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Review Article

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"Flavonoids and Brain Health: Chemical insights into Neurotherapeutic Benefits "

Wafa Mohammed Ali[1], Fathimathul Hisana Vattamkadathil[1], Fathima Hiba Kadambott[1], Fathima Wafa Thalappil[1] , Shifa thasni V[2] and Rashid Kootamkodan[3*]

[1]Department of Pharmacology, Moulana College of Pharmacy, Perinthalmanna 679321, Malappuram, Kerala, India

[2]Department of Pharmacy Practice, Jamia Salafiya Pharmacy College, Pulikkal 679637, Malappuram, Kerala, India

[3]Department of Pharmacology, Moulana College of Pharmacy, Perinthalmanna 679321, Malappuram, Kerala, India

ABSTRACT

Neurological and neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, poses significant health challenges due to their complex pathophysiology and unattainable curative treatments. Flavonoids, a diverse class of polyphenolic compounds, exhibit rich antioxidant and anti-inflammatory properties, modulate critical downstream effectors including ERK, PI3-kinase/Akt, and inhibit enzymes linked to amyloid plaque formation leading to mitigating neuronal apoptosis and oxidative stress. Due to their ability to penetrate blood-brain barrier, enhances their relevance in pointing neuroinflammation, cerebral ischemia, and even glioblastoma, as evidenced by preclinical and clinical studies. Specific flavonoids, including Genistein, quercetin and hesperidin have displayed beneficial effects in cognitive tests and pathological hallmarks in neurodegenerative diseases models. However, challenges of suboptimal bioavailability and metabolic instability limit their daily application. Emerging approaches, particularly nanotechnology-based delivery systems, offer innovative solutions to improve its systemically bioavailable. Although dietary flavonoids are generally safe to intake, excessive intake via supplements may pose risks, underscoring the need for rigorous safety evaluations. This comprehensive analysis addressing the dual role of flavonoids in neuroprotection and disease intervention, and encourages further studies to optimize their bioavailability and long-term safety in diverse populations. This review is Bridging traditional knowledge with modern pharmacological insights, flavonoids represent a convincing avenue for the development of novel neurotherapeutics in an era demanding safer, natural alternatives.

***Corresponding author**

Rashid Kootamkodan, Department of Pharmacology, Moulana College of Pharmacy, Perinthalmanna 679321, Malappuram, Kerala, India.

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Introduction

Neurological and neurodegenerative disorders represent significant health challenges in the modern era. Common conditions include nervous depression, while more severe diseases such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis are also prevalent. Although these disorders are often associated with aging, they are also linked to metabolic and immune system dysfunctions. They result in the progressive deterioration of neurons, often accompanied by the buildup of harmful substances, chronic inflammation, and cognitive decline. Despite notable advancements in pharmacology, definitive cures for these conditions remain elusive. As a result, there is growing interest in exploring natural substances for their potential role in prevention and supportive care.

Neurodegenerative Diseases (ND) are weakening conditions that affect the Central Nervous System (CNS), highly related to the aging of the world population. ND are characterized by the dysfunction and loss of the neuronal structure and function, as a result of uncontrolled neuronal death that leads to a progressive decrease in brain functions [1-3]. These diseases are connected with a wide range of clinical symptoms, including cognitive decline, memory loss and the impairment of motor functions [1-5]. Moreover, the severity of the ND symptoms gradually increase along with the disease development, leading to a decreased capability for independent living. As the average lifespan increased, the prevalence of CNS diseases tends to increase, with a high impact of the serious effects of such diseases on the quality of life as well as a high burden on healthcare systems worldwide [1-3].

Neurodegeneration is defined as a selective and progressive loss of the structure and function of specific populations of neurons, and is found in disorders such as Parkinson's Disease (PD),Huntington's Disease (HD), Alzheimer's Disease (AD),Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease), and glaucoma [6].

Most of the drug candidates have been developed as potentially effective neuroprotective agents based on discovery that indicate that pathological progression of ischemic stroke and subsequent I/R injury is caused by a variety of mechanisms, including inflammation and oxidative stress, etc. Although, adverse side effects and low therapeutic efficacy caused by insufficient entry into lesioned areas and nonspecific drug distribution are resulted in translational failure of those candidate drugs [7].

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While herbs and herbal remedies have a long history of traditional use, they are safe and effective but unfortunately received little scientific attention [8-12]. Many plants and their constituents are recommended in traditional practices of medicine to increase cognitive function and to reduce other symptoms of AD, including poor cognition, depression, and memory loss.

Flavonoids represent a various group of natural compounds which are biosynthesized from phenylalanine, and are present in green pigments in the plant kingdom [13]. Flavonoids have a long history of medical use for the treatment of numerous medical ailments [14]. So far, more than 7,000 flavonoids are reported from natural sources including medicinal plants, vegetables, fruits and wines. Flavonoids have the ability to bind with various body proteins and alter the transporters, enzymes, hormones, DNA, chelation of heavy metals and scavenge the free radicals; as a result, possess strong antioxidant properties. A myriad number of pharmacological studies have been reported about their use in the management of Diabetes Mellitus (DM), cancer, cardiovascular diseases, neurological disorders, inflammation and microbial diseases [15].

The effect of flavonoids rich foods like cocoa, green tea and blue berry can be attributed to the interactions of flavonoids and their metabolites with various cellular and molecular targets [16,17]. It has been reported that some flavonoid interactions with receptors within the ERK and PI3-kinase/Akt signalling pathways enhance the production of neuromodulatory and neuroprotective proteins and enhance the quantity and potency of certain neurone types [18-20]. Simultaneously, their helpful effects on the cerebrovascular system can enhance the cognitive performance of individuals via an increase in blood flow and stimulation of neurogenesis in brain. Several other mechanisms regarding the advantage of flavonoids have been recently documented [21,22]. Flavonoids weakened the initiation and progression of AD-like pathological symptoms and several neurodegenerative disorders. The mechanisms for these effects include the inhibition of neuronal apoptosis induced by neuro-inflammation, oxidative stress, inhibition of key enzymes included in the fabrication of amyloid plaques and other pathological products [23]. Flavonoids thus mediate their neuroprotective effects by keep up the neuronal quality and number in the key brain areas and thus inhibit the onset or progression of diseases responsible for the reduce in the cognitive function.

This review explores the neuroprotective effects of flavonoids, focusing on their chemical composition, the mechanisms through which they protect the nervous system, and their therapeutic potential in preventing or slowing neurodegeneration.

Methods

Recent scientific literature published in high quality journals were collected using PubMed, Web of Science, Scopus, and the academic search engine Google Scholar. The keywords employed included: flavonoids, classification of flavonoids, biosynthesis of flavonoids, dietary sources of flavonoids, and neuroprotective properties of flavonoid. Articles were screened based on their titles, abstracts, and the availability of full-text versions. Publications not in English were excluded from this review. No filters were applied regarding text availability, article type and publication date.

Biosynthesis of Flavonoids

Flavonoids are secondary metabolites of plants obtained from primary metabolic precursors which are generated via various biosynthetic pathways. The shikimate pathway includes various enzymes and six-step reactions for the biosynthesis of shikimic acid. It starts with the aldol condensation reaction of phosphoenolpyruvic acid and D-erythrose 4-phosphate [99, 100]. The end product of the shikimate pathway is chorismic acid which is further converted into the amino acid phenylalanine through the action of Prephenate-Aminotransferase (PhAT) and Arogenate-Dehydratase (ADT) enzymes [100]. Flavonoids primarily originate from two biosynthetic pathways (figure 1): the phenylpropanoid pathway, which generates the phenylpropanoid skeleton (C6-C3), and the polyketide pathway, which supplies polymeric C2 units [101]. The enzyme chalcone synthase facilitates the synthesis of the 2′-hydroxychalcone scaffold, which is chemically known as (E)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (Figure 1), by utilizing p-coumaroyl CoA and malonyl CoA. This intermediate further undergoes multiple enzymatic transformations to produce various flavonoids [102]. Several factors, including environmental conditions (such as light, water availability, and temperature), hormones like jasmonic acid, and physical damage, regulate the expression of genes involved in flavonoid biosynthesis, thereby affecting their production. [103].

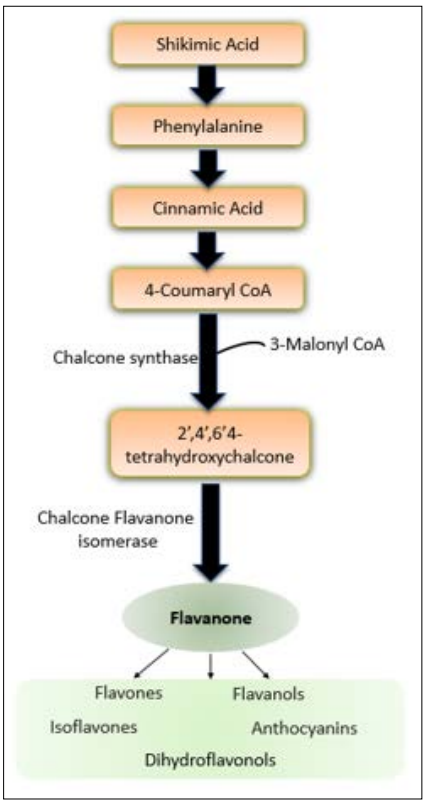


Figure 1: Biosynthesis of Flavonoids

Overview of Flavonoid Structure

Nearly all flavonoids present a C6-C3-C6 structure containing two benzene ring (A and B) connected by a heterocycle pyrene ring (C) that contains oxygen (figure 2). Flavonoids can be classified into two main groups based on the degree of central heterocyclic ring saturation [24]. For example, anthocyanidins, flavones, flavonols, and isoflavones contain a C2=C3 unsaturation, while flavanones, dihydroflavonols, and flavan-3-ols are examples of saturated flavonoids. However this classification is the most common one, flavonoids can also be classified based on molecular size, primarily due to the prevalence of biflavonyls in gymnosperms.Additionally regarding flavonoid structure is the degree of substituents on the A and B rings, groups involving like hydroxy, alkyl, and methoxy.

Moreover, in plants, flavonoids may be seen in the free form (aglycones) or linked to sugars. Glycosylated flavonoids are, in fact, the most prevalent form. For instance, glycosylated anthocyanidins are identified as a key class of flavonoids known as anthocyanins. Anthocyanidins themselves are sensitive to light and typically occur bound to sugars. Among flavonoid glycosides, O-glycosides are the most common, though C-glycosides are also present [25]. Glycosylation improves solubility, distribution, and metabolism by aiding in membrane transport, while methylation enhances flavonoid uptake into cells and provides protection [25].

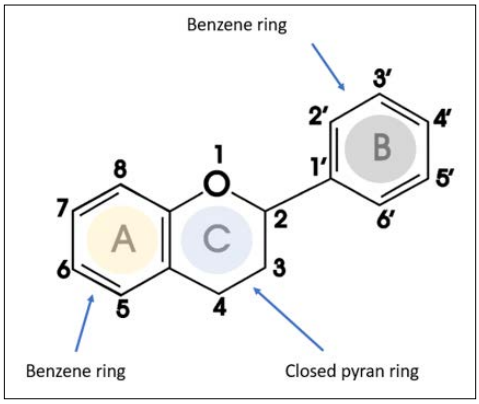


Figure 2: Basic Structure of Flavonoids

Classification of Flavonoids

Flavonoids are a diverse group of natural substances with variable phenolic structures [26]. Until now, more than 9,000 flavonoids have been discovered and are categorized into seven subgroups based on modifications to their core structure (figure 3). These subgroups include flavones, flavanones, isoflavones, flavonols, catechins, and anthocyanins [27-30].

Flavones

Flavones, a significant subgroup of flavonoids, are characterized by a 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one) structure (Figure 1A) and are commonly found in the leaves, flowers, and fruits of various plants, including celery, parsley, red pepper, chamomile, mint, and ginkgo [31-36]. They feature a C2′-C3′ double bond and a C-ring with a ketone group at the C4′ position [37]. Typically, flavones have a hydroxyl group on the A-ring at C5′, with additional hydroxylation frequently at C7′ on the A-ring and at C3′ and C4′ on the B-ring [38,39]. Glycosylation in flavones predominantly occurs at C5′ and C7′ on the B-ring, while methylation and acylation take place on the hydroxyl groups of the B-ring [40]. The most common flavones include apigenin, luteolin, baicalein, chrysin, and their derivatives [41].

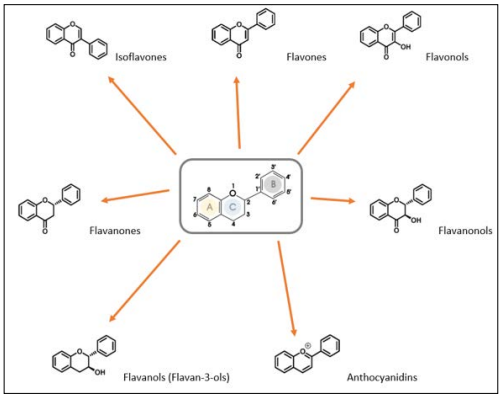


Figure 3: Types of Flavonoids

Flavonols

Flavonols, also referred to as 3-hydroxyflavones, feature a hydroxyl group at the C3′ position of the C-ring and exhibit varying degrees of glycosylation [42]. They serve as the fundamental units of proanthocyanidins and are widely present in fruits and vegetables like onions, lettuce, tomatoes, apples, and grapes [43-49]. The structural diversity of flavonols is primarily influenced by glycosylation and methylation processes [50, 51]. O-glycosides, the predominant substituents, are typically located at position 7 of the A-ring and position 3 of the C-ring, leading to the formation of flavonol glycosides, which include compounds such as kaempferol, quercetin, limocitrin, and isorhamnetin [52]. In the last 15 years, there has been a notable rise in the identification of flavonones [53]. Flavonols in the diet play a crucial role in human health, offering antioxidant, cardioprotective, antibacterial, antiviral, and anticancer benefits [54].

Flavanones

Flavanones, also known as dihydroflavones, are characterized by a saturated C-ring [55]. The primary structural difference between flavanones and other flavonoids is the absence of an unsaturated double bond between the C2′ and C3′ positions of the C-ring [56]. Flavanones are predominantly found in citrus fruits [57, 58], featuring hydroxyl groups at the C5′ and C7′ positions of the A-ring, along with hydroxyl or methoxy groups at the C3′ or C4′ positions of the B-ring [59]. The main substituent, O-glycoside, is typically attached at position 7 of the flavanone aglycone, resulting in flavanone glycosides [60]. These glycosides commonly include glucoside, rhamnoside, rutinoside, and neohesperidoside substituents [61]. Flavanones can be categorized based on their structural variations into types such as hesperetin, naringin, naringenin, eriodictyol, hesperidin, pinocembrin, and likvirtin [56-62]. Among these, naringenin and hesperetin are the most prevalent flavanones, commonly found in lemons, oranges, limes, tangerines, and grapefruits [63-65].

Isoflavonoids

Isoflavones are distinguished by a C-ring with the B-ring attached at position 3 (Figure 1D), which is the key structural difference from other flavonoids [66, 67]. They are primarily found in leguminous plants, where they play crucial roles in microbial signaling and the formation of root nodules in legumes [68]. Isoflavones are categorized into two main groups: genistein and daidzin, which occur in various forms such as aglycones, 7-O-glucosides, 6′-O-acetylglucosides, and 6′-O-malonylglucosides [69, 70]. These compounds exhibit strong antioxidant activity, helping to protect plant cells from free radical damage and enhancing their resistance to UV-B radiation, salt stress, and osmotic stress [71-73].

Neoflavonoids

Neoflavonoids are characterized by a 4-phenyl coumarin backbone and the absence of a hydroxyl group at the C2′ position. These compounds are uncommon in food plants [74]. Based on their core skeleton structure, neoflavonoids are classified into four subtypes: dalbergia phenols, dalbergia quinones, dalbergia lactones, and benzoyl benzenes [75, 76].

Flavanols, Flavan-3-ols, or Catechins

Flavanols, also known as dihydroflavonols or catechins, are 3-hydroxy derivatives of and are naturally occurring plant compounds valued for their antioxidant properties [77]. They are often referred to as flavan-3-ols because the hydroxyl group is consistently attached at position 3 of the C-ring [78]. Unlike other flavonoids, flavanols lack a double bond between the C2′

and C3′ positions of the C-ring [79-81]. These compounds are abundant in various fruits, including bananas, apples, blueberries, and pears [82-85], and can be categorized into several types: catechin, gallocatechin, catechin 3-gallate, gallocatechin 3-gallate, epicatechin, epicatechin 3-gallate, and epigallocatechin 3-gallate [86]. Flavanols and their metabolites contribute significantly to plant defense mechanisms against environmental stresses, owing to their strong antioxidant and free radical scavenging capabilities [87,88].

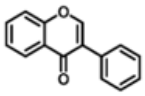
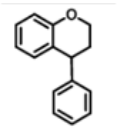
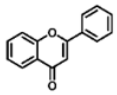
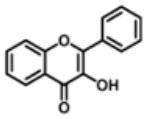
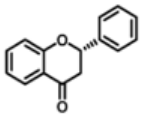
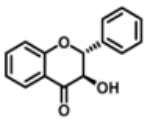
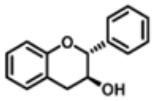
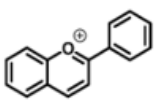
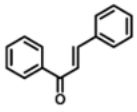
Anthocyanins

Anthocyanins are glycosylated polyphenolic compounds that function as soluble vacuolar pigments, producing a wide range of colors-including orange, red, purple, and blue-in both vegetative and reproductive parts of plants [89, 90]. To date, more than 650 anthocyanins have been identified across different plant species and are classified into six main groups: cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin, along with their derivatives [91-93]. Unlike most other flavonoids, with the exception of flavanols, anthocyanins lack a ketone group at position 4 of the C-ring . These pigments are predominantly located in the outer cell layers of many fruits and vegetables, such as black currants, grapes, and various berries [94-98].

Chalcones

Chalcones do not have a pyran ring but they are still classified as flavonoids on the basis of similarity in their synthetic approach with that of flavonoid. In chalcones, the pyran moiety is available as an open structure. The open structure has a carbonyl conjugated to a double bond making an α, β-unsaturated ring system, an ideal Michael acceptor for many organic reactions.

Table 1: Flavonoid Classes with Examples and Properties

Flavonoid Subclass	Structural Characteristics	Examples	Properties
Isoflavones		*Genistein, Daidzein, Glycitein*	Found in soybeans, exhibit estrogenic activity, antioxidant properties
Neoflavonoids		*Neoflavones, Neoflavenes*	Known for antidiabetic activity, found in *Echinops niveus*, *Dalbergia odorifera, Nepalese propolis*
Flavones		*Apigenin, Luteolin, Chrysin*	Found in various plants, exhibit antioxidant and anti-inflammatory properties
Flavonols		*Quercetin, Kaempferol, Myricetin*	Antioxidant activity, can exist as glycosides
Flavanones		*Hesperidin, Naringenin*	Found in citrus fruits, exhibit anti-inflammatory and antimicrobial properties
Flavanonols		*Taxifolin, Astilbin*	Antioxidant and anti-inflammatory effects
Flavanols (Flavan-3-ols)		*Catechin, Epicatechin, Gallocatechin*	Found in tea, cocoa, and fruits; strong antioxidant properties
Anthocyanidins		*Cyanidin, Delphinidin, Malvidin, Pelargonidin*	Impart color to plants (red, blue, purple hues), possess antioxidant activity
Chalcones		*Isoliquiritigenin, Butein*	Precursor to flavonoids, exhibit antimicrobial and anticancer properties

Neuropharmacological Benefits of Flavonoid

As stated, it has been determined for some time that certain flavonoids can cross the BBB; here, we will discuss the current treatments used for various brain diseases.

Neuroinflammation

Two major hallmark diseases centered around neuroinflammation are Alzheimer's Disease (AD) and Parkinson's Disease (PD) [99]. Neuroinflammation has been known to be a critical factor in these diseases; understanding the role of anti-inflammatory, antioxidant agents, such as flavonoids, could be beneficial in developing future treatments (figure 4). Recently, a clinical trial was performed for a therapeutic form of genistein, a well-defined flavonoid chemical, on prodromal Alzheimer's patients [100]. One study showed a simple fruit juice diet in middle-aged women with worsening cognition improved their cognitive performances on the Rey Auditory Verbal Learning Test [101]. This study further associated the presence of polyphenols in the blood and urine, which are known metabolites of fruit juice. Urine analysis in this study revealed higher levels of thyroxine and 3-methyladenine, which yield stability to pro-autophagic signaling associated with AD. Further clinical trials will elucidate additional mechanistic and therapeutic information regarding genistein and polyphenols and their role in neuroinflammatory diseases.

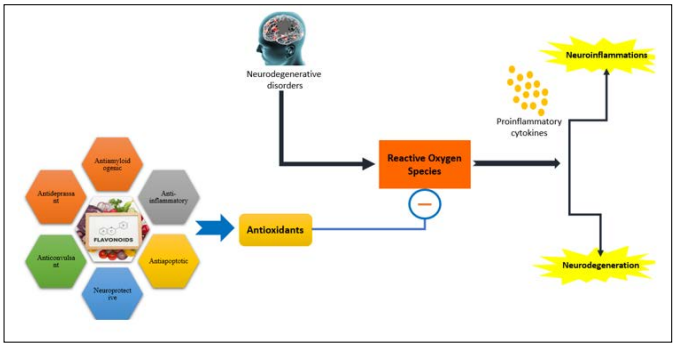


Figure 4: Neuroprotective Effects of Flavonoids with Mechanism.

Antiinflammatory Activity

The molecular mechanisms involved in the anti-inflammatory activities of flavonoids have been suggested to include: inhibition of pro-inflammatory enzymes, such as cyclooxygenase-2, lipoxygenase and inducible NO synthase, inhibition of NF-κB and activating protein-1 (AP-1) and activation of phase II antioxidant detoxifying enzymes, mitogen-activated protein kinase (MAPK), protein kinase C and nuclear factor-erythroid 2-related factor 2 [102]. Cyclooxygenase-2 is inhibited by quercetin and kaempferol in rat peritoneal macrophages [103]. Catechin weakly inhibits cyclooxygenase-2 but at a very high concentration (100 μM) with respect to the serum concentrations found following the ingestion of flavonoid-rich foods [104]. Flavonols such as kaemferol, quercetin, morin and myricetin were found to be better lipoxygenase inhibitors than flavones.

It has been observed that several flavonoids are able to decrease the expression of different pro-inflammatory cytokines/chemokines, including TNFα, IL-1β, IL-6, IL-8 and monocyte-chemoattractant protein-1, in different cell types such as RAW macrophages, Jurkat T-cells and peripheral blood mononuclear cells [105]. Quercetin and catechins coupled their inhibitory action on TNFα and IL-1β to an enhanced release of the anti-inflammatory cytokine IL-10 [105]. Molecular mechanisms involved in their cytokine-modulating activity, including polyphenol-mediated inhibition of transcription factors NF-κB and AP-1 and reduction of MAPK activity, have been suggested as relevant anti-inflammatory pathways [105-106].

Brain Cancer

A study showed the effects of several flavonoids on human GL-15 glioblastoma cells and found that all the flavonoids decreased the number of viable cells for cancer proliferation [107]. The anti-cancer effects shown by flavonoids indicate that flavonoids could have cytotoxic effects on cancer cells and could be a vital avenue of therapy for patients with early forms of brain gliomas.

Flavonoids and Stroke

Over the past few decades, many studies have been conducted, unveiling intriguing insights into using flavonoids as a remedy for stroke. These studies have explored the therapeutic potential of flavonoids, delving into their unique properties and mechanisms of action, aiming to harness their beneficial effects in mitigating the impact of stroke. According to a notable study published in the, evidence supports the association between high polyphenolic content in food and a reduced risk of stroke [108]. They found that individuals who regularly consumed higher amounts of fruits and vegetables, which are rich sources of polyphenols, exhibited a lower risk of experiencing a stroke.

Cerebral ischemia–reperfusion injury, a critical event in the pathogenesis of stroke, involves complex mechanisms such as apoptosis and Extracellular Matrix (ECM) accumulation. One study, for example, highlights the significance of apoptotic cell death in mediating the pathological consequences of acute brain ischemia and emphasizes the need for targeted therapeutic interventions to modulate apoptotic pathways to mitigate the detrimental effects of ischemic stroke [109-110]. This study allows for a target point of research to mitigate the impact of stroke, which was accomplished in a 2021 study by Wu et al. It provides valuable insights into the neuroprotective effects of icaritin and icariin in an experimental model of ischemic stroke. The findings highlight the ability of these flavonoids to mitigate neuronal apoptosis, preserve brain tissue integrity, and reduce the excessive accumulation of ECM following ischemic injury.

Hemorrhagic brain injury or Intracranial Hemorrhage (ICH), characterized by bleeding into the brain parenchyma or subarachnoid space, threatens neurological function and patient outcomes [111]. Shi et al. focused on baicalin, a specific flavonoid compound and active ingredient of the Chinese herbal medicine Scutellaria baicalensis, and its protective effects in a mouse model of subarachnoid hemorrhage [112]. Baicalin treatment was found to attenuate BBB disruption, which is a critical event that exacerbates brain edema and secondary brain damage following hemorrhage. Baicalin exerted its protective effects by modulating the expression of tight junction proteins and reducing vascular permeability, thereby preserving the integrity of the BBB.

ICH is a devastating condition that comprises 10–15% of all strokes and is associated with high morbidity and mortality [113]. While rutin, a dietary flavonoid, has demonstrated neuroprotective effects against cerebral ischemic stroke through its antioxidant and anti-inflammatory properties, its potential efficacy against ICH stroke remains unexplored [114]. The study highlights rutin's ability to alleviate oxidative stress, inhibit inflammatory processes, and maintain crucial signaling pathways involved in cellular homeostasis.

Table 2: Flavonoids and Their Neuropharmacological Activities

Flavonoid	Neuropharmacological activity	References
Hesperidin	Antidepressant Neuroprotective Cognitive	[137] [138] [139]
Silibinin and Naringenin	Neuroprotectants Antidepressant-like property	[140] [141]
Propolis	Antioxidant activity, and positive neurotrophic modulatory effects	[142]
Rutin and Hesperidin	Antidepressant	[143]
Aurones	Antioxidant	[144]
Apigenin	Neuroprotective effect	[145]
Gardenin A	Anxiolytic-like effects and Anticonvulsant actions	[146]
Isovitexin	Neuroprotective response	[147]
vitexin	Anticonvulsant effects	[148]
Quercetin	Anti-neuroinflammation Regulation of GABAC receptor channel activity.	[149] [150]
Morin	Neuroprotective	[151]
Epigallocatechin-3-gallate	Antialzheimer's Antiparkinsonian	[152]
Formononetin	Neuroprotective	[153]
Silymarin	Neuroprotection;	[154]
Chrysin and wogonin	Anxiolytic-like activity	[155]
Acacetin	CNS depressant activity	[156]
Genistein	Neuroprotective	[157-158]
Nattokinase, daidzein, genistein and glycitin	Antialzheimers	[159]

Antiplatelet Actions of Flavonoids

Flavonoids have been shown to inhibit thrombus formation, with their efficacy dependent on structural features like the 2,3-double bond, 4-keto group, and hydroxyl groups at positions 4 and 7. Structural modifications or glycosylation can weaken their antiplatelet activity. Their mechanism includes temporarily blocking thromboxane A2 receptor activation, enhancing eNOS activity, and promoting anticoagulant effects through platelet-endothelial cell adhesion molecules. Flavonoids also reduce p-selectin expression and microparticle release, while tea catechins lower platelet-activating factor production by inhibiting acetyl-CoA-acetyltransferase [115].

Flavonoids and the Blood Brain Barrier (BBB)

Flavonoids' ability to penetrate the BBB is crucial for their neuroprotective potential. Most flavonoids follow Lipinski's Rule of 5, predicting favorable pharmacokinetics. Molecular docking and in silico studies suggest their viability as brain therapeutics. Research on BBB models, including human and rodent brain endothelial cells, confirms flavonoid uptake. Further studies using ECV304/C6 cell models indicate that flavonoids can cross the BBB and reach various brain regions, though permeability varies. Naringenin crosses the BBB more effectively than quercetin, which may interact with p-glycoprotein, a key player in neurodegenerative diseases like Alzheimer's and Parkinson's. Overall, flavonoids exhibit promising BBB penetration, supporting their therapeutic use in brain disorders [115].

Anxiolytic Effects

Some natural molecules, such as flavonoids, produce anxiolytic-like effects in animal models, comparable to those produced by diazepam. At preclinical research, the flavonoid chrysin has verified anxiolytic-like effects mediated through the GABAA/Benzodiazepine receptor complex [116, 117]. However, unlike benzodiazepines, chrysin exert anxiolytic actions without inducing sedation or muscle relaxation [117].

Toxic Effects of Flavonoids

Consuming flavonoids in excessive quantities may lead to harm rather than providing protection. Most of the past researches have demonstrated the positive effects of flavonoids on various conditions, including neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, ischemic stroke, and traumatic brain injury. Nevertheless, it is crucial to acknowledge the possible adverse effects and toxicity linked to their intake. While flavonoids are generally viewed as safe and well-tolerated when obtained from dietary sources, it is advisable to consult a physician before consumption.

Emerging evidence highlights potential health risks associated with excessive flavonoid intake, particularly through supplements, which may contribute to adverse outcomes in vulnerable groups like older adults or those taking medications prone to interactions [118, 119]. Research suggests that high doses of certain flavonoids could trigger harmful biological processes. For instance, enzymatic reactions involving peroxidases may convert phenolic compounds in flavonoids into reactive radicals, which in turn damage cellular components like lipids, DNA, and antioxidants, generating oxidative stress [120-121]. These effects may explain why specific flavonoids, including luteolin, apigenin, quercetin, and genistein, have raised concerns regarding liver toxicity, hormonal disruption, and DNA damage in experimental models [122].

Human studies reveal broader systemic impacts, with documented cases of flavonoid-related harm to organs such as the liver, kidneys, and gastrointestinal tract [123]. Notably, a Japanese cohort study identified a dose-dependent correlation between isoflavone intake (genistein and daidzein) and elevated hepatocellular carcinoma risk in women [124]. While lab studies often flag quercetin's mutagenic potential, animal research has yielded inconsistent results, underscoring the complexity of translating in vitro findings to real-world scenarios [125]. Higher flavonoid doses may paradoxically act as pro-oxidants or interfere with hormone-regulating enzymes, necessitating deeper investigation into safe thresholds [124].

Despite widespread availability as supplements, many flavonoid products lack rigorous safety testing. Unlike pharmaceuticals, these formulations evade FDA scrutiny, leaving gaps in understanding their toxicity profiles and drug interaction risks [118]. Reports of kidney damage linked to quercetin and other flavonoid-rich botanicals further emphasize the need for standardized clinical evaluations [126-128]. Current evidence gaps underscore the urgency of systematic research to balance the therapeutic promise of flavonoids with their potential hazards, particularly as their popularity in consumer health products grows.

Limitations for Clinical Use of Flavonoids and Future Solutions
The practical application of flavonoids in medicine, pharmaceuticals, food, and cosmetics faces two major challenges. First, their chemical and biophysical limitations-including poor solubility, instability, low bioavailability, and unpredictable metabolic behavior during digestion and liver processing—hinder their effectiveness. Second, production hurdles arise from plants yielding minimal quantities of these secondary metabolites relative to overall biomass, compounded by inefficient extraction methods and difficulties in refining biosynthesis pathways [129].
A critical barrier lies in flavonoids' limited bioavailability. When consumed orally, only a fraction is absorbed early in the digestive tract, while much of the ingested dose interacts with gut microbiota in the colon. Others undergo significant transformation by liver enzymes, particularly cytochrome P450, which metabolizes them into active derivatives [129-132]. Absorption rates vary widely depending on molecular structure and environmental pH. Once absorbed, flavonoids are rapidly modified by intestinal and hepatic processes into conjugated forms like glucuronides, sulfates, or methylated metabolites.

Notably, smaller hydrophobic flavonoid aglycones enter the liver via the portal vein, where they undergo Phase I oxidation and Phase II conjugation reactions. In contrast, bulkier flavonoid glycosides—more water-soluble but harder to absorb-must first be broken down by gut bacteria into simpler aglycones or phenolic acids before entering systemic circulation [130, 131]. These metabolic complexities underscore the need for tailored formulations to optimize flavonoid delivery and efficacy across industries.

Emerging research suggests nanotechnology could revolutionize how we overcome flavonoid-related challenges. By leveraging nanoscale innovations, scientists aim to enhance the stability, solubility, and bioavailability of these compounds-key hurdles limiting their use in drugs, foods, and cosmetics. Nanoparticles' unique physical traits, such as their minute size and high surface-to-volume ratio, position them as ideal candidates for optimizing plant-derived therapeutics. For instance, they could enhance the potency of plant-derived compounds, boost the production of secondary metabolites, minimize unwanted side effects, and improve how efficiently the body absorbs these substances [133- 135].

Current studies focus on biocompatible delivery systems like liposomes, ethosomes, and solid lipid nanoparticles, alongside nanostructured carriers, cyclodextrins, and dendrimers-all engineered for compatibility with biological systems (figure 4). These platforms not only protect flavonoids from premature degradation but also enable targeted delivery, ensuring active compounds reach their intended sites more effectively. In pharmaceutical and agricultural contexts, such advances may streamline the extraction of high-yield plant metabolites while reducing reliance on resource-intensive purification methods [136].

By bridging gaps in flavonoid functionality, nanotechnology could unlock their full potential, transforming challenges like low bioavailability and metabolic instability into solvable engineering problems. This interdisciplinary approach underscores the growing synergy between material science and natural product research.

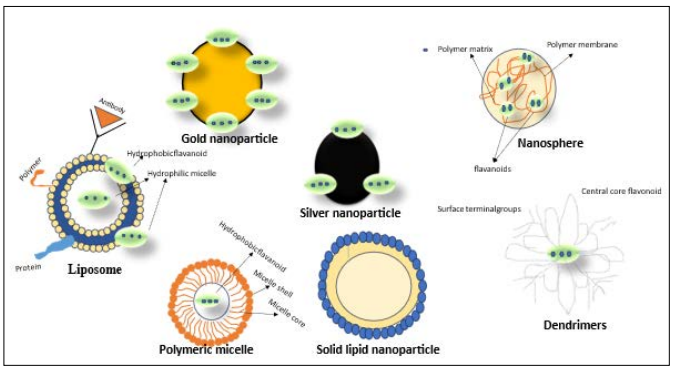


Figure 5: Biocompatible Delivery Systems of Flavonoids to Improve Bioavailability

Conclusions and Summary
As shown, flavonoids can exert their effects on many different biological pathways and have a strong therapeutic effect, mainly in antioxidants. While they are used in many different disease conditions, they also have shown a robust therapeutic impact on brain diseases and conditions. For example, when discussing neuroinflammation, certain flavonoids have shown that they can readily cross the BBB and modulate and control ROS levels. Lastly, they are relatively safe for consumption, as the sources of these flavonoids come from very commonly consumed food groups. While this information is promising, more studies regarding pharmacokinetics (absorption, distribution, metabolism and elimination) must be investigated to elucidate

the bioavailability in brain regions further. In doing so, analogue structures of the flavonoid can be synthesized for potential neuro-therapeutic bioavailability. Currently, some flavonoids are in clinical phases for drug development; genistein, for example, is currently in clinical trials and seems to have promising results for anti-inflammatory diseases such as Alzheimer's Disease.

Future studies will elucidate the length and degree of flavonoid therapy and the primary and secondary mechanisms in which they may be involved. While dietary lifestyle changes may lead to small changes, isolating the active flavonoid component and developing a therapy may lead to more drastic and larger-scale modifications in terms of therapy. Regarding brain injury, flavonoids could be a safe and productive means of ameliorating the oxidative stress symptoms associated with brain injury, specifically strokes. Flavonoids have presented themselves as a strong candidate for therapies for brain diseases. As clinical trials proceed, the Food and Drug Administration will examine each one closely for the potential of new drug development. As the FDA approves more flavonoids for brain disorders, it is essential to understand which disorders they can treat and the degree to which they can help. For example, as stated, flavonoids' therapeutic and anti-neuroinflammatory effects are worth investigating for treating certain diseases such as AD, PD, and strokes.

In conclusion, while flavonoids offer numerous benefits and have therapeutic potential for various neurological and neurodegenerative diseases, it is essential to consider their consumption's potential adverse effects and toxicity. The review summarized the significance of the neurologic and neurodegenerative disease, the lack of specific therapeutic agents, and the use of dietary flavonoids devoid of side effects when taken in moderate amounts. We also discussed the neuropharmacology of flavonoids and possible side effects when taken in higher concentrations. However, further research is needed to understand better the safety profile and potential risks of flavonoid intake, particularly at high doses, long-term use, and in specific populations.

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