Flavonoid Phytochemicals: A Promising Reservoir for Novel Antibiotic Discovery

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***Abstract*—Flavonoids are a major class of plant secondary metabolites that serve critical roles in plant defence, signalling, and bioactivity, contributing to both plant and human health, and therefore are gaining high attention from the pharmaceutical and healthcare industries. Plants synthesize flavonoids in response to microbial infection, and are found to be a potent antimicrobial agent against a wide range of pathogenic microorganisms in vitro. The substantially promising antibacterial flavonoids not only target bacterial cells selectively, but also inhibit virulence factors, as well as biofilm formation. Moreover, plant derived flavonoids can reverse antibiotic resistance by enhancing drug efficacy through direct destabilization of bacterial membranes, efflux pump inhibition, induction of ROS, interference with essential cellular pathways, and synergistic interactions with conventional antibiotics. These diverse mechanistic pathways underscore flavonoids' promise in combating multidrug resistant bacterial infection and would provide a molecular rationale for their continued exploration for developing potential antimicrobial drug candidate.**

***Index Terms*—: Medicinal plants; Phytochemicals; Flavonoids; Microbial resistance; Antibiotics**

I. INTRODUCTION

Plants have been an integral part of medicine and therapeutic agents for mankind. Several documentations are found throughout history about ancient healing practices, which primarily depended on the therapeutic properties of plant extracts. Long before the prehistoric era, mankind relied on the application of herbs for over 4000 years in the traditional medical system, which can be studied through Ayurveda, Unani manuscripts, Egyptian papyrus, as well as Chinese writings [1]. According to the World Health Organization 2019 report, about 80% of the world's population depends directly or indirectly on plant-based medicines for basic healthcare treatment. From ancient times to modern medicine, plants remain one of the most valuable reservoirs of therapeutic agents due to their production of secondary metabolites like phenolic acids, flavonoids, lignans, alkaloids, terpenoids and more. These compounds are unique as they act as defense molecules in plants while showing significant pharmacological activity in humans, which forms the molecular basis of developing modern drugs. The major usage of plant extracts as medicinal agents includes the isolation of bioactive compounds, which are directly used as drugs like morphine, reserpine, taxol, vinblastine, vincristine or used by improving the lead compounds into semi-synthetic novel formulations with higher efficacy or lower toxicity. Moreover, millions of years of plant evolution have generated an extensive diversity among secondary plant metabolites comparable to synthetic compounds in chemical libraries [2]. Thus, even in the modern pharmaceutical era, natural products and plant-derived compounds are irreplaceable due to the inherent chemical diversity, stereochemical complexities and overall potential for novel derivatives, which are difficult to replicate synthetically. These natural product scaffolds are opening new horizons in healthcare with their exceptional contributions and multifunctional bioactives, including antioxidant, antiviral, anticancer, anti-inflammatory and antimicrobial properties.

Despite decades of remarkable success in combating infectious diseases, antibiotics, once the core of modern medicine, are increasingly losing their therapeutic edge against evolving bacterial pathogens. This growing inefficacy represents one of the most pressing global health threats of the 21st century. Antimicrobial resistance (AMR) has rapidly undermined the effectiveness of available drugs, challenging healthcare systems worldwide. According to the World Health Organization's Global Antibiotic Resistance Surveillance Report 2025, approximately one in six laboratory-confirmed bacterial infections worldwide is now resistant to antibiotics, with resistance increasing by 5–15% annually since 2018 [3]. Gram-negative bacteria such as Escherichia coli, Klebsiella pneumoniae, and Acinetobacter species have shown the steepest rise in resistance, especially to essential and last-resort antibiotics like fluoroquinolones and carbapenems. The primary shortcoming of currently available antibiotics lies in their narrow spectrum of activity. Many agents target either gram-positive or gram-negative organisms, complicating empirical therapy when the causative pathogen is unknown [4]. The absence of rapid diagnostic tools in many healthcare settings often forces clinicians to prescribe broad-spectrum antibiotics empirically, even when the causative pathogen is unknown. This practice, although clinically justified in emergencies, significantly contributes to the misuse of antibiotics and accelerates resistance (AMR) development [5]. The progressive loss of efficacy against pathogens producing extended-spectrum beta-lactamases (ESBLs) has rendered drugs like ampicillin and cephalosporins ineffective in many settings, [6] while mutational changes in genes such as gyrA and parC have compromised the utility of fluoroquinolones [7]. Beyond genetic mutations, bacteria also employ many structural and physiological defense strategies such as biofilm formation and efflux pumps, reducing antibiotic penetration and intracellular concentration. Biofilm formation is a critical factor in chronic infections, where complex, surface-adhered microbial communities are encased in a protective extracellular matrix that often prevents antibiotic penetration and facilitates persistent survival and infection resulted by drug tolerance. Biofilm-embedded bacteria can withstand antibiotic concentrations 100–1000 times higher than their planktonic counterparts, leading to chronic conditions such as catheter-related infections, cystic fibrosis, and wound infections [8]. Additionally, certain bacterial species possess active efflux transporters or efflux pump systems, such as the AcrAB–TolC system in E. coli and MexAB–OprM in Pseudomonas aeruginosa, which actively expel antibiotics from bacterial cells, reducing accumulated intracellular drug concentrations, promoting multidrug resistance rendering many antibiotics—including tetracyclines, fluoroquinolones, and macrolides—ineffective even at high doses [9].

Another critical issue is the toxicity and adverse effect profile of many antibiotics. Agents such as cefuroxime, ceftriaxone, linezolid, and tedizolid are linked to systemic side effects including gastrointestinal disturbances, allergic reactions, neuropathies, myelosuppression, and, in severe cases, lactic acidosis [10]. These adverse effects limit antibiotic use in sensitive populations like children, pregnant women, and immunocompromised individuals, narrowing therapeutic choices further. Adding to these clinical challenges, antibiotic resistance has shifted beyond hospital settings, affecting community-acquired infections. Drugs such as amoxicillin and azithromycin, once mainstays of outpatient care, are showing reduced effectiveness due to resistance proliferation driven by inappropriate or excessive use [11]. Community-acquired drug resistance not only compromises treatment efficacy but also magnifies transmission risks, thereby deepening the crisis. The global pipeline remains thin, with most new drugs being just modified versions of odd ones rather than truly novel discoveries [12]. Innovation in antibiotic discovery has stagnated, with most new drugs being modifications of existing ones rather than novel classes. Horizontal gene transfer (HGT) further exacerbates this problem, allowing bacteria to acquire resistance genes via mobile genetic elements such as plasmids, transposons, and integrons. It allows even non-pathogenic strains to become reservoirs of resistance genes, facilitating rapid spread within microbial communities and healthcare environments, enabling rapid dissemination of resistance traits across species and environments [13]. Perhaps the most alarming shortcoming lies in the stagnation of antibiotic innovation. The global antibiotic development pipeline remains sparse and dominated by reformulations of older agents rather than novel classes WHO reports that Gram-negative

bacteria are becoming resistant much faster than new antibiotics can be developed, leading to a growing innovation gap. Because antibiotic research is costly, tightly regulated and offers limited economic return, major pharmaceutical companies have reduced investment [14]. Consequently, healthcare systems are being forced to depend on decades-old-drugs, many of which are losing their effectiveness andputting the world at serious risk of rising AMR-related deaths by 2050 if current trends continue [15] . In regions with underdeveloped health infrastructure, particularly in South Asia, Africa, and the Eastern Mediterranean, resistance affects one in three bacterial infections, severely undermining infection control and treatment accessibility [16]. Such disparities highlight that AMR is not merely a microbiological problem but a global equity and health-systems-crisis. Furthermore, most "new" antibiotics introduced in recent decades are merely just chemical modifications of older classes (e.g., β-lactams, macrolides), targeting the same cellular pathways that bacteria have already adapted to resist. The absence of novel mechanisms of action and molecular targets limits long-term efficacy and accelerates cross-resistance to develop rapidly [17]. A critical yet often overlooked limitation is weak antibiotic governance, particularly in developing regions that allows non-prescription sales and inappropriate use in both humans and livestock. Such Over-the-counter antibiotic sales and unregulated agricultural use continue to accelerate the resistance crisis intensifying selective pressure on bacteria and propagate resistance globally [18]. Pharmacokinetic and pharmacodynamic limitations also hinder antibiotic efficacy like poor absorption, low bioavailability, biofilms, limited tissue penetration, and inadequate drug concentration at infection sites often lead to incomplete bacterial clearance often diminishes antibiotic effectiveness. Additionally, sub-therapeutic drug concentrations at the infection site promote the selection of resistant mutants [19]. Compounding this, environmental contamination through medical and agricultural waste introduces antibiotic residues into soil and aquatic systems, promoting resistance even outside clinical settings. Large amounts of antibiotic residues enter aquatic and soil ecosystems through pharmaceutical discharge, hospital waste, and agricultural runoff. These residues create environmental "hotspots" for resistance development among soil and water microbiota, which can later transfer resistance genes to human pathogens. The antibiotics we rely on today are struggling to keep pace with bacterial evolution. Many possess a limited range of effectiveness and can cause harmful side effects and are losing their power as resistance spreads across communities. At the same time new drug development has slowed down, creating a dangerous gap in our ability to fight infections. To tackle this growing crisis, we need a united global effort - stronger antibiotic stewardship, better diagnostic tools, incentives for new drug research and firm policies that can help protect the effectiveness of antibiotics for the generation to come. Collectively, these challenges highlight the urgent need for coordinated global strategies that integrate antibiotic stewardship, rapid diagnostics, and renewed innovation to preserve the effectiveness of antimicrobial therapy for future generations. This global rise of antimicrobial resistance and the stagnation of new antibiotic development have accelerated the search for safer, natural alternatives.

In this context, flavonoid phytochemicals, a diverse group of plant-derived polyphenols, have gained increasing attention as promising antimicrobial candidates. These compounds exhibit broad-spectrum antibacterial activity and act through multiple mechanisms, including disruption of microbial membranes, inhibition of nucleic acid and protein synthesis, efflux pump suppression, and interference with biofilm formation [20,21]. Their multitargeted nature reduces the likelihood of rapid resistance development and offers a biologically inspired route to restoring therapeutic efficacy. Recent studies have also demonstrated that flavonoids can synergize with conventional antibiotics, enhancing their effectiveness against multidrug-resistant pathogens [22]. Thus, as conventional antibiotics lose their potency, exploring plant-based flavonoids represents a sustainable and innovative approach to bridging the current antimicrobial innovation gap and combating the global resistance crisis. With this background, the present review article is aimed to improve our understanding of flavonoids as a promising reservoir of novel antibiotic discovery.

Table 1. Major Flavonoid Phytochemicals with Reported Antibacterial Activity and Mechanisms of Action

Flavonoid (Subclass)	Natural Source(s)	Target Microorganisms	Proposed Mechanism(s) of Action	Reported MIC Range	Synergistic/Notable Features	Ref
Luteolin (Flavone)	Celery, thyme, green peppers	S. aureus, E. coli, K. pneumoniae	Membrane permeability alteration, inhibition of protein synthesis, anti-quorum sensing	16–128 µg/mL	Anti-biofilm; synergises with aminoglycosides in some reports.	[70,71,33]
Myricetin / Quercetin / Kaempferol	Berries, tea, walnuts	S. aureus, E. coli, P. aeruginosa, K. pneumoniae	Inhibits nucleic acid enzymes (DNA gyrase), membrane disruption, ROS induction	8–128 µg/mL	Efflux pump modulation; biofilm inhibition.	[72,73 74,63]
Morin (Flavonol)	Guava leaves, figs, almonds	E. coli, S. aureus, B. subtilis	Cell envelope disruption, oxidative stress induction, anti-quorum sensing	32–200 µg/mL	Biofilm modulatory activity.	[75,76]
Naringenin (Flavanone)	Citrus, tomato skin	S. aureus, E. coli, V. cholerae	Membrane perturbation, motility reduction, quorum sensing inhibition	31–250 µg/mL	Synergy with β-lactams/quinolones; anti-biofilm.	[77, 78,79]
Phloretin (Chalcone/dihydrochalcone)	Apple, pear, apple leaves	S. aureus, E. coli, P. aeruginosa	Membrane disruption, inhibits energy metabolism, reduces adhesion	16–128 µg/mL	Synergistic with vancomycin/β-lactams in some models.	[80, 81]
6-Amino-flavone (6-AF) (Flavonoid derivative)	Synthetic / semi-synthetic derivative	S. aureus, E. coli	Enzyme inhibition (putative gyrase/topoisomerase interference), membrane effects reported in vitro	8–64 µg/mL (screening data)	Derivative designed to enhance activity / drug-like properties.	[82]
3,2-Dihydroxyflavone (3,2-DHF) (Derivative)	Synthetic / plant-derived analogs	S. aureus, E. coli	ROS generation, membrane perturbation, enzyme inhibition (screening)	16–128 µg/mL (reported ranges)	Investigated as lead scaffold for optimisation.	[83]
2,2-Dihydroxy-4-methoxybenzophenone (DHMB) (Derivative)	Synthetic / plant derivative	Gram-positive / Gram-negative screening panels	Disrupts membrane integrity and metabolic pathways (in vitro)	16–128 µg/mL (screening)	Investigated as antibacterial benzophenone-flavonoid hybrid.	[84,85]
Total Flavonoids of Potentilla kleiniana (TFP)	Potentilla kleiniana (leaf/flower extracts)	S. aureus, E. coli, V. parahaemolyticus	Multimodal: membrane disruption, enzyme inhibition, inhibits motility/biofilm (extract-level effects)	Extract MICs reported 50–400 µg/mL (depending on fraction)	Fractionation yields active constituents; strong anti-biofilm activity reported.	[86,87]
Fisetin (Flavonol)	Strawberries, apples, persimmon	S. aureus,E. coli,B. subtilis	DNA gyrase inhibition, ROS induction, membrane effects	16–128 µg/mL	Reported antibacterial and anti-biofilm properties; antioxidant/host-modulatory activities.	[88,91]

Scutellarein (Flavone)	Scutellaria species, some medicinal herbs	S. aureus,E. coli	Inhibits bacterial enzymes, membrane destabilisation, anti-virulence effects	16–128 µg/mL	Reported synergy with β-lactams in vitro.	[89,90]
Licochalcone A (Chalcone)	Licorice root (Glycyrrhiza spp.)	MRSA,S. aureus,H. pylori	Disrupts membrane, inhibits cell wall biosynthesis enzymes, anti-biofilm	4–64 µg/mL	Notable anti-MRSA activity and β-lactam potentiation.	[92]
Galangin (Flavonol)	Alpinia officinarum, propolis	S. aureus,E. coli,H. pylori	Membrane damage, enzyme inhibition (glycolysis/energy pathways), anti-biofilm	8–128 µg/mL	Synergises with antibiotics vs Gram-positives.	[93]
Rutin (Flavonol glycoside)	Buckwheat, citrus peels	S. aureus,P. aeruginosa, A. baumannii	ROS generation, membrane depolarisation, metal complexation can enhance photodynamic killing	25–150 µg/mL	Rutin–Ga^{3+} photodynamic complexes show enhanced bactericidal activity.	[94,95]
Chrysoeriol (Flavone methylated)	Celery, oregano, some herbs	S. aureus,E. coli	Membrane perturbation, inhibits virulence factor expression	32–200 µg/mL	Methylation affects lipophilicity and activity.	[96]
Chrysosplenetin (Flavone derivative)	Certain medicinal plants (Asteraceae)	Gram-positive and Gram-negative screening panels	Enzyme inhibition, membrane effects (in vitro)	16–200 µg/mL	Reported antibacterial and antiparasitic effects in some studies.	[97]
Sophoraflavanone G (prenylated flavanone)	Sophora spp.	MRSA, S. aureus, Gram-negative screening	Strong membrane disruption, efflux pump inhibition, targets cell wall/peptidoglycan synthesis	2–32 µg/mL	Potent anti-MRSA activity; prenylation increases potency and lipophilicity.	[98]
Epicatechin gallate (ECG, Flavan-3-ol)	Green tea, cocoa	MRSA, E. coli,P. aeruginosa	Membrane disruption, FtsZ inhibition, efflux pump modulation	8–128 µg/mL	Related to EGCG; synergistic with β-lactams and aminoglycosides.	[99,100]
Dihydrochalcones (class; e.g., phloretin derivatives)	Apple family, some medicinal plants	S. aureus,E. coli,P. aeruginosa	Membrane disruption, energy metabolism inhibition, anti-adhesion	16–256 µg/mL (varies by derivative)	Certain derivatives show strong antibiofilm action.	[80, 101]
Chrysin (Flavone)	Propolis, passionflower	S. aureus,B. subtilis, E. coli	Inhibits cell wall biosynthesis, reduces virulence gene expression	25–150 µg/mL	Synergistic interactions reported with fluoroquinolones.	[102]
Biochanin A (Isoflavone)	Red clover, chickpea	S. aureus,E. coli, urinary pathogens	Inhibits nucleic acid synthesis, membrane effects	16–128 µg/mL	Isoflavone with reported antibiotic-potentiating properties.	[103]
Genistein (Isoflavone)	Soybean, legumes	E. coli,S. aureus,M. smegmatis	Inhibits DNA gyrase/ATP synthase, affects division	25–200 µg/mL	Reported structural similarity to fluoroquinolones' activity; potentiates	[104]

					antibiotics in some studies.	
5′-Methoxyhydnocarpin D (Flavonolignan)	Hydnocarpus, Berberis allied plants	Enhances activity of berberine and other antimicrobials vs S. aureus, E. coli	Efflux pump inhibitor (not strongly antibacterial alone — acts as resistance-modifier)	NA (active as adjuvant at low µg/mL)	Known as an efflux pump inhibitor that potentiates berberine; key example of adjuvant action.	[105]

Table 1: The spectrum of flavonoid phytochemicals exhibiting potent antibacterial activities through diverse mechanisms. These include inhibition of bacterial cell wall synthesis, disruption of cytoplasmic membranes, suppression of nucleic acid and protein synthesis, and interference with bacterial efflux pumps and quorum sensing systems. Representative compounds such as quercetin, luteolin, kaempferol, myricetin, apigenin, and naringenin demonstrate strong efficacy against both Gram-positive and Gram-negative pathogens, including Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Bacillus subtilis. Flavonoid derivatives like 6-amino-flavone, 3,2-dihydroxyflavone, and DHMB, along with complex plant extracts such as total flavonoids of Potentilla kleiniana, further expand the therapeutic scope by enhancing bacterial membrane permeability and modulating oxidative stress. Overall, the table highlights the multifaceted antibacterial potential of natural flavonoids and their derivatives, emphasizing their relevance as lead compounds for novel antibiotic development.

II. MECHANISMS OF ANTIMICROBIAL ACTION BY FLAVONOIDS

a. Inhibition of Biofilm formation

Biofilms are one of the most unique properties of bacteria, which significantly contribute to antimicrobial resistance. Biofilm formation differentiates these bacteria from other microbes, showing major changes in genetic and protein expressions [23]. Biofilm formation encases these microbial communities in self-producing extracellular polymeric substance (EPS), which is composed of polysaccharides, proteins, lipids and extracellular DNA. These unique features protect the resistant cells from environmental stresses as well as host immune response and often show signs of slowed metabolism, activated stress responses, along enhanced horizontal gene transfer. Therefore, antibiotics or antimicrobials, which usually show high activity on actively metabolizing cells, fail to act on non-metabolizing or biofilm-associated microbial communities [24], thus making biofilm synonymous with persistent and chronic infections. Biofilms comprise of communities of aggregation of bacterial cells (less than 10% of the dry mass) embedded in the EPS, which comprises about 90% of the total biofilm [25], making one of the root causes of life-threatening infection causing diseases. Biofilm formation is found in diseases causing bacteria, including both gram-positive and gram-negative bacteria, like Escherichia coli, Mycobacterium tuberculosis, Bacillus subtilis, Staphylococcus aureus, Klebsiella penumoniae, and Helicobacter pylori. Some specific ecological conditions, like stress, temperature, and nutrient limitation, initiate bacteria biofilm formation by activation of quorum sensing as well as some particular genetic expression. Along with providing protection and structural stability, the biofilm matrix entraps antimicrobials, forms complexes via chelating with antibiotics eventually degrades with the enzymes of the biofilm matrix. This is one of the classic methods by which biofilm successfully inhibits antimicrobials and antibiotic activity. Therefore, such antimicrobials are required that can successfully penetrate or diffuse through EPS without interacting with the EPS components.

Plant-derived antimicrobials like flavonoids have immense potential in inhibiting biofilms or acting on biofilm-associated bacteria, along with being eco-friendly, cost-effective and having no side effects. Many researchers till now have shown positive results of flavonoids inhibiting biofilm-forming bacteria. Flavone luteolin and flavonols, myricetin, morin, and quercetin are found to reduce the extracellular matrix of biofilm in Escherichia coli microcolony biofilms

[26]. Another mention can be found of the flavone naringenin and the chalcone phloretin, which significantly inhibit growth in the case of Bacillus subtilis. It is noteworthy to mention, all plant flavonoids don't generally show antimicrobial activity, but they are highly species specific. Although the exact mechanisms of different flavonoid actions on biofilm inhibition is still not known, there are various methods by which flavonoids regulate and inhibit bacterial biofilm and growth. The amyloid curli fibers and pEtN-cellulose are two of the major EPS components involved with bacterial attachment and biofilm formation, and some flavonoids show specific anti-amyloidogenic activities by interfering with the assembly of CsgA subunits into amyloid fibers, which results in the reduction of enteric biofilms [26]. Apart from these flavonoids, some flavonoid derivatives like 6-aminoflavone (6-AF), 3,2-dihydroxyflavone (3,2-DHF) and 2,2-dihydroxy-4-methoxybenzophenone (DHMB) have shown active biofilm initiation and suppression of virulence properties in the case of one of the most high-risk food-borne pathogens, Vibrio parahaemolyticus [27]. These flavonoid derivatives exert antibacterial and antibiofilm activities as well as interfere with metabolic activity, cell division, and membrane permeability of cells of Vibrio mixed species, Salmonella typhimurium, V. harveyi, and Staphylococcus aureus [27]. Total flavonoids of Potentilla Kleiniana Wight et Arn (TFP) have also shown successful antibiofilm and antimicrobial activities against a common opportunistic pathogen (Pseudomonas aeruginosa) via damaging cell membrane integrity, bacterial motility and virulence factors [28]. Other common mentions of secondary metabolites found in fruits and vegetables showing antibiofilm activities are fisetin and phloretin in the case of Acinetobacter baumanii, morin in case of Vibrio cholera [27]. Another interesting finding is the inhibition of biofilm by citrus flavonoid naringenin on Staphylococcus aureus ATCC 6538 where the flavonoid was successfully downregulating the expression of biofilm related genes. This in turn caused significant reduction in EPS production and surface hydrophobicity, two of the most vital contributing factors of biofilm formation [29]. Naringenin is a common flavonoid present in bergamot peel and found to inhibit various organisms, including E. coli, Salmonella enteritidis, Pseudonomas putide, Lactococcus lactis at minimum inhibitory concentrations [29]. Biofilm associated bacteria are known to cause havoc in oral hygiene and diseases like dental caries. Common antimicrobial compounds such as chlorhexidine or antimicrobial peptides, which are used in the case of oral healthcare, have plenty of limitations, including side effects and development of AMR. Cariogenic oral pathogen Streptococcus mutans has resistance mechanisms by developing biofilms. These pathogenic bacteria use some virulence enzymes like glucosyl transferase (Gtfs) and fructosyltransferase (Ftf) and synthesise eztra polysaccharides from dietary sugars. This sucrose is in turn converted to water soluble glucans (WSG) and water insoluble glucans (WIG) by Gtfs and hence produces biofilm matrix [30]. The natural flavonoid phloretin found in fruits like apple, pear etc, reduces expression of gtfB and gtfC genes, thus decreasing EPS/bacteria and WIG/WSG ratio [30]. Another research shows the efficacy of flavonoids rich Ziziphus jujuba (FZM) mill. Extract for inhibiting biofilm formation by Staphylococcus aureus and can successfully penetrate the biofilm matrix and act on the bacteria [31]. The flavonoids like quercetin, myricetin, and scutellarein have shown promising results in decreasing biofilm in case of Staphylococcus aureus via targeting Biofilm-Associated-Protein (Bap), which assembles the amyloid-like structure for biofilm formation [32]. Flavonoids also hold the potential to exhibit synergistic interactions with conventional antibiotics and open new avenues to treat MDR bacteria. Biofilm-associated infections nevertheless remain one of the formidable challenges in the fight against AMR and naturally occurring polyphenolic compounds like flavonoids have emerged as promising and versatile antibiofilm and anti- virulence agents.

b. Inhibition of the synthesis cell membrane and nucleic acid

Bacterial multidrug resistance (MDR) arises primarily from modifications that protect the cell envelope and genetic machinery from antibiotics. MDR strains such as Staphylococcus aureus, Pseudomonas aeruginosa, and Klebsiella pneumoniae develop through target mutations, enzyme secretion, and active efflux systems that expel drugs before they reach lethal concentrations [33,34]. The lipid bilayer of Gram-negative bacteria, reinforced by lipopolysaccharides and porins, acts as a selective barrier limiting

hydrophobic antibiotic penetration, while Gram-positive organisms thicken their peptidoglycan to delay uptake [35,36]. Simultaneously, genetic defense involves alterations of DNA gyrase and topoisomerase IV, the primary antibiotic targets, reducing binding affinity [20]. Collectively, these membrane-stabilizing and nucleic-acid-protective adaptations enable bacteria to survive a wide spectrum of antimicrobial agents.

Flavonoids exert antibacterial effects through dual interference with bacterial envelopes and nucleic-acid-related enzymes. Their amphipathic polyphenolic structures insert into lipid bilayers, increasing membrane permeability, dissipating proton gradients, and causing leakage of ions and metabolites [37,38]. Electron-donating hydroxyl groups and hydrophobic aromatic rings disrupt lipid packing, leading to morphological deformation and cytoplasmic disorganization [39]. In addition, flavonoids bind to membrane proteins such as ATP-synthetase, leading to energy depletion and cellular collapse [38].

At the nucleic-acid level, many flavonoids chelate metal ions essential for DNA-dependent enzymes or directly interact with the DNA double helix. Planar rings of compounds like quercetin and luteolin intercalate between base pairs, hindering replication and transcription [40,20]. Others inhibit bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, preventing supercoiling and segregation of genetic material [39,41]. These effects compromise cell division and genomic stability, ultimately leading to bacteriostasis or death.

Several structurally distinct flavonoids have been identified with potent activity against these two critical bacterial systems. Quercetin, a flavonol abundant in Allium cepa and Ginkgo biloba, destabilizes the cytoplasmic membrane and inhibits DNA gyrase and RNA polymerase, exhibiting broad efficacy against both Gram-positive and Gram-negative bacteria [40]. Epigallocatechin gallate (EGCG) from green tea binds to lipid bilayers and cell-wall peptidoglycan, while also suppressing nucleic-acid synthesis by interfering with ATP-dependent enzymes [20]. Luteolin and apigenin, typical flavones, form complexes with bacterial membranes, causing permeability alterations and inhibiting DNA and RNA polymerases [38,37]. Kaempferol and myricetin display strong inhibition of DNA gyrase catalytic subunits by binding to the ATP-binding pocket, comparable to fluoroquinolones [41]. Moreover, chalcones such as licochalcone A disrupt membrane potential and block nucleic-acid biosynthesis enzymes simultaneously, yielding synergistic bacteriostatic outcomes [20].

The inhibition of cell-membrane and nucleic-acid synthesis by flavonoids carries broad biomedical and ecological implications. First, these dual-action compounds target multiple bacterial pathways simultaneously, limiting the likelihood of resistance emergence [39,36]. Second, their natural origin and low toxicity make them ideal candidates for integration into antimicrobial coatings, food preservatives, and adjunct therapies with conventional antibiotics [41]. Synergistic interactions—such as quercetin with colistin or EGCG with tetracycline—restore antibiotic sensitivity in MDR strains by weakening membrane integrity and disabling efflux mechanisms [20]. Furthermore, by disrupting both envelope and nucleic-acid functions, flavonoids impose an energetic burden on bacteria, leading to oxidative stress and eventual cell death [37].

Consequently, flavonoids represent a sustainable route to counter antibiotic resistance through mechanisms distinct from traditional drugs. Their structural diversity allows chemical modification for improved bioavailability and potency, as recent nano-formulations have enhanced stability and cellular uptake [41]. Continued research integrating molecular docking, transcriptomic profiling, and delivery engineering will be essential to translate these plant-derived molecules into next-generation antibacterial therapeutics.

c. Inhibition of bacterial toxins

Bacterial toxins are harmful substances generated by bacteria which cause injury to host tissues either directly or by triggering strong immune responses as well as they can act locally at the site of infection or spread throughout the body leading to systemic effects. The mechanisms through which bacterial toxins act are enzymatic interference with host cell metabolism, destruction of host cell membranes and activation of immune cells that trigger tissue-damaging inflammatory responses. Endoxins, which are generated by gram-negative bacteria and Exotoxins, which are generated by gram-positive and a small number of gram-negative bacteria are the two main types of bacterial toxins [42].

Flavonoids, which are a significant group of plant secondary metabolites with a Polyphenolic structure, help to inhibit the growth of bacteria [43,41]. Many MDR (Multi Drug Resistance) mechanisms like overexpressed efflux pumps, altered membrane permeability, biofilm formation, toxin production decreases the effectiveness of antibiotics. Flavonoids simultaneously target several of these by inhibiting bacterial efflux pumps, increasing membrane permeability, disrupting biofilms and down-regulating virulence/toxin gene expression and thus producing measurable antibiotic potentiation in vitro and in vivo. Thus, Flavonoids are attractive antibiotic-potentiating adjuvants for combating MDR infections [44]. Flavonoids target both toxin production and their activities by several interconnected mechanisms like flavonoids can interact directly with bacterial toxins (like α-hemolysin) by altering their conformation or preventing their polymerization into functional pores and thus neutralizing toxin activity. For example, Myricetin prevents polymerization of Staphylococcus aureus α-hemolysin (αHL) monomers into active pores and directly neutralizes the toxin's haemolytic activity [45]. Flavonoids can modify host cell membranes to increase resistance against bacterial toxins. For example, lipophilic flavonoids such as quercetin incorporate into erythrocyte membranes, enhance the rigidity of the inner lipid layer and fluidize the outer layer and thereby making the membrane more resistant to toxin insertion and pore formation by Staphylococcus aureus α-hemolysin [45]. Flavonoids suppress the transcription of toxin genes and thereby lowering toxin production without necessarily killing the bacterium. For example, kaempferol has been shown to down-regulate the Hla (α-hemolysin) gene responsible for α-hemolysin production in Staphylococcus aureus [46]. Flavonoids interfere with QS (Quorum sensing) systems and in this way reduce toxin secretion and virulence factor expression. Since biofilm formation of bacteria increases toxin expression, flavonoids possess anti-biofilm effects that lead to a reduction in toxin production [41].

d. Inhibition of bacterial efflux pumps

The rise of multidrug-resistant (MDR) bacterial infections represents a major global health challenge, primarily driven by the overexpression of efflux pumps that expel antibiotics and toxic compounds out of bacterial cells, thereby reducing intracellular drug concentrations and compromising therapeutic efficacy. Efflux pumps are among the most important resistance mechanisms, capable of extruding diverse substrates including β-lactams, fluoroquinolones, macrolides, and tetracyclines. They are broadly categorized into five major families Major Facilitator Superfamily (MFS), ATP-Binding Cassette (ABC), Small Multidrug Resistance (SMR), Resistance-Nodulation-Division (RND), and Multidrug and Toxic Compound Extrusion (MATE) based on structural organization, substrate specificity, and energy utilization. A sixth family, the Proteobacterial Antimicrobial Compound Efflux (PACE) family, has also been described [9,47]. Among these, the AcrAB–TolC complex in Escherichia coli and MexAB–OprM in Pseudomonas aeruginosa are the most widely studied multidrug transporters, playing a crucial role in resistance to multiple antibiotic classes [9,49,50].

Efflux pumps are transmembrane protein complexes responsible for the active extrusion of a wide range of xenobiotics, including antibiotics, dyes, and detergents, thereby maintaining bacterial homeostasis under stress. These systems differ in their energy sources some rely on ATP hydrolysis (ABC family), while others use proton motive force or sodium ion gradients (MFS, RND, MATE, SMR). Notably, the RND-type systems, such as AcrAB–TolC, are tripartite complexes spanning both inner and outer membranes, contributing significantly to MDR in Gram-negative pathogens [9,47]. Thus, targeting efflux activity represents a promising strategy to restore intracellular drug accumulation and re-sensitize resistant pathogens to conventional antibiotics.

Flavonoids, a diverse class of naturally occurring plant-derived polyphenols, have gained significant attention as natural efflux pump inhibitors (EPIs). Evolved as part of the plant defense system, these compounds enhance the antimicrobial efficacy of phytochemicals by targeting bacterial efflux mechanisms [51,52]. Their mechanisms of action include (i) direct binding to efflux transporter proteins, (ii) disruption of membrane energetics such as the proton motive force, and (iii) transcriptional repression of efflux-related genes. Molecular docking and biochemical studies reveal that flavonoids like quercetin, genistein, and baicalein interact with efflux proteins such as NorA in Staphylococcus aureus and AcrB in E. coli, competitively blocking substrate transport [53,41]. Epigallocatechin gallate (EGCG), a

flavan-3-ol from Camellia sinensis, disrupts the proton motive force required for energy-dependent efflux, thus increasing intracellular antibiotic accumulation [54,55]. Apigenin, chrysoeriol, and chrysosplenetin, in turn, downregulate norA expression in S. aureus, further reducing efflux activity [41,56]. These actions collectively increase intracellular drug concentrations, restore antibiotic sensitivity, and significantly reduce the minimum inhibitory concentration (MIC) of several antibiotics.

Beyond these general mechanisms, structural variations among flavonoids define their efflux-inhibitory potency. Chalcones like phloretin and dihydrochalcones inhibit NorA pumps in S. aureus, increasing norfloxacin uptake [44]. Flavan-3-ols such as EGCG and epicatechin gallate inhibit CmeABC/CmeDEF in C. jejuni and NorA in S. aureus, reducing MICs of tetracycline and chloramphenicol [47,56]. Flavanones including naringenin, hesperetin, and sophoraflavanone G synergize with fluoroquinolones and suppress norA expression [44]. Flavones like apigenin and baicalein downregulate norA and tetK genes, restoring antibiotic efficacy [41]. Flavonols such as quercetin, kaempferol, and galangin inhibit RND/MFS pumps (AcrAB–TolC, AcrB) in E. coli and K. pneumoniae, enhancing ciprofloxacin and meropenem accumulation [47,57] . Flavonolignans like 5′-methoxyhydnocarpin D boost berberine retention in S. aureus [44], while Isoflavones such as biochanin A and genistein show strong binding to AcrB and MexB, suggesting broad Gram-negative inhibition [38,49]. Further, morin and kaempferol suppress acrA and tolC expression in E. coli and P. aeruginosa, reducing multidrug tolerance [57]. Naringenin and chrysin interfere with ATPase activity in K. pneumoniae and E. faecalis, disrupting energy-driven efflux [58]. Morin also enhances intracellular antibiotic retention [28]. Additionally, rutin and genistein interact stably with Rv1258c efflux transporters in M. tuberculosis, decreasing persistence [59]. Polyphenols from Terminalia spp. also inhibit efflux activity and induce ROS in gut pathogens [60].

An important advantage of flavonoid-based efflux inhibition lies in their low cytotoxicity and strong synergistic potential with conventional antibiotics. Several flavonoids–antibiotic combinations have demonstrated enhanced antibacterial efficacy, such as quercetin–ciprofloxacin and epigallocatechin gallate (EGCG)–β-lactam pairings, which significantly reduce bacterial viability and restore drug potency in resistant strains [53,54]. Co-administration of flavonoids with β-lactams or fluoroquinolones has been shown to reduce antibiotic MICs by up to eightfold in resistant strains [61]. This dual function—as resistance modulators and direct antimicrobials—offers a sustainable, biologically inspired strategy to restore antibiotic efficacy. Nonetheless, limitations such as poor aqueous solubility, rapid metabolism, and low bioavailability hinder clinical applications [41]. To address these, ongoing research focuses on nanoformulations, liposomal encapsulation, prodrug design, and structure–activity relationship (SAR) optimization to enhance pharmacokinetics and target engagement [56].

From an evolutionary perspective, the ability of plants to synthesize efflux-inhibiting flavonoids represents a natural adaptive strategy in the biochemical arms race between plants and microbes. As bacteria evolved efflux systems to evade phytochemical toxicity, plants in turn developed secondary metabolites capable of inhibiting those same systems, maintaining antimicrobial potency [47,56]. These co-evolutionary dynamic highlights the promise of flavonoid-based EPIs as adjuncts to antibiotic therapy. With growing molecular, proteomic, and in silico evidence [12,41], flavonoids hold strong potential as next-generation adjuvants to combat MDR infections and restore the therapeutic efficacy of existing antibiotics. Future work integrating computational docking, omics-based screening, and formulation science will be pivotal to translate these natural inhibitors into clinical use.

e. Antimicrobial action through ROS production

Flavonoids, one of the major groups of polyphenolic compounds, are known for their strong antioxidant and antimicrobial activities. Their antimicrobial action is closely related to their ability to modulate reactive oxygen species generation within microbial systems. Antioxidants, of which flavonoids form part, in preventing diseases that involve oxidative stress, are supported by literature studies showing their effect on halting cellular damage and the development of disease. Free radicals, or reactive oxygen species, are highly unstable molecules produced by living organisms, part of routine cellular metabolism. When the balance between oxidants and antioxidants is tilted towards oxidants, this is what is known as oxidative stress [62]. Flavonoids are effective antioxidants with

a variety of mechanisms contributing to their efficiency in neutralizing free radicals and preventing oxidative damage in the body. In microbial systems, excessive generation of ROS can damage membranes, proteins, and DNA, impairing cellular integrity and viability. Flavonoids exert their effects as free radical scavengers; they neutralize reactive oxygen species through their hydrogen atoms or electrons. Besides this, they have metal chelation properties. They bind to transition metals such as iron and copper, which would otherwise catalyze the generation of free radicals and, by this action, inhibit metal-induced oxidative stress. Reducing the availability of these redox-active metals inhibits microbial cells from generating hydroxyl radicals via Fenton reactions, hence reducing oxidative damage that sustains microbial metabolism and virulence. They can also inhibit the activity of enzymes that produce reactive species, such as xanthine oxidase and NADPH oxidase. This reduces the amount of ROS generated and impairs microbial redox homeostasis.

ROS can be generated in biological systems by exogenous and/or endogenous sources. Exogenous sources of ROS include high-energy radiation (X-rays, neutrons), chemotherapy, heavy smoking, heavy alcohol consumption, and other factors. Living systems produce endogenous ROS as a natural by-product of aerobic metabolism. Mitochondrial respiration is considered to be the primary endogenous source of ROS. ROS are also formed by a variety of enzymes such as xanthine oxidase, NADPH oxidases (NOXs), nitric oxide synthase (NOS), and others. The overproduction of ROS/reactive nitrogen species (RNS) is responsible for oxidative damage to all major cellular components, including biological membranes, proteins, and DNA. This state is termed oxidative stress/nitrosative stress and is the common denominator of many chronic diseases and aging. [63]. In microbial cells, oxidative stress plays a very critical role in the regulation of virulence, biofilm formation, and resistance mechanisms. The ability of flavonoids to suppress ROS production interferes with these oxidative pathways, thus weakening microbial defenses. Enhanced ROS/RNS formation, together with increased levels of redox metals (copper, iron) due to disturbed metal homeostasis, may have detrimental effects on all important biomolecules, such as proteins, lipids, and DNA. ROS/RNS-induced damage of lipids involves lipid peroxidation, which results in the formation of mutagenic compounds such as 4-hydroxynonenal (HNE) and malondialdehyde (MDA). ROS-induced DNA damage involves the formation of 8-oxo-7,8-dihydroguanine (8-oxo-guanine), a product of DNA interaction with hydroxyl radicals. An extensive amount of hydroxyl groups in the molecular skeleton of flavonoids, for example, quercetin, plays an important role in their radical scavenging and metal-chelating properties (Cu, Fe) manifested by suppressed ROS formation. [64].

Flavonoids like epigallocatechin-3-gallate (EGCG), quercetin, ,kaempferol , apigenin, luteolin and other like them modulate ROS through several specific mechanisms: EGCG may behave as a direct antioxidant through the chelation of transition metals-iron and copper-that catalyze the formation of ROS and function as a radical scavenger via hydrogen atom transfer (HAT) or single electron transfer (SET) reactions, mediated by its ortho-dihydroxyl and galloyl groups [65] .Moreover, EGCG inhibits the activities of ROS-producing enzymes such as NADPH oxidase, xanthine oxidase, COX-2, and iNOS, thus decreasing oxidative and inflammatory stress. Collectively, flavonoids regulate ROS through radical scavenging, inhibition of pro-oxidant enzymes, and modulation of redox-sensitive signaling pathways [62,64].

Quercetin has been demonstrated to possess significant antioxidant potential through various pathways that involve the regulation of GSH levels, modulation of key signaling pathways, and direct scavenging of ROS. It enhances endogenous antioxidant defense by stimulating enzymes like superoxide dismutase (SOD), catalase, and glutathione reductase, thus maintaining the balance of redox and preventing the induction of cellular injury by oxidative stress. Quercetin has also been shown to influence some crucial signaling pathways, including MAPK, NF-κB, AMPK, and PI3K/AKT, which cumulatively enhance the cellular antioxidant capacity and suppress the processes of inflammation, apoptosis, and mitochondrial dysfunction. In addition, quercetin directly scavenges ROS and reactive nitrogen species, thus protecting the biological systems from UVB-induced skin damage, PM2.5-related respiratory injury, radiation toxicity, and neurodegenerative oxidative stress. It prevents lipid peroxidation, stabilizes mitochondrial membranes, and restores redox homeostasis across tissues. Thus, with the

integration of enzymatic activation, gene regulation, and direct radical scavenging, quercetin acts as a multitarget antioxidant molecule against ROSmediated oxidative damage. [66]

Kaempferol is a polyphenolic flavonoid with powerful antioxidant and anti-inflammatory activities, suggesting its anti-atherosclerotic and cytoprotective properties. Indeed, mechanistically, kaempferol enhances the antioxidant defense by scavenging free radicals, inhibiting the activity of reactive oxygenase, and inducing antioxidant enzymes such as SOD and HO-1. It reduces the injury of oxidative stress through activation of the NRF2 signaling pathway, which maintains redox homeostasis and lowers intracellular accumulation of ROS. The activation of NRF2 suppresses pyroptosis mediated through NLRP3 inflammasome, thereby preventing the inflammatory cell death driven by ROS. Furthermore, kaempferol suppressed the MAPK pathway in LPS-stimulated monocytes, leading to decreased production of inflammatory mediators like MDC and IL-8. These combined actions reduce oxidative stress and inflammation along with lipid peroxidation, hence supporting vascular protection and reducing atherosclerosis risk. Generally, the regulation of ROS with NRF2/HO-1 and inhibition of the activation of NLRP3 inflammasome identify kaempferol as a potential therapeutic agent in oxidative stress-related inflammatory disorders. [67]

Apigenin, a natural flavonoid, shows protective effects against vitiligo by mitigating oxidative stress-induced melanocyte damage through modulation of critical antioxidant signaling pathways. Vitiligo is primarily linked to the loss of melanocytes that results from oxidative stress, which is characterized by an excessive accumulation of ROS that leads to DNA damage, disruption of melanin synthesis, and the induction of melanocyte apoptosis. Apigenin activates the Nrf2/ARE signaling pathway, an important cellular defense mechanism against oxidative damage. Following oxidative stimulation, apigenin leads to the dissociation of Nrf2 from Keap1, thereby facilitating its nuclear translocation and subsequent activation of downstream antioxidant genes like HO-1, GCL, and NQO1, thus enhancing cellular redox balance. The PI3K/Akt/mTOR pathway mediated by apigenin supports melanocyte survival and melanogenesis under conditions of oxidative stress. As a result, apigenin has effectively reduced the generation of ROS, recovered the activity of antioxidant enzymes, and hindered melanocyte apoptosis, thus contributing to repigmentation and recovering normal melanocyte functioning in lesions of vitiligo [68].

Luteolin is a naturally occurring flavonoid compound that exerts effective antioxidant activity by regulating different pathways to protect against ROS-induced cell injury. It increases the intrinsic antioxidant defense by upregulating the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1). Luteolin itself scavenges the free radicals and reduces the intracellular generation of ROS by inhibiting NADPH oxidase and other ROS-producing enzymes. Furthermore, it activates the Nrf2 pathway, inducing nuclear translocation of Nrf2 followed by subsequent transcription of various antioxidant response genes, thereby restoring the cellular redox balance. Thus, luteolin protects cells against oxidative damage, lipid peroxidation, and mitochondrial dysfunction, maintaining membrane integrity and inhibiting apoptosis. Altogether, the dual action of luteolin-direct scavenging of free radicals and indirect induction of cellular antioxidant defenses-provides impressive protection against oxidative stress and ROS-induced cell injury.[69].

In this respect, flavonoids act in a bidirectional manner: they inhibit the excessive generation of ROS for redox balance in the first instance or can induce controlled accumulation of ROS under certain conditions, thereby disrupting microbial homeostasis. By modulating oxidative pathways, flavonoids impair microbial energy metabolism, biofilm formation, and virulence factor expression. Thus, their antioxidant and ROS-inhibitory action contribute not only to cellular protection in higher organisms but also provides a key mechanism underlying their antimicrobial property.

Table 2. Mechanistic Pathways of Antibacterial Action of Flavonoid Phytochemicals

Mechanistic Pathway / Target	Representative Flavonoids	Mode of Action / Molecular Target	Representative Pathogens Affected	References
Cell wall synthesis inhibition	Quercetin, Luteolin, Morin, Kaempferol	Inhibits D-alanine–D-alanine ligase, transpeptidase activity; disrupts peptidoglycan crosslinking	S. aureus, B. subtilis	[74], [63], [107]
Cytoplasmic membrane disruption	Naringenin, Phloretin, EGCG, Apigenin	Alters membrane fluidity and permeability; causes leakage of ions and proteins	E. coli, P. aeruginosa, Listeria monocytogenes	[63], [20],[51], [116]
DNA gyrase and topoisomerase inhibition	Quercetin, Myricetin, Fisetin	Binds bacterial DNA gyrase and topoisomerase IV; prevents supercoiling and replication	E. coli, S. typhi	[108],[109], [110],[111],[112]
Efflux pump inhibition (EPI activity)	Baicalein, Chrysin, Licochalcone A, 5′-Methoxyhydnocarpi n D	Blocks NorA and AcrAB-TolC efflux systems; enhances antibiotic accumulation	S. aureus,E. coli	[60],[113], [114],[148]
Protein synthesis inhibition (ribosomal interference)	Kaempferol, Apigenin, Scutellarein	Binds bacterial ribosomal subunits, preventing peptide chain elongation	B. subtilis, E. coli	[67],[115], [75]
ROS (Reactive Oxygen Species) generation / oxidative stress induction	EGCG, Luteolin, Myricetin, Naringenin	Promotes intracellular ROS accumulation, leading to oxidative damage and cell death	S. aureus, P. aeruginosa	[62],[117],[118] , [119]
Quorum sensing (QS) inhibition	Naringenin, Quercetin, Genistein	Suppresses QS signaling (Las, Rhl systems); reduces biofilm formation and virulence gene expression	P. aeruginosa, Chromobacteriu m violaceum	[120],[121] [122],[106]
Biofilm disruption and inhibition	Phloretin, EGCG, Morin, Apigenin	Prevents EPS (extracellular polymeric substance) synthesis; destabilizes established biofilms	E. coli, S. aureus, K. pneumoniae	[56],[123],[124] , [125],[126]
ATP synthesis and energy metabolism interference	Luteolin, Fisetin, Rutin	Inhibits ATP synthase and metabolic enzyme activity, leading to energy depletion	E. coli, S. aureus	[127], [128],[129],[130]
Iron chelation and nutrient deprivation	Myricetin, Quercetin	Chelates Fe^{2+} ions, inhibiting bacterial metalloenzyme activity	E. coli, S. typhimurium	[75], [131],[45], [132]
Synergistic potentiation with conventional antibiotics	Quercetin, Baicalein, EGCG	Enhances β-lactam and fluoroquinolone efficacy; reduces MIC values	S. aureus, E. coli, MRSA	[133]– [137]
Epigenetic and regulatory modulation	3,2-DHF, 6-AF, DHMB	Alters bacterial signaling and gene expression linked to virulence and resistance	E. coli, P. aeruginosa	[138]-[141]
Multitarget action (polypharmacological effects)	Total flavonoids of Potentilla kleiniana, Licochalcone A, Chrysoeriol	Combines ROS generation, membrane damage, and efflux inhibition	S. aureus,E. coli	[28],[86],[142]– [148]

Table 2: Multifaceted antibacterial mechanisms of flavonoids, emphasizing their polypharmacological interactions with bacterial targets. Flavonoids exert bactericidal effects by disrupting cell walls and membranes, inhibiting essential enzymes like DNA gyrase, and interfering with efflux pumps and quorum sensing systems. Additionally, their ROS-inducing capacity and iron-chelating behavior impair bacterial viability. These mechanisms often act synergistically, enhancing the potency of conventional antibiotics and positioning flavonoids as promising scaffolds for the

development of next-generation antimicrobial therapeutics.

III. CONCLUSION

Interactions of flavonoids with proteins, like enzymes, receptors, transporters, and transcription factors exert the beneficial effects of flavonoids, along with their antibacterial property which has been thoroughly evaluated through various studies to discover more potent antibacterial agents as safe natural products. It can be concluded that several flavonoids' structural features may be important for imparting antibacterial effects, and therefore derivatisation and approaches towards new synthetic strategies, might play an important role to synthesize better antibacterial drugs to overcome stiff challenges associated with the treatment caused by multidrug resistant strains of bacteria.

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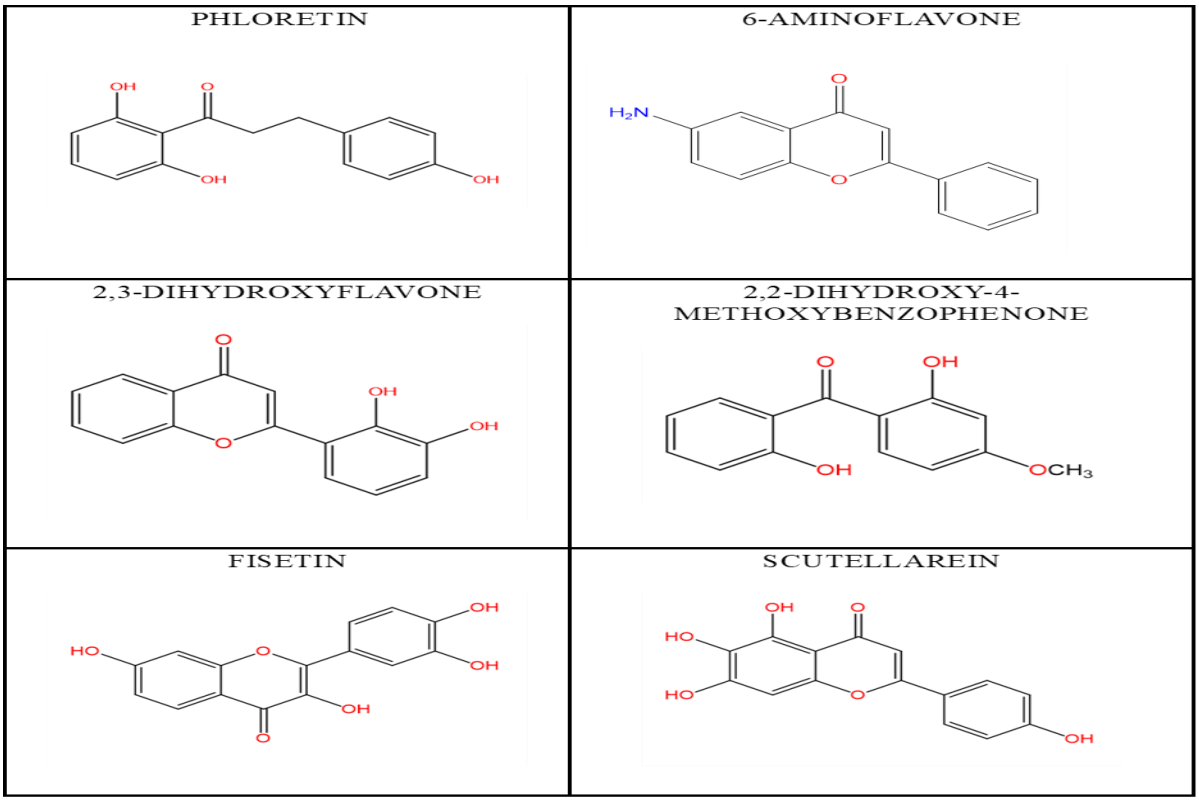
Author Contributions:
Bani Bala, Puspita Roy, Ruchira Swarnakar, Sivangi Srivastava, Sreeja Chakrabarti, Srijita Chatterjee contributed equally for this Review Article. Dipra Basu draws the chemical structures of the flavonoid phytochemicals. Subhalakshmi Ghosh conceptualized, finalized and reviewed the manuscript and communicated as the corresponding author.

V. STRUCTURE OF BIOACTIVE FLAVONOIDS



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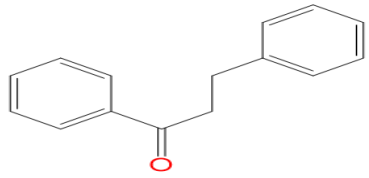
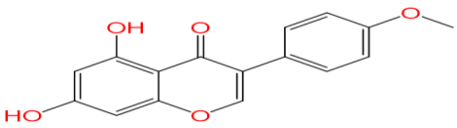
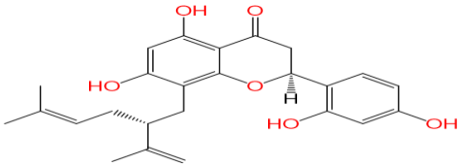


BIOCHANIN A



SOPHORAFLAVANONE G



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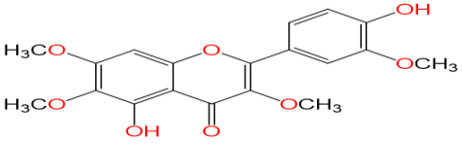

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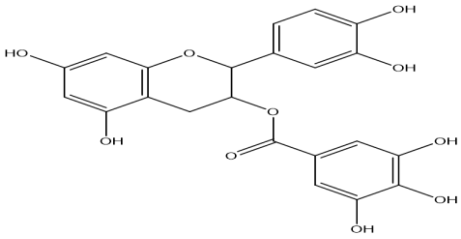
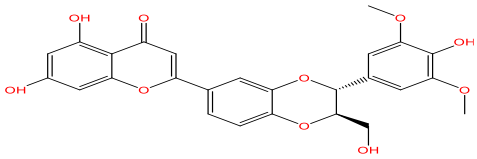


5′-METHOXYHYDNOCARPIN D



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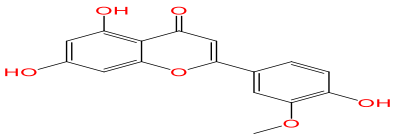

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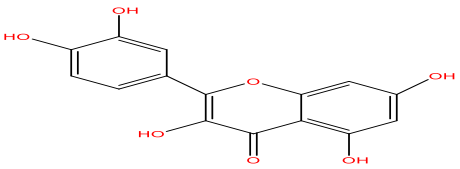

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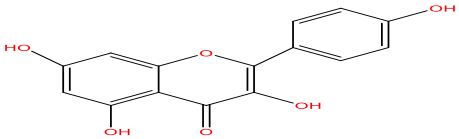
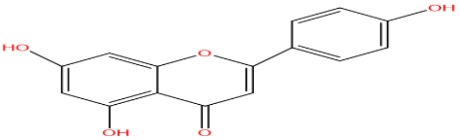
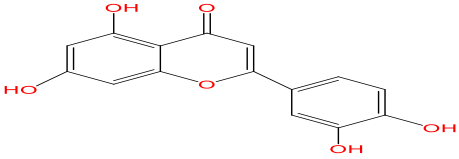


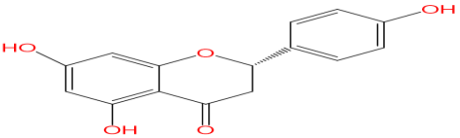
APIGENIN

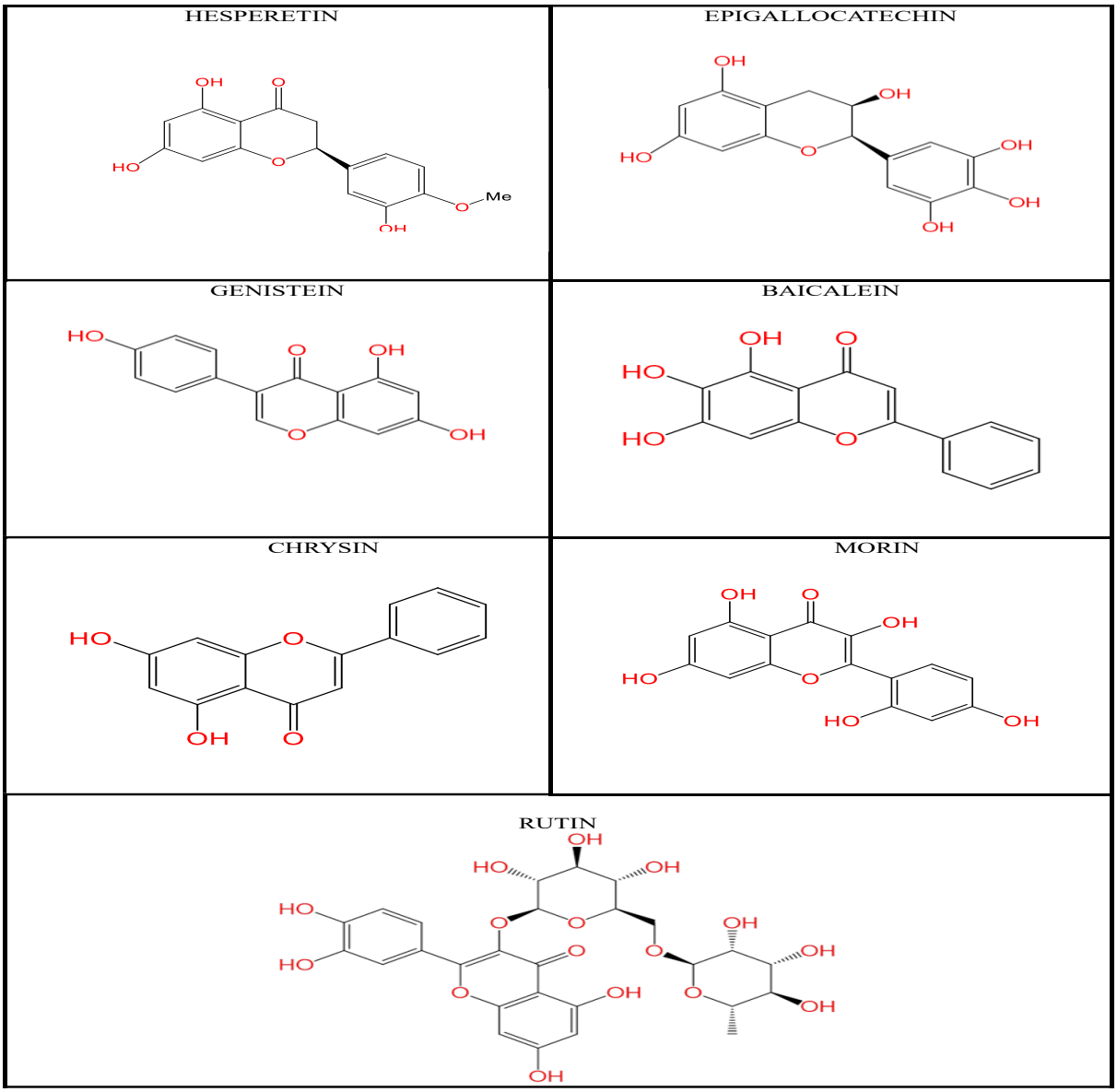


LUTEOLIN



NARINGENIN





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