Volume 1, Issue 1, April-June 2026

JOURNAL OF NOVEL PHARMACEUTICAL DISCOVERIES (JNPD)

e-ISSN: AWAITING

OPEN ACCESS

Publisher: Inscierra Edge Press

Journal homepage: https://jnpdglobal.com/index.php/files/index

Synergistic Effects of Antibiotics and Plant-Derived Phytochemicals Against Antimicrobial-Resistant Microorganisms: Mechanisms, Recent Advances, and Future Perspectives

Gayatri Shivanand Chavan[1] and Dhanashri Shivanand Chavan[2]

1. Smt. Kasturbai Walchand College of Arts and Science, Sangli.
2. Student, Dr. Shivajrao Kadam College of Pharmacy, Kasaba Digraj, Sangli.

Article Info

Submitted: 10-04-2026
Revised: 20-05-2026
Accepted: 15-06-2026
Published: 25-06-2026

*Gayatri Shivanand Chavan.
Smt. Kasturbai Walchand College of Arts and Science, Sangli.

Email:
gayatrichavan5231@gmail.com

ORCID: https://orcid.org/0009-0003-9991-4573

ABSTRACT

AMR represents one of the greatest public health challenges worldwide. Its emergence also threatens the effectiveness of existing antibiotics and severely limits the ability to manage infectious diseases. Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) pathogens are emerging at an unprecedented rate and call for urgent attention to the development of novel therapeutic strategies.

An area of immense promise is the use of phytochemicals (plant-derived compounds) in combination with conventional antibiotics. Bioactive compounds, including flavonoids, alkaloids, phenolic acids, terpenoids, tannins, saponins, coumarins, and essential oils, possess broad-spectrum antimicrobial activity, which can work through multiple mechanisms such as disruption of bacterial membranes, inhibiting efflux pumps, interfering with quorum sensing and biofilm formation, attenuating virulence factors, and inhibiting resistance enzymes.

In this review, we summarise the current evidence supporting the synergistic effects of antibiotic/phytochemical combinations against antimicrobial-resistant pathogens. Phytochemicals including curcumin, quercetin, epigallocatechin gallate, berberine, baicalein, thymol, carvacrol, eugenol, piperine, and allicin have been demonstrated to enhance the effective activity of beta-lactams, aminoglycosides, fluoroquinolones, tetracyclines, and glycopeptides against clinically relevant resistant pathogens. The antibiotic/phytochemical combinations reduce minimum inhibitory concentrations, increase antibiotic accumulation within cells, inhibit biofilm formation, and delay resistance development. While the preclinical data regarding these combinations is very promising; challenges remain due to limited clinical data regarding their standardisation, bioavailability, pharmacokinetics, herb-drug interaction, and potential side effects.

Nanotechnology, artificial intelligence, omics, and precision medicine will continue to accelerate the development of safe and effective combinations of antibiotics and phytochemicals in the fight against AMR.

Keywords: Antimicrobial resistance; Antibiotic synergy; Plant-derived phytochemicals; Multidrug-resistant bacteria; Combination therapy; Biofilm inhibition; Efflux pump inhibitors; Quorum sensing.

1. INTRODUCTION

The issue of Antimicrobial Resistance (AMR) has been on the rise and prevents us from being able to effectively treat all human infections. Resistance means that there is an increase in the ability of bacteria and other microorganisms to resist the effects of traditional antibiotics. The overuse of antibiotics in humans and

animals (including via agriculture) has resulted in the emergence of multi-drug resistant (MDR), extended drug resistant (XDR), and pan-drug resistant (PDR) pathogens. Some of the most well known resistant organisms include methicillin resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae, Escherichia coli and Enterococcus faecium, as well as many others [1].

and have a wide variety of chemical structures including but not limited to flavonoids, alkaloids, phenolic acids, tannins, terpenoids, essential oils, coumarins, lignans, quinones and saponins. Many of these phytochemicals have been shown to exhibit numerous biological activities including but not limited to antibacterial, antifungal, antiviral, antioxidan, anti-inflammatory and immunomodulatory activity [2].

In addition, numerous studies exist that demonstrate the combined utilization of phytochemicals and traditional antibiotics leads to a synergistic effect, meaning that the combination of both substances are more effective together compared to being used independently. The combination of antibiotics with phytochemicals may restore antibiotics' susceptibility to previously resistant bacteria, decrease minimum inhibitory concentrations (MIC) of drugs, decrease the biomass of biofilms, decrease bacterial virulence factors, inhibit quorum sensing, disrupt microbial membranes, inhibit efflux pumps and/or improve the intracellular accumulation of drugs. Thus, utilizing combination therapy with phytochemicals and antibiotics, it may be possible to decrease the total amount of antibiotics required for the treatment of infections, limit the number of adverse effects associated with antibiotic use, delay the development of antibiotic resistance and/or improve the overall treatment outcomes [3].

Several examples exist of phytochemicals potentiating the use of common antibiotics. For instance, the phytochemical epigallocatechin gallate (EGCG), which is found in green tea, enhances the activity of β-lactams (a type of antibiotic) against MRSA. Curcumin (a compound in turmeric that gives it the orange color) has been shown to strengthen the effectiveness of both aminoglycosides and fluoroquinolones by increasing their membrane permeability and producing reactive oxygen species. Furthermore, there are numerous other phytochemicals (including but not limited to berberine, quercetin, thymol, eugenol, carvacrol, piperine, baicalein and resveratrol) that have been demonstrated to possess antibiotic-enhancing properties against both resistant Gram-positive and Gram-negative organisms through multiple mechanisms [4].

Ongoing advances in nanotechnology, molecular biology, omics technologies and computational drug discovery have allowed researchers to assess and test the synergistic/complementary activity of

Due to the expanding concern surrounding antibiotic resistance, a substantial amount of research is underway to find alternative antimicrobial approaches. One of the most promising strategies for addressing antibiotic resistance is using phytochemicals from plants. Phytochemicals are naturally occurring secondary metabolites

phytochemicals and antibiotics. However, there are many barriers still inhibiting the encouragement of clinical utilization of phytochemicals as adjunctive therapy to antibiotics. Examples of barriers include but are not limited to the poor bioavailability of phytochemicals, the variability of phytochemical levels individual plant species, pharmacokinetic interactions, absence of standardized formulation, and limited clinical evidence to support efficacy [5].

The overall goal of this review is to provide an exhaustive overview of the available literature regarding the use of antibiotics combined with phytochemicals for the management of multi-drug resistant microorganisms. Included in this review will be a thorough analysis of the global impact of antimicrobial resistance, a description of the major categories of phytochemicals, descriptions of the mechanisms underlying the synergistic/antimicrobial properties of phytochemicals used in combination with antibiotics, evidence of efficacy, current barriers and additional avenues of future research required to establish greater clinical utilization of synergistic combinations of antibiotics and phytochemicals for the treatment of resistant pathogens [6].

2. GLOBAL BURDEN OF ANTIMICROBIAL RESISTANCE

One of the many global health crisis occurring today is the development of antimicrobial resistance (AMR). Due to this phenomenon, decades of therapeutic success previously achieved with the effective use of antibiotics have progressively returned to a state of being irrelevant or almost ineffective. One of the leading causes of morbidity and mortality in the world today is the rise of resistant microorganisms that have greatly reduced the efficacy of current antimicrobial agents causing longer length hospital stays, higher healthcare costs, more treatment failures, and higher mortality rates than anyone anticipated. Globally, it is estimated that more than 1.2 million deaths are caused directly by AMR annually, and an untold number of additional deaths occur as a result of drug-resistant infectious diseases. If no effective intervention is introduced, it will be predicted that AMR will continue to be among the top ten leading causes of death worldwide within the next few decades [7].

All of the issues associated with the emergence and spread of AMR are primarily due to the overuse and improper use of antibiotics for treating humans,

animals (livestock) and aquaculture, and for use in agriculture. Additional contributors to the emergence and spread of AMR include patients using antibiotics without a doctor's prescription (self-medicating), patients not using their medication as prescribed (non-compliance), healthcare providers prescribing antibiotics improperly, use of poor quality medications (substandard and counterfeit), inadequate infection control practices, globalisation and contamination of the environment with antibiotic residues. All of these issues have created a synergy of an increase in the rate of resistant bacterial organisms to be selected for and to spread throughout healthcare systems and communities [8].

The World Health Organisation has indicated that there are several bacterial pathogens that are high-priority and must be developed therapeutic alternatives as an urgent matter. These include carbapenem-resistant Acinetobacter baumanii, carbapenem-resistant Pseudomonas aeruginosa, third-generation cephalosporin-resistant Enterobacterales, methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus faecium (VRE), multidrug-resistant Klebsiella pneumoniae, and resistant Escherichia coli. These high-priority pathogens are responsible for severe healthcare-associated and community-acquired infections, including pneumonia, bloodstream infections, urinary tract infections, wound infections, and sepsis [9].

Microorganisms can evade the action of antibiotics by utilising many different mechanisms. One of the most often used mechanisms of evading the action of antibiotics is by enzymatic degradation or modification of antibiotics by enzymes, such as β-lactamases and carbapenemases. Another mechanism is developing a new target for the antibiotic that reduces the binding of the antibiotic to its target site as in MRSA and macrolide-resistant bacteria. Many organisms that are resistant to antibiotics have overexpressed multidrug efflux pumps that will pump antibiotics out of the bacterial cell causing decreased intracellular concentrations of the antibiotic. Additionally, the outer membrane of Gram-negative bacteria has decreased permeability due to modified outer membrane porins, which can further limit the ability of antibiotics to penetrate into the bacteria. Moreover, when bacteria are capable of producing biofilms, the biofilms act as a protective matrix that prevents the penetration of antibiotics into the bacterial cell and thereby protects the microorganisms from the host's immune system. Finally, bacteria can transfer drug resistance traits among themselves rapidly by horizontal gene transfer through plasmids, transposons, and integrons [10].

The dramatic rise in the number of multidrug-resistant (MDR), extensively drug-resistant (XDR) and pan-drug-resistant (PDR) microorganisms emphasises the need for innovative strategies for antimicrobial treatment. Rather than relying exclusively on the discovery of new antibiotics, contemporary research is focusing more on combination therapies, where conventional antibiotics are combined with bioactive phytochemicals. These types of synergistic approaches are designed to reverse existing resistance patterns, minimise or overcome the mechanisms of resistance, and to enhance the overall effectiveness of the antimicrobial treatment and reduce the potential for the future development of resistance [11].

Table 1. Major Mechanisms of Antimicrobial Resistance

Resistance Mechanism	Description	Representative Pathogens
Enzymatic inactivation	Production of β-lactamases, carbapenemases, aminoglycoside-modifying enzymes	*K. pneumoniae*, *E. coli*, *A. baumannii*
Target modification	Structural alteration of antibiotic binding sites	MRSA, VRE
Efflux pumps	Active extrusion of antibiotics from bacterial cells	*P. aeruginosa*, *E. coli*
Reduced permeability	Loss or modification of membrane porins limiting antibiotic entry	Gram-negative bacteria
Biofilm formation	Protective extracellular matrix reduces antibiotic penetration	*S. aureus*, *P. aeruginosa*
Horizontal gene transfer	Dissemination of resistance genes via plasmids, transposons, and integrons	Numerous bacterial species

3. PLANT-DERIVED PHYTOCHEMICALS AS ANTIMICROBIAL AGENTS

Vegetation is a great source of bioactive compounds that have a lot of variation in structure. For thousands of years, cultures around the world have used these compounds (collectively referred to as phytochemicals) from plants in their traditional medicine to combat infectious diseases. Phytochemicals are secondary metabolites of plants that many researchers believe to serve in the defence against herbivory, pathogenic microorganisms, insect predation and adverse environmental conditions [12].

Numerous studies over the past decade have demonstrated that phytochemicals have the potential to be used as alternative or adjunct to conventional antibiotics due to their broad-spectrum antimicrobial activity, multiple molecular targets and much lower rates of inducing antimicrobial resistance when compared to conventional antibiotics. Conventional antibiotics

typically act on one cellular aspect; whereas, phytochemicals generally affect several microbial pathways at the same time, making it more difficult for the microbes to develop resistance.

Phytochemicals can be classified into phenolic compounds, flavonoids, alkaloids, terpenoids, tannins, saponins, coumarins, lignans, quinones, and essential oils. Phytochemicals can be found in a variety of food and medicinal plants e.g., herbs and spices, fruits and vegetables, aromatic plants and a plethora of other plants that have long been used in many traditional forms of medicine including Ayurveda, Traditional Chinese Medicine and Unani Medicine [13].

Of the many phytochemicals, phenolic compounds represent one of the largest classes of phytochemicals with antimicrobial properties. Compounds such as gallic acid, caffeic acid, ferulic acid, chlorogenic acid, and ellagic acid exhibit antimicrobial properties by disrupting bacterial cell membranes, inducing oxidative stress, inhibiting critical metabolic enzymes, and disrupting nucleic acid synthesis within bacterial cells.The ability of flavonoids to have inhibiting effects on bacterial growth through several different mechanisms such as inhibiting the activity of bacterial efflux pumps and suppressing the metabolism of energy in bacteria, allows for the possibility of using these compounds in conjunction with conventional antimicrobials to restore bacterial susceptibility and increase the intracellular concentration of antimicrobials.

Many phytochemicals that fall under the umbrella of alkaloids exhibit strong antibacterial effects against both Gram-positive and Gram-negative bacteria. The ability of alkaloids such as berberine has shown to have synergistic properties with β-lactams, fluoroquinolones, and aminoglycosides by acting on bacterial efflux pumps to prevent bacterial cells from eliminating these antimicrobial compounds and by interfering with the processes needed for bacterial DNA replication. The bioavailability of piperine can also be enhanced with the use of various phytochemicals as they not only inhibit the efflux pump but also exhibit inherent antimicrobial and antibiofilm activity [14].

Essential oils and terpenoids can be classified as separate groups of phytochemicals; however, they comprise an important group of antimicrobial agents. Monoterpenoids such as menthol and phenolic terpenoids such as thymol can disrupt the membrane of the bacterial cell by increasing the permeability of their membranes, depleting the potassium gradient across the membrane, inhibiting the cell's capability to produce ATP, and introducing factors that would consequently increase bacterial permeability. Essential oils such as those from oregano, thyme, clove, cinnamon, tea tree, and peppermint have also been shown to exhibit antimicrobial properties against resistant bacterial pathogens [15].

In addition to flavonoids, alkaloids, terpenoids and essential oils, there are still many other phytochemicals that contribute significantly to the antimicrobial properties of phytochemicals, including tannins, saponins, coumarins, lignans, and quinones. Tannins inhibit the activity of some bacterial enzymes and can precipitate out membrane proteins, while saponins are capable of interacting with membrane sterols and increasing the permeability of the bacterial cell. Coumarins inhibit DNA synthesis in bacteria and interfere with the respiratory process, while quinones can induce oxidative stress in bacterial cells through the generation of reactive oxygen species [16].

The ability of phytochemicals derived from plants to target virulence factors of bacteria without affecting their viability provides an outstanding opportunity for the management of antibiotic resistance. Phytochemicals have been shown to inhibit bacterial quorum sensing and biofilm formation, reduce toxin production, and inhibit the adhesion of bacteria to host tissues. By targeting virulence factors of bacteria using phytochemicals in tandem with conventional antibiotics, the potential exists for phytochemicals to reduce the selective pressure for the development of resistance to antibiotics and enhance the overall efficacy of antibiotics [17].

Although many of the above mentioned phytochemicals exhibit moderate antimicrobial activity when administered alone, their therapeutic potential lies in the use of phytochemicals in combination with conventional antimicrobial therapy. Phytochemicals can also restore antibiotic susceptibility, decrease MICs, inhibit the activity of resistance mechanisms (e.g., efflux pumps, β-lactamases), and increase the permeability of the bacterial cell membrane when used in tandem with conventional antibiotics. As a result, phytochemicals are being evaluated as adjuvants to existing antimicrobial treatments for the purpose of restoring the effectiveness of treatment against multidrug-resistant organisms [18].

Table 2. Major Classes of Plant-Derived Phytochemicals with Antimicrobial Activity

Phytochemical Class	Representative Compounds	Major Antimicrobial Mechanisms
Phenolic acids	Gallic acid, Caffeic acid, Ferulic acid, Chlorogenic acid	Cell wall disruption, oxidative stress, enzyme inhibition
Flavonoids	Quercetin, EGCG, Kaempferol, Baicalein, Catechin	Membrane damage, efflux pump inhibition, biofilm inhibition, DNA gyrase inhibition

Alkaloids	Berberine, Piperine, Sanguinarine, Palmatine	DNA interference, efflux pump inhibition, enhanced antibiotic uptake
Terpenoids	Thymol, Carvacrol, Menthol, Citral	Membrane disruption, ATP depletion, leakage of intracellular contents
Essential oils	Clove oil, Thyme oil, Oregano oil, Tea tree oil	Cell membrane damage, protein denaturation, biofilm inhibition
Tannins	Tannic acid, Ellagitannins	Protein precipitation, enzyme inhibition, membrane destabilization
Saponins	Dioscin, Glycyrrhizin	Increased membrane permeability, cell lysis
Coumarins	Umbelliferone, Scopoletin	DNA synthesis inhibition, respiratory enzyme inhibition

4. SYNERGISTIC MECHANISMS BETWEEN ANTIBIOTICS AND PLANT-DERIVED PHYTOCHEMICALS

There are multiple means that can be utilized in combination to create an increased therapeutic effect when combined with an antibiotic or antimicrobial agent, such as the use of phytochemicals with antibiotics being used as combination therapy. Combination therapy makes use of two different, yet complementary mechanisms of action that can enhance the ability of the antibiotic or antimicrobial agent to combat bacterial resistance, while also increasing the effectiveness of the phytochemical against bacterial resistance. The synergy between the two agents typically reduces the number of bacteria that must be killed before an antibiotic will work, restores susceptibility to resistant bacteria, inhibits the virulence of bacteria, decreases biofilm formation and delays the development of new resistant strains of bacteria to that antibiotic. Commonly, synergy has been evaluated using a combination of checkerboard assays, FICI fractional inhibitory concentration index, time-kill assay or molecular assays [19].

Increased permeability of the bacterial cell membrane is one of the primary mechanisms responsible for the synergistic effect of antibiotics and phytochemicals. Phytochemicals, such as phenolic terpenoids (thymol, carvacrol, and eugenol), disrupt the integrity of the bacterial cell membrane by disrupting the phospholipids making up the bacterial cell membrane. This results in an increased release of intracellular protein, ions, nucleotides and ATP from within the bacterial cell. The additivity of one of the two agents aids in the increased accumulation of the antibiotic within the bacterial cell, especially with Gram-negative bacteria, due to their outer membrane being a barrier that prevents antibiotics from passing through the outer membrane into the bacterial cell [20].

For example, carvacrol has been shown to significantly enhance the antibacterial activity of aminoglycosides against Pseudomonas aeruginosa by increasing the permeability of the outer membrane of the bacterial cell and allowing for increased uptake of the aminoglycoside into the bacterial cell. Similarly, eugenol has been shown to augment the action of β-lactam antibiotics against methicillin-resistant Staphylococcus aureus through the disruption of the bacterial cell membrane [21].
Multidrug efflux pumps are the primary mechanism contributing to the emergence of antimicrobial resistance.Membrane Transport Proteins (Transporters) In Bacteria Create Antibiotic Resistance
Membrane transport proteins that extrude (i.e., "pump") antibiotics outside of the bacterium have been shown to reduce the intracellular concentrations of antibiotics to subtherapeutic levels.

Several naturally occurring phytochemicals act as "efflux pump inhibitors (EPI's)":

- Berberine
- Quercetin
- Baicalein
- Reserpine
- Piperine
- Epigallocatechin gallate (EGCG)

These phytochemicals inhibit major efflux systems in bacteria, including:

- NorA (Methicillin resistant Staphylococcus aureus (MRSA))
- AcrAB-TolC (Escherichia coli)
- MexAB-OprM (Pseudomonas aeruginosa)

The inhibition of efflux pumps allows antibiotics to accumulate in the bacterial cell and therefore may restore the effectiveness of antibiotics against bacteria resistant to that antibiotic. Although berberine has previously been found to have limited antibacterial activity due to efflux pump pumping, its antimicrobial potency increases significantly when combined with natural efflux pump inhibitors [22,23].

4.3 Phytochemicals Inhibit Biofilm Formation

Biofilms are organized communities of bacteria that are protected by an extracellular polymeric matrix, making these bacteria much more resistant to antibiotics and the host immune system. Bacteria that live in biofilms may show up to 1,000 times more tolerance to antibiotics than bacteria growing as planktonic cells [24].

Several naturally occurring plant compounds (i.e., phytochemicals) inhibit the various stages of biofilm development by:

- Preventing bacteria from adhering to surfaces
- Reducing extracellular polysaccharide (EPS) synthesis
- Disrupting established biofilms
- Inhibiting quorum sensing

Some of the most notably effective antibiofilm phytochemicals are:

- Cucumin
- Quercetin
- Epicatchin gallate (EGCG)
- Cinnamaldehyde
- Eugenol
- Thymol
- Carvacrol

By disrupting biofilms, antibiotics can penetrate into the bacterial community and kill more bacteria.

4.4 Phytochemicals Inhibit Quorum Sensing

Quorum sensing (QS) is a method of communicating between bacteria to regulate the expression of genes based on the number of bacteria present in the same area. Bacteria use quorum sensing to regulate many processes associated with virulence including:

- Toxin production
- Bacterial movement
- Biofilm formation
- Secretion of extra-cellular enzymes
- Tolerance to antibiotics

Many phytochemicals interfere with QS by interfering with recognized signaling molecules (e.g., acyl-homoserine lactones, AHL).

Some representative QS inhibitors are:

- Quercetin
- Cucumin
- Baicalien
- Cinnamaldehyde
- Ajoene from garlic
- Naringenin

Inhibition of quorum sensing severely limits bacterial virulence without directly killing bacteria, which reduces the pressure to develop resistance.

4.5 Phytochemicals Inhibit Antibiotic-Degrading Enzymes

Many resistant bacteria produce enzymes that degrade antibiotics before they reach the bacteria's target.

Examples of these enzymes include:

- β-lactamases
- Extended-spectrum β-lactamases (ESBL)
- Carbapenemases
- Aminoglycoside-modifying enzymes

Many phytochemicals inhibit these enzymes of resistance directly or indirectly.

Examples of phytochemicals that inhibit β-lactamases are:

- Gallic acid
- Catechin
- EGCG
- Baicalein
- Tannins

By inhibiting β-lactamases, the antibacterial activity of β-lactam antibiotics can be restored against resistant bacteria [25].

4.6 Phytochemicals Cause Oxidative Stress

Many phytochemicals increase the intracellular production of reactive oxygen species (ROS) in bacterial cells.

Increased levels of ROS cause:

- Damage to DNA
- Lipid peroxidation
- Oxidation of proteins
- Inactivation of enzymes
- Damage to membranes

Some well-recognized ROS-inducing phytochemicals include curcumin, catechin, resveratrol, and berberine.

When combined with bactericidal antibiotics, ROS enhances the rate of bacterial death using multiple complementary mechanisms [26].

4.7 Phytochemicals Inhibit Biological Properties (Virulence)

Most phytochemicals do not inhibit the growth of bacteria but they do inhibit the virulence associated with these pathogens.

Phytochemicals inhibit virulence through the inhibition of the production of:

- Hemolysins
- Proteases
- Elastases
- Exotoxins
- Adhesins
- Flagellins

By decreasing bacterial virulence, the effectiveness of antibiotics will be improved and the rapid clearance of the pathogen from the body by the host immune system will be enhanced [27].

4.8 Combining Multiple Targets for Resistance Prevention

Conventional antibiotics typically target one molecular target in the bacterial cell. Examples of targets for conventional antibiotics are:

- Bacterial cell wall synthesis
- Protein synthesis
- DNA synthesis
- Folate metabolism

Phytochemicals typically target multiple metabolic pathways simultaneously in bacteria, including:

- Bacterial membrane integrity
- Oxidative stress
- ATP synthesis
- Enzyme activity
- Quorum sensing
- Biofilm formation
- Efflux pumps.

Due to the presence of multiple simultaneous targets, the chance that bacteria will be able to acquire resistance by a single mutation is greatly decreased [28].

Table 3. Mechanisms Underlying Synergistic Activity Between Antibiotics and Plant-Derived Phytochemicals

Synergistic Mechanism	Representative Phytochemicals	Antibiotics Enhanced	Biological Outcome
Membrane disruption	Thymol, Carvacrol, Eugenol	Aminoglycosides, β-lactams	Increased antibiotic uptake
Efflux pump inhibition	Berberine, Quercetin, Piperine, EGCG	Fluoroquinolones, Tetracyclines	Increased intracellular antibiotic concentration
Biofilm inhibition	Curcumin, Quercetin, Cinnamaldehyde	Vancomycin, Ciprofloxacin	Improved penetration into biofilms
Quorum sensing inhibition	Curcumin, Ajoene, Baicalein	Multiple antibiotic classes	Reduced virulence and biofilm formation
β-lactamase inhibition	EGCG, Gallic acid, Catechin	Penicillins, Cephalosporins	Restoration of β-lactam activity
ROS generation	Curcumin, Resveratrol, Berberine	Aminoglycosides, Fluoroquinolones	Enhanced bacterial killing
Virulence suppression	Naringenin, Quercetin	Various antibiotics	Reduced pathogenicity
Multi-target action	Polyphenols and essential oils	Broad-spectrum antibiotics	Delayed resistance development

5. Recent Studies and Experimental Evidence (2020–2026)

Recent research has shown that there is strong evidence that a variety of phytochemicals, when used with a companion antibiotic, may prove effective in eliminating antimicrobial resistant microorganisms. Most studies have evaluated these combinations using methods such as checkerboard microdilution assays, FICI analysis, time-kill kinetics, biofilm inhibiting assays and electron microscopy to show evidence of the synergistic bacteria [29].

For example, the most commonly studied is the flavonoid baicalein isolated from Scutellaria baicalensis. In experimental studies, baicalein substantially increased the efficacy of doxycycline against multidrug resistant Gram-negative bacteria, including Acinetobacter baumannii and Klebsiella pneumoniae. The use of baicalein and doxycycline together lowered the effective dose of doxycycline dramatically and resulted in a high bactericidal activity on a number of multidrug resistant clinical isolates. In mechanistic studies, baicalein disrupted outer and inner membranes of the bacteria, increased the permeability of the membrane, and enhanced intracellular accumulation of the antibiotic, while suppressing mechanisms of resistance.

Thymol and carvacrol are two other phenolic monoterpenes and are the principle components found in the essential oils of oregano and thyme. Studies have demonstrated that combinations of these compounds with chloramphenicol, gentamicin and streptomycin, and other common antibiotics, have exhibited very strong synergy against MRSA and carbapenem-resistant Acinetobacter baumannii. These combinations resulted in reductions of the effective doses of antibiotics of 4 to 16 times, and primarily worked by disrupting the membrane integrity of the bacteria, increasing permeability to the intracellular portion of bacteria, and lowering the development of resistance.Allium sativum (garlic) is another medicinal plant that has well-established antimicrobial properties. Allicin, the sulfur-containing phytochemical found in garlic, was shown to have synergistic effects with a variety of conventional antibiotics against multidrug-resistant bacterial isolates (MDRBIs). Garlic extracts were shown to increase bacterial susceptibility due to their ability to disrupt cell membrane integrity, inhibit biofilm formation, and increase membrane permeability; therefore, they were proven capable of enhancing the effectiveness of antibiotics for combating resistant pathogens.

Recent studies have also shown that extracts from Bauhinia purpurea leaves have antibiotic-potentiating properties toward multidrug-resistant Staphylococcus aureus. B. purpurea leaf extracts exhibited a significant enhancement of β-lactam antibiotic activity by both inhibiting the mechanisms of bacterial resistance and increasing bacterial susceptibility to antibiotics. These findings further support the increasing interest in the use of extracts from various medicinal plants as

natural antibiotic adjuvants with the potential to restore the effectiveness of currently available antimicrobial agents.

In addition to the individual examples cited above, numerous reviews published from 2024 to 2026 have summarized supportive evidence demonstrating that flavonoids, alkaloids, phenolic compounds, terpenoids, and essential oils can enhance the activity of antibiotics through many complementary mechanisms. Common mechanisms of action include: disruption of bacterial membrane integrity; inhibition of multidrug efflux pumps; suppression of quorum sensing; inhibition of biofilm formation; interference with DNA and protein synthesis; attenuation of virulence factors; and induction of oxidative stress. This multitargeting significantly reduces the risk of developing drug resistance and improves the effectiveness of antibiotic therapy.

While laboratory studies show promising results, the majority of the currently available data are restricted to in vitro investigations. Only a limited number of studies have progressed to animal studies, and only a few combinations of phytochemicals and antibiotics have been upon clinical evaluation. Additionally, due to the variability in phytochemical extraction methods, geographic source of the plant material, chemical composition, dosage, formulation, and experimental protocol among studies, it has not been possible to compare data from these different studies directly. Standardization of plant extracts, pharmacokinetic characterization, toxicity evaluation, and well-designed randomized controlled clinical trials are key components to providing a scientific basis for the routine use of these medicinal plant–antibiotic combinations in clinical practice [30].

Table 4. Representative Studies Demonstrating Synergistic Activity of Plant-Derived Phytochemicals with Antibiotics (2020–2026)

Phytochemical / Plant Source	**Antibiotic**	**Target Resistant Pathogen**	**Proposed Mechanism**	**Major Outcome**
Baicalein (*Scutellaria baicalensis*)	Doxycycline	MDR *Acinetobacter baumannii*, *Klebsiella pneumoniae*	Membrane disruption, increased intracellular drug accumulation	Significant reduction in MIC; strong synergistic activity
Thymol	Gentamicin, Streptomycin	MRSA, *Acinetobacter baumannii*	Membrane permeabilization	4–16-fold reduction in antibiotic dose
Carvacrol	Chloramphenicol, Gentamicin	MRSA, *Acinetobacter baumannii*	Membrane disruption, resistance suppression	Potent synergistic antibacterial activity
Garlic (Allicin)	Various antibiotics	MDR bacterial isolates	Membrane damage, antibiofilm activity	Enhanced antibiotic susceptibility
Bauhinia purpurea extract	β-lactam antibiotics	MDR *Staphylococcus aureus*	Antibiotic potentiation, inhibition of resistance mechanisms	Improved antibacterial efficacy

The growing body of evidence indicates that plant-derived phytochemicals function as **antibiotic adjuvants** rather than direct replacements for antibiotics. Their ability to restore antibiotic susceptibility and interfere with multiple resistance pathways positions them as promising candidates for the development of next-generation combination therapies against multidrug-resistant bacterial infections.

1. Challenges and Future Perspectives

While experimental studies have demonstrated synergistic activity between phytochemicals and antibiotics, there remain several hurdles in the areas of science, funding and regulation which must be overcome for their use to become routine in clinical practice.

One major challenge is that there is currently no standardized method for the extraction and isolation of phytochemicals from plant sources. Pharmaceutical companies may experience a wide variability in the chemical makeup of phytochemical extracts, depending on species of plant, place of origin/where they were cultivated, how and when they were harvested, the method used for extraction, and how and where they are stored; this can make it difficult to reproduce results from previous experiments and compare studies. Therefore standardizing the extraction procedures and establishing an appropriate amount of quality control is essential.

Another consideration is the poor bioavailability associated with many phytochemicals. Phytochemicals like curcumin, quercetin, resveratrol and epigallocatechin gallate (EGCG) can exhibit very poor solubility in water, low absorption in the gastrointestinal tract, be rapidly metabolized, and have short halflives, all of which reduce their ability to provide an intended therapeutic effect in a living system. New methods of drug delivery (such as using nanoparticles, liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers (NLC), and nanoemulsions) may improve

the stability, bioavailability, and targeted delivery of bioactive molecules.

A major hurdle moving forward is the lack of in vivo and clinical evidence to support the use of phytochemicals in conjunction with antibiotics. Numerous in vitro studies have found that phytochemicals work together with antibiotics, but only a small number have been tested in animals; there are very few high-quality, randomized control trials supporting the clinical use of these combination products. Future efforts should focus on confirming the results of laboratory studies through appropriate preclinical studies and multicenter clinical trials confirming their safety, efficacy, appropriate dosing, and pharmacokinetic-pharmacodynamic (PK-PD) relationships.

Another factor that may influence overall success is the potential for herb-drug interactions. Some phytochemicals have been shown to interact with cytochrome P450 enzymes, drug transporters such as P-glycoprotein, and other metabolic pathways, thereby altering how co-administered antibiotics may be absorbed, distributed, metabolized, or eliminated. Therefore, proper toxicological assessments of the herb-drug combinations must be done using appropriate pharmacovigilance methods prior to clinical use.

Exciting new technological advances can provide great potential for speeding up the development of phytochemical-antibiotic combination therapies. Artificial intelligence (AI); machine learning; molecular docking; molecular dynamics simulations; systems biology; metabolomics; transcriptomics; proteomics; and high-throughput screening techniques can help identify new combinations of synergistic compounds, predict molecular interactions, and optimize lead compounds. Precision medicine approaches may also allow for individualized therapy targeting the specific pathogen's genotype or resistance profile and/or other host-specific factors.

Ultimately, phytochemicals derived from plants are not going to replace antibiotics in the near future, but they should be considered as adjuncts to antibiotics through (1) restoring the efficacy of antibiotics, (2) suppressing resistance mechanisms in bacterial pathogens, (3) lowering the required dose of antibiotic required to achieve a successful outcome, and (4) extending the clinical usefulness of current antimicrobial agents. Successful translation of laboratory findings into new treatments for patients will require continued interdisciplinary collaboration from microbiologists, pharmacologists, medicinal chemists, nanotechnologists, and clinicians.

7. Conclusion

Antibacterial resistance is considered one of the biggest challenges facing global health and therefore the development of new antibiotics alone is insufficient. Phytochemicals derived from plants are emerging as additional potential treatment options due to their broad spectrum activity against bacteria, multi-target mechanisms of action and capacity to enhance the effectiveness of traditional antibiotics. The research indicates that phytochemicals (flavonoids, alkaloids, terpenoids, phenolic acids and essential oils) can improve the antibacterial properties of antibiotics by: (1) increasing the permeability of bacterial membranes; (2) inhibiting bacterial efflux pumps; (3) inhibiting quorum sensing; (4) disrupting biofilm formation; (5) by inhibiting the production of beta-lactamase enzymes; and (6) by preventing or reducing the virulence of bacteria. Therefore, through these synergistic mechanisms, phytochemicals can render bacteria susceptible to previously drug-resistant bacteria, reduce the amount of antibiotics needed to treat an infection, and help prevent the development of new antibiotic resistance. However, there are multiple obstacles to utilizing phytochemicals as an antibiotic adjunct on a large scale, including the lack of standardization of phytochemical products, low bioavailability of many phytochemicals, limited pharmacokinetic information, toxicity, interactions between herbs and drugs, and little clinical data regarding effectiveness. The use of nanotechnology, computer-based drug discovery technologies, omics technologies and precision medicine should escalate the development of phytochemical and antibiotic combination therapies. Based on the current evidence from numerous scientific fields and systematic clinical trials, phytochemicals derived from plants have great potential as adjuncts to traditional antibiotics to help combat infections caused by antibiotic-resistant organisms.

Declarations

Ethics Approval and Consent to Participate

Not applicable. This review article is based exclusively on previously published literature and does not involve human participants, animals, or identifiable personal data. Therefore, ethical approval and informed consent were not required.

Consent for Publication

Not applicable.

Availability of Data and Materials

No new datasets were generated or analyzed during the preparation of this review article. All information presented has been obtained from published scientific literature cited in the reference list.

Funding

The authors declare that no specific funding was received from any governmental, commercial, or non-profit funding agency for the preparation of this review article.

Competing Interests (Conflict of Interest)

The authors declare that they have no known financial interests, personal relationships, or competing interests that could have appeared to influence the work reported in this manuscript.

Authors' Contributions

All authors contributed substantially to the conception and design of the review. Literature searching, data collection, critical analysis of the published literature, manuscript preparation, revision, and final approval of the manuscript were performed collaboratively by all authors. All authors have read and approved the final version of the manuscript.

Acknowledgements

The authors sincerely acknowledge their respective institutions for providing the necessary academic environment, library resources, and research support during the preparation of this review article. The authors also thank all researchers whose published work has contributed to the advancement of knowledge in the field of antimicrobial resistance and phytochemical-based combination therapy.

Data Availability Statement

Data sharing is not applicable to this article because no datasets were generated or analyzed during the current study.

Code Availability

Not applicable.

Ethical Statement

This manuscript is a narrative review based on published scientific literature. No human participants, animals, or clinical samples were involved in this study; therefore, institutional ethical approval was not required.

Declaration of Generative AI Use

During the preparation of this manuscript, the authors used generative artificial intelligence (AI) tools solely to improve language quality and assist with manuscript drafting. The authors carefully reviewed, edited, and verified all scientific content and accept full responsibility for the accuracy, originality, and integrity of the manuscript. The final content reflects the authors' scholarly judgment and has been critically evaluated against the cited literature.

Abbreviations

Abbreviation	Full Form
AHL	Acyl Homoserine Lactone
AI	Artificial Intelligence
AMR	Antimicrobial Resistance
ATP	Adenosine Triphosphate
CLSI	Clinical and Laboratory Standards Institute
DNA	Deoxyribonucleic Acid
EGCG	Epigallocatechin Gallate
EPI	Efflux Pump Inhibitor
ESBL	Extended-Spectrum β-Lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FICI	Fractional Inhibitory Concentration Index
FDA	Food and Drug Administration
MDR	Multidrug-Resistant
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-Resistant *Staphylococcus aureus*
NLC	Nanostructured Lipid Carrier
OMICS	Integrated Genomics, Transcriptomics, Proteomics, and Metabolomics Technologies
PBP	Penicillin-Binding Protein
PDR	Pan-Drug-Resistant
PK	Pharmacokinetics
PD	Pharmacodynamics
QS	Quorum Sensing
QSI	Quorum Sensing Inhibitor
ROS	Reactive Oxygen Species
RNA	Ribonucleic Acid
TEM	Transmission Electron Microscopy
VRE	Vancomycin-Resistant *Enterococcus*
WHO	World Health Organization
XDR	Extensively Drug-Resistant

Common Bacterial Species Mentioned

Abbreviation	Scientific Name
A. baumannii	*Acinetobacter baumannii*
E. coli	*Escherichia coli*
K. pneumoniae	*Klebsiella pneumoniae*

P. aeruginosa	*Pseudomonas aeruginosa*
S. aureus	*Staphylococcus aureus*

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