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Phytochemicals as antimicrobial agent to combat antibiotic resistance in microbial pathogens

Abstract

Antimicrobial resistance (AMR) represents one of the most pressing global health threats, primarily driven by the overuse and misuse of antibiotics in healthcare, animal farming, and other sectors. The rapid emergence of multidrug-resistant (MDR) pathogens has rendered many conventional antibiotics ineffective, creating an urgent need for alternative therapeutic strategies. In this context, the exploration of phytochemicals offers a promising and sustainable approach. These naturally occurring plant-derived compounds—such as curcumin, apigenin, ellagic acid, and thymol—have demonstrated broad-spectrum antimicrobial, anti-biofilm, and quorum-sensing inhibitory activities. Their mechanisms include disruption of microbial membranes, inhibition of virulence factors, and modulation of enzymatic pathways essential for bacterial survival and pathogenicity.

Furthermore, recent advances in drug delivery systems have significantly enhanced the efficacy of these phytochemicals. Innovative formulations such as nano emulsions, liposomes, and polymeric nanoparticles improve their bioavailability, stability, and targeted delivery, overcoming traditional limitations like poor solubility and rapid metabolism. These nanocarrier-based systems not only enhance the potency of phytochemicals but also enable synergistic interactions with existing antibiotics, potentially restoring their activity against resistant strains.

The review also provides insight into bacterial resistance mechanisms, including activation of efflux pumps, alteration, or loss of porin channels, and enzymatic degradation or modification of antibiotic molecules. Understanding these pathways is crucial for designing effective phytochemical-based interventions.

In conclusion, this review underscores the therapeutic potential of phytochemicals as safe, eco-friendly, and potent alternatives to synthetic antibiotics. Integrating phytochemistry with nanotechnology can pave the way for novel antimicrobial strategies, offering a sustainable route to mitigate AMR and safeguard global health. Such interdisciplinary approaches are essential to develop next-generation therapeutics capable of addressing the growing burden of drug-resistant microbial infections.

Keywords: antimicrobial resistance (AMR), phytochemicals, drug delivery technologies, antibiotic resistance mechanisms

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Introduction

Phytochemicals show strong potential as alternatives to conventional antibiotics because they can act on multiple bacterial resistance mechanisms. Antibacterial agents, in general, are substances used to prevent or treat infections caused by bacteria.

Nature provides a wide variety of antimicrobial peptides, derived from sources such as bacteria, fungi, plants, and invertebrates. Many of these compounds have demonstrated significant antimicrobial activity in both preclinical and clinical studies,[1,2] highlighting their role as promising antimicrobial agents. Historically, the period from 1940 to 1966 is considered the "Golden Age of Antibiotics," during which numerous drugs were developed that revolutionized infection treatment.[3]

Today, antimicrobial resistance (AMR) poses a serious global health challenge, as many bacteria no longer respond to available antibiotics. This limits treatment options and contributes to increased mortality rates.[4] Antibiotics, used in humans, animals, and even plants, remain essential tools for preventing and treating infectious diseases.[5] Their discovery marked a turning point in medicine and public health, making surgeries safer and dramatically reducing infant and maternal mortality. For example, the fungus *Penicillium* produces penicillin, a compound with bactericidal activity, illustrating how microorganisms naturally generate antibiotics as a defense against competing pathogens.[6] In recent years, however, antibiotics have been used extensively not only against bacteria but also in broader contexts, including fungal infections.

A major concern is the widespread misuse of antibiotics, both in human medicine and in livestock management. Large portions of these drugs are excreted unchanged into the environment, contaminating wastewater and continuously exposing pathogens to sub-lethal concentrations.[7] This persistent exposure accelerates selective pressure, driving the emergence of highly resistant bacterial strains.[8]

How microbes develop ab-resistance

Antibiotics are meant to enhance both the quality and longevity of human life-not only by treating infectious and life-threatening diseases but also by enabling advances in medical procedures. In the pre-antibiotic era, a breakthrough came with the discovery of the first antibiotic, penicillin, by Sir Alexander Fleming in 1928.[9] Nearly 11 years later, Florey and Chain succeeded in isolating and commercializing this powerful drug. While antibiotics revolutionized the treatment of bacterial infections, research has shown that bacteria can develop resistance. Misuse and overuse of antibiotics, often due

to a lack of knowledge about proper dosage, have contributed to the rise of resistant strains.[10,11] When antibiotics are used incorrectly or excessively, resistant bacteria are selectively favored, making diseases harder to treat and potentially lethal. Resistance can arise either from spontaneous DNA mutations that are passed down through generations or through horizontal gene transfer. Such genetic exchange occurs via mobile elements like phages, plasmids, and transposons. According to Fleming, conservation is the term for protection achieved by selecting the heart.[9] Another type of resistance is internal resistance. All members of specific bacteria are inherently resistant to antibiotics due to their function or structure. The culprits are genetic traits passed on by bacteria previously exposed to antibiotics. Drug resistance is a complex and constantly competing process, and the commitment to developing new drugs has made it difficult for pharmaceutical companies to invest in developing drugs for new diseases. Multidrug resistance (MDR) is characterized by the simultaneous development of resistance to more than one antibiotic, when bacteria have different strains (all bacteria are drug resistant) as they produce diseases that are resistant to several conventional medications, these bacteria are frequently referred to as "superbugs".[12] According to the Centers for Disease Control and Prevention (2019 report), there are over 35,000 vaccine-preventable fatalities and over 2.8 million vaccine-preventable illnesses in the United States each year. Pharmaceutical firms are therefore not sufficiently motivated to spend money on the creation of novel antibiotics.[13,14] Multidrug resistance (MDR), characterized by resistance to multiple classes of antibiotics simultaneously, can arise when a bacterial strain possesses various genes to resistance, each one conferring resistance to a different antibiotic, or when a single mechanism of resistance confers resistance to multiple antibiotics. Such bacteria are commonly referred to as "superbugs" because they cause infections that are resistant to conventional antibiotics.[15,16] As per the 2019 report from the Centers for Disease Control and Prevention regarding antibiotic resistance threats, the United States experiences over 2.8 million instances of antibiotic-resistant infections each year, resulting in the fatalities of more than 35,000 individuals (Table 1).[17]

Table 1 Description and features of a particular nanocarrier containing phytoactive antimicrobials

S.No.	Phytoactives	Mechanism of action	Nanocarriers	References
1	Apigenin	They destabilize the cell membranes of microorganisms and also impede	Liposomes	18
		the function of enzymes responsible for synthesizing microbial lipids, proteins, and nucleic acids, ultimately causing the demise of the microorganism.	Micelles	19
2	Capsaicin	It functions by attaching to particular proteins and disturbing the cell membrane of bacteria and other microorganisms, resulting in their demise.	Micelles	20
3	Carvacrol	The mechanism involves disturbing the cell membrane,	Nano emulsion	21
		changing its permeability,	Polymeric	22
		which causes leakage of cellular contentsand ultimately results in cell death.	NPs	
4	Curcumin	It works by suppressing the production ofvital enzymes necessary for microbial growth and causing damage to themicrobial cell membrane.	Liposomes Micelles Gold nanoparticles	23 24 25 26
5	Ellagic acid (EA)	It functions by inhibiting the biosynthesis of the bacterial cell envelope.	Micelles NPs	27
6	Menthol	It works by disrupting the cell membrane of the microorganism, causing it to leakout its contents and die.	Polymeri cNPs	28
7	Oregano, thyme, lemongrass	Act by inhibition of bacterial cellenvelope biosynthesis.	Nano emulsions	29
8	Quercetin	Act by inhibiting the growth of bacteriaand disrupting their cell membranes.	NLCs Gold nanoparticles	30 31
9	Rosemary essential oil	Act by disrupting the cell membrane of thebacteria.	NLCs	32
10	Thymol	Phenolic compound act by disrupting thecell membrane of bacteria	Micelles	33

Phytochemicals as a source of antimicrobial agents

Commercial demand for antibiotics derived from plants has increased steadily in recent years. These trends may reflect concerns about the side effects of synthetic AML drugs, as well as a global shift towards safer alternatives with fewer effects. Plants in general are believed to have many advanced phytochemicals. Many of these phytochemicals serve as protective mechanisms against various environmental stresses (such as free radicals, salinity and temperature changes) as well as pathogenic organisms (such as bacteria and fungi) and pests.[34–36]

Carotenoids, polyphenolics, alkaloids, sulfur containing groups, terpenes and terpenoids have many groups used to classify

phytochemicals. These compounds use different strategies to exert their antibacterial effects on bacteria.[37] The mechanism of action of phytochemicals against AML mainly includes changes in cell morphology, disruption of intracellular pH balance, membrane disruption leading to ion leakage, membrane reduction ability, inhibition of ATPase activity and enzymatic reactions, transcriptome and protein groups. Mutations include reduction of nucleic acid synthesis, inhibition of toxin biosynthesis, inhibition of biofilm formation, reduction of bacterial virulence, interference with quorum sensing, and pH control.[38,39]

Plant-derived bioactive compounds can interfere with multiple cellular activities, ultimately disrupting key processes required for microbial survival.[40] Numerous studies have shown that phytochemicals, particularly in extract form, exhibit antimicrobial activity against a wide range of microorganisms. Extracts from medicinal plants such as lemongrass, neem, aloe vera, thyme, rosemary, tulsi, and even bryophytes—obtained through different solvent extraction methods—have demonstrated antibacterial effects against both Gram-positive and Gram-negative bacteria.[41]

Additionally, solvent extracts of medicinal plants such as turmeric, birch, ginger and Tinospora cordifolia are effective against Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, E. coli, B. Bacillus subtilis and Proteus mirabilis. Berberine, curcumin, piperine, tomatine, reserpine, sanguinarine, anglimin, ergotin, squamine, allicin, ajoene, resveratrol Alcohol, baicalein etc.[42,43]

Nanocarriers designed to deliver aml phytochemicals

The emergence of antibiotic resistance is a result of the ability of bacteria to adapt to environmental changes. Taking steps to prevent the spread of these resistant bacteria is important for us and future generations. Although implementing a global strategy to control antibiotic use, conducting educational programs to educate end users, and developing new antibiotics are important preventive measures, they are not sufficient on their own.[24,25] To mount an effective attack, it is important to improve our antibiotic arsenal. This can be done by creating new forms of antibiotics, improving the quality of antibiotics through recycling, and using alternative methods. It is important to recognize the challenges that need to be overcome to develop new innovations in the fight against deadly diseases. Molecules or compounds that replace existing molecules or compounds should not be taken lightly (figure 1).[26]

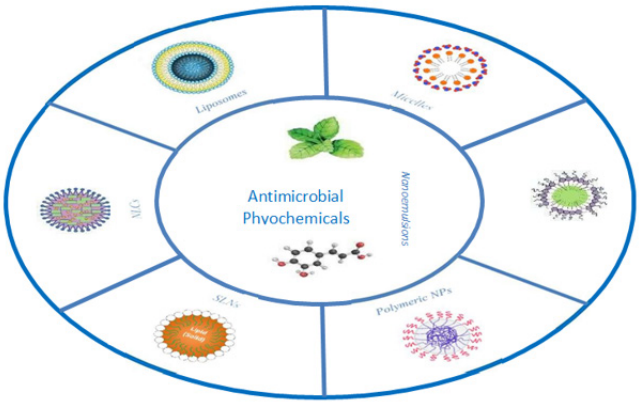

Figure 1 The potential of different nanocarriers as delivery systems for antimicrobial phytocarriers.

Antibacterial agents derived from plants

Infectious diseases pose a serious threat to human life worldwide. The World Health Organization has classified bacterial infections as priority, high and medium priority, based on the rate at which new drugs are developed to combat stymied drug resistance. Important pathogens include carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* strains, as well as carbapenem-and third-generation cephalosporin-resistant *Enterobacteriaceae* species.

Clinically important drug-resistant bacteria include *Enterococcus faecium* resistant to vancomycin, *Staphylococcus aureus* resistant to methicillin and vancomycin, *Helicobacter pylori* resistant to neomycin, and *Campylobacter* and *Salmonella* strains resistant to fluoroquinolones. In addition, third-generation cephalosporin-and fluoroquinolone-resistant *Neisseria gonorrhoeae* are also considered major threats.

The medium priority list includes penicillin-insensitive *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae,* and Shigella. Additionally, *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.[43] Some of the bacteria listed such as are also classified as ESKAPE bacteria due to the depletion of antibiotics. In the next section, we will examine the action process of natural products obtained from clinically important bacteria. Bacteria listed as most important include those resistant to carbapenems, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa,* as well as *Enterobacteriaceae*, which are resistant to carbapenems and third-generation cephalosporins. Important pathogens include vancomycin-resistant *Enterococcus faecium*, methicillin-resistant and vancomycin-resistant *Staphylococcus aureus*, clarithromycin-resistant *Helicobacter pylori,* and fluoroquinolone-resistant Campylobacter strains and *Salmonella* spp. and third-generation *Neisseria gonorrhoeae* resistant to cephalosporins and fluoroquinolones. The medium priority list includes penicillin-nonsusceptible *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae*, and Shigella Resistance to fluoroquinolones. Also included in this list are *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. Some bacteria such as are classified as ESKAPE bacteria because they can evade antibiotics.[44]

Plant-derived compounds targeting antimicrobial-resistant microorganisms

Historically, the medicinal properties of medicinal plants and their compounds have received widespread attention in the treatment of human diseases. This study expands our understanding of the antimicrobial properties of plant secondary metabolites (PSM) in the prevention of infectious diseases.[45–49] Phyto-AML's growth can be attributed to its unique features, comprehensive functionality, and excellent security track record. Phytochemicals are used to kill many types of harmful organisms by killing them directly or by destroying their defenses. This is an emerging and promising approach to combating persistent AML-R.[50–52]

What is antimicrobial resistance

Antibiotics are drugs or chemicals used to kill or inhibit pathogens that can cause disease in humans and animals. Antibiotics form the basis of modern medicine because they enable effective treatment of bacterial infections. While some bacteria are beneficial (e.g., *Lactobacillus* species used in fermented foods), others like

Salmonella can cause diseases such as typhoid fever. Antimicrobial resistance (AMR) also called drug resistance, occurs when bacteria, viruses, fungi, or parasites no longer respond to medicines that were once effective making infections harder to treat and increasing the risk of severe disease, prolonged illness, disability, and death. This resistance can develop naturally or be accelerated by anthropogenic activities like misuse or overuse of antibiotics in clinical, veterinary, and agricultural settings. Resistant microorganisms that survive drug exposure can spread to others, making common infections more difficult or even impossible to cure. There are various types of antimicrobials, each targeting specific classes of pathogens are - Antibacterials/Antibiotics target bacteria, Antivirals target viral pathogens, Antifungals act against fungal organisms, Antiparasitic are effective against parasitic infections. Resistance can occur across all these classes, making AMR a broad and complex public health challenge.[53]AMR has significant effects on the economy longer hospital stays, the need for intensive care, and the use of more costly or last-resort treatments result in higher expenditures for healthcare systems in addition to lost productivity from prolonged sickness. According to economic projections, AMR could cause a 1.1–3.8% decline in global GDP by 2050 and force millions of people into extreme poverty, particularly in low- and middle-income nations with inadequate health infrastructure. The financial burden that AMR places in addition to its health effects is highlighted by the expenses associated with higher healthcare utilisation, lost worker productivity, and the need for extra treatments for resistant infections in the European environment.[54]

How does resistance develop

1) *Irrational use of antimicrobials:* Misuse of antibiotics can lead to high selectivity against pathogens, resulting in increased resistance. Genetic changes in bacteria cause them to develop the ability to resist the effects of commonly used antibiotics.

2) *Genetic mutation:* When drugs target the most severely affected bacteria, they die quickly, while the most resistant bacteria survive, multiply, and become superbugs. When these serious infections occur, antibiotic resistance develops and antibiotics become ineffective.[22,23]

3) *Resilient bacteria replicate and evolve into superbugs*: When drugs target the most severely affected bacteria, they die quickly, while the most resistant bacteria survive, multiply, and become superbugs. When these serious infections occur, antibiotic resistance develops and antibiotics become ineffective.[22,23]

4) *Untreated disposal of sewage:* Improper wastewater treatment can lead to water contamination with antibiotic-resistant bacteria.

Social Factors

Relational factors such as self-medication, overuse of antibiotics over-the-counter drugs, and lack of knowledge about antibiotic use also contribute to the problem.[19–21]

Impact of Resistance

Antimicrobial resistance (AMR) significantly complicates the prevention and treatment of infectious diseases and undermines modern medical practice by reducing the effectiveness of existing treatments. As a result, resistant diseases sometimes necessitate more extensive diagnostic testing, longer hospital stays, and the adoption of more costly or harmful alternative medicines, which puts a pressure on health systems and raises healthcare expenses. AMR's extensive health burden was demonstrated by the projected 1.27 million deaths it directly caused worldwide in 2019 and the 4.95 million deaths it contributed to overall. The number of drug-resistant infection-related deaths worldwide is expected to increase significantly if appropriate mitigation measures are not implemented, possibly reaching approximately 10 million deaths year by 2050.[55]

Irrational use of antimicrobials

Antibiotic misuse, including improper prescription, over-the-counter, and dosage errors, results in significant selection pressure that permits resistant strains to persist and proliferate. AMR is accelerated by human overuse beyond what occurs naturally.

Genetic mutation and selection

Susceptible bacteria are eliminated by antibiotic pressure, whereas resistant variants will survive. Microbial populations are progressively dominated by these resistant bacteria as they multiply.

Horizontal gene transfer

By means of transformation, transduction or conjugation, resistance genes can proliferate among bacteria, increasing resistance in different populations.

Environmental contributions: Untreated sewage and improper wastewater disposal can discharge antibiotics and bacteria that are resistant to them into soil and water, which encourages the growth of resistance reservoirs in the environment.

Social and behavioural factors: The development of resistance is made worse by self-medication, excessive use of antibiotics without a prescription, and a lack of public awareness regarding safe antibiotic usage (Figure 2).[55]

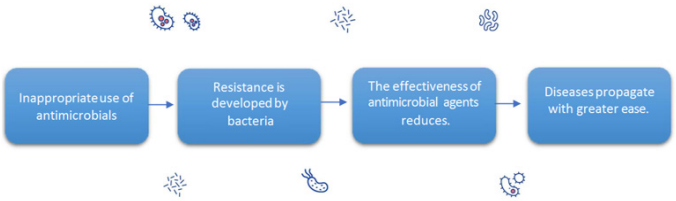

Figure 2 Schematic representation of the antimicrobial resistance (AMR) cycle showing how inappropriate or excessive use of antimicrobials leads to the development of bacterial resistance, reduction in drug effectiveness, and increased propagation of infectious diseases.

1) The challenge to preventing and treating infections poses a risk to essential medical procedures like chemotherapy, organ transplantation, and others.

2) The rise in healthcare expenses is attributed to extended hospital stays, increased diagnostic procedures, and the higher cost of medications.

3) AMR poses a significant threat to the continuation of modern medical practices.

4) There is a rise in the mortality rate among newborns and mothers.[18,19]

Prevention

Emphasizing the importance of prevention and health, he stated that prevention always and everywhere is important for public health.

1) Health reporting.

2) Supporting infection control in hospitals.

3) Use antibiotics carefully and only when necessary.

4) Use vaccination to reduce the spread of AMR.

Mechanism of antibiotic resistance

Mechanisms of antimicrobial resistance can be classified into four primary groups:

1) Enzymatic control/ inhibition

2) Porin changes

3) Excessive activation of efflux pump

4) Target change (figure 3)

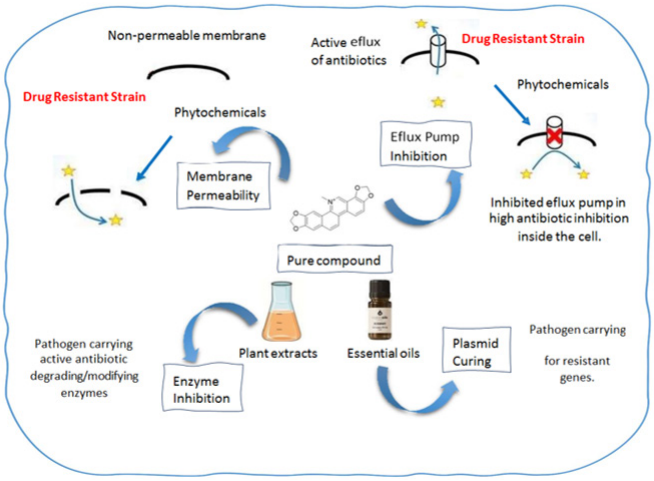

Figure 3 Mechanism of Phytochemicals against Antibiotic Resistant Microbes.

Mechanism

The pressure exerted by microbial antibiotics (AB)[56] triggers bacterial survival mechanisms, leading to resistance. This phenomenon, while continuously evolving, has become more significant in recent years due to the widespread and often irresponsible use of antibiotics. Bacterial genomes are generally small, compact, highly variable, and prone to rapid change. Resistance in infectious diseases develops through multiple pathways, classified as intrinsic or acquired.[57] Intrinsic resistance in bacteria arises from genes already present in their genomes that provide traits compatible with antibiotic survival. In microbial communities, bacteria may also carry resistance markers that alter their genomes, making them unresponsive to antibiotics (AB). [60,71] Acquired resistance can occur through genetic transfer either vertical or horizontal or a combination of both, often from other resistant bacteria. Such transfer can happen via several mechanisms: conjugation (plasmids and conjugative transposons), transformation (phage-mediated), or mutation (integration into chromosomal DNA or plasmids). Phenotypically, bacteria employ various strategies to resist antibiotics, including producing altered enzymes, modifying target sites, mutating porins, or overexpressing efflux pumps.[57,53]

Enzymatic control/ inhibition

Numerous bacterial enzymes can interact with various antibiotic classes (AB), resulting in group transfers, hydrolysis, or structural changes that lessen the medications' potency. The main cause of beta-lactam antibiotics' failure is hydrolysis.[58] The transfer of functional groups, including acyl, thiol, nucleotide, and phosphoryl groups, is mediated by enzymes called acyltransferases, thiol transferases, nucleotidyltransferases, and phosphotransferases in aminoglycosides. Enzymatic modification can also affect other antibiotics, including chloramphenicol, lincosamides, and macrolides. Furthermore, because they promote group transfer and hydrolysis processes, bacterial oxidoreductases and lyases are linked to antibiotic resistance, including to tetracyclines, rifampin, and streptogramins [59]

Alteration of porin

(Figure 4) In Gram-negative bacteria, the hydrophobic outer membrane, composed primarily of lipopolysaccharides, serves as a barrier that restricts the entry of hydrophilic compounds such as antibiotics (AB).[60] Porins, also known as outer membrane proteins (Omps), enable the passage of hydrophilic antibiotics through this lipid bilayer.[6] Specific porins, including Omp-E in *Salmonella Enteritidis* and Omp-C and Omp-F in *E. coli*, vary in expression depending on the bacterial strain.[61,62]

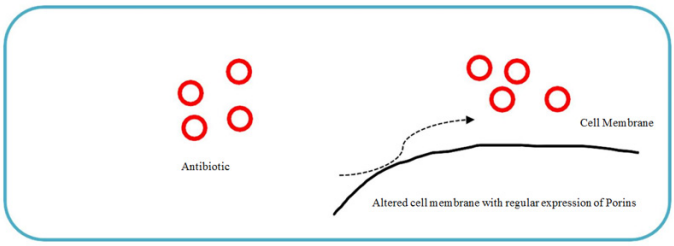

Figure 4 Bacterial mechanism conferring antibiotic resistance throughaltered cell permeability.

When porins are lost or inactivated, bacteria require a higher minimum inhibitory concentration (MIC) for hydrophilic antibiotics, leading to reduced susceptibility. Resistant pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Neisseria gonorrhoeae*, and *Klebsiella pneumoniae* have been shown to downregulate porin expression. [63]

Furthermore, in *Klebsiella pneumoniae*, replacement of OmpK35 (with a larger channel diameter) by OmpK36 (with a narrower channel) decreases sensitivity to β-lactam antibiotics. Similarly, the Omp36 G112D mutation in *B. aerogenes* disrupts porin function, thereby limiting cefepime uptake.[64]

Efflux pump hyperactivation

(Figure 5) Efflux pumps are one of the primary defense mechanisms bacteria use against antibiotics (AB). In resistant strains, pump overexpression actively expels antibiotics from the cell, lowering their intracellular concentration and rendering the drugs ineffective. These efflux systems can be encoded on either plasmids or chromosomes and may be selective for specific antibiotics or capable of expelling multiple drug classes, in which case they are termed multidrug efflux pumps.[65] Multidrug resistance (MDR) efflux pumps are classified into five major families based on their energy sources and structural features: the major facilitator superfamily (MFS), the small multidrug resistance (SMR) family, the multidrug and toxic compound extrusion (MATE) family, the resistance-nodulation-division (RND) family, and the ATP-binding cassette (ABC) family.[66,67]

Efflux pumps in Gram-negative bacteria form a complex system. These generally include three parts of the protein in the membrane; these include membrane fusion proteins that cross the periplasm, outer membrane efflux proteins, and transport proteins in the cytoplasmic membrane.[68]

Membrane fusion proteins in the periplasm and transport proteins in the cytoplasmic membrane.[69,70] Most Gram-positive bacteria have

carriers for drug use in the MFS, SMR, or ABC families. The best-known efflux pumps include NorA in Staphylococcus aureus and Bmr and Blt in Bacillus subtilis.[71,72]

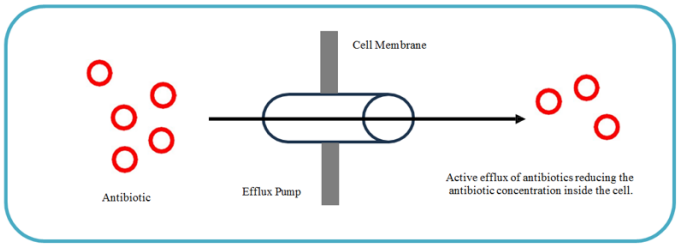

Figure 5 Bacterial mechanism conferring antibiotic resistance throughactive efflux pump.

Alteration at target site

(Figure 6)Most antibiotics (AB) target ribosomes, thus disrupting the protein production process.[73] Biochemical studies aimed at identifying the AB binding site have demonstrated direct interactions between ribosomal nucleotides and compounds such as lincosamides, streptogramins, and macrolides.[74] It has been shown that even a small change in the amino acid sequence in ribosomal proteins can cause changes in protein structure without affecting function, causing AB binding and subsequent further functioning. Resistance to antibiotics occurs due to changes in the amino acid sequence of ribosomal proteins.[75] Molecular targets for drugs are often derived from genetic modification. Changes in ribosomal RNA (rRNA), including post-translational modifications and mutations, are associated with drug resistance. The SOS response is a stress response caused by abnormal single-stranded DNA (ssDNA) and affects the growth and development of the reaction in addition to the processes described above.[76] The SOS response can also be activated by other factors, such as the presence of antibiotics such as beta lactams, fluoroquinolones, and other antibiotics in the environment. Studies have shown that the SOS response in bacteria such as Vibrio cholerae and Escherichia coli leads to the conversion of the 100 KB integral binding element sulfamethoxazole trimethoprim (SXT) and its related products.[77]

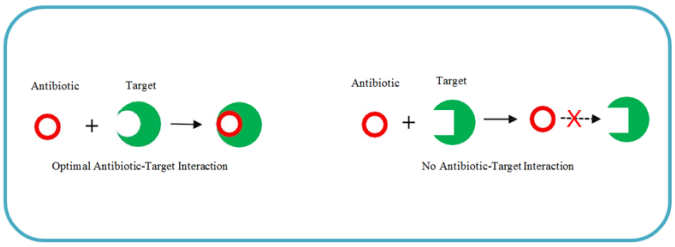

Figure 6 Bacterial mechanism conferring antibiotic resistance through target modification.

The main drivers of amr

One of the main causes of antibiotic resistance (AMR) is the excessive and inappropriate use of antibiotics, including antibiotics, antimicrobials, and antibiotics used in the prevention and treatment of human, animal, or plant diseases. The Basic Principles Guiding the Development of Antibiotics Address the Inappropriate and Overuse of Antibiotics in Humans, Animals, and Plants. [78]

The five compelling reasons why addressing anti microbial resistance (AMR) is of significant importance

1) Approximately 800,000 people are infected with antibiotics every year.
2) Antibiotic resistance (AMR) is found in animals, food, plants and the environment. Antimicrobial agents are used to treat livestock, aquaculture and livestock. They then enter the environment through human and animal waste, improper disposal of chemicals, and unhealthy use of fertilizers in agriculture. This can lead to residues in soil, water and plants, increasing the potential for disease.[79]
3) The fight against bacterial infections brings with it huge medical costs. 4. Antimicrobial resistance (AMR) disrupts the economy. The increase in illness and death is directly related to the economy.

Antimicrobial resistance (AMR) also affects the livestock and livestock economy by harming animal health and welfare and reducing productivity (Figure 7).[80]

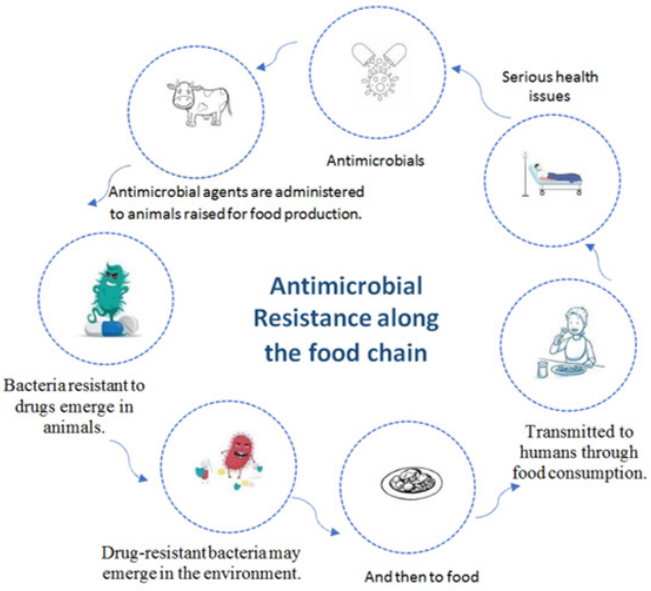

Figure 7 Antimicrobial Resistance along the food chain.

Plant derived antibacterial compounds

Plant-derived antibacterial compounds, or phytochemicals, are being researched extensively as alternative and supplemental treatments with potential efficacy against resistant microorganisms because antimicrobial resistance (AMR) reduces the efficiency of conventional antibiotics. Numerous phytochemicals such as alkaloids, flavonoids, terpenoids, phenolics, and tannins exhibit strong antibacterial activity. Compounds like curcumin, berberine, quercetin, thymol, carvacrol, and eugenol act through multiple mechanisms including disruption of bacterial cell membranes, inhibition of biofilm formation, interference with quorum sensing, and suppression of virulence factor expression. Unlike conventional antibiotics, phytochemicals often target multiple cellular pathways simultaneously, reducing the likelihood of resistance development. Some plant extracts also enhance antibiotic efficacy through synergistic interactions, restoring susceptibility in resistant strains. *Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli, Klebsiella pneumoniae*, and *Staphylococcus aureus* are among the WHO priority pathogens against which these classes have been regularly reported to demonstrate antibacterial action.[81]

Mechanisms of Action of Plant-Derived Antibacterial Compounds

Plant-derived compounds combat bacterial pathogens through multiple mechanisms, offering advantages over single-target conventional antibiotics

Cell wall and membrane disruption

Phytochemicals such as terpenes and phenols can weaken the integrity of the bacterial cell wall and membrane causing cell death and cellular leakage. Certain phytochemicals like berberine which inhibit enzymes that are essential for transcription and DNA replication which prevents cells from proliferation.[82]

Efflux pump inhibition

Antibiotic sensitivity is restored when some plant alkaloids, such as reserpine and piperine, inhibit the bacterial efflux pumps, which are mechanisms by which bacteria expel antibiotics.[83]

Quorum sensing disruption

Plant compounds can inhibit the bacterial communication systems that cause biofilm formation and virulence, thereby decreasing the pathogenicity of bacteria.[84]

Synergistic interactions

Phytochemicals can act synergistically with conventional antibiotics to enhance overall antibacterial efficacy and counter resistance.[84]

According to a recent systematic analysis, flavonoids made up roughly 24.8% of the antioxidant phytochemicals found in medicinal plants that have antibacterial properties. The most effective plant phytochemicals against bacteria that are resistant to drugs are polyphenols and terpenes, with membrane disruption serving as the main method of action. When paired with antibiotics, plant-derived metabolites such flavonoids, terpenes, alkaloids, and phenolic compounds have demonstrated antibacterial, antifungal, and synergistic effects (Table) (figure 8).[84]

Table List Plant-Derived Phytochemicals which shows Antibacterial Activity

Phytochemicals	Effects against MDR bacteria	Mechanism	References
Alkaloids	Broad activity, including against MDR strains	Efflux pump inhibition, DNA/RNA interference	83
Flavonoids	Inhibit biofilms, membrane disruption	Enzyme inhibition, membrane damage	81
Phenolics	Antioxidant + antibacterial effects	Multiple cellular targets	81
Terpenoids	Active against gram-positive & gram-negative bacteria	Cell wall/ membrane disruption	85
Tannins	Antibacterial & synergistic with antibiotics	Disrupt membrane and virulence pathways	81

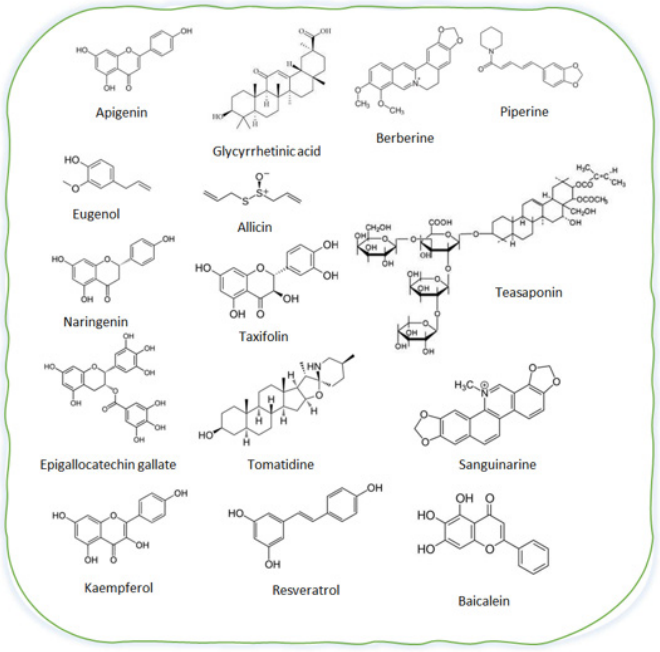

Figure 8 Potent phytochemicals used against the multidrug-resistant pathogens.

Diagnosis and Testing

People affected by PCP often experience symptoms such as fever, difficulty breathing, chest pain, and dry cough. Chest x-ray often shows areas of joint space and bilateral stromal infiltrates.[86,87] Histopathological examination shows that patients with PcP have alveoli containing eosinophilic exudate and Pneumocystis cystis. Pneumocystis jiroveci is frequently found in induced sputum or bronchoalveolar lavage (BAL) fluid, which is the standard for the diagnosis of pneumocystosis.[88,89] PCR tests generally detect PJP in patients by focusing on Pneumocystis jiroveci DNA in respiratory samples and blood samples. These tests generally use primers in a PCR well (Figure 9).[90]

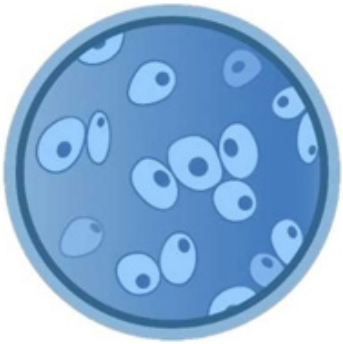

Figure 9 Pneumocystis jirovecii, the fungus that causes Pneumocystispneumonia.

Treatment and Outcomes

Primary treatment and prevention of PJP usually involves the combination use of trimethoprim and sulfamethoxazole.[91] But there are other drugs such as the combination of primaquine and clindamycin, pentamidine, atovaquone, and the combination of dapsone and trimethoprim.[93] Pneumocystis pneumonia can inhibit the phagocytic activity of alveolar macrophages and cause their apoptosis. During PJP, when there is more polyamine in the lungs and alveolar macrophages, they activate caspase.[92,93] This initiates the apoptotic process. Although trimethoprim-sulfamethoxazole remains the mainstay of current treatment, its effectiveness in treating and preventing PCP-related mortality is limited.[94,95] Hospitalized patients with PCP continue to have high mortality, indicating that current treatment is inadequate (figure 10).[96,97]

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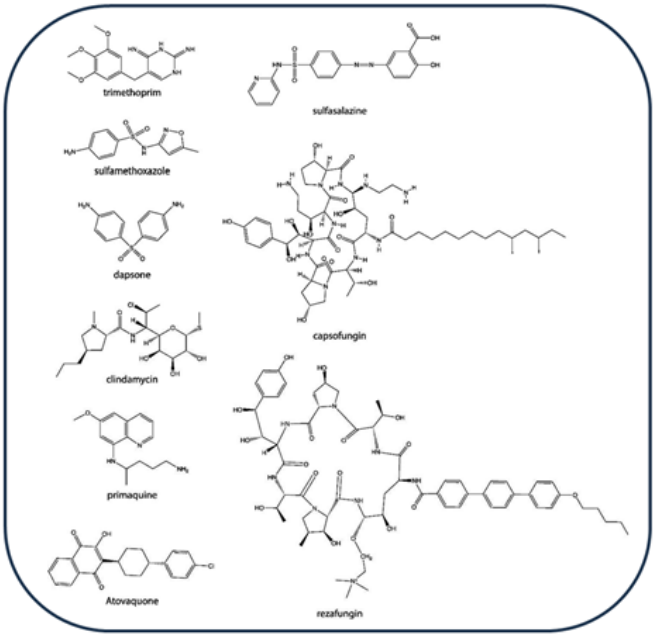

Figure 10 Displays the chemical compositions of drugs currently employed or under investigation for the prevention and treatment of Pneumocystis infection.[97]

Natural therapeutics and neutraceuticals for Pneumonia

Daidzein

(Table 2) Classified as a phytoestrogen, daidzein is a diphenolic compound found in many plants such as Pueraria mirifica, Pueraria lobata, soybeans, and soy products.[98] Recent studies have demonstrated its ability to prevent the growth of cancer cells, especially in breast cancer.[99] Daidzein is structurally similar to estradiol, a female hormone, and has properties that support collagen production, suggesting it may aid skin and wound healing.[100] Similarly, genistein, another isoflavone found in soybeans, has been shown to increase collagen synthesis in fibroblasts damaged by oxidative stress.[101] Genistein achieves this regeneration by modulating ERK1/2 signaling, demonstrating its ability to prevent oxidative damage and promote skin regeneration (Figure 11).[102]

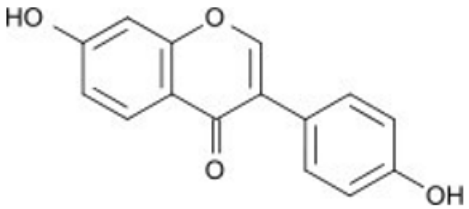

Figure 11 Structure of Daidzein.

Table 2 Ethnobotanical record of medicinal plants traditionally used for the treatment of pneumonia in different countries, highlighting plant parts utilized, preparation forms, modes of application, and traditional uses

S.No.	Plant names	Country	Plant parts used	Forms	Mode of application	Tradition aluse
1	Achyranth esaspera (Puthkand a)	Pakistan (Gujranwala)	Leaves	Decoction	Oral	Pneumonia
2	Achyranth esaspera	Pakistan (Soan Valley)	Root	Decoction, juice	Oral	Pneumonia
3	Adiantum capillus-veneris (Khati booti)	Pakistan (Soan Valley, Salt Range)	Whole part	Tea	Oral	Pneumonia
4	Amaranthus albus (So orBooti)	Pakistan (Punjab)	Whole parts	Decoction, juice	Internal	Pneumonia
5	Coccinia grandis (Voi gtGolkakri)	Nepal	Root	Root Extract	Oral	Pneumonia
6	Gentianod es tianschani ca	Pakistan (Baltistan)	Leaves	Infusion	Oral	Pneumonia
7	Helichrysum schimperi	Uganda	Leaves	Powder	Oral	Pneumonia
8	Justicia adhato da	India (Tripura)	Root, leaves	Decoction, juice	Oral	Pneumonia
9	Malva parviflora	Uganda	Leaves	Powder	Oral	Pneumonia
10	Planta go palmat a (Embatabata)	Uganda	Leaves	Powder	Oral	Pneumonia
11	Rubia cordifolia (Akaramata)	Uganda	Leaves	Powder	Oral	Pneumonia

Continuing the discussion of triterpenoids, ursolic acid and asiaticoside, they all belong to this group and are expected to have the following benefits: They have many biological effects.[103] In particular, ursolic acid has been shown to increase collagen synthesis and exert beneficial effects on skin and wound healing.[103,104] Similarly, triterpenoids such as madecassoside may have similar properties, but more research is needed to understand their mechanisms and effects on collagen production.[105]

Glycitein

This drug is a methoxy isoflavone characterized by having a methoxy group at the 6-position and a hydroxyl group at the 7- and 4'-position. It is obtained from the mycelium of the Cordyceps sinensis mushroom (Figure 12).[106]

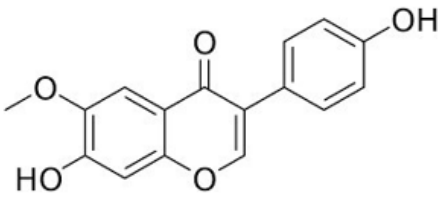

Figure 12 Structure of Glycitein.

The biological activity of daidzein, a little-known substance found in soy products, as well as the estrogen diethylstilbestrol

(DES) Isoflavones, was discovered when compared to well-studied isoflavones such as daidzein and genistein.[107]

1) Found in soy products: Gycitein is found in soy products and generally accounts for about 5-10% of the total isoflavones in foods.[108]
2) Biological activities: Although daidzein and genistein have been widely studied, the biological effects of daidzein have not been documented in previous studies.[109]
3) Studies in mice: The uterine weight of mice given daidzein, genistein and DES significantly increased compared to the control group.[110]
4) Competitive Binding Analysis: Daidzein showed moderate estrogenic effects similar to those observed for daidzein and genistein, but were weaker compared to DES and 17β-estradiol.[111]

The pharmacological potential of glycitein

However, genistein and daidzein (natural derivatives of isoflavones) have been found to inhibit important enzymes associated with Alzheimer's and Parkinson's diseases, such as human monoamine oxidase (hMAO), beta-secretase, beta-secretase, acylcholinesterase, and butylcholinesterase parent product. However, their pharmacological potentials among glycitein, aglycone variants found in soybeans and kudzu root have not been examined in detail. Kinetic studies show that daidzein inhibits a combination of all enzymes tested. Computational docking analysis showed that daidzein interacts with the main catalytic domain of hMAO-A. This suggests that it is an important phytochemical in the treatment of depression and dementia associated with neurodegenerative diseases.[111]

Nepetin

Nepetin is obtained by O-methylation of the flavonoid 6-hydroxyluteolin.[112] This study aims to evaluate the potential of nepetin, a flavonoid derived from O-methylation of 6-hydroxyluteolin, widely found in plants and known for its diversity of pharmacological effects, especially its anti-inflammatory effects (Figure 13).[113]

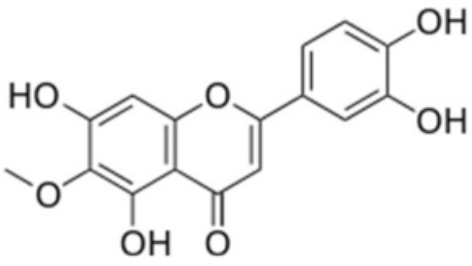

Figure 13 Structure of Nepetin.

Pharmacological properties of Nepetin

This research aimed to evaluate the potential of nepetin, a flavone derived from the O-methylation of 6-hydroxy luteolin and commonly present in herbal remedies known for their diverse pharmacological properties, particularly their anti-inflammatory effects.[115] The study investigated nepetin's ability to alleviate inflammatory responses in cultured keratinocytes and in a mouse model of atopic dermatitis (AD) induced by 2,4-dinitrochlorobenzene (DNCB).[114] Various methodologies, including cell viability assessments, flow cytometry, fluorometry, confocal microscopy, western blot analysis, ELISA techniques, and staining methods, along with scoring and evaluating scratch frequency, were employed to uncover the underlying mechanisms.[116] In keratinocytes treated with LPS, there was a gradual rise in inflammatory mediators and cytokines in a dose-dependent manner.[117]

However, treatment with nepetin prevented LPS-induced cell death and effectively suppressed the production of inflammatory mediators and cytokines in cultured keratinocytes. In the AD mouse model, nepetin treatment demonstrated a dose-dependent reduction in skin inflammation symptoms, leading to significant decreases in inflammation-related cytokines, skin lesions, and behavioral scores.[118] This comprehensive in vitro and in vivo investigation indicates that nepetin represents a safe bioactive compound with promising therapeutic potential for addressing AD-related skin lesions and adverse skin reactions.[119]

Dicaffeoylquinic Acid

The compound 4,5-dicaffeoylquinic acid exhibits inhibitory effects on prostate cancer cells by inducing cell cycle arrest. Additionally, it possesses anti-apoptotic, anti-injury, and anti-hepatitis B virus properties.[120] However, the effects of diCQAs, a group of polyphenolic antioxidant compounds naturally occurring in Arctium lappa extracts (AL), on stress hormone-induced depressive behavior and the underlying mechanisms are yet to be fully understood (Figure 14).[121]

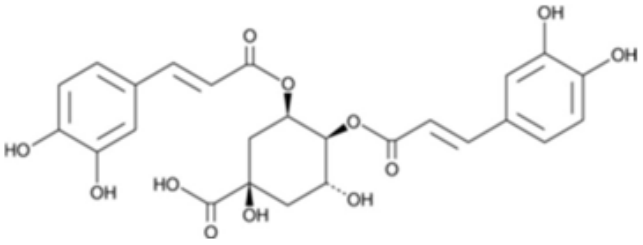

Figure 14 Structure of Dicaffeoylquinic acid.

Neutraceutical Effect of 4,5-Dicaffeoylquinic Acid

There is a pressing demand for anti-inflammatory agents that offer superior safety and efficacy compared to existing non-steroidal anti-inflammatory drugs.[63] While the isomer 4,5-diCQA of dicaffeoylquinic acid (diCQA) has been identified for its antioxidant properties and potential health advantages, its anti-inflammatory effects necessitate additional exploration.[122]

The objective of this research was to evaluate the anti-inflammatory characteristics of 4,5-diCQA, both in vitro employing RAW264.7 cells and in vivo utilizing a carrageenan-induced inflammation model [123]. In cell studies, pretreatment with 4,5-diCQA notably suppressed the expression of several inflammatory markers induced by lipopolysaccharide without inducing cytotoxic effects.[123]

The observed inhibitory effects were linked to the suppression of nuclear factor-κB nuclear translocation and the phosphorylation of mitogen-activated protein kinase (MAPK).[124] When orally administered at various doses, 4,5-diCQA effectively decreased carrageenan-induced edema and the expression of inflammatory markers in a dose-dependent manner.[125]

In summary, the results indicate that 4,5-diCQA demonstrates anti-inflammatory properties by regulating the nuclear factor-κB and MAPK pathways in vitro, while also reducing inflammation in vivo. These findings suggest its potential as a natural alternative to non-steroidal anti-inflammatory drugs.[126]

Identifying Potential Pharmacological Components in *GlycyrrhizaeRadix* for Combating Pneumonia

(Figure 15) Glycyrrhizae Radix et Rhizoma, a traditional Chinese medicine commonly referred to as Gan Cao (GC), is often prescribed in clinical settings to treat pneumonia.[127–130] Due to its pharmacological properties including antibacterial, anti-inflammatory, anti-tumor, and antiviral effects, Glycyrrhizae Radix et Rhizoma (GC) has been used clinically to treat various conditions such as cough, bronchitis, peptic ulcer, and dermatitis.[131–134] Existing studies on the treatment of pneumonia with Glycyrrhizae Radix et Rhizoma (GC) primarily concentrate on its general pharmacological effects or the mechanisms of action of its main constituent compounds. For instance, glycyrrhizin, a key component, has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its ability to target the angiotensin-converting enzyme 2 receptor. However, research investigating the specific compositions or active medicinal components of GC that are effective in treating respiratory diseases like pneumonia in vivo has not yet been conducted(Figure 16).

Figure 15 Dried root slices of Glycyrrhiza radix.

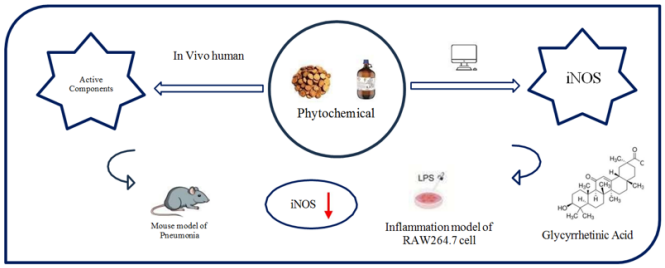

Figure 16 Phytochemistry, Pharmacology and mode of action of Glycyrrhetinic Acid in Glycyrrhizae Radix for combating pneumonia.

Conclusion

The global impact of antimicrobial resistance (AMR), directly attributable to the overuse and misuse of antibiotics, has urged the development of natural options to overcome this challenge. AMR threatens the already high burden of infectious diseases and leads to inadequate response to medical interventions, thereby contributing to high morbidity and mortality. As synthetic antibiotics prove ineffective against adaptable pathogens, phytochemicals are a sustainable, multi-target alternative. Plant-derived phytochemicals showed wide-ranging inhibitory influences on biofilm, antimicrobials, and modulation activities of enzymes, acting at several targets in pathogens. Compared to synthetic antibiotics, which frequently target one common site, phytochemicals have multiple mechanisms of action (alters cell membrane permeability, impede nucleic acid synthesis, inhibits biofilm formation), making development of resistance against these compounds less likely. Key compounds such as curcumin, apigenin, ellagic acid, and thymol have been shown to be effective against multidrug-resistant pathogens via pathogen-killing activity. The renewable characteristics of phytochemicals along with their low production cost and commitment to green healthcare not only provide advantages to human health but also to eco-nomics. Integration into mainstream medicine is challenged by variability in plant extracts, limited clinical trials, and regulatory hurdles. We must standardize extraction methods, engage in rigorous studies, and educate the public on the potential of alternative treatments. To sum up, phytochemicals appear to have a substantial scope as an eco-friendly substitute to tackle AMR. Research, innovation, and collaborative efforts across phytochemical, nanotechnological, and clinical medicine angles are key to managing AMR on a global health scale and securing better health outcomes for generations to come.

Abbreviations

hMAO	Human Monoamine Oxidase
PJP	Pneumocystis Jiroveci Pneumonia
MIC	Minimum Inhibitory Concentration
MDR	Multidrug Resistance
MFS	Major Facilitator Superfamily
SMR	The Small Multidrug Resistance
MATE	Multidrug and Toxic Compound Extrusion
RND	Resistance-nodulation-division
ABC	ATP-binding Cassette
MRSA	Methicillin-resistant Staphylococcus Aureus
VRSA	Vancomycin-resistant Staphylococcus Aureus
PcP	Pneumocystis Carinii Pneumonia
diCQA	Dicaffeoylquinic Acid
MAPK	Mitogen-activated Protein Kinase
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
AMR	Antimicrobial Resistance

Ethics, Consent to Participate, and Consent to Publish

This study did not involve human participants, animals, or sensitive data requiring ethical approval. Therefore, ethics approval, consent to participate, and consent to publish are not applicable.

Data Availability

No new data were generated or analyzed in this study. Data sharing is not applicable to this article.

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Conflicts of Interest

The authors declare that they have no competing interests.

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