https://doi.org/ 10.33472/AFJBS.6.Si2.2024.84-102

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Flavonoids and their Therapeutic Applications in Neurological Disorders

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Article History

Volume 6,Issue Si2, 2024

Received:22 Feb 2024

Accepted : 13 Mar 2024

doi: 10.33472/AFJBS.6.Si2.2024.84-102

Abstract

Flavonoids are a diverse class of polyphenolic compounds that occur widely in naturally occurring resources like fruits, vegetables, and plant-derived drinks which have potential therapeutic use in the treatment of several life-threatening neurological disorders. This review highlights the role of different flavonoids in various neurodegenerative disorders through their anti-inflammatory, antioxidant, and neuroprotective effects. They seem to have potential stimulatory and inhibitory effects in the mechanism of disease to either stop or delay the progression of various neurological diseases, including Parkinson's, Huntington's, Alzheimer's, and Multiple Sclerosis.

Flavonoids' role in the regulation of oxidative stress, modulation of signaling pathways as well as enhancement in neuroplasticity pose them as a possible neuroprotective agent against a disease in various clinical and models being conducted. Further, their potential to cross the blood-brain barrier and exert neural protective effect make them ideal for therapeutic roles against neurodegenerative disease.

This review highlights the mechanism of various neurodegenerative diseases, the potential of flavonoids to exert neuro-protective effects, their role in modulation of molecular pathways that can be used in combating neurodegenerative diseases, targeted course of action of flavonoids with specificity, and their future potentials in drug discovery and development.

Overall, elucidating the therapeutic potential of flavonoids in neurological disorders holds promise for developing novel therapeutic strategies aimed at improving neurological outcomes and enhancing the way of life for people affected by these debilitating conditions.

Keywords: *Flavonoid, antioxidant, neurological disorder, Parkinson's disorder, anti-inflammatory, Alzheimer's disease*

1. Introduction

Flavonoids being naturally procured secondary metabolites, consisting of polyphenolic compounds that have been observed to show therapeutic effects in cancer, cardiovascular diseases, diabetes, neurological and metabolic disorders. Flavonoids possess potential antimicrobial, antioxidant, anticancer, anti-proliferative, anti-inflammatory, and anti-apoptotic properties, and are extensively studied in lead discovery in drug discovery (Ullah et al., 2020).

They could be classified depending on their chemical structure, degree of saturation, and oxidation of carbon rings and thus further can be differentiated into different subgroups as flavanone, flavanol, flavanonols, flavans, and isoflavonoids (Panche et al., 2016a). These are produced in nature via the phenylpropanoid pathway, and their bioactivity is reliant on their route of absorption and bio-availability. The physicochemical characteristics, such as molecule size, solubility, configuration, lipophilicity, and pKa; influence the absorption of flavonoids(Youdim et al., 2003). Flavonoid glycoside or aglycan are the two types of flavonoids whose structures determine whether they are absorbed in may be in colon or small intestine. While flavonoid glycosides must first be transformed into aglycan to be absorbed, the aglycan portion of flavonoids is absorbed in the small intestine (Dabeek & Marra, 2019).

Our rapidly transforming lifestyles, high-caloric food habits, sedentary lifestyles, and stress have resulted in an increase in many metabolic diseases, cancer, and neurological disorders. Neurodegenerative conditions primarily affect people in their later years of life; a lot of people suffer from conditions such as Parkinson's disorder, Multiple Sclerosis, Huntington's disorder, and Alzheimer's disorder. The accumulation of abnormal proteins, oxidative stress, neuroinflammation, and mitochondrial dysfunction all of which have the potential to cause the degeneration of specific neurons within the brain and are some of the most significant pathophysiological bases of neurodegenerative diseases (Hamsalakshmi et al., 2022). Synaptic and cognitive dysfunction have an intrinsic relationship to major neurological disorders such as Parkinson's and Alzheimer's, which deteriorate with the loss of these neural cells and the signals that they generate.

The key causes of neurodegenerative diseases are oxidative stress and neuroinflammation. Numerous factors, including abnormal protein accumulation, disruptions in the peroxidation and imbalance in polyunsaturated fatty acid levels, and increased Ca2+ transmission across neurons, are contributors to oxidative stress. Increased oxidative stress triggers the activated interaction of numerous biochemical pathways that cause lipids, proteins, and DNA to undergo oxidative damage, which eventually results in neuronal cell death and neurodegeneration.

This overview provides of the natural flavonoids' resources, structural characteristics, processes, prospects, and potential future therapy approaches for neurological disorders. Employing a range of mechanisms that include molecular pathways and specific molecular targets linked to the pathophysiology of neurological disorders, including oxidative stress, inflammation, vascular remodeling, genetics, ionic channels, and cell proliferation, which with developments in this field would lead in drug discovery. The comprehensive mode of mechanism of several flavonoids were being highlighted against various life-threatening neurological disorders. Flavonoids' interactions with oxidative stress pathways, inflammatory mediators and several other biochemical compounds addressed its potential in having a neuroprotective effect, which either could be harnessed in drug discovery or facilitate the drug in medical treatment or side effects prevention. Further, it has been compared the selective and specific target of different flavonoids in the mechanism of a disease, and thus having a therapeutic action against the disease. The inhibitory and stimulatory effect of different flavonoids were being compared to each other, which would be crucial in knowing their course

of action. This study withstands with such comparisons that may be crucial in target selection, identification in drug discovery and development.

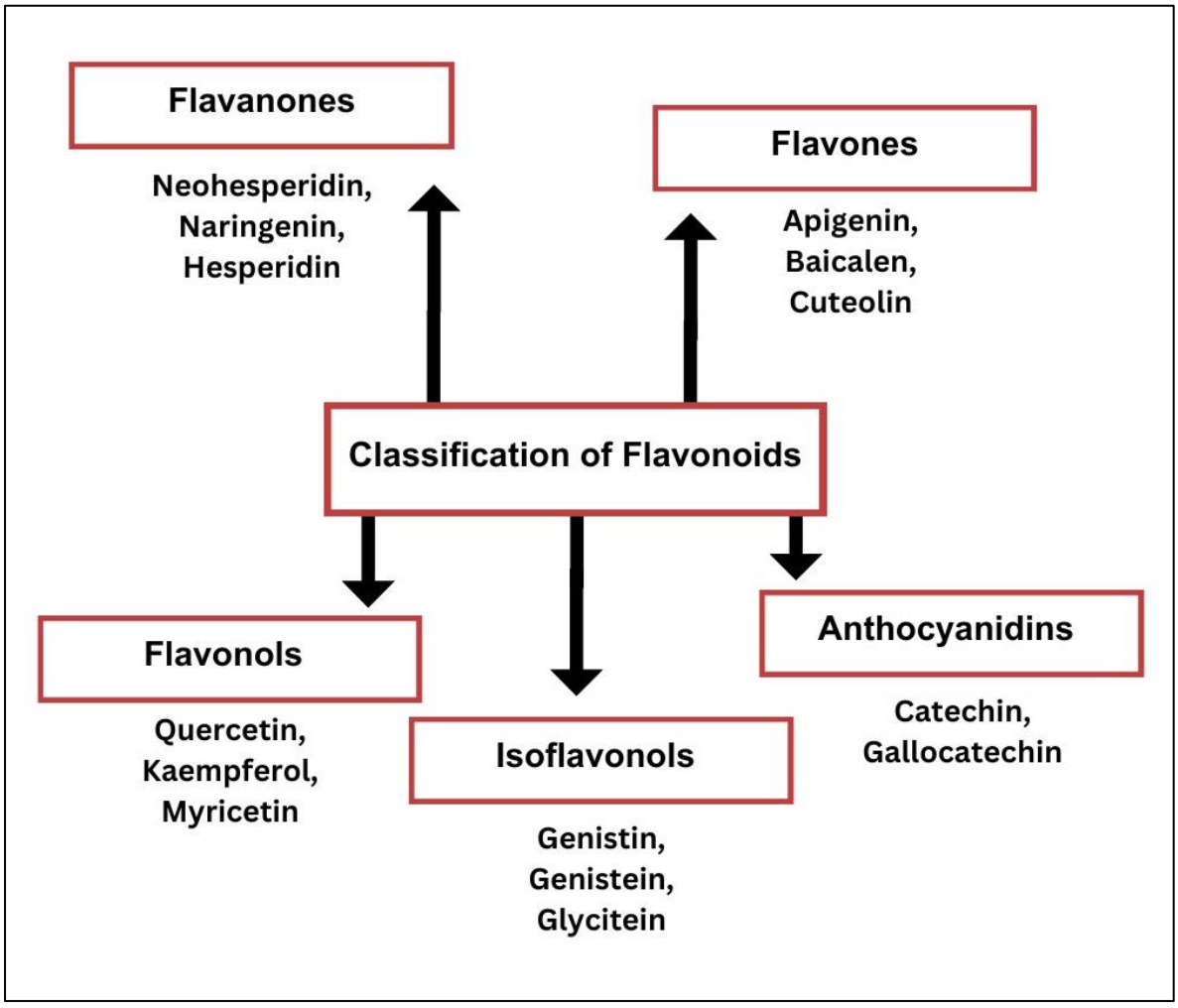

Figure 1: Classification of Flavonoids

2. Biochemical activities of Flavonoids

Plants possess substantial quantities of flavonoids, a sub class of polyphenolic compounds, especially in fruits, vegetables, grains, herbs, and beverages like tea and wine. Different characteristics of Flavonoids are:

2.1 Antioxidant Properties:

One of the most well-known characteristics of flavonoids is their potent antioxidant activity, that they scavenge free radicals and reactive oxygen species (ROS), thereby protecting cells from oxidative damage and reducing the risk of various chronic diseases, including cardiovascular diseases, cancer, and neurodegenerative disorders (Lobo et al., 2010).

2.2 Anti-inflammatory Activity:

Flavonoids possess anti-inflammatory properties, which contribute to their therapeutic potential in mitigating inflammation-associated diseases as they modulate inflammatory

pathways by inhibiting the production of pro-inflammatory cytokines, enzymes (such as cyclooxygenases and lipoxygenases), and signaling molecules involved in the inflammatory response (Rakha et al., 2022).

2.3 Neuroprotective Effects:

Flavonoids have been shown to have neuroprotective benefits in an array of neurological disorders experimental models as they protect neurons from damage caused by oxidative stress, inhibit neurological inflammation, promote neuronal survival, and enhance neuroplasticity these properties make flavonoids promising candidates for the prevention and treatment of neurodegenerative diseases like Alzheimer's and Parkinson's (Ayaz et al., 2019).

2.4 Cardioprotective Effects:

Several flavonoids have been linked to improvements for cardiovascular health. They improve endothelial function, reduce blood pressure, inhibit platelet aggregation, and lower LDL cholesterol levels, thus reducing the risk of cardiovascular diseases such as coronary artery disease and stroke (Ciumărnean et al., 2020).

2.5 Antimicrobial Activity:

Certain flavonoids exhibit antimicrobial properties, inhibiting the growth of bacteria, fungi, viruses, and parasites as they can be used as natural alternatives to conventional antimicrobial agents and may help combat microbial infections and antibiotic resistance (Vaou et al., 2021).

2.6 Potential Anti-cancer Properties:

The potential anti-cancer properties of flavonoids have sparked interest in the scientific community as they exert anti-proliferative, pro-apoptotic, and anti-angiogenic effects on cancer cells, inhibiting tumor growth metastasis, and may also be used to enhance the efficacy of conventional cancer therapies and reduce their side effects (Kopustinskiene et al., 2020).

S.No	Common Name	Plant	Class	Bioactive Compound	References
1	Apple	Malus pumila	Flavanols	Quercetin	(H. Khan et al., 2020)
2	Berries	Vaccinium corymbosum	Flavanols	Myricetin	(Zhu et al., 2020)
3	Broccoli	Brassica oleracea	Flavanols	Kaempferol	(Alam et al., 2020)
4	Cassava	Manihot esculenta	Flavanols	Kaempferol	(Baião et al., 2017)
5	Cassava	Manihot esculenta	Flavanols	Quercetin	(Uarrota et al., 2016)
6	Cassava	Manihot esculenta	Flavanols	Rutin	(Buschmann, 2000)
7	Cauliflower	Brassica oleracea	Flavanols	Kaempferol	(HERRMANN, 1976)

8	Cocoa nibs	Theobroma cacao	Flavones	Apigenin	(Häkkinen et al., 1999)
9	Grapes	Vitis vinifera	Flavanones	Hesperidin	(Egert & Rimbach, 2011)
10	Lemon	Citrus limon	Flavanones	Hesperidin	(Benavente-García & Castillo, 2008)
11	Mango	Mangifera indica	Flavanols	Quercetin	(H. Khan et al., 2020)
12	Onion	Allium cepa	Flavanols	Fisetin	(Sahu et al., 2014)
13	Orange	Citrus sinensis	Flavanones	Hesperidin	(Panche et al., 2016b)
14	Persimmons	Diospyros kaki	Flavanols	Fisetin	(Sahu et al., 2014)
15	Pomegranate	Punica granatum	Flavanols	Quercetin	(H. Khan et al., 2020)
16	Soybean	Glycine max	Isoflavones	Genistein	(Malenčić et al., 2012)
17	Soybean	Glycine max	Isoflavones	Glycitein	(Malenčić et al., 2012)
18	Strawberry	Fragaria ananassa	Flavanols	Kaempferol	(Alam et al., 2020)
19	Tea	Camellia sinensis	Flavanols	Myricetin	(Zhu et al., 2020)
20	Tomato	Solanum lycopersicum	Flavanols	Quercetin	(Panche et al., 2016b)

Table 1: Different Flavonoids and its sources

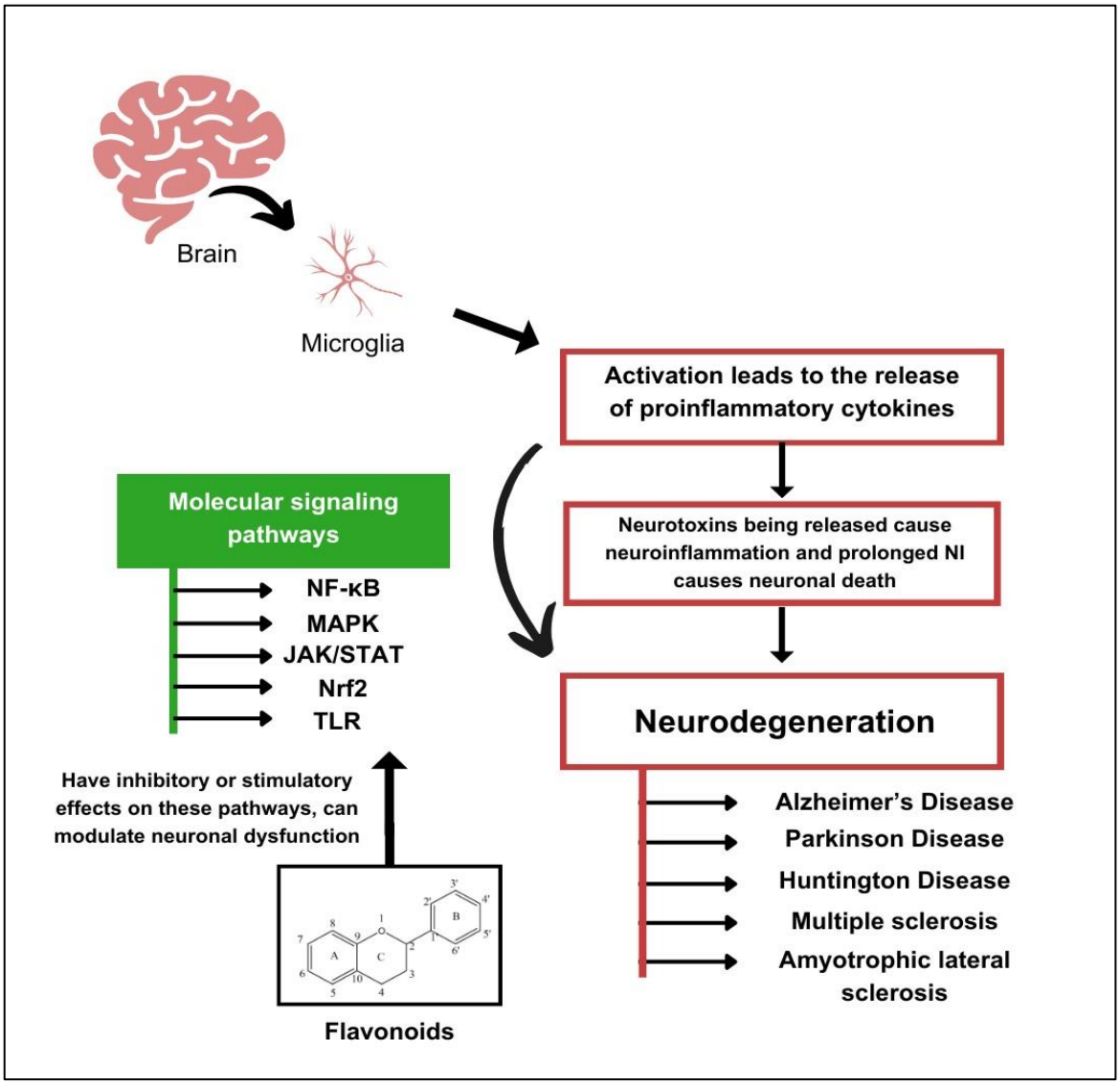

Figure 2: Schematic overview of Neurodegeneration and flavonoid actions

3. Neurological disorders and their current mechanisms

The Electron Transport Chain is usually characterized by producing reactive oxygen species in the bodies of human. Essential metabolic processes like protein phosphorylation, apoptosis, and activation of various transcriptional factors are being carried by Electron Transport Chain, but it is also responsible for lipid peroxidation that causes cell membrane damage. The potential difference exists in membrane of cells, with negative charges on the inner side and positive on the outer, the damage caused by Reactive oxygen species causes alteration in the osmotic pressure, and membrane potential thus causing cell death. The human defense system uses different mechanisms and enzymes to battle endogenous elevated Reactive oxygen species (Brunetti et al., 2013).

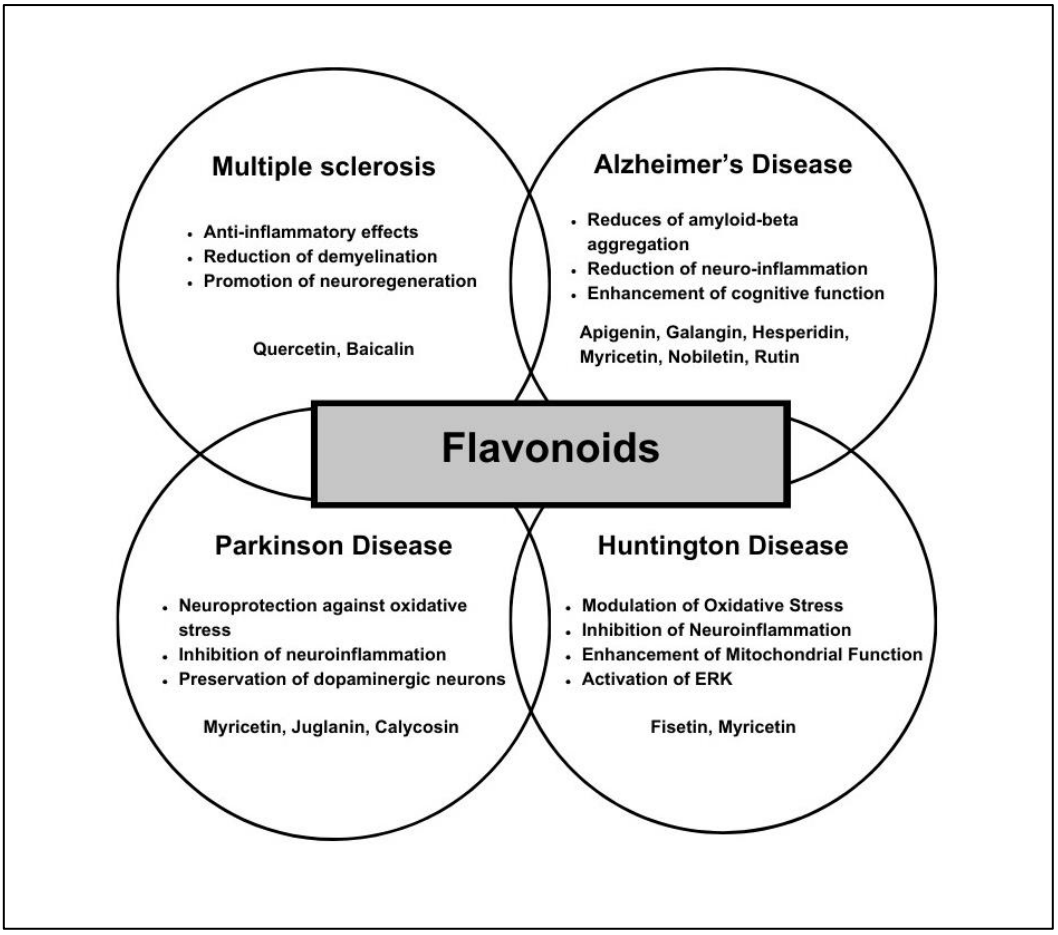

Figure 3: Main mechanism of actions of flavonoids as a neuromodulator

Neuronal interaction with microglia, astrocytes, and other Immunol signaling molecules plays a crucial role in neuroimmunol activation. Microglia are the central nervous system immune cells that usually perform sensing, housekeeping, and protective functions (Mitoma & Manto, 2019; Tchessalova et al., 2018). Microglia activation is an important factor of NI which promotes the release of pro-inflammatory cytokines resulting in progressive neuronal death (Qin et al., 2023). Neurotoxins released from microglia contrary to adverse neuroimmune function led to neurological inflammation and neuronal death and are considered to be the main cause of neurodegenerative diseases (W. Zhang et al., 2023).Neuroprotective therapies continue to be challenging in practice because neurodegeneration is caused by a variety of pathophysiological mechanisms. Thus, of this moment, there is no known cure for neurodegenerative disorders; the only available treatment focuses on symptom management.

Flavonoids appear to be potential leads, particularly for the treatment of neurological disorders. Several key molecular signaling pathways such as MAPK, CREB, Nrf2, NF-kB, JAK/STAT, and TLR are modulated by flavonoids. Inhibitory or stimulatory effects on these pathways by flavonoids significantly affect cellular functions by changing the phosphorylation state of target molecules and by modifying gene expressions (Mansuri et al., 2014; Pérez-Cano & Castell, 2016). These compounds also can modulate neuronal dysfunction through the activation of various metabolic pathways and are found to delay or prevent the onset of neurodegenerative diseases and provide neuroprotection (Makkar et al., 2020).

The antioxidant potential of flavonoids is associated with the molecular structure, and more precisely, with the location and total number of the –OH groups, the conjugation and resonance effects, the surrounding environment that modifies the thermodynamically favored antioxidant site, and the antioxidant mechanism for a compound (Zheng et al., 2019).

3.1 Alzheimer's disease

Somewhere five million individuals globally struggle with Alzheimer's disease, which makes it the most prevalent type of dementia. In Alzheimer there is the buildup of abnormal protein, increased production of amyloid beta production, and tau tangles which are responsible for causing impairment in synaptic loss, neuronal dysfunction and further leading to cognitive and memory dysfunction. The accumulation of amyloid beta leads to elevation of oxidative stress, neuroinflammation, and neurodegeneration (Williamson et al., 2018). Currently, there is no effective treatment available for the treatment and prevention of AD (Yiannopoulou & Papageorgiou, 2013). Nrf2 is a transcription factor binding to the antioxidant response element which controls oxidative response and regulates anti-inflammatory, antioxidant, and detoxifying genes (Ma, 2013). Nrf2 malfunction and its alternative localzation are common in most Neurodegenerative disorders including Amyotrophic lateral sclerosis, Alzheimer, and Parkinson. Nrf2 activation prevents our body from harmful stress by inhibiting inflammation, upregulating antioxidant defense pathways, and maintaining homeostasis (Villavicencio Tejo & Quintanilla, 2021). It was observed that Nrf2 was responsible for an array of critical roles to eliminate reactive oxygen species, preservation of redox homeostasis, and regulation of peripheral inflammatory responses thus has emerged as a promising therapeutic target and its seen flavonoids express their neuroprotective effects by inhibiting glutamate receptors and activating the Nrf2 (Moratilla-Rivera et al., 2023). However, some of the flavonoids have key potential for preventive and therapeutic effects.

3.1.1 Quercetin

Quercetin, a flavanol, possesses some pharmacological effects and has therapeutic effects. In various in vivo and in vitro models, it has been found that it protects neural cells by reducing oxidative stress and neurological inflammation. Some of the key properties that have a therapeutic effect include inhibition of amyloid beta aggregation, inhibition of tau phosphorylation, and restoration of acetylcholine levels through the inhibition of hydrolysis of acetylcholine by AChE enzyme (H. Khan et al., 2020).

3.1.2 Myricetin

Myricetin exhibits multifaceted neuroprotective effects by reducing the formation of amyloid beta 42 formations by blocking the conformational change, increasing the enzymatic activity of alpha-secretase and reducing that of beta-secretase countering the AD progression, suppressing neuroinflammation by inhibiting the activation of microglia and pro-inflammatory cytokines and mitigating oxidative stress (Taheri et al., 2020).

3.2 Parkinson’s Disorder

Parkinson's Disorder is the most common neurodegenerative disorder after Alzheimer’s disease and occurs due to the loss of dopaminergic neurons in the substantia nigra resulting in a decrease in the production of dopamine in the striatum and, subsequently, motor dysfunction (de Andrade Teles et al., 2018). The exact cause of Parkinson’s disease is unknown, but it

occurs due to the accumulation of abnormal proteins, oxidative stress, environmental toxins, and accumulation of alpha-synuclein (Dias et al., 2013; Jo et al., 2019). During neuroinflammatory diseases including Multiple sclerosis and Parkinson, it has been observed that JAK/STAT behaviour differently. JAK/STAT pathway initiates Dysregulation which generates oncological, metabolic, neurological, or other types of diseases to create disorders. The abnormalities are being regulated by JAK/STAT pathway inhibitors during the treatment of neurological disorders (Yan et al., 2018). Flavonoids possess potential in reduction of the phosphorylation of TYK2, STATs ; reduction in the translocation of nuclear STAT1 and STAT3; inhibition of COX-2 NO, iNOS, and proinflammatory cytokines such as TNF-alpha, interleukin 6 and 1beta in macrophages. Reactive oxygen species synthesis delivers the antioxidant properties of Flavonoids (S.-M. Qi et al., 2018).

3.2.1 Myricetin

Myricetin has shown some of the key neuroprotective effects that could be crucial against Parkinson's disorder are through inhibiting the activation of microglia and other proinflammatory cytokines, suppressing intracellular production of reactive oxygen species, inhibiting the formation of alpha-synuclein and destabilizing it, and re-establishing the mitochondrial transmembrane potential (Taheri et al., 2020).

3.2.2 Calycosin

Calycosin has been shown to have crucial neuroprotective effects against Parkinson's disorder by preserving and enhancing mitochondrial biogenesis, reducing oxidative stress-induced damage, and modulating and inhibiting TLR/NF-kB, and MAPK pathway (Yang et al., 2019).

3.3 Huntington’s Disease

Another neurodegenerative illness that causes involuntary movements, cognitive impairments , psychiatric disturbances, and dementia is Huntington's disease (HD). Genetically it is associated with the expansion of cytosine adenine guanine trinucleotide repeats in the Huntingtin gene (Hung et al., 2016; Velusamy et al., 2017). There is no treatment available for the management of HD (Frank, 2014).

3.3.1 Myricetin

Myricetin has been shown to interact with RNA, especially the CAG motif to inhibit the translation and destabilize the aggregates of mutant huntingtin protein, potentially reducing their cytotoxicity (E. Khan et al., 2018).

3.4 Multiple Sclerosis

In multiple sclerosis, chronic inflammation contributes to demyelination and neuronal damage. The activation of NF-kB plays a major role in many inflammatory diseases such as MS (Tak & Firestein, 2001). NF-kB is involved during functionating of the brain especially NDs (O’Neill & Kaltschmidt, 1997). Flavonoids play a significant role in providing the anti-inflammatory and antioxidant effect by hindering the NF-kB signaling pathway (Jones et al., 2012). Thus, NF-kB pathway targeting offers a novel treatment method and potential for neurodegenerative disorders.

S .No	Flavonoid	Disease	Action	References
1	*Apigenin*	Alzheimer disease	Inhibits the MAPK Pathway	(Zhao et al., 2013)
2	*Galangin*	Alzheimer disease	Docking studies revealed interaction with BChE active site forms H bonds and thus inhibits it	(Katalinić et al., 2010)
3	*Hesperidin*	Alzheimer disease	Reduces the increased levels of Tumour necrosis factor-alpha and Interleukin-1beta levels	(Ciftci et al., n.d.)
4	*Icariside II*	Alzheimer disease	Increase the antiapoptotic activity by the MAPK pathway	(He et al., 2018)
5	*Myricetin*	Alzheimer disease	Reduced the formation of amyloid b 42 formation by blocking the conformation change	(Fiori et al., 2012)
6	*Nobiletin*	Alzheimer disease	Reducing the level of soluble A1–40, reactive oxygen species, NF-kB ,and MAPKs	(G. Qi et al., 2019)
7	*Rutin*	Alzheimer disease	Decrease the amyloid beta induced ROS levels	(Moghbeli nejad et al., 2014)
8	*Quercetin*	Alzheimer disease	inhibition of amyloid beta aggregation and tau phosphorylation	(H. Khan et al., 2020)
9	*Fisetin*	Amyotrophic lateral sclerosis	Reduced ROS levels and activation of ERK	(Wang et al., 2018)
10	*Myricetin*	CNS	minimizes the accumulation of various abnormal proteins and gets rid of different harmful proteins connected to neurological disorders. stimulates Hsp70 molecular chaperone's physiological activities and lowers misfolded protein levels	(Joshi et al., 2019)
11	*Fisetin*	Huntington Disease	Activation of ERK	(Maher et al., 2011)
12	*Myricetin*	Huntington Disease	Interaction with RNA, especially CAG motif, and thus decrement in the huntingtin protein translation and	(E. Khan et al., 2018)

			sequestration that reduces cytotoxicity in HD.	
13	*Galangin*	Inflammation and free radicals	Decreased levels of pro-inflammatory cytokines, reduced levels of Nrf2 and HO-1, ERK and p38 pathways	(Y.-C. Huang et al., 2017)
14	*Quercetin*	Multiple sclerosis	Inhibits interleukin 12; STAT 3,4; TYK2	(Muthian & Bright, 2004)
15	*Baicalin*	Multiple sclerosis	Inhibits Th1,17; JAK/STAT; NF-kB	(Liu et al., 2014)
16	*Fisetin*	Neuroinflammation	Reduced the interleukin 6, NF-kB, TNF-alpha, NF-kB levels	(Chen et al., 2018)
17	*Nobiletin*	Neuroinflammation	Decrease in pro-inflammatory cytokine	(Cui et al., 2010)
18	*Quercetin*	Neuroinflammation	Inhibits the MAPK Pathway, NF-kB, NO	(Sun et al., 2015)
19	*Myricetin*	Parkinson Disease	Suppresses intracellular ROS production, re-establishes mitochondrial trans-membrane potential and also impedes MKK4 and JNK activation	(K. Zhang et al., 2011)
20	*Myricetin*	Parkinson Disease	Reduces the activation of microglia (neuroinflammation), and expression of pro-inflammatory mediators.	(B. Huang et al., 2018)
21	*Juglanin*	Parkinson Disease	Inhibits TLR4/NF-kB pathway	(F.-X. Zhang & Xu, 2018)
22	*Calycosin*	Parkinson Disease	Inhibits MAPK pathway	(Yang et al., 2019)

Table 2: Different Flavonoids and its therapeutic actions

4. Discussion and Future Directives

Flavonoid's ability to reach the target site (i.e. brain) in effective concentrations and exert its neuroprotective effects is hindered due to factors like low solubility, fast metabolic rate, and limited absorption in the gastrointestinal tract. Adsorption of flavonoids and delivery to specific target sites has been a challenge and needs innovative novel strategies to overcome. Delivery

systems such as nanoparticles, liposomes, or microemulsions could be used to deliver at the target site. These novel delivery systems possess the potential to improve the stability and solubility of flavonoids, improving in absorption and bioavailability of flavonoids having neuroprotective effects to cross the blood-brain barrier and reach the target site.

Complex structures and diversity in flavonoids pose challenges in understanding precise mechanisms of action and determining in optimal dosage to have therapeutic effects and metabolic activity. Flavonoids' distinct structural properties, bioactivities, and mechanisms make it difficult to find specific flavonoids that would modulate, stimulate, and interact with the abnormal proteins at the target site and cause a neuroprotective effect. This specificity and selective limitations could be overcome by conducting structure-activity relationship studies to know the peculiarities of flavonoids for their neuroprotective effects. Advanced computational tools and molecular docking technologies must be deployed in predicting the flavonoids' interactions with biological targets and pathways, these could further guide drug development efforts.

Flavonoid interactions with other medications or bio compounds are less known and could be affecting their efficacy or causing adverse effects. These potential side effects and interactions with other bio compounds are crucial to know as would have deteriorative effects on individuals having multiple diseases or some underlying health conditions. Preclinical and clinical studies could be conducted to find out the potential interaction of flavonoids with medications. Devising specialized systems to monitor the adverse effects related to flavonoid therapeutic action, to ensure timely detection and antidote for the side effects.

To summarize, flavonoids show immense promise in treating Neurological Disorders, but several limitations warrant further exploration. Firstly, leveraging tools in drug discovery, such as computer-aided design and high-throughput screening, can enhance understanding of flavonoids' safety, biochemical activity, and targeted mechanisms of action. Secondly, investigating the modifications in structure of these compounds is crucial for optimizing their efficacy. Lastly, conducting scientific clinical trials and comprehensive evaluations of potential side effects are essential to determine both the specificity and safety of flavonoids in treating Neurological Disorders. By continuing to advance our understanding, overcoming barriers, and translating research findings into clinical practice, we can harness flavonoids’ full potential in promoting brain health and combating neurological diseases.

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