PHARMACIA

Pharmacia 72: 1–12
DOI 10.3897/pharmacia.72.e140059

Review Article

Essential oils – a review of the natural evolution of applications and some future perspectives

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Received 23 October 2024 ♦ **Accepted** 1 December 2024 ♦ **Published** 16 January 2025

Citation: Ivanova S, Gvozdeva Y, Staynova R, Grekova-Kafalova D, Nalbantova V, Benbassat N, Koleva N, Ivanov K (2025) Essential oils – a review of the natural evolution of applications and some future perspectives. Pharmacia 72: 1–12. https://doi.org/10.3897/pharmacia.72.e140059

Abstract

Since ancient times, essential oils (EOs) have been used, thoroughly explored, and regarded as products of great importance for humanity. Currently, EOs represent not only an important part of the contemporary pharmaceutical and cosmetic industry but are also considered as sources for novel drug candidates. The article discusses the applications of EOs in historical terms, the current applications, and the future perspectives. Although there are many studies that involve EOs, the therapeutic potential of EOs is not fully investigated. In the next decades it is highly likely that some compounds, isolated from EOs, could be included in the composition of novel drug candidates with targets in neurology, cardiology, or oncology. Moreover, EOs represent important key points in the development of novel environmentally friendly preservatives and pesticides.

Keywords

biopesticides, essential oils, folk medicine, phytopharmaceuticals, plants, skin recovery

Introduction

Since ancient times, essential oils (EOs) have been used, deeply explored, and regarded as products of great importance for human society. According to some sources, humanity has known and utilized these products since the Neolithic Age (before 4000 A.D.) (Cimino et al. 2021). EOs were mainly used for spiritual rituals, beauty treatments, and medicinal applications, but with time the use of EOs expanded deeply. Nowadays, EOs take an important place in the cosmetic, pharmaceutical, and food industries and in agriculture (Fig. 1).

According to some sources, the term "essential oil" originates from "*Quinta essentia*" (Dhifi et al. 2016). However, this fact is not still clarified.

EOs could be described as non-polar liquids with characteristic odour, obtained from an aromatic raw plant material, either by steam distillation or by mechanical processes from the epicarp of Citrus, or "dry" distillation. EOs could be separated from the aqueous phase by different physical methods (Dhifi et al. 2016).

In general, most of the aromatic plants are well known by humanity and have been used since approximately 5000 A.D. as preservatives, medicines, spices, and flavorings

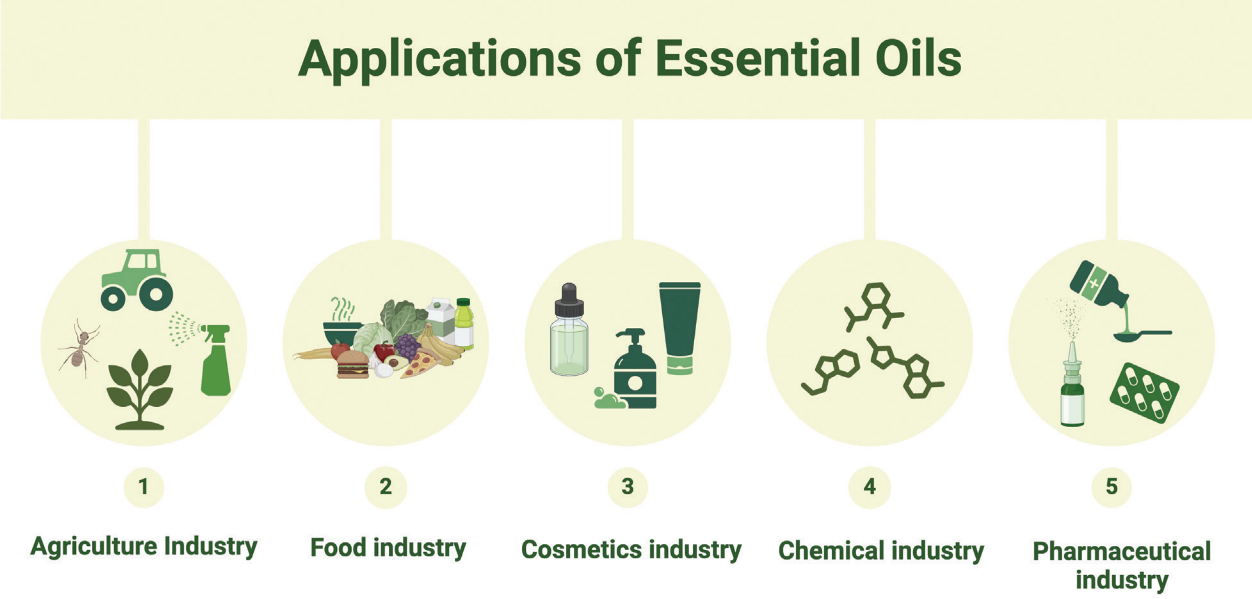

Figure 1. Applications of essential oils in different industries. Created with BioRender.com (accessed on 21 October 2024).

(Christaki et al. 2012). Nowadays, it is considered that the number of aromatic plant species is about 17,000 (Prakash et al. 2015). Some of the most important plants from the point of EOs belong to the families Asteraceae, Lamiaceae or Labiateae, and Apiaceae.

Most parts of the aromatic plants contain EOs: flowers, leaves, roots (vetiver), rhizomes (ginger, sweet flag), fruits (fennel, anise), seeds, including wood and bark (cinnamon, sandalwood, rosewood) (Dhifi et al. 2016). There are great variations in the levels of the EO's content between the different parts of the aromatic plants. In plant organisms, EOs are stored in complex secretary structures, including glandular trichomes, resin ducts, and secretory cavities. It is considered that the main function of the EO for plant organisms is protection against pests, predators, and pollination (Sharifi-Rad et al. 2017).

EOs are complex mixtures that might contain more than 300 different compounds. Normally, these compounds have low molecular weight (below 300) and belong to various chemical classes like alcohols, aldehydes, ethers, ketones, esters, amines, amides, heterocycles, phenols, and mainly terpenes (Dhifi et al. 2016; Sharifi-Rad et al. 2017), which are synthesized in cytoplasm and plastids of plant cells (Prakash et al. 2015).

Most of the EOs are classified as GRAS (Generally Recognized as Safe) or completely safe and, therefore, are the subject of intense research (Ruiz-Navajas et al. 2015).

In the last years, EOs gained great attention in the food industry research due to their antioxidant, antimicrobial, and antifungal properties. Currently, EOs are used and studied as safe natural flavoring agents and preservatives, and it is considered that they have a great potential to extend the shelf life of different foods (Holley and Patel 2005; Prakash et al. 2015). The increase in the shelf life of food products is due to compounds such as vanillin, linalool, thymol, cinnamaldehyde, etc. These compounds are associated with the suppression of the development of microorganisms and food spoilage (Pinto et al. 2023). It is considered that the demand for plant antimicrobials in the food industry would become significantly higher because of the constant consumers' requirements for environmentally friendly products (Pinto et al. 2023). The current trends include the replacement of the synthetic preservatives with natural ones. Likely, this would be an area in which the research of EOs will achieve serious results.

However, one of the most valuable characteristics of the EOs is their therapeutic potential, and for ages EOs have been studied, especially in this direction. The therapeutic potential of EOs could be described as quite diverse: relieving chronic pain, antibacterial, antiviral, and antifungal activity, skin recovery effects, etc. Although the synthesis of novel molecules evolves daily, the interest in EOs is still considerable. Moreover, some EOs and their compounds, such as β-caryophyllene, are studied as novel drug candidates for the management of neurodegenerative diseases like Alzheimer's disease (Machado et al. 2018).

In the next decades it is highly likely that some compounds, isolated from EOs, could be included in the composition of novel drug candidates with targets in neurology, cardiology, or oncology.

The aim of the present manuscript is to summarize data about the natural evolution of the utilization of EOs, the current trends, and their future applications. Data about the limitations of the EOs are also included.

Utilization of essential oils in the past

One of the earliest data about the use of EOs dates from the period of the Neolithic Age (4000 A.D.). In this period the use of the EOs was limited mainly to folk medicine and spiritual rituals. Some of the earliest evidence about the use of EOs in folk medicine was discovered in Mesopotamia (2600 A.D.) and Egypt (2551–2528 A.D.). The ancient Egyptians included the EOs not only in their medical and spiritual practices but also in beauty treatments and in the mummification procedures. It was considered that EOs allowed good preservation of the mummies. This is one of the earliest usages of the EOs as preservatives (Valiakos et al. 2015; Dhifi et al. 2016; Cimino et al. 2021).

EOs represent an important part of traditional Chinese medicine. The Chinese book "Shennong's Herbal," which is considered one of the oldest medical books (2700 A.D.), includes guidelines for the usage of more than 300 medical plants. Currently, China is one of the world's leading producers and consumers of EOs. The EOs are considered a fundamental part of Indian folk medicine, which is based on more than 5000 years of traditions. The book Ayurveda describes the usage of more than 700 medical and religious plants (Valiakos et al. 2015; Cimino et al. 2021). In addition, EOs had a special place in the Ancient Greek culture. Because of their stimulating and calming properties, some EOs were used in many temples. Hippocrates – the father of modern medicine – described the medicinal application of over 300 plants and strongly believed in the benefits of fumigation with EOs for some medical conditions. Another of his beliefs was that the topical application of some medicines containing EOs could produce systemic effects (Cowan 1999; Lardos 2006; Valiakos et al. 2015; Dhifi et al. 2016).

Romans used the EOs for SPA and medical procedures. In the Middle Ages, Avicenna described the distillation method to produce EOs. In 1928, Rene-Maurice Gattefossé introduced for the first time the term "aromatheraphie" and described the healing properties of the lavender EO (Cowan 1999; Lardos 2006; Valiakos et al. 2015; Dhifi et al. 2016). Nowadays, EOs are already established as essential products for the pharmaceutical and cosmetics industries. Currently it is believed that some EOs could be used as environmentally friendly alternatives to some pesticides and environmentally friendly preservatives.

Biological activities of essential oils

Antibacterial activity of EOs and future directions

One of the most urgent health concerns nowadays is antimicrobial resistance (AMR). Since the mid-1950s, it has become a common practice in agriculture to include antibiotics in animal feedstuff to increase animal flesh production and to reduce the economic losses. This practice and the high levels of antibiotic prescriptions contributed to the extensive spread of the antibiotic resistance all over the world. Hospital, industrial, and domestic wastes are considered as other important factors for the widespread of this concern (Dimitrova et al. 2014). Other contributing factors are the mutations of the microorganisms and their ability to pass on to other hosts in different ways (Fournomiti et al. 2015).

According to the World Health Organization (WHO), it was estimated that AMR contributed to the death of almost 5 million people on a global level in 2019. It was predicted that this trend would get more serious in the next years (Breijyeh and Karaman 2023) (WHO).

Although in the last decade some new antibiotics and combinations were introduced, including eftolozane/tazobactam, meropenem/vaborbactam, ceftazidime/avibactam, imipenem/cilistatin/relebactam, cefiderocol, plazomicin, eravacycline, and omadacycline, the necessity for the discovery of novel antibacterial agents is still urgent (Matlock et al. 2021).

Many researchers consider that EOs could be successfully used as antibacterial agents for many different applications. Moreover, it was established that the synergy between EO compounds and antibiotics could be a new direction for the production of novel antibacterial agents (Langeveld et al. 2014).

Numerous studies investigated the mechanism of action of EOs and their main compounds as antibacterial agents. For example, it was established that *Origanum vulgare* L. EO is associated with reduction in lipase and coagulase activity and enzyme inhibition in bacteria (Carneiro De Barros et al. 2009).

The antibacterial activity of the phenolic monoterpenoid carvacrol is expressed in the membrane disruption of the bacterial microorganisms, inhibition of ATPase activity, membrane destabilization, leakage of cell ions, fluidization of membrane lipids, and reduction of proton motive force (Langeveld et al. 2014). Normally this compound is present in the component composition of the EOs isolated from *Origanum vulgare* L., *Thymus vulgaris* L., *Lepidium flavum*, *Citrus aurantium bergamia*, and numerous other plants. Clinical studies in healthy subjects confirm the safety of the compound (Sharifi- Rad et al. 2018).

In 2023, Sepideh Asadi and colleagues reported a successful combination between cefixime and carvacrol against *Escherichia coli* (Asadi et al. 2023). The research team reported that carvacrol is associated not only with antibacterial activity but also with anti-biofilm activity. The study indicated that this combination could become a novel alternative for treatment of *Escherichia coli* infections. (Asadi et al. 2023).

Thymol is another example of a natural monoterpenoid with significant antiseptic properties. The compound has a pleasant aroma and is naturally found in the EOs isolated from *Thymus vulgaris* and other plants. Thymol causes membrane disruption with potential intracellular targets and citrate metabolic pathway disruption as well. Other compounds, isolated from EOs, which also cause membrane disruption in bacteria, are *p*-cymene, cinnamaldehyde, cinnamic acid, eugenol, and gamma-terpinene (Chouhan et al. 2017).

A study published in 2013 reported that carvacrol and eugenol could effectively be used as wash treatments to reduce *Salmonella enteritidis* on shell eggs (Upadhyaya et al. 2013).

Currently, carvacrol, thymol, and eugenol are some of the most studied EO compounds. Numerous studies have associated these compounds with diverse biological activity: antibacterial, antioxidant, analgesic, and anti-inflammatory. In general, these compounds are considered safe for humans, although some studies reported that carvacrol, thymol, and eugenol may cause potential toxicological effects like pulmonary and renal damage, skin irritation, ulcer formation, and others. However, these effects are associated with a prolonged exposure/intake (Fuentes et al. 2021). Other in vivo studies suggest that carvacrol and thymol are not only safe but may also improve gut health (Michiels et al. 2010). However, the safety of these compounds should be better analyzed.

Essential oils isolated from plant species belonging to the Lamiaceae family are some of the best examples of well-expressed antibacterial and antifungal activity. For example, *Origanum vulgare* L., *Thymus vulgaris* L., *Salvia sclarea* L., and *Lavandula angustifolia* Mill exhibit different biological activities, including antibacterial and antifungal. Oregano, thyme, clove, and arborvitae EOs are associated with significant antibacterial activity against *Escherichia coli*, *Yersinia enterocolitica*, *Salmonella typhimurium*, *Listeria monocytogenes*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Bacillus cereus*, *Arthrobacter protophormiae*, and *Pseudomonas fragi*, and anti-fungal activity against *Chaetomium globosum*, *Penicillium chrysogenum*, *Alternaria alternate*, *Cladosporium cladosporoides*, and *Aspergillus fumigatus*. Studies suggested that these EOs might be used as broad-spectrum antimicrobial agents for external use, for decontaminating indoor environments, or for disinfection of contaminated surfaces and equipment (Puškárová et al. 2017). Some researchers suggest that EOs could be included in novel eco-friendly disinfection strategies. Moreover, it was established that some EOs could prevent the formation of *Listeria monocytogenes* and *Salmonella enterica* biofilm on stainless steel surfaces (Puškárová et al. 2017).

Some double-blinded randomized controlled studies evaluated the benefits of the inclusion of EOs in mouthrinse products. These studies were focused on the evaluation of the antimicrobial effects of the EOs against oral pathogens and the levels of reduction of gingivitis. It was reported that this type of disinfection showed important clinical benefits,

Table 1. Data about some studies that investigated the antibacterial activity of different EOs.

Plant material	Study design	Results	References
Echinophora tenuifolia L. subsp. *sibthorpiana*	In vitro study	Antimicrobial activity against *Bacillus cereus* and *Staphylococcus* spp.	(Gokbulut et al. 2013)
	In vitro study	Antimicrobial and antifungal activity against *Fusarium oxysporum*, *Rhizoctonia solani*, and *Alternaria alternata*.	(Sanli and Ok 2023)
Echinophora orientalis Hedge & Lamond	In vitro study	Antimicrobial effect of *E. orientalis* essential oil against *Staphylococcus aureus* in a food model	(Farzanehnia et al. 2017)
Origanum vulgare L.	In vitro study	*K. oxytoca* is a sensitive organism to *Origanum vulgare EO*, with a mean value of MIC of 0.9 μg/mL. MIC for *K. pneumoniae* – 73.5 μg/mL.	(Fournomiti et al. 2015)
	In vitro study	Chemical profile: carvacrol (61.08–83.37%), *p*-cymene (3.02–9.87%), and *γ*-terpinene (4.13–6.34%). Antibacterial activity against *Escherichia coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Bacillus subtilis*. *B. subtilis* was the most sensitive and resistant strain.	(Béjaoui et al. 2013)
	In vitro study	The carvacrol-rich EOs had a potent inhibitory effect against *S. aureus*. The average DIZ value was 29.1 (±0.6) mm, and the MIC and MBC of EOs against *S. aureus* were 0.125 and 0.25 mg/mL, respectively.	(Hao et al. 2021)
	In vitro study	Antimicrobial and bactericidal activity, with MIC ranging between 128 μg/mL and 256 μg/mL and MBC between 256 μg/mL and 512 μg/mL, on the tested *K. pneumoniae*.	(Silva et al. 2023)
Salvia officinalis L.	In vitro study	No antibacterial activity against *E. coli*, *K. oxytoca*, or *K. pneumoniae*.	(Fournomiti et al. 2015)
	In vitro study	Antibacterial activity against the Gram-positive pathogens (*S. aureus* and *M. luteus*) and very good activity against *B. cereus* and *B. subtilis*.	(Ben Khedher et al. 2017)
	In vitro study	Antibacterial activity of EOs extracted from *Rosmarinus officinalis*, *Salvia officinalis*, and *Thymus satureioides*, individually and in combination with conventional antibiotics against *S. typhi* – MIC values ranging from 2 to 85 μg/mL.	(Rafya et al. 2022)
Thymus vulgaris L.	In vitro study	*K. oxytoca* – MIC of 8.1 μg/mL. MIC for *K. pneumoniae*: 9.5 μg/mL.	(Fournomiti et al. 2015)
	Animal	*Thymus vulgaris* EO at 0.4% concentration may negatively affect intestinal integrity and the probiotic strain *E. faecium* AL41.	(Placha et al. 2010)
Zingiber officinale Rosc.	In vitro	Ginger EO was reported to possess excellent antibacterial activity against two foodborne microorganisms: *S. aureus* and *E. coli*. This study reported that the antibacterial mechanism of the EO seems to be associated with damage to the bacterial cell membrane, leakage of macromolecular substances such as bacterial proteins and nucleic acids, and decline of bacterial metabolic activity.	(Wang et al. 2020)

*MIC: minimum inhibitory concentration;
DIZ: the average diameter of the inhibitory zone;
MBC: minimum bactericidal concentration.

including reducing plaque and gingival inflammation and bleeding without altering basic salivary parameters and decreasing the gingival bleeding index (Botelho et al. 2007; Cortelli et al. 2009; Marchetti et al. 2017).

A randomized, double-blind, controlled study reported that toothpaste containing *Lippia sidoides* Cham. EO reduced significantly the levels of salivary *Streptococcus mutans* in children with caries after 5 days of treatment (Lobo et al. 2014). The main compounds found in this EO were caryophyllene (3.59%) and thymol/carvacrol (93.36%) (Lobo et al. 2014).

In 2021, Maria Rejane Cruz de Araújo and colleagues reported data from a randomized, controlled, and blinded clinical trial, conducted with 36 participants with oral candidiasis. The aim of the study was to evaluate the efficacy of cinnamon EO for the treatment of oral candidiasis. The participants were divided into two groups: the *C. zeylanicum* group (0.5 mg/mL) and the nystatin group (100,000 IU/mL). Each group included 18 participants. According to this study, both *C. zeylanicum* EO and nystatin exhibited significant clinical efficacy. *C. zeylanicum* use was associated with a reduction of 61% and 33% of *Candida* spp. (de Araújo et al. 2021).

Most of the clinical studies that investigate EOs are in the field of dentistry. It seems that the evaluation of the antibacterial potential of different EOs will expand in dentistry in the next few years. It is highly likely some novel products based on EOs will be introduced in the dental practice soon.

Although some EOs could become promising antibacterial agents, there are some limitations for internal use because of toxicity and genotoxicity on the mammalian cell level. The potential toxic effects of plant extracts, including EOs, on humans should not be underestimated and better studied.

Anti-inflammatory and antioxidant activity

Inflammation is regarded as a complex protective response against harmful exogenous stimuli or endogenous signaling. However, the persistence of this response in the absence of harmful stimuli has no biological relevance and is associated with severe tissue damage (De Sousa et al. 2023). Several studies investigated the applications of EOs in controlling the inflammatory response. It is considered that the possible anti-inflammatory mechanism of EOs involves regulation of the release of inflammatory cytokines involved in multiple signalling pathways (Zuo et al. 2020). Currently, there are many herbal medicines based on EOs for local topical treatment of different injuries and chronic pain.

EOs could be regarded as rich sources of molecules with different biological activity, including the anti-inflammatory. However, it is important to consider the full chemical profile, not only the sole molecules. Some of the molecules associated with significant anti-inflammatory potential include carvacrol, α-phellandrene, bergapten, β-caryophyllene, and others (De Sousa et al. 2023).

In 2021 a randomized, double-blind, clinical trial reported that treatment with carvacrol for two months significantly improved the cytokine levels in serum and supernatant in asthma patients. Authors suggested that carvacrol could be successfully involved as a novel therapeutic agent for asthma because of its anti-inflammatory and antioxidant activity (Ghorani et al. 2021a).

A placebo-controlled trial investigated the effects of carvacrol on inflammatory mediators and respiratory symptoms in veterans exposed to sulfur mustard. The authors reported that a two-month treatment with carvacrol significantly reduced inflammatory cytokines and chemokines while it increased the anti-inflammatory cytokines and improved respiratory symptoms and forced expiratory volume-one second value in sulfur mustard-exposed patients (Ghorani et al. 2021a).

In recent years, the high efficiency of many EOs with antioxidant activity has been increasingly reported. Additionally, EOs and their constituents have been investigated as alternative additives in aromatherapy and the food industry, highlighting their advantages over synthetic antioxidants that often have negative health effects (Tit and Bungau 2023).

In a study by Mot et al., the chemotyping, antioxidant activity of EO from *Salvia officinalis*, and its effect in aromatherapy conducted in a hospital setting were determined. According to this research, the EO has limited antioxidant capacity, but hospitalized patients may find that inhaling the high borneol content of the oil increases their comfort/pleasure (Mot et al. 2022). A study conducted by S. Kammoun El Euch et al. shows that antioxidant activity may be due to the greater abundance of the two compounds 1,8 cineole (22.22%) and terpinen-4-ol (0.8%) in the essential oil of the Tunisian cultivar of *S. officinalis* and also due to the presence of some minor components, such as α-pinene (1.71%), terpinen-4-ol (0.8%), or linalool (0.28%), considered to be among the most powerful scavengers of free radicals (El Euch et al. 2019). In another study by Khedher et al., it was reported that the antioxidant activity is due to the presence of monoterpenes such as α-pinene and several sesquiterpenes. It is assumed that the contribution of minor and major compounds contributes to this activity, and not just one or a few active molecules (Ben Khedher et al. 2017).

Minchán-Herrera et al. suggested that volatile *Valeriana pilosa* components that act as potential CYP2C9 gene and xanthine oxidase inhibitors may contribute to the observed antioxidant effect (Minchán-Herrera et al. 2022). The pharmacological effects of *Scutellaria edelbergii* EOs were initially documented by Shah et al. The findings point to the presence of methyl abiet-7-en-18-oate, a bioactive compound that may serve as an effective pain reliever, antioxidant, and anti-inflammatory agent (Shah et al. 2022).

Neuroprotection

Globally, neurodegenerative diseases are a cause of disability and mortality. Despite advances in medicine, current treatments for these diseases are still limited and often ineffective (Qneibi et al. 2024). This leads to a growing interest in alternative and complementary therapies. One part of the studies focused on properties of EOs and their potential application in neurodegenerative diseases (Qneibi et al. 2024).

The neuroprotective effects are due to their ability to modulate various signaling pathways and neurotransmitter systems involved in neuronal survival and function. EOs exert their neuroprotective effects by acting as antioxidants (Tongnuanchan and Benjakul 2014). Ayaz M. and colleagues, in their study, proved that EOs modulate the activity of the glutamatergic system, which is critical for learning and memory in the brain (Ayaz et al. 2017). Studies have shown that EOs can also modulate the activity of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Majlessi et al. 2012), which are important for synaptic plasticity and learning and memory processes. By modulating AMPAR activity, EOs can potentially improve cognitive function and memory and provide new therapeutic approaches for neurodegenerative diseases (Qneibi et al. 2024; Lee et al. 2016). Several studies have indicated that lavender and rosemary EOs have neuroprotective properties and can potentially be used to treat several neurological disorders and conditions, such as depression, Alzheimer's disease (AD) (Williams et al. 2011; Ayaz et al. 2017; Majlessi et al. 2012), dementia, Parkinson's disease (PD) (Loizzo et al. 2013), etc.

Limitations of essential oils and encapsulation strategies

The main limitations of the EOs are related to their chemical instability: they are highly volatile and easily oxidized under the influence of light and oxygen and require special storage conditions. EOs evaporate quickly and pass into the body easily and quickly through the skin (Stoleru and Brebu 2021). EOs must be stored appropriately to prevent rancidity.

The shelf life, the quality, and the beneficial properties largely depend on the storage of the EOs. When stored in the correct conditions (including appropriate container, temperature, etc.), the EOs can reach their maximum shelf life with a conservative estimate of at least one year. Properly maintained EOs can even last for ten years or more, depending on the type and storage conditions of the EOs. The quality of the EOs declines gradually with the oxidation process, causing loss of aroma and nourishing benefits. Not all EOs break down at the same rate. For example, the citrus EOs oxidize faster than the others. EOs with earthy or woody aromas, like patchouli and sandalwood, tend to smell even better with time. Thus, the oil's shelf life can vary greatly depending on the quality of the vintage and the storage method (Xu et al. 2017).

The stability of essential oil compounds is of great interest since it is related to quality and delivery in the organism. Despite their diverse biological effects, the practical use of EOs is constrained by their inability to dissolve in water, their tendency to evaporate, and their lack of stability (Xu et al. 2017). EOs are said to possess irritating characteristics within the human organism, and enzymes in the body may deactivate them when identified as foreign substances. These obstacles can be surmounted by employing an effective drug delivery mechanism utilizing lipid-based delivery systems, inclusion complexes with cyclodextrins, microcarriers, or nanocarriers. Encapsulating EOs within a drug delivery system reduces their volatility and toxicity while enhancing their stability, bioavailability, and biological efficacy (Cimino et al. 2021). Encapsulation offers robust protection against moisture, oxygen, light, and unwanted interactions, thus extending the shelf life and potency of essential oils. The outcome of encapsulation is the production of particles in various sizes, ranging from a few micrometers to several millimeters, presented as particles, capsules, droplets, or complexes (Nguyen et al. 2021). Encapsulation techniques involve processes like spray-drying, emulsification, complexation, coacervation, and nanoprecipitation. The choice of encapsulation method primarily relies on various factors, including particle size, physical and chemical characteristics of both the core and the wall materials, intended application of the encapsulated product, mechanisms for controlled release, and cost considerations. Spray drying, dating back to the 1930s, is one of the earliest encapsulation techniques employed to create the first encapsulated flavor compounds. Its widespread adoption in the pharma industry today can be attributed to its cost-effectiveness, availability of diverse encapsulating materials, ability to retain and stabilize volatile compounds, and capacity for large-scale production (Nguyen et al. 2021) (Veiga et al. 2019). The procedure involves five primary steps: first, preparing the oil and the water phase; second, dispersing the emulsion (such as lipids in a concentrated solution of wall material); third, homogenizing the dispersion; fourth, subjecting the feed dispersion to spray drying; and finally, dehydrating the spray-dried particles. Encapsulation commonly employs a variety of wall materials, including carbohydrates such as starches, maltodextrins, sucrose, cyclodextrin, cellulose, and chitosan. Gums like acacia, agar, sodium alginate, and carrageenan are also frequently used, alongside lipids such as waxes, paraffin, stearic acid, tristearin, mono- and diglycerides, oils, and fats. Additionally, proteins like gluten, casein, gelatine, albumin, and peptides are utilized in the encapsulation process (Veiga et al. 2019). Carbohydrates and proteins serve as the primary classes of wall materials for the encapsulation of essential oils via spray drying, with gum arabica emerging as one of the widely utilized options (Jafari et al. 2008). In the emulsification process, proteins undergo a conformational change and align themselves at the oil-water interface, enhancing stability by contributing to repulsive forces that deter emulsion breakdown. Gelatin, a protein derived from collagen, possesses film-forming characteristics and water solubility. Alterations in the pH of the aqueous solution can induce polycationic and polyanionic effects within the gelatine, which are harnessed in coacervation processes (Bakry et al. 2016). Complex coacervation involves the phase separation of two biopolymers with opposite charges, resulting in the formation of coacervates within a narrow pH range. These coacervates consist of a modified layer surrounding oil-in-water emulsion droplets as the core. Through the introduction of a cross-linking agent, the layer transforms into a robust membrane. Microcapsules generated through this technique typically exhibit lower surface oil and higher oil content, along with enhanced stability, compared to those produced via spray-drying (Bakry et al. 2016). Liposomes represent a vesicular system characterized by one or more bilayers composed of phospholipids, enclosing an aqueous core. Initially explored as drug delivery systems in the 1970s, liposomes serve as carriers for both lipophilic and hydrophilic molecules, owing to the presence of both hydrophilic compartments and lipophilic bilayers. Encapsulating EOs within liposomes provides protection from degradation and enhances solubility, making them a versatile tool for drug delivery (Musthaba et al. 2009). Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are the most recent essential oil carriers. Solid lipid nanoparticles emerged in the early 1990s as a solution to the limitations associated with liposomes. They consist of physiological lipids combined with surfactants and water, offering a promising alternative for essential oil delivery with enhanced stability and controlled release properties. Nanostructured lipid carriers constitute a second generation of lipid nanoparticles, introduced in 1999 to address the shortcomings of SLNs, including their restricted loading capacity and the risk of drug expulsion during storage. NLCs offer improved EO encapsulation efficiency and enhanced stability, making them a promising advancement in essential oils delivery technology (Bakry et al. 2016).

Encapsulated EOs are increasingly recognized as a viable alternative to conventional antibiotics for combating multidrug-resistant pathogens, which have emerged due to the indiscriminate use of antibiotics. Research indicates that essential oils loaded in NLCs exhibit antibacterial activity and demonstrate in vivo wound-healing effects. Moreover, the encapsulation of EOs has been explored for the development of anticancer delivery systems, showcasing the versatility and potential therapeutic applications of this approach (Nguyen et al. 2021). Encapsulation of EOs facilitates their incorporation into various dosage forms and enables precise control over their release kinetics, which is necessary for determining their effectiveness.

Essential oils as biopesticides

The volatile compounds, isolated from EOs, seem to present great importance for the agriculture industry due to their applications as biopesticides. Plant protection in modern agriculture requires intensive application of pesticides. Their use increases yields, but this leads to the accumulation of pesticides in agricultural products and the environment, polluting the ecosystem and causing adverse health effects. Currently, the demand for green pesticides/eco-friendly pesticides seems to be higher than ever.

An alternative to the use of chemical products for plant protection is biopesticides, which are part of organic farming and allow limiting negative impacts on the environment and achieving high yields (Lahlali et al. 2022; Ayilara et al. 2023; Gostin and Popescu 2023). Compared to synthetic pesticides, the main advantage of biopesticides is to achieve pest control without polluting the environment (Ntalli et al. 2022). Synthetic chemicals have also traditionally been used to protect bee colonies from pest infestations, but they often have poor selectivity, resulting in high toxicity to bees and humans and the development of resistance by the target beekeeping pests. Current European policy promotes the use of ecological methods to control bee pests, and international research highlights plant secondary metabolites as relevant candidate alternatives (Ntalli et al. 2022). Biopesticides must achieve an effect caused by a naturally occurring substance or its synthetic equivalent that is derived from a plant or animal source (Valiakos et al. 2015).

The biopesticides production is regarded as one of the essential future directions for the use of EOs (Samada and Tambunan 2020).

Nowadays, it is regarded that some volatile compounds isolated from EOs are able to improve not only the crop yield but also soil health, plant growth, and to enhance plant resistance against pests and pathogens (Ventura-Aguilar et al. 2024).

The most studied EOs as biopesticides are thyme, clove, cinnamon, rosemary, eucalyptus, oregano, and lemongrass oils (Gostin and Popescu 2023). However, currently the number of commercial biopesticides based on EOs remains low (Mossa 2016).

Among the plant families with promising essential oils used as repellents are *Cymbopogon* spp., *Ocimum* spp., and *Eucalyptus* spp. Some of the compounds with significant repellent activity are α-pinene, limonene, citronellol, citronellal, camphor, and thymol (Nerio et al. 2010).

Some monoterpenes, such as *α*-pinene, cineole, eugenol, limonene, terpinolene, citronellol, citronellal, camphor, and thymol, are common constituents of a number of EOs described in the literature as presenting mosquito repellent activity (Nerio et al. 2010). Among the sesquiterpenes, *β*-caryophyllene is the most cited as a strong repellent against *A. aegypti* (Gillij et al. 2008). Although the repellent properties of several EOs regularly appear to be related to the presence of monoterpenoids and sesquiterpenes (Jaenson et al. 2006), other authors, Odalo et al. (Odalo et al. 2005), have found that phytol, a linear diterpene alcohol, has a high repellent activity against *Anopheles gambiae*. Furthermore, the oxygenated compounds phenylethyl alcohol, b-citronellol, cinnamyl alcohol, geraniol, and *α*-pinene isolated from the essential oil of *Dianthus caryophyllum* showed a strong repellent activity against ticks (*I. ricinus*) (Tunón et al. 2006).

Thymus vulgaris EOs and their main volatile compounds are some of the most prominent examples of strong repellent activity. The monoterpenes carvacrol, *p*-cymene, linalool, alpha-terpinene, and thymol were reported to provide repellence against the mosquito Culex pipiens pallens (Silva et al. 2021). Although all five compounds effectively repelled mosquitoes, based on a human bioassay, carvacrol and *α*-terpinene were reported to provide a significantly greater repellent activity than a commercial formulation that contained N, N-diethyl-m-methylbenzamide. This compound is one of the oldest and most effective repellents. It is called diethyltoluamide, or DEET. Currently, it is a common active ingredient in many commercial repellents (Samada and Tambunan 2020). It was established that thymol can provide a similar repellent activity to that of N, N-diethyl-m-methylbenzamide. Moreover, the duration of repellence after application for carvacrol, *p*-cymene, linalool, *α*-terpinene, and thymol was similar to or higher than that of DEET.

Recently it was established that at the same concentration, *β*-caryophyllene oxide provides a stronger repellent and irritant effect than DEET. The repellent activity was evaluated against laboratory strains of female *Aedes aegypti* and *Anopheles minimus* (a major malaria parasite vector) (Nararak et al. 2019). These findings represent an important and significant step in future malaria prevention.

The studies published in the last decade indicate that EOs may serve as an eco-friendly and much safer alternative to the classic mosquito repellents (Jaenson et al. 2006).

Essential oils market trends and regulatory requirements in the EU

EOs have traditionally found extensive application in the areas of food and beverage manufacturing, as well as within the field of aromatherapy. Nevertheless, in recent years, the growing use of EOs in various sectors, including pharmaceuticals, cosmetics, and personal care, significantly increased their sales (Bolouri et al. 2022). The European EOs market size was valued at an estimated USD 11.72 billion in 2023 and is expected to expand at a compound annual growth rate of 8.4% from 2024 to 2030. In 2023, the European region contributed to 49.4% of the global EO market's total revenue. The highest share belongs to orange EOs (Market Analyses Report 2024).

The regulatory requirements for EOs vary depending on their intended uses, including raw materials, cosmetic products, food and food supplements, or medicinal products. Raw material EOs are regulated under the consolidated version of the Regulation (EC) No 1272/2008 on the classification, labeling, and packaging of substances and mixtures (CLP Regulation 2008) as well as Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the registration, evaluation, authorization, and restriction of chemicals (REACH) (REACH Regulation 2006), provided that production exceeds 1 tonne annually.

EOs are commonly incorporated into a range of cosmetic products, including moisturizers, lotions, cleansers, creams, hair care products, perfumes, etc. (Bolouri et al. 2022). When EOs are included in cosmetic products, they must comply with specific regulations related to labeling, safety for human health, and the disclosure of allergen information. In this context, the requirements outlined in European cosmetic legislation, such as Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products regulation (EC) No 1223/2009, and Regulation (EU) 2023/1545 (Commission Regulation 2023) regarding labelling of fragrance allergens in cosmetic products, must be followed.

There are many herbal medicinal products on the pharmaceutical market containing EOs successfully used in conditions in which self-medication is applied, such as insomnia, cough, irritable bowel syndrome, urinary tract infections, headache, etc. (Sattayakhom et al. 2023; Elsebai and Albalawi 2022). Given their widespread availability and popularity, EOs used as active pharmaceutical ingredients (APIs) must comply with specific standards for efficacy, quality, and safety. As APIs, EOs can be incorporated into herbal preparations used in both herbal medicinal products and traditional herbal medicinal products for human use (Petina 2023). At the EU level, a simplified registration process for traditional herbal medicinal products was established in 2004 with the adoption of Directive 2004/24/EC, also known as the Herbal Directive (European Parliament 2004). The quality requirements for EOs can be found in monographs of the European Pharmacopoeia and in scientific guidelines provided by the Committee on Herbal Medicinal Products (EMA 2024).

Conclusion

Although the synthesis of novel molecules evolves daily, the demand for natural and safe products seems to be considerable. The utilization of EOs dates to antiquity and has deep traditions in human society. However, the scientific attention to EOs and the number of studies involving EOs seems to be significant. Some of the main directions for expanding EOs' applications seem to be the development of novel green pesticides, repellents, and natural preservatives. The synergy between EOs compounds and the antibiotics could be an important direction for research programs for novel antibacterial agents. Neuroprotection seems to be another important area that could be explored more deeply in the next years, and it is highly likely novel therapeutic agents will be developed based on some natural molecules, isolated from EOs.

Acknowledgements

We would like to express our gratitude to the program "Research, Innovation and Digitalisation for Smart Transformation" 2021–2027, Project BG16RFPR002-1.014-0007 Center for Competence "PERIMED-2" for supporting this article.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.
The authors declared that no experiments on humans or human tissues were performed for the present study.
The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
The authors declared that no experiments on animals were performed for the present study.
The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Funding

This research received no external funding.

Author contributions

Conceptualization: SI; methodology: SI, KI and NB; investigation: NB, VN, RS, KI and NK; data colection: SI, RS, YG, writing – original draft preparation: SI, RS, YG; writing – review and editing: SI, DG-K; visualization: VN; supervision: DG-K and SI.

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Data availability

All of the data that support the findings of this study are available in the main text.

References

Asadi S, Nayeri-Fasaei B, Zahraei-Salehi T, Yahya-Rayat R, Shams N, Sharifi A (2023) Antibacterial and anti-biofilm properties of carvacrol alone and in combination with cefixime against *Escherichia coli*. BMC Microbiology 23: 55. https://doi.org/10.1186/s12866-023-02797-x

Ayaz M, Sadiq A, Junaid M, Ullah F, Subhan F, Ahmed J (2017) Neuroprotective and anti-aging potentials of essential oils from aromatic and medicinal plants. Frontiers in Aging Neuroscience 9: 168. https://doi.org/10.3389/fnagi.2017.00168

Ayilara MS, Adeleke BS, Akinola SA, Fayose CA, Adeyemi UT, Gbadegesin LA, Omole RK, Johnson RM, Uthman QO, Babalola OO (2023) Biopesticides as a promising alternative to synthetic pesticides: A case for microbial pesticides, phytopesticides, and nanobiopesticides. Frontiers in Microbiology 14: 1040901. https://doi.org/10.3389/fmicb.2023.1040901

Bakry AM, Abbas S, Ali B, Majeed H, Abouelwafa MY, Mousa A, Liang L (2016) Microencapsulation of oils: A comprehensive review of benefits, techniques, and applications. Comprehensive Reviews in Food Science and Food Safety 15: 143–182. https://doi.org/10.1111/1541-4337.12179

Béjaoui A, Chaabane H, Jemli M, Boulila A, Boussaid M (2013) Essential oil composition and antibacterial activity of *Origanum vulgare* subsp. *glandulosum* Desf. at different phenological stages. Journal of Medicinal Food 16: 1115–1120. https://doi.org/10.1089/jmf.2013.0079

Ben Khedher MR, Ben Khedher S, Chaieb I, Tounsi S, Hammami M (2017) Chemical composition and biological activities of Salvia officinalis essential oil from Tunisia. EXCLI Journal 16: 1611–2156. https://doi.org/10.17179/EXCLI2016-832

Bolouri P, Salami R, Kouhi S, Kordi M, Asgari Lajayer B, Hadian J, Astatkie T (2022) Applications of essential oils and plant extracts in different industries. Molecules 27: 8999. https://doi.org/10.3390/molecules27248999

Botelho MA, Bezerra Filho JG, Correa LL, Fonseca SGDC, Montenegro D, Gapski R, Brito GAC, Heukelbach J (2007) Effect of a novel essential oil mouthrinse without alcohol on gingivitis: a double-blinded randomized controlled trial. Journal of Applied Oral Science 15: 175–180. https://doi.org/10.1590/S1678-77572007000300005

Breijyeh Z, Karaman R (2023) Design and synthesis of novel antimicrobial agents. Antibiotics 12: 628. https://doi.org/10.3390/antibiotics12030628

Carneiro De Barros J, Lúcia Da Conceição M, Gomes Neto NJ, Vieira Da Costa AC, Siqueira JP, Basílio ID, Leite De Souza E (2009) Interference of *Origanum vulgare* L. essential oil on the growth and some physiological characteristics of Staphylococcus aureus strains isolated from foods. LWT – Food Science and Technology 42: 1139–1143. https://doi.org/10.1016/j.lwt.2009.01.010

CLP Regulation (2008) CLP Regulation. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1272 [22.10.2024]

Chouhan S, Sharma K, Guleria S (2017) Antimicrobial activity of some essential oils – present status and future perspectives. Medicines 4: 58. https://doi.org/10.3390/medicines4030058

Christaki E, Bonos E, Giannenas I, Florou-Paneri P (2012) Aromatic plants as a source of bioactive compounds. Agriculture 2: 228–243. https://doi.org/10.3390/agriculture2030228

Cimino C, Maurel OM, Musumeci T, Bonaccorso A, Drago F, Souto EMB, Pignatello R, Carbone C (2021) Essential oils: pharmaceutical applications and encapsulation strategies into lipid-based delivery systems. Pharmaceutics 13: 327. https://doi.org/10.3390/pharmaceutics13030327

Commission Regulation (2023) Commission Regulation (EU) 2023/1545 of 26 July 2023 amending Regulation (EC) No 1223/2009 of the European Parliament and of the Council as regards labelling of fragrance allergens in cosmetic products (Text with EEA relevance). http://data.europa.eu/eli/reg/2023/1545/oj

Cortelli SC, Cortelli JR, Holzhausen M, Franco GCN, Rebelo RZ, Sonagere AS, Queiroz CDS, Costa FO (2009) Essential oils in one- stage full- mouth disinfection: double- blind, randomized clinical trial of long- term clinical, microbial and salivary effects. Journal of Clinical Periodontology 36: 333–342. https://doi.org/10.1111/j.1600-051X.2009.01376.x

Cowan MM (1999) Plant products as antimicrobial agents. Clinical Microbiology Reviews 12: 564–582. https://doi.org/10.1128/CMR.12.4.564

De Sousa DP, Damasceno ROS, Amorati R, Elshabrawy HA, De Castro RD, Bezerra DP, Nunes VRV, Gomes RC, Lima TC (2023) Essential oils: chemistry and pharmacological activities. Biomolecules 13: 1144. https://doi.org/10.3390/biom13071144

De Araújo MRC, Maciel PP, Castellano LRC, Bonan PRF, Alves D da N, de Medeiros ACD, de Castro RD (2021) Efficacy of essential oil of cinnamon for the treatment of oral candidiasis: A randomized trial. Special Care in Dentistry 41: 349–357. https://doi.org/10.1111/scd.12570

Dhifi W, Bellili S, Jazi S, Bahloul N, Mnif W (2016) Essential oils' chemical characterization and investigation of some biological activities: A critical review. Medicines 3: 25. https://doi.org/10.3390/medicines3040025

Dimitrova M, Petrova G, Tachkov K, Bozhkova MK, Kamusheva M, Mitov K (2014) Economic consequences of the vaccination against hepatitis A in the Bulgarian healthcare setting. Biotechnology & Biotechnological Equipment 28: 366–371. https://doi.org/10.1080/13102818.2014.909654

El Euch SK, Hassine DB, Cazaux S, Bouzouita N, Bouajila J (2019) Salvia officinalis essential oil: Chemical analysis and evaluation of anti-enzymatic and antioxidant bioactivities. South African Journal of Botany 120: 253–260. https://doi.org/10.1016/j.sajb.2018.07.010

Elsebai MF, Albalawi MA (2022) Essential oils and COVID-19. Molecules 27: 7893. https://doi.org/10.3390/molecules27227893

EMA (2024) Herbal medicinal products. https://www.ema.europa.eu/en/human-regulatory-overview/herbal-medicinal-products [accessed on 20.10.2024]

European Parliament (2004) Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. http://data.europa.eu/eli/dir/2004/24/oj [accessed on 20.10.2024]

European Parliament (2009) Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast) (Text with EEA relevance). http://data.europa.eu/eli/reg/2009/1223/oj

Farzanehnia E, Ghajarbeygi P, Mahmoudi R, Mardani K (2017) Phytochemical and antibacterial properties of *Echinophora orientalis* essential oil against *Staphylococcus aureus* in Soup. Journal of Biology and Today's World 06. https://doi.org/10.15412/J.JBTW.01050803

Food Additives & Ingredients (2024) Essential Oils Market Size, Share Analysis, By Type (Citrus (Orange, Lemon, Grapefruit, Lime, and Others), Eucalyptus, Lavender, Rosemary, Tea Tree, Peppermint, and Others), By Application (Food & Beverages, Personal Care & Cosmetics, Spa & Relaxation, Pharmaceuticals & Medicinal Formulations, and Others), By Distribution Channel (Direct Distribution, MLM Distribution, and Retail Distribution), and Regional Forecast, 2024–2032. https://www.fortunebusinessinsights.com/industry-reports/essential-oils-market-101063 [accessed on 20.10. 2024]

Fournomiti M, Kimbaris A, Mantzourani I, Plessas S, Theodoridou I, Papaemmanouil V, Kapsiotis I, Panopoulou M, Stavropoulou E, Bezirtzoglou EE, Alexopoulos A (2015) Antimicrobial activity of essential oils of cultivated oregano (*Origanum vulgare*), sage (*Salvia officinalis*), and thyme (*Thymus vulgaris*) against clinical isolates of *Escherichia coli*, *Klebsiella oxytoca*, and *Klebsiella pneumoniae*. Microbial Ecology in Health & Disease 26. https://doi.org/10.3402/mehd.v26.23289

Fuentes C, Fuentes A, Barat JM, Ruiz MJ (2021) Relevant essential oil components: a minireview on increasing applications and potential toxicity. Toxicology Mechanisms and Methods 31: 559–565. https://doi.org/10.1080/15376516.2021.1940408

Ghorani V, Alavinezhad A, Rajabi O, Boskabady MH (2021a) Carvacrol improves pulmonary function tests, oxidant/antioxidant parameters and cytokine levels in asthmatic patients: A randomized, double-blind, clinical trial. Phytomedicine 85: 153539. https://doi.org/10.1016/j.phymed.2021.153539

Ghorani V, Alavinezhad A, Rajabi O, Mohammadpour AH, Boskabady MH (2021b) Safety and tolerability of carvacrol in healthy subjects: a phase I clinical study. Drug and Chemical Toxicology 44: 177–189. https://doi.org/10.1080/01480545.2018.1538233

Gillij YG, Gleiser RM, Zygadlo JA (2008) Mosquito repellent activity of essential oils of aromatic plants growing in Argentina. Bioresource Technology 99: 2507–2515. https://doi.org/10.1016/j.biortech.2007.04.066

Gokbulut I, Bilenler T, Karabulut I (2013) Determination of chemical composition, total phenolic, antimicrobial, and antioxidant activities of *Echinophora tenuifolia* essential oil. International Journal of Food Properties 16: 1442–1451. https://doi.org/10.1080/10942912.2011.593281

Gostin IN, Popescu IE (2023) Evaluation of the essential oils used in the production of biopesticides: assessing their toxicity toward both arthropod target species and beneficial pollinators. Agriculture 14: 81. https://doi.org/10.3390/agriculture14010081

Hao Y, Li J, Shi L (2021) A carvacrol-rich essential oil extracted from oregano (*Origanum vulgare* "Hot & Spicy") exerts potent antibacterial effects against *Staphylococcus aureus*. Frontiers in Microbiology 12: 741861. https://doi.org/10.3389/fmicb.2021.741861

Holley RA, Patel D (2005) Improvement in shelf-life and safety of perishable foods by plant essential oils and smoke antimicrobials. Food Microbiology 22: 273–292. https://doi.org/10.1016/j.fm.2004.08.006

Jaenson TGT, Garboui S, Pålsson K (2006) Repellency of oils of lemon eucalyptus, Geranium, and lavender and the mosquito repellent MyggA natural to *Ixodes ricinus* (Acari: Ixodidae) in the laboratory and field. Journal of Medical Entomology 43(4): 731–736. https://doi.org/10.1093/jmedent/43.4.731

Jafari SM, Assadpoor E, He Y, Bhandari B (2008) Encapsulation efficiency of food flavours and oils during spray drying. Drying Technology 26: 816–835. https://doi.org/10.1080/07373930802135972

Lahlali R, El Hamss H, Mediouni-Ben Jemâa J, Barka EA (2022) Editorial: The use of plant extracts and essential oils as biopesticides. Frontiers in Agronomy 4: 921965. https://doi.org/10.3389/fagro.2022.921965

Langeveld WT, Veldhuizen EJA, Burt SA (2014) Synergy between essential oil components and antibiotics: a review. Critical Reviews in Microbiology 40: 76–94. https://doi.org/10.3109/1040841X.2013.763219

Lardos A (2006) The botanical materia medica of the Iatrosophikon – A collection of prescriptions from a monastery in Cyprus. Journal of Ethnopharmacology 104: 387–406. https://doi.org/10.1016/j.jep.2005.12.035

Lee K, Goodman L, Fourie C, Schenk S, Leitch B, Montgomery JM (2016) AMPA receptors as therapeutic targets for neurological disorders. Advances in Protein Chemistry and Structural Biology 103: 203–261. https://doi.org/10.1016/bs.apcsb.2015.10.004

Lobo PLD, Fonteles CSR, Marques LARV, Jamacaru FVF, Fonseca SGDC, De Carvalho CBM, De Moraes MEA (2014) The efficacy of three formulations of *Lippia sidoides* Cham. essential oil in the reduction of salivary *Streptococcus mutans* in children with caries:

A randomized, double-blind, controlled study. Phytomedicine 21: 1043–1047. https://doi.org/10.1016/j.phymed.2014.04.021

Loizzo MR, Ben Jemia M, Senatore F, Bruno M, Menichini F, Tundis R (2013) Chemistry and functional properties in prevention of neurodegenerative disorders of five *Cistus* species essential oils. Food and Chemical Toxicology 59: 586–594. https://doi.org/10.1016/j.fct.2013.06.040

Machado KDC, Islam MT, Ali ES, Rouf R, Uddin SJ, Dev S, Shilpi JA, Shill MC, Reza HM, Das AK, Shaw S, Mubarak MS, Mishra SK, Melo-Cavalcante AADC (2018) A systematic review on the neuroprotective perspectives of beta-caryophyllene. Phytotherapy Research 32: 2376–2388. https://doi.org/10.1002/ptr.6199

Mączka W, Twardawska M, Grabarczyk M, Wińska K (2023) Carvacrol – A natural phenolic compound with antimicrobial properties. Antibiotics 12: 824. https://doi.org/10.3390/antibiotics12050824

Majlessi N, Choopani S, Kamalinejad M, Azizi Z (2012) Amelioration of Amyloid β-Induced Cognitive Deficits by *Zataria multiflora Boiss*. essential oil in a rat model of Alzheimer's disease. CNS Neuroscience & Therapeutics 18: 295–301. https://doi.org/10.1111/j.1755-5949.2011.00237.x

Marchetti E, Tecco S, Caterini E, Casalena F, Quinzi V, Mattei A, Marzo G (2017) Alcohol-free essential oils containing mouthrinse efficacy on three-day supragingival plaque regrowth: a randomized crossover clinical trial. Trials 18: 154. https://doi.org/10.1186/s13063-017-1901-z

Market Analyses Report (2024) Europe Essential Oils Market Size, Share & Trends Analysis Report By Product (Orange, Eucalyptus), By Application (Medical, Spa & Relaxation), By Sales Channel, By Country, And Segment Forecasts, 2024–2030. https://www.grandviewresearch.com/industry-analysis/europe-essential-oils-market-report

Matlock A, Garcia JA, Moussavi K, Long B, Liang SY-T (2021) Advances in novel antibiotics to treat multidrug-resistant gram-negative bacterial infections. Internal and Emergency Medicine 16: 2231–2241. https://doi.org/10.1007/s11739-021-02749-1

Michiels J, Missotten J, Van Hoorick A, Ovyn A, Fremaut D, De Smet S, Dierick N (2010) Effects of dose and formulation of carvacrol and thymol on bacteria and some functional traits of the gut in piglets after weaning. Archives of Animal Nutrition 64: 136–154. https://doi.org/10.1080/17450390903499915

Minchán-Herrera P, Ybañez-Julca RO, Quispe-Díaz IM, Venegas-Casanova EA, Jara-Aguilar R, Salas F, Zevallos-Escobar L, Yáñez O, Pino-Rios R, Calderon PB, Benites J (2022) *Valeriana pilosa* roots essential oil: chemical composition, antioxidant activities, and molecular docking studies on enzymes involved in redox biological processes. Antioxidants 11: 1337. https://doi.org/10.3390/antiox11071337

Mossa A-TH (2016) Green pesticides: essential oils as biopesticides in insect-pest management. Journal of Environmental Science and Technology 9: 354–378. https://doi.org/10.3923/jest.2016.354.378

Mot M-D, Gavrilaș S, Lupitu AI, Moisa C, Chambre D, Tit DM, Bogdan MA, Bodescu A-M, Copolovici L, Copolovici DM, Bungau SG (2022) *Salvia officinalis* L. essential oil: characterization, antioxidant properties, and the effects of aromatherapy in adult patients. Antioxidants 11: 808. https://doi.org/10.3390/antiox11050808

Musthaba SM, Baboota S, Ahmed S, Ahuja A, Ali J (2009) Status of novel drug delivery technology for phytotherapeutics. Expert Opinion on Drug Delivery 6: 625–637. https://doi.org/10.1517/17425240902980154

Nararak J, Sathantriphop S, Kongmee M, Mahiou-Leddet V, Ollivier E, Manguin S, Chareonviriyaphap T (2019) Excito-repellent activity of β-caryophyllene oxide against *Aedes aegypti* and *Anopheles minimus*. Acta Tropica 197: 105030. https://doi.org/10.1016/j.actatropica.2019.05.021

Nerio LS, Olivero-Verbel J, Stashenko E (2010) Repellent activity of essential oils: A review. Bioresource Technology 101: 372–378. https://doi.org/10.1016/j.biortech.2009.07.048

Nguyen TTT, Le TVA, Dang NN, Nguyen DC, Nguyen PTN, Tran TT, Nguyen QV, Bach LG, Thuy Nguyen Pham D (2021) Microencapsulation of essential oils by spray-drying and influencing factors. Journal of Food Quality 2021: 1–15. https://doi.org/10.1155/2021/5525879

Ntalli NG, Spochacz M, Adamski Z (2022) The role of botanical treatments used in apiculture to control arthropod pests. Apidologie 53: 27. https://doi.org/10.1007/s13592-022-00924-7

Odalo JO, Omolo MO, Malebo H, Angira J, Njeru PM, Ndiege IO, Hassanali A (2005) Repellency of essential oils of some plants from the Kenyan coast against Anopheles gambiae. Acta Tropica 95: 210–218. https://doi.org/10.1016/j.actatropica.2005.06.007

Petina O (2023) Comparative Analysis of the EU Regulatory Requirements for Essential Oils as Ingredients for the Pharmaceutical, Cosmetic Products and Feed Additives. https://www.dgra.de/media/pdf/studium/masterthesis/master_petina_olga_2023.pdf

Pinto L, Tapia-Rodríguez MR, Baruzzi F, Ayala-Zavala JF (2023) Plant antimicrobials for food quality and safety: recent views and future challenges. Foods 12: 2315. https://doi.org/10.3390/foods12122315

Placha I, Simonova MP, Cobanova K, Laukova A, Faix S (2010) Effect of *Enterococcus faecium* AL41 and *Thymus vulgaris* essential oil on small intestine integrity and antioxidative status of laying hens. Research in Veterinary Science 89: 257–261. https://doi.org/10.1016/j.rvsc.2010.03.006

Prakash B, Kedia A, Mishra PK, Dubey NK (2015) Plant essential oils as food preservatives to control moulds, mycotoxin contamination and oxidative deterioration of agri-food commodities – Potentials and challenges. Food Control 47: 381–391. https://doi.org/10.1016/j.foodcont.2014.07.023

Puškárová A, Bučková M, Kraková L, Pangallo D, Kozics K (2017) The antibacterial and antifungal activity of six essential oils and their cyto/genotoxicity to human HEL 12469 cells. Scientific Reports 7: 8211. https://doi.org/10.1038/s41598-017-08673-9

Qneibi M, Bdir S, Maayeh C, Bdair M, Sandouka D, Basit D, Hallak M (2024) A comprehensive review of essential oils and their pharmacological activities in neurological disorders: exploring neuroprotective potential. Neurochemical Research 49: 258–289. https://doi.org/10.1007/s11064-023-04032-5

Rafya M, Zehhar N, Hafidi A, Benkhalti F (2022) Investigation of the High-order Effect of *Rosmarinus officinalis*, *Salvia officinalis*, and *Thymus satureioides* essential oils with antibiotics on the membrane integrity of *Salmonella typhi*. Journal of Essential Oil-Bearing Plants 25: 939–952. https://doi.org/10.1080/0972060X.2022.2128896

REACH Regulation (2006) Regulation (Ec) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. https://eur-lex.europa.eu/legal-content/en/TXT/HTML/?uri=CELEX:02006R1907-20231201

Ruiz-Navajas Y, Viuda-Martos M, Barber X, Sendra E, Perez-Alvarez JA, Fernández-López J (2015) Effect of chitosan edible films added with *Thymus moroderi* and *Thymus piperella* essential oil on shelf-life of cooked cured ham. Journal of Food Science and Technology 52: 6493–6501. https://doi.org/10.1007/s13197-015-1733-3

Samada LH, Tambunan USF (2020) Biopesticides as promising alternatives to chemical pesticides: A review of their current and future status. OnLine Journal of Biological Sciences 20: 66–76. https://doi.org/10.3844/ojbsci.2020.66.76

Sanli A, Ok FZ (2023) Chemical composition and antimicrobial activity against phytopathogenic fungi of essential oils obtained from *Echinophora tenuifolia* subsp. *sibthorpiana* Grown in wild and cultivated conditions in Turkey. Molecules 28: 585. https://doi.org/10.3390/molecules28020585

Sattayakhom A, Wichit S, Koomhin P (2023) The effects of essential oils on the nervous system: A scoping review. Molecules 28: 3771. https://doi.org/10.3390/molecules28093771

Shah M, Bibi S, Kamal Z, Al-Sabahi JN, Alam T, Ullah O, Murad W, Rehman NU, Al-Harrasi A (2022) Bridging the chemical profile and biomedical effects of *Scutellaria edelbergii* essential oils. Antioxidants 11: 1723. https://doi.org/10.3390/antiox11091723

Sharifi-Rad J, Sureda A, Tenore G, Daglia M, Sharifi-Rad M, Valussi M, Tundis R, Sharifi-Rad M, Loizzo M, Ademiluyi A, Sharifi-Rad R, Ayatollahi S, Iriti M (2017) Biological activities of essential oils: from plant chemoecology to traditional healing systems. Molecules 22: 70. https://doi.org/10.3390/molecules22010070

Silva AS, Tewari D, Sureda A, Suntar I, Belwal T, Battino M, Nabavi SM, Nabavi SF (2021) The evidence of health benefits and food applications of *Thymus vulgaris* L. Trends in Food Science & Technology 117: 218–227. https://doi.org/10.1016/j.tifs.2021.11.010

Silva SL, Araújo FSM, Silva POA, Silva EVA, Bezerra MMSL, Diniz AF, Oliveira DM, Jesus HO, Nascimento Junior BB, Medeiros LADM, Oliveira Filho AA (2023) Evaluation of the antimicrobial effect of the *Origanum vulgare* L. essential oil on strains of *Klebsiella pneumoniae*. Brazilian Journal of Biology 83: e269317. https://doi.org/10.1590/1519-6984.269317

Stoleru E, Brebu M (2021) Stabilization techniques of essential oils by incorporation into biodegradable polymeric materials for food packaging. Molecules 26: 6307. https://doi.org/10.3390/molecules26206307

Tit DM, Bungau SG (2023) Antioxidant activity of essential oils. Antioxidants 12: 383. https://doi.org/10.3390/antiox12020383

Tongnuanchan P, Benjakul S (2014) Essential oils: extraction, bioactivities, and their uses for food preservation. Journal of Food Science 79. https://doi.org/10.1111/1750-3841.12492

Tunón H, Thorsell W, Mikiver A, Malander I (2006) Arthropod repellency, especially tick (*Ixodes ricinus*), exerted by extract from *Artemisia abrotanum* and essential oil from flowers of *Dianthus caryophyllum*. Fitoterapia 77: 257–261. https://doi.org/10.1016/j.fitote.2006.02.009

Upadhyaya I, Upadhyay A, Kollanoor-Johny A, Baskaran SA, Mooyottu S, Darre MJ, Venkitanarayanan K (2013) Rapid inactivation of *Salmonella* Enteritidis on shell eggs by plant-derived antimicrobials. Poultry Science 92: 3228–3235. https://doi.org/10.3382/ps.2013-03126

Valiakos E, Marselos M, Sakellaridis N, Constantinidis Th, Skaltsa H (2015) Ethnopharmacological approach to the herbal medicines of the “Antidotes” in Nikolaos Myrepsos’ Dynameron. Journal of Ethnopharmacology 163: 68–82. https://doi.org/10.1016/j.jep.2015.01.005

Veiga RDSD, Aparecida Da Silva-Buzanello R, Corso MP, Canan C (2019) Essential oils microencapsulated obtained by spray drying: a review. Journal of Essential Oil Research 31: 457–473. https://doi.org/10.1080/10412905.2019.1612788

Ventura-Aguilar RI, Lucas-Bautista JA, Arévalo-Galarza MaDL, Bosquez-Molina E (2024) Volatile organic compounds as a diagnostic tool for detecting microbial contamination in fresh agricultural products: mechanism of action and analytical techniques. Processes 12: 1555. https://doi.org/10.3390/pr12081555

Wang X, Shen Y, Thakur K, Han J, Zhang J-G, Hu F, Wei Z-J (2020) Antibacterial activity and mechanism of Ginger essential oil against *Escherichia coli* and *Staphylococcus aureus*. Molecules 25: 3955. https://doi.org/10.3390/molecules25173955

Williams P, Sorribas A, Howes M-JR (2011) Natural products as a source of Alzheimer’s drug leads. Natural Product Reports 28: 48–77. https://doi.org/10.1039/C0NP00027B

Xu L, Yu X, Li M, Chen J, Wang X (2017) Monitoring oxidative stability and changes in key volatile compounds in edible oils during ambient storage through HS-SPME/GC–MS. International Journal of Food Properties 20: S2926–S2938. https://doi.org/10.1080/10942912.2017.1382510

Zuo X, Gu Y, Wang C, Zhang J, Zhang J, Wang G, Wang F (2020) A systematic review of the anti- inflammatory and immunomodulatory properties of 16 essential oils of herbs. Evidence-Based Complementary and Alternative Medicine 2020: 8878927. https://doi.org/10.1155/2020/8878927