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PHYTO-THERAPEUTICS IN BATTLE OF MULTIDRUG-RESISTANT INFECTIONS: A SYSTEMATIC REVIEW

Tamalika Chakraborty [*1], Sumana Chatterjee [2], Lopamudra Datta [2] and Ranjana Shaw [1]

Department of Biotechnology [1], Department of Pharmacy [2], Guru Nanak Institute of Pharmaceutical Science & Technology, 147/F, Nilgunj Road, Panihati, Kolkata - 700110, West Bengal, India.

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Correspondence to Author:
Ms. Tamalika Chakraborty

Assistant Professor,
Department of Biotechnology,
Guru Nanak Institute of Pharmaceutical Science & Technology, 147/F, Nilgunj Road, Panihati, Kolkata - 700110, West Bengal, India.

E-mail: tamalika.chakraborty@gnipst.ac.in

ABSTRACT: Background: The unprecedented overuse and illogical prescribing of antibiotics for various illnesses has accelerated the evolution of antibiotic-resistant bacteria, which has contributed to the resurgence of pathogenic strains with strengthened resistance to conventional therapies. Rising resistance has threatened human health and increased the expense of treating diseases, compromising the treatment procedure for a wide range of antibiotics. Microbes are diversifying quickly due to rapid evolution, which makes it difficult to develop management strategies. This favours the use of plant-derived antimicrobials obtained from medicinal plants to treat diseases. Over the last two decades, an abundance of plant-derived antimicrobials with a wide spectrum of activity against numerous pathogens that cause human infections have been discovered via extensive research. There are various compounds with active components that have been found and are marketed. They have great antibacterial power and can be utilised as antibiotic resistance modifiers or antimicrobials. The current study focuses on the characteristics of plant antimicrobials, their mechanisms of action in combating the rise in microbial resistance, and, in particular, the varied impacts of plant compounds on virulence factors, which are crucial for pathogenicity within the host. Creating new alternatives is necessary due to the very challenging condition of antibiotic resistance that develops amongst bacteria exposed to antibiotics. Due to their high antibacterial action, plant-based antimicrobials have the potential to be utilized in the manufacturing of medicines.

INTRODUCTION: Infectious diseases have emerged significantly in the past years due to human population growth and its effects on the environment worldwide [1, 2]. The second greatest cause of death worldwide is infectious disease, which is brought on by pathogenic microorganisms such as bacteria, viruses, fungi and parasites [3]. Pathogenic *Escherichia coli, Campylobacter spp., Pseudomonas aeruginosa, Vibrio cholerae, Enterococcus faecalis, Klebsiella pneumoniae, Staphylococcus aureus, etc*., are the most prevalent bacterial etiologic agents that cause infections [3]. Antibiotics have been essential in treating these fatal infectious illnesses and enhancing human health [4, 5]. However, due to incorrect, infrequent, and excessive use of antibiotics, antimicrobial resistance has grown, making them adaptive.

The growth of multidrug-resistant bacteria makes treating infectious disorders more difficult, which dramatically reduces the effectiveness of the antibiotic arsenal and speeds up the pace of therapeutic failure [6]. Efflux pump-mediated resistance is the main contributor to MDR. A special pump can make bacteria resistant to various chemicals with various structural characteristics. Therefore, inhibiting them offers hope for ending the bacterial resistance phenomena. Other bacterial

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resistance mechanisms include modifications to cell permeability, changes in the drug target, biofilm formation, and the ability to make spores, which serve as drug defense and aid in the survival of bacterial resistance in challenging environmental settings [7]. Additionally, bacterial cell wall components, including capsular polysaccharides, offer resistance to the host immune system, and microbiological toxins harm the host tissue [8, 9]. Phytochemicals are great substitutes as resistance-modifying agents. They can interact with the key pathogenicity events or directly kill bacteria, preventing them from developing resistance. Numerous plants have notable efflux pumps' inhibitory activities. Edible plants are gaining popularity. In addition to mutations, mobile genetic elements such as insertion sequences, integrative conjugative elements, plasmids, and transposons are essential for the spread of bacterial class-specific tolerance [10]. Bacteria with resistance genes are more likely to spread and persist in new environments [11]. The three primary methods that bacteria use to develop antibiotic resistance and develop multidrug resistance are as follows:

Site Modification at the Target: Antibiotics work by changing their target sites chemically, typically through the action of constitutive and induced enzymes [12]. Many harmful bacteria use this tactic to lower the affinity of drugs for their binding site. Additionally, target site variants are brought about by haphazard mutations in bacterial chromosomes. Examples include cellular enzyme mutations that cause resistance to quinolone and rifamycin, such as DNA gyrase and RNA polymerase. Pathogenic Streptococcus species have developed resistance to antibiotics such macrolides and streptomycin B due to methylation of adenine residue of the N6 amino group in 23S Rrna [13].

Enzyme Inactivation: Pathogenic bacteria frequently develop specific enzymes such as hydrolytic enzymes and a group of transferases to combat the effects of antibiotics. P-lactamases have been associated with gram-negative and gram-positive bacterial resistance to P-lactam antibiotics [14]. These enzymes significantly increase the bacteria's resistance to antibiotics [15].

Antibiotic Efflux Pump: It is generally acknowledged that intestinal antibiotic resistance is mostly caused by the constitutive production of "efflux pump proteins" encoded by the housekeeping genes, which are abundant in bacterial genomes [16]. Drug extrusion lowers the antimicrobial's intracellular concentration, allowing the bacterium to survive in environments with high antimicrobial concentrations. Both gram-positive and gram-negative bacteria contain multidrug resistance efflux pumps, which can be chromosomally or plasmid-encoded proteins [17]. Since, these proteins are naturally present in bacteria, the persistent presence of the substrate causes their over-expression [18], which results in the development of the acquired resistance. *Staphylococcus aureus*, a gram-positive pathogenic bacteria, is an illustration of a chromosomally encoded pump of the NorA protein [19]. This sparked the hunt for an effective therapeutic strategy to fight these illnesses. Therefore, this study aims to examine the antibacterial characteristics of such an approach, for instance, medicinal plants, by examining its elements' actions against various multidrug-resistant organisms.

The global spread of multidrug-resistant bacterial strains is reducing the effectiveness of current strains and increasing the risk of infection treatment failure [20]. Antimicrobial drug resistance is a financial concern [8] since it affects physicians, patients, healthcare administration, pharmaceutical businesses, and the general public. The scarcity of and high price of the most recent generation of antibiotics with a short duration of efficacy have been caused by increased morbidity and mortality [21].

Consequently, proper care is necessary. Finding more potent antimicrobial agents among plant-based components has resulted from this search for more potent antimicrobial agents. For centuries, plants have been essential to the growth and prosperity of human society. Finding potentially helpful active components that could be used as a starting point for synthesizing novel antibacterial drugs [22]. A sizable variety of medicinal plants are acknowledged as a valuable source of organic antibacterial compounds [23]. Phytochemicals found in therapeutic plants suppress bacterial pathogens [24]. Organic solvents are employed for bioactive chemical extraction [25].

Excess plant products have been utilised as food preservatives, flavour enhancers, and dietary supplements to preserve food quality and to maintain human health. Additionally, herbal medicine extensively uses plant extracts for illness prevention and treatment, both prophylactically and therapeutically. Most of these substances are secondary metabolites and result from interactions between animals, plants and microorganisms [26]. The main benefit of using antimicrobials produced from plants for medical treatment is that they don't have the adverse effects that come with using synthetic chemicals [27]. Examples of plant-derived antimicrobials include quinones, terpenoids, tannins, coumarins, flavonoids, alkaloids, lectins and polypeptides.

TABLE 1: PLANT-DERIVED ANTIMICROBIALS ARE CATEGORIZED BASED ON THEIR CHEMICAL COMPOSITION AS FOLLOWS

S. no.	Plant-derived antimicrobials	Description	Example	Antimicrobial Spectrum
1.	Quinones	Quinones are chemical molecules with aromatic rings at their core. They are bacteriostatic, which causes the pathogen to become inactive [28-30]	Naphthoquinone Benzoquinone Anthraquinone	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Bacillus subtilis*
2.	Terpenoids	Terpenoids being one of the biggest groups of secondary bioactive molecules that cause membrane disruption in microorganisms [31-33].	Terpinene Carotenoids	*Vibrio cholera* *Pseudomonas aeruginosa* *Salmonella typhi*
3.	Tannins	Tannins are a class of oligomeric, water-soluble chemicals with strong astringent qualities that render bacterial adhesins as well as transport proteins of cell envelope inactive [34, 35]	Tannic acid Gallic acid	*Staphylococcus aureus* *Salmonella enterica* *Campylobacter jejuni*
4.	Coumarins	A class of aromatic benzopyrones known as coumarins possess anti-inflammatory as well as antifungal properties [36-39]	Agasyllin Ostruthin Ammoresinol	*Escherichia coli* *Vibrio parahaemolyticus* *Listeria monocytogenes*
5.	Flavonoids	Flavonoids are pigmented compounds that interact with the proteins in bacterial membranes, increasing membrane permeability and causing membrane rupture. This category of catechins has inhibitory effects on a wide range of species [40-44]	Flavones like rutin, chrysin. Catechins like catechin. Flavanones like naringenin. Anthocyanins like cyanidin.	*Salmonella enterica* *Pseudomonas aeruginosa* *Vibrio cholera* *Klebsiella pneumonia*
6.	Lectins and polypeptides	Peptides are small fragments of amino acids and lectins are proteins that bind to sugars. Peptides and lectins generate ion channels in the cell membrane as part of their mode of action[45-47].	Concanavalin A Fabatin Mannose-specific agglutinin	*Bacillus subtilis* *Candida albicans* *Pseudomonas aeruginosa* *Escherichia coli*

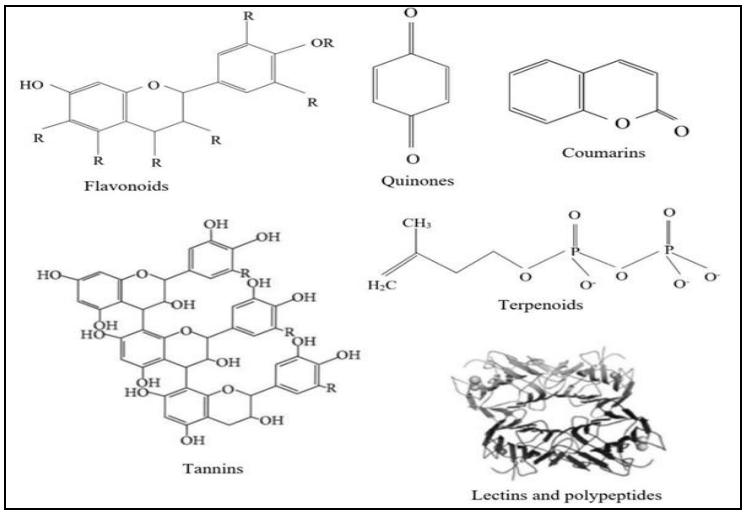

FIG. 1: CHEMICAL STRUCTURES OF MAJOR GROUPS OF PLANT-DERIVED ANTIMICROBIALS

Antimicrobial Properties of Plant-derived Antimicrobials:

Antibiofilm Activity: Bacterial biofilms are intricate communities of surface-associated microbes that are encased in an extracellular matrix made of proteins, lipids, extracellular DNA as well as exopolysaccharides [48, 49, 1, 2]. Bacteria persist in the microenvironment for however long the conditions are favourable, one of the most important characteristics of bacterial biofilms [3]. The extracellular polymeric material, also called the matrix, is a collection of different biopolymers created by the organisms themselves [4]. These give the cells an additional layer of defense against many pressures, resulting in bacteria in the biofilm being resistant to antibiotics, environmental challenges and even extinguished host immunological responses, which poses severe issues for both industrial and therapeutic settings [50, 51].

Plant-derived antimicrobials are reported to modulate bacterial gene transcription [52-56] at subinhibitory concentrations in several pathogens such as *Pseudomonas aeruginosa*, *Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus*. Antimicrobials are secreted from plants to prevent the development of biofilm. For instance, trans-cinnamaldehyde, an aromatic aldehyde molecule derived from bark of cinnamon trees, was discovered to prevent *Cronobactersakazakii* from forming a biofilm [57].

Bacterial Membrane Disruption: Catechins, carvacrol, eugenol and thymol are plant-derived antimicrobials that interact with the bacterial cell membrane, causing membrane disruption that results in loss of membrane potential, loss of cellular contents, impaired ATP synthesis, chelation of metal ions, and altered permeability of the membrane, all of which affect the normal physiology of the bacteria, resulting in cell death[58-64]. The well-known antibacterial compound cinnamaldehyde, derived from plants, has also been shown to interfere with ATPase-dependent energy metabolism and glucose uptake and use, which disrupts bacterial membranes [59, 62, 63, 65].

Inhibition of Bacterial Capsule Production: The polysaccharide capsule in many pathogenic bacteria, including *Streptococcus pneumonia* [66-68], *Klebsiella pneumoniae* [69], *Bacillus anthracis* [70] is a significant virulence determinant [71, 72]. It prevents the bacteria from phagocytosis [73] and thus increases the survival of bacteria within the host [74]. The existence of a capsule also improves bacterial adhesion and the formation of biofilms[75] in the environment [76, 77]. In different pathogens like *Staphylococcus aureus*, salicylic acid or its derivatives like bismuth subsalicylate [78], sodium salicylate [79] and bismuth dimercaprol [80] modulate the expression of regulators that are involved in the regulation of capsular synthesis, which significantly slows down capsule development.

Inhibition of Bacterial Quorum Sensing: Quorum sensing is one of many virulence factors that mediate the pathophysiology of microbial infection in a host and are expressed at different phases of infection to cause the disease. Bacteria can exchange data about cell density and adjust gene expression through the cell-cell communication technique called quorum sensing. Quorum sensing controls the expression of genes that encode various virulence factors in numerous bacteria [81, 82]. According to studies, plants produce antiquorum-sensing substances that prevent cell-to-cell contact and lower the expression of virulence genes in bacteria [83–85]. For instance, trans-cinnamaldehyde, an antiquorum sensing substance, reduced the expression of luxR, the transcriptional regulator for quorum sensing in *Cronobacter sakazakii* [53].

Reducing Production of Toxin: Toxins produced by microorganisms act as chemical agents that promote host virulence and pathogenesis and are the focus of therapeutic interventions. Exotoxins (secreted by bacteria) and endotoxins, among other types of toxins, are emitted by bacteria (released after bacterial lysis). Plants are effective against the bacterial toxins produced by *Escherichia coli* and *Staphylococcus aureus*. For instance: Using a dihydroisosteviol produced from a natural plant effectively prevents intestinal fluid secretion caused by the cholera toxin [86].

Three Lines of Bacterial Infections that Lead to Multidrug-Resistant Infections:

Bacterial Persister Cells: Bacterial communities develop persistent cells that are not mutants but phenotypic variants of the wild-type cells [87].

Environmental and intracellular stressors trigger the persistence phenomenon. They do not expand or die in the presence of bacterial agents and thus show multidrug resistance [88]. Persistent gene expression profiles included toxin-antitoxin systems and other genes that could block essential cellular functions such as translation, preventing antibiotics from destroying their targets, and contributing to multidrug-resistant cells. Overproduction of RelE toxin, a translation inhibitor, triggered a drastic increase in persisters [89].

Functional expression of a HipA toxin also improved persistence [90], while deletion of the hipBA system triggered a decrease in persistence in stationary and biofilm populations. The purpose of these specialized persister dormant cells is to ensure the survival of the kin cell population in the presence of lethal factors [91]. Persisters in *Escherichia coli* are non-growing cells, pre-existing in a population [92].

Persistent cells in all pathogens contribute significantly to the difficulties in treatment and the recalcitrant nature of chronic infections [93]. Active efflux pump is the main phenomenon through which bacteria release compounds detrimental to their survival, including antibiotics, outside their cells [94]. Pumps include recognition, fixing, and transport of efflux substrates. Reversal of it *via* inhibition of efflux pumps is promising to increase the concentration of intracellular drugs, restore drug activity against resistant strains, and reduce further production of resistant strains [95].

A small efflux pump in *Escherichia coli* is formed by EmrE protein [96] from *Escherichia coli and* needs serious therapeutic attention as it is a common cause of urinary tract, urinary tract sepsis, neonatal meningitis, acute enteritis, bloody diarrhoea, *etc*. One such therapeutic approach is the use of medicinal plants.

Numerous experiments on medicinal plant extracts have shown the existence of putative molecules that block efflux pumps in *Escherichia coli* and potentially restore the efficacy of antibiotics, enabling antibiotics to achieve a sufficient concentration within the bacteria for a bactericidal impact. Hence, it plays a significant role in combating such infections.

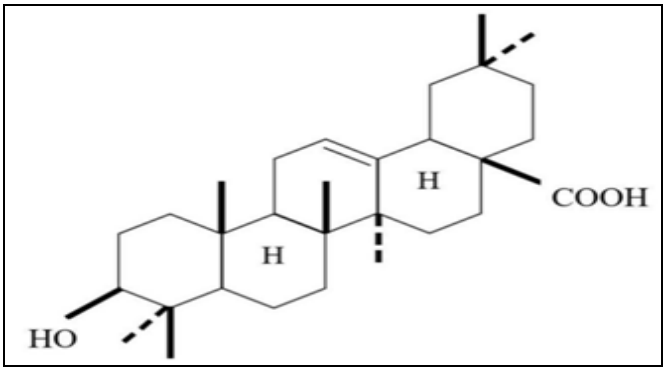

FIG. 2: STRUCTURE OF OLEANOLIC ACID

Mode of Action of Plant-derived Antimicrobial to Inhibit Persister Cells: *Carpobrotus edulis* from the Aizoaceae family is a succulent plant native to South Africa that invades coastal habitats in many parts of the world [97]. Triterpenoids are the most representative group of phytochemicals [98], one such is produced by this plant named Oleanolic acid as drawn in **Fig. 2**. It is a pentacyclic triterpenoid that occurs in nature in free acid form [99]. This compound possesses a range of fascinating pharmacological functions such as anti-inflammatory, antioxidant, anticancer, *etc* [100] which is utilized to suppress multidrug resistance in bacterial persister cells. However, tolerance may be the trait of an entire population that is destroyed slowly and of a single cell that manages to survive extensively.

Many efflux systems use energy from H+ and Na+ electrochemical gradients for their activity; the key mode of action is the targeting of the H+/Na+ incentive force of the efflux mechanism or the competitive/non-competitive inhibition of the binding substrate [101]. Other modes of action include: Ionic gradient dissipation through the cell membrane, decreased regulation of the transcription pathway of the genes encoding the efflux pumps, and interference with the hydrolysis of ATP which in turn compromises the activation of the efflux pumps and increases the permeability of the outer membrane in the structure of the said bacteria, conformational changes in efflux protein structures, also compromising the assembly of multi-component pumps [102].

Bacterial Tolerant Cells: Usually, tolerant cells do not begin to grow until after antibiotic exposure. Bacteria can withstand treatment durations that kill more susceptible bacteria due to tolerance

characteristics. These tolerance-related factors could be hereditary or environmental [103]. Tolerance is the capacity of the bacterial population to resist prolonged treatments with brief exposure to bacterial antibiotics [103]. Human commensal Enterococcus faecalis has the potential to spread disease [104]. It can thrive in hospital environments and result in serious nosocomial infections because of its robustness [105]. Although it is naturally tolerant to many antibiotics like penicillin and vancomycin, which implies that these generally bacterial medications only have a bacteriostatic effect, it may evolve various drug resistance determinants. Therefore, a vancomycin-susceptible *Enterococcus faecalis*' resistance to vancomycin contributes to treatment failure [106]. Numerous therapeutic herbs have demonstrated effectiveness against this resistant bacterium species. The Piper species are unique in this sense. They are culinary spices made from fragrant plants whose secondary metabolites have biological impacts on human health [107]. One kind of Piper, the *Piper nigrum*, is particularly abundant in essential oils, which may be found in this plant's fruit, seeds, leaves, branches, roots, and stems [108]. It is employed in conventional medicine [109] to treat a variety of medical conditions. It contains a lot of bioactive phytochemicals. One of the most popular chemical alkaloids extracted from this plant is piperine, which is depicted in Figure 3. Piperanine, piperline A, piperoline B, and pipericine are only a few of the similar alkaloids that have been discovered [110]. As a result, it is crucial in the fight against *Enterococcus faecalis*.

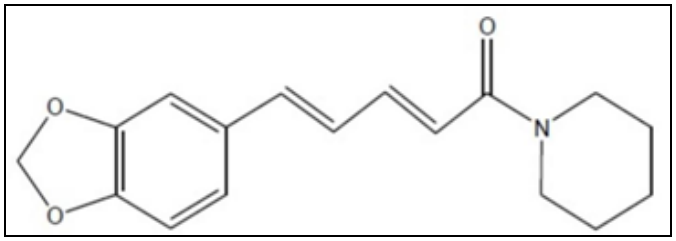

FIG. 3: STRUCTURE OF PIPERINE

Mode of Action of Plant-derived Antimicrobial to Inhibit Tolerant Cells: The antioxidant properties of *Piper nigrum* are often brought on by phenolic chemicals [111]. These plant extracts' effectiveness as good superoxide, hydrogen peroxide, and free radical scavengers can be attributed to their strong hydrogen-donating capacity, metal-chelating ability, and antioxidant processes [112]. Tolerance to penicillin and vancomycin depends on the presence of *Enterococcus faecalis* superoxide dismutase [104]. This phenolic substance scavenges the superoxide radical, which in turn decreases the tolerant capacity of *Enterococcus faecalis*.

Bacterial Resistant Cells: Some bacteria are naturally immune to antibiotics. For example, if a bacterium does not have a cell wall, it does not affect the antibiotic. This phenomenon is known as innate resistance [113]. Also, a bacterium previously susceptible to antibiotics develops resistance, called acquired resistance [113]. As a result, the bacteria survive and multiply continuously, causing more harm. *Staphylococcus aureus* is a prevalent natural microorganism in the human population [114], many of which are asymptomatic carriers. It can also cause life-threatening infections, and its strains have become resistant, leading to the development of Methicillin-resistant *Staphylococcus aureus*, which is a result of variations occurring inside the said strains as they acquired the Staphylococcal Cassette Chromosome Mec strain, which possesses the mecA gene [115]. The gene encodes the penicillin-binding protein that confers resistance to all β-lactam antibiotics, making this strain a resistant bacterial cell population [115]. Previously, vancomycin was used to treat these infections, but now it shows reduced vancomycin susceptibility [116,] limiting the treatment options. Hence, better treatment like medicinal plants is required to combat such infections. *Acacia catechu* from the Fabaceae family is a deciduous forest tree and an important medicinal plant. It is known for its antioxidant, antiproliferative, and DNA protective activities [117]. The methanolic extract [118] obtained from the leaves of this plant suppresses the Methicillin-resistant *Staphylococcus aureus.*

Mode of Action of Plant-derived Antimicrobial to Inhibit Resistant Cells: Leaf extract of *Acacia catechu* possesses antimicrobial activity, has been mentioned in **Fig. 4**, due to the presence of terpenes in high amounts. Terpenes are a single class of aromatic compounds found in essential oils [119]. The antimicrobial activity of terpenes depends on hydrophobic activity, cytoplasmic membrane disturbance, electron flow disturbance, active transport, and cell material coagulation [120].

Other mechanisms include the disruption of the pH gradient and the electrical potential of the proton-motive force [121]. It interacts with the lipids in the cell membrane. It can pass through the cytoplasm due to its lipophilic character, leading to disruption of intracellular constituents as well as the cytoplasmic matrix, which in turn combat the Methicillin-resistant *Staphylococcus aureus* [119]. Another phytochemical constituent of this plant is flavonoids, a phenolic compound. They can form complex soluble and extracellular proteins to bind to bacterial cells, through which they can disrupt bacterial cell membranes [119]. Another phytoconstituent is tannins, a class of water-soluble oligomeric molecules with strong astringent qualities that render cell envelope transport proteins and microbial adhesins inactive [119]. Together, all of these phytochemical components of this plant work to inhibit the pathogen mentioned above.

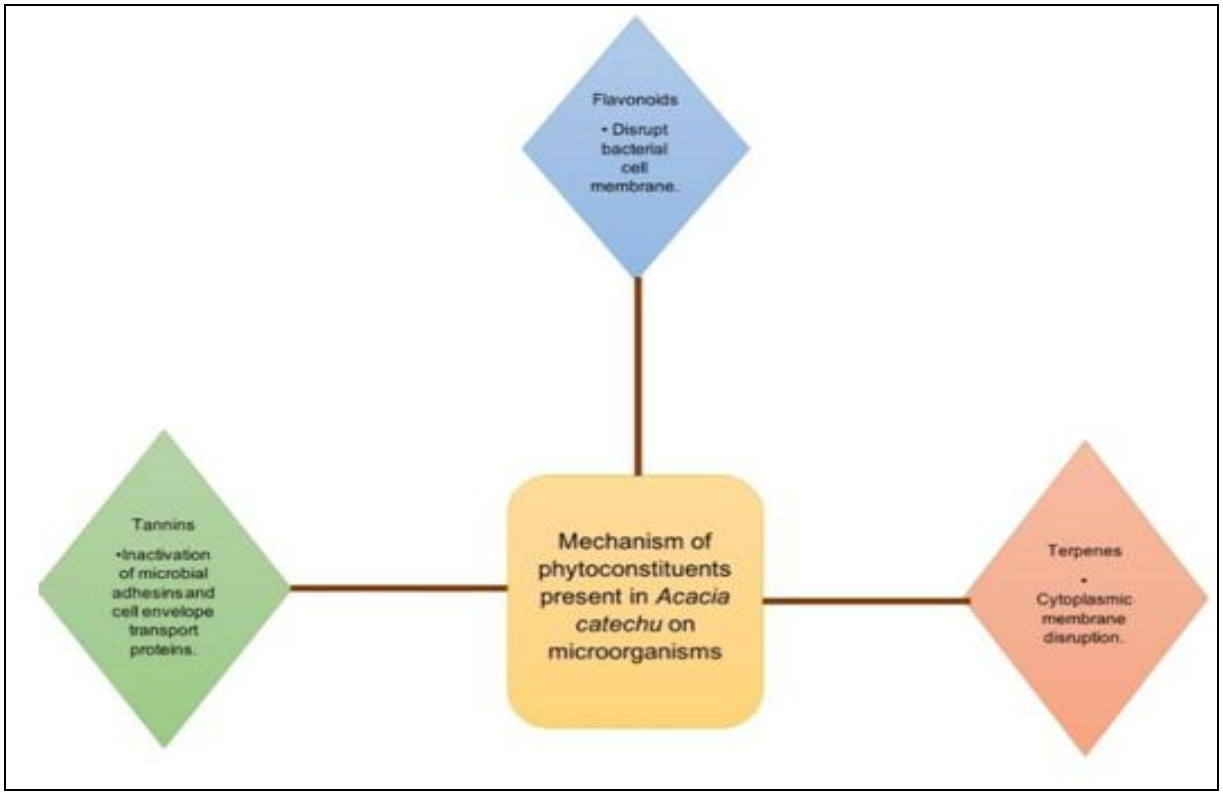

FIG. 4: MECHANISMS OF ANTIMICROBIAL ACTIVITY OF *ACACIA CATECHU*

TABLE 2: MECHANISM OF ACTION RELATED TO MAJOR CLASSES OF PLANT-DERIVED ANTIMICROBIALS

S. no.	Scientific name	Common name	Compound	Class	Mechanism	Antimicrobial Spectrum
1.	*Lawsonia inermis* *Senna italica*	Henna Senna	Lawsone Anthraquinone	Quinones	Quinones are thought to form an irreversible combination with the nucleophilic amino acids in a protein, which can occasionally cause the protein to lose its function and become inactive in the microbial cells. Additionally, it can prevent the microbes from accessing the substrate [119, 122]	*Mycobacterium tuberculosis* *Pseudomonas aeruginosa*
2.	*Laurusnobilis* *Centella asiatica*	Bay Gotu kola	Essential oils Asiatocoside	Terpenoids	Terpenoids are thought to work by a process that involves the membrane degradation of lipophilic substances found in microbial cells, though this mechanism is not fully understood [119, 122]	*Salmonella typhi* *Mycobacterium leprae*
3.					Tannin is a name used to describe a	

	Salixalba *Eucalyptus globulus*	Willow Eucalyptus	Salicin Tannic acid	Tannins	class of polymeric phenolic compounds that have the astringent ability to tan leather or precipitate solution gelatine. They can transport proteins for cell envelopes, enzymes, deactivate microbial adhesins, etc. They may combine with the bacterial cell wall to produce a complex, which could break the membrane [119, 122]	*Escherichia coli* *Proteus vulgaris*
4.	*Galium odoratum* *Rumex crispus*	Woodruff Yellow dock	Essential oil Essential oil	Coumarins	Coumarins act through the stimulation of macrophages that may indirectly negatively affect multidrug-resistant infections. It also interacts with the eucaryotic DNA[119, 122]	*Streptococcus mutans* *Escherichia coli*
5.	*Camellia sinensis* *Podocarpus nagi*	Greentea Treebard	Catechin Totarol	Flavonoids	Their ability to interact with soluble and extracellular proteins as well as adhesins found on bacterial cell walls, which in turn rupture microbial membranes, are key components of their function [119, 122]	*Shigella* *Propionibacteriu macnes*
6.	*Aesculushippocastanum* *Allium sativum*	Horsechestnut Garlic	O-glycan α(1→3) Man	Lectins and Polypeptides	Their mode of action is by creating ion channels in the microbial membrane to prevent it from existing. Additionally, the disruption of the microbial membrane via competitive suppression of microbial protein attachment to host polysaccharide receptors [119, 122, 123]	*Pseudomonas* *Staphylococcus aureus*

Synergistic Activity of Plant-derived Metabolites and Antibiotics: A recent trend in the production of new sources of antibiotics is the study of the combination of natural plant derivatives and standard antibiotics to improve their efficacy by bacterial synergism [119]. For example, the pluripotent activity of phytochemicals may stimulate the antimicrobial activity of quinolones, aminoglycosides, macrolides, tetracyclines. In multidrug therapy, the results may be negligible, additive, synergistic, or antagonistic. In the case of a synergistic effect, the behaviour of a combination of compounds is higher than the total of the effects of each compound [124].

Also, the resistance in efflux pumping of multidrug resistant (MDR) bacteriocin be treated with synergistic combinations of an antimicrobial with an efflux pumpinhibitor [125-127]. It has been shown that *Punica granatum* extracts in combination with chloramphenicol, ampicillin, gentamicin, tetracycline, oxacillin has a synergistic impact on methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria. Berberine alkaloid berberine has strongly synergistic activity with β-lactam antibiotics against MRSA [124].

Challenges Related to Plant-derived Anti-microbials in Combating Multidrug-Resistant Infections: The effectiveness of plant-derived antimicrobials depends on different intrinsic and extrinsic variables in controlling pathogens in the environment. The physicochemical properties such as aqueous solution solubility, hydrophobicity, biodegradability, stability are major challenges that hinder their use in the environment as natural biocontrol agents [128, 129].

Environmental temperature and atmospheric composition also modulate their antimicrobial efficacy [130]. Plant-derived antimicrobial's ability is checked to know its potential to inhibit the pathogens. This is a critical factor in combating multidrug resistant infections. The analysis of the composition of the plant extract is done significantly to allow the activities to be reproducible for successful application in further works that contribute to the effective exploitation

of medicinal plant extracts. The complex nature of medicinal plant extracts represents a challenge that deals with the synergism or antagonism effects [131]. Therefore, a detailed analysis of this activity is of extreme importance.

Furthermore, during the formulation of a plant-derived antimicrobial drug, its nutritional value should be checked so that it gets easily digested and does not cause any harm to the individual who is taking it [132]. Also, the bioavailability and bioactivity should be stringently monitored. The ingested compounds interact, leading to some notorious effects that represent a challenging situation. Hence, toxicity, carcinogenicity, and mutagenicity should be monitored, and efforts should be made to overcome that. Finally, a systematic study of the in vivo toxicity of the most promising extracts is a major obstacle to their use in treating multidrug-resistant *Salmonella* infections [133].

Future Directions: Plants consisting of many bioactive compounds are renowned natural laboratories for developing natural products that are structurally distinct, diverse, complex. However, less than 10 percent have been tested for discovering natural products in plants, especially angiosperms [134].

This paves the pathway of fascinating more bioactive compounds from flowering plants that will yield novel drugs to combat antimicrobial-resistant infections. So, more integrative research is needed for the successful discovery of this. Isolation of this natural product from the plant is difficult, but the plants promote it due to its diverse nature.

Moreover, for the production of natural therapeutic agents, the use of digestion models that provide useful value has been developed. It should be introduced to assess components, drug safety, and comprehension of the fate of microorganisms under digestive conditions. To increase the efficacy of plant antimicrobial components, emerging technologies, such as bio-adhesive technology such as hydrogel formulations and packaging materials in combination with plant bioactive components, nanotechnology, and the high-throughput assay should be considered. Hence, these plant-derived active principles can be used for further study to convert this information into potential therapeutic drugs. However, the fundamental use of medicinal plants for the drug discovery program threatens its existence, so farming of medicinal plants must be instigated to ensure future transparency [135].

CONCLUSION: The development of multidrug resistance in human pathogenic bacteria and the adverse side effects of some antibiotics has given rise to a great deal of interest in discovering new antimicrobial drugs of plant origin. Plants have historically been used to prevent and treat various diseases since ancient times. Plants are a promising alternative to treating medically difficult pathogens and combating the increasing number of bacteria resistant to traditional antibiotics. Moreover, with the increased negative attitudes of consumers toward chemical preservatives, the use of antimicrobial plant extracts has become a particularly interesting option.

Plant cells produce many phytochemicals, particularly secondary metabolites, to protect microorganisms, parasites, and herbivores. These bioactive compounds are found in all plant materials, such as roots, stems, leaves, flowers, fruits, and seeds are responsible for their medicinal properties and health benefits. The arrangement of the antimicrobial secondary metabolites describes the variety of metabolites. The mechanisms by which these compounds function against microbial cells are different cellular architectures and functional target classes. Antimicrobial compounds in plants surpass the restricted specificity of antibiotics. A recent trend in the production of new sources of antibiotics is the study of the combination of natural plant derivatives and standard antibiotics to improve the action of these using bacterial synergism. Hence, plants play an important role in combating multidrug-resistant infections and can be used to discover new antibacterial agents.

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