THE ROLE OF MEDICINAL PLANTS IN COMBATING INFECTIOUS DISEASES: A COMPREHENSIVE REVIEW OF PLANT-DERIVED ANTIMICROBIAL AGENTS

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ABSTRACT:

Many different infectious diseases are treated and prevented with the use of medicinal herbs. Infectious diseases are caused by pathogenic microorganisms, which include bacteria, viruses, parasites, and fungus. It is possible for diseases to spread from one person to other both directly and indirectly. Infectious infections are the second leading cause of death worldwide. Approximately 25% of the drugs we consume are derived from plants that grow in rainforests. Nevertheless, very few medicinal plants have been the focus of substantial research in the scientific community. The emergence of antibiotic resistance in microorganisms necessitated the development of novel antibacterial drugs. India's rural and impoverished communities use a variety of plants as herbal remedies to combat infectious diseases.Plants that come from the families Lamiaceae, Rubiaceae, Fabaceae, Rosaceae, Plantaginaceae, and Malvaceae have anti-bacterial and anti-infectious qualities. The main objective of this study was to evaluate the antibacterial activity and screen phytochemicals of medicinal plants used to treat infectious disorders.

KEYWORDS: Medicinal plant, Anti-bacterial activity, Anti-microbial activity, Medicinal plant extract, Infectious diseases.

INTRODUCTION:

The World Health Organization (WHO) states that traditional medicines made from medicinal plants continue to help 80% of people in the underdeveloped nations [1]. Of the estimated 374,000 species of plants, people use 28,187 different types of plants for medical purposes. Moreover, the World Health Organization has identified over 20,000 varieties of medicinal plants and cataloged them, acknowledging their potential as sources of novel pharmaceuticals [2]. Regulations concerning medicinal plants have been developed in over 100 nations. It has been estimated that more than 1340 plant species possess antibacterial properties, and over 30,000 antimicrobial chemicals have been extracted from plants [3]. Furthermore, 74% of plant-derived bioactive chemicals have been shown to have therapeutic applications in conventional medicine, and it is predicted that 14–28% of higher plant species have medicinal qualities [4].

The overuse of antibiotics, which is extensive, inappropriate, irregular, and indiscriminate, has caused antimicrobial resistance to develop, making many commonly used medications ineffective[5]. The World Health Organization (WHO) has identified this trend as potentially the most urgent issue in medical science[6]. Consequently, there is a growing need to create new antimicrobial drugs that can prevent the development of resistance and reduce the reliance on antibiotics. As a result, researchers are exploring and identifying new bioactive compounds from plants that can combat microbial resistance. It is also important to note that approximately half of all current medications and nutraceuticals are derived from natural sources[7].Bioactive compounds can be obtained from medicinal plants in abundant quantities, and various techniques have been explored to assess their effectiveness as antimicrobial agents. However, there hasn't been a comprehensive analysis of the compounds yet[8]. Natural antimicrobial substances can be employed independently or in conjunction with antibiotics to enhance their antibacterial effects against various pathogens. Ongoing research aims to discover emerging treatments as many medicinal plants still possess unidentified antibacterial properties[9].

In order to assess the effectiveness of potentially significant medicinal plants and demonstrate their antibacterial properties, it is crucial to have reliable and well-validated data. This review thoroughly examined key research on validating the antimicrobial properties of medicinal herbs, the underlying mechanisms of action, bacterial resistance mechanisms, challenges associated with plant-derived chemical compounds that exhibit such properties, and the future prospects of using herbal extracts to address drug resistance[10].

1. Antimicrobial Activity of Medicinal Plant Extract:

Studies have demonstrated that medicinal plant extracts have a range of biological properties, including anti-inflammatory, antibacterial, and antioxidant properties. In contrast to the antimicrobials we currently use, chemicals derived from these plants can inhibit the growth of bacteria, fungi, viruses, and protozoa [11]. This implies that they might be helpful in treating infections brought on by bacteria that are resistant to the antibiotics that are currently in use. When combined with other antibiotics, some of these compounds can help combat antibiotic

resistance in bacteria, even though they might not be as effective as antibiotics alone. Furthermore, some of these substances can change antibiotic resistance and naturally have antibacterial qualities. Because complex chemical structures have fewer side effects and are less likely to develop resistance than manufactured drugs, they have a lot of potential for use in medicine [12]. Similar to how antibiotics function, if medicinal plant-based treatments contain only one active ingredient, bacteria may become immune to them. Given the paucity of research on the topic, it is imperative to learn more about how bacteria withstand plant-based therapies. Furthermore, how well the active ingredients in plant extracts interact affects their capacity to inhibit bacterial growth. The ability of compounds to target multiple pathways, substances that can inhibit bacterial resistance, and improvements in the absorption, solubility, and toxicity reduction of plant extracts are some of the reasons for this collaboration [13].

Numerous chemical compounds found in medicinal plants have been shown in laboratory experiments to have the capacity to eradicate bacteria. There are too many plants and substances with potent antibacterial qualities to discuss them all in this review. The following section of this discussion, however, will concentrate on some of the most important substances present in medicinal plants [14].

Research on plant chemicals has identified a number of compounds, including spermidine, rutin, quercetin, tocopherol, and carotenoids, in caper plants that can fight off bacteria, reduce oxidative stress, reduce inflammation, and combat viruses. Due to the presence of quaternary ammonium and glucosinolate compounds, extracts from Capparis decidua seeds have demonstrated antibacterial and antifungal qualities. While some herbs, like lemon balm, garlic, and tea tree, are known for their broad-spectrum antimicrobial properties, natural remedies, such as those derived from bearberry and cranberry, are well known for their use in treating urinary tract infections. Phenolics, alkaloids, flavonoids, triterpenes, and steroids are among the powerful substances with strong antimicrobial qualities that have been discovered in Cameroonian plants [15]. Research on plant chemicals has identified a number of compounds, including spermidine, rutin, quercetin, tocopherol, and carotenoids, in caper plants that can fight off bacteria, reduce oxidative stress, reduce inflammation, and combat viruses. Due to the presence of quaternary ammonium and glucosinolate compounds, extracts from Capparis decidua seeds have demonstrated antibacterial and antifungal qualities. While some herbs, like lemon balm, garlic, and tea tree, are known for their broad-spectrum antimicrobial properties, natural remedies, such as those derived from bearberry and cranberry, are well known for their use in treating urinary tract infections. Phenolics, alkaloids, flavonoids, triterpenes, and steroids15 are among the powerful substances with strong antimicrobial qualities that have been discovered in Cameroonian plants. Additionally, it has been discovered that extracts from Cistusmonspeliensis, Punicagranatum, and Berberis vulgaris exhibit strong anti-Enterococcus faecalis, anti-Enterococcus cloacae, and anti-Staphylococcus aureus properties. Furthermore, extracts from these plants have demonstrated significant activity against Staphylococcus aureus, Enterobacter cloacae, and Enterococcus faecalis [16].

Certain compounds were found in a fungus that lived inside a plant called Hypericumacmosepalum. These compounds included hyperenoneA, hypercalin B, hyperphorin, and emodin. In addition to other bacteria such as Pseudomonas aeruginosa, Salmonella enterica, Escherichia coli, Mycobacterium tuberculosis, Aspergillusniger, and Candida albicans, these substances were found to be effective against bacteria that have developed antibiotic resistance. Hypericumolympicum essential oil contains three main active ingredients: e-anethole, β-farnesene, and spathulenol. Other ingredients include E-caryophyllene, germacrene D, different kinds of terpenes, and a special kind of acylphloroglucinol. Although it demonstrated a wide range of activity, the crude methanol extract from Hypericumolympicum exhibited the strongest antibacterial effects against Salmonella enteritidis and Klebsiellapneumoniae. Medicinal plants were the main source of natural resins with antibacterial and antiprotozoal qualities. Propolis extract high in flavonoids, specifically galangin and pinocembrin, showed superior efficacy against Streptococcus pyogenes strains. The study investigated Korean propolis's antibacterial properties with regard to Streptococcus mutans. The fungus Diaporthaceae sp. from a marine sponge produced diaporthalasin, a strong antibacterial compound that was effective against methicillin-resistant Staphylococcus aureus (MRSA) as well as Staphylococcus aureus. Essential oils from aromatic medicinal plants, such as peppermint, fennel, lavender, and thyme, have been shown to be effective against fungi, viruses, and both Gram-positive and Gram-negative bacteria. These oils contain a range of volatile substances, including phenylpropanoids, sesquiterpenes, and monoterpenes [17].

2. Antimicrobial Activity Mechanisms of Medicinal Plant Derived Chemical Compound:

2.1. Alkaloids

Alkaloids are a broad class of complex nitrogen-based compounds that have analgesic, muscle-relaxant, and antimicrobial qualities. In particular, a number of studies indicate that alkaloids are essential for combating a variety of infections [18]. While quinine is well-known for its ability to effectively combat the malarial parasite, other alkaloids, such as indoquinoline alkaloids, have demonstrated efficacy against Gram-negative bacteria and fungi. Most alkaloids work by preventing the actions of enzymes.A powerful intercalator in various microorganisms, berberine is an isoquinoline alkaloid that selectively enters cells according to the electrical charge of the cell membrane. It also targets the cell's nucleic acid and enzymes that aid in DNA replication, including RNA polymerase, gyrase, and topoisomerase IV. As a result, by increasing bacterial permeability, berberine modifies the membrane's structure [19].

2.2. Phenolic Compounds/Polyphenols

Medicinal plants contain a wide variety of bioactive secondary metabolites called phenolic chemicals, which are frequently used to combat harmful bacteria [20]. Their effects, however, are typically mild and wide-ranging. Flavones, flavanols, flavonoids, quinones, and tannins are all members of this group. It has been demonstrated that these substances have a variety

of effects on various bacterial species. Although their exact mechanisms are still unknown, some known ones include inhibiting the activity of enzymes, altering the cell membrane's ability to let substances in or out, altering the activities occurring within the cell by interacting with enzymes, or weakening the bacterial cell wall's structure through different reactions with the cell membrane [21]. Flavones in particular are known to be an antimicrobial agent that weakens the membrane of bacteria. Conversely, flavanols interact with the bacterial cell wall and deactivate some bacterial enzymes, most likely through indirect interactions with proteins or by reacting with sulfhydryl groups [22]. Organic compounds called flavonoids have strong antiviral, antibacterial, and anti-inflammatory properties. Pseudomonas aeruginosa, Klebsiellapneumoniae, Mycobacterium tuberculosis, and Escherichia coli have all been shown to be effectively inhibited by certain flavonoids. It is thought that flavonoids' ability to interact with bacterial cell membranes and external proteins accounts for their antibacterial properties. Therefore, by inhibiting virulence factors such as QS signaling receptors and enzymes, rupturing and weakening the bacterial cell membrane, interfering with the activity of external microbial enzymes, and blocking vital nutrients for bacterial growth like iron and zinc [23], flavonoids can lessen the virulence of bacteria. Quinones can bind to nitrogen-containing amino acids in bacteria's proteins and produce stable radicals, which frequently results in a loss of protein function. Conversely, tannins work well against both gram-positive and gram-negative bacteria. The breakdown of the cell wall and membrane, the inhibition of oxidative phosphorylation that affects bacterial metabolism, the binding of base pairs in DNA, and the inhibition of bacterial enzymes, which generally influence gene expression, inhibit RNA production, and cause cell death are all credited with this activity [24].

2.3. Sulfur-Containing Compounds

The antibacterial, antifungal, antiviral, and antiprotozoal qualities of sulfur-rich compounds obtained from plants with high levels of polysulfides have been extensively studied [25]. Ajoene, isothiocyanates, and allicin are the main compounds of interest. These compounds have shown efficacy against Helicobacter pylori and other bacterial species, including both Gram-positive and Gram-negative ones [26]. Sulfur-containing substances may kill bacteria by inhibiting the activity of enzymes that use sulfhydryl groups and by partially preventing the synthesis of proteins and DNA. Furthermore, some substances have the ability to weaken the cell wall, which allows the contents of the cell to leak out. These substances' capacity to combat fungi is associated with lowering their oxygen consumption, boosting the accumulation of reactive oxygen species within the cell, and increasing the positivity of the mitochondria's outer membrane [27].

2.4. Coumarins

Both natural and synthetic coumarins are naturally occurring phenols that have antibacterial qualities [28]. In particular, Salmonella entericaTyphi, Enterobacteraerogenes, Enterobacter cloacae, Bacillus subtilis, Klebsiellapneumoniae, Staphylococcus aureus, MRSA, and Helicobacter pylori can all be effectively combatted by extracts of numerous medicinal plants that contain coumarins [29]. Bacterial pathogens' capacity to generate small signaling molecules, form biofilms, and produce virulence factors can all be impacted by coumarins'

ability to block the QS network [30]. Furthermore, certain coumarins are potent DNA gyrase inhibitors and block the MRS EP system. Additionally, studies have demonstrated that coumarins can activate macrophages, which may indirectly lower infection [31].

2.5. Terpenes

Terpenoids are chemical relatives of terpenes that contain additional elements, usually oxygen. Terpenes are also known as isoprenoids. They serve a wide range of purposes, from supporting cellular processes to assisting in cell structure, making them the most diverse group of naturally occurring compounds [32]. The primary constituents of essential oil blends that give plants their distinct scent are terpenes. Because essential oils' constituents work together rather than alone, they have shown stronger antibacterial qualities. They have demonstrated antibacterial properties against a number of bacteria, including Salmonella sp., Vibrio parahaemolyticus, Helicobacter pylori, Staphylococcus aureus, Escherichia coli, and Enterococcus faecalis [33]. Furthermore, they have shown differing levels of antibacterial activity against various fungal species. Terpenes exhibit a considerable amount of activity, particularly against Gram-positive bacteria, despite their limited solubility making it difficult for them to function as antibacterials. With a focus on Mycobacterium TB, several terpenoid compounds, such as diterpenoids, have demonstrated antibacterial activity against bacteria, fungi, viruses, and protozoa [34]. Terpenes' affinity for lipids, which enables them to penetrate bacterial cell walls, is intimately related to their antibacterial properties. The primary ways that monoterpenes impact the membrane are by increasing its fluidity and permeability, changing the structure of proteins, and stopping the respiration process [35]. Although it is unclear exactly how terpenoids function as antibacterials, it is thought to entail using lipid-soluble chemicals to break down the cell membrane, interfering with the cellular machinery, and causing the aggregation of cellular materials [36].

Table 1: Plant Containing Antimicrobial Activity

Sr. No.	Common Name	Scientific Name	Compound	Class	Activity
1	Aloe	*Aloe vera*	Latex	Complex mixture	Salmonella, Streptococcus, S.aureus
2	Apple	*Malussylvestris*	Phloretin	Flavonoid derivative	General
3	Ashwagandha	*Withaniasomniferum*	Withafarin A	Lactone	Bacteria, Fungi
4	Basil	*Ocimumbasilicum*	Essential oils	Terpenoids	Salmonella, bacteria
5	Black pepper	*Piper nigrum*	Piperine	Alkaloids	Fungi, lactobacillus, E. coli, Micrococcus
6	Blueberry	*Vaccinium spp.*	Fructose	Monosaccharide	E. coli
7	Clove	*Syzygiumaromaticum*	Eugenol	Terpenoid	General
8	Coca	*Erythroxylum coca*	Cocaine	Alkaloids	Gramm-

					negative and – positive cocci
9	Cranberry	*Vaccinium spp.*	Fructose	Monosaccharide	Bacteria
10	Dill	*Anethumgraveolens*	Essential oil	Terpenoids	Bacteria
11	Garlic	*Allium sativum*	Allicin, ajoene	Sulfoxide, Sulfated terpenoids	General
12	Ginseng	*Panaxnotoginseng*	-	Saponins	E. coli, Staphylococcus, Trichophyton
13	Green tea	*Camellia sinensis*	Catechin	Flavonoids	General, shigella, Vibrio, Viruses, S. mutans
14	Henna	*Lawsoniaintermis*	Gallic acid	Phenolic	S. aureus
15	Legume	*Millettiathonningii*	Alpinumisoflavone	Flavone	Schistosoma
16	Licorice	*Glycyrrhizaglabra*	Glabrol	Phenolic alcohol	S. aureus, m. tuberculosis
17	Onion	*Allium cepa*	Allicin	Sulfoxide	Bacteria, Candida
18	Papaya	*Carica papaya*	Latex	Terpenoids. Organic acids, alkaloids	General
19	Peppermint	*Menthapiperita*	Menthol	Terpenoid	General
20	Poppy	*Papaversomniferum*	Opium	Alkaloids and others	General
21	Quinine	*Cinchona sp.*	Quinine	Alkaloid	Plasmodium spp.
22	Rauwolfia	*Rauvolfiaserpentina*	Reserpine	Alkaloid	General
23	Rosemary	*Rosmarinusofficinalis*	Essential oil	Terpenoid	General
24	Senna	*Cassia angustifolia*	Rhein	Anthraquinone	S. aureus
25	St. John’s wort	*Hypericumperforatum*	Hypericin, others	Anthraquinone	General
26	Tansy	*Tanacetumvulgare*	Essential oil	Terpenoid	Helminths, bacteria
27	Thyme	*Thymus vulgaris*	Caffeic acid, Thymol, Tannins	Terpenoids, Flavones, Phenolic alcohol	Viruses, bacteria, fungi
28	Turmeric	*Curcuma longa*	Curcumin, Turmeric oil	Terpenoids	Bacteria, Protozoa

3. Mechanisms of Action of Antimicrobial Agents:

An agent's antimicrobial activity is explained by two fundamental processes: avoiding the conventional mechanisms of resistance to antibacterial agents and chemically interfering with the production or operation of vital bacterial components. However, bacteria may develop an innate resistance to specific antimicrobials due to selection pressures or by learning the

resistance mechanism from neighboring microbes. The following mechanism is consistent with well-known antimicrobial medications (Fig. 1).

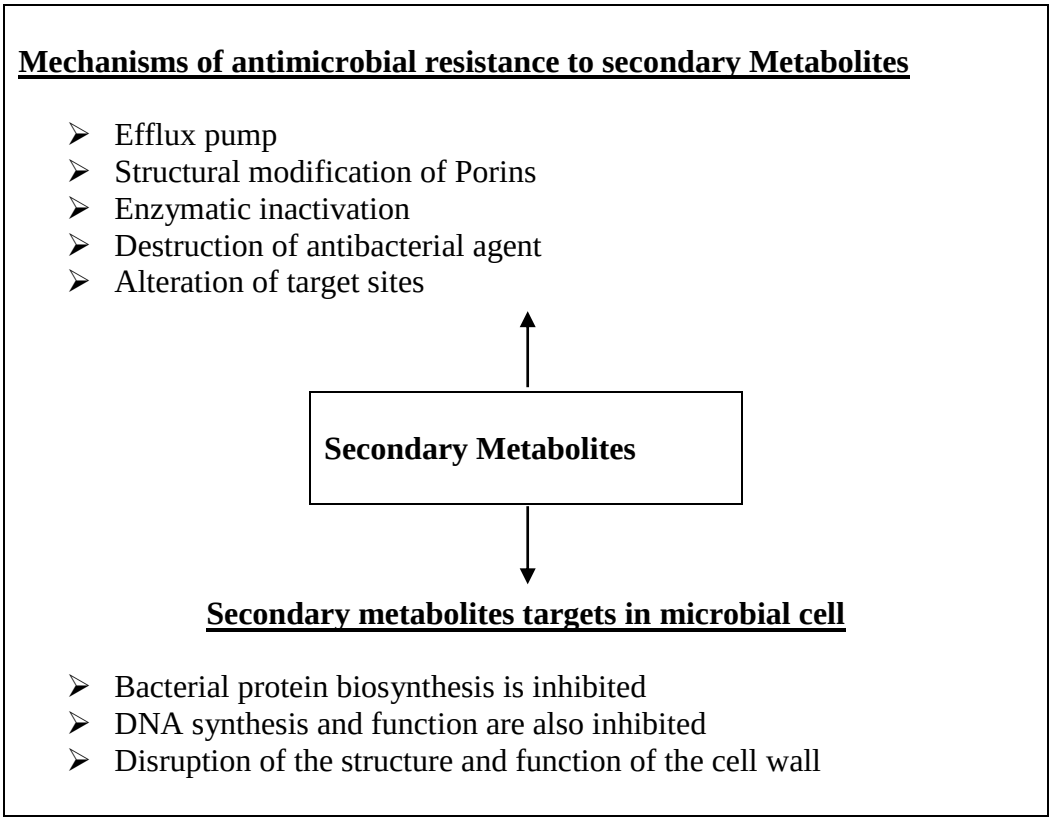

Figure 1: Mechanisms of antimicrobial agents and resistance by pathogens.

3.1. Bacterial Protein Biosynthesis

Reducing protein synthesis by focusing on the ribosomal subunits of bacteria is a useful strategy against bacterial infections. This mechanism enables the production of antibiotics with antibacterial activity, such as tetracyclines, aminoglycosides, macrolides, and oxazolidinones. Amikacin inhibits the synthesis of proteins by altering the structure of the ribosome and preventing it from correctly reading the mRNA codon. In order to do this, it forms an irreversible bond with the 30 S component of the bacterial ribosome's RNA-binding S12 protein and 16 S rRNA. It also inhibits the region that engages with the tRNA anticodons oscillating base [37].

3.2. Inhibition of Nucleic Acid Synthesis

The enzyme DNA gyrase is essential for bacterial DNA synthesis, replication, repair, and transcription. This makes gyrase a prime target for antibacterial medications called fluoroquinolones, such as ciprofloxacin and nalidixic acid. Ciprofloxacin inhibits type II topoisomerase (DNA gyrase) and topoisomerase IV, which are necessary for bacterial DNA separation and, consequently, cell division [38].

3.3. Cell-Wall Biosynthesis

Bifunctional enzymes called transglucosylases and transpeptidases are crucial for the development of the bacterial cell wall and may be the target of bactericidal medications like cephalosporins, vancomycin, and penicillin. These antibiotics can obstruct an enzyme process by binding to the peptide substrate of the peptidoglycan layer. Vancomycin, for instance, functions by stopping Gram-positive bacteria from correctly synthesizing their cell walls. Vancomycin is a large hydrophilic molecule that can form hydrogen bond interactions with the terminal D-alanyl-D-alanine moieties of N-acetylmuramic acid (NAM)/N-acetylglucosamine (NAG) peptides. By binding to the D-Ala-D-Ala, vancomycin prevents the synthesis of the lengthy polymers of NAM and NAG, which are responsible for creating the backbone strands of the cell wall [39].

3.4. Destruction of Bacterial Cell Wall

Various antibiotics, such as polymyxins, can bind to the fat portion of lipopolysaccharide, changing its structure by exchanging phospholipids. A water concentration imbalance and the rapid death of bacteria could result from this. By attaching itself to a negatively charged region of the lipopolysaccharide layer, which is attracted to the positively charged portions of the cyclic peptide portion, polymyxin B facilitates the passage of bacteria through their outer membrane. The outer membrane becomes unstable as a result. Additionally, when the fat portion of the lipopolysaccharide dissolves in the nonpolar portion of the cell membrane, the membrane breaks down, releasing the contents of the cell and halting the cell's energy production process [40].

4. Mechanisms of Resistance to Antimicrobial Agents:

The development of multidrug resistance (MDR) in various pathogenic bacteria is directly caused by the extensive and improper use of antibiotics [41]. Resistance genes and their ensuing effects are the main causes of antimicrobial resistance, which presents a complicated and important global public health concern. These traits may arise naturally from bacterial DNA mutations, be inherited, or be picked up from other pathogens. To effectively control the emergence and spread of infectious organisms resistant to currently available antimicrobial medications, no one or straightforward strategy will be adequate [42]. The urgent need to preserve the efficacy of existing drugs is highlighted by the current dearth of novel antimicrobials to replace ineffective ones. Numerous processes, each covered separately in figure 1, can cause bacteria to become resistant to antibacterial agents.

4.1. Efflux Pump

The interbacterial concentration is much lower than the effective level because the antibacterial agent is released faster than it takes for it to diffuse into bacterial cells. Particularly in the case of EP-mediated inhibitors of protein synthesis systems, the reduction in concentration within bacteria frequently permits unhindered bacterial protein synthesis processes, including ribosomes [43]. Numerous dangerous bacteria and fungi, including Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacterbaumannii, and Candida albicans, can develop antibiotic resistance as a result of EPs [44]. The combination of EPs and decreased drug uptake brought on by the multi-membrane layer is the main cause of the high intrinsic and acquired antibiotic resistance frequently seen in Gram-negative bacteria.

Consequently, it is frequently thought that using EP inhibitors in conjunction with antibacterial agents is a successful way to fight microbial infections [45].

4.2. Structural Modification of Porins

Proteins called porins create water-filled channels that allow molecules to passively pass through lipid bilayer membranes, thereby regulating the entry of antibiotics. Changes in membrane permeability brought about by variations in porin structure provide an alternative to antibacterial medications. Pseudomonas spp. and Acinetobacter spp. are two examples of Gram-negative bacteria that commonly exhibit this kind of antibiotic resistance [46].

4.3. Enzymatic Inactivation

Three different kinds of enzymes alter functional groups in gram-negative bacteria, causing them to become resistant to aminoglycosides. Protein synthesis is ultimately inhibited by the altered components' reduced affinity for RNA, which keeps them from attaching to ribosomes [47].

4.4. Destruction of Antibacterial Agent

Another tactic used by bacteria to resist antibiotics is chemical degradation or modification of the antibiotics' chemical makeup. Penicillin, cephalosporins, and carbapenems are broken down more easily when the hydrolytic enzyme β-lactamase bonds to the β-lactam ring [48].

4.5. Alteration of Target Sites

Another way that resistance develops is through changes to the drug-binding site, which make it more difficult for the antibacterial agent to interact with the target bacterial site and, as a result, less effective against bacteria. Vancomycin-resistant enterococci species display vancomycin-resistance through a mechanism involving van HAX genes, which generate enzymes that cause structural changes in the peptidoglycan structure from amide linkage to ester linkage, decreasing antibiotic-binding affinity [49].

The rise of various antibiotic-resistant pathogenic species is one of the largest problems we are currently facing. Growing in prevalence, multidrug-resistant bacteria pose a major risk to public health worldwide. The probability of effectively treating infections is significantly decreased, and it also raises the morbidity and mortality linked to common bacterial illnesses [50]. The use of antibiotics has been associated with the emergence of antibiotic resistance since the 1928 discovery of penicillin. Furthermore, resistance of bacterial strains to newly developed antibiotics has been observed on a regular basis. As a result, fighting antibiotic resistance is still an ongoing endeavor that calls for a number of approaches. Because bacterial resistance is still developing and antibiotic development is slowing down, the situation is alarming. Bacteria use a range of defense mechanisms against antibiotics, such as target modification, enzymes, efflux pumps, low outer membrane permeability, and biofilm formation. Horizontal gene transfer is a common method used in these strategies to acquire new genetic elements [51].

Table 2. Antimicrobial Resistance mechanisms against antibiotic different classes

Sr. No.	Drug	Drug uptake limitation	Drug target modification	Drug inactivation	Efflux Pumps
1	B-Lactams	+	+	+	+
2	Carbapenems	+	-	-	-
3	Cephalosporins	+	-	-	-
4	Glycopeptides	+	+	-	-
5	Lipopeptides	-	+	-	-
6	Aminoglycosides	+	+	+	+
7	Tetracyclines	+	+	+	+
8	Chloramphenicol	-	+	+	+
9	Lincosamides	-	+	-	+
10	Macrolides	-	+	-	+
11	Oxazolidinones	-	+	-	+
12	Streptogramins	-	-	-	+
13	Fluoroquinolones	-	+	-	+
14	Sulfonamides	-	+	-	+
15	Trimethoprim	-	+	-	+

Since more than 80% of recorded antibiotics in the last 20 years have come from various terrestrial sources like plants, fungi, and lichen, Figures 2 and 3 demonstrate the important role that natural products and their semi-synthetic equivalents play in the development of antimicrobial drugs. Nature-derived compounds have been the focus of special attention due to their potential to fight a variety of microorganisms, despite their obvious effects on safety. In the fight against resistant infections, a variety of pure natural compounds and their recently created synthetic counterparts have proven to be effective substitute antimicrobial agents [52]. Furthermore, using natural antimicrobial agents to replace ineffective antibiotics has attracted a lot of attention.

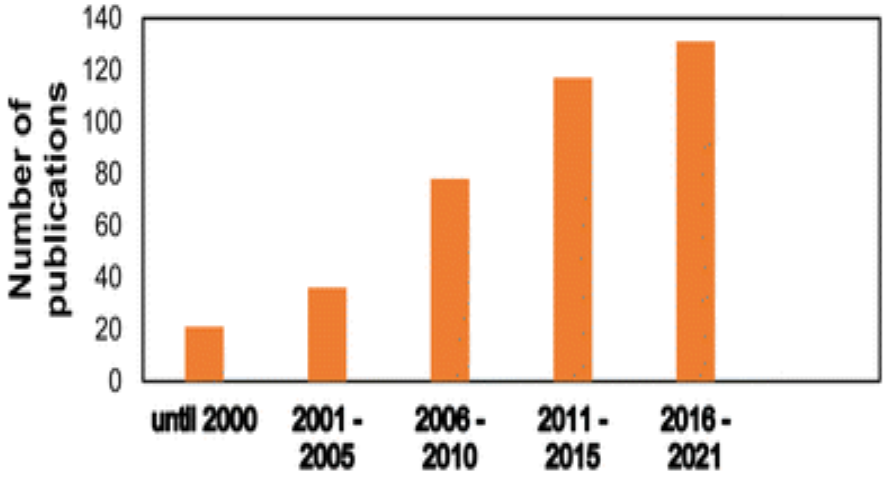

Figure 2: Distribution of publications covering antimicrobial agents derived from natural products in the last period of research

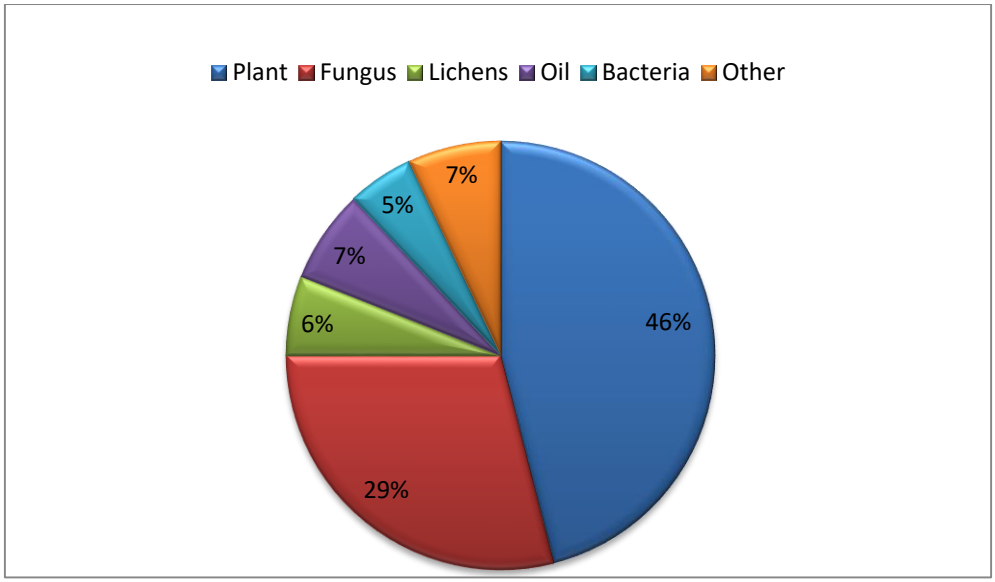

Figure 3: Natural products against drug resistant bacteria from diverse terrestrial sources

5. Use of Antimicrobials from Medicinal Plant Extracts:

Antimicrobial-containing medicinal plant extracts are more readily available, less expensive, and natural than synthetic alternatives, which makes them a safer and more cost-effective option for treatment with potential therapeutic benefits [53]. Furthermore, plant extracts with medicinal properties may be a helpful treatment option when dealing with a range of side effects and drug resistance [54].

Future applications of medicinal plant-derived antibacterial compounds against microorganisms are not fully represented by the current rate of approved antibacterial compound production. There are definitely some inherent difficulties when using natural plant extracts as antimicrobial medications:

- Recent research indicates that it is important to be cautious when using medicinal plant compounds without clear evidence of their effectiveness. It is uncommon to find thoroughly conducted toxicological and clinical studies that are both double-blind and well-controlled to demonstrate the efficacy and safety of products [55].
- The use of medicinal plants raises problems that hinder the development of new antimicrobials, such as adulteration, subpar cultivation techniques, inconsistent preparation, and unsuitable storage conditions. The concentrations and mechanisms of various substances in extracts can be affected by various factors, including the time of harvesting, the growth location, the plant components used, and the extraction technique. Because of this, it can be difficult to compare data from the literature regarding the antimicrobial activity of plant extracts because the composition of these extracts varies depending on the local climate and environmental factors. Different geographical areas have different amounts of rainfall and humidity, which can cause variations in the compounds' composition and yield when the same medicinal plant species is grown in different places. Furthermore, the worldwide climate change is an additional obstacle affecting the weather and putting at risk the formation and output of compounds, even in the same areas [56].

- Mapping the complex interactions between the various compounds in a medicinal plant is difficult for scientists. Because plant extracts contain many different components, it can be difficult to determine their exact composition and interpret the results. It could take a long time and possibly require a large amount of plant material to isolate individual compounds that have antimicrobial qualities. Problems may also arise if the same compounds are found again in different sources. As a result, while difficult, standardization, stability, and quality control are achievable. However, the chance to investigate many unknown compounds may result in a renewed interest in medicinal plants [57].
- The interaction of compounds in a complex mixture poses challenges due to the lack of advanced technology for studying multiple compounds affecting various biological targets simultaneously.
- Securing access to medicinal plant species can prove challenging, particularly in a global context. Rules for gathering and trading plants vary based on the location of the research being carried out [58].

SUMMARY:

The rise of multi-drug resistance in bacteria that harm humans and animals, along with negative reactions to some antibiotics, has sparked a high level of curiosity in the quest for new plant-derived antimicrobial medications. Due to side effects and antibiotic resistance, numerous scientists are now focusing on extracts and bioactive compounds from plant species utilized in herbal remedies. There is a growing number of reports on the antimicrobial properties of medicinal plants from various regions worldwide. Antimicrobials can play a crucial role in treating resistant strains of microbes, making them clinically valuable. Specifically, plant oils and extracts have been utilized for various purposes such as preserving raw and processed food, creating pharmaceuticals, practicing alternative medicine, and providing natural therapies due to their antimicrobial properties. Reports indicate that higher plants have demonstrated potential as a source for new antimicrobial agents. It is determined that medicinal plants have the potential to act as antimicrobial agents in developing new drugs to treat infectious diseases in humans.

CONCLUSION:

The antimicrobial activity of medicinal plants offers a new opportunity to fight against the growing threat of antimicrobial resistance. Hence, it is crucial to discover and separate new bioactive substances from medicinal plants, which have not been fully researched. The wide range of these substances has shown promise in treating infections and combating antimicrobial resistance.

The utilization of novel bioactive compounds remains difficult. It is important to highlight that thorough in vitro and in vivo testing is necessary to ensure the identification of effective and safe antimicrobial compounds derived from plants. Harnessing the potential synergies or antagonisms between compounds in medicinal plant extracts poses a significant challenge. With the progress of biotechnology, it becomes clear that we will have the ability to delve deeper into the chemical makeup of medicinal plants and create more advanced methods for extracting, separating, and pinpointing bioactive compounds with various chemical structures and modes of operation. Standardization of extraction and in vitro testing methods would be beneficial for a more systematic approach to the search and easier interpretation of results.

Furthermore, reference models have not been utilized in investigating plant extract combinations and their suitability for this method will be explored in future research.

Research on how extracts work, their interactions with other drugs or plants, and their effects in the body should be top priority.This review and the identified challenges in this field are anticipated to aid in the development of faster, more effective, and simpler methods for utilizing new therapeutic medicinal plants against microbes.

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