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The Role of Phytochemicals in Combating Antimicrobial Resistance

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ABSTRACT

Antimicrobial resistance (AMR) has become a worldwide health danger because it makes many typical antibiotics less effective. The public health emergency stemming from resistant pathogens requires new and additional approaches for treatment. Plants produce bioactive compounds known as phytochemicals that show great potential against microorganisms because of their multiple chemical arrangements along with broad antimicrobial effect. Phytochemicals demonstrate resistance-blocking behaviours through their ability to damage microbial membranes as well as their effectiveness against biofilm development and their control of efflux pumps and their capacity to boost standard antibiotic effects. This examination details the primary groups of phytochemical substances showing antimicrobial potential namely alkaloids and flavonoids and terpenoids and phenolics and tannins while discussing their methods of combating multidrug-resistant organisms. The review explores preclinical and clinical evaluation findings that demonstrate phytochemical effectiveness as well as the use of phytochemical combinations in therapy and technical obstacles in their drug advancement. Learning how phytochemicals interact with resistant microbes will enable the development of plant-derived solutions to combat antimicrobial resistance in medical practice.

INTRODUCTION

1.1. Overview of Antimicrobial Resistance (AMR):

Antimicrobial resistance (AMR) enables bacterial and fungal and viral and parasitic microorganisms to prevent medicine treatments which were formerly effective against infections. The development and propagation of antibiotic resistance happened quickly because of different drivers including human-animal antibiotic abuse and agriculture misuse alongside deficiency of infection control methods and insufficient antibiotics in pipeline development(1, 2). Bacteria develop resistance by using different genetic systems including mutations and horizontal gene transfer using plasmids as well as mobile genetic elements that acquire resistance genes (3). The formation of resistant bacteria strains results in antibiotic breakdown enzymes and drug target modification as well as increased efflux activity and diminished membrane permeability which render therapeutic measures useless (4). AMR represents both a scientific microbiological obstacle and a fundamental societal health as well as economic issue worldwide.

1.2. Global Impact and Statistics:

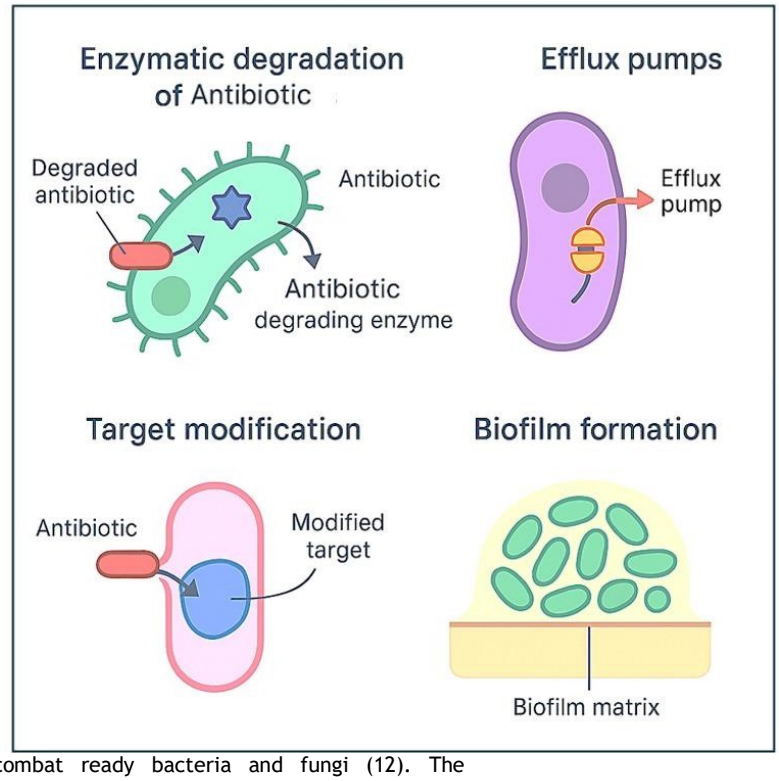
The worldwide AMR situation remains critical because it escalates with each passing year. The Global Research on Antimicrobial Resistance (GRAM) Project projected those drug-resistant bacterial infections caused 4.95 million deaths during 2019 with AMR leading to 1.27 million of these fatalities(5). The World Health Organization (WHO) ranks AMR among the 10 most dangerous worldwide public health threats for humanity (6). SMCs along with their insufficient quality care systems and limited diagnostic capacities and wide antibiotic misuse face a critical

situation in low- and middle-income countries (7). The United Nations Interagency Coordination Group (IACG) on AMR released a recent warning that without intervention the yearly deaths from AMR will reach 10 million by 2050 while global economic losses could exceed USD 100 trillion (8). Healthcare costs rise from resistant infections which also lengthens hospital stays and weakens both surgical procedure efficacy and outcomes of cancer chemotherapy (9).

1.3. Need for Alternative Strategies:

Recent antibiotic resistance and diminished new antibiotic development rates compel the world to explore new antimicrobial approaches as alternative treatment methods. Era traditional antibiotics lose potency, and pharmaceutical companies demonstrate diminished enthusiasm for new antimicrobial research due to its high expense and small financial gains as well as fast resistance emergence (10, 11). Phytochemicals which exist naturally within plants now attract high interest as tools to fight antimicrobial resistance (AMR) because of their inherent antimicrobial properties of many phytochemicals extend to broad-range activity, and they utilize multiple modes of action, which reduce the possibility of resistance becoming established (13). Phytochemicals demonstrate
improved antibiotic effectiveness when combined with standard medications to treat antibiotic- resistant strains (14). The wide chemical diversity found in plant secondary metabolites along with their defensive evolutionary purpose makes phytochemicals an attractive source for developing new antimicrobial medications and resistance-modifying components(15). The identification of phytochemicals in combination with their proper characterization followed by their integration into antimicrobial treatment approaches presents sustainable solutions to face the increasing antibiotic resistance.

Figure 1: ***Mechanisms of Antimicrobial Resistance: Enzymatic degradation of antibiotics, efflux pump activation, target site modification, and biofilm formation.***



properties in combat ready bacteria and fungi (12). The

2. Mechanisms of Antimicrobial Resistance:

Evolutionary adaptations generate antimicrobial resistance by employing various sophisticated and intricate defines mechanisms in microbes. Knowing the mechanisms behind drug- resistance allows healthcare providers to establish better methods against infections that defeat antibiotics. Antimicrobial resistance in microbes mainly occurs through antibiotic enzyme degradation and drug efflux pump activation and drug target modification as well as biofilm formation and other mechanisms.

2.1. Enzymatic Degradation of Antibiotics:

The generation of enzymes that destroy antibiotics through modification before they can accomplish their target constitutes a notable and medical-level resistance mechanism. ß- Lactamases succeed in inactivating penicillin's along with cephalosporins and carbapenems by breaking down their ß-lactam ring (16, 17). Studied ß-lactamase enzymes include extended- spectrum ß-lactamases (ESBLs) together with carbapenems represented mainly by KPC (Klebsiella pneumoniae carbapenems), NDM (New Delhi Metallo-ß-lactamase), and OXA- types which pose the greatest risk to patient treatment (18). The enzymes show a rapid dispersion among Gram-negative bacteria that especially affect Escherichia coli and Klebsiella pneumoniae. Alteration of aminoglycoside antibiotics through the actions of aminoglycoside-modifying enzymes (AMEs) including acetyltransferases and nucleoli Dyl transferases and phosphotransferases causes ribosome binding impairment in bacteria(19). Multiple Enterobacteriaceae strains practice acetylation as their means of inactivating chloramphenicol through chloramphenicol acetyltransferase (CAT).

2.2 Efflux Pumps:

Membrane proteins called efflux pumps expel bacterial cells' antibiotics and toxic substances by active transport which results in suboptimal drug levels inside the cell. Such pumps generate multidrug resistance (MDR) when they appear at elevated expression levels. Neutrophilic ß- lactam antibiotics and fluoroquinolones along with chloramphenicol become less effective in Pseudomonas aeruginosa through the functioning of the MexAB-OprM efflux pump system(20). The E. coli AcrAB-TolC pump operates as a resistance mechanism against tetracyclines, fluoroquinolones and macrolides (21). Several pivotal efflux families exist including the Resistance-Nodulation-Division (RND) family together with Major Facilitator Superfamily (MFS), ATP-Binding Cassette (ABC) transporters and Multidrug and Toxic compound Extrusion (MATE) family and Small Multidrug Resistance (SMR) family(22). Treatment strategies become more challenging due to overexpressed proteins of resistance genes which are regulated by global stress responses particularly in cases of hospital-acquired infections (23).

2.3 Target Modification:

Revised antibiotic binding sites cause resistance mechanisms when they reduce drug affinity to its targeted protein. The modification of penicillin-binding proteins (PBPs) within Staphylococcus aureus cells produced methicillin-resistant S. aureus (MRSA) through which PBP2a with reduced affinity for ß-lactam antibiotics is encoded by the mecA gene(24). The targets DNA gyrase and topoisomerase IV in E. coli and Salmonella spp. become resistant to fluoroquinolones when mutations occur(25). Blood cells modify ribosomes through methylation as a resistance-causing pathway. The erm gene produces a methyltransferase enzyme that adjusts the 23S rRNA attachment site thus causing resistance to the antibacterial class called macrolide-lacosamide-streptogramin B (MLSB)(26). The transfer of DNA from transmissible pANS elements leads Enterococcus faecalis to express the vanA and vanB gene clusters which convert the drug target D-Ala-D-Ala into D-Ala-D-Lac resulting in strong resistance to vancomycin (27).

2.4 Biofilm Formation:

Biofilm represents a structured microbial community which develops its polymeric surface binding matrix on catheters and other implant surfaces as well as tissues. The antibiotic resistance of bacteria in biofilms reaches 1,000 times higher than their resistance when they exist as planktonic cells(28). Bacteria acquire antibiotic resistance through two main factors: limited antibiotic penetration and a change in environmental pH and oxygen conditions as well as reduced cell growth rate and activated stress response elements(29). Biofilm development marks the essence of persistent infections because it occurs frequently in pathogens including Staphylococcus epidermidis and P. aeruginosa and Candida albicans and Acinetobacter baumannii (30). During cell-to-cell communication through quorum sensing (QS) these organisms use the signalling mechanism to control biofilm development and resistance expression. Scientists now focus on attacking both the quorum sensing control systems and biofilm matrix components as an innovative way to fight antibiotic resistance (31, 32). Pathogens develop reduced outer membrane permeability especially in Gram-negative bacteria due to damaged or altered OmpF porin channels in E. coli strains (33). Some pathogens create bypass pathways with additional metabolic processes which allow them to avoid antibiotic effects including the sulphonamide resistance system based on alternative folate synthesis enzymes (34).

3. Phytochemicals: An Overview

Phytochemicals are naturally occurring bioactive compounds found in plants, primarily responsible for their colour, flavour, and resistance to pathogens. These compounds have gained significant attention in recent years due to their potent antimicrobial, anti-inflammatory, antioxidant, and immunomodulatory properties(35). Unlike conventional antibiotics, phytochemicals target multiple pathways and microbial mechanisms, making them promising agents in mitigating antimicrobial resistance (AMR). Phytochemicals are broadly classified into phenolics (flavonoids, tannins, phenolic acids), alkaloids, terpenoids, organosulfur compounds, and saponins, among others. These compounds act either by directly killing or inhibiting pathogens or by enhancing host immune responses. For instance, flavonoids such as quercetin and catechin disrupt bacterial membranes and inhibit nucleic acid synthesis(36), while alkaloids like berberine interfere with DNA replication and efflux pump activity. Several studies have demonstrated the synergistic action of phytochemicals with antibiotics. For example, curcumin from Curcuma longa enhances the activity of antibiotics like ciprofloxacin and tetracycline against Staphylococcus aureus and Pseudomonas aeruginosa (37). Eugenol, a phenolic compound from clove (Syzygies aromaticum), shows inhibitory activity against Gram-positive and Gram-negative bacteria and potentiates the effect of ß-lactam antibiotics
(38). Similarly, thymol and carvacrol, monoterpenes from thyme and oregano oils, disrupt cell membranes and increase antibiotic uptake. Moreover, phytochemicals often target bacterial communication pathways such as quorum sensing, which is crucial for biofilm formation and virulence factor expression. For instance, resveratrol and furanones inhibit quorum sensing in
P. aeruginosa, thereby reducing pathogenicity and enhancing antibiotic sensitivity.

4. Classes of Phytochemicals with Antimicrobial Properties

4.1 Alkaloids

The antimicrobial properties of alkaloids represent important nitrogenous secondary metabolites that contain natural chemical compounds. Bacterial cell membranes together with nucleic acids experience interference from these compounds(39). The anti-bacterial properties of berberine and is quinoline alkaloid derived from Berberi's species reach high levels of effectiveness against Staphylococcus aureus E. coli and Mycobacterium tuberculosis bacteria through its action against DNA gyrase and efflux pumps leading to MIC results between 16 to 64 µg/mL. The mixture of ß-lactam antibiotics with berberine proved effective against MRSA strains by decreasing the MIC of oxacillin from 64 µg/mL to 8 µg/mL which exhibits synergistic antibiotic restorative properties(40).

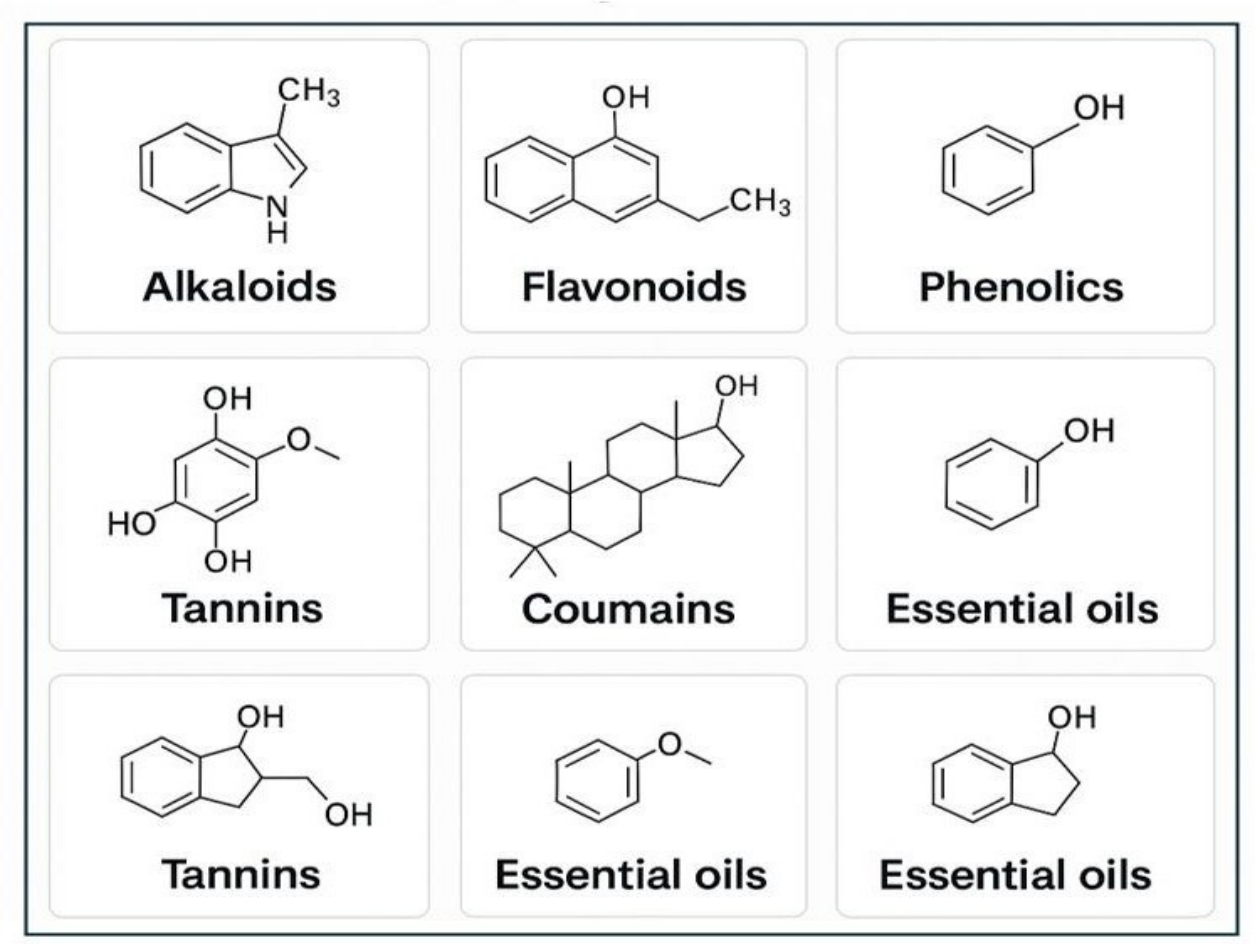


Figure 2: ***Classes of Phytochemicals with Antimicrobial Properties, including Alkaloids, Flavonoids, Terpenoids, Phenolics, Tannins, Saponins, Coumarins, and Essential Oils, each represented with characteristic chemical structures.***

4.1. Flavonoids:

Bacterial membrane interference and DNA and RNA synthesis inhibition occurs through the mechanism of flavonoids which belong to polyphenolic compounds(13). Both S. aureus and E. coli exposure to quercetin and catechin revealed an MIC value between 25 to 50 µg/mL which led to bacterial membrane disruption and subsequent leakage of cellular materials(41). In a recent study demonstrated that quercetin prevented Pseudomonas aeruginosa biofilm development to the extent of 65% and restricted quorum sensing gene expression by more than 50% indicating its promising anti-virulence action.4 Research demonstrated that the combination of apigenin with kaempferol alongside tetracycline made E. coli antibiotic- resistant strains sensitive to treatment by reducing the MIC to a range of <32 µg/mL to values less than >128 µg/mL(42).

4.2. Terpenoids:

The lipophilic properties of terpenoids help these compounds damage bacterial membranes while interrupting their metabolic functions(43). The antimicrobial compounds carvacrol and thymol found in Thymus vulgaris and Origanum vulgare depolarize bacterial membranes through their effect on ATP leakage to achieve more than 90% bacterial death in Listeria monocytogenes and Bacillus cereus cells at concentrations of 100 µg/mL within one hour (44).Research using poultry demonstrated how dietary carvacrol reduced impairments of Broilers by 60% during Salmonella typhimurium intestinal colonization when administered to control groups.

4.3. Phenolics:

The antimicrobial function of phenolic compounds occurs through their ability to damage enzymes during oxidation reactions. In vitro experiments showed three phenolic acids such as gallic acid, ferulic acid and caffeic acid created ROS-mediated oxidative stress in both E. coli and S. aureus microorganisms but exhibited MIC ranges from 32 to 64 µg/mL(45). Green tea extracts from Camellia sinensis that contained high amounts of phenolic compounds proved effective against the growth of Helicobacter pylori by 80% while effectively suppressing urease activity at 50 µg/mL thus showing potential as natural treatment against gastric infections.

4.4. Tannins:

High-molecular-weight polyphenols known as tannins connect to proteins as they prevent bacterial enzymes from functioning(46). Hydrolysable tannins extracted from Terminalia chebula showed medium inhibitory concentration values between 64 to 128 µg/mL while affecting the protein synthesis and cell wall structure of both Staphylococcus aureus and Klebsiella pneumoniae(47). The biofilm biomass of P. aeruginosa was decreased by 50% using tannins while they simultaneously prevented bacterial adhesion to epithelial surfaces according to research findings.

4.5. Saponins

The antimicrobial activity of saponins occurs through their formation of pores in bacterial membranes due to their foaming properties as glycosides(48). The antimicrobial effects of Quillaia saponins on Bacillus cereus and Listeria monocytogenes became evident through MIC values between 32 and 64 µg/mL as they caused harm to bacterial membrane sterol equilibrium. Therefore, these compounds activated innate immune responses through enhanced macrophage function and cytokine production to boost defense mechanisms(49).

4.6. Coumarins

The chemical group known as coumarins displays multiple biological features such as both antimicrobial properties and anti-quorum sensing properties based on their structure as benzopyrone derivatives(50). The MICs of antibacterial compounds Umbelliferon and aesculetin fell below 100 µg/mL against E. coli, Proteus mirabilis along with Streptococcus pyogenes by disrupting DNA gyrase activity and perturbing

electron transport mechanisms. The research on P. aeruginosa showed that coumarins controlled quorum sensing-regulated gene expression while simultaneously decreasing vital pathogenic characteristics such as pyocyanin production and motility(51).

4.7. Essential Oils

Essential oils consist of components that include terpenes together with phenolic compounds which demonstrate potent antibacterial properties(52). Clove oil containing eugenol in combination with oregano oil yielding carvacrol showed at least 90% inhibition against multidrug-resistant Acinetobacter baumannii and MRSA at 100 µg/mL through membrane disruption and ATPase inhibition(53). A 2022 research study demonstrated that using tea tree oil successfully decreased Candida albicans biofilms by 70% while simultaneously lowering metabolic cellular processes by 60% showing strong antifungal effectiveness in medical environments.

5. Mechanisms by Which Phytochemicals Combat AMR:

5.1. Inhibition of Bacterial Efflux Pumps:

Phytochemicals prevent antibiotic resistance by blocking bacterial operators that lead bacteria to eject antibiotics while diminishing antibiotic retention inside cells(39). The microbial activity of berberine alkaloid increased substantially after pairing it with 5′- methoxyhydnocarpin which acts as a plant-derived efflux pump inhibitor through a synergistic interaction leading to a significant reduction of Staphylococcus aureus MIC level from 64 to 8 µg/mL. The efflux pump inhibitor Pipeline from Piper nigrumtalented NorA efflux pump activity thus raising the intracellular ciprofloxacin levels while decreasing its MIC value from 32 µg/mL to 4 µg/mL in MRSA(54). The research shows that phytochemicals demonstrate efficacy as resistance sensitizer agents which decrease MIC of conventional antibiotics because they diminish resistance-mediating transporters in bacterial cells.

5.2. Disruption of Microbial Cell Membranes:

Phytochemicals contain lipid properties which enable them to merge with microbial membranes to destroy membrane structure(55). The two primary terpenes found in oregano and thyme essential oil terpenes known as carvacrol and thymol damaged E. coli and Listeria monocytogenes cells by creating large ATP and ion leaks that killed the cells within thirty minutes at 100 µg/mL concentration. Transmission electron microscopic data from 2021 showed tea tree oil affects membrane structure in Candida albicans cells while also condensing cytoplasmic matter which led to more than 90% loss of viability(56). These phytochemicals produce permanent damage to membranes thus establishing themselves as efficient weapons against pathogens resistant to drugs.

5.3. Inhibition of Biofilm Formation:

Microbial biofilms protect bacterial cells through a defensive environment making them more resistant to antibiotic treatment. Several phytochemicals demonstrate their capacity to break down biofilm development while disrupting biofilm structure(41). Portions of catechin along with quercetin slowed down Pseudomonas aeruginosa biofilm development beyond 60% while reducing expression of quorum sensing genes lasR and rhlR. The compound gallic acid demonstrated double anti-biofilm effects against Staphylococcus epidermidis and Escherichia coli by preventing them from creating EPS and disrupting adhesion protein activity(57). Scientific evidence confirms how phytochemicals enable the control of microbial populations which resist elimination by antibiotics as standalone treatment elements.

5.4. Modulation of Microbial Virulence:

Most phytochemicals demonstrate additional antibacterial functions by diminishing the production of harmful microbial elements(58). Aesculetin among coumarin compounds demonstrated anti-virulence properties by reducing P. aeruginosa production of pyocyanin and elastase activity and motility factors without influencing bacterial growth to a significant extent. The activity of S. aureus's quorum-sensing system Agar gets regulated by baicalein and luteolin which prevents the organism from producing homolysing and enterotoxin. The compounds lower disease-causing properties while creating no selective advantage which can contribute to resisting pathogen adaptation(59).

5.5 Synergistic Effects with Conventional Antibiotics:

The strongest advantage of phytochemicals emerges from their ability to work together with antibiotics which simultaneously amplifies their effectiveness and minimizes dose requirements. The combination of resveratrol with tetracycline or erythromycin resulted in a 16-fold reduction of minimum inhibitory concentration through in vitro checkerboard assays when testing MDR E. coli and K. pneumoniae. The addition of eugenol together with fluconazole reduced the fluconazole-resistant MIC of Candida albicans from an initial value of
>128 µg/mL down to 16 µg/mL. Phytochemicals show synergy with antibiotics to restore their effectiveness, and they become strong complementary agents for antimicrobial treatment(60).

6. Phytochemicals in Combating Specific Resistant Pathogens:

6.1. Methicillin-resistant *Staphylococcus aureus* (MRSA):

Research demonstrates that phytochemicals show strong potency in fighting MRSA strains(39). The phytochemical berberine which belongs to the is quinoline alkaloid category demonstrated minimum inhibitory concentrations between 16–64 µg/mL for MRSA isolates. The combination of berberine with 5'-methoxyhydnocarpin resulted in a fourfold decrease of berberine's MIC value while using plant-derived efflux pump inhibitor(61). The biofilm formation capability of MRSA was inhibited by epigallocatechin gallate (EGCG) from green tea which reduced biomass amounts up to 70% when applied at non-bactericidal concentrations.

6.2. Multi-drug-resistant *Escherichia coli:*

The anti-MDR E. coli properties of phytochemicals were noted in the published research(62). Resveratrol a polyphenolic compound achieved an MIC measurement of 64 µg/mL against MDR E. coli strains. When ciprofloxacin combined with the treatment the efficacy was enhanced because it decreased ciprofloxacin's MIC value by factor eight(37). The phytochemical Curcumin obtained from turmeric killed MDR E. coli while its MIC measured 125 µg/mL and additionally destroyed bacterial membrane structures.

6.3. Vancomycin-resistant *Enterococci* (VRE):

The antibacterial activities of phytochemicals have been studied specifically against VRE. Allicin from garlic produced VRE strain inhibitory effects that appeared in MIC values measuring between 32–64 µg/mL. The bactericide effect of thymol was observed against VRE through its concentration-dependent membrane destruction, which caused cellular substance
leakage at 100 µg/mL(63).

6.4. Carbapenem-resistant *Klebsiella pneumonia:*

Researchers have identified specific phytochemicals which show promise in dealing with carbapenem-resistant K. pneumoniae infections. Research has shown that phenolic compound eugenol extracted from clove oil exhibits an MIC value of 256 µg/mL against carbapenem- resistant K. pneumoniae strains (64). The combination of meropenem with the antibiotic produced a synergistic outcome that lowered meropenem MIC values by fourfold. Baicalein represented a flavonoid that demonstrated antibacterial effects toward carbapenem-resistant K. pneumoniae including an MIC measurement of 128 µg/mL and imipenem potency enhancement.

Table 1: Preclinical and Clinical Studies on Antimicrobial Phytochemicals

Sr. No	Study Type	Phytochemical / Source	Trial Phase	Result / Outcome	Reference

1.	In vitro	Phytol (from *Adhatoda vasica*)	Preclinical	Inhibited *Bacillus licheniformis*; reduced fish mortality in goldfish model	(65)
2.	In vitro	Methanolic extract of *Centaurea damascena*	Preclinical	MICs ranged from 60–1100 µg/mL against various bacteria	(66)
3.	In vitro	*Hibiscus sabdariffa* extract	Preclinical	Synergistic effect with chloramphenicol against *S. aureus*	(12)
4.	In vitro	Extracts of *Pleurotus florida*	Preclinical	Effective against *Bacillus subtilis* and *E. coli*	(67)
5.	In vitro	Ethanolic extract of *Bacopa monnieri*	Preclinical	Antibacterial activity against *S. aureus* and *E. coli*	(68)
6.	In vitro	Endophytic fungi from *Rosmarinus officinalis*	Preclinical	Significant activity against *P. aeruginosa* and *S. aureus*	(69)
7.	In vitro	Traditional herbal formula (*Althaea officinalis*, *Tilia cordata*, *Psidium guajava*)	Preclinical	Synergistic antibacterial and antibiofilm activities	(69)
8.	In vitro	Thymoquinone	Preclinical	Effective against *S. aureus*, *E. coli*, and *P. aeruginosa*; inhibited biofilm formation	(70)
9.	In vitro	Extracts of *Canarium patentinervium*	Preclinical	Significant activity against MRSA and *P. aeruginosa*	(71)
10.	In vitro	Extracts of *Cleome spinosa*	Preclinical	Broad-spectrum activity; synergistic with oxacillin against S. aureus	(72)
11.	In vitro	Extracts of *Albizia odoratissima*	Preclinical	Antioxidant and antimicrobial activities; effective against various pathogens	(73)
12.	In vitro	Extracts of *Habenaria digitata*	Preclinical	Anti-inflammatory and antioxidant activities; potential antimicrobial effects	(74)
13.	In vivo	Carvacrol	Preclinical	Inhibited carbapenem-resistant *K. pneumoniae* in mouse model	(75)
14.	In vivo	Baicalein + Linezolid	Preclinical	Synergistic effect against MRSA biofilms in mice	(76)
15.	In vivo	Curcumin, EGCG, Allicin	Preclinical	Reduced bacterial load and inflammation in animal models	(77)
16.	Clinical	Beta-sitosterol	Phase II	Improved weight gain and lymphocyte counts in TB patients	(78)

17.	Clinical	Silymarin	Phase II	Decreased liver function tests and viral load in hepatitis C patients	(79)
18.	Clinical	Alpha-Viniferin	Phase I	Reduced S. aureus levels in nasal passages; maintained nasal flora	(80)
19.	Clinical	Nigella sativa extract	Phase I	Effective against Propionibacterium acnes; reduced infection symptoms	(81)
20.	In vitro	Usnic acid	Preclinical	Altered MRSA resistance; downregulated peptidoglycan biosynthesis	(82)

7. Challenges and Limitations:

7.1. Bioavailability and Pharmacokinetics:

Phytochemicals face multiple challenges due to their bad absorption levels and poor solubility in addition to their instability within biological environments. Plant-derived compounds including flavonoids and polyphenols undergo rapid excretion after absorption while also ending up with deficient therapeutic bloodstream levels because of poor gastrointestinal absorption and rapid metabolism(83). The strong antimicrobial properties demonstrated by turmeric phytochemical curcumin in laboratory conditions become limited by poor absorption and rapid metabolism in human biological systems which requires enhancement systems through nanoparticles and liposomes to improve therapeutic outcomes (84, 85).

7.2. Toxicity and Safety Concerns:

At usual doses and typical periods of usage phytochemicals are generally safe to use however they may show toxic behaviour when consumed in excessive amounts. The biological activity strength of alkaloids leads to neurotoxicity as well as hepatotoxicity and genotoxicity during specific exposure conditions (86). The haemolytic potential of selected saponins and essential oils together with their ability to induce mucosal tissue irritation has generated concerns about exposure safety parameters and maximum permissible levels based on experimental studies(87, 88) . Serious toxicological analysis needs to be thoroughly conducted before transferring drugs into clinical practice.

7.3. Standardization and Regulatory Hurdles:

The current difficulty in achieving standardization exists for both the extraction process of phytochemicals and their formulation development along with dosage delivery methods. The composition of plant extracts shifts according to the geographical region, harvesting period and extraction procedures which results in dissimilar outcomes between different plant batches(88). The insufficient regulation of herbal medicines across different countries delays and complicates the clinical review and approval of phytochemical substances because fertilizer testing methods usually are less strict than synthetic drug standards (89). Endorsing universal guidelines plus creating approved analytical procedures remain critical for achieving dependable results with ensured safety.

8. Future Perspectives and Research Directions:

8.1. Novel Phytochemical-Based Formulations:

The development of new therapeutic formulations represents the key path for fighting antimicrobial resistance (AMR) through phytochemicals. The effectiveness of phytochemicals becomes improved through co-formulation processes that align agents for synergy and involve bio-enhancers and polyherbal formulas to decrease resistance formation (90). Combining curcumin with piperine leads to improved antimicrobial functionality and pharmacokinetics because piperine restricts drug-metabolizing enzymes and efflux transporters (91). Research groups are studying combined antibiotic and phytochemical drugs to revitalize antibiotic effectiveness against resistant bacteria populations like MRSA and carbapenem-resistant Enterobacteriaceae (14).

8.2. Nanotechnology for Delivery Enhancement:

The industry of nanotechnology shows great potential for solving problems involving phytochemical delivery as well as stability and bioavailability challenges. Studies prove the use of nanocarriers including liposomes and solid lipid nanoparticles (SLNs) and polymeric nanoparticles to encapsulate berberine and eugenol and quercetin enhances antimicrobial potential by providing controlled release and reduced toxicity(92, 93). In vitro and in vivo studies showed that quercetin-loaded chitosan nanoparticles demonstrated better biofilm fighting ability against Pseudomonas aeruginosa that indicates their potential to treat chronic infections.

8.3. Genomics and Metabolomics in Phytochemical Discovery:

The discovery and enhancement of antimicrobial phytochemicals now benefit from modern genomic and metabolomic and transcriptomic and proteomic methodologies. Fast screening methods of plant genomes and metabolomes help researchers discover new bioactive compounds along with their biosynthetic pathways(94). Research can identify antimicrobial activity by linking phytochemical profiles through metabolomic fingerprinting which leads to better standards in selecting elite chemotypes (95). Scientists are currently using CRISPR/Cas9 tools together with genome editing to boost the production levels of significant antimicrobial secondary metabolites in medicinal plants(96). The developed tools support the development of novel antimicrobial medications through precision phototherapeutic techniques.

CONCLUSION

The worldwide surge of antimicrobial resistance emerges as a critical health problem so scientists must study alternative treatments which are effective and safe. Phytochemicals show great promise against drug-resistant pathogens because they possess various chemical structures which use multiple antibacterial mechanisms including blocking efflux pumps and destroying microbial membranes to prevent biofilms growth while working well with traditional antibiotic treatments. Scientific research has established the antimicrobial potential of multiple compounds which belong to flavonoids, alkaloids, terpenoids and essential oils classes against resistant pathogens like MRSA, VRE and carbapenem-resistant Klebsiella pneumoniae when tested both in test tubes and living organisms. The medical implementation of phytochemical compounds remains challenging due to their poor bioavailability problems alongside

variable drug levels in the bloodstream and toxicity risks and lack of standardized guidelines. Research into the future should focus first on improved delivery methods including nanotech-based delivery carriers and then it should apply omics technologies to identify and improve phytochemical treatment possibilities. The combination of both traditional wisdom and contemporary pharmaceutical methods will speed up the process of creating antimicrobial drugs from phytochemical sources. Phytochemicals show great potential for combating antimicrobial resistance as an important resistance-fighting weapon. The realization of phytochemical usefulness for resisting infections requires strategic funding of research programs along with regulatory alignment among global institutions and translational science development.

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