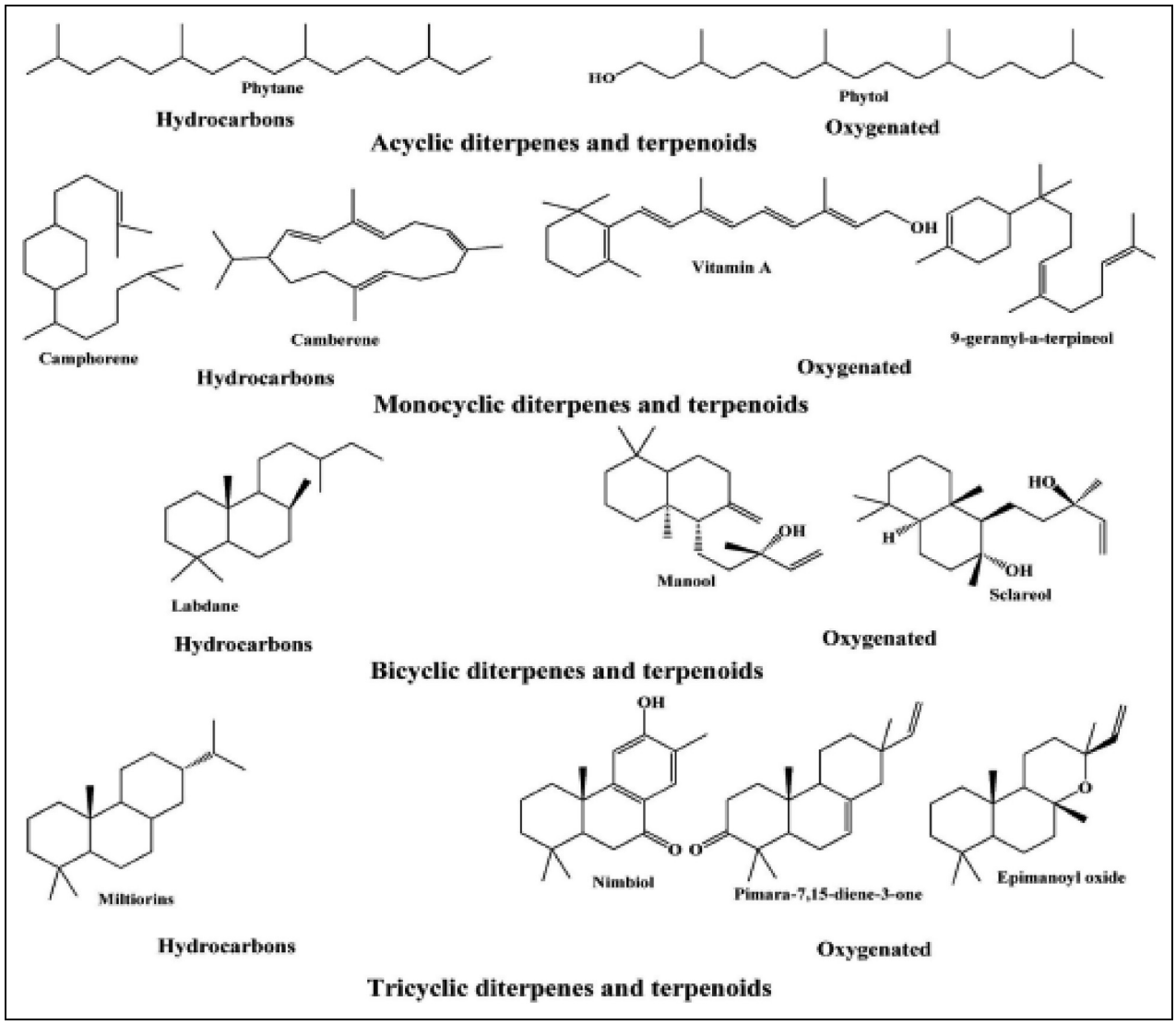

Figure 5. Some of the diterpene and diterpenoid constituents of EOs.

of antimicrobial drug resistance, researchers face the challenge of developing new molecules to target human pathogens.[42] EOs are gaining popularity as an alternative because they do not have the same unpleasant side effects, such as nephrotoxicity or ototoxicity, associated with many synthetic drugs. Additinally, EOs offer a viable approach to controlling multidrug-resistant pathogenic microorganisms and combating various infectious diseases.[43]

Antibacterial Activity. The antibacterial activity of EOs is characterized by their ability to inhibit or inactivate bacterial growth.[2,44] Numerous studies have demonstrated the potent inhibitory effects of EOs from plants such as *Syzygium aromaticum*, *Thymus vulgaris*, *Salvia rosmarinus*, *Origanum vulgare*, *Cinnamomum verum*, and *Pimenta dioica* against various bacterial pathogens.[45–48] The phenolic compounds present in EOs, such as eugenol, carvacrol, and thymol, are primarily responsible for their antibacterial action against bacteria such as *Staphylococcus aureus*, *Bacillus cereus*, *Streptococcus pneumoniae*, and *Escherichia coli*. The aromatic nature of these phenolics contributes significantly to the antibacterial activity of EOs.[49–52]

EOs exhibit stronger antibacterial effects against Gram-positive bacteria compared to Gram-negative bacteria.[52,53] *Chrysopogon zizanioides* and *Santalum album* EOs showed limited inhibition of Gram-negative bacteria but are more effective against Gram-positive strains. The hydrophobic nature of EOs allows them to interact with bacterial cell membranes, disrupting their structure and increasing permeability, which can lead to cell death. Additionally, some compounds in EOs also affect drug tolerance mechanisms in Gram-negative bacteria, further enhancing their antibacterial efficacy.[54,55]

EOs from *S. aromaticum*, *T. vulgaris*, *S. rosmarinus*, *O. vulgare*, *C. verum*, and *P. dioica* were noted for their strong antibacterial activity against pathogens like *S. aureus* and *P. aeruginosa*, with

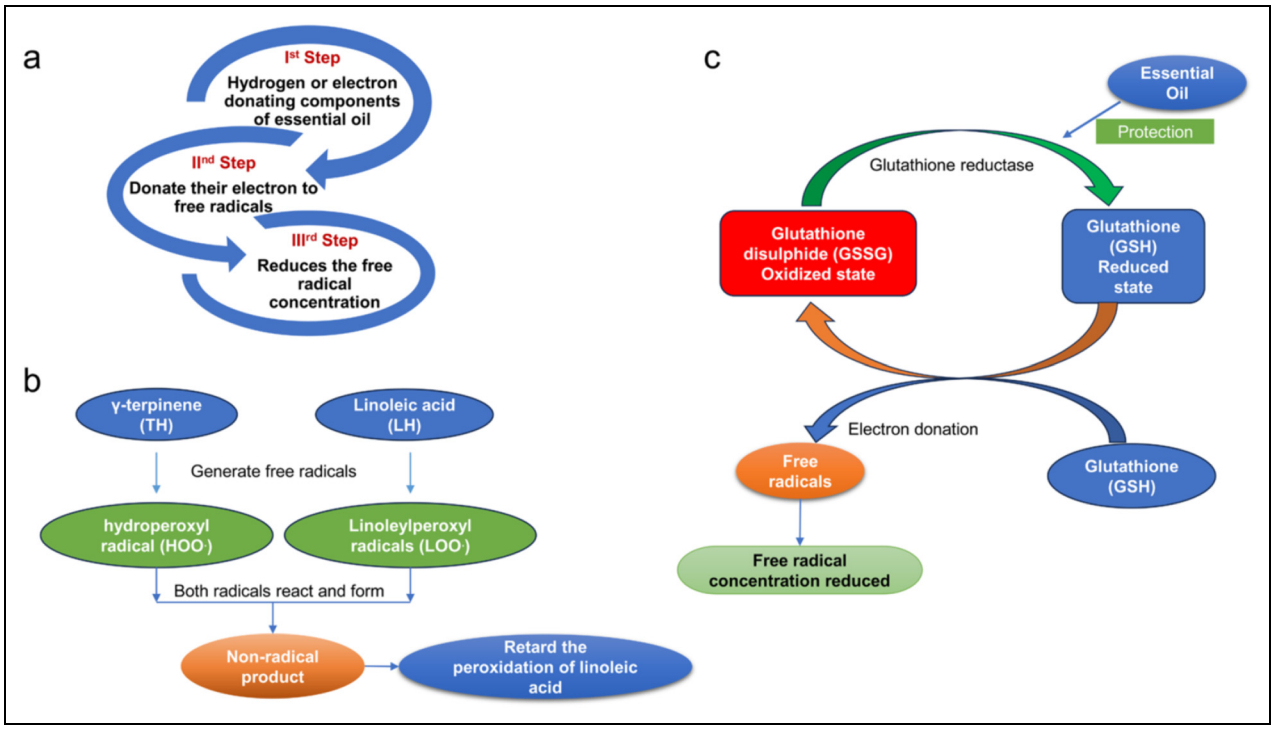

Figure 6. Antioxidative role of EOs. (a) Free radical scavenging by EOs. (b) Lipid peroxidation inhibition by EOs. (c) Protection of glutathione reductase by EO.

S. aromaticum oil being particularly effective.[56] The antibacterial efficacy of these oils is often linked to their major components, such as eugenol and thymol.[57] *S. aromaticum* EO has been shown to affect *Listeria monocytogenes* by altering respiratory metabolism and cell membrane permeability.[58] Other studies have evaluated EOs from *Ocimum basilicum*, *Elettaria cardamomum*, *S. rosmarinus*, and other herbs against various microorganisms.[59] High concentrations of EOs can suppress bacterial growth, with Minimum Inhibitory Concentration (MIC) values for *O. vulgare* and *T. vulgaris* ranging from 0.25% to ≥2% v/v against pathogens like *Salmonella* and *E. coli*.[60]

EOs from *S. officinalis*, containing camphor and α-thujone, inhibit human bacterial pathogens such as *Providencia stuartii* and *S. aureus*.[61] *Mentha pulegium* EO had a notably low MIC of 1 µg/mL for several pathogens.[62] *Achillea ligustica* exhibited inhibitory activity against *S. mutans* with MIC values ranging from 155 to 625 µg/mL. Additionally, EOs from *Ocimum tenuiflorum* and *Struchium sparganophora* have shown activity against various pathogens.[63,64]

Furthermore, EOs from various sources, such as *O. vulgare*, *O. basilicum*, *S. rosmarinus*, *P. crispum*, *Coriandrum sativum*, *Pimpinella anisum*, and *E. cardamomum*, have demonstrated significant antimicrobial activity against saprophytic microbes.[64] One study indicated that *O. vulgare* EO effectively inhibits the growth of *S. typhimurium*, *Yersinia enterocolitica*, and *E. coli*.[65] *O. vulgare* EO not only slowed bacterial growth but also reduced lactic acid production. Additionally, *O. vulgare* and *Lavandula angustifolia* EOs exhibited a bactericidal effect on *Klebsiella pneumoniae* with an MIC of 63,000 µg/mL.[66] *C. zeylanicum* EO has been shown to induce oxidative stress in *K. pneumoniae*, leading to cell viability loss.[67] These findings highlight the significant antibacterial potential of *O. vulgare* and *C. zeylanicum* EOs, with numerous studies confirming their antimicrobial efficacy against various species. *Echinophora platyloba* DC EO demonstrated strong activity against bacteria, with *S. aureus* and *L. monocytogenes* being the most sensitive, exhibiting MIC values of approximately 6250 and 12,500 µg/mL, respectively.[68] In a study testing the antimicrobial activity of seven EOs against resistant bacterial strains and fungi, *O. vulgare* EO exhibited antibacterial activity against *S. aureus* and *S. pyogenes* with the lowest MIC of 25 µg/mL, while other oils were effective at higher concentrations against all microorganisms tested.[69] A study by Thanissery et al.[70] demonstrated that EOs from *S. aromaticum*, *S. rosmarinus*, and a *T. vulgaris* – *O. vulgare* blend effectively inhibited *Campylobacter* and *S. enterica*, with *T. vulgaris* oil showing the highest inhibition against *Salmonella*, achieving zones of 18.5 mm. Sutili et al.[71] found that EOs from *Hesperozygis ringens*, *Ocimum gratissimum*, and *O. americanum* significantly inhibited *Aeromonas hydrophila*.

The antibacterial properties of EOs are primarily attributed to their ability to disrupt bacterial cellular architecture. Research has shown that EOs significantly enhance bacterial membrane permeability, leading to the leakage of intracellular components such as ions, nucleotides, and other metabolites, which are crucial for cellular homeostasis.[72,73] This increased permeability also results in a reduction in membrane potential, which is

essential for the operation of proton pumps and ATP synthesis. The disruption of these proton pumps leads to ATP depletion, further impairing cellular metabolic activities.[74] Moreover, the impact of EOs on the cell membrane initiates a series of downstream effects that compromise the function of intracellular organelles. The cumulative effect of these disruptions ultimately leads to cell death.[74] These findings highlight the multifaceted mechanisms by which EOs exert their antibacterial effects, offering potential as alternative antimicrobial agents, particularly in the face of rising antibiotic resistance. Likewise, the EO of *C. medica* L. has demonstrated significant antibacterial effects on *E. coli* and *S. aureus*. These effects include alterations in cell structure, such as the development of wrinkles, the formation of surface perforations, and the disruption of the plasma membrane. These structural changes, as reported by Li et al.,[75] indicate the potential of *C. medica* L. EO to compromise bacterial integrity, leading to the breakdown of cellular functions and, ultimately, bacterial cell death.

Due to their hydrophobic nature, EOs likely interact with the lipids in the bacterial plasma membrane or mitochondria, disrupting their function by increasing proton permeability, as evidenced by membrane electrical conductivity assays.[76] The EO of mustard was found to cause damage to the bacterial cell membranes of *E. coli* and *S. typhi*, leading to the loss of essential cellular structures, ATP depletion, and a decrease in intracellular pH.[77] The EO of *Origanum compactum* Benth. can induce the dissipation of potassium ion gradients, resulting in the loss of membrane potential in *Pseudomonas aeruginosa*.[78] Scanning electron microscopy showed that *O. compactum* Benth. EO caused damage to the cell walls of *E. coli* and *B. subtilis*.[79] Furthermore, the diverse chemical composition of essential oils enhances the likelihood of components that can disrupt protein synthesis. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis, coupled with Western blotting, demonstrated that carvacrol and p-cymene can reduce protein synthesis in *E. coli*.[80]

EOs may also exhibit mutagenic properties, which can be explored through gene modulation studies.[81] RNA sequencing of *Salmonella* cells treated with thymol revealed differential expression of several key genes in metabolism, suggesting that EO components can interfere with bacterial metabolic pathways, leading to cell death.[82]

Antifungal Activity. In addition to their well-documented antibacterial effects, EOs also exhibit significant antifungal activity. The volatile components of EOs have been extensively tested for their efficacy against various fungi, including *Aspergillus niger* and *A. flavus*, as well as for their potential to extend the shelf life of foods.[83] For instance, *Putranjiva roxburghii* EO has demonstrated potent fungicidal properties without adversely affecting plant health.[84] Additionally, EOs have applications in pharmaceuticals, cosmetics, and skin-care products, highlighting their versatility as antifungal agents.[85,86]

Antifungal agents, including EOs, combat fungal infections using various strategies by targeting crucial components within fungal cells.[87] One major approach is targeting the fungal cell membrane, specifically ergosterol, a key component. Drugs or EOs may bind directly to ergosterol or inhibit its production, compromising membrane integrity and leading to cell death. Another strategy involves disrupting cell wall formation by targeting beta-glucans, which weakens the cell structural framework and results in cell destruction. Additionally, some antifungal agents affect mitochondria, which are responsible for energy production. Disruption of the mitochondrial electron transport chain reduces membrane potential and ATP levels, leading to cell death due to energy deficits. Inhibiting efflux pumps, which expel drugs from the cell, can also enhance antifungal efficacy by allowing drugs to accumulate within the fungal cell, thus improving effectiveness and potentially reducing drug resistance. EOs from *Anethum graveolens* and *C. sativum* exhibited these mechanisms.[88,89] *A. graveolens* EO affects the fungal cell membrane by increasing proton pumping activity and acidification, particularly in the presence of glucose. This reduces intracellular ATPase activity, possibly through interactions with mitochondrial dehydrogenases, and increases reactive oxygen species (ROS) production, indicating apoptosis.[90,91] Furthermore, EOs may inhibit cell wall formation by targeting enzymes such as delta-14-sterol reductase and 1,3-β-glucan synthase.[92] Rich in linalool and gamma-terpinene, *C. sativum* EO exhibited broad antifungal activity, highlighting the efficacy of these monoterpenes.[93,94]

Antiviral Activity. EOs have demonstrated activity against various DNA and RNA viruses, including herpes simplex virus type-1 (HSV-1) and type-2 (HSV-2), poliovirus, adenovirus, dengue virus type-2, yellow fever virus, influenza virus, respiratory syncytial virus, Zika virus, coronaviruses, coxsackievirus B-1, and Junin virus.[95–98] EOs derived from oregano and clove exhibited significant antiviral activity against non-enveloped DNA and RNA viruses such as adenovirus type 3, coxsackievirus B1, and poliovirus.[99] EOs from *Melaleuca alternifolia*, *Eucalyptus globulus*, and *T. vulgaris* also proved highly effective against HSV-1, achieving nearly 96% inhibition.[100] These EOs, along with *manuka* and Australian *eucalyptus*, displayed notable antiherpes properties.[101–103]

Specific EO components like phenylpropanes, sesquiterpenes, and triterpenes exhibited potent antiviral activity against rhinovirus and herpes viruses.[104,105] EOs also exhibited efficacy against other viruses. *Eupatorium patens* and *Artemisia douglasiana* EOs were active against the dengue virus,[106] while *Lippia junelliana* and *L. turbinata* EOs showed antiviral activity against the Junin virus. *Pogostemon cablin* EO was effective against the H2N2 influenza-A virus,[107] and *Fortunella margarita* EOs demonstrated activity against the avian influenza virus H5N1.[108] *M. officinalis* EO, combined with oseltamivir, exhibited enhanced inhibition of H9N2 avian influenza virus replication.[109]

The antiviral efficacy of EOs was often linked to their ability to disrupt viral entry by damaging the viral envelope, disintegrating the capsid, or blocking viral attachment to host cell receptors. For instance, 4% *O. vulgare* EO caused expansion

of murine norovirus particles, leading to capsid disintegration and loss of viral infectivity.[110] Similarly, *M. alternifolia* EO and its component terpinen-4-ol prevented influenza virus entry by disrupting endolysosomal acidification.[111] EOs such as marjoram, clary sage, *T. vulgaris*, *C. zeylanicum*, *C. bergamia*, and *P. anisum* showed antiviral activity against influenza virus, with low IC50 values.[112,113] The EO component germacrone, found in *Curcuma amada*, demonstrated significant antiviral activity against influenza virus.[114,115] Additionally, EOs from *T. vulgaris*, *Cymbopogon citratus*, and *Rosmarinus officinalis* were shown to destabilize the Tat/TAR-RNA complex necessary for HIV replication.[116] *Cymbopogon nardus* EO inhibited HIV-1 reverse transcriptase, an effect attributed to α-citronellol.[117]

Antiparasitic Activity. EOs have shown significant anthelmintic activity against various parasitic species, demonstrating their potential as natural treatments for parasitic infections. The EOs of *M. piperita*, *Lippia alba*, and *Zingiber officinale* have effectively controlled the acanthocephalan parasite *Neoechinorhynchus buttnerae*, which causes substantial economic losses in *Colossoma macropomum* fish in the Amazon region.[118] Similarly, EOs from *Piper hispidinervum* and other Piper species have provided effective treatment, with *P. hispidinervum* EO showing the most effective dose-response result when applied at 0.78 mg/L for 15 min.[119] In controlling parasites like *Anacanthorus spathulatus*, *Notozothecium janauachensis*, and *Mymarothecium boegeri* in Serrasalmidae fish, the EOs of *Cymbopogon citratus*, *Pterodon emarginatus*, *L. origanoides*, *L. sidoides*, and *L. alba* have been used. Among these, *L. sidoides* EO was particularly effective, demonstrating 100% efficacy when applied at 320 mg/L for 10 min.[120] For *Dactylogyrus* spp., which are common pathogens in cultured freshwater fish, *Lippia alba*, *Lippia origanoides*, and *Lippia sidoides* EOs have shown 100% efficacy when applied at 100 mg/L for 5 min against *Dactylogyrus minutus* and *D. extensus*.[121] Additionally, *Cichlidogyrus* species affecting cichlid fish have been effectively managed using *L. sidoides* and *M. piperita* EOs, with both demonstrating complete efficacy at specific concentrations and times.[122] The EOs of *M. piperita* and *O. americanum* have also proven effective against other parasites such as *Dawestrema cycloancistrium*, *D. cycloancistrioides*, and *Gyrodactylus* spp. The former was treated with *M. piperita* EO at 160 and 320 mg/L for 30 min, resulting in 100% efficacy,[123] while the latter showed high efficacy with *O. americanum* EO at 50 mg/L for 1 h.[124] For protozoan parasites, *L. angustifolia* and *Lavandula intermedia* EOs have demonstrated 100% efficacy against *Hexamita inflata* when applied at concentrations of 1% and 0.5% for 30 min.[125]

The EO from *M. piperita* EO showed high efficacy against the dinoflagellate *Piscinoodinium pillulare* in *Colossoma macropomum* juveniles, with 40 mg/L achieving up to 79.91% parasite removal.[126] EOs from *P. diospyrifolium* and *P. mikanianum* also exhibited strong antiparasitic effects, particularly against *Leishmania* spp. and *Trypanosoma cruzi*, with EO achieving 35.34% inhibition and EO showing 94.25% mortality at certain concentrations.[127] Additionally, *Myrtus communis* EO showed potent antiparasitic activity against chronic toxoplasmosis in mice, significantly reducing *Toxoplasma gondii* cysts and enhancing immune response.[128]

T. vulgaris EO showed significant antiparasitic effects against *Trypanosoma cruzi*, *Trichinella spiralis*, and *Haemonchus contortus*, exhibiting high efficacy in inhibiting growth and development of these parasites.[129,130]

Insecticidal and Larvicidal Activity. Plants produce defensive chemicals known as allelochemicals, which serve to deter predators, microbes, and vertebrates due to similarities in neuronal signaling across various animal species.[131] The presence of secondary metabolites in plants can provide extended protection against herbivores and pests, offering a broader defense compared to individual compounds. These metabolites physical characteristics further contribute to their prolonged defense capabilities. According to Shaalan & Canyon,[132] plants contain a diverse array of phytochemicals, including steroids, terpenoids, phenolics, alkaloids, and EOs, all of which exhibit insecticidal properties. EOs from aromatic plants are increasingly explored as alternatives to conventional insecticides.[133]

EOs have been utilized to manage pests through various mechanisms, including acute toxicity, repellency, and antifeedant effects. This approach helps in protecting crops and preserving food. Recent interest in EOs has surged due to consumer demand for residue-free, healthy food and heightened environmental concerns, driving research into plant-derived compounds for insecticide development.[134] EOs are recognized as promising alternatives to synthetic pesticides.[13]

Research into EOs for pest management has revealed that their insecticidal effectiveness depends on the chemical structure and characteristics of their components, their ability to penetrate biological membranes, and their action mechanisms.[135] EOs from plant families such as Lamiaceae,[136] Asteraceae,[137] Apiaceae,[138] Myrtaceae,[139] and Rutaceae[140,141] exhibit significant insecticidal properties. These EOs have been studied for various effects, including attractant, repellent,[142,143] antifeedant,[144] fumigant,[145,146] and contact[147] against different insect life stages across multiple orders.[148]

Mechanistic studies have investigated how EOs affect insects. EOs can disrupt cellular processes by impairing respiration, reducing cell membrane permeability, and affecting Golgi bodies and mitochondria.[149–151] Neurotoxic effects include blocking octopamine receptors, inhibiting acetylcholinesterase (AChE), and interfering with γ-aminobutyric acid (GABA) receptors.[152,153] EOs also impact cytochrome P450 monooxygenase and insect pheromone and hormone systems.[154] Disruptions in octopamine can impair insect nervous system functions, while symptoms induced by EOs, such as hyperactivity and paralysis, resemble those caused by carbamate and organophosphate insecticides.[155]

Several studies have demonstrated the efficacy of EOs against various mosquito larvae, particularly *Aedes aegypti*. Martianasari & Hamid[156] reported 100% mortality within one hour using *Piper betle* L. EOs at 500 ppm. Scalvenzi et al.[157]

observed 100% mortality with *P. aduncum*, *O. campechianum*, and *Ocotea quixos* EO at varying concentrations after 24 h. Cheng et al.[158] demonstrated 100% larval mortality with *Eucalyptus camaldulensis* and *E. urophylla* EOs at concentrations of 100 g/ml and 200 g/ml, respectively. Similarly, studies by Marques et al.[159] found high larvicidal activity with 100% mortality rates in *Ottonia anisum*. Ivoke & Odii[160] and Nwankwo et al.[161] also reported significant mortality rates at various concentrations.

EOs and their components exhibit a wide range of insecticidal activities across various insect species. 1,8-cineole, found in *R. officinalis*, *E. lehmannii*, and *E. astringens*, showed both fumigant and contact toxicity against insects such as *Ectomyelois ceratoniae*, *Ephestia kuehniella*, *E. cautella*, *Callosobruchus maculatus*, *Rhyzopertha dominica*, and *Tribolium castaneum*.[162,163] Similarly, α-pinene, present in *Pistacia lentiscus*, demonstrated efficacy against *Tribolium castaneum* and *Lasioderma sericorne*.[164] α-Terpineol, derived from *L. angustifolia*, *Juniperus virginiana*, and *Cinnamomum camphora*, has been reported to possess repellent properties against *Resseliella oculiperda*.[165] Camphor, found in *Perovskia abrotanoides* was effective as both a fumigant and in topical applications against *Sitophilus oryzae* and *Tribolium castaneum*.[166] Cinnamaldehyde from *C. osmophloeum* showed contact activity against *Coptotermes formosanus*,[167] while citronellal from citrus peel EOs exhibited fumigant toxicity against *Callosobruchus maculatus*.[168] Estragole in *Foeniculum vulgare* demonstrated insecticidal effects against *Sitophilus oryzae*, *C. chinensis*, and *Lasioderma sericorne*.[169] Eugenol, found in various EOs, displays effectiveness in topical application, contact toxicity, fumigation, and repellency against *Spodoptera litura*.[170] Geranial from *L. alba* and *Callistemon lanceolatus* shows repellent action against *Callosobruchus chinensis*.[171]

Limonene from *C. aurantium* exhibits fumigant and anticholinesterase activities against *Bemisia tabaci*.[140] Linalool in *Laurus nobilis* and *C. sativum* demonstrates repellent and fumigant properties against *Rhyzopertha dominica*, *T. castaneum*, *S. oryzae*, and *Lasioderma sericorne*.[172,173] L-Menthol from *M. piperita* showed contact toxicity against *Culex quinquefasciatus* and *Aedes aegypti*.[174] Myrcene, a pure monoterpene hydrocarbon, demonstrated contact toxicity towards *Leptinotarsa decemlineata*.[175] Piperitone from *Cymbopogon schoenanthus* exhibited insecticidal toxicity against *Callosobruchus maculatus*.[176] Pulegone in *M. pulegium* showed fumigant and repellent potentials against *T. castaneum* and *Lasioderma sericorne*.[177] 1-Butyl-3,4-methylenedioxybenzene from *Piper corcovadensis* demonstrated fumigation, contact, and ingestion toxicity against *Sitophilus zeamais*.[178]

Toxicology, an essential aspect of pharmacology, examines the adverse effects of phytochemical compounds on living organisms before their use in drugs or industrial applications. Subha and Geetha[179] showed the importance of toxicity analysis to ensure the safety of plant-based products, considering the potential harmful effects from prolonged exposure. This analysis aids in determining the safety of chemicals in various applications and clarifying mechanisms of toxicity. According to Arome et al.,[180] toxicity tests are integral to chemical toxicology in ecotoxicology. Lethal concentration (LC) tests, including LC50 and LC95, are utilized to assess toxicity thresholds. These tests have been applied to evaluate the larvicidal activity of *Azolla pinnata* extracts against *Aedes* mosquitoes, offering insights into the effectiveness of plant extracts in controlling mosquito larvae.[181]

Anti-inflammatory Activity. Inflammation, a protective response to harmful stimuli, involved the immune system efforts to eliminate causes and maintain tissue homeostasis[182] (Figure 7). However, prolonged inflammation without persistent harmful stimuli could result in tissue damage and contribute to conditions such as cancer and obesity, which necessitated clinical

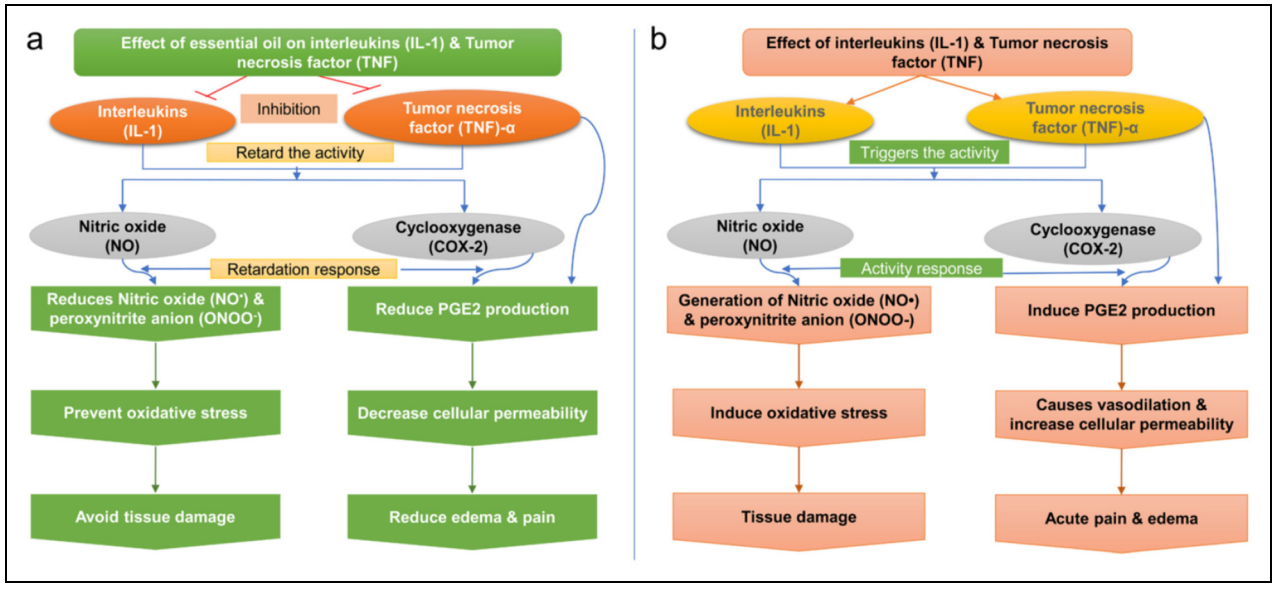

Figure 7. Inflammatory response involving interleukins and TNF, along with the therapeutic mechanisms of EOs. (a) Impact of essential oils on interleukins and TNF levels. (b) Roles of interleukins and TNF. PGE2 refers to prostaglandin E2.

intervention.[183,184] This process was marked by the release of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-8, which activated immune cells and increased vascular permeability, potentially leading to tissue injury if not properly regulated.[185]

Research indicated that EOs could modulate inflammatory responses by affecting pro-inflammatory cytokines and enzymes, suggesting their potential as natural anti-inflammatory agents.[8] *Pelargonium graveolen* EO, particularly through its component citronellol, was shown to significantly reduce β-hexosaminidase secretion in IgE-stimulated mast cells, indicating its potential in treating allergic reactions by inhibiting mast cell degranulation.[185,186]

α-Phellandrene, another EO component, demonstrated protective effects against ifosfamide-induced hemorrhagic cystitis and wound healing. It inhibited leukocyte influx, neutrophil adhesion, and reduced pro-inflammatory cytokines like TNF-α and IL-6.[187,188] Bergapten, found in *C. bergamia* EO, showed promise in treating skin disorders by reducing colonic lesions and edema in colitis models.[189]

Carvacrol and its derivative, carvacryl acetate, exhibited anti-inflammatory effects by interacting with the TRPA1 receptor, which was involved in detecting cell damage.[190,191] Molecular docking studies confirmed that carvacrol bound strongly to the TRPA1 receptor, enhancing its anti-inflammatory effects.[192,193] Eucalyptol, another EO, was shown to reduce paw edema and pro-inflammatory cytokines in various inflammation models, with its effects dependent on the TRPM8 receptor.[194–196]

C.aurantium L. EO inhibited pro-inflammatory cytokines and COX-2 expression in macrophages, acting through suppression of the NF-κB and MAPK signaling pathways.[197] Similarly, *Eucalyptus* EO, particularly its subfraction F, reduced NO production, pro-inflammatory cytokines, and COX expression, with components like methylsyringol and menthol contributing to its efficacy.[198] *L. angustifolia* EO, containing linalool and linalyl acetate, improved psoriasis severity by reducing skin inflammation.[199] Additionally, β-eudesmol and β-caryophyllene interacted with COX-2 and CB-2 receptors, respectively, showing anti-inflammatory effects with high safety margins.[200–203] Camphor regulated TLR4 and Nrf-2, enhancing antioxidant activity and reducing pro-inflammatory cytokines.[204,205] Cinnamaldehyde from *Cinnamomum* exhibited anti-inflammatory properties through the MyD88-dependent TLR2/TLR4 signaling pathway and accelerated wound healing by disrupting bacterial membranes.[206] α-Pinene, a bicyclic terpenoid, provided relief from neuritis-induced damage by reducing pro-inflammatory cytokines and apoptotic gene expression.[207] Ar-turmerone from turmeric alleviated inflammation by scavenging reactive oxygen species and inhibiting PGE2 and TNF-α production.[208,209] *M. alternifolia* reduced IL-6 and TNF-α expression in mastitis models.[210] However, the practical use of EOs in vivo was challenged by their volatility and instability, which could cause stress and abnormal behaviors in animals.[211] In pathogen-infected wound models, *M. piperita* L. EO showed conflicting results, increasing IL-1β levels and decreasing VEGF and FGF2, which contradicted its typical anti-inflammatory effects.[212]

In vitro studies often used lower concentrations of PEOs (1-100 μg/kg) compared to *in vivo* studies (approximately 100 mg/kg) to assess their biological activities and effects on cell morphology.[213–215]

Clinical and epidemiological research was necessary to fully understand the therapeutic and preventive roles of EOs. They showed promise in treating conditions like rheumatoid arthritis,[216] migraine,[217] and anxiety.[218] EOs were also used in mouthwashes to inhibit dental plaque and reduce chronic periodontitis.[219] However, more research was needed to assess their efficacy, particularly regarding their digestion and absorption, as current studies mainly focused on stomatitis and aromatherapy.[220,221] *Cuminum cyminum* L. EO capsules were found to reduce TNF-α and CRP levels in type II diabetes patients, indicating the need for further inflammatory models to support EO clinical applications.[222]

Anti-diabetic Activity. Glucose metabolism plays a crucial role in regulating insulin secretion, beginning with glucokinase-mediated phosphorylation of glucose to glucose-6-phosphate, which produces ATP that inhibits ATP-sensitive potassium channels. This inhibition activates L-type voltage-dependent calcium channels, causing an increase in intracellular calcium that triggers insulin release.[223] Additionally, gut-derived hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) enhance pancreatic insulin secretion, though they are quickly inactivated by dipeptidyl peptidase-4.[224,225] A high-fat diet exacerbates the situation by inducing inflammation and adipose tissue dysfunction, stimulating the production of pro-inflammatory cytokines like TNF-α and interleukins (IL-6, IL-1β), which contribute to insulin resistance and type 2 diabetes mellitus.[226]

EOs demonstrated anti-diabetic properties by scavenging free radicals, inhibiting glucose oxidation, and reducing protein glycation, while modulating signal transduction pathways linked to glucose metabolism, including MAPK, GLUT4, and Caspase-3[227] (Figure 8). They reduced pro-inflammatory markers like TNF-α and ILs, enhanced insulin levels, and boosted antioxidant enzymes such as SOD, catalase, and GPx.[228,229] Modulation of MAPK pathways, including ERKs, JNKs, and p38/SAPKs, restored AQP7 function, promoted insulin secretion, and inhibited Caspase-3 to reduce β-cell apoptosis.[215,230,231] Insulin signaling enhanced GLUT4 translocation, facilitating glucose metabolism.[232,233] Inhibiting prostaglandins, cytokines, α-amylase, and α-glucosidase reduced insulin resistance, improved glycoprotein enzyme activity, and stabilized glucose levels.[234–236] Additionally, AMPK activation enhanced GLUT4 expression, reduced inflammation, and improved insulin resistance.[237]

Several studies highlighted the anti-diabetic potential of EOs in animal models. *Pelargonium graveolens* EO significantly reduced blood glucose and increased hepatic glycogen in alloxan-induced diabetic rats, showing superior results to glibenclamide.[238] Similarly, *C. sinensis* EO, when administered intraperitoneally, reduced fasting blood glucose and increased

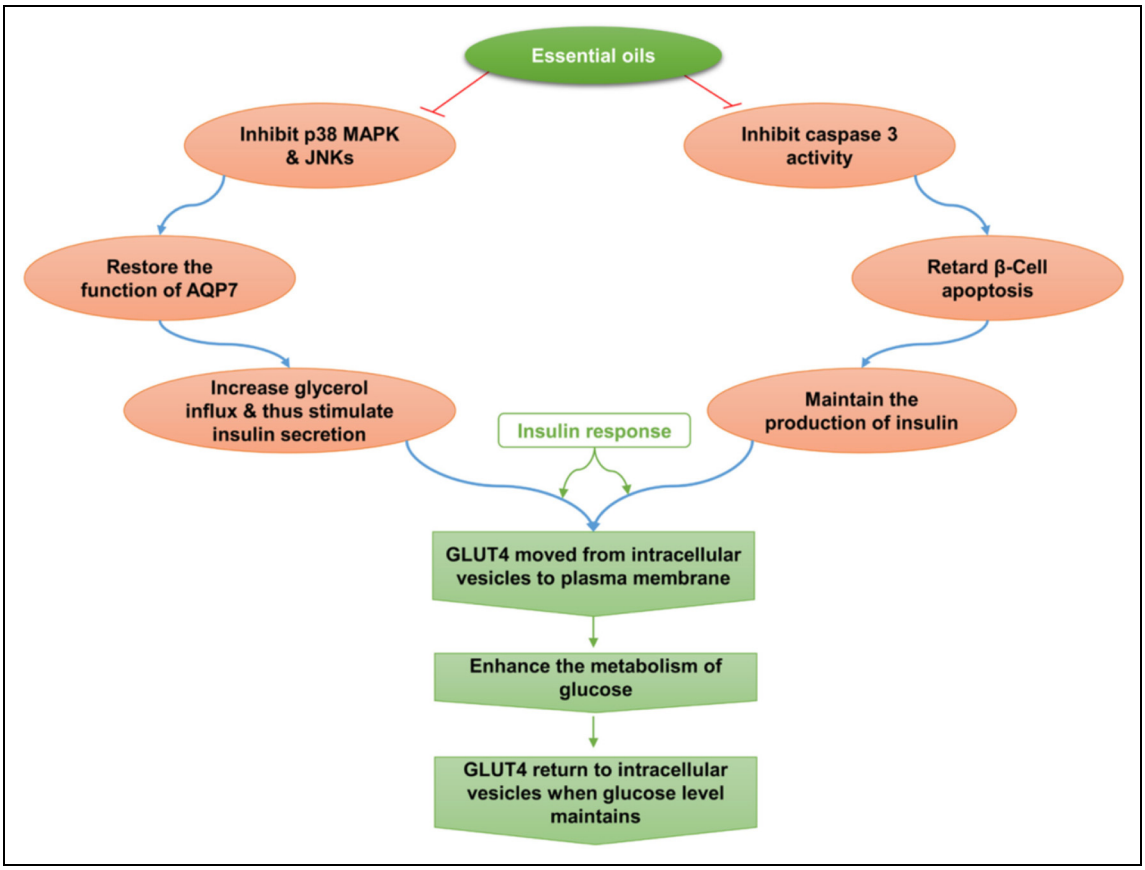

Figure 8. Mechanism by which EOs exhibit anti-diabetic effects via signaling pathways. AQP refers to aquaporin; GLUT4 denotes glucose transporter type 4; JNKs are jun N-terminal kinases; MAPK stands for mitogen-activated protein kinase.

hepatic glycogen in diabetic rats, likely due to its monoterpene content, which mimics insulin.[239] Additionally, EOs of *Salvia officinalis* and *M. suaveolens* inhibited α-amylase and α-glucosidase, helping to manage postprandial hyperglycemia.[240] *C. sativum* EO demonstrated protective effects on kidney and pancreatic cells in streptozotocin-induced diabetic rats, improving insulin secretion and lowering blood glucose levels.[241] Similarly, *Myrtus nivellei* EO significantly reduced blood sugar and triglyceride levels in diabetic rats.[242] *S. aromaticum* EO showed significant anti-diabetic effects by lowering blood glucose levels and influencing glucose metabolism.[243]

Anti-cancer Activity. EOs have emerged as potential agents in cancer treatment, a field where nearly half of traditional chemotherapy drugs were plant-derived. Paclitaxel, known for inhibiting cell division by targeting tubulin, was widely used in chemotherapy.[244] Recent studies suggested that EOs, such as (+) -citronellal, might disrupt microtubule formation, indicating their possible therapeutic role in cancer.[245] However, further research was necessary to confirm their effectiveness and safety.

The anticancer mechanisms of EOs are diverse and multifaceted (Figure 9). They included disrupting the cell cycle to halt proliferation, inducing apoptosis, and interfering with cell signaling pathways and angiogenesis.[11] EOs could also cause oxidative damage by disrupting the redox balance of tumor cells and altering cell membrane properties, leading to instability and loss of cell function.[246] The effects of EOs varied with cancer type and the specific composition of the EO.[247] While there was considerable potential, further *in vivo* and clinical studies were needed to confirm their efficacy and safety.[248] Limited research existed on the mechanisms of whole EOs or their constituents in cancer treatment, and assessing the toxicity of essential oil components was crucial to ensure safety.[249,250]

Despite significant advancements in cancer research, multidrug resistance (MDR) remained a major challenge. MDR was driven by cellular plasticity and prolonged exposure to drugs.[251–254] EOs, recognized for their antitumor properties, demonstrated cytotoxic effects against various tumor cell lines *in vitro*. Active compounds such as phenols, alcohols, and aldehydes exhibited significant antitumor activity.[255,256]

Effective cancer therapies needed to induce apoptosis and inhibit cell proliferation, addressing cancer hallmarks like resistance to apoptosis and sustained proliferative signaling.[257] EOs were shown to activate both intrinsic (mitochondria-dependent) and extrinsic (death receptor-dependent) apoptosis pathways. Camphene from *P. cernuum* EO induced apoptosis in melanoma cells by activating the caspase-3 pathway and triggering ER stress signaling.[258] Similarly, carvacrol from oregano and

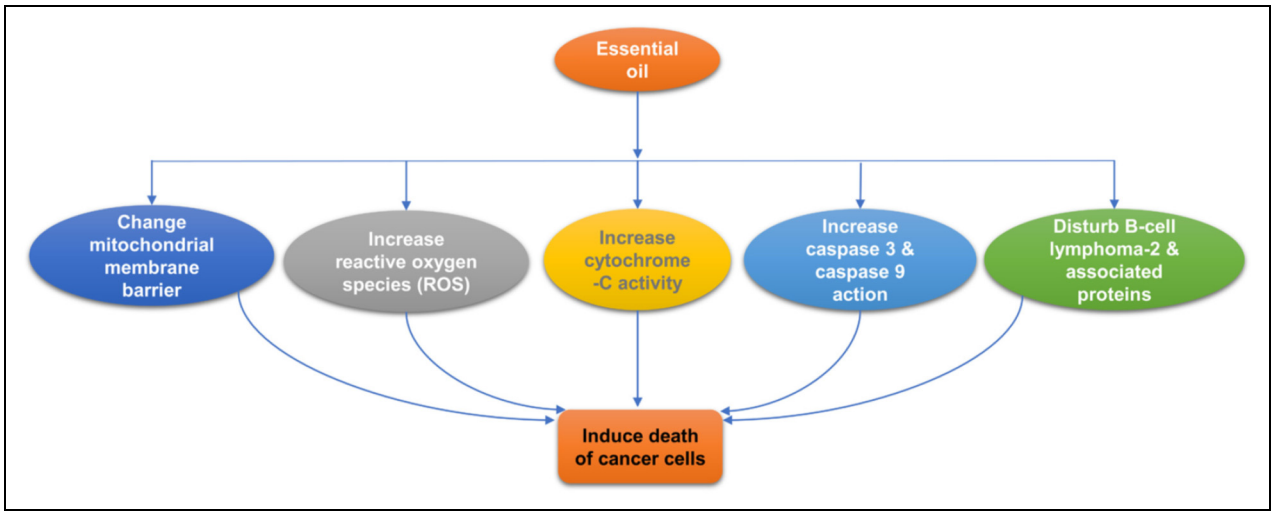

Figure 9. Mechanism of induction of cancer cells death by EOs.

thyme EOs promoted apoptosis in breast cancer cells through mitochondrial membrane permeabilization and caspase activation.[259] Frankincense EO from *Boswellia sacra* selectively induced apoptosis in cancer cells, demonstrating PARP cleavage in breast cancer cells.[260] Citral, a component of various EOs, also triggered caspase activation and apoptosis in colorectal and glioblastoma cells.[261–265]

Protein kinase B (PKB) played a crucial role in cell metabolism, transcription, and survival.[266] EOs like *Litsea cubeba* seed oil induced cell cycle arrest and apoptosis in non-small cell lung carcinoma cells by inhibiting mTOR and PPDK1, leading to PKB dephosphorylation and caspase-dependent apoptosis.[267]

Carvacrol demonstrated significant antitumor activities across various models, including cell cycle arrest, apoptosis, antioxidant activity, and inhibition of DNA synthesis.[268] Geraniol exhibited antitumor effects through cell cycle arrest, apoptosis induction, and inhibition of RhoA activation.[269] Limonene showed activity by stimulating apoptosis, affecting detoxification enzyme activities, and influencing gap junctions.[270] Thymol showed cell cycle arrest, apoptosis induction, and antioxidant activity.[271] Thymoquinone suppressed Akt phosphorylation, promoted apoptosis, and regulated the PPAR-γ pathway.[272]

A significant advantage of EOs was their selective cytotoxicity towards cancer cells while sparing healthy cells. *T. fallax* EO exhibited selective cytotoxicity against colorectal cancer cells with minimal effects on fibroblast cells.[273] Similarly, *Boswellia sacra* EO showed cytotoxic effects on breast cancer cells while being noncytotoxic to normal breast cells.[274]

EOs could also enhance the efficacy of conventional chemotherapy drugs. For example, limonene increased the sensitivity of prostate cancer cells to docetaxel, reducing the required dose and associated toxicity.[275] β-Caryophyllene, though not cytotoxic alone, enhanced paclitaxel activity in colorectal cancer cells by increasing cell membrane permeability.[276]

Combining EOs with conventional chemotherapy or targeted therapies offered a promising approach by improving drug specificity and reducing side effects. Citronellol, a major component of a Chinese herbal medicine complex, was shown to mitigate neutropenia, a common side effect of chemotherapy, while exhibiting antioxidant and anticancer properties.[277] Geraniol was also found to increase cancer cell sensitivity to 5-fluorouracil and reduce DNA damage in animal models.[278]

Neuropharmacological Activity. Recent pharmacological research has demonstrated the nootropic effects of certain aromatic Chinese medicines, including rosemary[7]

Cao[279] found that rosemary EO enhanced learning abilities in C57BL/6 mice with olfactory epithelial damage by influencing the expression of AChE and GluR1. Conversely, Hancianu et al.[280] reported that *L. angustifolia* EO improved learning and memory in rats, attributing this to its antioxidant and anti-apoptotic properties, which reduced malondialdehyde (MDA) levels and increased reduced glutathione (GSH), suggesting benefits for memory and learning. EOs from *Acorus tatarinowii* Schott and *C. limon* have also shown promise in enhancing learning and memory. Zhou et al.[281] found that Acorus EOs improved spatial learning and memory in rats, while Ogeturk et al.[282] reported that *C. limon* EO enhanced memory and attention in rats.

EOs also exhibit effects on sedation and hypnotic properties. *L. angustifolia*, *Valeriana officinalis*, and *Rosa damascena* EOs have been noted for their sedative effects.[283] *L. angustifolia* EO significantly reduced locomotor activity and sleep latency in mice,[284] while *Styrax benzoin* EO was found to have a wake-promoting effect by shortening sleep duration.[285] However, Cheaha et al.[286] and Komori et al.[287] noted that the effects of EOs on sleep can vary, with valerian and *Rosa* spp. EOs prolonging sleep duration, whereas *C. limon* EO had the opposite effect.

Dementia, particularly Alzheimers disease (AD), is marked by cognitive impairments such as memory loss and judgment difficulties. Various EOs have shown potential in alleviating AD symptoms by targeting factors like amyloid-beta toxicity and acetylcholine reduction. For instance, Watson et al.[288] and Postu et al.[289] found that *C. limon* EO and *Pinus halepensis* EO improved memory and reduced physical aggression in AD patients. *S. rosmarinus* EO has also been shown to inhibit acetylcholinesterase, enhancing memory in AD models. EOs like *C. bergamia* and *Pistacia chinensis* demonstrate antioxidant and anti-inflammatory effects beneficial for AD treatment.[290,291]

In the realm of anxiety, characterized by excessive worry, EOs have shown promise. *L. angustifolia* EO, in particular, has been studied for its anxiolytic properties, with Zamanifar et al.[292] and López et al.[49] highlighting its effectiveness in reducing anxiety among different groups. Other EOs, such as *P. graveolens* and *propolis*, have also demonstrated anxiolytic effects through various mechanisms, including modulation of serotonin and GABA receptors.

Depression, a major psychological condition, has seen encouraging results from EOs as alternative treatments. Research by Shen[293] and Conrad & Adams[294] revealed that *S. rosmarinus* and *C. citratus* EOs significantly reduced depressive symptoms, while *L. angustifolia* EO alleviated depressive behavior in mice through increased expression of neurotransmitters in the brain. Other EOs, including *R. damascena* – *L. angustifolia* and geranium, have also shown antidepressant effects.[295] Regarding pain management, EOs like *L. angustifolia*, *C. bergamia*, and bornyl alcohol have proven effective. Silva et al.[296] demonstrated that *L. angustifolia* EO alleviated pain similarly to conventional analgesics, while *C. bergamia* EO and bornyl alcohol EO reduced pain in models of formalin-induced and acetic acid-induced pain, respectively.[297,298]

In epilepsy management, *Mentha* × *piperita* EO and its components such as menthol and limonene have shown potential in controlling seizures. Shimada & Yamagata[298] highlighted that *Mentha* × *piperita* EO reduced seizure frequency and intensity. Other EOs, like borneol, have also been effective in protecting neurons and reducing oxidative stress in epilepsy models.[299] However, caution is warranted as some EOs, such as camphor and eucalyptus, may potentially exacerbate epileptic symptoms.[300]

Other Activities

Application of Essential Oils in Food Products

EOs have garnered significant attention in health, cosmetics, crop protection, and the food industry, primarily due to their potent antimicrobial, antioxidant, and antifungal properties. Their natural, safe, eco-friendly, cost-effective, renewable, and biodegradable characteristics make them attractive alternatives for food preservation.[301] EOs have demonstrated remarkable antimicrobial properties, making them effective in extending the shelf life and enhancing the safety of various food products. *Cuminum cyminum* EO nano-emulsions combined with chitosan have been shown to reduce bacterial populations such as *S. typhimurium*, *E. coli*, and *Listeria monocytogenes* in refrigerated beef loins, while also boosting antioxidant activity.[302,303] Similarly, *S. aromaticum* EOs applied to cold-stored prawn shrimp in combination with deacetylated chitosan reduce aerobic bacteria proliferation, minimize color changes, and prevent melanosis.[303] *Trachyspermum ammi* EOs, when paired with chitin nanofibers and carboxymethyl cellulose, are effective against molds, yeast, and bacterial pathogens like *S. aureus* and *Pseudomonas* spp., thereby preserving the sensory characteristics of cold-stored raw beef.[303] *Allium sativum* EOs, used with whey protein and chitosan in vacuum-packed sausages and cheese slices, inhibit spoilage bacteria and reduce fat oxidation.[302] Additionally, nano-emulsions of resveratrol and *O. vulgare* EOs in pectin-edible coatings prevent microbial growth in fresh pork, extending its shelf life and enhancing sensory attributes.[304]

These examples illustrate the potential of EOs, particularly when used in combination with various biopolymers, to act as natural preservatives, offering a safer alternative to synthetic additives in food preservation. Cerrón-Mercado et al.[305] investigated the chemical composition and bioactivities of *Tagetes elliptica* EO, identifying 27 compounds, with cis-tagetenone, trans-tagetenone, dihydrotagetone, and trans-tagetone as the primary constituents. The study demonstrated that *T. elliptica* EO possesses substantial antioxidant and antibacterial properties, surpassing standard synthetic antioxidants, and highlighting its potential as a natural food preservative. While these findings are promising, further research is needed to isolate and explore the specific active compounds responsible for these effects, ensuring the EO efficacy and safety in food applications.

Encapsulation technologies have emerged as a vital method for enhancing the stability and controlled release of EOs in food systems. However, challenges remain, particularly in material selection, retention of biological activity, and scalability. Kong et al.[306] addressed these issues by developing anti-*S. aureus* inclusion complexes using Hinoki EO (HEO) with β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD). This approach achieved a high recovery yield and significant antibacterial activity, though further research is necessary to better understand the release characteristics of HEO under varying environmental conditions. Similarly, Prasad et al.[307] demonstrated the enhanced antifungal, antiaflatoxigenic, and antioxidant activities of encapsulated *C. khasiana* × *C. pendulus* EO (CKP-25-EO) in a chitosan nanoemulsion. The encapsulated EO effectively inhibited lipid peroxidation and aflatoxin B1 secretion in stored *Syzygium cumini* seeds, without compromising sensory qualities. This study emphasizes the potential of EO encapsulation as a strategy for maintaining the quality and safety of food products, particularly in long-term storage.

The search for sustainable alternatives to conventional plastic packaging has led to innovative solutions such as k-carrageenan films infused with EOs. Santos et al.[308] produced such

films using *C. winterianus* EO, which exhibited significant antioxidant and antibacterial properties. The films effectively reduced *L. monocytogenes* biofilms and inhibited quorum sensing, offering a transparent and slightly hydrophobic alternative to plastic packaging. These findings contribute to the growing body of research advocating for environmentally friendly packaging options in the food industry. De Bruno et al.[309] explored the application of natural antioxidants and EOs in edible coatings, specifically evaluating their impact on the shelf life of strawberries. The study found that coatings enriched with *C. bergamia* pomace extract and EO effectively preserved the quality of strawberries for up to 14 days, maintaining high levels of ascorbic acid and consumer acceptability. This research highlights the role of natural antioxidants and EOs in extending the shelf life and safety of fresh produce, aligning with circular economy principles and sustainability goals.

Traditional food preservation techniques, such as chilling, freezing, drying, salting, smoking, and fermentation, have been long-standing methods in food processing.[310] However, as consumer demand for low-salt foods increases, methods like fermentation, brining, and salting have come under increased scrutiny.[311] In response to health concerns associated with chemical preservatives such as nitrate salts, sulfites, and chlorides-commonly used in the meat industry but linked to carcinogenic effects-there is growing interest in replacing these preservatives with natural alternatives.

Lucera et al.[312] reviewed various natural preservatives, including lactoferrin, lysozyme, bacteriocins, chitosan, organic acids, EOs, and plant extracts, noting the increasing focus on EOs as natural bio-preservatives. While much of the research has concentrated on EOs from herbs and spices, there is a burgeoning interest in EOs derived from fruit peels and other plant sources. These studies have demonstrated the effectiveness of EOs in extending the shelf life and inhibiting pathogens across various food products, such as fresh-cut vegetables, lettuce, fruit juices, and ready-to-eat meats. Fernandez-Lopez & Viuda-Martos[6] provided an extensive review of over 2,400 publications on the antimicrobial activity of EOs, highlighting their application across a wide range of food products, including fruits, vegetables, fish, meat, dairy, and baked goods. Additional reviews have explored the use of rosemary extract in meat, the synergistic effects of EOs in seafood preservation, and their application in active packaging.

Recent studies have also focused on the preservation of fruits and vegetables using EOs through methods such as spraying, dipping, coating, and impregnation. He et al.[313] demonstrated that thyme EO nanoemulsion (TEON) effectively inhibited *E. coli* on cherry tomatoes, with enhanced efficacy when combined with ultrasound treatment. Kang & Song[314] similarly found that cinnamon leaf EO nanoemulsion reduced bacterial counts on mustard leaves, with comparable results for kale leaves. These findings indicate that EOs can effectively reduce bacterial populations in fresh-cut vegetables, fruit juices, and meat products, without negatively impacting sensory qualities.

In meat products, research has shown that EOs such as *Pistacia vera*, *M. alternifolia*, *S. aromaticum*, and *T. vulgaris* possess significant antimicrobial properties. *S. aromaticum* EO has exhibited bactericidal effects in ground beef, while *T. vulgaris* EO has proven effective against various pathogens in beef.[315,316] Recent studies suggested that EO nanoemulsions can inhibit pathogens in turkey fillets, rainbow trout, and chicken breast fillets, reinforcing their potential as natural preservatives in diverse food matrices.

Citrus EOs, rich in bioactive compounds like limonene, citral, and linalool, are valuable in the food industry for their antimicrobial, antioxidant, and preservative properties. Extracted from citrus peels, which were once considered waste, *Citrus* EOs enhance flavor, extend shelf life, and improve nutritional quality in food products. Their natural insecticidal effects also protect stored foods from pests. This sustainable approach transforms waste into valuable inputs, contributing to food safety, quality, and eco-friendly practices.[317]

Despite these promising findings, challenges remain in the widespread application of EOs in the food industry. Stability issues, potential impacts on sensory qualities, and the need for more in-depth research into specific active compounds and their mechanisms of action are ongoing concerns. Future research should continue to explore innovative encapsulation techniques, the synergistic effects of EOs with other natural preservatives, and the development of sustainable packaging solutions. The expanding role of EOs in food preservation reflects a broader trend towards natural and environmentally friendly solutions, aligning with consumer demand for safer and more sustainable food products.

Factors Influencing Biological Activities of Essential Oils

The biological efficacy of EOs is governed by a complex set of factors, each critically influencing the chemical profile and therapeutic potency of these compounds. A primary determinant is the plant species and its associated growing conditions.[318] The specific genotype, along with abiotic factors such as soil composition, climate, altitude, and the phenological stage at harvest, can induce substantial variability in the phytochemical composition of the EO.[319,320] These variations in the concentration and presence of bioactive constituents directly impact the EO biological activities, including its antimicrobial, antifungal, and antioxidant properties.[321,322]

Another significant determinant is the extraction methodology utilized to isolate the EOs. Techniques such as steam distillation, cold pressing, and solvent extraction yield oils with diverse chemical compositions and varying levels of purity. The extraction process influences the concentration of specific volatile and non-volatile constituents, thereby affecting the biological activity of the EO. Consequently, the selection of an appropriate extraction method is crucial for optimizing the therapeutic properties of the EO.[323–325]

The stability and preservation of EOs are heavily dependent on their storage conditions. Factors such as light exposure, oxygen levels, and temperature fluctuations can accelerate the degradation of volatile compounds, leading to a reduction in

the o EO bioactivity. EOs are best maintained in opaque, airtight containers at controlled, low temperatures to minimize oxidative degradation and preserve the integrity of active constituents. Improper storage not only diminishes the therapeutic efficacy of the EOs but may also result in the formation of undesirable by-products, such as peroxides, which can have negative biological effects.[317]

The synergistic interactions among the various constituents within an EO significantly contribute to its overall biological efficacy. EOs comprise a complex mixture of bioactive compounds, and their therapeutic effects often emerge from the synergistic interplay between these components.[326] Such synergistic effects can enhance the biological activity, producing a combined effect greater than the sum of the individual actions of the constituents. This phenomenon is particularly evident in the antimicrobial and antioxidant properties of EOs, where multiple compounds work in concert to disrupt microbial integrity, inhibit enzymatic processes, or scavenge free radicals more effectively than isolated compounds.[327,328] Understanding and leveraging these synergistic interactions is essential for maximizing the therapeutic potential of EOs in clinical and pharmacological applications.

Safety Considerations and Regulatory Standards in Essential Oil Use

EOs offer a variety of therapeutic advantages, yet their application requires stringent safety measures and adherence to regulatory standards.[329] While generally considered safe, EOs can induce adverse effects such as skin irritation, sensitization, or systemic toxicity if misused or applied in excessive amounts.[330] Certain individuals might also experience allergic reactions triggered by specific compounds, such as terpenes or phenols, which can lead to hypersensitivity.[331] To control the risk of adverse reactions, it is crucial to account for individual sensitivities and conduct patch tests prior to topical application.

The therapeutic efficacy of EOs is highly dependent on their proper use. Due to their concentrated nature, EOs must be diluted appropriately or used in controlled quantities to prevent adverse effects. Inappropriate usage, such as ingesting EOs meant for topical application or using them in excessive doses, can result in severe health issues, including organ toxicity or hormonal imbalances. It is essential to provide accurate guidance on the correct methods of application, whether for inhalation, topical use, or diffusion, to ensure both safety and therapeutic effectiveness.

Regulatory oversight plays a critical role in the safe use of essential oils. Regulatory bodies such as the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe establish and enforce standards for the production, labeling, and marketing of EOs.[332] These regulations are intended to ensure product quality, purity, and consumer safety. Manufacturers must comply with rigorous testing for contaminants, precise ingredient labeling, and accurate representation of the product's intended uses. Furthermore, any therapeutic claims made about EOs must

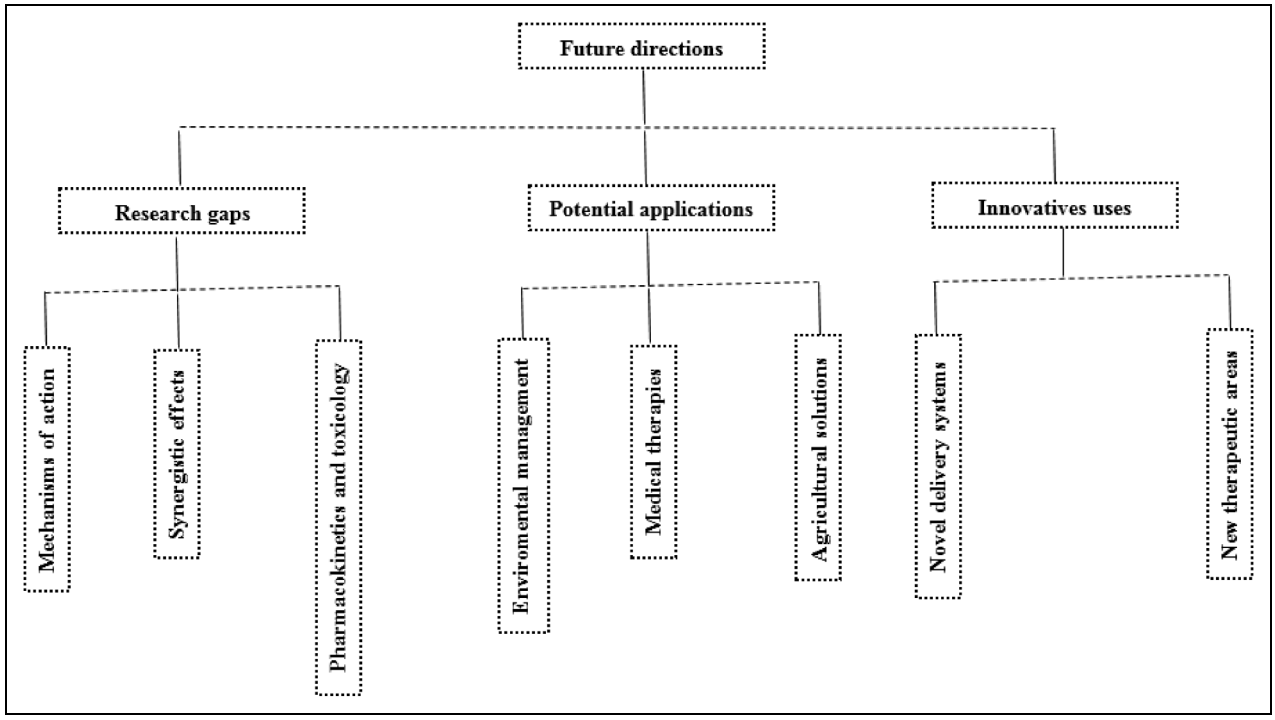

Figure 10. Advancing EOs: Research priorities and emerging opportunities.

be supported by scientific evidence to avoid misleading or deceptive advertising. Adherence to these regulatory requirements is crucial for safeguarding consumer health and maintaining the credibility of EOs efficacy.[329]

Future Directions

There is a critical need to investigate the specific molecular mechanisms and targets through which EOs exert their biological effects (Figure 10). Understanding these mechanisms will provide valuable insights into how EOs interact with biological systems, guiding their effective application. Comprehensive studies on the pharmacokinetics and toxicology of EOs are also needed to clarify their absorption, distribution, metabolism, excretion, safety, and potential toxicity. Additionally, exploring the synergistic effects of EOs in combination with other therapeutic agents could enhance their effectiveness and broaden their range of applications.

EOs hold significant promise in the development of medical therapies, particularly for infectious diseases, including those caused by antibiotic-resistant pathogens. In agriculture, they can be used as natural pesticides and growth enhancers, offering eco-friendly alternatives to synthetic chemicals. Furthermore, EOs have potential applications in environmental management, such as bioremediation, where they can aid in sustainably breaking down pollutants.

Innovative delivery systems, such as advanced formulations, can improve the stability and bioavailability of essential oils, maximizing their therapeutic potential. There is also growing interest in exploring new therapeutic areas, such as neuroprotection and mental health management, where the diverse bioactivities of essential oils may lead to novel treatments and approaches.

Conclusion

EOs are a diverse class of bioactive compounds with numerous applications in medicine, agriculture, and food preservation. This review emphasized the broad spectrum of biological activities exhibited by EOs. These effects are intrinsically linked to the chemical composition of EOs and their complex interactions with biological systems, highlighting their potential as viable alternatives or adjuncts to traditional therapies, particularly in light of the growing issue of antimicrobial resistance.

EOs also contribute significantly to extending the shelf life of food products and improving their quality, as well as demonstrating efficacy in pest management and sustainable agricultural practices. However, despite their promising potential, challenges such as understanding their mechanisms of action, ensuring their stability, and enhancing their bioavailability must be addressed to fully harness their therapeutic benefits. Future research should focus on elucidating the intricate dynamics of EOs in various biological contexts, refining their practical applications, and overcoming the barriers to their widespread adoption.

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