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Review Article

The Role of Plant-Derived Compounds in Amplifying Antibiotic Effectiveness

Elham Nikouie[1], Nadia Kazemipour[1]*, Farokh Rokhbakhsh-Zamin[1]

[1] Department of Microbiology, Ke.C., Islamic Azad University, Kerman, Iran.

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ABSTRACT

Today we are facing an increasing problem related to the antibiotic resistance due to the inappropriate and excessive using antimicrobial drugs. The World Health Organization has declared the antibiotic resistance crisis as one of the greatest threats to global health, and therefore, it is essential to employ effective new methods to combat life threatening infections. Accordingly, researchers are striving to find effective alternatives to address this problem. One promising approach is the use of herbal medicines with antimicrobial properties accompanying with conventional antibiotics. The potential synergistic effects of using antibiotics with medicinal plants can provide more effective treatment option for dangerous infectious disease caused specially by multidrug resistant bacteria. This research was conducted to draw a clear view about the synergism antibiotics and plants with acceptable effects against important human pathogenic bacteria. Using various herbal essential oils in combination with antibiotics were investigated recently on certain bacteria and it revealed that the synergistic interactions between plant compounds and antibiotics enhance antioxidant and antimicrobial activities. This type of combinations and their dual usage not only increase their antioxidant and antibacterial effects but also significantly reduce the active dose of antibiotics. Outer membrane of Gram-negative bacteria act as an effective barrier against amphipathic agents, making them more resistant to these types of drugs. But their simultaneously plants and antibiotics usage surprisingly permeate the outer membrane making mentioned bacteria more sensitive. Purified plant components in combination with antibiotics enhance their efficacy against target bacteria and provide promising compounds for the development of new effective way for better curing the infectious diseases.

Keywords: Antibiotics, Antimicrobial activity, Medicinal plants, Synergism.

* *Corresponding Author:*
E mail: kazemipour@iau.ac.ir
ORCID ID: 0000-0002-1569-5744

BACKGROUND

Infectious diseases are a significant cause of mortality and disability, accounting for one-third of deaths worldwide. The discovery of antibiotics was a crucial part of the fight against bacterial infections. Antibiotics are vital tools in combating bacterial infections and can be beneficial for human health. However, commonly used antibiotics over time have diminished their effectiveness against specific infections due to the emergence of drug-resistant strains. The rapid development of multidrug-resistant (MDR) bacteria is a major problem occurring globally from now on. Medicinal plants, with a long history of use in traditional medicine for treating infectious diseases, have been transformed into innovative antimicrobial agents by extracting their active chemical compounds, which are effective in preventing some infections. Plant-derived compounds can exhibit direct antibacterial activity or indirectly enhance the effectiveness of commonly used drugs as antibiotic resistance-modifying compounds when combined with antibiotics (1). Biofilm-forming bacteria pose a significant challenge for the healthcare sector; for example, infections with antibiotic-resistant *P. aeruginosa* complicate the treatment of various conditions, from non-healing skin wounds to complex chronic respiratory diseases (2). The synergy between plant extracts and antibiotics significantly reduces the MIC of the used antibiotics, and the synergy of plant extracts with antibiotics can be an effective therapeutic agent against antibiotic resistance as well as biofilm formation (3). Antibiotic resistance is an example of the high capacity for natural evolution and adaptation of bacteria under various conditions. The reasons for the increasing number of antibiotic-resistant bacteria in humans include inadequate infection control in hospitals and a lack of sufficient quantity and duration of antibiotic therapy. The rising rate of resistance in bacteria leads to a decrease in the effectiveness of existing antibiotics, as indicated in Figure 1. (4).

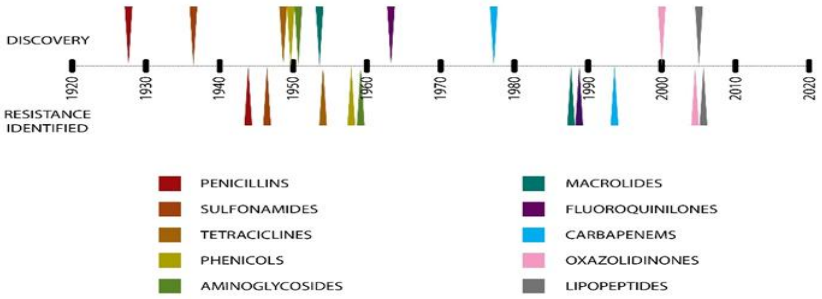

Fig. 1 Approximate dates of the discovery of new classes of antibiotics and the identification of bacterial resistance.

Plant metabolites, by synergistic traits with antibiotics in some cases, have a better effect on MDR pathogens. Essential oils are volatile, natural, and complex compounds recognized as secondary metabolites produced by aromatic plants. The properties of essential oils are typically identified by the compounds they contain. They are commonly used as bactericide, virucide, fungicide, antiparasitic, insecticide, and antioxidant. Plant-derived chemicals

accompanying antibiotics may enhance the efficacy of antibiotics. This is an appropriate method to overcome bacterial resistance (5). The use of essential oils as antimicrobial compounds has also advantaged such as minimal side effects, high tolerance, biodegradability, and low cost. Furthermore, essential oils are safe and can be used as substances that enhance antibiotic activity. Numerous studies have shown that essential oils administered with common antibiotics can increase effectiveness, and they reduce bacterial resistance (6).

REVIEW OF THE LITERATURE

Antimicrobial activity of plants

Research on alternative or complementary treatments to antibiotics has been extensively discussed and examined. Antimicrobial products obtained from natural origins have garnered attention due to their high chemical diversity and inherent properties.

Plant compounds with antimicrobial activity

Plants produce a large number of secondary metabolites (Table 1) with inhibitory or killing effects against pathogenic microbes. Throughout scientific improvement, some structures of secondary metabolites can be modified to show better effects on harmful microbes (6).

Table 1

Some plant compounds have antimicrobial activity

Common name	Scientific name	Combinations	Activity	Reference
Onion	*Allium cepa*	Allicin	Antibacterial, Antifungal	7
Garlic	*Allium Sativum*	Allicin	Antibacterial, Antifungal	8
Bell Pepper	*Capsicum annuum*	Oleoresin	Antibacterial, Antifungal, Antiviral	9
Jujube	*Ziziphus jujuba*	Phenol Flavonoid Proanthocyanidins	Antibacterial	10
Black Cumin	*Nigella sativa*	Thymoquinone	Antibacterial, Antifungal	11
cinnamon	*Cinnamon zeylanicum*	Alkaloid Steroid Terpenoid	Antibacterial	12
Ginger	*Zingiber officinale*	Jingjerol Shogaol	Antibacterial, Antifungal, Antiviral	8
Apple	*Dovyalis cafra*	Phenol Flavonoid	Antibacterial, Antifungal, Antiviral	13
Lemon	*citrus lemon*	Flavonoid, carotenoid, limonoid, tannin, terpenoid	Antibacterial	14
Sweet Cherry	*Prunus avium L.*	Phenol	Antibacterial	15

Main classes of plant antimicrobial compounds

Different plants have an unlimited capacity for synthesizing some aromatic substances,

including the majority of phenol compounds. Plants produce a wide range of metabolites without importance for primary metabolism, but they have an important role in both biotic and abiotic environmental conditions, and these organic compounds are biologically dynamic and behave as secondary metabolites working as defensive components by intervening in the molecular targets of pathogens (16). Some main classes of antimicrobial compounds in plants are listed in Table 2.

Table 2

Different classes of obtained antimicrobial compounds from plants

Class	Subclass	Example	Mechanism of action	Reference
Terpenoid & Essential Oils	Monoterpenes	Carvacrol	Increased membrane permeability Disruption of ion balance across the membrane	17
		Terpinen-4-ol	Change in phospholipids Binding to the bacterial membrane and coagulation of the cytoplasmic membrane Disrupting the enzyme system and the synthesis of genetic material	
	Phenylpropanoid	Vanillin	Disturbing the balance of ions, lipids, and membrane proteins	
Phenols	Flavonoids	lignan	changes in the plasma membrane	
		Magnolol	Disturbance in the formation of biofilm and cytoplasmic	
	Tannic acid		Binding to cell membrane proteins Binding to phospholipids Interfering with the metabolism and absorption of substances in bacteria Decreased cell membrane permeability	18
Alkaloid	Isoquinoline	Berberine	Increased membrane permeability	19

The antimicrobial effect of plant compounds

Some extracts of plants have high efficacy in antimicrobial activities, with their various volatile and organic biological materials inhibiting or killing bacteria and fungi. The bioactive properties of plant extracts are evaluated by their main components with potential applications as supplements, additives,

or antibacterial agents (16). The use of medicinal plants with synergistic effects with antibiotics is helpful to slow the resistance of pathogens. Plant extracts can also enhance the antibacterial properties of chemotherapeutic agents. For example, Beta- lactamase- producing *Staphylococcus aureus* (*S. aureus*) is sensitive to methanolic nutmeg extract (20). Rosemary extract has a good effect on *S. aureus* and *Escherichia coli* (*E. coli*) (21). *S. aureus* strains are affected by clove extract as they suffer significant leakage of intracellular components and reduction at their metabolic level, which significantly inhibits the respiratory metabolism by suppressing the tricarboxylic acid cycle pathway (22). Nutmeg extract is the other example with antimicrobial property against β-lactam-resistant *Streptococcus pyogenes* (*S. pyogenes*) (23). Biochemical studies of thyme indicate that it can act as a key agent in combating respiratory diseases and has antimicrobial properties against *S. pyogenes* (24). Red ginger has also shown antibacterial activity against *S. pyogenes* (25). There are many studies about the antibacterial effects of nutmeg extract on *Klebsiella pneumoniae* (*K. pneumoniae*) and *Acinetobacter baumannii* (*A. baumannii*) strains producing broad-spectrum beta-lactamases (26). Cinnamon and tea tree oil extracts also possess antimicrobial and bactericidal agents against *K. pneumoniae* and affect bacterial biofilms (27). Some plant extracts are effective against *K. pneumoniae*, primarily due to their resistant nature. The use of various plant extracts is effective in reducing and even eliminating biofilm formation by *K. pneumoniae* (28). Many plants are used in medical aspects due to their antibacterial properties related to the secondary metabolites, with constituents such as phenolic compounds present in essential oils and tannins. Effectiveness of metabolites is related to three items as bacterial and plant species, and type of extracted active principles (29).

Synergism of medicinal plants and antibiotics

Different parts of Plants especially oils were used for a verity of human purposes as a long time. They can be utilized for their pleasant aroma, flavor, and antibacterial properties. They are employed in various plants for their protective role against microorganisms, insects, or microbial flora attacks. Essential oils are considered good natural alternatives to antibiotics. The synergistic combination of antibiotics and plant compounds represents a promising strategy with multiple clinical benefits. Some plant compounds have a direct antimicrobial activity against antibiotic-resistant bacteria, especially in combination with inert antibiotics, in a synergistic relationship to plant metabolites, which can be changed to more powerful antibiotics. So, some plant compounds can enhance the effects of antibiotics in various ways, such as facilitating their entry into the cell by destabilizing the cytoplasmic membrane, inhibiting efflux pumps, or dispersing biofilms. Some of the synergistic interactions between secondary metabolites and antibiotics include increased efficacy, lower doses of antibiotics, reduced side effects, and enhanced stability. Certain polyphenols, like catechins, can deeply penetrate the lipid bilayer structure of bacterial membranes, destabilizing the cellular structure of the cytoplasmic membrane by lipophilic hydrocarbons present in plant extracts, increasing its permeability, and interacting with the hydrophobic regions of proteins, which can enhance the effect of specific antibiotics against resistant bacteria (4).

Synergism of medicinal plants and the antibiotic ampicillin against different microbial strains

Combinations of plant essential oils and the standard antibiotics, such as ampicillin, with synergistic interactions can lead to a reduction in their MIC values of the drug. There are new information about the evaluation of the chemical composition and antibacterial activity of essential oils of *Cymbopogon citratus* (CCEO), *Cymbopogon khasianus* (CKEO), and *Mentha arvensis* (MAEO) against two Gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*) and three Gram-positive bacteria (*Staphylococcus aureus*, *Micrococcus luteus*, *Bacillus subtilis*) separately and in combination with selected antibiotics such as chloramphenicol, ampicillin, and erythromycin. Accordingly, synergistic behavior was successfully observed (30). The effects of antibiotics can be attributed to the presence of hydrophobic components in plant essential oils that have the ability to interact with membrane lipids, thereby disrupting cellular structure and increasing membrane permeability, allowing antibiotics to easily cross the membrane barrier, resulting in enhanced antibacterial effects, especially at lower doses. Another possible mechanism of synergism involves the inhibition of efflux pumps caused by plant essential oils, resulting in the inability of efflux pumps to pump out antibiotics, leading to the retention of antibiotics within bacterial cells and consequently reducing their effective dose (31).

Synergism of medicinal plants and antibiotics against some Gram-negative bacteria

Using the extracted oil from *Pelargonium endlicherianum* (*P. endlicherianum*) combined with four common antibiotics (penicillin, ampicillin, ciprofloxacin, and gentamicin) increase membrane permeability and enhancing phagocytic activity in human leukocyte cells resulting better treatment of bacterial meningitis against *Neisseria meningitidis* and *Haemophilus influenzae* (32). The oil extracted from *P. endlicherianum* showed a synergistic effect in combination with cefepime and gentamicin against *K. pneumoniae* (33).

The combined effects of the essential oils of *Drypetes gosswelleri* (*D. gosswelleri*), *Echinops giganteus* (*E. giganteus*), *Melaleuca leucadendron* (*M. leucadendron*), and the antibiotics ciprofloxacin and ceftriaxone were effective against strains involved in infectious diseases, including *Pseudomonas aeruginosa* (*p. aeruginosa*), *K. pneumoniae*, and *Salmonella enteritidis* (34). The maximum eradication of *P. aeruginosa* biofilm was achieved using the oil extracted from pomegranate/rosemary and its combination with antibiotics such as ceftazidime, gentamicin, imipenem, and levofloxacin (3).

Additionally, derived metabolites from the plant *Callistemon citrinus* and *Vernonia adoensis* enhancing the efficacy of antibiotics synergistically against *P. aeruginosa* (5). The synergism of the extracts of *Allium cepa* (*A. cepa*) and *Allium sativum* (*A. sativum*) accompanying with the antibiotics tetracycline and ampicloxacillin resulting strong antibacterial activity against bacterial pathogens such as *E. coli* (35).

The synergy of peppermint essential oil with the antibiotic chloramphenicol inhibits *E. coli* and *P. aeruginosa* (36). *E. coli* has a sensitivity to the combination of *Ramarinas officinalis* (*R. officinalis*) with neomycin, gentamicin, metronidazole, amikacin, nystatin, and amphotericin. *P. aeruginosa* can be inhibited by one of the species of lavender through synergy with chloramphenicol, ciprofloxacin, fusidic acid, and nystatin (37).

The combination of *Matur cammunis* extract with polymyxin B and ciprofloxacin can be an

effective combination for treating *A. baumannii*. The synergistic effects of methanolic extracts of sage and rosemary with ceftazidime against *E. coli* has been also well demonstrated (38). *A. baumannii* is sensitive to the combination of *Arctostaphylus vaccinium* with the antibiotic meropenem (39).

The combination of plant extracts from *Mentha pulegium L.* (*M. pulegium*) and *Artemisia herba-alba* (*A. herba-alba*) with the antibiotics (cefoxitin and amikacin) have valuable effects on imipenem-resistant *A. baumannii* (40).

Synergism of medicinal plants and antibiotics on some Gram-positive bacteria

Synergistic combinations of essential oils extracted from the peels of *C. reticulata* (CREO) and *C. aurantifolia* (CAEO) with gentamicin can successfully inhibit Methicillin-resistant *S. aureus* (MRSA) (41). The antibacterial activity of the ethanolic extract of black cumin and co-trimoxazole also exhibits a synergistic effect against MRSA (42). Additionally, MRSA exhibit a change in phenotypic antibiotic resistance and reducing antibiotic resistance to the related antibiotic after synergism of oil extracted from *Thymus zygis* accompanying with the antibiotics (ampicillin, ciprofloxacin, or vancomycin) (43). The usage of essential plant oils from *D. gosswelleri*, *E. giganteus*, and *M. leucadendron* with the antibiotics such as ciprofloxacin and ceftriaxone were effective against different pathogenic as *S. aureus* and *Bacillus cereus* (34). The synergy of extracts from *A. cepa* and *A. sativum* with the tetracycline and ampicloxacillin demonstrated strong antibacterial activity against *S. aureus* (35). The synergy usage of peppermint essential oil with the chloramphenicol inhibits *S. aureus* (36). The combination of plant extracts from *M. pulegium* and *A. herba-alba* with cefoxitin and amikacin demonstrated synergy against penicillin-resistant *S. aureus* (40). *S. aureus* strains have better sensitivity to the combination of *R. officinalis* with neomycin, gentamicin, metronidazole, amikacin, nystatin, and amphotericin. A species of lavender, through synergy with chloramphenicol, ciprofloxacin, fusidic acid, and nystatin, can inhibit *S. aureus* (37). The combination of essential oil from wild thyme with ciprofloxacin and gentamicin show synergistic effect against methicillin-resistant strains of *S. aureus* (MRSA) and significantly inhibit their biofilm formation (44). The combination of ethanolic extract of *Peganum harmala* seeds with clindamycin has a suitable antibacterial effect against *Streptococcus sanguinis*, an important species residing in the mouths of individuals responsible for heart damages (45). The combination of cinnamon essential oil with aminoglycosides can inhibit *Enterococcus faecalis* (46).

Synergism of medicinal plants and antibiotics on Candida albicans suppression

A species of lavender, through synergy with chloramphenicol, ciprofloxacin, fusidic acid, and nystatin, is able to inhibit *Candida albicans* (*C. albicans*), and these strains showed sensitivity to the combination of *R. officinalis* with neomycin, gentamicin, metronidazole, amikacin, nystatin, and amphotericin (37). The synergistic antifungal and antibiofilm effects of gypenosides with fluconazole against resistant *C. albicans* have been proven (47). Berberine hydrochloride, as a common traditional herbal medicine in China, has a synergistic effect with fluconazole against *C. albicans* (48). Clove essential oil, through synergy with chlorhexidine and cetylpyridinium chloride, is also effective against pathogenic Candida species (49).

Synergism of bioactive compounds from plants with common antibiotics

Medicinal plants used in traditional medicine produce a variety of compounds with therapeutic significance. Researchers have shown that the use of rutin and quercetin, which are present in the human diet as components of fruits and vegetables, in adjunct therapies combined with antibiotics against drug-resistant bacteria represents a promising therapeutic strategy against superbug infections (50).

Berberine, as an alkaloid salt found in barberry, in combination with ciprofloxacin and imipenem, is an effective agent to reduce bacterial resistance to the common antibiotics (51). Carvacrol, a phenolic monoterpenoid compound derived from the essential oils of the Lamiaceae family, including thyme, wild oregano, and marjoram, introduces this agent as a natural antibacterial drug and significantly enhances the antibacterial properties of cefixime. Therefore, carvacrol can introduce an effective compound for increasing the antibacterial potency of cefixime (52). Black seed is rich in polyphenols and tocopherols, and its oil contains linoleic, oleic, palmitic, and stearic acids.

The results of simultaneous use of black seed oil and chloramphenicol showed that it has a synergistic effect on certain pathogenic bacteria (53). *Thymus atlanticus* contains carvacrol and borneol, and its use with ciprofloxacin and fluconazole on some gram-positive and gram-negative bacteria and fungi has been proved with the maximum synergistic effects against *K. pneumoniae* (54). *Pelargonium graveolens L.* contains citronellol, geraniol, and isomenthone, which showed significant synergism with antibiotics against *Streptococcus pneumoniae* (55). The antibacterial effects of thymoquinones in combination with common antibiotics against *K. pneumoniae*, *S. epidermidis*, and *S. aureus* have also been proven by some researchers (56).

DISCUSSION

The mechanisms of action of plant-derived metabolites involve six achievable modes of antimicrobial activities, which include disrupting the outer membrane of gram-negative bacteria by depleting lipopolysaccharides, interacting with membrane proteins, disrupting the proton motive force with ion leakage, interfering with the normal function of cellular components, and inhibiting enzyme synthesis.

The results obtained from essential oils, along with their bioactive compounds, primarily disrupt the cell membrane of microorganisms. Lipophilic monoterpenes derived from essential oils significantly affect the lipid bilayer structure. Many scientists have investigated the significance of the synergistic effects of plant-derived compounds and antibiotics. The synergistic interaction between two agents, where one agent enhances the effect of the other and they work more effectively together than individually, has prompted many researchers to evaluate the importance of the synergistic effects of plant-derived compounds and traditional antibiotics.

This can lead to change resistant bacteria to sensitive forms facing antibiotics. Numerous studies in laboratory conditions revealed a combination of some plant extracts and antibiotics exhibiting synergistic effects, resulting in a significant reduction in the minimum inhibitory concentration (MIC) of antibiotics (5).

The antibacterial activity of henna, pomegranate, peanuts, and sesame extract, as well as their potential use as agents to enhance antibiotic activity (1). The combination of fresh garlic extract with gentamicin and ciprofloxacin

can inhibit drug-resistant bacteria to the mentioned antibiotics, enhancing their effectiveness (57).

Synergistic interactions between thyme (*Thymus broussonnetii*) and streptomycin and ciprofloxacin also exhibit higher inhibitory activity against some pathogenic bacteria (58). Combination of plant-based antimicrobial products with drugs is a research necessity for several reasons, especially for commercial advantages. The development of new antibiotics requires extensive, expensive, time-consuming evaluations for their effectiveness, but a combination of plant extracts and antibiotics does not have these limitations. So, application of common antibiotics in medical and clinical use can be extended for a longer time with less reduced activity (4).

CONCLUSION

Treatment of infectious disease by a combination of common antibiotics and plants is a good way to change antibiotics from an ineffective state to their previous potent form. There are many problems with traditional methods for finding new drugs. The traditional methods for biosynthesis of new antimicrobial compounds facing big problems such as high costs as well as too much time consuming. But fortunately, combination of antibiotics with plants does not have above mentioned problems and they have attractive reasonable market price. On the other hand, lower doses of specific antibiotics are necessary in the combined drugs with reduced side effects. Experimental data suggest that resistance in bacterial infections may be reduced by some drug combinations with plants instead of monotherapy. Other advantages are the possibility of shortening the treatment duration and expanding the activity spectrum. In the recent years, Scientists expand their views to use different ways for interrupting infectious disease and now it is believed that both attempt to find new antibiotics and in parallel try to find good combinations of synergistic antibiotics and plant constituents are golden strategies for our future research works.

Transparency declaration

There is no conflict of interests.

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