

Antibacterial And Synergistic Effect Of Medicinal Herbs As Potential Activity Against Antibiotic Resistant-Bacteria : A New Strategy For Control Or Reducing Antibiotic Resistant Bacteria

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Abstract

Drug resistance in bacteria became a great global problem. This review suggested to use medicinal herbs to increase susceptibility to antibiotics as a new strategy for control of antibiotic resistance. The proliferation of bacteria that are resistant to antibiotic treatment poses a substantial challenge to the development of effective treatments for microbial infections. The prospect of humans returning to a time before the widespread use of antibiotics has caused scientists to express growing anxiety. Therefore, it is essential to look for other ways to combat germs in today's world. Certain bacteria have the ability to withstand antibiotic treatment of their own accord, whereas other bacteria develop resistance to antibiotics due mostly to the improper use of antibiotics and the development of new resistant versions through mutation. Plants have been a primary source of both conventional pharmaceuticals and alternative medicines for treating a wide variety of ailments ever since ancient times. Secondary metabolites such as alkaloids, quinones, tannins, terpenoids, flavonoids, and polyphenols are abundant in plant foods because plants are such a rich source of these compounds. Numerous studies have concentrated their attention on the secondary metabolites of plants as a possible source of antibiotics. They possess the necessary structural qualities and are capable of acting via a variety of methods. There are many applications of medicinal plants including, antibacterial, antifungal, antiviral, anti-depression, antioxidant, anti-inflammatory, anti-insecticidal because plants possess many active compounds. Eucalyptus contains cineole as active compounds with an area of 85.82%. Lemongrasses possess geraniol with an area of 34%. Clove contains eugenol with 85% area. Rosemary possesses cineol with 23% area.

Keywords: Drug resistance, Medicinal herbs, antibiotic, Antibacterial.

1. INTRODUCTION

The rise in antibiotic resistance has received a lot of attention in recent years. Many diseases have become more difficult to treat as more microbial species and strains are becoming resistant. Due to using inappropriate antibiotics and often their over-prescription in several human medicine therapies are considered to be the main conditions for increasing bacterial resistance to antibiotics [1] [2], [3]. Antibiotic resistance is essentially developed by bacteria through natural selection or as a survival mechanism in severe environments, but irrational use has amplified the resistance and spread infectious diseases [4], [2]. Antimicrobial resistance (AMR) can occur in different ways, but the most important distinction is between intrinsic and acquired resistance. Intrinsic resistance is usually limited to a few antibiotics and often only to a single type of action mechanism. Acquired resistance is the result of genetic mutation or horizontal gene transfer [5].

Multidrug-resistant gram-negative bacteria are rapidly spreading throughout the world [6], [7]. In the last years with the spread of viral diseases the complication of drug resistance has increased, as the significant use of antibiotics in COVID-19 patients is a major reason for the spread of antimicrobial resistance [8]. An international hazard to human health comes from ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) which acquisition of antimicrobial resistance genes [9]. The global threat of antimicrobial resistance (AMR) and infections caused by AMR bacteria has raised the need for urgent therapeutic discoveries and improvement of existing infection control and antimicrobial practices [10].

Nowadays researchers have been looking for new molecules coming from plant material, emerged as powerful potential therapeutic tools [11]. The main of this review article is to focus on the antimicrobial activity of essential oils of some plant species and their synergic effect with antibiotics against pathogenic bacteria as an alternative solution to the development of new antibiotics, and take advantage of these natural and safe oils for humans and the environment.

ANTIMICROBIAL RESISTANCE MECHANISMS

Fundamentally, prokaryotic cells can develop five different AMR mechanisms these are:

Production Of Enzymes That Destroy Antibiotics

The most frequent enzymes are called β -lactamases, and they are responsible for rendering β -lactam antibiotics like penicillin ineffective by destroying a molecular structure of those medications [12] .

Slowing Down Or Preventing The Antibiotic From Entering The Cell

This is typically the result of changes in electrical charges on the cell surface, which lead to limited permeability of the outer membrane. This confers resistance against broad-spectrum antibiotics such as tetracycline, as well as narrow-spectrum antibiotics such as penicillin[13] .

Altering the receptor to which the antibiotic binds.

This method is primarily observed in infections that have evolved resistance to drugs that obstruct the translation of proteins in prokaryotic cells[12] .

(4) Changing The Cell Metabolism,

For instance, by ceasing production of particular enzymes, which an antibiotic would ordinarily target for destruction [14]

(5) Developing Transport Mechanisms

that remove antibiotics from prokaryotic cells before it is possible for them to have an effect on their target site [15] .

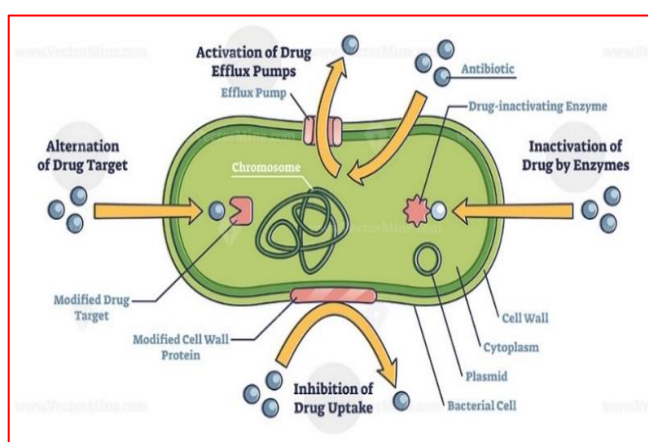


Figure 1: mechanism resistance in bacteria

2. PLANTS ESSENTIAL OILS

In response to environmental conditions such as herbivore attacks, abiotic stress, and interspecific interactions, plants develop an invaluable source of secondary metabolites. [16] . Plant secondary metabolites are a significant source of bioactive substances. Due to the increasing development of microorganism resistance patterns to most currently used antimicrobial drugs, scientific interest in these metabolites has increased today with the search for new therapeutic agents from plant sources [17] . Monoterpenes and sesquiterpenes are the major terpenoids found in essential oils. Terpenes have a strong antibacterial effect, according to reports [18]

Many of these plant compounds are generally recognized as safe (GRAS) for human consumption [19] . Essential or volatile oils are naturally occurring plant extracts of petals, seeds, leaves, stems, or roots [20] . Chinese and Egyptians used plant oil extracts for therapeutic purposes [21] .

Essential oils (EOs) play a crucial role in the protection of plants they may attract some insects to aid in the spread of pollens and seeds or resist other undesirable insects [22] . Commercial uses of EOs includes pharmaceuticals, perfume fragrance, and cosmetics, products for personal care, and drinks and foods [23] .

Essential oil have been studied for their antibacterial and antifungal potential, because these properties are used in preserving foods in addition to their antioxidant effect [24] . Essential oils (EOs) derived from plants appear to be a promising alternative to common antibiotics [25].

Essential oils have multiple effects on the bacterial cell this is due to it possesses many effective compounds [26]. Essential oils (EOs), biosynthesized by aromatic medicinal plants as secondary metabolites, are the oily liquids that contain a mixture of compounds [27] . The majority of antimicrobial chemicals identified in essential oils are terpenoids and phenylpropenes, with phenols being the most active. However, several aldehydes and non-phenolic compounds also exhibit promising antibacterial action [28] . The chemical composition can of essential oil depend on different factor such as plant's physiology, climate characteristic, or even soil condition where the plant grow [29]. Different extracted components from EOs such as carvacrol, thymol, eugenol, perillaldehyde, and cinnamaldehyde have been reported as antibacterial agents [30]. Previous studies reported the antimicrobial, antifungal, anti-inflammatory, anti-parasitic, and insecticidal activities of E.Os [31] [32] [33].

3. MECHANISM OF ACTION OF ESSENTIAL OIL

Terpenoids and phenylpropanes make up the vast bulk of the antimicrobial compounds that have been isolated from essential oils, with phenols being the most effective of the group. Nevertheless, there are a number of aldehydes and non-phenolic compounds that show promise as potential antibacterial agents. [34]. In point of fact, the mechanisms of action of Eos include the breakdown of the cell wall, the disruption of the integrity of the cytoplasmic membrane, and the coagulation of the cytoplasm. [22], damaging the membrane proteins, increased permeability leading to leakage of the cell contents, reducing the proton motive force [35], reducing the intracellular ATP pool via decreased ATP synthesis and augmented hydrolysis that is separate from the increased membrane permeability and reducing the membrane potential via increased membrane permeability [36] [37]. Moreover, EOs contain hydroxyl group and it may prevent the genetic material synthesis [38]. Many plants contain fatty acids that play an important role as antimicrobial as shown in figure:

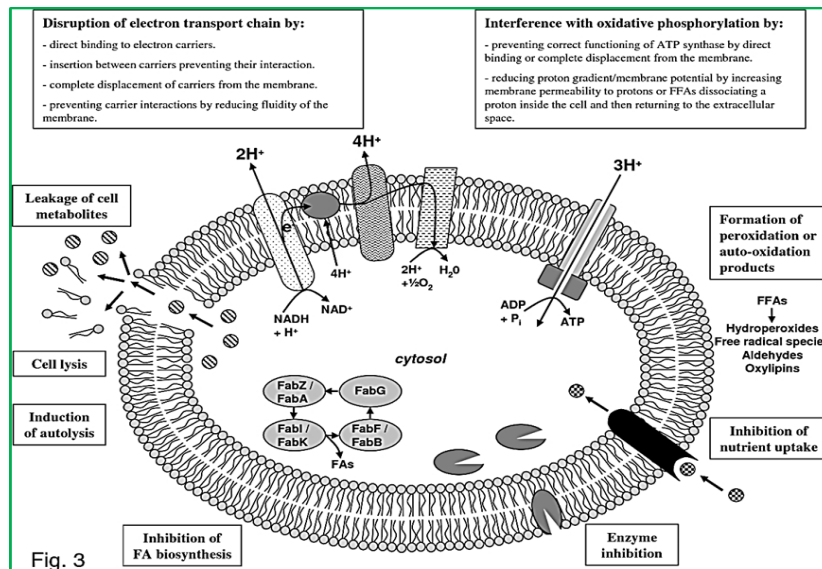


Figure 2: Schematic representation of possible cell targets and mechanisms of antibacterial action of free fatty acids (FFAs).

They may affect bacterial energy production by disrupting the electron transport chain and/or interfering with oxidative phosphorylation. FFAs can cause leakage of cell metabolites from the cell, complete cell lysis and autolysis. Membrane and cytosolic enzymes, including those required for fatty acid biosynthesis, can be inhibited by FFAs. They can impair active nutrient uptake by acting directly on the transport protein or as an indirect result of the cell's inability to produce ATP. Peroxidation and auto-oxidation products of FFAs may also have deleterious effects on the bacterial cell and play a role in cell killing. For clarity, only the bacterial inner cell membrane is shown. Image cited by Desbois & Smith, (2010)

3.1. Eucalyptus

The Eucalyptus genus (eucalypt) is a tropical and subtropical tree in the Myrtaceae family. It consists of about 900 species, most originally from Australia [40]. It is commonly used in traditional medicine around the world as an anti-inflammatory, analgesic, and antipyretic cure for respiratory infections like colds, flu, and sinus congestion [41].

Essential oils from *Eucalyptus* exhibit antibacterial, antifungal, analgesic and anti-inflammatory properties and have also been widely used in pharmaceutical, food, and cosmetics products [42]. The oil, well known as 'eucalyptus oil' commercially, has been produced from the leaves [43]. Several studies indicated that the antimicrobial activity of eucalyptus essential oil could be associated with the presence of 1,8-cineole, linalool, and pinocarveol. 1,8-Cineole as well as linalool are well-known substances with pronounced antimicrobial properties [44] [45]. Several studies have been conducted on eucalyptus oil to study the antimicrobial properties, including a study by [46] that confirmed antimicrobial properties of essential oils from *E. globulus* and *E. camaldulensis* that showed significant growth inhibition for *S. aureus* and *E. coli* tested whose the problem relates to the emergence of strains that possess multiple resistance to a range of antibiotics, thereby making them difficult to treat. Other study was done by Diloksumpun et al [47] on *Eucalyptus urophylla* show that all *E. urophylla* oils in mention study were more potent against Gram-positive bacterial strains than Gram-negative bacterial strains. [48] his study on oil *Eucalyptus globulus* leaves show that the Gram (-) bacteria (*P.aeruginosa* and *P.mirabilis*) was the most resistant to the oils in comparison with the Gram (+) bacteria (*S. pyogenes* and *S. aureus*). The low susceptibility of Gram-negative bacteria is probably due to the presence of an outer lipopolysaccharide membrane which acts a physical barrier to lipophilic compounds including essential oils [49].

While the results of study was done in Iraq show the higher sensitivity of the gram negative bacteria [50]. The antimicrobial activity of *E. globulus* essential oil is due to the presence of a mixture of monoterpenes and oxygenated monoterpenes [51].

Table 1. Chemical composition of the leaf essential oil of *Eucalyptus globulus* [52]

Compound	(%)
α -Pinene	7.16
Camphene	trace
β -Pinene	1.10
β -Myrcene	1.52
α -Phellandrene	0.55
<i>p</i> -Cymene	trace
Limonene	0.85
1.8 Cineole	85.82
γ -Terpinene	1.16
α -Terpinene	0.11
Linalool	0.43
Pinocarveol	0.44
Terpinen-4-ol	0.49
α -Terpineol	0.14

3.2. Cymbopogon Citratus

Lemongrass is an herb which belongs to gramineae family. Scientifically it is called as *Cymbopogon citratus*, are primarily cultivated for their essential oils. The genus lemongrass comprises about 180 species, is one of medicinal plant which has been shown potential as a source of chemotherapeutic compounds. [53]. The prefix lemon derives from its characteristic lemon-like odor, which is caused by the presence of citral, a cyclic monoterpene. Lemongrass contains phytochemical constituents such as tannins, flavanoids, alkaloids, and a variety of essential oils [54].

Antimicrobial property of lemongrass (*Cymbopogon citratus*) oil against pathogenic bacteria isolated from pet turtles [55] Besides the medicinal use, lemon grass can be also used in the food industry, as well as in cosmetics and pharmaceutical industries [56]. Lemongrass essential oil has been shown to effectively inhibit the growth of many different bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), and gram negative bacteria [57]. According to Onawunmini (1989), the essential oil of *C. citratus* has three main components in its composition, which are: alpha citral (geranial), beta-citral (neral) and myrcene. That study showed that alpha and beta citral showed antimicrobial activity against Gram-positive and Gram-negative bacteria. However, the component myrcene showed no antimicrobial activity alone [58].

Other study show that Lemongrass essential oil has a significant inhibitory effect on *Staphylococcus aureus*, *Bacillus cereus* and *Escherichia coli* [59]. Study conducted in Pakistan was reported the role of lemon grass for treating UTI infection [60]. In a study conducted to examine antimicrobial activity of Lemongrass oil against some selected pathogenic bacteria was found that the investigated oil was effective against all the test organisms except *P. aeruginosa* [61].

Table 2. Percentage compound composition of the West Indian lemongrass essential oil (*Cymbopogon citratus*) [62].

Name of Compounds	Presence in %
Camphene	0.8
Limonene	1.3
Linalool	2.6
Verbenol	0.4
α -Terpineol	1.7
Carveol, trans	0.5
Carveol, cis	1.0
Neral	26.1
Geraniol	4.3
Piperitone	0.6
Geranial	34.5
Geranyl formate	0.7
Neryl acetate	0.7
β -Caryophyllene	1.0
Cadinene	1.4
Calamenene	0.6
Caryophyllene-oxide	4.7

3.3. Syzygium aromaticum

Clove (*Syzygium aromaticum*) in the family Myrtaceae, it is a herbal plant, oils, seeds, flowers, leaves and stems were used in ancient times to make medicine. [63] [64]. The activity of clove against bacteria is due to the presence of the following compounds (biflorin, kaempferol, rhamnocitrin, myricetin, gallic acid, ellagic acid and oleanic acid) [65]. While another study mentioned that Eugenol the major compound of clove essential oil which has anti-bacterial activity against *Staphylococcus aureus* [66] [67]. This difference in the chemical content of the active substances may be due to several factors, including geographical location and other factors such as soil and water, as well as the season of oil collection [68]. Antimicrobial properties of clove volatile oil were tested and showed inhibitory activity to *Listeria monocytogenes*,

Campylobacter jejuni, *Salmonella enteritidis*, *Bacillus cereus*, *Escherichia coli*, and *Staphylococcus aureus* [69]. In many studies Clove essential oils show markedly antibacterial activity and have inhibitory effect on *Klebsiella pneumoniae* [70] Essential oils of *Syzygium aromaticum* had bacteriostatic effect on extended-spectrum beta-lactamases-producing *Escherichia coli* strains [71].

Table 3:Chemical composition of the essential oil from *Syzygium aromaticum* [72]

Compounds	%
α -Pinene	3
Camphene	0.21
Camphor	0.29
Eugenol	82.16
Caryophyllene	0.79
Acetyeugenol	16.55

3.4. Rosmarinus Officinalis L.

This type is considered an important medicinal plant that belongs to the Lamiaceae family, and because it contains anti-bacterial, anti-fungal, anti-inflammatory and antioxidant substances, interest in it has increased recently [73]. Nowadays the importance of focusing on essential oils and their effectiveness against bacteria to discover new agents and means to reduce the effectiveness of multidrug-resistant strains such as *P. aeruginosa* strains. Rosemary leaves contain essential oils that are characterized by their fragrant smell and yellow color, its ratio ranges between (1.0%–2.5%) [74]. Antimicrobial activity of rosemary essential oils depends on the presence of phenolic compounds and small terpenoids (carvacrol, eugenol and thymol), which in pure state have high antimicrobial activity [75]. Terpenes and terpenoids can break the lipopolysaccharide chain in the membrane because they are lipophilic, and if the damage is severe enough, it can reach the cytoplasm and impair essential cell functions [76].

The antioxidant and antibacterial properties of rosemary vary according to the use of the technique of extracting extracts from the plant, geographical region, the period of maturity of the plant and climatic conditions [77]. Rosemary oils exhibited strong activity against various pathogens [78] [37]

Table 4: Chemical composition of rosemary oil [79]

Compound	%
cis-3-Hexanol	0.08
α -Thujene	0.14
α -Pinene	9.94
Camphene	5.83
1, Octan-3-ol	0.44
Sabinene	0.26
Myrcene	4.86
α -Terpinene	0.13
P-Cymene	0.91
Limonene	3.08
β -Phellandrene	1.65
1, 8-Cineole	23.40
γ -Terpinene	0.51
cis-Sabinene-hydrate	0.53
Terpinolene	0.42
Linalool	1.24
trans-Sabinene hydrate	0.11
Filifolone	0.06
Chrysanthenone	0.14
Camphor	26.40
Borneor	2.05
Terpinene-4-ol	1.46
α -Terpineol	2.68
Myrtenol	0.43
Verbenone	3.32
p-Mentha-1,8-dien-3-one	0.14
Bornyl acetate	3.97
Eugenol	0.17
Methyl eugenol	0.16
β -Caryophyllene	0.40
α -Humulene	0.39
Caryophyllene oxide	0.16
Total	96.29

3.5. Lavandula

Lavandula common name : Lavender, is a flowering plant in the family Lamiaceae, native to the western Mediterranean, primarily the Pyrenees and other mountains in northern Spain is among the most significant medical genera, with various medicinal and biological actions. The *Lavandula* genus includes 28 species and provides useful essential oils primarily for the food (flavoring), skincare products, and cosmetic industries, as well as essential oils [80]. Antibacterial, antifungal,

antioxidant, anti-inflammatory, depressive, sedative, hypnotic, analgesic, and anti-cancer properties are all present in lavender essential oil [81] [82]. Lavender oil has been proved to be effective against a broad spectrum of bacteria, such as antibiotic-resistant strains like methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* [83]. Lavender essential oil is composed mainly of monoterpenoids and sesquiterpenoids, the much more dominant that are linalool and linalyl acetate, camphor and 1,8-cineole are moderate to low in content, while lavandulyl acetate, terpinen-4-ol, and lavandulol are medium level elements [84]. lavender oil recorded high antimicrobial potential. Lavender oil has antibacterial activity on *E. coli*, *S. aureus*, *L. monocytogenes* and *P. mirabilis* in study conducted by [85].

Table 4: Chemical analysis of *Lavandula angustifolia* Essential Oil by GC-MS [86]

Compounds	%
p-cymene	0.9
Limonene	0.8
1,8- Cineol	21.5
Linalool	44.94
Camphor	5.6
Menthone	4.2
Roesfuran epoxide	9.3
Isomenthol	4.8
Dihydrocarvone	3.8

Table 5 Studies demonstrating activity of essential oils from different plant families against multi drug resistant bacteria

Essential oil	Major components	Method for study of antibacterial activity	Test bacteria	Countr y	Ref.
<i>Eucalyptus gomphocephala</i>	tannins, flavonoids, saponins and steroids/triterpenes	agar well diffusion method	<i>Pseudomonas aeruginosa</i>	Morocco	[87]
<i>Eucalyptus globulus</i>	citronellol, citronellal and 1,8-cineole.	broth microdilution method.	<i>Acinetobacter baumannii</i>	Germany	[43]
<i>Eucalyptus globulus</i>	pinene, limonene, terpinenol, piperitone and globulol	Disk Diffusion method	<i>Streptococcus mutans</i>	India	[88]
Lemongras	/	Micro dilution method	<i>Staphylococcus aureus</i>	Thailand	[89]
<i>Cymbopogon citratus</i>	/	disk diffusion method	<i>S.aureus</i> , <i>S. epidermidis</i> , <i>E. coli</i> , <i>K. pneumonia</i>	South Africa	[90]
<i>Cymbopogon citratus</i>	/	broth dilution assay	<i>Staphylococcus spp.</i> , <i>Streptococcus mutans</i> and <i>Candida spp.</i>	Brazil.	[91]
<i>Syzygium aromaticum</i>	Eugenol Caryophyllene Gamma-humulene Caryophyllene oxide	disk diffusion method	<i>streptococcus suis</i>	Thailand	[92]
<i>Syzygium aromaticum</i>	eugenol, β -caryophyllene and α -humulene	microdilution method	<i>S. aureus</i>	Iran	[93]
<i>Syzygium aromaticum</i>	/	disk diffusion method	<i>S. aureus</i> <i>E. coli</i>	Iraq	[94]
<i>Rosmarinus officinalis</i>	α -pinene, 1,8-cineole, camphor, verbinone and borneol	broth microdilution method	<i>Staphylococcus aureus</i> <i>Bacillus subtilis</i> <i>Escherichia coli</i>	Morocco	[95]
<i>Salvia rosmarinu</i>	in 1,8-cineole and α pinene	broth microdilution method	<i>Mycobacterium smegmatis</i> <i>Bacillus subtilis</i>	Morocco	[96]
<i>Rosmarinus officinalis</i>	α -pinene 1,8-cineole linalool	Disc diffusion method	<i>E. coli</i> <i>S. aureus</i> <i>L. monocytogenes</i>	Iran	[97]
<i>Lavandula angustifolia</i>	/	disk diffusion method	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> and <i>Enterococcus faecalis</i>	India	[98]
<i>Lavandula angustifolia</i>	linalool and 1,8-Cineol	microdilution broth assay	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Bacillus cereus</i> , <i>Salmonella typhimorium</i> and <i>Listeria monocytogenes</i>	Iran	[86]
<i>Lavandula angustifolia</i>	linalool ,cineole ,camphor ,linalyl acetate , borneol, and α -terpineol	disc diffusion test	<i>E. coli</i> and <i>P.aeruginosa</i>	Morocco	[99]

3.6. Synergistic Interactions Between The Essential Oil And Antibiotic:

Antibiotics combined with plant extracts have a combination effect on resistant bacteria, opening up new avenues for the treatment of pathogenic disorders [100].

Synergy therapies may lead to a reduction in the active daily dosage of antibacterial agents needed for treatment, as well as decreased side effects. One of the most recent techniques for trying to combat multidrug resistant bacteria is the combined antimicrobial action of antimicrobials and essential oils. Due to the non-availability of new antibiotics into the market and an increase in antibiotic-resistant pathogenic

[101]. There are many studies about synergy between essential oils of different plant species and Antibiotics [102]. The synergistic effect of a mixture of oils with each other was also studied, synergistic effect between essential oils has been demonstrated, and the optimal mixtures that show the lowest MIC values against tested bacteria [103]

In study conducted about the combination of *Cymbopogon khasianus* essential oil with streptomycin against *E. coli* showed total synergistic effect [104]. Clove Volatile oil exhibited synergistic effect when combined with (Ceftazidimim, Cefepime and Ceftriaxone) [70] When lavender and neomycin were combined, they produced antimicrobial synergisms against *Staphylococcus aureus*, *E. coli*, *Streptococcus spp.*, and *Pseudomonas aeruginosa* [105]. Other study conducted in Iraq show that antimicrobial activity of gentamicin and ciprofloxacin against *E. coli* were increased when combined with rosemary essential oil [106]. The combination between antibiotic and *Eucalyptus globulus* essential oil against *Pseudomonas aeruginosa* isolates from respiratory tractinfections show synergistic effect [107]. This synergistic effect differs according to the tested bacterial isolates, as well as the different components of the essential oil [108].

4. CONCLUSIONS

In conclusion, the present review is organized to display some studies that studied the bacterial activity of essential oils of some medicinal plants and their synergistic effect with some antibiotics used to treat bacterial infections. Through the presented studies, we concluded that the active substances in each plant differ between the species of one genus, as well as there are several factors that affect the quality and quantity of these substances, such as soil, water, season, as well as the country. However, further studies need to be performed in order to identify and quantify the active substances in these oils that have not yet been studied. We, as researchers, looking forward to the possibility of developing a drug that overcomes the resistant bacteria to the by use of the active substances available in these essential oils.

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