CHAPTER

11

ESSENTIAL OILS: A NATURAL ALTERNATIVE TO COMBAT ANTIBIOTICS RESISTANCE

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INTRODUCTION

Antibiotics are probably the drug most used in human medicine, and over the last few years, abuse in the use of these drugs has created multidrug resistance (MDR), which puts at serious risk the effective treatment of a growing number of infections caused by pathogenic microorganisms.[1] MDR is the result of a number of convergent factors, among which are the inappropriate use of antibiotics caused by suspension of treatment, use of inadequate doses, and genetic improvement of microorganisms, among others.[2]

Currently, bacterial infections represent a serious risk around the world,[3] especially bacterial infections that are resistant to drugs and affect a large number of patients; these diseases are usually more severe compared with the same infections caused by microorganisms (nonresistant) and thus are more difficult to be treated and eventually be cured.[1,2] This is a problem that not only confounded medical specialists, but also many governments because the costs and impact are high. It has been estimated that resistance to antibiotics is responsible for about 50,000 deaths per year only in the United States and Europe[4]; there is no reliable record in other countries, but this issue is estimated to cause large numbers of deaths, especially in developing countries where control over the sale of antibiotics is poor.

This situation requires some effort to help combat such problems. One possible solution is to search for alternative therapies to control these diseases. An alternative is the use of essential oils to achieve control over antibiotic-resistant microorganisms.[5,6]

Essential oils are liquid, volatile, natural, and complex mixtures of low-molecular-weight compounds and are formed by aromatic plants as secondary metabolites, which are naturally synthesized by plants in response to attacks by insects, herbivores, and other organisms.[5] Essential oils are characterized by a strong odor. They are usually extracted by steam or hydrodistillation or solvent extraction.[7,8] This type of oil can be produced by all plant organs (ie, seeds, flowers, leaves, buds, stems, fruits, roots, wood, or bark), and are stored in oil ducts, resin ducts, glands, or trichomes of the plants.[7,8] They are commonly used as flavoring agents in food products, drinks, perfumeries, pharmaceuticals, and cosmetics. The essential oil alone or in combination possesses significant medicinal properties; hence, it may be used for chemotherapy of infectious and noninfectious diseases.[5] The presence of different compounds in the oil makes it possible to use it as an antimicrobial agent that offers a low risk of microbial resistance development.[6]

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In this chapter, the essential oils as a natural alternative to fight MDR pathogens are presented, natural sources of essential oils, predominant chemical composition in these fractions and the mechanisms of action of essential oil are showed. Finally some of the most commonly used essential oils against multidrug-resistant microorganisms such as citrus, rosemary, oregano, basil, and mentha, are presented.

NATURAL SOURCES OF ESSENTIAL OILS AND ITS COMPOSITION

There are around 3000 known essential oils, of which only 300 are commercially important for the pharmaceutical, agronomic, food, sanitary, cosmetic, and perfume industries.[5,8,9] Plants producing essential oils belong to various genera in about 60 families, including Alliaceae, Apiaceae, Asteraceae, Lamiaceae, Myrtaceae, Poaceae, and Rutaceae.[5]

Essential oils are very complex natural mixtures; the concentration of each component can vary.[8] The essential oil components include terpenoids and phenylpropanoids, and other components like aromatic and aliphatic constituents also may be present. Within the terpenes group are found monoterpenes, sesquiterpenes, and oxygenated derivatives, all of which are characterized by low molecular weight. Major components are responsible for the biological properties of essential oils,[8] but sometimes a combination of molecules modifies their activity to significant effect.[5,9]

The antimicrobial and other biological activities of essential oils are directly correlated with the presence of bioactive volatile components. The composition of the essential oil of any particular plant depends on the plant part used, whether it be flowers, green parts (ie, leaves and stems), bark, wood, whole fruits, pericarp, seed, or roots.[7] Terpenoids, discussed in the next section, are the major constituents of essential oils; other important compounds are aromatic and aliphatic constituents.

TERPENES

Terpenoids are naturally occurring hydrocarbons produced by a wide variety of plants. Terpenes are grouped in different types according to their structure and function; they are classified based on five-carbon (isoprene) units. The main terpenes are monoterpenes (C10) and sesquiterpenes (C15), but hemiterpene (C5), diterpenes (C20), triterpenes (C30), and tetraterpenes (C40) are also important, and they represent around 90% of essential oils.[8] More than 55,000 terpene molecules have been discovered to date. The bioactivities of a particular essential oil is based on these molecules most of the time, but sometimes biological activity cannot be attributed to only one compound[5,9] (Fig. 11.1).

AROMATIC COMPOUNDS

Aromatic compounds present in essential oils are usually derived from phenylpropane, and they are in lower concentration than terpenes. Aromatic compounds comprise aldehyde, alcohol, phenols, methoxy derivatives, and methylene dioxy compounds. The syntheses of phenylpropanoic derivatives and terpenes generally are separated in plants but may coexist in some cases.[3]

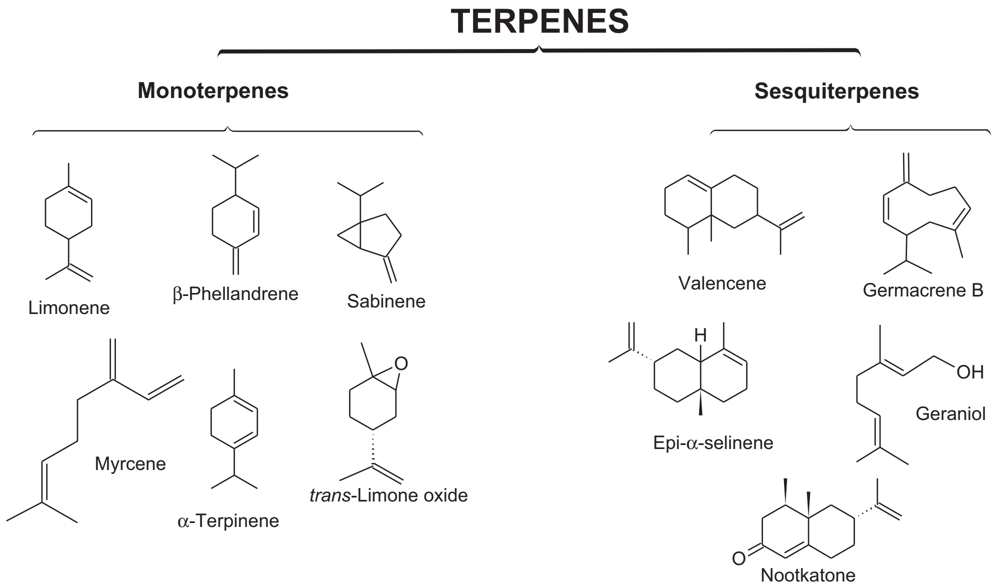

FIGURE 11.1

Examples of some terpenes (monoterpenes and sesquiterpenes) found in essential oils.

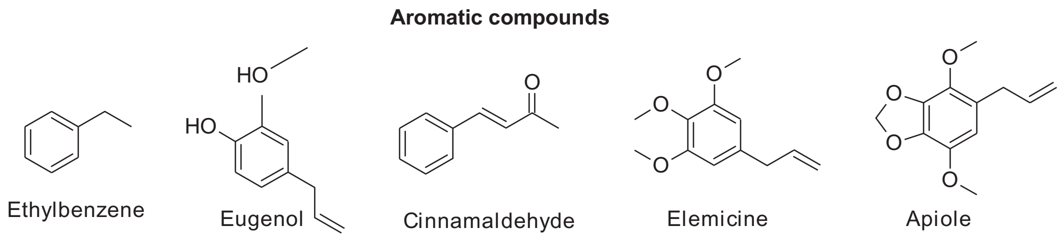

FIGURE 11.2

Examples of some aromatic compounds found in essential oils.

Some examples of aromatic compounds include cinnamaldehyde, cinnamic alcohol, chavicol, eugenol, anethole, elemicine, estragole, methyleugenols, apiole, myristicine, and safrole[8] (Fig. 11.2).

MECHANISM OF ACTION OF ESSENTIAL OILS

The antimicrobial effect of essential oils has been demonstrated with a wide range of microorganisms. Numerous mechanisms of action have been proposed, but none have been completely understood.[10,11] In most of the mechanisms, only the action of chemical compounds present in essential oils is explained, and antibacterial activity involves different mechanisms used to attack pathogenic bacteria.[12]

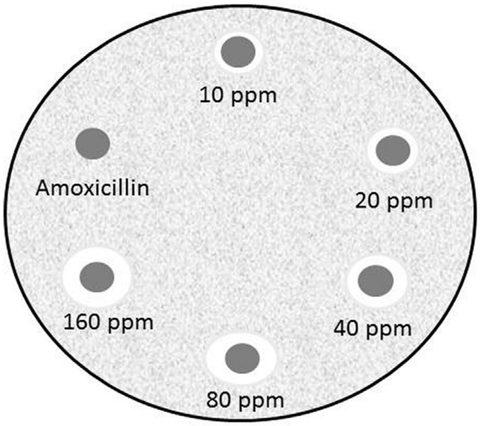

FIGURE 11.3

Schematic effect on the activity of basil essential oils against MDR bacteria.

The mechanism of antimicrobial action of terpenes is associated with their high affinity for lipids because of their hydrophobic nature. Their antibacterial properties are evidently associated with this lipophilic character and by the outer microorganism structures.[13] This allows monoterpenes to penetrate membrane structures inside the cell, which increases membrane fluidity and permeability, changes the topology of membrane proteins, and induce disturbances in the respiration chain.[14,15]

Phenolic compounds present in essential oils disrupt the cell membrane, resulting in the inhibition of cell functional properties and eventually causing leakage of internal cell content.[16] It has been reported that the phenolics thymol and carvacrol also inhibited growth of Gram-negative bacteria by disrupting the outer cell membrane.[17] Other processes associated with the cell membrane include electron transport, ions, protein translocation, phosphorylation, and other enzyme-dependent reactions. The disrupted permeability of the cytoplasmic membrane can result in cell death.[2] Interaction of essential oils with microbial cell membranes results in growth inhibition of some Gram-positive and Gram-negative bacteria.[7] It has been reported that Gram-positive bacteria appear to be more susceptible to the antibacterial properties of essential oil compounds than Gram-negative bacteria. This is expected, as Gram-negative bacteria have an outer layer surrounding their cell wall, limiting the access of hydrophobic compounds (Fig. 11.3).

DIFFERENT ESSENTIAL OILS USED AGAINST MDR

CITRUS ESSENTIAL OIL

The genus *Citrus* has different species, including orange (*Citrus sinensis*), mandarin (*Citrus reticulata*), lime (*Citrus aurantifolia*), grapefruit (*Citrus paradisi*) among others. These fruits have different chemical components, and within the fruit peel, essential oils can be found.

Citrus essential oils contain an extremely wide variety of compounds.[18] Approximately 400 compounds have been identified in citrus oils.[7] The analysis, extraction, and content of the components depend on the seasonal variation, ripeness, and geographical region, the specific citrus type, and even the separation and extraction methods used.[7,10] Around 85−99% are volatile compounds; the remaining ones are nonvolatile compounds.[18] The major components are monoterpenes (representing around 97% of the citrus essential oil), and 1.8−2% represent alcohols, aldehydes, and esters.[10]

Essential oils derived from the citrus industry have been screened for their antimicrobial properties against diverse foodborne pathogens such as *Escherichia coli* O157:H7, *Salmonella* Typhimurium, *Staphylococcus aureus*, *Listeria monocytogenes*, *Campylobacter* sp., and others. Several have shown to possess antimicrobial activity.[19,20] The major component of citrus oils is limonene (ranging from 32% to 98% depending on the citrus type), with sweet orange containing 69−98% and lemon containing 45−76%.[10] The chemical, physical, and biological properties of limonene have an important impact on the biological properties of the major components of essential oil.[18]

Limonene has shown to be effective against *S. aureus*, *L. monocytogenes*, *Salmonella enterica*, and *Saccharomyces bayanus*, as well as other microorganisms.[7] It was found to be effective against strains of *E. coli*,[10] *Klebsiella pneumoniae*,[21] *Mycoplasma pneumoniae*,[7] and *Staphylococcus epidermidis*.[21] This component can exert potent, broad-spectrum antimicrobial activity.[7] However, limonene is also susceptible to oxidative degradation, which causes a reduction of activity.[7] Linalool exhibits antimicrobial properties against *Shigella sonnei*, *Salmonella flexneri*,[10] *Staphylococcus epidermidis*,[21] *Arcobacter butzleri*,[22] *Campylobacter jejuni*, *E. coli* O157, and *L. monocytogenes*.[23] Citrulline exerts potent, broad-spectrum antimicrobial activity.[7] α-Terpineol has an important effect on *E. coli*, *Salmonella* Typhimurium, *L. monocytogenes*, and *S. aureus*.[24] Citral was reported with power against *A. butzleri*,[22] *C. jejuni*, *E. coli*, *Salmonella* Typhimurium, *L. monocytogenes*, and *S. aureus*.[23] Another important terpene that can be used in antimicrobial therapy is (4R)-(+)-carvone (monoterpene), which was effective against *L. monocytogenes* and showed activity against *Enterococcus faecium* and *E. coli*.[13]

In addition to the use of citrus essential oil components against pathogenic microorganisms, complete essential oils have been tested. Pathan et al.[25] indicated that *Citrus aurantifolia* showed high activity against *K. pneumoniae* and *S. aureus*. Mandarin essential oil has been reported to have antimicrobial effects against *E. coli*, *K. pneumoniae*, and *Salmonella enterica*.[26] Lemon oil was reported to have properties against *Lactobacillus plantarum* and *L. monocytogenes*, which showed inhibition percentages around 99.9%[26,27] and against *Candida albicans*, *Bacillus subtilis*, *E. coli*, *K. pneumoniae*, and *Salmonella enterica*.[26,28,29] In addition, some studies demonstrated inhibition and reduction of the numbers of foodborne pathogens such as *Salmonella* spp., *E. coli* O157:H7, and *L. monocytogenes* by citrus essential oils.[26] It has been observed that the activity of the essential oil used also depends on its concentration. Recently, it has been found that in lemon peel, the maximum concentration of volatile compounds occurs when the fruit is at the intermediate maturation stage.[18]

ROSEMARY ESSENTIAL OIL

Rosemary (*Rosmarinus officinalis* L.) is a herb that belongs to the mint family. It is an evergreen aromatic shrub[30] grown in many parts of the world, and it has been cultivated for a long time for use in folk medicine, cosmetics, and phytocosmetics.[31] Recent studies on rosemary essential oil have focused on its antimicrobial activity against several pathogenic microorganisms.[1]

Chemical analysis of rosemary essential oil revealed the presence of terpenes and terpenoids. The major constituents of this essential oil include α-pinene, myrcene, 1,8-cineole, camphor, camphene, α-terpineol, and borneol.[1,31] There have been some reports on the antimicrobial activity of this essential oil. For instance, Jiang et al.[30] indicated that rosemary essential oil was very active against *Staphylococcus epidermidis*, *S. aureus*, *B. subtilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, and *E. coli*. The minimum inhibitory concentration (MIC) was found to range from 0.03% (v/v) to 1.0 (v/v) for all the test microorganisms. Other investigations reported that rosemary essential oil had a strong antimicrobial activity against *S. aureus*,[32] and detailed the antimicrobial efficiency of the main rosemary essential oil components. For example, among α-pinene, myrcene, 1,8-cineole, camphor, and borneol compounds, only α-pinene was able to inhibit *S. aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *E. coli* ATCC 35218, and *K. pneumoniae*, with the MIC ranging from 0.8 to 8 μL/mL.[31] It also has been discussed that the antimicrobial activities of rosemary essential oil were superior to α-pinene and 1,8-cineole.[30] It is difficult to attribute the antimicrobial effect of an essential oil to one active compound or a few, because extracts are a mixture of different chemical compounds with diverse biological properties.

At present, there is a growing interest in enhancing the antibiotic activity of bioactive plant products, and numerous efforts have been made to increase its effectiveness against microorganisms. Studies about the effect of rosemary essential oil with tetracycline, gentamycin, sulfazotrim, chloramphenicol, cefepime, and tetracylcline have showed a synergistic effect against *S. aureus* and *E. coli*.[1]

OREGANO OIL

The *Origanum* (Lamiaceae) genus is an annual, perennial and shrubby herb that is predominantly distributed around the Mediterranean, Euro-Siberian, and Iran-Siberian regions.[33] Its use in traditional medicine has given rise to numerous studies that confirmed the benefits of oregano for human health, and its oil has been used to treat respiratory and gastrointestinal disorders, as well as an oral antiseptic and in dermatological applications.[34] *Origanum* has around 39 species, of which *Origanum vulgare* L. is the most studied. Its essential oil has been reported to have several biological properties, such as antioxidant, antimicrobial, and antimutagenic.[35]

Origanum vulgare essential oil is composed of different compounds. Most of them are thymol and carvacrol, but other compounds include ρ-cymene, thymoquinone, and γ-terpinene.[35,36] It has been reported that oregano essential oils have a powerful antimicrobial action against bacteria (Gram-positive and Gram-negative), yeast and fungi.[34] Oregano (*Origanum vulgare* subsp. vulgare) essential oil showed activity against *Sarcina lutea*, *S. aureus*, *C. albicans*, *E. faecalis*, and *Bacillus cereus*, resulting in inhibition halos of 34.67, 26.67, 24.67, 22.33, and 20.33 mm, respectively.[35] Lv et al.[37] reported that oregano essential oil has high activity against *S. aureus* (27.4 ± 0.5 mm), *B. subtilis* (27.4 ± 0.7 mm), *E. coli* (18.2 ± 0.8 mm), and *Saccharomyces cerevisiae* (27.2 ± 0.6 mm). In the same study, the MIC was determined for all tested microorganisms, they found that MIC was the lowest with 0.625 μL/mL, in all bacterial strains.[37] Hammer et al.[29] reported similar results, MIC values of oregano oil against *E. coli* and *S. aureus* were from 0.5 to 1.2 μL/mL. Actually, oregano has been used against pathogenic bacterial strains such as *E. coli* O157:H7, and when it was in direct contact with *Salmonella* Typhimurium DT104, this microorganism was inactivated.[38]

Oregano essential oil has been tested for use as a cleaning agent in the treatment of antibiotic-resistant bacteria on organic leafy greens; an investigation demonstrated that with a treatment of 0.5% oregano oil, the greatest microorganism population reductions (up to 4.9-log) was seen on all leafy greens, and even biological activity increased over time in storage.[39] In this context, it was investigated the disinfection efficacy of oregano oil on *Salmonella* Typhimurium inoculated into iceberg lettuce. Washing lettuce leaves with oregano oil led to a significant reduction in numbers of *Salmonella* Typhimurium as compared with chlorinated water. The best result occurred at a 75-ppm concentration, with a reduction of 1−92 log CFU/g. The authors stated that oregano oil could be used as a natural alternative to chlorine without affecting sensory properties.[34]

Some studies have reported the effect of oregano oil in combination with other essential oils like marjoram, where the reduction in the maximum specific microbial growth rate achieved was approximately threefold higher than that with the oregano oil alone.[36] Investigations have further examined the effect of oregano essential oil on lag phase duration; when *E. coli* was exposed to oregano in combination with basil, the results indicated that the time of the lag phase increased by 7.44 h with respect to the increase with oregano alone.[36]

BASIL ESSENTIAL OIL

Common basil (*Ocimum basilicum* L.) belongs to the Lamiaceae family, and it has been considered an important herb traditionally used worldwide. More than 150 species of this genus have been recognized, and basil is the most commercially important of these around the world.[40,41] It has been used as a food ingredient for flavoring, in cosmetics, and in traditional medicine for treating coughs, inflammations, and pains.[41,42] Basil essential oil has been indicated to possess high antioxidant, antimicrobial, antihypertensive, anticancer, and antiinflammatory activities.[40] Different authors have described the antibacterial properties of this essential oil as well.

The chemical composition of *O. basilicum* essential oil differs according to the season. These essential oils have oxygenated monoterpenes (60.7−68.9%), followed by sesquiterpene hydrocarbons (16.0−24.3%) and oxygenated sesquiterpenes (12.0−14.4%).[41] Around 29 compounds representing 98.0−99.7% of the oil composition have been reported by Hussain et al.[41] Linalool was the main constituent of essential oils (56.7−60.6%), followed by epi-α-cadinol (8.6−1.4%), α-bergamotene (7.4−9.2%), γ-cadinene (3.3−5.4%), germacrene D (1.1−3.3%), and camphor (1.1−3.1%). In addition, components like methylchavikol, methylcinnamat, linolen, eugenol, camphor, *cis*-geraniol, 1,8-cineole, α-bergamotene, β-caryophyllene, germacrene D, γ-cadinene, epi-α-cadinol, and viridiflorol have been reported as important components.[41,42]

The essential oil obtained from *O. basilicum* has showed strong antimicrobial activity against a wide number of microorganisms. This strong effect has been demonstrated using *O. basilicum* in different seasons. *S. aureus* and *B. subtilis* were two of the tested microorganisms, and these bacteria showed significant sensitivity in the presence of basil essential oil, with low MIC values for *S. aureus* (0.9−1.5 mg/mL) and *B. subtilis* (0.8−1.4 mg/mL). These findings showed that basil essential oil is a strong antimicrobial agent.[41]

Opalchenova and Obreshkova[42] reported on the antimicrobial activity of basil against drug-resistant bacterial strains from *Staphylococcus*, *Pseudomonas*, and *Enterococcus* genera. Other investigations reported that *L. monocytogenes* and *B. cereus* were sensitive to basil essential oil. The viability of these two bacteria treated with 0.1% basil essential oil was 0.16% and 0.08%, respectively. In the same study, *Vibrio* spp. and *Aerobacter hydrophila* showed high sensitivity too; with 0.01% basil essential oil concentration, the viability varied from 0.014% to 3.64%.[43]

A number of studies have discovered the effect of basil essential oil on drugs such as amoxicillin and flumequine. It has demonstrated antimicrobial activity comparable to these drugs, presenting a strong effect against Gram-positive and Gram-negative bacteria. This effect increased when the essential oil is produced in the autumn and winter, when linalool content is in higher concentrations.[41] Also, essential oil from *O. basilicum* L. has been shown to possess an inhibitory effect on fungi like *Aspergillus ochraceus*.[42]

MENTHA ESSENTIAL OIL

Mentha is a well-known genus (in the Lamiaceae family) that has medicinal and aromatic value. The *Mentha* genus includes 25−30 species that are widely grown in temperate areas around the world, particularly in Europe, North America, North Africa, Asia Minor, Northern parts of Iran and near East (Syria, Ethiopia), but nowadays, it is cultivated throughout all regions of the world.[44−46] *Mentha piperita* is a perennial plant that is 50−90 cm high, normally quadrangular, and a prototypical member of the mint family.[44]

Mentha spp. is a plant that exhibits important biological activities. For that reason, it has been used through the years as a remedy for respiratory diseases like bronchitis, sinusitis, tuberculosis, and the common cold. The plant acts as an excellent expectorant.[46] These bioactivities are due to the essential oil extracted from different parts of the plant, like aerial parts of the flowering plant, dried leaves, and fresh flowering.[44]

The composition of the Mentha essential oil directly affects the effectiveness of its antimicrobial activity,[45] which have displayed differences in its constituents depending on the growing area. The chemistry of mentha oil is very complex and highly variable. Analysis by gas chromatography−mass spectrometry (GC-MS) revealed that the prominent components are menthol, isomenthone, limonene, iso-menthanol, menthol acetate, carvone, β-pinene, α-pinene, 1,8-cineole, α-terpineol, isopulegol, pulegone, piperiton, piperitone oxide, and β-phellandrene.[45−47] Both the in vivo and in vitro antimicrobial power of these components on *Streptococcus mutans* and *Streptococcus pyogenes* have been evaluated, showing outstanding activity.[45] In addition, the oil exhibited bactericidal effects against *S. aureus*, *Staphylococcus epidermidis*, *B. cereus*, and *E. coli* 4.7. The MIC of the *M. piperita* essential oil was determined against various bacterial strains and varied from 1.13 to 2.25 mg/mL; the MIC of Gram-positive bacteria (*B. subtilis* and *S. aureus*) was lower than that of Gram-negative bacteria (*E. coli*, *P. aeruginosa*, and *Pseudomonas fluorescens*).[45]

The antimicrobial activity of Mentha oil against different microorganisms in a disk diffusion assay showed significant effects against *S. aureus*, *Staphylococcus epidermidis*, *B. cereus*, *C. albicans*, and *Vibrio cholerae*, with an inhibition zone in a range of 13−21 mm.[46] On the other hand, Singh et al.[44] reported that *S. aureus* and *Staphylococcus pyogenes* were sensitive to this essential oil, with an inhibition zone of 17.2 and 13.1 mm, respectively, which is greater than that of gentamycin.

CONCLUSIONS

The antimicrobial activity of essential oils are of great interest in the food, cosmetic, and pharmaceutical industries, since their possible use as natural additives emerged from the tendency to replace antibiotics due to the high resistance shown by a number of different pathogens. Although essential oils appear to be the answer to the problem of antibiotic resistance, additional investigations need to be performed to confirm the safety of each essential oil and evaluate the appropriate concentration of each one for human consumption.

One of the most important points to be consider for the use of essential oils in fighting pathogenic bacteria resistant to antibiotics is to perform studies to achieve greater yields of oils. Although essential oils are widely distributed by nature, they appear only in low concentrations. Future studies should focus on extraction methodologies that are technically and economically viable in order to improve recovery yields, and also ensure that the methodologies do not harm the bioactive components of the essential oils. Furthermore, it is important to make efforts to evaluate the synergistic effect of the combination of essential oils and pH values to enhance antimicrobial activity and to study the effect of combining water activity and essential oils in order to develop formulations that allow the essential oils to be used to replace specific antibiotics. Studies in vivo and clinical trials are needed to evaluate the potential of these essential oils as antibiotic substitutes or as interveners in this type of treatment.

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