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# An Updated Review on the Therapeutic Potential of Plant-derived Compounds as Natural Anti-diabetic Agents against Multidrug-resistant Pathogens

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## Abstract

**Background:** The increasing prevalence of diabetic multidrug-resistant (MDR) pathogens has reduced the effectiveness of conventional antibiotics, highlighting the need for alternative therapies such as *Ayurveda*-derived plant bioactive compounds. **Aim:** This review aims to evaluate the potential of *Ayurveda* plant-derived natural bioactive compounds in combating diabetic multidrug-resistant (MDR) pathogens amid the growing global threat of antibiotic resistance. **Methods:** A comprehensive analysis of previous literature was conducted to examine the antibacterial efficacy of plant-derived bioactive compounds and their mechanisms of action against resistant pathogens. Emerging therapeutic strategies, including major plant materials and bioactive compounds, bacteriophages, nanotechnology, CRISPR-Cas systems, and probiotics, were also reviewed. **Results:** Plant-derived compounds demonstrate significant antimicrobial activity against MDR pathogens, including Gram-negative *bacilli* and Gram-positive cocci. These pathogens are responsible for infections that are increasingly difficult to treat with conventional antibiotics such as antifungal, antibacterial, and antiparasitic agents. Resistance mechanisms include efflux pumps, enzymatic degradation, and target site modification. Bioactive compounds such as alkaloids, flavonoids, terpenes, phenolic compounds, essential oils, and polysaccharides contribute to antimicrobial activity. **Conclusion:** Medicinal plant-derived compounds hold strong potential as alternative therapeutic agents against diabetic multidrug-resistant pathogens. However, variability in phytochemical activity and limitations in clinical validation highlight the need for standardisation, advanced technologies, and well-structured clinical trials. Global collaboration is needed to translate plant-based compounds into approved clinical treatments. Emphasis on personalised medicine may further enhance the effectiveness of these therapies in targeting specific microorganisms.

**Major Findings:** Medicinal plant-derived bioactive compounds exhibit very strong antibacterial activity against diabetic multidrug-resistant microorganisms by targeting multiple resistance mechanisms, indicating their potential as effective alternative therapeutic options.

**Keywords:** Alkaloids, Essential Oils, Flavonoids, Phenolic Compounds, Plant-derived Compounds, Polysaccharides

**Abbreviations:** AMR – Antimicrobial Resistance; CFU – Colony Forming Unit; CRISPR – Clustered Regularly Interspaced Short Palindromic Repeats; ESBL – Extended-Spectrum Beta-Lactams; EDTA – Ethylenediaminetetraacetic Acid; MBC – Minimum Bactericidal Concentration; MDR – Multidrug Resistant; MIC – Minimum Inhibitory Concentration; MRSA – Methicillin Resistant *Staphylococcus Aureus;* VRE – Vancomycin Resistant *Enterococcus;* WHO – World Health Organisation.

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## 1. Introduction

Antibiotic resistance is a global problem that needs to be dealt with right away, and more people need to know about multidrug-resistant organisms (MDR). In one instance, an MDR case was verified in a hospital patient and given top priority for basic care and management. In severe or prolonged instances where patients persist in antibiotic consumption, antimicrobial-resistant (AMR) genes may emerge and disseminate. These genes could get into the environment through medical sewage, which would pollute the ecosystem's water and soil sources[1]. Antibiotics, such as antifungal, antibacterial, and antiparasitic agents, are fundamental to contemporary medicine and are employed to treat diverse infections. For almost 50 years, they worked very well, and this time is often called the "golden era" of antibiotics[2]. Even though the World Health Organisation and other groups have strongly warned against the dangers of over-prescribing antibiotics, it is still a big problem around the world[3]. A study conducted in India found that rising population density is contributing to an increase in multidrug-resistant pathogens such as *Pseudomonas* species, vancomycin-resistant *Enterococcus* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae* and *Escherichia coli*. The World Health Organisation has already identified antimicrobial resistance as one of the top global health threats[4]. As a result, infections such as pneumonia and urinary tract infections (UTIs) are becoming more difficult to treat. Routine surgeries and medical procedures are also becoming riskier due to the threat of untreatable infections[5].

Day by day, the number of organisms that are resistant to antibiotics is growing, which is a big worry for the World Health Organisation (WHO). Taking too many antibiotics or not using them properly has led to the rise of multidrug-resistant (MDR) bacteria, which are also known as "superbugs"[6]. These infections are hard to treat, and they can make surgeries and other medical procedures very dangerous, especially for patients with weak immune systems, who may not be able to get rid of or treat these infections. Medicinal plant-derived compounds, CRISPR-Cas systems, nanotechnology, and phage therapy are all promising alternatives to traditional antibiotics that could help stop and treat MDR infections. We need to act right away. Research centres, government agencies, and drug companies need to work together to speed up the development of new treatments. Public awareness campaigns are also important to encourage the responsible use of antibiotics[7].

It can be hard to plan antibiotic research. Medicinal plants have been known for a long time to be a good source of bioactive compounds that could be used to treat diseases. Plant extracts and their constituents exhibit antibacterial and antifungal properties, rendering them suitable subjects for investigation against diverse pathogens[8]. Medicinal plants produce numerous active compounds with phytochemical characteristics, including flavonoids, alkaloids, terpenes, terpenoids, essential oils, phenolic compounds, and polysaccharides, which demonstrate antimicrobial efficacy against a wide range of pathogens. Recent *in vitro* studies targeting multidrug-resistant organisms have shown that these plant-derived compounds work well when used with traditional therapies[9].

## 2. Summary of Pathogens that are Resistant to More Than One Drug

Over the past few decades, the increasing number of multidrug-resistant (MDR) pathogens, especially Gram-negative bacteria, has had a big impact on the way infectious diseases spread[10]. *Klebsiella pneumoniae* is a Gram-negative bacillus that ferments lactose and is often linked to infections of the urinary tract and bloodstream. It often doesn't respond to antibiotics like carbapenems and extended-spectrum beta-lactams (ESBL) because it can make enzymes that break down these drugs. This resistance is a big problem in hospitals and other places where people get medical care. Imipenem, meropenem, ertapenem, and colistin are all types of carbapenem antibiotics[11]. *Pseudomonas aeruginosa* is a Gram-negative bacillus that does not ferment lactose. It is known for causing pneumonia and wound infections, especially in burn patients. It is frequently resistant to various classes of antibiotics, especially carbapenems and aminoglycosides, including gentamicin, amikacin, and netilmicin. *Acinetobacter baumannii* is a Gram-negative coccobacillus that does not ferment lactose. It is linked to infections that people get in hospitals, such as ventilator-associated pneumonia and sometimes bacteremia. Carbapenem

antibiotics like meropenem and imipenem are often used to treat it. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a Gram-positive coccus bacterium that is resistant to methicillin, cefoxitin, and numerous other beta-lactam antibiotics. It is often linked to infections of the skin and soft tissues, especially wounds in people with diabetes, as well as infections of the bloodstream[12]. *Candida auris* is a fungal pathogen that is resistant to many drugs. It is a budding yeast-like organism that is Gram-positive and can cause serious infections, such as vaginal and urinary tract infections. It is a big problem in healthcare settings because it doesn't respond to many antifungal drugs. *C. auris* was first discovered in Japan in 2009 and has since become a worldwide healthcare-associated pathogen[13]. In clinical environments, these multidrug-resistant pathogens pose significant challenges that require stringent infection control protocols and the immediate advancement of innovative antibiotic treatments[14].

## 3. How Bacteria Become Resistant

Antibacterial resistance mechanisms include (1) altering membrane permeability, (2) modifying target sites, (3) inactivating drugs, (4) utilising efflux pumps for inherent resistance to limit uptake, and (5) disrupting cell membrane integrity. Drug inactivation's and drug efflux are resistance processes that may involve modifications to drug targets due to structural variability. There are different types of mechanisms that Gram-negative bacteria use. Gram-negative bacteria, constituting all four mechanisms, in contrast to Gram-positive bacteria, typically exhibit reduced limitations on drug uptake due to the absence of an LPS outer cell membrane and the lack of capacity for one or two types of drug efflux pump mechanisms[15,16].

### 3.1 Efflux Pump

This pump creates antibacterial properties. The antibiotic must be present in high enough amounts and stay stable for a long time to work[17]. Many bacteria that are resistant to more than one drug fight drugs by using efflux pumps. The efflux pump is a protein-based transporter that stays stable in the cytoplasmic membrane and works as a regulator of the microbial internal environment[18]. All bacteria eliminate toxins and antibiotics, with the resistance gene initially identified as the efflux pump acting as a causative agent. *E. coli* resistance to tetracycline was also a major cause of resistance[19]. Resistance-nodulation-division (RND) is a family-specific characteristic found in Gram-negative bacteria[20]. Adenosine triphosphate is an affinity cassette supergroup (ABC), a multi-drug and toxic compound extrusion (MATE), and a major facilitator superfamily (MFS), as well as a small multi-drug resistant family (SMR)[21]. They are all efflux pumps that move large groups of Gram-negative and Gram-positive bacteria around. Bacteria can make efflux pumps work faster than normal, which helps them get rid of antibacterial agents. It won't take long for this agent to get to the target site at a steady concentration. Bacterial efflux pumps are coded by resistance genes found in mobile genetic elements like plasmids and transposons, which are present in all microorganisms, including humans, and are based on chromosome[22]. The resistance gene is one of the 20 genes that make up a bacterial efflux pump. Most of the pump is found in MGEs, and it changes the resistance of most Gram-positive bacteria. Different MDR efflux pumps in the *Enterobacteriaceae* group of organisms and *P. aeruginosa* belong to the RND family and affect the extrusion of tetracycline drugs[23]. Resistance to RND efflux pumps can also occur with two or more antibiotics, like chloramphenicol, beta-lactams, fluoroquinolones, and fusidic acid. *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and certain Gram-positive bacteria exhibit resistance to macrolides via an efflux pump associated with the ABC family located within the chromosome. This resistance mechanism was initially discovered in *S. epidermidis*[24]. Antibiotic resistance via efflux mechanisms is also observed in A. The AdeABC and RND efflux pumps in *A. baumannii* let antibiotics like aminoglycosides, tigecycline, beta-lactams, chloramphenicol, erythromycin, and tetracycline out of the bacterial cells. The results show that drug accumulation at the specific site is lower, and the minimum inhibitory concentrations of antibiotics are higher, making them less effective[25].

### 3.2 Changes to the Target Site

There are many compounds in bacterial cells that antibacterial agents could target. The bacterium can also change many of these targets to make them resistant to drugs. Mechanisms of resistance to β-lactam antibiotics

are predominantly associated with Gram-positive bacteria and involve penicillin-binding proteins[26]. They are transpeptidases that work with peptidoglycan in the walls of cells. A change in the number of PBPs can lead to a decrease in drug-binding affinity or a decrease in PBPs; along with normal antibiotics binding to PBPs, which means that only a small amount of drug can bind to that target. Changes in the structure of cells, like PBP2a in *Staphylococcus aureus* getting the mecA gene, could make it harder for drugs to bind or stop drug binding altogether[27].

The glycopeptides that belong to vancomycin work by stopping the synthesis of cell walls, and the lipopeptides that belong to daptomycin work by depolarising the cell membranes. Gram-negative bacteria have a thick LPS layer that makes them naturally resistant to these drugs[28]. *Enterococcus* species (Vancomycin-Resistant *Enterococcus*) and *Staphylococcus aureus* (MRSA) are two of the main problems with vancomycin resistance. This is caused by the acquisition of genes that change the morphology of peptidoglycan substances, which makes it harder for vancomycin to bind; daptomycin necessitates the detection of calcium for binding. The mutation in genes like mprF changes the charge of the cell wall membrane surface to positive, which stops calcium from binding to daptomycin[29].

Resistance to drugs that target ribosomal subunits may arise from ribosomal mutations in aminoglycosides, oxazolidinones, and other ribosomal subunits, such as methylation. Aminoglycosides and macrolides affect Gram-positive bacteria, while oxazolidinones and streptogramins are synthetic antibiotics. Most of the involved genes or ribosomal protections (tetracycline) hinder the drug's ability to bind to the ribosome[30]. Antibiotics target nucleic acid synthesis. Fluoroquinolones are resistant to some modifications in DNA gyrase in Gram-negative bacteria (e.g., gyrA) or topoisomerase IV in Gram-positive bacteria (e.g., grlA), which cause mutations that change the structure of gyrase and topoisomerase. This decreases or removes the drug's ability to attach to these substances[31]. Drugs that can inhibit metabolic pathways are resisted by causing mutations in enzymes involved in DHPS (dihydropteroate synthase) and DHFR (dihydrofolate reductase) that enter the folate biosynthesis pathways or by producing more resistant DHPS and DHFR enzymes. Sulphonamides inhibit DHPS, and trimethoprim inhibits DHFR; both enzymes bind to their respective substances because they are structural analogues of natural substances. These drugs work by competitively inhibiting enzymes by binding to their active sites. These enzyme mutations are located in or near the active site[32].

### 3.3 Modification of Permeability of Membranes

Gram-negative bacteria have an outer membrane, which acts as a barrier and protective layer against harmful substances[33]. Porins are proteins found in the outer membrane of bacteria. They form holes that are filled with water and allow materials and nutrients to pass through this membrane. They are one of the possible targets for drugs that kill germs. Porins were first found in *E. coli*[17]. Porin divided into two types of activity specific and non-specific. Specific porins are selective compounds, such as LamB, that specifically take up maltose, maltodextrin, and Feb A, which are iron complexes. On the other hand, nonspecific or general porins are involved in membrane permeability and are linked to bacterial resistance to antimicrobial properties[34]. Based on their structure, porins can be classified into three groups: monomeric, dimeric, and trimeric. There are three types of porins: those that are specific for antibiotic transport (LamB, YddB), those that are specific for membrane integrity (OmpA), and those that are not specific and react to both antibiotic transport and membrane safety (OmpC, OmpF). The porin structure is linked to a rise in bacterial resistance to antibiotics, for example. OmpF porin is responsible for transporting several antibiotics, including β-lactam and fluoroquinolone antibiotics like ciprofloxacin, levofloxacin, and ofloxacin; this porin protects *E. coli, K. pneumoniae,* and *P. aeruginosa*. It is resistant to carbapenems by lowering the levels of porins like OmpF and OmpC. This changes the integrity of the outer membrane, making it resistant to colistin[35]. *P. aeruginosa* has two kinds of antibiotics: intrinsic and acquired (adaptive). The alteration of the primary component of the outer membrane involves lipopolysaccharides (LPS), exemplifying intrinsic resistance mechanisms through which *P. aeruginosa* combats antibiotics such as β-lactams, quinolones, and aminoglycosides[36].

### 3.4 Destruction of Antibiotics or Drugs that make them Less Effective

A group of enzymes is involved in making the bacterial cell wall, nucleic acids, and metabolites. Some antibacterial agents specifically target those enzymes as a primary aspect of their mechanism. The bacterium may develop antibiotic resistance through morphological alterations or modifications of structural components influenced by antibiotics, such as ribosomes via methyltransferases[37]. Bacteria that are either Gram-positive or Gram-negative release enzymes that break down antibiotic molecules and make them useless. Numerous antibiotics rendered inactive by these mechanisms inhibit bacterial protein synthesis[38]. Three main types of enzymes are known to make antibiotics less effective: β-lactamase enzymes break down the lactam ring in penicillin, cephalosporins, and carbapenems. There are 300 different types of β-lactamases, and they are all different in terms of their structure and function[39]. Second, the enzyme acetyltransferase acetylates the hydroxyl group in chloramphenicol, which stops it from binding to the target site correctly. *H. influenzae* is a Gram-negative coccobacillus belonging to the *Enterobacteriaceae* family, including *Acinetobacter* species and *P. aeruginosa*, which exhibit resistance to chloramphenicol through this mechanism[40]. Aminoglycosides are a group of antibiotics that change the way enzymes work in *S. aureus*, *K. pneumoniae*, and *E. coli*. *E. faecalis* is a microorganism that combats antibiotics by producing modified drug molecules through certain enzymes, thereby enhancing its affinity for binding to 30S subunits[41].

### 3.5 Damage to the Integrity of the Cell Membrane

The antimicrobial properties of plant-derived compounds are frequently linked to their capacity to compromise bacterial cell membrane integrity. In Gram-positive bacteria, negatively charged components like teichoic acids interact with bioactive compounds, which destabilise the membrane, cause intracellular contents to leak out, and eventually kill the cell. These compounds can target lipopolysaccharides

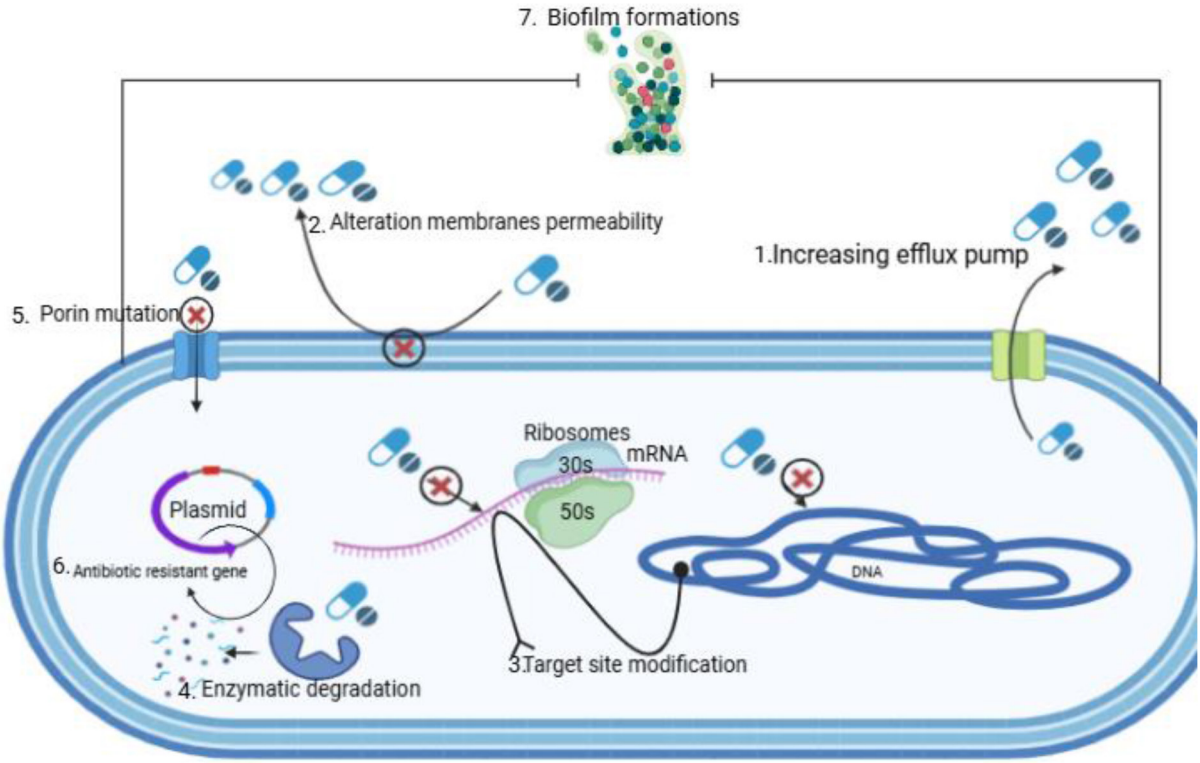



**Figure 1.** Systematic development of bacterial antibiotic resistance, incorporating resistance mechanisms. **(1).** Increasing the efflux pump; **(2).** Changing the permeability of membranes; **(3).** Changing the target site; **(4).** Enzymatic degradation; **(5).** Porin mutations; **(6).** Antibiotics resistant gene; **(7).** Making biofilms.

in the outer membrane of Gram-negative bacteria. This makes the membrane more permeable and lets more substances into the cell. Research on polyphenols, flavonoids, and essential oil constituents has shown that damaging both the outer and inner membranes causes cytosolic material to leak out and microbial cells to die. Similar mechanisms have been documented for various plant-derived microspheres and nanoparticles, underscoring their potential to disrupt bacterial membrane integrity and exhibit bactericidal effects (Figure 1)[42].

## 4. Compounds from Plants that Target Multidrug-resistant Pathogens

Plants are made up of two kinds of metabolites: primary and secondary. Primary is necessary for plant survival, while secondary pertains to plant interactions with other plants and the environment. Primary metabolites are the end products of glycolysis, shikimate pathways, and tricarboxylic acid cycles that help with nutrition and reproduction[43]. They are the precursors to thousands of secondary metabolites that are made at different points

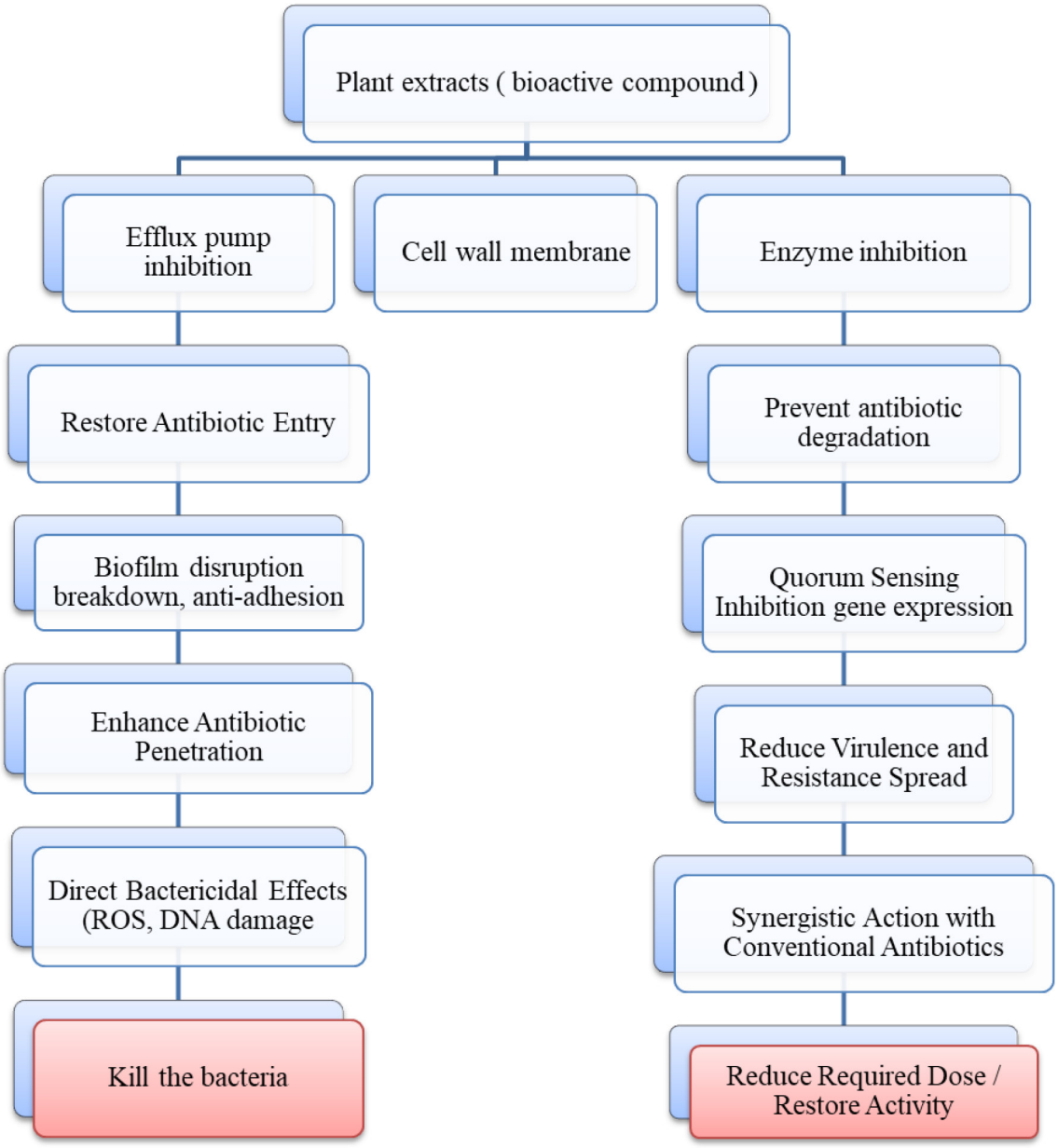



**Figure 2.** Mechanisms of plant extracts against multidrug-resistant (MDR) pathogens – diagrammatic representation.

in primary metabolic pathways. The goal of enzymatic activity against primary metabolites is to make new compounds that help plants adapt to biotic factors like bacteria, fungi, insects, and infections, as well as abiotic factors like injury, temperature, moisture, and stress[44]. A plant-derived compound is a secondary metabolic product found in various plant parts, including roots, leaves, bark, flowers, and seeds, exhibiting a wide range of structural diversity. Plant-derived compounds are utilised in the pharmaceutical industry for their natural antibiotic properties or as potential sources for new antibacterial agents targeting various pathogens[45]. Plant phytochemicals can be classified into terpenoids, polyketides, phenylpropanoids, and alkaloids. In the update, plant-derived phytochemicals exhibited antimicrobial activity and mechanisms of action against various multidrug-resistant microorganisms. In the study, the compounds were divided into alkaloids, polyphenols, terpenoids, and sulfur-rich compounds from plant material. These plants show a strong effect on antibiotic-resistant bacteria, which are called multidrug-resistant bacterial pathogens. Ancient civilisations recognised plant-derived compounds for their potential in combating microbial infections. These phytochemicals have exhibited antibacterial and antifungal properties, serving as effective medicinal alternatives through their antimicrobial activity (Figure 2)[46].

## 4.1 Alkaloids

Alkaloids, proteins, amino acids, peptides, nucleotides, nucleic acid antibiotics, and amines are all chemicals that contain nitrogen and have important effects on drugs. Many alkaloids are used to treat different infections because they have antimicrobial properties. Sanguinarine is one of these alkaloids that can kill bacteria. Sanguinarine, a benzophenanthridine alkaloid extracted from the rhizomes of *Sanguinaria canadensis*, has been acknowledged for its antibacterial properties, capacity for DNA intercalation, and anti-inflammatory effects. *In vitro* studies have demonstrated that sanguinarine can impede bacterial adhesion to dental surfaces[42]. A recent study examined the efficacy of sanguinarine, EDTA, and vancomycin, as well as their combinations with sanguinarine, EDTA, and streptomycin, against Gram-positive cocci in clusters, Gram-negative bacteria, and multidrug-resistant (MDR) bacteria. The studies indicate that sanguinarine exhibits significant efficacy against all tested strains, with a minimum inhibitory concentration (MIC) ranging from 0.5 to 128 g/ml. Additionally, synergistic effects were observed for the combinations of sanguinarine + EDTA and sanguinarine + EDTA + vancomycin against persistent Gram-negative bacteria. The combination of sanguinarine with EDTA and streptomycin exhibited synergistic activity against all strains, except for methicillin-resistant *S. aureus*. Alkaloids extracted from berberine, classified as isoquinoline derivatives, have been studied for their efficacy against oral pathogens, particularly in inhibiting the growth of *Streptococci* species and other endodontic pathogens, as well as in multispecies biofilm tooth examinations. The initial antibacterial effect was noted against *S. sanguinis* (MIC: 512 g/ml), with a significant synergistic effect identified when combined with penicillin, clindamycin, and erythromycin. When combined with 1% chlorhexidine, the processed pathogens in vitro have a bactericidal effect that is similar to that of NaOCl[47,48]. Research investigated tomatidine, a steroid alkaloid derived from tomato plants, as a potential virulence-attenuating agent for *S. aureus* single colony variant phenotypes implicated in chronic infections. Numerous studies indicate that tomatidine exhibits anti-virulence activity against typical *S. aureus* strains and additionally functions synergistically with aminoglycoside antibiotics[49]. Berberine inhibited the adhesion of *S. epidermidis* and biofilm formation on titanium alloy disks. The study demonstrated that berberine, at a concentration of 63.5 g/ml, effectively reduced biofilm growth in various *K. pneumoniae* clinical isolate samples[50].

Spathullin A and B, which were taken from a culture broth of *Penicillium sapthulatum* Em19, are two natural products that kill bacteria. Both Gram-negative and Gram-positive bacteria, including *E. cloacae,* were tested against these compounds. *P. aeruginosa*, *A. baumannii, K. pneumoniae,* and *S. aureus*. Spathullin B was more effective than spathullin A against all of the tested microbial pathogens, including bacteria, with a MIC of 1 g/ml against *S. golden*. The minimum inhibitory concentrations of meropenem and ciprofloxacin against *S. aureus* were 0.5 and 0.25 g/ml, indicating that spathullin B exhibited significant antimicrobial activity (Table 1)[51].

## 4.2 Flavonoids

Flavonoids are found in many foods, including fruits, vegetables, nuts, seeds, stems, flowers, tea, wine, propolis, and honey. They are also found in cells that perform photosynthesis. These compounds act as active ingredients that fight human pathogens. Flavonoids possess antifungal, antiviral, and antibacterial properties that have been identified by various research institutions. Furthermore, recent studies have demonstrated the efficacy of active flavonoids in chemotherapeutic applications; plants high in flavonoids, such as Hypericum, Capsella, and Chromolaena, have been isolated, and their structures identified. They have also been shown to have antimicrobial activity. Flavonoids are available for commercial production, including compounds such as apigenin, galangin, pinocembrin, ponciretin, genkwanin, sophoraflavanone, luteolin, luteolin 7-glycoside, quercetin, 3-O-methylquercetin, quercetin glycosides, kaempferol, isoflavones, flavanones, isoflavans, flavonols, and chalcones. The antimicrobial activity of these compounds has been confirmed, along with identification[52]. Flavonoids administered via *in vivo* methods, specifically oral administration of either 142.9 mg/kg quercetin or 214.3 mg/kg quercetin, protect guinea pigs from induced *Shigella* species bacterial infections, which are lethal to untreated control animals[53]. Furthermore, it has been demonstrated that intraperitoneal injections of either 1.58 mg/kg sophoraisoflavone A or 3.16 mg/kg 6,8-diprenylgenistein conferred significant protection to mice challenged with approximately 9.5 × 10^8 colony-forming units of *S. typhimurium*, a foodborne pathogen[54]. Bacteria generate enzymes, including tyrosyl-tRNA synthetase, which were inhibited by the artocarpin compound derived from the leaves of *A. anisophyllus* against *B. cereus*, *E. coli*, and *P. putida*[55]. The baicalein compound has been investigated for its ability to diminish the secretion of inflammatory cytokines IL-1β, IL-6, IL-8, and TNFα induced by *P. aeruginosa*, which are crucial for inflammatory injury following *P. aeruginosa* infections and diseases. Baicalein at concentrations of 32 and 64 μg/ml effectively downregulated the quorum sensing regulators agrA, RNAIII, and sarA, influencing the gene expression associated with intracellular adhesion in methicillin-sensitive *Staphylococcus aureus* during biofilm formation[56]. Gancaonin G and semilicoisoflavone B are both compounds from *Glycyrrhiza uralensis* that were tested on vancomycin-resistant *Enterococcus* bacteria[57]. The minimum inhibitory concentration values for these compounds were 32 and 64 μg/ml, respectively. Neocyclomorusin and neobavaisoflavone, two of the 19 natural compounds from the methanolic extract of Cameroon plants that belong to the terpenoids, alkaloids, thiophenes, and phenolics, were effective against Gram-negative bacteria *(K. pneumoniae* and *E. cloacae)*[58].

## 4.3 Terpenes

Geraniol is a notable agent against resistant strains of Gram-negative pathogens, specifically through the inhibition of efflux pumps in *Enterobacter* species[59]. The study examined the effects of four monoterpenes - acyclic monoterpenes, monocyclic monoterpenes, bicyclic monoterpenes, and monoterpenoid derivatives - on the biomembranes of *S. aureus* and *E. coli* using differential scanning calorimetry. The study examines the relationship between thymol, carvacrol, p-cymene, gamma terpenes, and dimyristoylphosphatidylcholine in the context of transport. The mention of thymol has a bactericidal effect on *S. aureus*. Carvacrol and p-cymene have consistently demonstrated effective inhibitory action against *E. coli*. The effects of compounds are dependent on their concentrations. The study showed that these monoterpenes may work against MDR infections by breaking down membrane lipids. The effect was strongly affected by the lipid makeup of the bacterial membrane[60]. Carvacrol, cinnamaldehyde and thymol were used in the study mouthwash with chlorhexidine (0.004 mgml. Flow cytometry and confocal microscopy results showed that these chemicals work well to stop bacterial growth *in vitro* through disruption of membrane integrity, and also carvacrol, thymol and cinnamaldehyde may affect microbial biofilm formation at concentrations equal to or more than 0.5-5 mg/mL. Some people think that the hydroxyl group in carvacrol and thymol is involved in this process by stopping microbial enzymes from working and connecting with the cell membrane. As a result, intracellular component leakage would be heightened[61]. Retinol, found in vitamin A, and its activated form, retinoic acid, are another type of terpene present in most vegetables such as carrots, sweet potatoes, pumpkin, squash and cantaloupe[62].

More than one study has confirmed its activity in treating skin-related diseases. Vitamin A is one of the contributes to gene expression through two types of receptors: Retinoic Acid Receptors (RAR) and retinoid X receptors (RXR), which are the lot of in the skin. A novel synthetic compound, retinoid CD437, was evaluated for its potential bactericidal effect against *E. faecalis*[63]. This compound exhibited anti-biofilm activity against this microorganism and demonstrated significant synergy when combined with gentamicin. Conversely, another study showed that CD437's ability to kill bacteria was linked to the breaking of the lipid membrane[64]. This study evaluated the bactericidal efficacy of two synthetic retinoids, CD437 and CD1530, against MRSA.

## 4.4 Phenolic Substances

The HPLC/DAD method was used to find phenolic compounds and measure them as caffeic acid, verbascoside, oleuropein, luteolin-7-O-glucoside, rutin, apigenin-7-O-glucoside, and luteolin-4-O-glucoside. Olive leaf extracts at low concentrations demonstrated a unique combination of antibacterial and antifungal properties. The assessment was conducted *in vitro* against various microorganisms that may be responsible for human intestinal, respiratory, and Urinary Tract Infections (UTIs). The pathogens tested were Gram-positive bacteria (*B. cereus, B. subtilis,* and *S. aureus*), Gram-negative bacteria (*P. aeruginosa*, *E. coli*, and *K. pneumoniae*), and fungi (*C. albicans* and *C. neoformans*). These findings suggest that olive leaf extracts possess significant potential as nutraceuticals, especially as a source of phenolic compounds[65]. The antibacterial efficacy of 18 phenolic compounds, including hydroxycinnamic acid, hydroxybenzoic acid, stilbenes, flavan-3-ols, flavonoids, and other phenolic substances, was assessed against lactic acid bacteria isolates from wine, specifically *Oenococcus oeni*, *Lactobacillus hilgardii*, and *Pediococcus pentosaceus*, to determine which phenolic compounds exhibited the most significant inhibition of bacterial growth[66]. Investigating the antimicrobial efficacy of 15 phenolic compounds, including phenolic acids, stilbenes, and flavonoids derived from grapes, against spoilage yeasts and acetic acid bacteria in wine fermentation. Pterostilbene, resveratrol, and luteolin exhibit significant inhibitory effects on the tested microorganisms, while phenolic acids such as myricetin, p-coumaric acid, and ferulic acid demonstrate selective antimicrobial activity based on the species of yeast and bacteria tested[67]. Phenolic compounds are phytochemicals present in all plants, including simple phenols, benzoic and cinnamic acids, coumarins, tannins, lignins, and flavonoids. To find and measure certain phenolic compounds, scientists use spectrophotometric and chromatographic methods. To find total phenolics, they use chemical processes. These phenolic compounds have been present for the last 25 years. They may have properties that could enhance health[68]. Phenolic compounds exhibit diverse antimicrobial activities, including the permeabilisation and destabilisation of the plasma membrane, as well as the inhibition of extracellular enzymes. This mechanism acts against pathogens that are resistant to many drugs[69]. Dihydroguaiaretic acid, 4-epi-larreatricin, 3-demethoxy-6-O-demethylisoguaiacin, and 5,4-dihydroxy-7-methoxyflavone exhibit substantial microbial growth inhibition potential against certain bacterial strains, with minimum inhibitory concentration values ranging from 12.5 to 50 g/ml. This MIC value of 500-1000 g/ml was reported for 7-hydroxycoumarin (umbelliferone) against *S. aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA*), E. coli,* and *P. aeruginosa*[70]. Mango was isolated from gallotannins through kernel inhibition of the growth of *B. subtilis* and other food pathogens such as *E. coli*. The inhibition of gallotannins may be attributed to their ability to interact with proteins, hinder enzyme activity, and exhibit iron-complexing properties[71].

## 4.5 Oil of Essential Oils

Natural products have been investigated for their biological properties. Consequently, this study aimed to evaluate the antibacterial activity of 27 essential oils (EOs) used in aromatherapy, a natural therapy currently employed to combat *Pseudomonas* species*, E. coli,* and *S. aureus* strains of *P. aeruginosa*. The agar dilution method was used to determine the minimal inhibitory concentration (MIC 50% and MIC 90% values) that killed 50% and 90% of microorganisms. The MIC 90% of copaiba *(Copaifera officinalis)* essential oil is 26.52 mg/mL, while the MIC 90% of tea tree *(Melaleuca alternifolia*) and black pepper (*Piper nigrum*) is 0.21 mg/

mL. The strains of *aureus* were very easy to infect. Clove (*Syzygium aromaticum*) and cinnamon (*Cinnamomum cassia*) essential oils were effective against *P. aeruginosa* (8.29 mg/mL, *E. coli* (2.0 mg/mL). So, it has been found that Gram-positive bacteria are more susceptible than Gram-negative bacteria and that their antibacterial properties are very different from each other[72]. Secondary essential oil SEO of menthe citrate exhibits antibacterial activity against eight strains of Gram-positive bacteria, including *S. aureus*, *S. epidermidis*, and *S. mutans,* all sourced from MTCC. Additionally, it demonstrates efficacy against Gram-negative bacteria such as *P. aeruginosa, K. pneumoniae, E. coli*, and *S. typhimurium*, with a reported MIC value of 50-1000 µg/mL. In contrast, the primary essential oil shows activity against seven strains, with a MIC value of 250-1000 µg/mL[73]. Essential oils contain bicyclogermacrene (19.42%), isocaryophyllene (16.70%), valecene (12.94%), and germacrene D (12.34%). These compounds were tested for antimicrobial and modulatory activity against multidrug-resistant strains like *E. coli* and *S. aureus* using a microdilution test. The data show that the substance stops the growth of *E. coli* (MIC 512 µg/ml) and *S. aureus* (MIC 256 µg/ml). The synergy between the essential oil compound and aminoglycosides resulted in a significant reduction of MICs (7×, 1250-5 µg/ml) against *E. coli*[74]. There are 44 known compounds in the essential oil of *Hofmeisteria schaffneri*, which make up about 90% of its composition. The thymol analogues make up the largest group (about 65%). The plant had selective antimicrobial properties, working mostly against yeast and Gram-positive bacteria. The infusion stopped *S. aureus* and *B. subtilis* at MIC levels of 64 mg/ml, while the essential oils worked against *S. aureus* with MIC values between 48 and 192 mg/ml. On the other hand, there was no activity against Gram-negative bacteria (*P. aeruginosa*, *E. coli, and S. typhi*), with MIC values higher than 1024 mg/ml. The infusion (MIC = 128 mg/ml) and essential oil from batch I (MIC = 192 mg/ml) both showed moderate antifungal activity against *C. albicans*. The organic extract, on the other hand, was inactive (MIC = 1024 mg/ml). Compounds 8 and 38 had the strongest antibacterial activity against Gram-positive strains (MIC = 32–64 mg/ml). Compounds 6 (from the infusion) and 10 (found in all preparations) were the most effective against yeast, with lower MIC values (128 mg/ml) than the other tested compounds (256–512 mg/ml). In general, the results show that *H. Schaffneri* oils and infusions, abundant in thymol analogues, exhibit significant efficacy against Gram-positive bacteria and *C. albicans*, but do not work against Gram-negative pathogens[75].

## 4.6 Polysaccharides

The increasing antimicrobial efficacy of polysaccharides in derived compounds such as chitosan has been documented in numerous studies, indicating a 65.55% antibacterial activity attributed to sulphated algal polysaccharides, alginate, β-glucan, pectin, xanthan gum, xylan, agar, maltodextrin, and various others, despite polysaccharides being cultivated from natural sources. Depolymerised polysaccharides exhibited superior inhibitory activity against *E. coli*. In addition, low molecular weight (<10 kDa) anionic and non-ionic polysaccharides were more effective than chitosan (10–100 kDa) in this case. It is difficult to comprehend the implications of the current meta-analysis, which exhibits substantial variability in results (I2 > 80%)[76]. Plants have a lot of polysaccharides, like starch, cellulose, and pectin, which are usually safe and not harmful. They have a lot of positive biological effects, such as being antimicrobial, antioxidant, and immune-modulating, as well as having other health benefits[77]. The walls of Gram-positive bacteria are thick and made of peptidoglycan. The walls of Gram-negative bacteria are made of lipopolysaccharides (LPS), which make their surface charge more negative. This makes cationic chitosan bind more strongly to other things, especially when the pH is low. Some studies indicate increased susceptibility in Gram-negative bacteria, whereas others demonstrate that Gram-positive bacteria are more sensitive. Teichoic acids that are negatively charged also affect how chitosan works, and removing them from *S. aureus* makes it more resistant. The antibacterial efficacy of chitosan is contingent upon both the structural characteristics of the cell wall and the molecular attributes of chitosan[78]. Broth microdilution assays are often used to find the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of polysaccharide extracts. The MIC is the lowest concentration that stops visible growth, and the MBC

**Table 1.** *In vitro* tests of plant-based antimicrobials combined with antibiotics show effective antimicrobial action against clinically significant microorganisms

| Bioactive Compound | Dose / Concentration | Target Microorganisms | Outcomes/Mechanism of action: | References |
|---|---|---|---|---|
| Quercetin | 142.9–214.3 mg/kg (oral, *in vivo*) | *Shigella* spp. | Outcomes: Protected Guinea pigs from infection; killed bacteria in untreated controls<br>Mechanism of action: Likely inhibits bacterial growth and virulence factors | [53] |
| Sophoraisoflavone A | 1.58 mg/kg (i.p., *in vivo*) | *Salmonella typhimurium* | Outcomes: Provided significant protection in mice against ~$9.5\times10^8$ CFU<br>Mechanism of action: Antimicrobial activity, possibly immune modulation | [54] |
| 6,8-Diprenylgenistein | 3.16 mg/kg (i.p., *in vivo*) | *Salmonella typhimurium* | Outcomes: Provided significant protection in mice<br>Mechanism of action: Antimicrobial activity, possibly immune modulation | [54] |
| Olive leaf phenolics (caffeic acid, verbascoside, oleuropein, luteolin-7-O-glucoside, rutin, apigenin-7-O-glucoside, luteolin-4-O-glucoside) | Low concentrations | Gram-positive bacteria *(B. cereus, B. subtilis, S. aureus*), Gram-negative bacteria *(E. coli, P. aeruginosa, K. pneumoniae*), fungi *(C. albicans, C. neoformans*) | Outcomes: Mixed antibacterial and antifungal activity<br>Mechanism of action: Likely disrupts cell membranes and interferes with microbial metabolism | [65] |
| Berberine | 63.5 (µg/mL) | *S. epidermidis, K. pneumoniae* | Outcomes: Inhibited adhesion and biofilm formation on titanium disks; reduced biofilm growth<br>Mechanism of action: Inhibits bacterial adhesion and biofilm formation | [50] |
| Retinol (Vitamin A) | Not specified | Skin-associated pathogens | Outcomes: Protective and antimicrobial effect in skin infections<br>Mechanism of action: Modulates gene expression via retinoic acid receptors (RAR) and retinoid X receptors (RXR) | [65] |
| Gallotannins (from mango kernel) | Not specified | *B. subtilis, E. coli,* other food pathogens | Outcomes: Inhibition of bacterial growth<br>Mechanism of action: Interacts with proteins, inhibits enzymes, iron chelation | [71] |
| 7-Hydroxycoumarin (Umbelliferone) | 500–1000 µg/mL | *S. aureus,* MRSA, *E. coli, P. aeruginosa* | Outcome: Growth inhibition<br>Mechanism of action: Likely membrane permeabilisation and enzyme inhibition | [70] |
| Bicyclogermacrene, Isocaryophyllene, Valecene, Germacrene D (EO components) | MIC = 512 µg/mL (*E. coli*), 256 µg/mL (*S. aureus*) | MDR *E. coli, S. aureus* | Outcomes: Growth inhibition; synergy with aminoglycosides (MIC reduction 1250→5 µg/mL)<br>Mechanism of action: Potentiates antibiotics, disrupts membranes | [74] |

**Table 1.** Continued...

| Bioactive Compound | Dose / Concentration | Target Microorganisms | Outcomes/Mechanism of action: | References |
|---|---|---|---|---|
| Tomatidine (steroidal alkaloid) | | *S. aureus*, *P. aeruginosa* | Outcomes: Antibacterial and anti-virulence activity effective against chronic infections; synergistic effect with aminoglycosides<br>Mechanisms of Action: Reduces virulence factor production. | 49 |
| Hydroxycinnamic and hydroxybenzoic acids, stilbenes, flavan-3-ols, flavonoids | Not specified | Lactic acid bacteria (*O. oeni, L. hilgardii, P. pentosaceus*) | Outcomes: Strong inhibition of bacterial growth<br>Mechanism of action: Likely inhibition of extracellular enzymes and membrane destabilisation | 66 |
| *H. schaffneri* infusion (thymol analogues ~65%) | MIC = 64 mg/mL (*S. aureus, B. subtilis*); MIC = 128 mg/mL (*C. albicans*) | Gram+ (*S. aureus, B. subtilis*), yeast (*C. albicans*) | Outcomes: selective activity; moderate antifungal effect<br>Mechanism of action: Thymol analogues disrupt membranes and biofilm | 75 |
| *H. schaffneri* essential oil | MIC = 48–192 mg/mL (*S. aureus*); MIC = 192 mg/mL (*C. albicans*) | Gram+ bacteria, *C. albicans* | Outcomes: Antibacterial and antifungal activity<br>Mechanism of action: Membrane disruption | 75 |
| *H. schaffneri* compounds 8 and 38 | MIC = 32–64 mg/mL | Gram-positive strains | Outcomes: Strong antibacterial activity<br>Mechanism of action: Likely cell membrane destabilisation | 75 |
| *H. schaffneri* EO / infusion | MIC > 1024 mg/mL | Gram-negative bacteria (*P. aeruginosa, E. coli, S. typhi)* | Outcomes: No activity observed<br>Mechanism of action: Gram– outer membrane barrier prevents activity | 75 |
| Berberine (Isoquinoline alkaloid) | 512 (µg/mL) | *S. sanguinis*, oral pathogens, endodontic pathogens | Outcome: Antibacterial activity; significant synergistic effect with penicillin, clindamycin, erythromycin; comparable bactericidal effect with 1% chlorhexidine<br>Mechanism of action: Inhibits bacterial growth and biofilm formation | 47, 48 |
| Isothiocyanates (horseradish root) | Fungal MIC: 0.52 mg/ml; Bacterial MIC: 1.25 mg/ml | *Lactobacillus*, *Streptococcus*, *Enterococcus*, *F. nucleatum*, *P. nigrescens*, *S. aureus* | Outcomes: High antimicrobial potency toward oral pathogens and anaerobes.<br>Mechanism of action: Disrupts cell membrane integrity. | 81 |
| Benzyl-isothiocyanate (*Moringa oleifera* seeds) | Not specified | *E. casseliflavus*, *S. aureus* | Outcomes: Active against *E. casseliflavus* and *S. aureus*.<br>Mechanism of action: Blocks bacterial expansion | 82 |
| Alkaloids from *Rauwolfia* sp. | MIC: 15.6 µl/m | *K. pneumoniae* | Outcomes: Active against *K. pneumoniae*.<br>Mechanism of action: Regulates and reduces biofilm formation, limiting bacterial survival and persistence. | 83 |

**Table 1.** Continued...

| Bioactive Compound | Dose / Concentration | Target Microorganisms | Outcomes/Mechanism of action: | References |
|---|---|---|---|---|
| Myricetin, p-coumaric acid, ferulic acid | Not specified | Yeasts and bacteria (species-dependent) | Outcomes: Selective antimicrobial activity<br>Mechanism of action: Likely affects membrane integrity and microbial metabolism | 67 |
| Pterostilbene, resveratrol, luteolin | Not specified | Wine spoilage yeasts and acetic acid bacteria | Outcomes: Significant antimicrobial activity<br>Mechanism of action: Likely membrane disruption and enzyme inhibition | 67 |
| Tea tree oil (*Melaleuca alternifolia*) | $MIC_{90}$ = 0.21 mg/mL | *S. aureus* | Outcomes: High susceptibility of Gram-positive strain<br>Mechanism of action: Disrupts membrane integrity, leakage of cell contents | 72 |
| Black pepper oil (*Piper nigrum)* | $MIC_{90}$ = 0.21 mg/mL | *S. aureus* | Outcomes: Strong antibacterial activity<br>Mechanism of action: Alters cell membrane permeability | 72 |
| Clove oil (*S. aromaticum*) | MIC = 8.29 mg/mL | *P. aeruginosa* | Outcomes: Effective inhibition<br>Mechanism of action: Disrupts bacterial membrane, enzyme inhibition | 72 |
| Gancaonin G<br>Semilicoisoflavone B | 32 µg/mL<br>64 µg/mL | Vancomycin-resistant *Enterococcus* (VRE) | Outcomes: Inhibited bacterial growth<br>Mechanism of action: Likely disrupts bacterial replication or metabolism | 57 |
| Artocarpin | Not specified | *B. cereus, E. coli, P. putida* | Outcomes: Inhibited bacterial growth.<br>Mechanism of action: Inhibits tyrosyl-tRNA synthetase enzyme | 55 |
| Piperine (*P. nigrum*) | 0.5–10 µg/ml | *E. coli*, *Proteus* spp. | Outcomes: Limits Uro-pathogen colonization.<br>Shows adjunct potential in urinary tract infection (UTI) management.<br>Mechanisms of action: Interferes with virulence factors, reducing colonisation ability. | 84 |
| Allyl-isothiocyanate | MIC: 51 ppm;<br>MBC: 412 ppm | *E. coli*, *S. aureus*, *Listeria monocytogenes* | Outcomes: Exhibits both bactericidal and bacteriostatic effects.<br>Mechanisms of action: Induces oxidative stress and cellular damage. | 85 |
| Berberine | MIC: 0.3125 mg/ml | *Actinobacillus pleuropneumoniae* | Outcomes: Exhibits antimicrobial potential against pathogens<br>Mechanisms of action: Disrupts cell membrane integrity. | 86 |
| Tomatidine (Steroid alkaloid) | Not specified | *S. aureus* (SCV phenotypes) | Outcome: Anti-virulence activity; synergistic effect with aminoglycosides<br>Mechanism of action: Virulence attenuation; inhibits chronic infection phenotypes | 49 |

**Table 1.** Continued...

| Bioactive Compound | Dose / Concentration | Target Microorganisms | Outcomes/Mechanism of action: | References |
|---|---|---|---|---|
| Neocyclomorusin and Neobavaisoflavone | 4–8 µg/mL | *K. pneumoniae, E. cloacae* | Outcomes: Effective against Gram-negative bacteria<br>Mechanism of action: Likely targets bacterial cell wall or protein synthesis | 58 |
| Baicalein | 32–64 µg/mL | *P. aeruginosa*, methicillin-sensitive *Staphylococcus aureus* (biofilm) | Outcomes: Reduced inflammatory cytokines (IL-1β, IL-6, IL-8, TNFα); inhibited biofilm formation<br>Mechanism of action: Downregulates quorum sensing genes (agrA, RNAIII, sarA), reduces adhesion | 56 |
| Menthe citrate essential oil (SEO) | MIC = 50–1000 µg/mL | Gram-positive: *S. aureus, S. epidermidis, S. mutans;* Gram-negative: *P. aeruginosa, K. pneumoniae, E. coli, S. typhimurium* | Outcomes: Broad-spectrum antibacterial activity<br>Mechanism of action: Likely membrane destabilisation | 73 |
| Primary menthe citrate EO | MIC = 250–1000 µg/mL | 7 bacterial strains (Gram+ and Gram−) | Outcomes: Antibacterial activity, but weaker than SEO<br>Mechanism of action: Membrane disruption | 73 |
| Carvacrol | Concentration-dependent | *E. coli* | Outcome: Inhibited bacterial growth; biofilm inhibition at ≥0.55 mg/mL.<br>Mechanism of action: Disrupts membrane integrity; hydroxyl group interferes with microbial enzymes, increases intracellular component leakage | 61<br>60 |
| Cinnamaldehyde | ≥0.55 mg/mL | Oral pathogens (used in mouthwash studies) | Outcomes: inhibited bacterial growth; biofilm inhibition.<br>Mechanism of action: Disruption of membrane integrity | 61 |
| Gliricidin-7-O-hexoside and Quercetin-7-O-rutinoside (fern metabolites) | Not specified | *Proteus mirabilis*, *P. aeruginosa*, *P. vulgaris, etc.* | Outcomes: Provides antimicrobial shielding against several pathogenic species<br>Mechanisms of action: Suppresses production of virulence enzymes and toxins | 87 |
| Spathullin A and B | 1g/ml | *E. cloacae, E. coli, P. aeruginosa, A. baumannii, K. pneumoniae, S. aureus* | Outcomes: Spathullin B more effective than Spathullin A; strong antimicrobial activity.<br>Mechanism of action: Likely disrupts microbial growth (specific MOA not reported) | 51 |
| Geraniol | Not specified | Gram-negative pathogens (*Enterobacter* species, MDR strains) | Outcomes: Inhibited bacterial growth; efflux pump inhibition<br>Mechanism of action: Inhibits bacterial efflux pumps, enhancing intracellular accumulation of antibiotics | 59 |

**Table 1.** Continued...

| Bioactive Compound | Dose / Concentration | Target Microorganisms | Outcomes/Mechanism of action: | References |
|---|---|---|---|---|
| Thymol | Concentration-dependent | *S. aureus* | Outcomes: Bactericidal effect<br>Mechanism of action: Disruption of bacterial membrane lipids | 60 |
| p-Cymene | Concentration-dependent | *E. coli* | Outcomes: Inhibited bacterial growth<br>Mechanism of action: Likely membrane disruption | 60 |
| CD437 (synthetic retinoid) | Not specified | *E. faecalis,* MRSA, *S. aureus* | Outcomes: Anti-biofilm and bactericidal effect; synergistic with gentamicin<br>Mechanism of action: Rupture of bacterial lipid membrane; anti-biofilm activity | 66 |
| CD1530 (synthetic retinoid | Not specified | MRSA, *S. aureus* | Outcomes: Bactericidal effect<br>Mechanism of action: Likely membrane disruption similar to CD437 | 64 |
| Dihydroguaiaretic acid, 4-epi-larreatricin, 3-demethoxy-6-O-demethylisoguaiacin, 5,4-dihydroxy-7-methoxyflavone | 12.5–50 µg/mL | Various bacterial strains | Outcomes: Strong growth inhibition<br>Mechanism of action: Likely membrane destabilisation and enzyme inhibition | 69 |
| Sanguinarine | 0.5–128 (µg/mL) | Gram-positive cocci in clusters, Gram-negative bacteria, MDR bacteria | Outcome: Inhibited bacterial growth; synergistic effects with EDTA, vancomycin, and streptomycin.<br>Mechanism of action: DNA intercalation, inhibits bacterial adherence, anti-inflammatory | 42 |
| Chitosan (10–100 kDa) | Reported in ~65.55% of studies | *E. coli*, *S. aureus*, Gram-positive and Gram-negative strains | Outcomes: Antibacterial effect depends on bacterial type; moderate activity compared to low-MW forms<br>Mechanism of action: Electrostatic interaction with negatively charged cell walls; disrupts membrane integrity | 76 |
| Plant polysaccharides (starch, cellulose, pectin, xanthan, gum, agar, maltodextrin, xylan) | Safe, non-toxic; variable MIC/MBC | Broad spectrum (Gram+ and Gram−) | Outcomes: Antimicrobial, antioxidant, immune modulatory, and health-promoting effects<br>Mechanism of action: Multiple cell wall disruption, ROS modulation, immune activation | 76 |

is the lowest concentration that kills 99% of bacteria. The MBC/MIC ratio is used to tell if the effect is bactericidal (≤2) or bacteriostatic (>2)[79]. The broth micro-dilution method is commonly utilised to assess the antibacterial efficacy of new formulations. In this technique, bacterial cultures are standardised to McFarland turbidity, diluted in Mueller–Hinton broth, and subjected to serial dilutions of test compounds in

96-well plates. After incubation, colony-forming units (CFUs) are measured on agar plates to see how well the formulations work against untreated controls[80].

## 5. Current and Developing Research Trends

### 5.1 Advantages of Plant-derived Nanoparticles for Antimicrobial Uses

Plant-based nanoparticles are important in nanotechnology because they are better at killing bacteria. These nanoparticles have antifungal, antibacterial, anticancer, and antioxidant properties, which make them useful in medicine[88]. Plant-based nanoparticles, which are often called "green synthesis", are made by combining plant materials with nanoparticles in a way that is safe for the environment and the body, without using harmful chemicals[89]. Nanoparticles made from plants are cheap, easy to work with, and their small size makes them more effective against microbes. They can break down microbial membranes and make reactive oxygen species (ROS), which is better than regular antibiotics because it slows down the development of resistance. These methods focus on sustainable and renewable resources like biomass, agricultural waste, and plant extracts. They use less energy and produce less waste, while also making stable, targeted nanoparticles[90]. Plant-derived nanoparticles are a promising way to make new antimicrobial therapies that work better as antibiotic resistance grows. This is because they can be made, stored, and delivered in the best way possible[91].

### 5.2 *In Silico* Methods for Finding Possible Targets

Molecular docking studies are an essential instrument in drug discovery and computational biology[92]. This computational method predicts how a ligand will bind to a target protein and how strong the interaction will be. A ligand–protein complex is more stable when the binding energy is lower. Docking looks at different types of molecular interactions, such as hydrogen bonds, hydrophobic interactions, van der Waals forces, and electrostatic interactions. It gives a score that shows how strong the interaction is. Molecular docking is very important for nutraceutical research and for making new medicines to treat infections[93]. As a powerful *in silico* method, it speeds up the process of finding good targets while lowering the cost of experiments. New docking methods, like better scoring functions and the addition of protein flexibility, make predicted binding affinities more accurate and better mimic real biological conditions.

### 5.3 Ethnobotanical Surveys

For hundreds of years, the deep knowledge of plants that indigenous people have had has led to new medicines. Ethnobotanical surveys offer a methodical means of recording traditional knowledge, especially regarding medicinal plants utilised for the treatment of infectious diseases, typically comprising over 100 face-to-face participant interviews[94]. Plants used in indigenous medicine often have a lot of different bioactive compounds, such as unique secondary metabolites that fight bacteria. Ethnobotanical knowledge can help us find new ways to fight pathogens that are resistant to multiple drugs. Ethnobotanical leads also help with sustainable drug development by adding to the pharmaceutical pipeline and making it less dependent on synthetic compounds. These studies also support cultural and bio-cultural conservation by encouraging respect for indigenous knowledge and making sure that medicinal plants are used in a way that will last[95].

### 5.4 Genomic and CRISPR Studies

CRISPR and genomic studies are very useful for figuring out how compounds from plants affect the genetics of bacteria[96]. Researchers can use the CRISPR system to make very precise changes to the DNA of bacteria. This lets them see how certain genes react to plant compounds. Scientists can study how bacterial genes affect survival, metabolism, or resistance when they are exposed to these compounds by knocking them out or turning them on. This method helps find genes that are linked to antibiotic resistance, the metabolism of molecules from plants, and pathogenicity. CRISPR technologies, such as prime editing and other advanced endogenous editing techniques, are giving scientists more and more tools to study different pathogens[97]. The implications of this research transcend microbiology, advancing CRISPR-based therapies, synthetic biology, and biotechnology. For instance, bacteria can be genetically modified to have better metabolic functions

for use in industry or medicine[98]. In agriculture and bio-control, CRISPR is used to design beneficial bacteria that promote plant growth while suppressing harmful pathogens. Plant secondary metabolites such as flavonoids, alkaloids, and polyphenols possess antimicrobial properties that can influence bacterial survival, evolution, and adaptation[99].

Recent advances in genomics and CRISPR/Cas technologies have significantly enhanced the discovery and optimisation of plant-derived bioactive compounds with antidiabetic and antimicrobial properties. Whole-genome sequencing and metagenomic analyses enable identification of biosynthetic gene clusters and resistance-associated genes, facilitating targeted therapeutic development[100,101]. CRISPR/Cas-based genome editing further allows precise manipulation of metabolic pathways to enhance phytochemical yield and bioactivity in medicinal plants[102]. Moreover, CRISPR-driven antimicrobial strategies can selectively target resistance genes or virulence determinants in multidrug-resistant pathogens, offering a precision approach to combat AMR-associated diabetic complications[102-104].

## 6. Conclusion and Future Perspectives

Traditional knowledge, cultivated through generations, possesses significant insights in health, agriculture, and environmental management. Its integration with contemporary scientific methodologies can augment sustainability, foster innovation, and facilitate global problem-solving. Multidisciplinary research that includes local communities as active partners, standardises documentation, and legally protects traditional knowledge can help this integration work well. Plant-based compounds can help fight multidrug-resistant pathogens by breaking down bacterial cell walls, stopping resistance mechanisms, making antibiotics work better, and stopping biofilm from forming. Berberine, for example, makes β-lactams work better against *S. aureus*; piperine makes rifampicin work better against MDR *M. tuberculosis*; and ginger compounds make biofilm-related resistance lower. To fight antimicrobial resistance, countries around the world need to work together by improving surveillance, funding research, sharing data openly, and using the One Health approach, which links human, animal, and environmental health. Plant-based therapies are cheaper, more sustainable, and more accurate than regular antibiotics. Ongoing investigation into phytochemicals and customised plant-derived therapeutics from stems, roots, leaves, and bark can aid in surmounting resistance, suppressing virulence factors, and providing innovative therapies for multidrug-resistant infections.

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## Author Contribution

Govindharasan Palani: Literature search, data curation, and drafting of the manuscript; N. Anuradha: Sata collection and critical revision of the manuscript; Ponnulakshmi Rajagopal: Literature search and interpretation of the literature; Ramya Murali: Literature search and preparation of tables and figures; Chella Perumal Palanisamy: Data interpretation and critical revision of the manuscript; Vishnu Priya Veeraraghavan: Critical evaluation of the literature and revision of the manuscript; Selvaraj Jayaraman: Conceptualization, study design, supervision, critical review, editing, and final approval of the manuscript. All authors contributed to the preparation and critical revision of the manuscript and approved the final version for publication.