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A REVIEW OF FLAVONOIDS, BIOSYNTHESIS, SOURCES AND THEIR USE IN INFECTIOUS DISEASES

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Abstract

Flavonoids are the plant's secondary metabolites and majority of them are effective medicinal agents. These flavonoids can improve human health when a person is afflicted with a variety of infectious diseases. Flavonoids are extensively employed in food, medicines, and nutraceuticals due to their safety and protective properties, which encompass antibacterial, antiviral, antifungal, and antiparasitic potential. The production of flavonoids from plants necessitates complex extraction processes and downstream handling with potentially dangerous compounds. Flavonoids are a diverse group of plant compounds that can be broken down into several main subgroups. These subgroups contain variety of compounds possessing many medicinal as well as

anti-infection properties. This review will delve into the various subgroups of flavonoids, highlighting their diverse compounds and the wide array of medicinal and anti-infection properties they possess. We will summarize their sources, biosynthesis, mechanisms of action, and their application against infectious diseases, drawing upon previously reported studies.

Introduction

Phenolic chemicals have the most evidence supporting their therapeutic potential when it comes to lowering the risk of acquiring chronic or degenerative diseases. Secondary metabolism of plants produces phenolic compounds (PCs), which are non-essential components of the human diet [1]. Flavonoids make up the largest group of the PCs found in the human diet [2]. More than 9000 flavonoid derivatives have been found in different plants, which are further categorized into distinct subfamilies based on changing in their fundamental structures [3, 4]. Plants are the primary source of flavonoids, which are polyhydroxy compounds. They offer a key defense mechanism that shields plants from infections and other abiotic stress [5]. Clinical, animal and epidemiological studies have demonstrated that flavonoids can improve human health when a person is afflicted with a variety of ailments [6-8].

Chemical substances known as polyphenols are produced by plants' secondary pathways and includes coumarins, tannins, lignans, flavonoids, and phenolic acids [9, 10]. The plants can only synthesize flavonoids in a limited quantity so they cannot fulfill the required need of flavonoids. For this reason, the production of flavonoids from plants necessitates complex extraction processes and downstream handling with potentially dangerous compounds [11]. Furthermore, the production of flavonoids is limited due to raw material accessibility issues, insufficient plant availability and low yield output. They are made chemically, with limited selectivity, and under harsh production circumstances [12]. Flavonoids found in plants have not only role in severe stress conditions such as drought, heat, and freezing tolerance but also act as signaling molecules, help filtering UV rays, and are scavengers of reactive oxygen species (ROS) [13].

The therapeutic effects of plants are due to the bioactive phytochemicals they contain. The majority of flavonoids are recognized as effective medicinal agents [14]. Bioflavonoids is a common term for flavonoids having biological effects [15]. In addition to their other bioactivities, such as anti-aging and anti-inflammation properties, flavonoids also exhibit beneficial biochemical effects on various diseases, such as atherosclerosis and cardiovascular

disease [16]. Furthermore, studies provide information related to flavonoids which offer protection against abiotic stresses via ROS detoxification, including UV-B radiation, salt, dehydration, low temperatures and heavy metal stress [17-21].

This comprehensive review delves into the significant role of plant-derived flavonoids in combating a wide array of human infectious diseases. The study provides a foundational understanding of these natural compounds by summarizing their classification into distinct subgroups based on their chemical structure, their widespread occurrence in various plants, and the complex biosynthetic pathways through which plants produce them.

The central focus of this review is to meticulously examine the mechanisms of action by which flavonoids exert their therapeutic effects against various pathogens in humans. It explores their potent antibacterial properties, which include disrupting bacterial cell wall synthesis, inhibiting biofilm formation, and compromising cell membrane integrity. Furthermore, the review investigates the antiviral activities of flavonoids, highlighting their ability to interfere with viral replication and key viral proteins. The discussion also extends to their effectiveness as antifungal agents against various fungal pathogens and their potential as antiparasitic agents.

Sources of flavonoids

Flavones

Flavones represent an important class within the broader flavonoid family. Notable sources of flavones include celery, parsley, red peppers, chamomile, mint, and ginkgo biloba [22-24]. Tangeretin, luteolin, and apigenin are also members of this subclass of flavonoids [25]. Apigenin is among the most varied flavonoids found in plants, encompassing spices and herbs [26, 27]. The other plant sources of apigenin include parsley, celery, citrus fruits, and different herbs like chamomile and thyme. Highest concentration is present in chamomile tea ranging from 0.8%-1.2% v/w [28]. The fungus *Cunninghamella elegans* NRRL 1392 was reported to produce apigenin when chrysin substrates are present [29]. Studies demonstrate that apigenin contains various activities such as antioxidant, anticancer, anti-inflammatory, cardioprotective and other related activities [30].

Baicalein is usually derived from the root of *Scutellaria baicalensis Georgi (Lamiaceae*) and Indian burdock *(oroxylum indicum*) [31]. This herb also has a cooling effect that is used as herbal tea. Besides these plants, baicalein also found in *Thymus vulgaris*, *Lamiaceae* (common thyme); *Caryota urens*, *Arecaceae* (fish-tail palm); *Vicia unijuga*, *Fabaceae* (Chinese vetch);

and *Kaempferia galanga*, *Zingiberaceae* (galangal) [32]. Baicalein was found to be in the metabolites of endophytic fungus *Aspergillus* sp. Gbtc 2 and *Isaria fumosorosea* KCH J2 strain which was extracted from Ginkgo biloba roots [33, 34] which exhibits different pharmacological activities [31]. Luteolin has a similar natural distribution to apigenin and is also used as a food preservative [35]. Luteolin encompasses activity such as anti-inflammatory, antioxidant, anti-apoptotic, cardioprotective [36] and neurodegenerative diseases also [37].

Flavonols

Fruits, vegetables, and certain beverages, such as tea and red wine, serve as primary sources of flavonols [38]. The most common flavonols found in food include myricetin, fisetin, kaempferol, quercetin, and certain derivatives of glycosides and methylated compounds that makes diversity of flavonols [39, 40]. Additionally, certain microbes' metabolites contain these chemicals. The fermentation broth of *Trichoderma asperellum* TJ01 was reported to contain isorhamnetin [41], kaempferol from *Epicoccum nigrum* metabolites [42], myricetin from *Xylaria papulis* BCRC 09F0222 endophytic fungus [43], and quercetin from *Psathyrella candolleana* endophytic fungus (isolates from Ginkgo biloba seeds) [44]. Isorhamnetin (ISOR) is an essential active component of ginkgo biloba and sea buckthorn fruit [45]. The phytochemical profile of the *Duguetia furfuracea* leaves was investigated that is a native shrub to Brazilian ceraddo through various chromatographic techniques and was identified to contain the two important flavonoids such as kaempferol and isorhamnetin [46]. Isorhamnetin exhibits a range of anticancer properties [47] as well as anti-inflammatory [48], antioxidant [49], antibacterial , antiviral [50], and immunity-regulating properties [51].

Myricetin is the most common substance extracted from the leaves of *Myrica rubra* and *Turbinaria conoides* seaweeds and exhibits various pharmacological activities [52]. Quercetin flavonol is also constituted in berries such as elderberry, blackberry, chokeberry and juniper berry [53]. In terms of specific food sources, cranberries exhibit the highest quercetin content at 149 mg per 100 g, followed by onions at 65 mg per 100 g. Green tea and red wine contain mean quercetin contents of 2.5 mg/100 mL and 1.6 mg/100 mL, respectively [38]. Quercetin is also reported to be supplemented at 1000 mg/d [54].

Anthocyanidins

The most common anthocyanidins, like cyanidin and delphinidin, are found in varying amounts in fruits, vegetables, grains, and legumes with different proportions [55]. Suresh *et al*. successfully isolated cyanidin from floral bracts acquired from *Musa acuminata* Colla (AAA cultivar group containing red variant especially) [56]. Delphinidins are one of the major classes of anthocyanidins that are present in high quantity in Maqui berry, a fruit of maqui (*Aristotelia chilensis).* Yamazaki *et al*. investigated maqui berry extract and delphinidins against blue light exposed organelle damage and concluded that MBE can be useful against that oxidative damage [57]. Delphinidin is a purple-blue pigment that gives flowers their blue color. Pelargonidin, distinct from most anthocyanidins, is a red pigment in nature, giving an orange or red pigmentation to flowers and fruits [58]. Malvidin exhibiting a purple pigment is common in blue flowers and is primary coloring agents in red wine. Petunidin is a dark red or purple pigment found in plants like blackcurrants and purple petaled flowers [58].

Flavanones

Flavanones, also called dihydroflavones, have a saturated C-ring [59]. These are abundant in citrus fruits earning them the name citroflavonoids. They are also found in smaller amounts in herbs such as mint and rosemary, albeit in lesser quantities [60]. Eriodictyol, hesperitin, and naringenin are frequently encountered by flavanones. In a separate line of research, Zhao and colleagues identified eriodictyol as one of the metabolites produced by *Enterococcus* sp. [61]. Researchers Vibgedor *et al*. successfully isolated eriodictyol from the bark of *Afzelia africana* and demonstrated its biological potential. The isolated compound was active against *Staphylococcus aureus* and *Bacillus subtilis* [62]. Hesperitin is commonly derived from citrus fruit [63-65] and is found to be a metabolite of endophytic fungus *Aspergillus* sp. [34]. Salunkhe *et al*. conducted a study using naringinase producing *Neurospora* sp. to covert naringin into naringenin from citrus peel waste as a source and the naringenin conjugate with gold and silver attributed with enhanced antimicrobial activities [66]. Naringenin exhibits a range of activities including antiviral antioxidant effects [67].

Anthocyanins

Anthocyanins are pigments found throughout the plant kingdom in various colored grains, fruits, and vegetables, with their concentrations varying significantly among different plants. Fruits are the most abundant source of the anthocyanins [68]. The highest concentrations of anthocyanins

are typically found in berries, currants, and grapes, as well as some tropical fruits. Among vegetables, leafy grains, roots, and tubers contain the most significant amounts. Anthocyanins are not limited to the edible portions and are also present in other parts of the plant [69]. Anthocyanins are also found in processed foods and drinks like red wine, juices, and jellies. The most prevalent anthocyanins in foods are glycosides of six common anthocyanidins. A single glass of red wine, for instance, contains glycosides of cyanidin, delphinidin, pelargonidin, peonidin, and malvidin. Glucose serves as primary sugar in glycosylating anthocyanins, resulting in the formation of 3-O substituted derivatives [70]. In one study, Kruszewski *et al*. used ultrasound-assisted extraction to isolate these compounds from blackcurrant pomace [71].

Flavanols

Cacao beans are a primary source of phenolic compounds, with flavanols being particularly abundant. In non-fermented cocoa beans, the monomeric flavanols particularly epicatechin and oligomeric flavanols constitute approximately 60% of the total polyphenols [72]. Cheng Wu *et al*. described that catechin can be produced by endophytic fungus *Annulohypoxylon elevatidiscus* BCRC 34014 [73]. Along with cocoa, dark chocolate is also the primary source of flavanols, with cocoa containing 3411 mg per 100 g and dark chocolate containing 1590 mg per 100 g. Berries, including black chokeberry, blueberry, and blackcurrant, are also significant sources, providing 659, 330, and 139 mg per 100 g, respectively [38].

Isoflavones

Isoflavones are primarily found in *Leguminosae* family [74, 75]. Isoflavones provide estrogenic activity [76] similar to those of estradiol hormones [77]. Genistein is an isoflavone that is found to be in green tea and possesses antiestrogenic activity. Daidzein is found in vegetables like soyabeans, chickpeas, clover, lentils, and beans [78]. Daidzein and genistein molecules have reportedly been found in the metabolites of the *Streptomyces* sp. TPU1401A [79] and YIM GS3536 strain [80], as well as *S. xanthophaeus* [81] and *Micromonospora* sp. [82].

Chalcones

Most naturally occurring chalcones are polyhydroxylated aromatic compounds, which are widely present in products including tea, coffee, red wine, beer, and fruits as well as grains, legumes, and vegetables [83]. For example, a naturally occurring chalcone isobavachalcone (IBC) is mostly extracted from *Psoralea corylifolia* seeds[84]. Chalcones are already isolated from

different plant families like *Leguminosae, Asteraceae, and Moraceae* and exhibit various biological activities [85]. For instance, chalcones bearing chlorine atom exhibits strong antimicrobial activity [86].

Biosynthesis of flavonoids

Phenylalanine is formed via the shikimate pathway, whereas flavonoids are produced from phenylalanine via the phenyl-propanoid pathway [87]. The biosynthesis of flavonoids in plants takes place via two different pathways, the acetate pathway (shown by ring A), and the shikimate pathway (represented by ring B), and the connecting chain (represented by ring C), which generates the C6-C3 component [88]. Flavonoids are produced by phenylpropanoid pathway and cinnamic acid is synthesized by the deamination of L-phenylalanine by phenylalanine ammonia lyase (PAL) [89] (Figure 1). The trans-cinnamic acid is then hydroxylated to yield p-coumaric acid by cinnamic acid hydroxylase (C4H), a hydroxylase that is dependent on cytochrome P450. 4-coumaric acid is catalyzed by the 4-coumaric acid CoA ligase (4CL) to produce 4-coumaroyl CoA, an essential step in the production of flavonoids [90] and lignin [91]. The addition of p-coumaroyl-CoA to the flavonoid biosynthesis pathway signifies the synthesis of certain flavonoids, which begins with the creation of chalcones [92].

One p-coumaroyl CoA and three malonyl-CoA molecules are converted into naringenin chalcone by the enzyme chalcone synthase (CHS), the fundamental component of naturally occurring substances including fatty acids, polyketides, and flavonoids [93]. Chalcone is the first significant intermediate product in the metabolism of flavonoids, which serves as the essential building block for the creation of subsequent flavonoids [87]. Naringenin chalcone is converted to naringenin through chalcone isomerase (CHI), a general precursor of all flavonoid compounds [94]. Naringenin is then converted to flavones and isoflavones by the action of flavone synthase I and II and isoflavone synthase respectively [95, 96]. Naringenin is catalyzed to dihydroflavonols by the action of flavanone-3-hydroxylase [97, 98]. Flavanols are formed by the action of dihydroflavonol-4-reductase (DFR) from naringenin [99]. The dihydroflavonols are converted to flavonols by the action of flavonol synthase and are also converted to leucoanthocyanidins by dihydroflavonol-4-reductase [100]. Leucoanthocyanidin dioxygenase converts leucoanthocyanidins to anthocyanidins that is catalyzed by uridine diphosphate glucose flavonoid-3-O-glycosyltransferase to anthocyanins [101]. The leucoanthocyanidins also form

flavanols through leucoanthocyanidin reductase [102, 103]. Glycosylation, methylation, and acylation modifications stabilize anthocyanins [104].

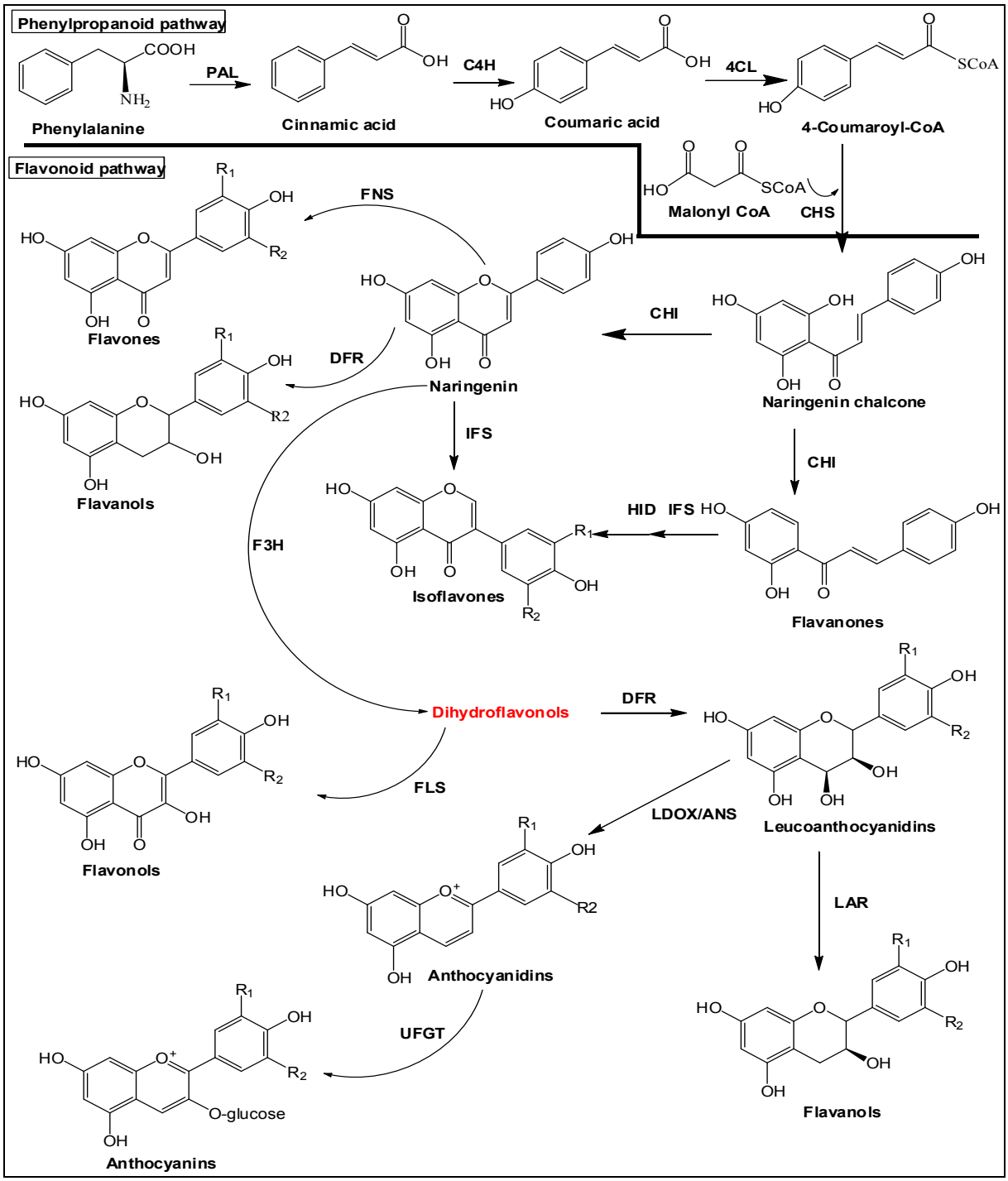

Figure 1: Schematic diagram of biosynthesis of flavonoids.

Structure and classification of flavonoids

Chemically, flavonoids possess a fundamental C6-C3-C6 skeleton [105] which consists of two benzene rings (A and B) connected by a three-carbon heterocyclic pyran ring (C). The vast diversity within this family arises from different groups—such as hydroxyl, methoxy, and glycosides—that attach to this core structure, along with an oxo group often found at the C4 position of the C ring.

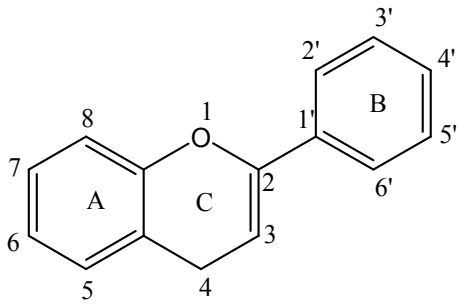

Figure 2: Basic skeleton of flavonoids.

Flavonoids are classified into subclasses based on the structural variations of the C ring, including its oxidation state, unsaturation, and the attachment point of the B ring [106]. The seven main subclasses are flavones, flavonols, flavanones, isoflavones, anthocyanins, flavanols, and chalcones [22, 107-110]. The most abundant flavonoids, including flavones, flavonols, and flavanones, are distinguished by structural variations in their central C ring [111]. Flavones are characterized by a double bond between the C2 and C3 carbons [112, 113] and an oxo group at the C4 position [106]. Flavonols are very similar, sharing these features but with the addition of a hydroxyl group at the C3 position [106]. Flavanones are distinct because they lack the C2–C3 double bond. Other subclasses are defined by different core structures. In isoflavones and neoflavanoids, the B ring attaches to the C3 or C4 position of the C ring, respectively, instead of the usual C2 position. [106]. Anthocyanidins are unique due to their characteristic oxonium ion called as 2-phenylbenzopyrylium [114]. Finally, chalcones are open-chain flavonoids, where the two aromatic rings are connected by a three-carbon α,β-unsaturated carbonyl system [115].

Mechanism of action

Antiviral activity

Flavonoids act as antioxidants, enzyme inhibitors, and cell membrane disruptors [116]. Flavonoids inhibit the attachment of viruses and block their entrance into the host cells and their disruption to replication, transcription and translation of the viral genome [117]. Badshah *et al*.

demonstrated antiviral properties of flavonoids in various testing contexts such as luteolin inhibiting the spike protein just like baicalein in corona virus [118].

Antibacterial activity

Flavonoids display antibacterial action through different mechanisms. Primarily, they work by inhibiting the synthesis of nucleic acids (DNA and RNA) and altering the function of the cytoplasmic membrane like permeability and pore formation, inhibition of energy metabolism, reduction in biofilm formation and cell attachment [119]. A number of flavonoids possess antibacterial activity such as apigenin [120] through membrane depolarization against *E.coli* and catechin [121] through nucleic acid synthesis inhibition and baicalein by inhibiting biofilm formation [122].

Antiparasitic activity

Different plant extracts containing flavonoids possess potent antiparasitic activities [116, 123]. Soto-Sánchez, J. *et al.* establish the the mechanism of antiparasitic activity by golgi damage, mitochondrial dysfunction, morphological alterations like chromatin condensation, DNA fragmentation, accumulation of acidocalcisomes and glycosomes, negative regulation of enzymes, and other vital enzymes like arginase that is necessary for parasite survival [124]. Tang *et al*. assessed the water and ethyl acetate extracts' *in vitro* parasiticidal efficacy against *T. piriformis* in 22 specific traditional Chinese medicines (TCMs). The most effective extract of ethyl acetate was of *Psoralea corylifolia* with minimum parasiticidal concentration of 100 mg/L in under three hours and it was further analyzed [125].

Antifungal activity

Flavonoids inhibit fungal growth through multiple mechanisms, including disruption of the plasma membrane, causing mitochondrial dysfunction, and inhibiting essential cellular processes like cell wall formation, cell division, and the synthesis of RNA and proteins. They also interfere with the fungus's efflux pump systems [126]. They combat fungal infections by inhibiting spore germination and disrupting fungal cell functions. Baicalein, a flavone found in *Scutellaria baicalensis*, shows promising antifungal activity against *Candida* species [116].

Flavonoids showing antibacterial activity

Apigenin

Apigenin's lipophilic nature also allows it to disrupt microbial membranes, making it effective against various bacteria [127]. Research indicates that the bacterial targets of the apigenin could be the DNA or RNA processing enzymes of cell membrane/wall. One of the studies describe that the apigenin disturbs the cell membrane/wall synthesis pathways to make the bacteria vulnerable [128]. The apigenin 7-O-Glucoside also depict antibacterial activity through anti-biofilm mechanism. It was demonstrated that A7G possess strong antibiofilm and antibacterial activity against gram positive and gram-negative bacteria. It was discovered that A7G inhibits biofilm through inhibition on quorum sensing (QS), cell surface hydrophobicity (CSH), and exopolysaccharides (EPS) [129]. Apigenin has been discovered the most potent antibacterial properties against *Proteus mirabilis*. It is bactericidal to gram-positive and gram-negative bacterial species [130]. Apigenin also efficiently prevented *Enterococcus caccae* upregulating the genes associated with stress response, cell wall synthesis, DNA repair and protein folding [131].

Galangin

Galangin is often present in propolis samples and has shown inhibition against distinct fungal strains [132]. Galangin exhibits broad-spectrum antibacterial effects, inhibiting both Gram-positive and Gram-negative bacteria. Galangin forms complexes with bacterial proteins, inhibiting their function and disrupting bacterial cell membranes leading to inhibition of bacterial growth and proliferation [127]. Reports have shown some disadvantages of galangin like light sensitivity, pH, temperature, semi permeability to GIT barriers, but these disadvantages can be overcome by making micro or nanoparticles of galangin [133].

Flavone and flavonol glycosides

Flavone and flavonol glycosides are glycosylated forms of flavonoids prevalent in fruits and vegetables [134]. Their antibacterial action stems from their ability to bind with bacterial proteins and damage microbial membranes.These compounds effectively suppress the growth of numerous bacterial species making them valuable in combating bacterial infections [135].

Isoflavones

Isoflavones are found in soybeans and other legumes exhibiting antibacterial activity against a broad spectrum of microorganisms [135]. Formononetin is an isoflavone that exhibits many activities including antibacterial activity [136]. Similarly daidzein and genistein isoflavones

interfere with the biofilm formation of bacteria thus inhibiting bacterial action [13]. Conversely, prenylated isoflavones exhibited antibacterial effects against Gram-positive bacteria by disrupting their cell membrane integrity [137]. Prenylated isoflavones are multifunctional compounds known for a spectrum of biological activities, including antioxidant, antimicrobial, antidiabetic, and anticancer properties. Their key mechanism of antibacterial action is attributed to the disruption of bacterial biofilms [138].

Flavanones

Flavanones are abundant in citrus fruits and possess significant antibacterial activity. Naringenin has been demonstrated the antibacterial activity against gram positive and gram negative bacteria through biofilm inhibition [139]. Eriodictyol a flavanone exhibited bacteriostatic potential against *Methicillin resistant Staphylococcus aureus (MRSA)* [140]. Hesperidin is a flavanone glycoside that possesses various pharmacological activities. Hesperidin damages bacterial cell walls and induces macromolecule leakage by generating reactive oxygen species [141].

Flavonoids showing antiviral activity

Green tea extracts (GTE) and Epigallocatechin (EGC)

Green tea extracts, particularly Epigallocatechin (EGC), demonstrated significant inhibitory effects against influenza viruses. Studies confirmed GTE's ability to slow virus growth, with EGC being a prominent antiviral agent. GTE inhibited early viral infection stages, particularly within 5-15 minutes post-infection [118]. The antiviral activity of EGC against influenza A(H1N1)pdm09 viruses is promising when tested *in vitro*. Despite showing the ability to inhibit viral replication in laboratory assays, EGC treatment was ineffective in a ferret model of influenza. It failed to reduce the viral load in either the upper or lower respiratory tracts and offered no additional benefit when combined with OST treatment [142]. The *in vitro* antiviral experiments of green tea against tobacco mosaic virus has also decreased the induced local necrotic lesions of TMV with increased concentration of the extracts active compounds [143]. EGC is also effective against Porcine reproductive and respiratory syndrome virus (PRRSV), a single-stranded RNA virus, by inhibiting its replication within porcine alveolar macrophages [144].

Elderberry extracts and flavonoids

Flavonoids from elderberries (*Sambucus nigra*) can prevent the influenza virus from infecting host cells, thereby halting the progression of the flu. Additionally, *Sambucus nigra* flavonoids' accumulation inhibits the virus competitively and then endocytoses it to prevent influenza infection [145]. European black elderberry extract is highly effective against the original SARS-CoV-2 strain and its variants. The mechanism involved viral cycle inhibition in later stages after the host cell penetration [146]. The elderberry extract also possesses antiretroviral reverse transcriptase activity against HIV-2 [147].

Quercetin derivatives

Quercetin and its derivatives have the capacity to lower the amount of viruses in the body by blocking their entry into cells. Quercetin binds to the functional areas of viruses, stopping them from using host cell resources for their own purposes and limiting their ability to multiply [148]. Quercetin derivatives reduce COVID-19 severity by targeting the AT1R pathway or endoplasmic reticulum stress [149, 150]. Quercetin also shows antiviral activity against various zoonotic viruses by inhibiting their entry into host cell [151]. Quercetin derivatives like quercetin-3-O-rutinose and rhamnose also possess activities [152]. It was also active against Dengue Virus Type-2 (DENV-2) [118].

Baicalein

Baicalein's antiviral action involves three mechanisms: modulating key signaling pathways, regulating antiviral protein expression, and inhibiting virus-induced cell death. All of these mechanisms of action may also be linked to baicalein's potential antiviral activity [32] Baicalein also displayed potent antiviral activity against JEV. It inhibited various stages of viral replication, including adsorption and has virucidal effects [153]. Baicalein also inhibited infectious bronchitis virus at 20 μg/mL by reducing mRNA expression and viral titers [154]. On the other hand, it also showed potent activity against Chikungunya Virus (CHIKV) [155].

Fisetin, and quercetagetin

Fisetin, and quercetagetin showed potent antiviral activity against Chikungunya virus. These flavonoids inhibited viral replication and entry into host cells, with baicalein being the strongest inhibitor. They demonstrated dose-dependent inhibition of virus attachment, entry, and intracellular replication [118].

Flavonoids showing antiparasitic activity

Apigenin

Cutaneous leishmaniasis, which results in skin lesions, has around 1.2 million cases reported each year. The parasite responsible for cutaneous leishmaniasis, *Leishmania amazonensis*, is commonly found in Brazil, particularly in the Amazon region [156]. Pentavalent antimonial are the primary drugs for treating leishmaniasis, with amphotericin B used as a secondary option [157]. In case to check activity of flavonoid against leishmania, the apigenin's antileishmanial potential was evaluated for 24 h *in vitro*. Apigenin suppressed cell growth and increased reactive oxygen species production [158] via concentration dependent inhibition against *L. infantum* with IC_{50} value of 29.9μM. The apigenin potential via long term and short term schemes was also evaluated against murine visceral leishmaniasis *in vivo*, which demonstrated 94% and 99.7% decrease in liver parasite load in long term and short term schemes respectively [131]. Apigenin isolated from *Larrea divaricata* was evaluated and illustrated trypanocidal activity by different possible mechanisms like redox imbalance or may be disturbing metabolic function [159].

Kaempferol

Kaempferol, a compound that is found in certain plants. In a study chromatographic fractionation was used to extract three flavonoids from the MeOH extract of *Myriophyllum mattogrossense* aerial parts including kaempferol and was tested *in vitro*. Kaempferol possessed anti-*Schistosoma mansoni* effect at EC_{50} value of 81.86 μM. The kaempferol activity was also investigated *in vivo* against the infected mice using single dose of 400 mg/kg and it reduced the worm burden by 25.5% [160]. Kaempferol derivatives, such as tiliroside, have shown significant anti-amoebic activity against *E. histolytica* trophozoites. Through docking studies, it was found that tiliroside, like kaempferol, can directly interact with PFOR and G/FBPA, with potent inhibition constant values similar to those of metronidazole, a commonly used anti-amebic drug. The activity differences between kaempferol and its derivatives may be attributed to the number of OH groups or the presence of sugar molecules, affecting their effectiveness [161]. Kaempferol reduces the antioxidant enzyme expression of *E. histolytica* and therefor is an effective drug. The susceptibility of kaempferol was investigated in hamster model and caused decreased amoebic vitality with 150 μM after 90 mints of incubation [162].

Catechin

Azadirachta indica, has long been used to cure parasite illnesses, however its mechanism and antiparasitic compounds are unclear. There are two basic enzyme targets for the survival of parasites, such as acetylcholinesterase and lactate dehydrogenase. The screened compounds catechin and epicatechin displayed anticholinesterase activity. The compound Carnosol displayed dual inhibitory activity against both enzymes [163]. Epicatechin triggers cell death and alters the cellular structure of amoebas. It also affects the functioning of certain proteins in the amoebas, leading to disruptions in processes like adhesion, cytolysis, and phagocytosis [161].

Flavonoids showing antifungal activity

Quercetin

Although quercetin's antifungal effects are less documented compared to its antibacterial properties, it has been shown to have antifungal activity against *Aspergillus fumigatus* (with an effective range of 16–64 μM) and *Aspergillus niger* [164]. Quercetin's antifungal properties stem from its ability to disrupt fungal growth by inducing oxidative stress and altering the structure of the fungal cell membrane. Additionally, quercetin can enhance the effectiveness of other antifungal medications, particularly in cases of resistant fungal infections [165]. The quercetin gold nanoparticles have strong antifungal activities against *Aspergillus fumigatus* [166]. Vulvovaginal candidiasis is a common infection in humans caused by the fungus *Candida albicans* and quercetin has demonstrated antifungal activities against *Candida albicans*. Quercetin was evaluated *in vitro* against the fungus, significantly reducing the biofilm formation of *Candida albicans* as well as the fungus' adherence and invasion to VK2/E6E7 cells. Furthermore, in a mouse model of vulvovaginal candidiasis, orally administered quercetin effectively protected against *C. albicans* infection without any adverse effects [167]. In another study the combination of HATi (Histone acetyltransferase inhibitors) anacardic acid and quercetin inhibited the biofilm formation of *Aspergillus tropicalis* and their co-administration also downregulated the drug resistant gene expression [168].

Baicalein

Baicalein is originally derived from the root of the *Scutellaria baicalensis* and is considered a favorable medicine in Chinese pharmacopoeia. Baicalein is used as an antifungal agent in case of *Candida albicans* infection [169]. Baicalein encompasses several apoptotic characteristics like externalization of phosphatidylserine, activation of meta caspase, nuclear condensation and DNA

fragmentation. BE additionally affected mitochondrial functioning and elevated intracellular ROS levels. BE can causes *Candida auris* to undergo apoptosis by altering ribosome related pathways indicating that ribosomes may become novel targets for antifungal medications [170]. To fully comprehend the mechanism of action of BE against *C. auris*, more investigation is required [171]. The ribosomal abnormalities can cause ribotoxic stress response (RSR), which diminishes cell viability and hinders protein synthesis [172]. According to a study, ribosomal disability caused an increase in both MPP and mitochondrial reactive oxygen species levels [173]. Fu, Z., *et al*. has shown the combined effect of amphotericin B and biacalein. Amphotericin B exhibit apoptotic activity but because of poor membrane permeability, an increased amount is given that causes side effects. To mitigate these side effects a combination was given of amphotericin B and biacalein. Biacalein enhanced the apoptotic and caspase activity of the amphotericin B [169].

Glabridin

Glabridin is a compound found in licorice root that has strong antifungal properties against certain types of fungi. It works by causing changes in the structure of the fungal cell walls, making them smaller and more permeable [174]. In a recent study the antifungal activity of glabridin alone and combined with other antifungals was evaluated against *Aspergillus fumigatus*. The researchers used a broth microdilution method to assess its activity against both free-floating (planktonic) cells and biofilms at different stages of maturity. Glabridin inhibited the formation of both immature and mature biofilms and damaged the fungal cell wall and membrane on planktonic cells. Glabridin demonstrated a powerful synergistic impact against *A. fumigatus* when combined with either natamycin or amphotericin B [175]. Glabridin also showed antifungal activity against Sclerotinia stem rot caused by *Sclerotinia sclerotiorum,* affecting tyrosine metabolism of *S. sclerotiorum* [176].

Conclusion

In summary, this review underscores the significant therapeutic promise of phenolic compounds, especially flavonoids, in addressing various infectious diseases. Abundantly found in fruits, vegetables, and medicinal plants, flavonoids possess a wide range of biological properties, including the ability to combat bacteria, viruses, fungi, and parasites. Furthermore, the extensive range of dietary sources containing flavonoids underscores their accessibility and potential as

natural remedies. These compounds function through antioxidant effects, inhibiting enzymes, disrupting microbial membranes, and altering the host's immune responses. Studies reviewed here demonstrate the efficacy of specific flavonoids, such as apigenin, quercetin, and kaempferol, against various pathogens. This research points to promising new strategies for developing treatments, particularly for emerging infectious diseases and the challenge of antimicrobial resistance.

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