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Antimicrobial activity of Plant derived extracts on disease causing strains of bacteria: *Escherichia coli, Staphylococcus aureus, Pseudomonas aureus.*

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Abstract:
The need for novel antimicrobial remedies is highlighted by the rising incidence of drug-resistant microorganisms. Medicinal plants have the potential to provide new avenues for fighting pathogenic microorganisms by supplying novel bioactive chemicals. This review looks at the modes of action and chemical variety of chemicals derived from plants that have antibacterial characteristics. It also discusses the inconsistent results of antimicrobial susceptibility tests and the difficulties in optimizing extraction methods, which differ depending on the species of plant. Though more investigation is required to fully understand their pharmacokinetic and pharmacodynamic characteristics, medicinal plant extracts continue to hold promise for the development of antimicrobial agents despite these obstacles. In parallel, this review delves at the background of antibiotic discovery, the emergence of antibiotic resistance, and the processes via which bacteria.

Keywords: *Antimicrobial activity, Drug-resistant bacteria, Medicinal plant compounds, Bioactive substances, antimicrobial susceptibility, Antibiotic discovery, Resistance mechanisms, plant-based antimicrobials.*

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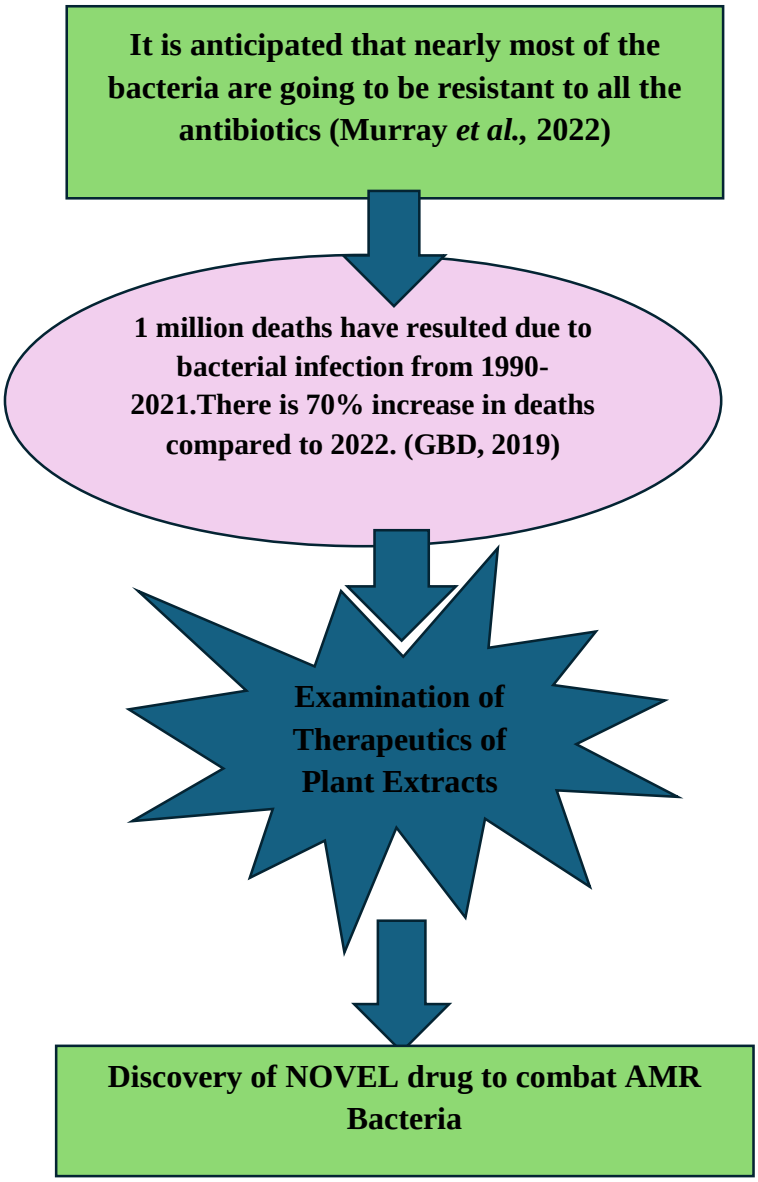
I. INTRODUCTION:

Microbes are tiny living organisms that inhabit a wide range of environments, including water, soil, the Earth's crust, and extreme conditions like acidic hot springs and radioactive waste (Madigan *et al.*, 2012). The discovery of microscopic organisms occurred between 1665 and 1683, attributed to pioneers like Robert Hooke and Antoni van Leeuwenhoek (Lane, 2015). Some microbes are harmful and cause illness, while others are essential for maintaining human health (Lloyd-Price *et al.*, 2016). Researchers estimate that the human body hosts around 10,000 different microbial species (Qin *et al.*, 2010). One significant role of gut microbes is aiding digestion, affecting how food is metabolized and stored (Turnbaugh *et al.*, 2006). Microbes also play a vital role in protecting the skin from illness and injury, acting as a first line of defense (Grice & Segre, 2011). There is strong evidence that microbes in the female reproductive tract help protect against diseases (Ravel *et al.*, 2011). Additionally, microbes contribute to the production of essential nutrients like Vitamin K2, particularly menaquinone-4 and menaquinone-7 (Conly & Stein, 1992). In food and medicine, microbes are indispensable for producing items like bread, cheese, yogurt, wine, and medical products like insulin and the HPV vaccine (Buchanan & Gibbons, 1974; Frenkel, 2020). There is a small fraction of millions of microbes on the planet that cause serious illness and even death, and such harmful microbes are referred to as pathogens (Kumar *et al.*, 2014). Among viruses, the influenza virus is the causative agent of the flu, while viral hemorrhagic fevers (VHF) are among the world's most dangerous infections (Ergonal *et al.*, 2018). HIV causes AIDS by interfering with the body's ability to fight infections, and the herpes virus leads to various viral skin infections (Bannister *et al.*, 2006). Fungi like *Aspergillus fumigatus* cause aspergillosis, a serious lung infection, while *Candida albicans* commonly infects the skin and mucous membranes (Latge, 1999). Bacteria, including *Mycobacterium tuberculosis*, which causes tuberculosis, and *Pseudomonas aeruginosa*, responsible for infections like hot tub folliculitis, also pose health risks (Stover *et al.*, 2000). *Streptococcus aureus* causes strep throat, and bacteria such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* lead to sexually transmitted infections (STIs), causing symptoms such as itching and genital discharge (Van Grewan *et al.*, 2022). Microbial diseases like tuberculosis, polio, smallpox, and diphtheria once caused dramatic increases in morbidity and mortality rates (Baker *et al.*, 2021). More recently, the 2009 swine flu pandemic, the 2012 MERS coronavirus outbreak, and the 2013-2016 Ebola epidemic in West Africa resulted in significant global health impacts (WHO, 2020). In 2019, bacterial infections were responsible for 13% of global deaths, with E. coli accounting for 8.8% of mortality in India (Murray *et al.*, 2022). In Kashmir,

outbreaks of diseases like measles, hepatitis, and influenza have been reported frequently since 2005 (Khan *et al.,* 2013).

Certain bacterial species like *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* are of special interest in clinical microbiology due to their roles in infections and antibiotic resistance (Prajescu *et al.,* 2023).

- ***Escherichia coli*** is a gram-negative, rod-shaped bacterium with cells measuring 2.0 μm in length and 0.25-1.0 μm in diameter (National Academies Press (US), 1999). It causes a range of diseases including gastroenteritis and urinary tract infections, with symptoms such as severe abdominal cramping, diarrhea, and vomiting (Croxen & Finlay, 2010).
- ***Pseudomonas aeruginosa*** is a gram-negative, aerobic, non-spore-forming rod bacterium that is notorious for its ability to infect both healthy and immunocompromised individuals (Pang *et al.,* 2019). It is highly adaptable and difficult to treat due to its antibiotic resistance mechanisms and dynamic defenses. The bacterium is typically 0.5–1.0 μm wide and 1–5 μm long, with a genome size ranging between 5.2 and 7 million base pairs (Mbp) (Stover *et al.,* 2000). The production of beta-lactamase enzymes, encoded by plasmids like TEM, OXA, and PSE, significantly contributes to its resistance to antibiotics (Oliver *et al.*, 2015). While *P. aeruginosa* rarely infects healthy individuals, it is opportunistic, often colonizing those with weakened immune systems, such as patients with cancer, AIDS, or cystic fibrosis (Lyczak *et al.*, 2000). The virulence factors it produces are capable of causing tissue damage, and infections are often chronic and life-threatening. This pathogen is also associated with severe eye diseases (Fleiszig *et al.,* 2012).
- ***Staphylococcus aureus*** is a gram-positive, spherical bacterium that is a natural part of the human microbiota (Lowy, 1998). It is a well-known pathogen, responsible for a wide range of infections, from minor skin conditions like impetigo to severe diseases like pneumonia, infective endocarditis, and osteomyelitis (Tong *et al.,* 2015). The *S. aureus* genome, first mapped from the strain NCTC 8325, has approximately 2,900 open reading frames and a G+C content of 33%, with 85% of its DNA being coding sequences (Kuroda *et al.*, 2001). Virulent strains such as methicillin-resistant *S. aureus* (MRSA) have posed significant challenges in both healthcare and community settings due to their resistance to multiple antibiotics (Otto, 2012).
- Antibiotics, a class of antimicrobial agents, have been pivotal in combating bacterial infections since their discovery. Penicillin, discovered by Alexander Fleming in 1928, revolutionized the treatment of bacterial infections (Fleming A; 1929). The greatest medical discovery of the 20th century has been the development of antibiotics for clinical use (Katz & Baltz, 2016). By the turn of the 20th century, it was known that bacteria generate a new and powerful source of antibacterial and antifungal activities (Maiyo *et al.*, 2010). Despite of the great efficacy of commercially available antibiotics the world is at higher risk of infections due to the ability of bacteria to develop the antibiotic resistance. Antimicrobial resistance has emerged as a result of the widespread, improper, irregular, and indiscriminate use of antibiotics, rendering many currently prescribed drugs useless (WHO, 2014; Baym *et al.*, 2015; Davies and Davies, 2010). It is anticipated that by 25 years, nearly all bacteria will be resistant to the majority of pharmaceutical antibiotics (Kaur Sodhi and Singh, 2022; Murray *et al.*, 2022). Due to this rising global issue the world has shifted its interest to natural plant products for inhibiting the activity of bacteria or to combat resistance issue.
- Plant extracts, including Azadiracta indica (Biswas *et al.*, 2002), Curcuma longa (Kim *et al.*, 2014), Pisidium guajava L. (Lutterodt, 1999; Ahmad and Ansari., 2001), Salvia officinalis L., and Ziziphus spina-Christi (Shahat *et al.*, 2001), all have medicinal properties. These findings suggest that plant extracts with antimicrobial properties could serve as promising candidates for the development of natural antimicrobial agents. They offer a potential alternative to synthetic antibiotics, especially in the context of increasing antibiotic resistance. Additionally, these extracts could be integrated into natural preservative systems for food and cosmetics, contributing to the reduction of microbial contamination and spoilage. Despite the promising results, several limitations were noted. The variability in antimicrobial potency among different extracts and preparations highlights the need for standardization in extraction methods and concentration.
- Moreover, the mechanisms underlying the antimicrobial activity of these plant extracts are not fully understood, warranting further investigation to elucidate how these compounds interact with microbial targets. Future research should focus on exploring the synergistic effects of plant extracts when used in combination with conventional antibiotics. This method could enhance the efficacy and stability of these antimicrobial agents. Clinical trials are also necessary to evaluate the safety and effectiveness of these extracts in real-world applications, providing a clearer understanding of their potential therapeutic benefits. Overall, the antimicrobial activity of plant extracts offers a valuable avenue for developing natural alternatives to conventional antibiotics. As research progresses, these natural products could play a crucial role in addressing the challenges of antimicrobial resistance and promoting health through sustainable and effective treatments.



II. REVIEW OF LITERATURE:

1. ANTIBIOTICS:

From the French terms "antibiose" and "antibiotique," which were defined by Vuillemin in the late 19th century to describe compounds that exert harmful consequences on living things, especially microbes (Laskin and Laskin, 2002). Later on, in 1947, Selman A. Waksman gave a thorough explanation of antibiotics as substances created chemically by microbes with the ability to hinder the development and cause the demise of microorganisms such as bacteria (Waksman, 1947; Sodhi and Singh, 2022). The earliest known medical record is the Eber's papyrus, which dates to 1550 BC and lists therapeutic soil and moldy bread among its treatments (Hass, 1999). An Anglo-Saxon recipe from 1000 years ago has also recently been shown to kill MRSA (methicillin-resistant *Staphylococcus aureus*) (Harrison, 2015). Paul Ehrlich is largely credited with developing the synthetic arsenic-based pro-drugs salvarsan (salvation arsenic) and neo-salvarsan approximately 100 years ago to treat *Treponem*a *pallidum*, the causative agent of syphilis (Gelpi *et al.*, 2015). The discovery of penicillin, which Alexander Fleming witnessed on a contaminated Petri dish in 1928, significantly eclipsedthe usage of sulfonamides, which were the first really effective, broad-spectrum antimicrobials in clinical use and are still in use today (Fleming, 1929). It was Louis Pasteur, who postulated that germs could release substances capable of destroying other microorganisms (Brunel, 1951). By the turn of the 20th century, it was known that bacteria could produce diffusible and heat-stable chemicals (Frost, 2016) and their potential to combat infectious diseases had been investigated. *Pseudomonas aeruginosa* (then known as *Bacillus pycyaneus*) extract was used to treat hundreds of patients by Emmerich and Low in the 1890s, in what is arguably the earliest documented therapeutic use of an antibiotic. This extract, known as pyocyanase, was in useuntil the 1910s (Emmerich and Low, 1899).

The majority of antibiotics undergoing clinical trials today are not novel classes of antibiotics, but rather are synthesized or recognized classes of NP compounds. The genus Streptomyces produced half of all antibiotics discovered between 1945 and 1978 (Embly, 1994). There are no. of theories suggesting that soil microbes produce several NP antibiotics. The most plausible hypothesis is that these NP antibiotics serve a variety of purposes in these microbes, including using chemical weapons to eliminate rivals in the ground, either as signalling molecules to close relatives or to facilitate connections with eukaryotic host, they can be either offensive or defensive in their predation (Seipke, 2012) (Klassen, 2014; Traxler and Kolter, 2015). The greatest medical discovery of the 20th century has been the development of antibiotics for clinical use (Katz and Baltz, 2016).

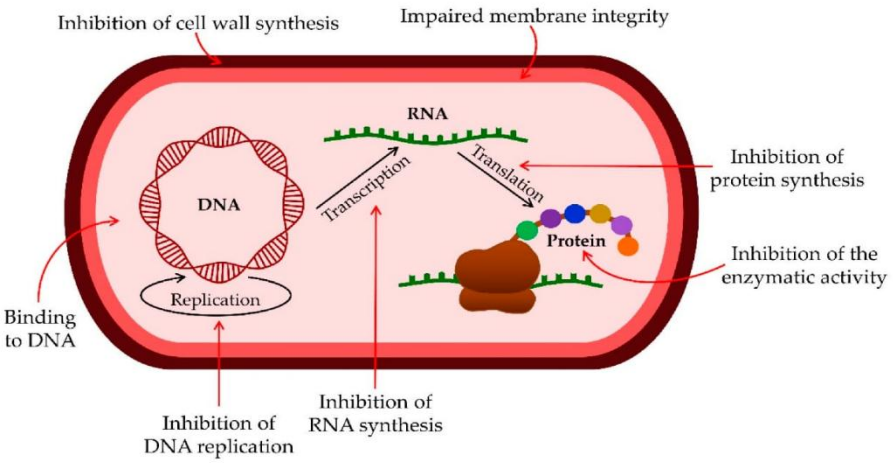
According to Sodhi and Singh (2022), there are four main mechanisms by which antibiotics work. These mechanisms include the inhibition of DNA replication (Fabrega *et al.*, 2009), protein biosynthesis (Tenson *et al.*, 2003), cell wall biosynthesis (Cho *et al*., 2014) and folic acid metabolism (Donnelly, 2001).

1.1. Antibiotics inhibit DNA replication: The process of making duplicate copies of DNA is called DNA replication (Gilbert, 2001). The replication process involves several enzymes to carry out synthesis of two new DNA strands complementary to old DNA, enzymes like DNA polymerase (Li and Araki, 2013), DNA helicase, DNA gyrase (Alt *et al.*, 2011) are involved. Certain antibiotics inhibit replication by affecting activity of these very crucial enzymes.

1.2. Antibiotics inhibit protein biosynthesis by targeting the ribosomal 30S or 50 S subunits which includes Aminoglycosides antibiotics whose target is the 16s rRNA of the 30s, which they bind to via hydrogen bonds. This binding inhibits protein biosynthesis before it can be completed (Vicens and Westhof, 2003), Tetracycline antibiotics which targets the highly conserved sequence of the 16S rRNA present in the ribosomal 30S subunit, Chloramphenicol antibiotics which inhibit peptidyl transferase, an enzyme located on the 50S ribosomal subunit that is necessary for protein synthesis. This inhibition prevents t-RNA from connecting to the ribosomal A site, leading to the inhibition of protein synthesis (Syroegin *et al.*, 2022), Macrolide antibiotics and Oxazolidinone antibiotics also bind to 50S ribosomal subunit and inhibit protein synthesis.

1.3. Antibiotics inhibit folic acid metabolism where Sulfonamide antibiotics target dihydropteroate and trimethoprim antibiotics target dihydrofolate reductase enzymes in the pathway (Capasso and Supuran, 2014).

1.4. Antibiotics inhibit cell wall synthesis which involves Beta lactams antibiotics comprising all cephalosporins and penicillins having the beta-lactam ring chemical structure (Fernandes *et al*., 2013). Because of their unique structure, they can bind to enzymes that cross-link peptidoglycans, like transpeptidase and carboxypeptidase, which inhibits the formation of bacterial cell walls and prevents cross-linking (Cho *et al.*, 2014). This inhibition of cell wall production results in the bacterial cell's death (Cho *et al.*, 2014). Glycopeptide antibiotics prevent cross linking of Precursors of peptidoglycan by creating non-covalent connections with the terminal carbohydrates. The process eventually results in the breakdown of bacterial cell walls, which causes the cells to be destroyed and eliminated (Kang and Park; 2015).



Source: https://doi.org/10.3390/antibiotics11101417

Fig.1: Mechanism of Antibiotic action of antibiotics.

Table 1: All classes of clinically used antibiotics and their source

Class	Discovery reported	Introduced clinically	Example (and producing organism)	Molecular target
Aminoglycosides	**1944**	**1946**	**Kanamycin A (*Streptomyces kanamyceticus*)**	**Protein synthesis: 30S ribosomal subunit**
Tetracyclines	**`1948**	**1948**	**Tetracycline (*Streptomyces aureofaciens)***	**Protein synthesis: 30S ribosomal subunit**
Amphenicols	**1947**	**1949**	**Chloramphenicol *(Streptomyces venezuelae*)**	**Protein synthesis: 50S ribosomal subunit**
Macrolides	**1952**	**1952**	**Erythromycin (*Saccharopolyspora erythraea*)**	**Protein synthesis: 50S ribosomal subunit**
Streptogramins	**1953**	**1965**	**Pristinamycin (*Streptomyces pristinaespiralis***	**Pristinamycin (*Streptomyces pristinaespiralis* subunit.**
Polypeptides	**1939**	**1941**	**Gramicidin A (*Bacillus brevis)***	**Cell wall: forms ion channels that increase the permeability of the bacterial cell membrane.**
Penicillins	**1929**	**1943**	**Semi-synthetic derivative of penicillin (*Penicillium chrysogenum).***	**Cell wall synthesis: penicillin-binding proteins**
Sulfonamides	**1932**	**1936**	**Mafenide**	**Folate synthesis: inhibition of dihydropteroate synthetase.**
Oxazolidinones	**1987**	**2000**	**Linezolid**	**Protein synthesis: 50S ribosomal subunit.**

2. MECHANISM OF ANTIBIOTIC RESISTANCE:

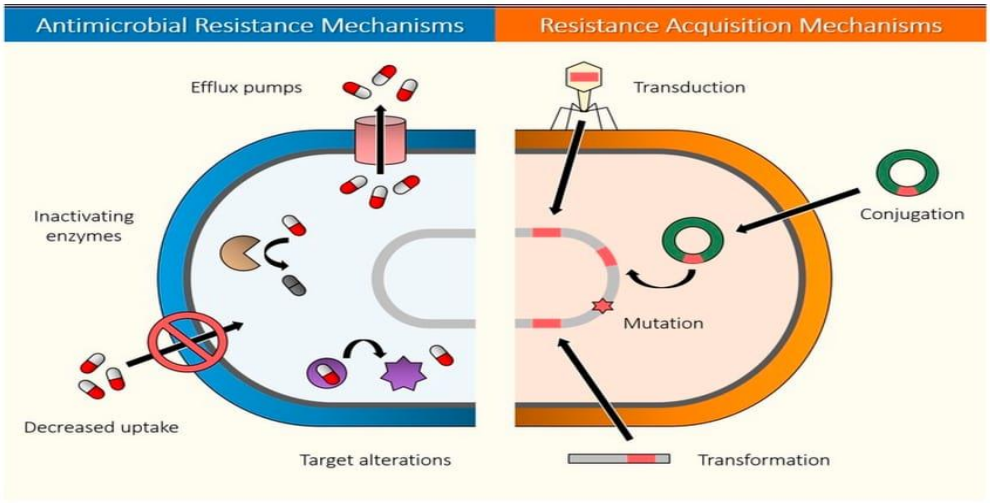
Resistance is more likely to develop when a patient is unable to obtain the antibiotic concentration required to either suppress or kill the bacterium (Tenovar, 2006). A century of advancements in healthcare and the accomplishment of sustainable development objectives are seriously threatened by the global epidemic of antibiotic resistance, according to Dr. Tedros Adhanom Ghebreyesus, CEO of the World Health Organization (WHO) (Sarkar *et al.,* 2021). Antimicrobial resistance has emerged as a result of the widespread, improper, irregular, and indiscriminate use of antibiotics, rendering many currently prescribed drugs useless (WHO, 2014; Baym *et al.,* 2015; Davies and Davies, 2010). It is anticipated that by 25 years, nearly all bacteria will be resistant to the majority of pharmaceutical antibiotics (Sodhi and Singh, 2022; Murray *et al.,* 2022). Additionally, experts estimate that by the middle of the twenty-first century, antimicrobial resistance-related mortality could account for 10 million deaths annually, up from the present total of over 700,000 (Romandini *et al.,* 2021). According to WHO, microbes exhibiting highest trend in resistance observed in 2017 are as; *Acinobacter baumannii, Pseudomonas aeruginosa, Enterobacteriaceae, Enterococcus faecium, Helicobacter pylori, Salmonella species, Campylobacter species, Staphylococcus aureus, and Nisseria gonorrhoeae.* Bacteria employ three primary mechanisms to counteract the effects of antibiotics (Zhou *et al.,* 2015). Antibiotic resistance can be acquired by microorganisms through exposure or can be innate (Premlatha, 2019). Gene mutations or direct transfer of resistance genes can lead to the development of resistance (Sodhi *et al.,* 2023). These genes can be carried on plasmids (mobile genetic elements) and transmitted through conjugation (Sodhi and Singh, 2022; Shree *et al.,* 2023) alternatively, equivalent DNA can be transferred directly through transformation (Shree *et al.,* 2023) or similar DNA can be transferred through bacteriophages (Kaur Sodhi and Singh, 2022; Shree *et al.,* 2023), a process known as transduction. Genetic material, particularly genes resistant to antibiotics, can spread quickly even amongst bacteria of different species (Džidić *et al.,* 2008). According to reports, biofilm development (Shree *et al.,* 2023) and heavy metals (Sodhi *et al.,* 2023) promote the spread of antibiotic resistance in bacteria.

THE MECHANISMS ARE AS FOLLOWS:

1. **Bacteria prevent antibiotic accumulation in their cells**: Gram-negative bacteria have porin channels in their outer membrane (Kang and Park, 2015) which acts as gatekeepers allowing only certain antibiotics like B-lactams and quinolones to enter the bacterial cell. By reducing these bacterial porins it can hinder the entry of these antibiotics into the cell, leading to increased resistance to these drugs (Darby *et al.,* 2023). Also, Bacterial cytoplasmic membranes contain efflux pumps, which are essential for preserving the solute balance inside of bacterial cells. Nevertheless, by removing medications from bacterial cells before they can reach their intended targets, these pumps also contribute to antibiotic resistance (Džidić et al., 2008).
2. **Bacteria modify the target molecule of antibiotics:** Antibiotics are intended to bind to certain molecules, but even minute changes can prevent them from doing so, which can result in the development of

antibiotic resistance (Kang and Park, 2015; Shree *et al.,* 2023). Antibiotics such as aminoglycosides, tetracycline, macrolides, chloramphenicol, lincosamides, and streptogramin (Tenover, 2006; Fernández *et al.,* 2023) affect protein production by modifying their ribosomal 30S or 50S subunits (Sodhi and Singh, 2022; Sodhi *et al.*, 2023). Changes in the structure or function of transpeptidases enzyme also known as Penicillin-Binding Proteins (PBPs) which is responsible for crosslinking peptidoglycan precursors in order to build bacterial cell wall can lead to bacterial resistance to these drugs (Sodhi and Singh, 2022; Sodhi *et al.,* 2023). The enzymes DNA gyrase and topoisomerase are involved in DNA replication (Hirsch and Klostermeier, 2021). Because these two enzymes are especially targeted by quinolone antibiotics, structural changes to them may result in bacterial resistance to the antibiotics (Fabrega *et al.,* 2009). Tetracycline antibiotics are known to target the ribosomal 30S subunit, but the ribosome has defense mechanisms that can resist their action (Kang and Park, 2015). Changes to this D-alanyl-D-alanine residue have the potential to make bacteria resistant to medications that work against it (Dzidic *et al.,* 2008). Mutations in the rpoB gene, which encodes the beta-subunit of RNA polymerase, can confer resistance to rifampicin (Patel *et al.,* 2023) which is common antibiotic used to treat bacterial infections.

3. Bacteria inactivate the antibiotic by enzyme: Three key enzymes are responsible for antibiotic inactivation and these areas; first is Beta-lactamases enzymes have the ability to break down all B-lactam antibiotics that are bonded with ester and amide thus provide resistance to bacteria that produce this very enzyme (Fernandez-Billon *et al.,* 2023). Secondly, Aminoglycoside modifying enzymes (AGES) have been found to prevent the attachment of aminoglycoside antibiotics to their ribosomal target (Strateva and Yordanov 2009) and lastly Chloramphenicol-acetyl transferases enzymes cause acetylating of hydroxyl group of antibiotic Chloramphenicol resulting in an altered form of the antibiotic that is unable to bind to its ribosomal target. Bacteria possessing these enzymes are resistant to chloramphenicol antibiotics, rendering them ineffective (Varela *et al.,* 2021).



Source: https://doi.org/10.3390/biomedicines8100405

Fig. 2: Different Mechanism of Antibiotic Resistance.

4. Antimicrobial activity of different herbal plant extracts:

Infectious diseases continue to be a major worldwide health concern, accounting for 41% of all disease cases, as assessed in Disability-Adjusted Life Years (DALYS) (Noah and Fidas, 2000). One of the primary causes of this issue is the global spread of acquired bacterial resistance to antibiotics, which poses a major threat to public health worldwide today (Chopra, 2000) and results in both epidemics and pandemics of antibiotic resistance (Chanda *et al*., 2010, Osman *et al*., 2012). The issue of antibiotic resistance has led to a shift in focus towards biologically active components extracted from plant species that are used in herbal medicine. These components have the potential to generate a new and powerful source of antibacterial and antifungal activities. (Maiyo *et al*., 2010; Erfan and Marouf, 2019). The capacity of plants to produce several secondary metabolites with antibacterial activity from very complicated structures is linked to their antimicrobial qualities (Matasyoh *et al*., 2009; Souza *et al*., 2005). These compounds are present in the roots, stems, leaves, flowers, fruits, and seeds of plants. They have been shown to have good inhibitory effects on foodborne bacteria and fungi in addition to other advantageous qualities like food preservation, anti-aging, antioxidant, and anti-cancer properties (Masyita *et al*., 2022). To increase antimicrobial activity against a variety of microorganisms, natural antimicrobial compounds can work

alone or in conjunction with antibiotics (Fazley *et al*., 2016; Fazley *et al*., 2018). It is well known that *Azadiracta indica* (leaf, bark, and seed) has antiviral, antibacterial, and antifungal properties against a variety of pathogenic microorganisms (Biswas *et al.,* 2002). It has been demonstrated that neem's leaf, bark, and seed oil all have a wide range of pharmacological actions, such as anti-inflammatory, anti-mutagenic, anticarcinogenic, antioxidant, antimalarial, antihyperglycemic, antiulcer, and anti-diabetic qualities (Talwar *et al*., 1999). In India, China, and South East Asia, turmeric *(Curcuma longa*) is widely used as a spice, food preservative, and coloring agent. The rhizome of *C. longa* contains a variety of sesquiterpenes and curcuminoids that have been identified and linked to a broad range of biological activities, including wound healing (Maheshwari *et al*. 2006), anticancer (Kim *et al*. 2012), antibacterial activity (Gupta and Sadhana 2005; Naz *et al*., 2010), and anti-inflammatory (Sandur *et al*., 2007; Aggarwal and Harikumar 2009). A fruit plant in the Myttacea family, guava (*Pisidium guajava L*.) is used to treat and prevent diarrhea (Lutterodt, 1989; Alnieida *et al*., 1995). It also exhibited strong antibacterial activity against bacteria that cause food-borne diarrhea, such as *Pseudomonas*, *Shigella*, and *Staphylococcus* species (Alnieida *et al*., 1995, Jaiarj *et al*., 1999). In addition, guava is used as an antibacterial and anti-inflammatory to treat respiratory conditions, diabetes, hypertension, pain fever, gastroenteritis, diarrhea, and dysentery (Gutierrez *et al.,* 2008). Salvia officinalis L., a fragrant herb belonging to the Lamiaceae family, is utilized in conventional medicine to address various conditions such as oral and throat inflammation (Baricevic *et al*., 2001). It also functions as an antimutagenic and anticarcinogenic agent (Craig, 1999; Simic et al., 2000). According to Loannides (2002), it is also used as a diuretic, tonic, local styptic, antibacterial, antifungal, and pain reliever for spasms. A plant in the Rhamnaceae family, Rhamnus (*Ziziphusspina Christi)* was used in Egyptian folk medicine to treat a variety of conditions, such as diarrhea, diabetes, and gastrointestinal tract disorders. Its extracts also demonstrated antiviral, antifungal, and antibacterial properties (Shahat *et al*., 2001). In addition to being used to cure fever and headaches, mulberries (*Moursalba L*.) can also be used to treat chronic digestive tract illnesses and increase appetite. Hepatitis and chronic gastritis are two other conditions it is utilized to cure. Oedema, dyspepsia, cough, and oligurea can all benefit from it (Sunil and Ammani, 2009). El-Beshbishy *et al.* (2006) reported that *M. alba* had anti-inflammatory, antiviral, antibacterial, and antioxidant effects based on recent investigations. The pharmaceutical application of olive tree (*Oleaeuropaea L.*) leaves is extensively investigated; the leaves are significant due to their secondary metabolites, such as secoiridoid chemicals, which have hypotensive and hypoglycemic properties (Hansen *et al*., 1996) (Gonzalez *et al*., 1992). According to a number of studies, plants can ease arrhythmia, reduce blood pressure, and stop intestinal muscle spasms (Samuelsson, 1951; Garcia *et al*., 2000). There have been publications on the use of cranberry juice (*Vaccinium macrocarpon*) and bearberry (*Arctostaphylos ura-ursi*) to treat urinary tract infections, and broad-spectrum antimicrobial agents include garlic (*Allium sativum*), tea tree (*Melaleuca alternifolia*), and lemon balm (*Melissa officinalis*) (Joshi, 2017). Myrtus communis showed significant effectiveness against *Pseudomonas aeruginosa*. The oils from tea trees (*Melaleuca alternifolia*) and carrots (*Daucus carota*) exhibit antibacterial action against *Mycoplasma pneumoniae* and *Helicobacter pylori*, respectively (Wangchuk *et al*., 2011).

The majority of bioactive molecules generated from plants that have therapeutic effect are secondary metabolites. Plant metabolism produces secondary metabolites, which can be intermediate or final products (Stefanovic, 2010). The structure, quantity, and location of substituent groups, the existence of glycosidic connections, the alkylation of OH groups, the geography and climate of the area of origin, and other factors all contribute to their broad range of antimicrobial action. In fact, the antibacterial action of bioactive secondary metabolites varies depending on the kind and concentration of the microbial strains they affect (Merkl *et al*.,2010; Arima *et al*.,2002; Assob *et al*.,2011).

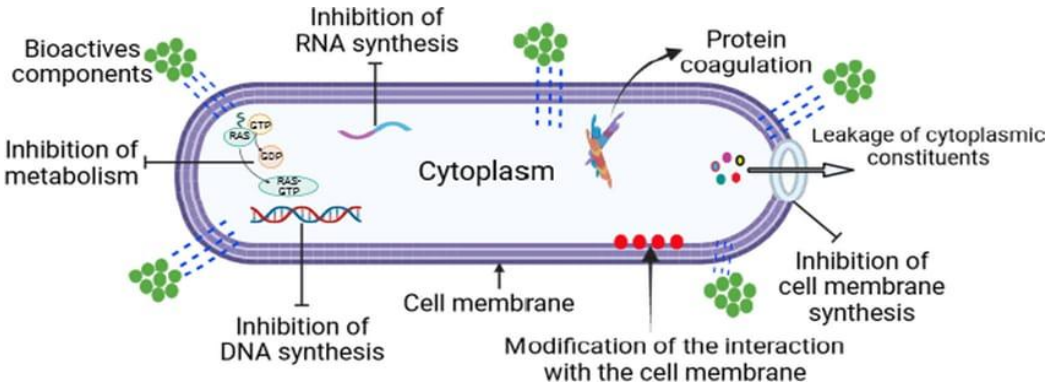
Table 2: Bioactive molecules derived from respective plant species.

Plant Derived Drugs/Molecules	Plant Species
Aspirin	*Filipendula ulmaria* (L.) Maxim
Codeine	*Papaver somniferum* L.
Papaverine	*Papaver somniferum* L.
Colchicine	*Colchicum autumnale* L.
Digoxin and digitoxin	*Digitalis purpurea* L.
Cannabidiol	*Cannabis sativa* L.
Tetrahydrocannabinol	*Cannabis sativa* L.
Vinblastine and vincristine	*Catharanthus roseus* (L.) G. Don
Artemisinin	*Artemisia annua* L.
Galantamine (Reminyl®)	*Galanthus woronowii* Losinsk

Apomorphine hydrochloride (Apokyn®)	*Papaver somniferum* L
Tiotropium bromide (Spiriva®)	*Atropa belladonna* L.
Paclitaxel (Taxol®)	*Taxus brevifolia* Nutt.
Paclitaxel	*Taxus brevifolia* Nutt. & *Taxus chinensis* (Pilg.) Rehder
Camptothecin	*Camptotheca acuminate* Decne
Allicin (diallylthiosulfnate)	*garlic* (*Allium sativum* L.)

5. MECHANISM OF ACTION OF PLANT DERIVED EXTRACTS:

There are various ways in which these chemicals can impact the microbial cell. Bioactive substances generally target the cytoplasmic membrane as their major target, altering its permeability, functioning, and structural integrity in various way (Stefanovic, 2012). Plant extracts may naturally include EP inhibitors in their composition, according to several suggestions. It has been proposed that the composition of plant extracts may include EP inhibitors (Savoia, 2012). One of the most promising modes of action for bioactive chemicals against MDR pathogens has also been described as the disruption of normal cell communication, or quorum sensing (QS). In addition to being chemically stable enough to withstand the metabolic and disposal processes of the host organism, QS inhibitors should be able to reduce the expression of QS-controlled genes Savoia, 2012; Radulovic *et al.,* 2013; Saleem *et al*.,2010). Certain substances have the ability to alter or block protein-protein interactions, making them useful regulators of the immune system, mitosis, and apoptosis (Vadhana *et al.,* 2015). Furthermore, they can disrupt or prevent the formation of biofilms, which provide pathogens with a protective advantage during infection (Lau and Plotkin, 2013) interfere with intermediate metabolism (Vadhana, *et al*., 2015) and cause the coagulation of cytoplasmic components (Omar *et al.,* 2017) Medicinal plant extracts include several antiviral components that interact with distinct viral proteins at different phases of the virus's reproduction (Rajasekaran *et al.,* 2014) Based on the chemical structures, chemical composition, biosynthetic pathway, or the solubility of the compounds extracted from plants are classified into several main groups that include alkaloids, phenolic compounds, sulfur-containing compounds, coumarins, terpenes/essential oils, and lectins and polypeptides (Kabera *et-al*., 2014; Alamgir, 2017).



Source: https://doi.org/10.1007/s13399-023-04856-9

Fig.3: Possible antimicrobial mechanisms of action of plant extracts.

6. INTERACTION BETWEEN PLANT EXTRACTS AND ANTIBIOTICS:

Medicinal plant extracts have shown significant potential in enhancing the efficacy of conventional antibiotics, particularly when used synergistically. Studies have demonstrated that plant-derived compounds, such as α-mangostin from mangosteen fruit, can inhibit bacterial β-lactamase enzymes, reactivating β-lactam antibiotics in resistant bacterial strains (Phitaktim *et al*., 2016). These plant extract-antibiotic combinations can significantly reduce the minimum inhibitory concentration (MIC) of antibiotics, a phenomenon termed resistance-modifying activity (RMA) (Gibbons *et-al*., 2003) (Al-hebshi *et al*., 2006). Synergistic effects are observed when plant extracts increase antibiotic permeability or inhibit efflux pumps, allowing higher antibiotic accumulation in bacterial cells, as seen with isoflavones from *Lupinus argentens* enhancing the activity of berberine and norfloxacin (Morel *et al*., 2003). Additionally, combinations of plant extracts and antifungals, such as ketoconazole with *Agastache rugosa* essential oil, have shown enhanced antifungal activity (Shin, 2003; Aiyegoro et al., 2009) However, pharmacokinetic and pharmacodynamic interactions, such as synergism or antagonism, depend on specific plant extracts, antibiotics, and their concentrations (Aiyegoro *et al*., 2009). For example, *Camellia sinensis* extract with nalidixic acid reduced the MIC eightfold against *Salmonella Typhi, (*Farooqui *et*

al., 2015) while thymol exhibited antagonism with penicillin against MRSA (Gallucci et al., 2006). Understanding both synergistic and antagonistic effects is crucial to maximizing the benefits of these combinations (Oliveira *et-al*., 2006) (Van Vuuren *et al*., 2009).

7. CHALLENGES OF USING PLANT EXTRACTS FOR ANTIMICROBIAL PURPOSE:

Medicinal plant extracts offer a natural and often safer alternative to synthetic antimicrobials, providing accessible, cost-effective treatment options with significant therapeutic potential (Ghosh *et-al*., 2008) (Pandey and Kumar, 2012). They can be particularly valuable for addressing issues like drug resistance and side effects associated with conventional medications (Pandey and Tripathi, 2014) (Ingle *et-al*., 2017). However, several challenges hinder their effective use as antimicrobial agents. Firstly, the current approval rate of antibacterial compounds derived from medicinal plants does not fully reflect their potential. The lack of well-controlled, double-blind toxicological and clinical studies often leaves a gap in proving their efficacy and safety (Deutch, 2017) (Calixto, 2000). Additionally, the quality of plant extracts can be compromised by factors such as adulteration, poor cultivation practices, lack of standardization, and inadequate storage, all of which can affect the development of new antimicrobials (Njume and Goduka, 2012). Variability in plant extract composition due to factors like harvest season, cultivation region, and processing methods adds to the complexity. Differences in local climate, including rainfall and humidity, can alter the chemical profile of the same plant species grown in different locations, and climate change further exacerbates these variations (Radulović *et-al*., 2013)

Moreover, understanding the complex interactions among the numerous compounds in medicinal plants is challenging. Isolating and studying single compounds often requires extensive resources and can be time-consuming. Rediscovery of compounds from various sources and ensuring standardization, stability, and quality control remain significant hurdles (Rodrigues and Barnes, 2013). The potential for synergistic effects among compounds within a plant extract also presents difficulties, as current technology to study multiple compounds targeting various biological pathways is still developing. Additionally, logistical issues such as obtaining access to plant species and navigating differing regulations for plant collection and export/import further complicate research efforts (Bhardwaj *et al*., 2018). Plant extracts can contain hundreds or even thousands of compounds, making it difficult to identify which ones are responsible for antimicrobial effects (Wagner and Ulrich-Merzenich, 2009) (Efferth and Koch, 2011) (van Vuuren and Viljoen, 2011). Another significant hurdle is assessing the toxicity of medicinal plant extracts, as many have not been evaluated by regulatory agencies like the U.S. Food and Drug Administration (Stermitz *et al*., 2003) (Kengni *et al*., 2016). Without official toxicity data, the risk of adverse effects remains a concern, emphasizing the need for strict regulation and quality control of plant extracts. Financial constraints and limited high-quality research further complicate the understanding of structure-activity relationships of individual compounds (Mahmood and Mahmood, 2013).

8. Conclusions:

The antimicrobial activity of medicinal plants offers a promising avenue to address the escalating problem of antimicrobial resistance. This potential emphasizes the urgent need to identify and isolate novel bioactive compounds from medicinal plants, many of which remain unexplored. The diverse range of these compounds demonstrates significant therapeutic potential as antimicrobials and as modifiers of antimicrobial resistance. However, harnessing this potential presents several challenges. Comprehensive in vitro and in vivo testing are crucial to ensure that the selected plant-derived compounds are both effective and non-toxic. Additionally, understanding and managing the potential synergistic or antagonistic interactions among compounds within and between plant extracts is a major challenge. Advancements in biotechnology are expected to enhance our ability to analyze the chemical composition of medicinal plants more deeply. Developing more sophisticated techniques for extraction, fractionation, and identification of bioactive compounds with varied chemical structures and mechanisms of action will be beneficial. Standardizing extraction methods and in vitro testing protocols could make the search for new antimicrobials more systematic and facilitate result interpretation. Future studies should also focus on reference models to better understand plant extract mixtures. Further research is needed on the mechanisms of action of these compounds, their interactions with antibiotics or other medicinal agents, and their pharmacokinetic and pharmacodynamic profiles. This review and the identified challenges should guide efforts to develop efficient, successful, and straightforward methods for utilizing medicinal plants as new therapeutic agents against microbial infections.

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