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Review Article

Flavonoid-Mediated Neuroprotection in Epilepsy: A Holistic Review on Anticonvulsant and Inflammation-Modulating Action from Experimentally Induced Epileptic Models

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ABSTRACT

Approximately seventy million individuals worldwide suffer from epilepsy, a chronic neurological condition marked by recurring seizures. The most popular pharmaceuticals used to treat epilepsy are antiepileptic ones. In roughly sixty to seventy percent of cases, they aid in seizure control. Scientists are searching for natural chemicals that can either prevent seizures or enhance the effectiveness of medications in add-on therapy while minimizing side effects because the remaining patients have drug-resistant epilepsy. At the moment, natural products are highly valued. This group includes flavonoids, which may enhance the effects of other medications when used to treat epilepsy. According to reports, these substances have a number of pharmacological characteristics, such as reducing inflammatory reactions in neurological conditions like epilepsy. Flavonoids are a promising choice for epilepsy-related clinical trials because of the excellent outcomes of preclinical research. The article provides an overview of literature reports from the last ten years, primarily in vivo preclinical research on different models of experimental epilepsy using specific flavonoids, emphasizing their mechanism of modulating anti-inflammatory responses in various forms of epilepsy, as demonstrated by preclinical studies conducted on multiple epilepsy models.

INTRODUCTION

Spontaneous and recurrent seizures (SRS) are a common feature of epilepsy, a persistent brain condition. There are many different kinds of epilepsies; some are caused by brain damage, some are influenced by genetic predispositions, and some have an unidentified underlying cause. Unsynchronized GABA and glutamatergic activity and excessive excitatory glutamatergic

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electrical activity are the causes of epileptic seizures [1]. In addition to endangering the normal electrical activity of the brain, spontaneous electrical discharges during seizures can cause strange sensations or involuntary movements of different body parts. Anxiety, depression, sleep issues, emergency seizures, cognitive and memory issues, low self-esteem, and poor social skills are just a few of the psychological and social challenges that people with epilepsy face on a daily basis. Approximately seventy million people worldwide suffer from epilepsy, a severe neurological condition [2].

Aging, mutations of genes, homoeostasis of central nervous system, and brain stressors such as oxidative stress, neuroinflammation, and traumatic injury of brain appear to have an impact on the etiology of epilepsy. However, little is understood about the mechanisms of Pathophysiology behind the development and recurrence of seizures, pathological alterations, and related comorbidities. Nonetheless, research on humans has shown that neuroinflammation has a role in the onset and progression of different types of epilepsy [3]. Therefore, the evidence points to a complex relationship between neuroinflammation and seizure occurrence. Furthermore, it has been documented that repeated seizures enhance production of inflammatory mediators, which may raise neuronal excitability and lead to degeneration of neurons.

While sixty to seventy percent of patients respond well to antiepileptic medication (AED) therapy, thirty to forty percent of patients do not have seizure control. The International League Against Epilepsy defines drug resistance in epilepsy as the inability to control seizures with two appropriately administered and well-tolerated AEDs for a long enough period of time [4]. There is still much to learn about the mechanism underlying medication resistance. Both hereditary and environmental variables most likely have an impact. Even half of patients with drug-resistant epilepsy (DRE) experience depression due to a variety of pharmacological side effects, memory problems, stigmatization that becomes a social issue, and the absence of anticipated treatment outcomes. Henceforth, increasing the duration of seizure control, reducing adverse effects, and enhancing quality of life are the primary objectives of drug-resistant epilepsy therapy. The utilization of natural compounds with antiepileptic qualities as supplements to conventional antiepileptic medications in the treatment of DRE is currently the subject of several research investigations, and flavonoids may represent a class of natural medications that enhance the effects of widely used anticonvulsants [5].

Plant components called polyphenols are secondary metabolites that are resorted in distinct tissues and vacuoles. Lignans, phenolic alcohols, flavonoids, and phenolic acids are some of important polyphenols that are known to offer a number of health advantages. They are powerful antioxidants that can alter cell signaling pathways and are useful against disorders linked to oxidative stress [6].

Flavonoids are polyphenolic compounds with strong anti-inflammatory and antioxidant qualities. Several studies show that flavonoids anti-inflammatory qualities coexist with their neuroprotective benefits via a variety of pathways. Numerous flavonoids have been shown in preclinical research to have anti-epileptic qualities, which appear to be influenced by their anti-inflammatory effects [7]. The current study's goal was to emphasize our current knowledge of flavonoids' possible anti-seizure effects in various epileptic models.

Flavonoids

Flavonoids are the most common group of natural polyphenolic compounds in dietary foods and vegetables. These substances share a C6-C3-C6 phenyl benzopyran backbone, which comprises two phenyl rings linked by a three-carbon heterocyclic ring. Evidence from preclinical research demonstrates flavonoid's antioxidant, anti-cancer, antidiabetic, and neuroprotective properties [8,9]. Additionally, flavonoids have reduced the risk of neurodegenerative diseases and alleviated neuroinflammation. These compounds can influence inflammatory pathways by inhibiting glial cell activation, cytokine release, NO generation, NADPH oxidase activity, and iNOS expression [10].

Table 1: Classification of flavonoids

Flavonoids				
Flavanones	***Isoflavones***	***Flavonols***	***Chalcones***	***Flavones***
Naringin	Genistein	Morina	Arbutin	Baicalin
Hesperidin	Daidzein	Mirecitin	Phloretin	Diosmetin
Naringenin		Quercetin	Chalconaringenin	Apigenin
hesperedine		Rutin	Phloridzin	Luteolin
		Kemferol		

Flavonoids with Anticonvulsant and Anti-inflammatory mechanisms used in Epilepsy

Naringin/Naringenin

In mice with pilocarpine-induced seizures, naringenin, a naturally occurring phenolic chemical found in citrus species and Chinese herbs including Drynaria fortunei and Citrus medica, had anticonvulsant effects. According to their findings, seizures decreased in comparison to the control group after receiving naringin (40 mg/kg and 60 mg/kg) for 15 days and pilocarpine on the final day of treatment. It has been demonstrated that naringenin inhibits seizure onset and duration in a dose-dependent way. In contrast to the higher dose (60 mg/kg), which lowered seizure length by 2 minutes and postponed seizures by 27 minutes, naringin at a dose of 20 mg shortened seizure duration by approximately 1 minute and delayed seizures by 12 minutes [11]. One of the best flavonoids for reducing TNF-α production during PTZ-induced seizures is naringin. Naringin treatment delayed the onset of seizures and decreased the frequency of SRS in male C57BL/6 mice following KA injection. Naringin therapy also prevented an increase in TNF-α in activated microglia, maintained hippocampal CA1 neurons, and decreased autophagic stress [12].

Hesperidin

Neuroprotective, anti-inflammatory, analgesic, antiviral, antifungal, antibacterial, anti-hypercholesterolemic, and anti-cancer effects have all been demonstrated for hesperidin. Research has evaluated hesperidin's effects on mice with PTZ-induced epilepsy, both by itself and in conjunction with gabapentin and diazepam. The results showed that hesperidin (100 mg/kg) administered 30 minutes before to PTZ injection considerably postponed the onset of seizures. It has also been demonstrated that the protective effect is enhanced when hesperidin (50 mg/kg) is combined with either gabapentin (10 mg/kg) or diazepam (0.2 mg/kg) as opposed to when these medications are administered alone [13]. These findings imply that hesperidin's antioxidant qualities and its synergy

with the ligands at the GABA-A-benzodiazepine receptors may be linked to its neuroprotective effects against PTZ-induced convulsions. Hesperidin therapy may also increase seizure latency, lessen hyperactive reactions in PTZ-mediated seizures in zebrafish larvae, and alter BDNF and IL-10 expression, according to recent studies. In-silico studies further revealed hesperidin's affinity for a number of receptors, including IL-10 [14,15].

Apigenin

The primary source from Asteraceae has been identified as apigenin. Because of its neuroprotective, anxiolytic, sedative, anticonvulsant, and depressive qualities, apigenin has drawn special attention. It's interesting to note that apigenin can also improve memory impairment associated with Alzheimer's. Apigenin at doses of 25 and 50 mg/kg given 15 minutes before to picrotoxin (6 and 8 mg/kg) delayed the onset of convulsions, according to studies by Avallone et al., [16] demonstrating the strong anticonvulsant efficacy of apigenin in picrotoxin-induced seizures in Sprague-Dawley male rats. It's interesting to note that apigenin (25–50 mg/kg) administered for five days, followed by a KA injection on the final day, was demonstrated to decrease the frequency and duration of seizures in rats [17]. Additionally, it was discovered that apigenin inhibited KA-induced cerebral cortex electroencephalogram discharge activity [18].

Quercetin

Apples, blueberries, almonds, grapes, onions, and chamomile all contain quercetin. In a rat PTZ kindling model, Nassiri-Asl et al. examined the potential impact of quercetin on oxidative stress and memory retrieval. The results showed that pretreatment with 100 mg/kg of quercetin reduced the mean seizure stages in comparison to the control group, hence attenuating seizure severity from the start of the kindling procedure [19]. Furthermore, compared to the control rats, quercetin at a dose of 100 mg/kg markedly enhanced the step-through latency of the passive avoidance reaction. A study by Mkhize et al. claims that quercetin can treat febrile seizures because, when prenatal stress is present, it downregulates the expression of many pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. Additionally, a recent study found that quercetin stimulates NF-kB in glial cells and suppresses the production of pro-inflammatory cytokines like TNF-α and IL-1β [20]. In the rat model of hypoxia-induced neonatal seizure, Wu et al. recently showed that quercetin reduces anxiety-related behavior, memory deficits, and later-life seizure susceptibility [21,22].

Rutin

Quercetin's essential derivative is rutin. This bioactive substance is flavonol glycoside, which contains rutinose and quercetin. Rutin successfully stops seizures in animal models of epilepsy, according to mounting data. A recent study examined the potential anti-seizure mechanism of rutin in rats treated with KA. The researchers found that pretreatment with rutin (100 and 200 mg/kg) for seven days boosts glutamate levels in the hippocampus, reverses neuronal loss, and lessens the severity of seizures. Additionally, rutin reduced the protein levels of pro-inflammatory molecules like IL-1β, IL-6, TNF-α, HMGB1, IL-1R1, and TLR-4, prevented astrocyte activation, and raised the levels of anti-inflammatory molecules like IL-10 [23,24,25]. Overall, the study discovered that via inhibiting the IL-1R1/TLR4-related neuroinflammatory cascade, rutin lessens KA-induced seizures and neuronal death in rats [26].

Baicalein

Scutellarin baicalensis and Scutellarin lateriflora roots are the source of the flavone baicalein. A study by Qian et al. found that baicalein therapy improves cognitive deficits and preserves hippocampus neurons in temporal lobe epilepsy mice after episodes start. Furthermore, studies have demonstrated that baicalein lowers inflammatory and oxidative stress markers (TNF-α and IL-1β) in the hippocampus and serum of TLE rats [27]. Baicalein (100, 200, and 400 mg/kg) administered orally reduced the expression of the insulin-like growth factor 1 receptor, suppressed inflammation, reduced microglial proliferation, and alleviated the symptoms of epilepsy [28]. They demonstrated that pretreatment baicalin (100 mg) reduced animal mortality and postponed seizures caused by pilocarpine in rats. Furthermore, compared to the Pilocarpine group, baicalin dramatically decreased nitrite, glutathione, and lipid peroxidation, reversing the alterations in oxidative stress levels in the hippocampus [29,30].

Kaempferol

Fruits and vegetables like broccoli, apples, strawberries, and beans contain kaempferol, a naturally occurring flavonol. According to the literature now in publication, kaempferol may be able to treat a number of human illnesses, such as cancer, inflammatory conditions, cardiovascular conditions, neurological conditions, etc [31]. According to a recent study by Ahmed et al., kaempferol therapy reduces the intensity of seizures, improves behavioral abnormalities, and repairs cellular damage in PTZ epileptic rats. Additionally, the study found that kaempferol increases the expression of anti-inflammatory cytokines like IL-1, IL-4, and IL-10 while decreasing the expression of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and NF-kB [32,33]. Therefore, kaempferol's ability to decrease pro-inflammatory molecules while boosting anti-inflammatory ones may go hand in hand with its anti-epileptic potential.

Luteolin

Pepper, celery, broccoli, thyme, and chamomile tea are just a few of the foods and drinks that contain luteolin, a flavone. This bioactive substance has a variety of biological functions, including neuroprotection, and can pass through the brain [34]. Lin et al. examined luteolin's anti-inflammatory properties in rats experiencing convulsions brought on by kainic acid. In the hippocampus of rats given kainic acid, the study demonstrated that luteolin prevents neuronal death, suppresses glial activation, and increases Akt activation [35]. In rats given PTZ, pretreatment with luteolin (100 mg/kg i.p.) reduced seizure frequency, decreased iNOS and MMP-2 activity, and increased e-NOS activity. Because luteolin can pass through the blood-brain barrier, it can be used to treat conditions affecting the central nervous system, such as brain tumours [36]. In a PTZ-induced seizure test in mice, Tambe and colleagues assessed luteolin's antiepileptic potential. In compared to the PTZ control mice, the results demonstrated that the administration of luteolin at a dose of 10 or 20 mg/kg postponed the incidence of myoclonic seizures, clonic seizures, and hind limb extension [37,38].

Myricetin

Another significant flavonoid that is categorized as a flavonol is myricetin. It is an essential part of many human foods and drinks, such as fruits, vegetables, and teas. Its iron-chelating, antioxidant, anti-inflammatory, and anti-cancer qualities are its most well-known attributes [39]. Numerous nervous system conditions, such as cerebral ischemia, Alzheimer's disease, Parkinson's disease, epilepsy, and glioblastoma, have been shown to benefit from myricetin intake.

When given orally to mice for 26 days before each PTZ injection, myricetin (100 or 200 mg/kg) decreased seizure and mortality rates, downregulated the production of apoptotic proteins, and restored GABA and glutamate levels [40,41]. Furthermore, after PTZ-kindling, it has downregulated MMP-9 expression, indicating that myricetin's anti-seizure ability is linked to its MMP-9-mediated immunomodulatory characteristics [42].

Table 2: Anticonvulsant and inflammation modulating properties of selected flavonoids in experimental models of epilepsy

Flavanoid	Animal model	Results/Effects	References
Apigenin	Kainic Acid model (rats)	Lowered the frequency of seizures	[43, 44]
	PTZ model (mice)	Delayed the incidence of seizures	
Kaempferol	PTZ kindled model (rats)	Decreases the expression of TNF-α, IL-1β, and enhances the expression of IL-10, IL-4	[45]
Rutin	PTZ model (rats/mice)	Reduced seizure severity, delayed seizure onset, improved behavioral and cognitive impairments	[46]
Myricetin	Picrotoxin induced model (rats/Zebrafish larvae)	Downregulated MM-9 expression	[47]
Baicalein	Kainic acid induce model (mice)	Decreases TLR4, NF-kB, and IL-1β expression	[48]
Luteolin	PTZ-model (mice/rats)	delayed the onset of myoclonic jerks, onset of clonic seizures and onset of hind limb extension, protection against mortality, neuroprotective effect	[49]
	Pilocarpine model (mice)	delayed the onset of seizures and shortened the duration of clonic seizures, improvement of cognitive functions	

Naringenin	Pilocarpine model (mice)	Decreased the intensity of seizures	[50, 51, 52]
	PTZ model (rats)	Improved cognitive deficits, reduced seizure intensity	
	Kainc acid model (mice)	Reduced the severity of seizures	
Quercetin	MES model (mice)	Supressed seizures	[53,54,55]
	PTZ model (rats)	Reduced the onset of grand mal seizures	
	6Hz model (mice)	Reduced seizure severity and improved behavioural impairments	
	PTZ kindled model (rats/mice)	Delayed the onset of seizures and improved cognition	
Hesperidin	PTZ model (mice/zebrafish)	Significant neuroprotective effect, delayed the onset of seizure and reduced the seizure severity	[56,57]
	Kainic acid induce TLE in mice	Supressed TNF-α, IL-1β, iNOS expression	

CONCLUSION

Patients who are resistant to one pharmacological treatment only need a second anticonvulsant, which bears the risk of worsening adverse effects, despite the widespread availability of multiple generations of AEDs. It has been demonstrated that flavonoids have a broad range of activities and a potent pharmacological effect. The results of preclinical studies that targeted neuroinflammatory pathways in epilepsy with flavonoids are presented in this review paper. As a result, the review sheds light on a potentially effective treatment for epilepsy that targets both strong anticonvulsant action and neuroinflammation. Flavonoids may therefore be helpful in creating novel therapeutic approaches for the treatment of epilepsy. There is a strong need to include flavonoids as antiepileptic drugs in clinical trials, even though their anticonvulsant effects have been confirmed in preclinical research.

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