Emerging avenues of flavonoids in defying antibiotic resistance


Dhruv Sanjay Gupta & Divya Suares*

Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's NMIMS, V.L. Mehta Road, Vile Parle (W), Mumbai - 400056, India

divyasuares@gmail.com; divya.suares@nmims.edu

1.Introduction

Antibiotic resistance is a critical issue in the clinical use of antibiotics for the management of bacterial infections, as well as more serious conditions such as cancer (1). The growing development and spread of multidrug resistant infections has accelerated the demand for novel antibiotics, directing research focus towards natural compounds, such as flavonoids (2).

Flavonoids are bioactive with tremendous health potentials and are widely present in a variety of food materials, such as fruits and vegetables. Some of the most studied benefits include antioxidant and anti-inflammatory activities, and their impact on biological functioning has been validated through a variety of preclinical and clinical studies (3). The topic at hand deals with the possibilities of harnessing flavonoids in the management of antimicrobial resistance, and the authors have aimed to provide a structured understanding of the phenomenon and prospective intervention strategies.

At the outset, the authors have discussed the various types of antibiotic resistance with an insight into the mechanisms that may be responsible for their occurrence. Additionally, the prime role played by efflux pump and transport proteins during the onset of resistance have also been touched upon (4). Moreover, the potential adjuvant treatments for bacterial infections using actives that exhibit inhibitory activity towards these pathways, i.e., the therapeutic role of flavonoids will be delved (5). Nevertheless, the claims discussed have been suitably backed by recent preclinical and clinical studies, to further support the use of flavonoids in reducing dependence on synthetic compounds and minimizing the growing burden on healthcare systems, and in turn, improving the quality of life of patients.

Finally, in order to present the most recent developments on this front, the authors offer a discussion on nanotechnological interventions, aimed at improving targeted delivery and offering other allied benefits, such as improved bioavailability and lowering of dose (6). The authors have concluded the article with a short discussion on the key challenges and future perspectives that will prompt continued research efforts and further ones understanding on the plethora of benefits offered by flavonoids.

2.Brief overview of types of antibiotic resistance and resistance mechanisms

Antibiotic resistance exhibited by bacteria may be broadly classified into three sub-types, i.e. intrinsic, acquired, and adaptive (7). Intrinsic resistance primarily entails the resistance that is seen to develop owing to the inherent properties, such as glycopeptide resistance that is widely seen in case of gram-negative pathogens (8). Acquired resistance, on the other hand, develops due to sensitisation over time. This phenomenon is seen to arise due to bacterial gene mutations, or horizontal gene transfer (9). The major mechanisms involved in bacterial gene transfer include chromosomal incorporation due to transformation, genetic transduction and conjugation, mediated by physical contact (10).

Adaptive resistance occurs due to exposure to environmental factors, such as ionic or nutrient concentrations, surrounding pH and the presence of stressors. This type of resistance is a transient, largely reversible process, mediated by epigenetic modulations (11). Some mechanisms that have been attributed to adaptive resistance include DNA methylation, modified expression of porin channels and efflux pumps (12).

In order to obtain a holistic understanding of antimicrobial resistance, other key mechanisms that are explored include, (a) the inactivation or modification of chemical structure of antibiotics, for e.g., acetylation of gentamicin by Pseudomonas aeruginosa (13). (b) The alteration of target site of the antibiotic, which is widely observed in case of beta-lactam antibiotics, such as vancomycin. (c) Staphylococcus aureus resistance due to transpeptidase mutations, which is a cause for clinical concern (14). Such mutations prevent binding of the antibiotic moiety to the target site, permitting retention of the integrity of cellular structure. Efflux pumps also play a crucial role in the mechanism of antimicrobial resistance. They mediate the elimination of antibiotics from bacterial cells, for e.g., AcrAD efflux pump is responsible for aminoglycoside resistance in Escherichia coli (15).

3.Therapeutic significance of flavonoids

An extensive literature analysis undertaken by Biharee et al. sheds light on various mechanisms of flavonoids that may explain their benefits in the management of antimicrobial resistance. Some of these include the prevention of development of cell envelops, regulating the activity of efflux pumps, preventing biofilm formation, triggering membrane rupture, as well as by slowing down bacterial motility (16).

Addressing resistance to antibiotics in cancer management is another emerging avenue. Flavonoids offer a cost-effective, non-toxic alternative, and have been observed to elicit positive health outcomes through a variety of pathways. With a special focus on neoplasms, flavonoids, chiefly flavonolignans, have been seen to inhibit Adenosine triphosphate Binding Cassette (ABC)-transporters. Flavonoids are also responsible for modulating the action of other transporters involved in the pathogenesis, including glucose transporters, small multidrug resistance (SMR) and toxic compound extrusion (MATE) transporters (17).
In addition to this, biotransformation reactions including hydroxylation and conjugation have been observed to improve the biological activity of these agents. Flavonoids such as quercetin and naringenin have been observed to inhibit cell wall synthesis, control DNA replication and

enable the targeting of multiple sites in bacteria. This, in turn, improves the sensitivity of cells to these compounds, minimising the possibility of resistance (18). Isoflavones (such as equol, daidzein), flavonones (naringenin, hesperitin) and flavonols (quercetin, galangin) include someof the most widely studied classes of compounds in combating opportunistic fungal resistance, majorly those belonging to the Candida species (19). The usage of these bioactives, as monotherapy or in combination with widely used antibiotics, may be explored as an effective strategy in the management of antimicrobial resistance. Their usage has been linked with a reduction in the ability of microorganisms to adapt to treatment regimens, opening up the doors for exciting research opportunities (20). Figure 1 depicts the skeleton structure of flavonoids, alongside the representative structure from certain classes discussed, and their members.

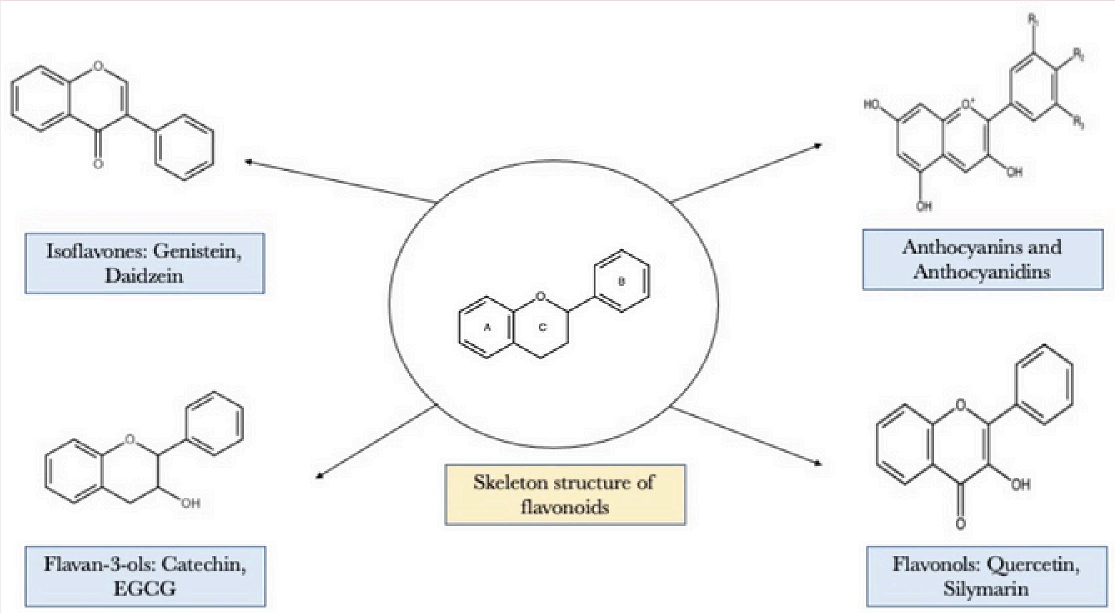

Figure 1. Skeleton structure of flavonoids, alongside the representative structure from certain class and their members

4. Supporting evidence from preclinical studies

This section aims to offer an overview of recent preclinical studies that elucidate the role of flavonoids as antimicrobials. Some of the key mechanisms explored in preclinical trials include the inhibition of cell envelop formation, arrested synthesis of key biomolecules such as nucleic acids, and lowered bacterial motility.

A study by Zhang et al. highlighted the potentials of flavonoids such as quercetin and apigenin in inhibiting cell envelop synthesis, by inhibiting the dehydrase enzyme that catalyses the process (21). With respect to bacterial motility, flavonoids have been observed to arrest swarming movement, thereby reducing pathogen adhesion to target cells. Naringenins and catechins have been widely explored in this domain, and have been linked with a suppression of biofilm formation, resulting from lowering of quorum sensing among bacterial populations (22). Bacterial endotoxins and exotoxins are of particular interest with respect to disease onset and progression, and have been explored as a potential target. A study by Silva et al. reported the usage of fisetin, genistein and luteolin, among other compounds, against the haemolysins produced by S. aureus (23).

A study by Cuccioloni et al. aimed to understand the benefits of epigallocatechin gallate (EGCG) in the inhibition of bacterial folic acid that revealed key enzyme inhibition across different species, including Streptomonas, Mycobacterium and Escherichia sp. (24). These studies highlight the potentials for further exploration, and clinical validation of preliminary outcomes. Figure 2 offers a diagrammatic representation of the major mechanisms of flavonoids in the management of antibiotic resistance, based on insights from preclinical studies.

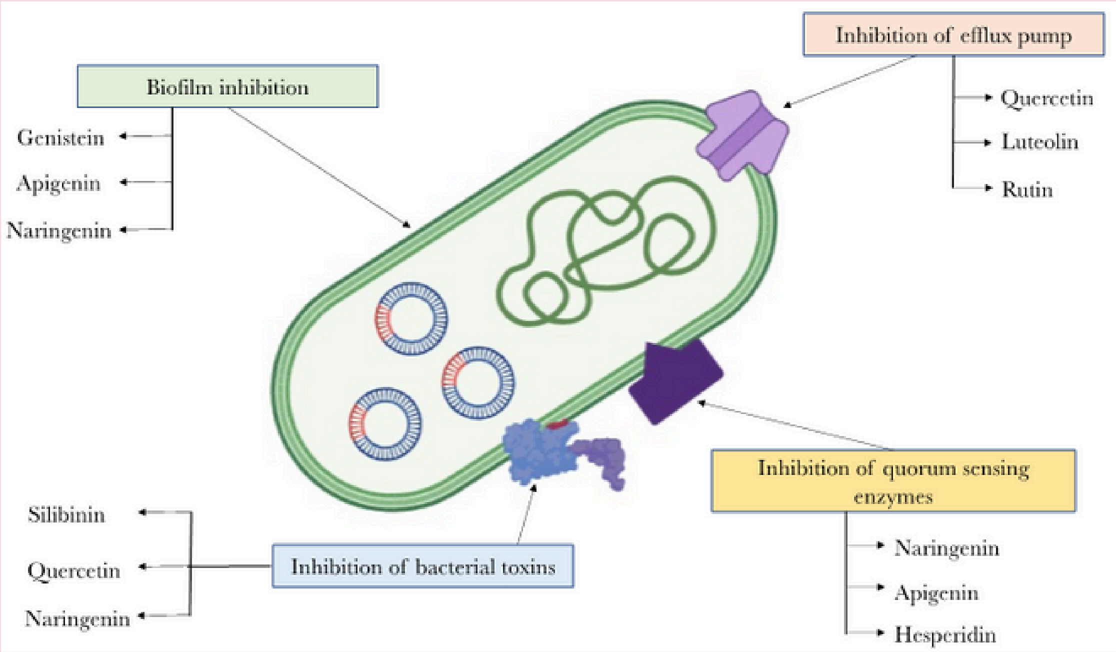

Figure 2. Mechanisms of flavonoids in the management of antibiotic resistance, gleaned from preclinical studies (16) (Created using Biorender)

5. Clinical picture

While results from preclinical studies are a crucial stepping-stone in evaluating the benefits of flavonoids in disease management, it is pertinent to include relevant data from clinical trials. Table 1 offers an insight into the outcomes and inferences from recently conducted clinical trials, to further support the usage of phytoconstituents such as flavonoids in the management of the condition at hand. While there have been a number of studies over the last decade, there is a need for a greater number of focused trials, exploring combinations of different agents to establish their pharmacodynamic profiles, safety as well as possibilities for exploring newer targets.

6.Nanotechnological interventions

While natural actives are widely distributed across various dietary food materials and provide a wide range of health benefits, their usage is marred by a number of limitations, including degradation owing to poor stability, and low solubility. Nanotechnological strategies aim to pave the way for improved delivery, as well as lowered side effects. This section offers an exploration of recent advances in the domain, focused on the delivery of nanocarrier loaded with flavonoids for their antimicrobial benefits.

A study by Das et al. explored the application of flavonoid-loaded gold nanoparticles for controlling the growth of gram-negative bacteria. The antioxidant benefits of quercetin were harnessed to hamper microbial growth, and a synergistic effect with gold assisted cell

Table 1. Insight into recently conducted clinical trials to establish the clinical efficacy of flavonoids in antimicrobial resistance

Dose and duration	Volunteers	Design	Outcome	Conclusion	Ref
Cranberry proanthocyanidins (Doses 1-18.5 mg, twice a day), for 24 weeks	145 healthy women with history of Urinary tract infections (UTIs)	Randomized, controlled clinical trial	Decrease in the incidence of infections, no major adverse effects reported.	Proanthyocyanidin administration was associated with protective effects, and reduced rate of recurrence. No significant benefits observed with higher dosing.	(25)
Naringenin (5mg/ kg) v/s Azithromycin, over a 5 day period	180 children with bronchial pneumonia	Randomized, controlled clinical trial	Decreased latency period, lowered inflammation, satisfactory safety profile (compared to azithromycin) and overall health improvement.	Naringenin may be clinically employed in pneumonia management, owing to its anti-inflammatory and antimicrobial benefits.	(26)
Cranberry juice (rich in proanthocyanidins), at concentrations 17 and 35%, for a period of 8 weeks	522 *Helicobacter pylori* positive adults	Double-blind, randomized, placebo-controlled trial	Satisfactory patient compliance, no adverse effects observed, lowered positivity rates over an 8-week period.	Intake of foods rich in flavonoids, such as cranberries, may be beneficial in suppressing microbial growth and proliferation.	(27)
Silymarin (140mg/ day), in combination with oral doxycycline (100mg/ day), over 4 months	60 patients with acne vulgaris	Randomised, controlled clinical trial	Therapeutic synergism, lowered occurrence of lesions on combining a flavonoid moiety with synthetic therapy.	While work remains to be done in evaluating the benefits of silymarin monotherapy, it may be used as adjunct therapy with conventional treatment regimens.	(28)
Plantago lanceolata herbal tea (prepared from its flowers and leaves), infusion	44 healthy adolescents	Randomised, controlled clinical trial	Inhibition of growth of cariogenic bacteria (*Streptococci*, *Lactobacilli*),	Phytochemicals such as flavonoids, coumarins and tannins may be used in checking the growth of cariogenic	(29)

membrane disruption (30). Li et al. evaluated the usage of nanoparticles and nanofibers loaded with actives from Chinese traditional medicine, in order to elicit an antibacterial effect. It was observed that the combination of flavonoid glycosides with nanoparticles enhanced bacteriostatic activity, offering interesting opportunities for drug delivery and combating antimicrobial resistance (31).

Nanotechnological interventions have also been employed to improve the pharmacokinetic profiles of natural actives, thereby improving their bioavailability (32). By the process of valorization, products that would have otherwise been treated as waste are now finding biomedical applications. Pomegranate peel, known to be rich in anthocyanins among other polyphenols, offers a host of antimicrobial benefits. Various strategies such as nanoemulsions and lipid nanoparticles have been utilised to deliver pomegranate peel extract to target sites, offering advantages such as easy production, low cost and promising biocompatibility (33). As interest in this domain continues to grow, other biological compounds such as peptides have also been explored for their benefits as natural nano-antibiotics (34).

7.Conclusion

Antimicrobial resistance is a growing issue in the medical space, affecting millions across the globe. This has sparked the need for exploring alternative strategies for its management. Extensive research and development in the domain has permitted the discovery of potential targets and mechanisms, and nanotechnology offers interesting opportunities for targeted delivery, minimising the occurrence of side effects. Notwithstanding the massive number of benefits offered and prospects for future development, a greater number of focused studies are necessary, to further support and scale-up the usage of these agents.

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