PERSPECTIVE

Perspective: Therapeutic Potential of Flavonoids as Alternative Medicines in Epilepsy

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ABSTRACT

Epilepsy is a chronic neurological disorder that affects many people worldwide. Temporal lobe epilepsy is the most common and most studied type of epilepsy, but the pathological mechanisms underlying this condition are poorly understood. More than 20 antiepileptic drugs (AEDs) have been developed and used for the treatment of epilepsy; however, 30% of patients still experience uncontrolled epilepsy and associated comorbidities, which impair their quality of life. In addition, various side effects have been reported for AEDs, such as drowsiness, unsteadiness, dizziness, blurred or double vision, tremor (shakiness), greater risk of infections, bruising, and bleeding. Thus, critical medical needs remain unmet for patients with uncontrolled epilepsy. Flavonoids belong to a subclass of polyphenols that are widely present in fruits, vegetables, and certain beverages. Recently, many studies have reported that some flavonoids elicit various beneficial effects in patients with epilepsy without causing the side effects associated with conventional medical therapies. Moreover, flavonoids may have a property of regulating microRNA expression associated with inflammation and cell survival. These findings suggest that flavonoids, which are more effective but impose fewer adverse effects than conventional AEDs, could be used in the treatment of epilepsy. *Adv Nutr* 2019;10:778–790.

Keywords: epilepsy, granule cell dispersion, flavonoids, antiepilepsy, antiepileptic drugs

Introduction

Epilepsy is a chronic neurological disorder that affects >70 million people worldwide. Globally, an estimated 2.4 million people are diagnosed with epilepsy per year (1, 2), and the adult epilepsy patient population in the United States has increased ≥30%, from ∼2.3 million in 2010 to 3 million in 2015. During the same period, pediatric patient diagnoses have increased from 450,000 to 470,000 (3). In addition to epilepsy and the associated comorbidities (e.g., depression and anxiety), many epilepsy patients also experience social discrimination and alienation. Currently, epilepsy is classified into 4 types depending on the onset of seizures: focal, generalized, combined generalized and focal, and unknown (4). Focal seizures arise in 1 brain hemisphere only, whereas generalized seizures arise in both brain hemispheres. Temporal lobe epilepsy (TLE) was defined in 1985 by the International League Against Epilepsy. It is the most common type of epilepsy, with recurrent, unprovoked focal seizures originating from the medial or lateral temporal lobe. Several studies have demonstrated that recurrent seizures affect cognitive function, including memory, attention, language, praxis, executive function, judgment, insight, and problem-solving (5, 6). These cognitive impairments have been suggested to result from changes in neural circuitry by seizure-induced structural and functional changes in the brain (7). More than 20 antiepileptic drugs (AEDs) have been developed, including valproic acid, lamotrigine, phenobarbital, gabapentin, felbamate, and topiramate (8). Despite the fact that >10 different epilepsy treatments are available, ∼30% of patients respond poorly to treatment

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Abbreviations used: AED, antiepileptic drug; BBB, blood–brain barrier; DG, dentate gyrus; GABA, γ-aminobutyric acid; GCD, granule cell dispersion; GSH, glutathione; KA, kainic acid; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; MDA, malondialdehyde; miRNA, microRNA; PTZ, pentylenetetrazol; TLE, temporal lobe epilepsy.

(9). In contrast, 70% of patients can achieve long-term remission under AED treatment. However, many AEDs are associated with adverse side effects that are experienced by a considerable number of patients. These include somnolence, dizziness, gastrointestinal events, psychotic episodes, behavioral problems, depression, impaired cognition, osteoporosis, and leukopenia (10). Furthermore, previous clinical trials reported that treatment with AEDs could lead to seizure worsening, and AED therapeutic effects were not significantly different from placebo treatments (11–14). Thus, significant unmet medical needs still must be overcome for the effective and safe treatment of epilepsy.

Recently, there has been increasing evidence for the pharmacological effects of plant-derived flavonoids on epilepsy. Flavonoids are most widely found in plant-based products such as fruits, vegetables, grains, nuts, seeds, tea, and traditional medicinal herbs. More than 8000 different flavonoids have been isolated from natural sources. In general, flavonoids are compounds of low molecular weight containing 2 benzene rings linked by a heterocyclic pyran or pyrone ring (15). Flavonoids have been considered as novel AED candidates because they have many relevant biological and medicinal properties, including antioxidative, anti-inflammatory, and neuroprotective properties. We previously reported that the flavonoids naringin (16, 17), naringenin (18), eugenol (19), silibinin (20), morin (21), and hesperetin (22) attenuated epileptic symptoms. These effects seemed to be taking place via 2 main mechanisms: *1*) by the alleviation of hippocampal structural changes, including through granule cell dispersion (GCD) in the dentate gyrus (DG), and *2*) by the reduction of inflammatory responses, which is well represented in TLE, by inhibiting the expression of pro-inflammatory cytokines in kainic acid (KA)-induced seizure model mice. These findings suggest that flavonoids can be used as an alternative medicine for the treatment of epilepsy. In this review, we discuss the beneficial effects of flavonoids as potential antiepileptic agents with less adverse effects than conventional AEDs.

Basic Mechanisms Underlying TLE

TLE is frequently associated with Ammon's horn sclerosis. The latter is characterized by loss of principal neurons in the CA1 and CA3 regions of the hippocampus and in the hilus of the DG, where widening of the granule cell layer is typical (23–26) and was named GCD by Houser (23). GCD is associated with hippocampal sclerosis in ~40% of epilepsy patients, but its underlying pathological mechanisms and clinical significance are poorly understood. Nevertheless, it has been implicated in the decreased expresstion of the extracellular matrix protein Reelin in the hippocampus of TLE patients (27) and seizure model mice (28–31). Hyperactivation of the mammalian target of rapamycin (mTOR) signaling pathway in the hippocampi of human patients and animal models has also been associated with GCD (18, 20, 32, 33); in some cases, treatment with rapamycin, which inhibits the activity of mTOR, suppressed GCD in vivo (33, 34).

Currently Available Epilepsy Treatments

Many studies have suggested that imbalances between excitatory and inhibitory signals may cause epilepsy (35–37). AEDs currently used to stop epileptic seizures act mostly by blocking ion channels and inhibiting neuronal excitability (**Table 1**). The targets of AEDs include voltage-gated sodium channels [for carbamazepine (38–41), felbamate (42), lacosamide (42), lamotrigine (43), oxcarbazepine (42), phenytoin (44–47), rufinamide (46, 48), topiramate (49), valproic acid (50–52), and zonisamide (42, 53)] and T-type calcium channels [for valproic acid (42)]. Other AEDs reduce abnormal excitatory action potentials via the inhibition of synaptic neurotransmitter release. These targets and drugs include the synaptic vesicle ligands, glycoprotein 2A [for levetiracetam (42)], the $\alpha_2\delta$ subunit of the voltage-gated calcium channel [for gabapentin (54) and pregabalin (55)], and glutamate receptors [e.g., *N*-methyl-D-aspartate (NMDA) receptor for felbamate (42)]. Approximately 70% of epilepsy patients become seizure-free after receiving medication, but 30% of patients are often resistant to AED treatment. When seizures are not successfully controlled by single-drug treatments, multiple-drug treatments are typically attempted. However, a study demonstrated that 1 such combination therapy elicited a positive therapeutic effect in only 3% of patients (9). In addition, current treatments with AEDs exert only transient effects on recurrent seizures and insufficient suppression of GCD in TLE model animals (56, 57). Rapamycin, which was approved by the FDA as an anticancer drug, has been demonstrated as another potential antiepileptic agent with broader clinical relevance (58, 59). Unfortunately, rapamycin can inhibit cell proliferation and motility; thus, the safety of long-term rapamycin treatments must be assessed in advance. Nevertheless, the role of the mTOR inhibition strategy for the treatment of epilepsy remains viable.

In addition to poor efficiency, AEDs can induce a variety of dose-related side effects, such as drowsiness, unsteadiness, dizziness, blurred or double vision, tremor (shakiness), greater risk of infections, bruising, and bleeding (60). Thus, there is a critical need for effective and safe alternative drugs to use in the treatment of epilepsy.

Therapeutic Advantages of Flavonoids in Neurological Diseases

With respect to neurological disorders, many flavonoids are known to provide neuroprotective effects, including in Alzheimer's disease (61, 62), Parkinson's disease (63–66), and ischemic stroke (67, 68). Emerging evidence suggests that the beneficial effects of flavonoids on these neurological diseases may be associated with modulation of γ-aminobutyric acid (GABA) receptors (69–71); mitochondrial dysfunction (72, 73); and regulation of antioxidative and anti-inflammatory mediators such as glutathione (GSH), superoxide dismutase, and cytokines (74–76). Furthermore, some flavonoids prevented mossy fiber sprouting, GCD formation, and mTOR activation in the hippocampi of KA-induced TLE model mice

TABLE 1 Current AEDs used in epilepsy[1]

Agent	Mechanism of action	Advantage	Adverse effects	References
Carbamazepine	Sodium channel blocker Action on monoamine, acetylcholine, and NMDA receptors	Highly effective Suitable in adults and children for many types of epilepsy	Diplopia, dizziness, ataxia, hyponatremia, dermatological, hepatic, hematological toxicity	(38–41)
Ethotoin	Calcium channel blocker	Highly effective	Dizziness, fatigue, headache, insomnia, numbness, rash, diarrhea, chest pain, diplopia, nystagmus, lymphadenopathy, ataxia, vomiting or nausea	(77)
Felbamate	NMDA antagonist Sodium channel conductance	Powerful broad-spectrum action	Occasional case of severe hepatic and aplastic anemia Used only by specialists as last-resort therapy	(42)
Gabapentin	Unknown; possibly GAD modulation	Lack of side effects at low doses	Seizure exacerbation at high doses	(54)
Lacosamide	Sodium channel blocker	Highly effective	Dizziness, diplopia, tremors, sleepiness, headache, loss of coordination, nausea	(42)
Lamotrigine	Sodium channel blocker	Moderate efficacy	High instance of rash (occasionally severe) Dizziness, diplopia, tremors, sleepiness, headache, loss of coordination, nausea	(43)
Levetiracetam	Action via binding to the SV2A synaptic vesicle protein Action via binding to the SV2A synaptic vesicle protein	Highly effective and generally well tolerated; mode of action not shared by other drugs	Mood and behavioral changes	(42)
Oxcarbazepine	Sodium channel, potassium conductance blocker NMDA antagonist	Powerful antiepileptic action An alternative to carbamazepine	Adverse event profile is different and involves fewer drug interactions than does carbamazepine. Higher incidence of hyponatremia than that with carbamazepine	(42)
Phenobarbital	Enhances activity of $GABA_A$ receptor Depresses glutamate excitability and affects sodium, potassium, and calcium conductance	Highly effective and low-cost AED Highly effective well-tested AED	Sedation Rash	(42)
Phenytoin	Sodium channel blocker	Highly effective Low cost	Teratogenic and carcinogenic Sedation, dizziness, ataxia, gingival hyperplasia	(44–47)
Pregabalin	Calcium channel modulation Reduces release of glutamate	Effective and well tolerated	Dizziness, vertigo, incoordination, balance disorder, ataxia, diplopia, blurred vision, amblyopia, tremor, somnolence, confusional state, disturbance in attention, thinking abnormal, euphoria, asthenia, fatigue, edema, peripheral edema, dry mouth, constipation	(55)
Rufinamide	Sodium channel modulation	Highly effective	Dizziness, headache, nausea, somnolence, double vision, fatigue, ataxia, vomiting, abnormal vision	(46, 48)
Tiagabine	Inhibits GABA reuptake	Highly effective	Dizziness, asthenia, somnolence, nausea, irritability, tremor, abdominal pain, difficulty with concentration	(78, 79)
Topiramate	AMPA/kainic acid antagonist Inhibition of voltage-gated sodium channels	Powerful antiepileptic action Rare serious adverse effects	Weight loss, anorexia, somnolence and fatigue, sedation, cognitive complaints, paresthesia	(49)

(*Continued*)

TABLE 1 (*Continued*)

Agent	Mechanism of action	Advantage	Adverse effects	References
	Potentiation inhibitor of benzodiazepine $GABA_A$ receptor Inhibition of high-voltage calcium channels			
Valproate	GAD modulation Effects on GABA	A wide spectrum of activity	Weight gain, nausea, tremor, hair loss Hepatic disturbance in children, teratogenicity	(50–52)
Vigabatrin	GAD modulation Inhibition of GABA transaminase activity	Highly effective antiepileptic drug Excellent effect in West syndrome	Adverse effect on visual fields and potential for cognitive effects	(42)
	Inhibition of GABA transaminase activity	Excellent effect in West syndrome	Because of visual field effects, prescriptions are currently restricted to last-resort use in partial epilepsy.	
Zonisamide	Sodium channel blocker Inhibition benzodiazepine $GABA_A$ receptor	Highly effective	Drowsiness, dizziness Problems with memory or concentration Loss of coordination, trouble walking Renal stones, oligohydrosis, hypersensitivity, teratogenicity	(42, 53)

[1] AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; NMDA, *N*-methyl-D-aspartate.

(16–22). Antiepileptic effects of flavonoids have been verified in some preclinical studies, but the effects of flavonoids as antiepileptic agents for the treatment of epilepsy have not been reported in clinical trials (80).

Blood–brain barrier (BBB) penetration is the largest obstacle for drugs targeting the central nervous system. Several studies have demonstrated that flavonoids can penetrate the BBB and exert effects in the brain (81–86). Both naringenin and naringin were detected in the cortex after intravenous administration of naringenin (20 mg/kg) (81). In addition, the concentration of morin in the brain was measured as 10 μg/mL at 3 h post intranasal administration with 160 mg/40 μL morin, indicating that morin may have the ability to cross the BBB (86). Another study reported that quercetin was significantly elevated in the brain tissue of quercetin-fed rats (after 1 mo compared with 1 wk of quercetin feeding); the actual amounts of brain quercetin were ∼8% (83). Despite flavonoids being safer than conventional drugs, there is little evidence regarding the specific mechanisms whereby they enter the brain. It has been suggested that flavonoids may penetrate the BBB via mechanisms such as transcellular diffusion, carrier-mediated transcellular transport (87, 88), or paracellular diffusion through tight junctions between the endothelial cells of the BBB (82). Yang et al. (89) used an in vitro BBB model to investigate the rates of transportation of some lipophilic or lipophobic flavonoids, including rutin, hesperidin, quercetin, genistein, and apigenin. Their results showed that the transportation rates of flavonoids increase linearly with their concentration. However, saturation was not observed, indicating that the permeation process may be mainly driven by the concentration gradient for these flavonoids.

Using Flavonoids to Treat Epilepsy and Seizures

Apigenin

Apigenin (5,7,4′-trihydroxyflavone) is a dietary flavonoid present in large amounts in many fruits and vegetables. Han et al. (90) reported that pretreatment with apigenin (25 and 50 mg/kg, intraperitoneally) for 5 d reduced the seizure scores and delayed the convulsion onset time in KA-injected mice; it also blocked the KA-induced electroencephalography changes in the cortex. In addition, increases in GSH concentrations in hippocampal neurons after KA-induced seizures were significantly prevented by apigenin pretreatment; this resulted in a significant reduction in the amount of mitochondrial reactive oxygen species and degree of apoptotic neuronal cell death in vitro and in vivo. In picrotoxin-induced seizure model rats, apigenin (25 and 50 mg/kg, intraperitoneally) significantly reduced the latency of seizure onset (91).

Luteolin

Luteolin (3′,4′,5,7-tetrahydroxyflavone) is a flavonoid commonly present in many fruits, vegetables, and medicinal herbs. According to a previous report (92), pretreatment with luteolin (50 and 100 mg/kg/d by oral administration for 36 d) reduced seizure onset, frequency, and severity after pentylenetetrazol (PTZ) injection; in addition, it significantly reduced the amount of mitochondrial reactive

oxygen species, resulting in protection of hippocampal neurons against PTZ toxicity. Furthermore, luteolin led to the expression induction of brain-derived neurotrophic factor and activation of protein kinase A and cAMP response element binding protein in the hippocampus of PTZ-injected rats. Tambe et al. (93) investigated the effects of pretreatment with luteolin (5, 10, and 20 mg/kg, intraperitoneally) in PTZ-induced, acute and chronic epilepsy model mice. They found that luteolin attenuated the malondialdehyde (MDA) concentrations, restored concentrations of reduced GSH, and inhibited kindling behavior induced by PTZ injection.

Genistein

Genistein (4',5,7-trihydroxyisoflavone) is an isoflavone found in soybeans and known to exhibit, among others, anti-inflammatory, antioxidative, and antitumorigenic biological properties. The effects of genistein on KA-induced behavioral and neuronal dysfunctions in ovariectomized rats have been reported (94). Pretreatment with genistein (0.5 mg/kg, intraperitoneally once a day for 4 consecutive days) significantly improved seizure-induced spatial learning and memory impairments, early long-term potentiation deficits, and damage to hippocampal neurons 7 d post-seizure onset. In another study, pretreated genistein (10 mg/kg, intraperitoneally 30 min before PTZ injection) exerted anticonvulsant effects against PTZ-induced seizure in ovariectomized mice, which might have been mediated via the estrogenic/serotonergic systems (95). Elsayed et al. (96) also tested the anticonvulsant effects of genistein on PTZ-induced epilepsy in ovariectomized rats. Pretreatment with genistein (10 and 20 mg/kg, intraperitoneally 30 min before PTZ injection) delayed seizure onset, reduced seizure duration, reduced the concentrations of oxidative stress indicators such as MDA and GSH, decreased estrogen receptor expression, reduced apoptosis, and improved histopathological patterns.

Baicalin

Baicalin (7-glucuronic acid, 5,6-dihydroxyflavone) is a major flavonoid component of the herbal medicine prepared from *Scutellaria baicalensis*. A previous study (97) found that administration of baicalin (100 mg/kg, intraperitoneally injected twice at 1 and 8 h after seizure onset) significantly reduced the expression of cleaved caspase-3 and induced the expression of B cell lymphoma 2, resulting in reduction of neuronal cell death in the hippocampus of KA-treated mice. Furthermore, treatment of KA upregulated the expression of microRNA-497 (miR-497) in the hippocampus, but baicalin significantly attenuated this effect. In another study, Liu et al. (98) showed anticonvulsant effects of baicalin in pilocarpine-induced epilepsy model rats. Baicalin (100 mg/kg, administered intraperitoneally 30 min before pilocarpine) significantly delayed the onset of pilocarpine-induced seizures. In addition, baicalin significantly reduced nitrite/nitrate and MDA concentrations while upregulating the GSH concentration in the hippocampus of pilocarpine-injected rats, which is indicative of its antioxidant properties.

Silibinin

Silibinin [2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-6-(3, 5, 7-trihydroxy-4-oxobenzopyran-2-yl)-benzodioxin] is a flavonoid extracted from milk thistle seeds. A recent report (99) demonstrated that silibinin has beneficial effects in lithium–pilocarpine-induced seizure model rats. The authors administered silibinin intragastrically 30 min before (at 100 mg/kg) pilocarpine injection and daily for 13 d thereafter (at 100 mg/kg for days 1–3 and at 50 mg/kg for days 4–13). Under these conditions, silibinin significantly downregulated the mRNA expression of hypoxia-inducible factor-1α, TNF-α, IL-1β, and IL-6. Furthermore, these effects resulted in the reduction of neuronal loss in the hippocampus of rats after seizure induction. In a separate study, we reported positive therapeutic effects of silibinin in KA-injection-induced epilepsy model mice (20). Treatment with 200 mg/kg of silibinin (intraperitoneally injected 1 d and 1 h before KA injection and daily for 35 d thereafter) significantly attenuated seizure susceptibility, spontaneous recurrent seizure frequency, and GCD, a morphological alteration characteristic of the DG. Moreover, silibinin significantly reduced the expression of apoptotic, autophagic, and pro-inflammatory molecules that are normally produced after KA injection, resulting in neuroprotection of hippocampal neurons in the KA-injected mice.

Naringin and its metabolite, naringenin

Naringin (4′,5,7-trihydroxyflavanone-7-rhamnoglucoside) and its metabolite, naringenin (4′,5,7-trihydroxyflavanone), are flavanone glycosides found in grapes and citrus fruits that have strong antioxidative and anti-inflammatory properties. Golechha et al. (100, 101) reported on the effects of naringin in both KA- and PTZ-induced epileptic rat models. Pretreatment with naringin (20, 40, and 80 mg/kg, intraperitoneally) for 7 d significantly delayed the latency of seizure and reduced the expression of TNF-α induced by KA injection in a dose-dependent manner. Naringin pretreatment (40 and 80 mg/kg) also increased GSH concentrations and prevented lipid oxidation in the hippocampus of KA-treated rats, supporting the antioxidant effects of naringin (100). Similar to the observations in the KA-induced model rats, pretreatment with naringin (80 mg/kg, intraperitoneally) for 7 d significantly attenuated oxidative damage, inflammation, and cognitive impairment in PTZ-induced seizure model rats. In addition, rats pretreated with the GABA receptor antagonist flumazenil showed a significant decrease in the latency of myoclonic jerks compared with naringin-treated rats, indicating that naringin may have GABA receptor modulation properties (101). Moreover, 80 mg/kg of naringin (administered intraperitoneally 1 d before KA injection and daily for 6 d thereafter) could delay the onset of KA-induced seizures and attenuate autophagic stress and GCD in KA-treated mice via the regulation of mTOR complex 1 (mTORC1) activity (16, 17). The beneficial effects of naringenin have also been reported in various other epileptic models. Khodayar et al.

(102) investigated the anticonvulsant effect of naringenin on both maximal electroshock and PTZ-induced seizures in mice. Naringenin (200 mg/kg, intraperitoneally 30 min before seizure onset) reduced the duration of hindlimb extension in the maximal electroshock-induced seizure model and decreased the duration of myoclonic jerks in the PTZ-injected mice. In another study (103), naringenin (20 and 40 mg/kg) was administered orally for 15 d before pilocarpine-induced seizure onset in mice. Under these conditions, naringenin restored the antioxidant status and reduced lipid peroxidation in the hippocampus. Our previous report (18) showed that pretreatment with naringenin for 8 d (100 mg/kg/day, intraperitoneally) reduced the extent of morphological alterations of the DG and attenuated the expression of neurotoxic inflammatory cytokines such as TNF-α, IL-1β, and inducible nitric oxide synthase in the hippocampus of KA-treated mice. Furthermore, a mild binding affinity of naringenin for the $GABA_A$ receptor benzodiazepine site (104, 105) indicates that naringenin may act as an agonist of GABA receptors.

Morin

Morin [2-(2, 4-dihydroxyphenyl)-3, 5, 7-trihydroxy-4H-1-benzopyran-4-one], is a flavonoid isolated from *Maclura pomifera* (Osage orange), *Maclura tinctoria* (old fustic), and the leaves of *Psidium guajava* (common guava). Kandhare et al. (106) showed that morin has antiepileptic effects in PTZ-induced seizure model mice. Morin (20 and 40 mg/kg, intraperitoneally 45 min before PTZ injection) significantly reduced seizure behavior and improved the locomotor impairment caused by PTZ-induced seizures. In addition, morin significantly limited the seizure-induced reductions in GABA, dopamine, and Na^+/K^+-ATPase concentrations and the seizure-induced increases in xanthine oxidase activity and oxidonitrosative stress. Therefore, the authors suggested that the anticonvulsive effects of morin were elicited via modulation of the concentrations of GABA, Na^+/K^+-ATPase, and antioxidant status. Moreover, we recently reported (21) that the activation mTORC1 due to KA-induced seizure in mice was inhibited by treatment of morin (80 mg/kg; orally 1 d and 1 h before KA injection and daily for 2 d thereafter). Decreases in inflammation, mossy fiber sprouting, and GCD formation were also observed in the hippocampus of the KA-treated mice after administration of morin for 7 d.

Rutin

Rutin (3, 3′, 4′, 5, 7-pentahydroxyflavone-3-rhamnoglucoside) is a flavonoid of the flavonol type that is an important dietary component of foods and plant-based beverages. Nassiri-Asl et al. (107) showed the antiseizure effects of rutin on PTZ-induced model rats. Pretreatment with rutin (at 50 and 100 mg/kg, intraperitoneally for 14 d and up to 30 min before PTZ injection on day 14) led to a reduction in seizure severity and significantly increased the step-through latency in the passive avoidance paradigm. In another study with KA-induced seizure model mice (108), rutin treatment (at 100 and 200 mg/kg, intraperitoneally for 7 d and up to 30 min prior to KA injection) had anticonvulsant effects and attenuated oxidative stress indicators such as MDA concentrations.

Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is one of the most widely occurring flavonoids and is often present in vegetables and fruits. Nassiri-Asl et al. (109) investigated the anticonvulsant and antioxidant effects of quercetin in PTZ-induced seizure model rats. Quercetin (administered at 25, 50, or 100 mg/kg/day, intraperitoneally for 15 d and up to 30 min before PTZ treatment) resulted in anticonvulsant effects; although protection against memory impairment was observed at a dose of 50 mg/kg, no antioxidant effects were observed. On the other hand, it was reported that quercetin treatment (at 10 mg/kg, intraperitoneally 30 min before PTZ injection in rats) significantly prolonged the onset and reduced the severity of the seizure (110). In that study, 20 mg/kg of quercetin administered 30 min before picrotoxin injection had anticonvulsant effects. Moreover, in another study with KA-induced model mice, it was shown that quercetin administration (50 and 100 mg/kg/d, intraperitoneally for 7 d) decreased seizure severity in a dose-dependent manner; in addition, it reduced the expression levels of the $GABA_A$ α_5 mRNA (111). Other studies have also reported an increase in $GABA_A$ α_5 expression in KA and pilocarpine models (112–114), suggesting that compensatory mechanisms are involved in disease pathogenesis (114).

Hesperidin and its aglycone, hesperetin

Hesperidin is a natural flavone that is predominantly and abundantly found in citrus fruits. Hesperidin and its aglycone, hesperetin (3′,5,7-trihydroxy-4′-methoxyflavanone), have been shown to exert beneficial effects in the treatment of epilepsy. Kumar et al. (115) reported that 7 d of pretreatment with hesperidin (100 and 200 mg/kg, orally) prolonged the latency of onset of clonic and tonic phases of convulsion and increased the concentrations of antioxidant enzymes such as glutathione, superoxide dismutase, and catalase in PTZ-induced model mice. Another study (116) suggested that hesperidin pretreatment (10 and 50 mg/kg, intraperitoneally) attenuated neuronal loss in the hippocampus of KA-treated rats via reduction of glutamate release. We previously (22) showed that hesperetin (20 mg/kg/d, administered orally 1 d before KA injection and 7 d after seizure onset) prevented structural and functional abnormalities such as GCD and mTORC1 activation in the hippocampus of KA-injected mice.

Vitexin

Vitexin (5, 7, 4-trihydroxyflavone-8-glucoside) is a C-glycosylated flavone, which has been found in various plants such as *Passiflora* sp., bamboo leaves, pigeon pea leaves, and mung bean. Abbasi et al. (117) investigated the neuroprotective effects of vitexin on PTZ-induced model rats. In

TABLE 2 Preclinical studies of the effects of flavonoids on epileptic models[1]

Flavonoids	Study model	Dosage	Main targets	References
Apigenin	KA-induced mouse model	25, 50 mg/kg, i.p.	Antioxidant	(90)
	Picrotoxin-induced rat model	Pretreatment, 25, 50 mg/kg, i.p.	GABA receptor antagonism	(91)
Luteolin	PTZ-induced rat model	50 or 100 mg/kg/d, p.o.	Antioxidant, induction of trophic factor	(92)
	PTZ-induced mouse model	5, 10, 20 mg/kg, i.p.	Antioxidant effects, inhibition of kindling behavior	(93)
Genistein	KA-induced rat model (ovariectomized)	Pretreatment, 0.5, 5 mg/kg/d, i.p. for 4 consecutive days	Seizure-induced spatial learning and memory impairment, early long-term potentiation deficit, damage to hippocampal neurons	(94)
	PTZ-induced mouse model (ovariectomized)	Pretreatment, 10 mg/kg, i.p. 30 min before PTZ injection	Inhibition of estrogen and serotonin system	(95)
	PTZ-induced rat model (ovariectomized)	Pretreatment, 10, 20 mg/kg, i.p. 30 min before PTZ injection	Antioxidative stress (MDA and GSH), inhibition of estrogen receptor expression	(96)
Baicalin	KA-induced mouse model	100 mg/kg, i.p. twice at 1 and 8 h after KA treatment	Antiapoptotic effects via inhibition of miR-497	(97)
	Pilocarpine-induced rat model	Pretreatment, 100 mg/kg, i.p. 30 min before pilocarpine injection	Antioxidant effects	(98)
Silibinin	Lithium–pilocarpine induced rat model	Pretreatment, 100 mg/kg, p.o. 30 min before pilocarpine injection and 100 mg/kg at 1–3 d and 50 mg/kg at 4–13 d post onset	Anti-inflammatory effects	(99)
	KA-induced mouse model	200 mg/kg, i.p. 1 d and 1 h before KA injection and daily treatment for 35 d	Antiapoptotic, autophagic, inflammatory effect and anti-GCD effect	(20)
Naringin	KA-induced rat model	Pretreatment, 20, 40, 80 mg/kg/d for 7 d, i.p.	Antioxidant and anti-inflammatory effects	(100, 101)
	PTZ-induced rat model		Modulation of GABA receptor and ameliorate cognitive impairment (80 mg/kg)	(16, 17)
	KA-induced mouse model	80 mg/kg, i.p. 1 d before KA injection and daily treatment for 7 d	Anti-autophagic stress and GCD Modulation of mTORC1 activity	
Naringenin	Maximal electroshock and PTZ-induced mouse model	200 mg/kg, i.p. 30 min before seizure onset	Anticonvulsant effects	(102)
	Pilocarpine-induced mouse model	20, 40 mg/kg, p.o. for 15 d before seizure onset	Antioxidant effects	(103)
	KA-induced mouse model	Pretreatment, 100 mg/kg/d i.p. for 8 days	Anti-inflammatory effects and anti-GCD	(18)
Morin	PTZ-induced mouse model	20, 40 mg/kg, i.p. 45 min before seizure onset	Preservation of GABA, dopamine, and Na^+/K^+ ATPase concentrations and antioxidant effects	(106)
	KA-induced mouse model	80 mg/kg, p.o. 1 d and 1 h before KA injection and daily treatment for 2–7 d	Inhibition of GCD formation via mTORC1 inhibition, anti-inflammatory and anti-apoptotic effects	(21)
Rutin	PTZ-induced rat model	50, 100 mg/kg/d, i.p. for 14 d 30 min before PTZ injection	Prevention of seizure behaviors	(107)
	KA-induced mouse model	100, 200 mg/kg/d, i.p. for 7 d	Prevention of seizure behaviors and antioxidant effects	(108)
Quercetin	PTZ-induced rat model	50 mg/kg/day, i.p. 30 min before PTZ injection for 15 days	Anticonvulsant effects and protection against memory impairment	(109)
	PTZ- or picrotoxin-induced rat model	10, 20 mg/kg, i.p. 30 min before seizure onset	Anticonvulsant effects	(110)
	KA-induced mouse model	50, 100 mg/kg/d, i.p. for 7 d	Anticonvulsant effects and reduction in the expression of the $GABA_A\ \alpha_5$ mRNA	(111)
Hesperidin	PTZ-induced mouse model	Pretreatment, 100, 200 mg/kg, p.o. for 7 d before seizure onset	Anticonvulsant effects and modulation of antioxidant enzymes concentrations	(115)

(*Continued*)

TABLE 2 (*Continued*)

Flavonoids	Study model	Dosage	Main targets	References
	KA-induced rat model	Pretreatment, 10, 50 mg/kg, i.p.	Neuroprotection, reduction of glutamate release	(116)
Hesperetin	KA-induced mouse model	20 mg/kg/day, p.o. 1 d before KA injection and 7 d after seizure onset	Prevention of GCD and inhibition of mTORC1 activity	(22)
Vitexin	PTZ-induced rat model	100, 200 μM, i.c.v. 30 min before PTZ injection	Anticonvulsant effects and GABA receptor modulation	(117)

[1]GABA, γ-aminobutyric acid; GCD, granule cell dispersion; GSH, glutathione; i.c.v., intracerebroventricular; KA, kainic acid; MDA, malondialdehyde; p.o., oral administration; PTZ, pentylenetetrazol.

that study, vitexin (100 and 200 μM, administered intracerebroventricularly 30 min before PTZ injection) exerted anticonvulsant effects by significantly reducing minimal clonic seizure and generalized tonic–clonic seizure. In addition, the authors showed that such antiepileptic effects of vitexin were abolished by pretreatment with flumazenil, indicating that vitexin may act as a $GABA_A$ receptor modulator.

Modulation of microRNAs as a Potential Target of Flavonoids in Epilepsy

MicroRNAs (miRNAs) are small endogenous noncoding RNAs critical for the post-transcriptional regulation of most mRNAs. miRNA biogenesis is a conserved process, which generates 21–25-nucleotide-long products that regulate gene expression by complementary binding to the

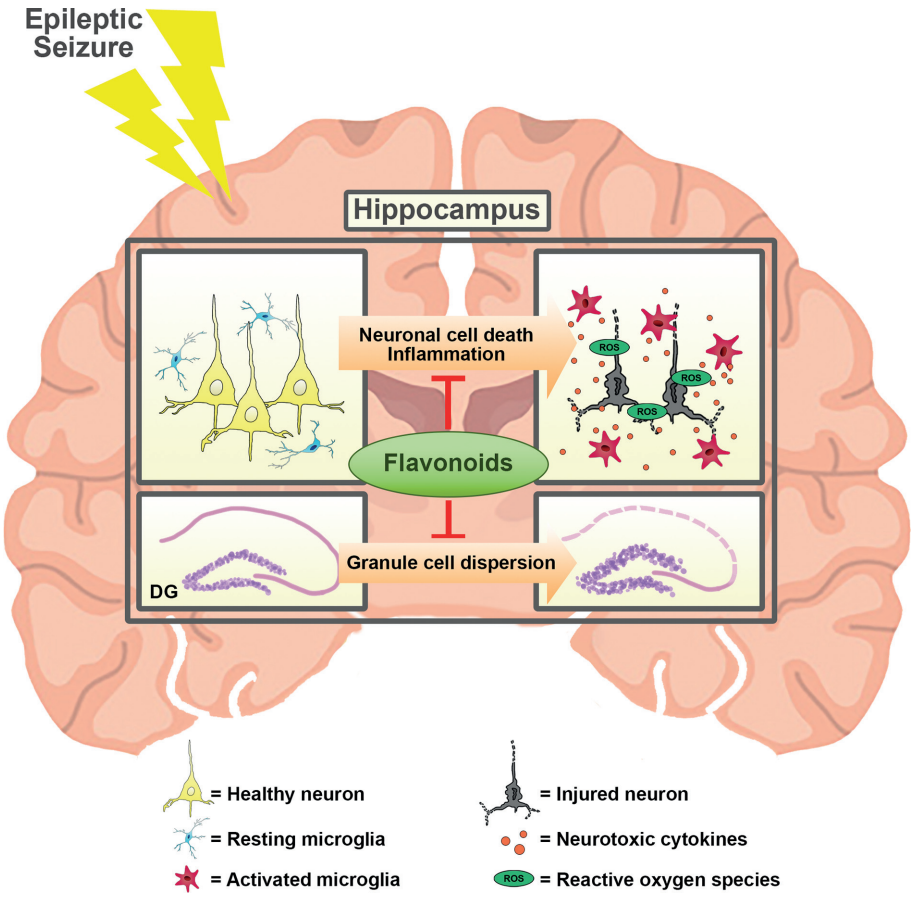

FIGURE 1 Schematic of the beneficial effects of flavonoids in the hippocampus with epilepsy in vivo. The treatment with various flavonoids, such as apigenin, silibinin, and naringin, may provide antioxidative and anti-inflammatory effects and reduce granule cell dispersion in the hippocampus, resulting in attenuation of status epilepticus. DG, dentate gyrus; ROS, reactive oxygen species.

target mRNA. Some studies have profiled alteration of miRNAs in the hippocampus of animal models and patients with TLE (118–130). Peng et al. (123) demonstrated that the expression of miR-132, which belongs to the miR-212/132 family, is increased in the hippocampus of human TLE patients and experimental models. miR-132 could modulate neurite outgrowth and dendritic morphology via regulation of the protein kinase A-mediated cAMP response element binding protein signaling pathway. Han et al. (118) measured the miRNA profile in the hippocampus of rats after lithium–pilocarpine-induced epilepsy using microarrays and qPCR. This approach revealed the presence of 4 upregulated miRNAs (miR-146a, -210, -34a, and -27a) and 2 downregulated miRNAs (miR-135b and -33) in the hippocampus of TLE model rats. This work highlighted a role for miR-34a in TLE-associated neuronal cell death. In addition, it showed that miR-34a antagomir treatment significantly inhibited the activity of caspase-3 and led to an increase in neuronal survival 7 d post-epilepsy in the rat hippocampus (122). Liu et al. (126) found that miR-344a expression was downregulated in the hippocampus of PTZ-induced epilepsy model rats. Overexpression of miR-344a by intracerebroventricular injection of miR-344a agomir significantly reduced neuronal cell death and the seizure behaviors associated with TLE in the PTZ-injected rats. Alsharafi et al. (124) investigated the miRNA expression patterns in the hippocampus of patients with TLE and pilocarpine-induced model rats. The results showed that the expression of miR-139–5p was significantly downregulated in both TLE patients and pilocarpine-induced model rats. These findings suggested that alternation of miRNA expression may play an important role in epileptogenesis.

Several studies found that miR-155 expression was increased in the hippocampus of epilepsy model rats and TLE patients (128, 131–133). In addition, the TNF-α and phosphoinositide 3-kinase/Akt/mTOR epileptogenic pathways were regulated by miR-155 in epilepsy model rats and TLE patients (128, 131, 132). Another study showed that silencing miR-155 reduced apoptotic cell death associated with pilocarpine-induced seizure in the CA3 hippocampal area of rats (133). The effects of silibinin on miR-155 expression were evaluated in cell cultures of MCF-7, which is a breast cancer cell line. Treatment with 100 μg/mL of silibinin significantly downregulated expression of miR-155, resulting in inhibition of cell proliferation and migration (134). Arango et al. (135) reported that apigenin (50 mg/kg, intraperitoneally) prevented LPS-induced inflammatory activity by reducing miR-155 expression in murine macrophage culture and lung tissue. Quercetin (10 μmol/L) significantly decreased the mRNA and protein expression of TNF-α through the downregulation of miR-155 in LPS-stimulated murine macrophages (136). In another in vivo study, elevation of miR-497 expression was observed in the hippocampus of KA-injected mice at 12 h post-seizure onset (97). However, double treatment with baicalin (100 mg/kg) by intraperitoneal injection at 1 and 8 h after seizure onset significantly inhibited the expression of miR-497 in the mouse hippocampus.

There are few studies on miRNAs as molecular targets of flavonoids in TLE model animals. However, there are several studies on the miRNA-related mechanisms of action of plant-derived compounds, including flavonoids, in human diseases such as hypertension, diabetes, atherosclerosis, metabolic disorders, and cancer. Therefore, further studies are required to examine the extent of correlation between flavonoids and miRNA in the treatment and prevention of TLE.

Conclusions

Although there are some medications to control epilepsy that successfully regulate seizures, 30–40% of epilepsy patients do not respond to typical treatments with AEDs. In addition, current AEDs have a narrow therapeutic window due to several adverse effects, such as dose-related neurotoxicity and impaired systemic processes. Therefore, alternative effective and safe medical treatments of epilepsy are highly desirable. In recent years, studies have reported beneficial effects of flavonoids, particularly TLE, in epilepsy (**Table 2**), including reductions in neuronal cell death, neurotoxic inflammation, mossy fiber sprouting, and GCD formation, as well as modulation of miRNA expression in the hippocampus (**Figure 1**). Current understanding of the specific molecular mechanisms preventing structural changes and mossy fiber sprouting in the hippocampus is limited. In addition, there are insufficient data from clinical trials on the therapeutic and adverse effects of flavonoids. Nevertheless, the beneficial effects of many flavonoids described recently suggest that various flavonoids have the potential to become effective and safe alternative medicines. Thus, flavonoids could be useful for developing novel therapeutic strategies for the treatment of epilepsy.

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