Flavonoids and antiepileptic drugs: a comprehensive review on their neuroprotective potentials

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ABSTRACT
Flavonoids have more potent therapeutic efficacy for the treatment of epileptic disorders. Certain flavonoids possess significant synergistic effects and can be taken with particular antiepileptic drugs (AEDs) to reduce the possibility of drug resistance. The combination of herbal and traditional medicines may not only prevent adverse effects but also increase the drug effects in overall comprehensive efficacy. The present study reviewed the potential efficacy of active constituents of selected flavonoids. Furthermore, in recent years, various researches have been attentive to specific flavonoids for their neuroprotective potential in in-vitro and in-vivo models. We have selected some specific flavonoids that have already proven therapeutic potential in animal epileptic models. Certain flavonoids possess significant synergistic effects and can be taken with particular AEDs to reduce the possibility of drug resistance. Some flavonoids are shown to exhibit their neuroprotective effects in Parkinson's disease, Alzheimer's disease, and ischemic stroke, which are the most common examples of neurological disorders. The major outcomes of flavonoids on progressive neurological disorders may be correlated to the regulation of gamma-aminobutyric acid (GABA) receptors. It has been reported that the neuroprotective actions of naringenin in experimental strokes are mediated by a reduction in NF-B-induced neuroinflammation. These discoveries appear to suggest that some flavonoids are more effective than conventional antiepileptic medicines, which have fewer side effects and can be used for the cure of epileptic seizures. Recently, in many research studies, it has been found that plant-derived flavonoids provide synergistic pharmacological action in experimental models of severe epilepsy.

Keywords: Flavonoid, Therapeutic efficacy, Traditional medicine, Neuroprotective effect, Alternative therapy.

INTRODUCTION
Epilepsy is a severe neurological condition that affected millions of people throughout the world⁴. The most frequent type of epilepsy is temporal lobe epilepsy, but the pathological causes that trigger it and still poorly understood⁵. For the treatment of seizures, more than 20 antiepileptic medications (AEDs) have been synthesized and are currently in use⁶. Some flavonoids have already been studied for their anticonvulsant properties, and few selected flavonoids have been found as new chemicals that are effective natural inhibitors of convulsions⁷. Epileptogenesis is the process that results in the development of seizures. Lamotrigine is a prominent antiepileptic drug that has been primarily used in anti-epileptogenic research studies⁸. Kindling models have been suggested as potentially important and useful methods for the identification of antiepileptogenic therapies⁹. Previous research studies have shown that lamotrigine efficacy in the electrical kindling model is controversial. Another kindling model is chemical kindling such as the pentylenetetrazol (PTZ) model¹⁰. Mostly Flavonoids are polyphenol that can be present in a variety of natural vegetables, including dietary foods, fruits, and some beverages. Various recent studies have discovered that certain flavonoids have a variety of therapeutic properties for epileptic patients without any adverse effects linked with traditional health systems¹¹. Additionally, some flavonoids have the ability to regulate microRNA expression, which is linked with inflammation and cellular survivability. Natural sources can give approximately 8000 distinct flavonoids. Flavonoids are low-molecular-weight chemicals that comprise 2 benzene rings linked by a heterocyclic pyrone or pyran ring. AEDs potentially cause a wide range of dose-related adverse reactions including sleepiness, dizziness, vertigo, blurred/double vision, tremors (uncontrollable shaking), increased infections risk, bruising, and hemorrhages. As a result, there is significantly essential for active and harmless alternative medications for the management of epileptic seizures. The
BBB (blood-brain barrier) is the most complex obstacle to pass instead of medications that target the central nervous system\(^{9}\). Few research investigations have shown that some flavonoids can easily penetrate into BBB and provide pharmacological action in the hippocampus region of the brain\(^{10}\). Quercetin is a natural flavonoid and a polyphenol compound mainly found in fruits and vegetables. It can be an effective antioxidant and radical scavenger in the search for new therapeutic approaches. It has been found that quercetin exhibits anti-blood coagulation, anti-inflammatory, and anti-ischemic properties. Flavonoids are usually classified such as Anthocyanins, Flavanones, Flavones, Chalcones, Flavonols, Isoflavonoids (In figure.2)\(^{11}\). These discoveries specify that flavonoids can be utilized as an alternative treatment for epilepsy. In this review, we have explored the efficacy of selected flavonoids as a promising effect with fewer adverse effects than conventional AEDs\(^{12}\).

**Figure 1**: Diagrammatically explain the neuro-protective effect of flavonoids

**Figure 2**: Major Classes of Flavonoids

- **Anthocyanins**
- **Flavanones**
- **Flavones**
- **Chalcones**
- **Flavonols**
- **Isoflavonoids**

**Figure 3**: Chemical Structures of Some Flavonoids

- **Luteolin**
- **Apigenin**
- **Baicalin**
- **Hesperidin**
- **Rutin**
- **Quercetin**
- **Vitexin**
- **Wogonin**
- **Morin**
- **Naringenin**
- **Hispidulin**
Alternative therapeutic approaches for the treatment of epilepsy

According to the new finding, some flavonoids are shown to exhibit neuroprotective effects in neurological illnesses such as Alzheimer's disease and Parkinson's disease[13]. The major outcomes of flavonoids on progressive neurological disorders may be correlated to the regulation of gamma-aminobutyric acid (GABA) receptors. It has been reported that the neuroprotective actions of naringenin in experimental strokes are mediated by a reduction in NF- B-induced neuroinflammation[14]. Cannabis seems to have the ability to produce over 400 different chemical compounds, including terpenes, flavonoids, and more than 100 Phyto cannabinoids[15]. Cannabidiol (CBD) and Tetrahydrocannabinol (THC) are the two most common Phyto-cannabinoids. Several countries use cannabis-based products as medications[16]. Some inhibitory and excitatory neurotransmitters are responsible for causing epileptic seizures that can be regulated by the use of alternative therapy for epilepsy inpatients[17]. These 5 types of alternative treatment are as follows.

Herbal treatments

Traditional herbal remedies maintain the natural and biological actions of their active constituents. Natural medicines have no toxic or minimum side effects. Furthermore, animals do not even acquire the benefits of drug resistance, so the use of natural compounds in animals usually leaves no drug residue and causes no potential health risks. When compared with the conventional drug generally recommended for the treatment of epileptic seizures, the properties of natural medicaments are complex and difficult. Even though a particular drug doesn't have a high therapeutic efficacy but they have minimal harmful side effects that can decrease a patient's level of illness. Some of the most widely used plants for epilepsy are peony, skullcap, tree of heaven, valerian, lily of the valley, mistletoe, mug wort, and others[18].

Dietary changes

Specific dietary changes may also benefit seizure management. The most well-known diet is the ketogenic diet, which focuses on ingesting a higher ratio of protein and fats. The ketogenic diet is a limited, moderate eating plan. The ketogenic diet is frequently used to treat children with epilepsy. Many people find the constraints difficult to accept. However, this type of diet may be used in combination with some other treatment options to help reduce convulsions[19]. The proper protein diet may have neuroprotective capability includes the synthesis of calcium-binding proteins, like para-albumin regulating cellular calcium homeostasis that is necessary for brain cell activity. Some enzyme production regulates by getting an optimum diet, meditation that can be cure stress circumstances and diseases such as Alzheimer's, Parkinson's disease, multiple sclerosis, severe encephalomyelitis as well as other disorders and AIDS[20].

Vitamins

Certain vitamins may contribute to minimizing the frequency of seizures caused by epilepsy. Vitamin B-6 is mainly used to suppress pyridoxine-dependent seizures, a rare kind of epilepsy. This type of epilepsy usually appears during pregnancy or shortly after birth. It is caused by your body's inability to properly digest vitamin B-6. Although the results are promising, more research is needed to see whether supplementing with vitamin B-6 helps patients with some other neurologic disorders. The vitamin D studies related to the first indications of a possible involvement between vitamin D and seizures and thus raised scientists’ attention for further studies in this field. Neuroscientists from the UK and Denmark reported an annual history of newborn epilepsy. They observed that epileptic birth incidence is maximum in January and minimum in September. The administering of vitamin D can reduce the frequency of chemically induced seizures and increase the effect of some anti-epileptic drugs like phenytoin and valproate. In few clinical studies found that treatment with vitamin D has synergistic effects and positive outcomes in an epileptic patient. vitamin D can recover 30 percent of cases related to a neurological disorder[21].

Self-control and biofeedback

To minimize the occurrence of seizures, some patient with epilepsy tries to regulate their brain activity. The theory is that if you can identify the beginning of a seizure, you could be able to prevent it. Aura symptoms appear in many people with epilepsy about 20 minutes before they have a seizure. People may feel unusual odours, notice abnormal lights, or experience blurry vision. People may develop symptoms for several days before the incident. These signs include anxiety, depression, drowsiness, and severe headaches[22].

Acupuncture and chiropractic care

Acupuncture and chiropractic therapies are often suggested as alternatives to the traditional treatment of seizures. Acupuncture's underlying mechanism is unknown, but ancient Chinese therapy is used to treat chronic pain and other medical issues. According to specialists, they think that the body can heal itself by placing fine needles in specific areas of the body. Acupuncture does have the potential to change cognitive function and hence prevent convulsions. Acupuncture may help to control epilepsy by raising parasympathetic activity and altering autonomic dysfunction[23].

Currently available treatment of allopathy drugs for epileptic disorders

Several researchers have indicated that excitatory and inhibitory transmission abnormalities may cause epileptic fits. AEDs that are now being prescribed to treat epileptic seizures work primarily by blocking signaling pathways and inhibiting neuronal excitability. Voltage-gated sodium channels are the primary targets of AEDs, including lacosamide, oxcarbazepine, topiramate, lamotrigine, carbamazepine, rufinamide, phenytoin, felbamate, zonisamide,
valproic acid. Other AEDs inhibit synaptic neurotransmitter release, which reduces excessive neuronal excitability. Around 70% of epileptic patients experience seizure-free phases after initiating medication, whereas 30% of patients are resistant to AEDs. When single-drug treatments are ineffective for controlling seizures in this condition, multiple-drug therapy is usually attempted. Furthermore, current anticonvulsant medications only have a temporary effect on recurrent seizures. Rapamycin is an anticancer drug that has been officially approved by the FDA, is another promising anti-seizure drug with wider therapeutic potential

In addition, rapamycin inhibits cellular proliferation and motility. As a result, the continuing efficacy of rapamycin therapy can be determined for prophylactic effect. Nonetheless, the function of mTOR reduction in the management of convulsions is still unknown. Apart from ineffectiveness, AEDs can cause fatigue, dizziness, vertigo, blurred or double vision, tremors (uncontrollable shaking), a higher possibility of infection, hemorrhage, and bruises. As a consequence, safe and effective alternative medications for the treatment of epilepsy are desperately required. Recognition Receptors (PRRs) that are abundantly present on phagocytes have played a significant role in defense system. These receptors initially differentiate self from non-self in a coordinated immune response. Scientists from Batson to Tokyo have published a series of papers that give a clear image of how the elegant system of phagocyte cell Pattern Recognition Receptors (PRRs) that detect Microbe Associated Molecular Patterns (MAMPs) and Damage Associated Molecular Patterns (DAMPs) is disrupted when any kind of flaw in the signaling cascade occurs.

<table>
<thead>
<tr>
<th>Anti-epileptic drugs</th>
<th>Therapeutic efficacy</th>
<th>Idiosyncratic effects</th>
<th>Effects on the fetus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>Highly effective</td>
<td>skin rash, aplastic</td>
<td>increased bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>anemia, jaundice, and</td>
<td>tendency due to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hepatitis.</td>
<td>decreased vitamin K</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Moderate efficacy</td>
<td>skin rash</td>
<td>May cause severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>effect in heart</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Highly effective</td>
<td>bone-marrow, depression,</td>
<td>Increased congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hepatitis</td>
<td>heart malformations</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Highly effective</td>
<td>hepatitis, jaundice, fever,</td>
<td>congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>skin rashes</td>
<td>malformations</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Moderate effective</td>
<td>Thrombocytopenia, hair loss</td>
<td>congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>malformations</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Highly effective</td>
<td>Lack of side effects at low doses</td>
<td>harm to an unborn baby</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Moderate effective</td>
<td>dry mouth, swollen arms/legs, blurred vision</td>
<td>increased risk of preterm birth</td>
</tr>
<tr>
<td>Ethotoin</td>
<td>Highly effective</td>
<td>Dizziness, tiredness, numbness/tingling</td>
<td>Lack of side effects on the fetus</td>
</tr>
</tbody>
</table>

Cytokines are the most important signaling molecules among them, as they signal and warn the entire immune system to recruit an army of cells and proteins to fight the foreign invader. Cytokines influence cell differentiation, the production of other cytokines, and the activation of specific cells. If, for example, more cytokines are generated following a signal than required for an appropriate immune response, this might result in a cytokine storm or cytokine toxicity, which in turn can lead to septic shock and trauma to normal bodily tissues.

**Neuro-protective efficacy of flavonoids in epilepsy**

Antiepileptic drugs (AEDs) have potential effects for the prevention of seizures, with nearly 70% of children can achieve satisfactory treatment with only medications. Although the satisfying inventory of new and old AEDs is increasing, approximately 30% of epileptic patients still have seizures. Flavonoids are polyphenolic molecules containing 15 carbons and a 3-bridge [C6–C3–C6] linking two aromatic rings. Nutritional flavonoids are described as flavanones, flavones, anthocyanidins, flavonols, or isoflavones, while dihydroflavonols, coumarins, chalcones, dihydrochalcones, and aurones are relatively small constituents of food. Fruits, vegetables, cereal, teas, and fruit liquids have all been better sources of flavonoids.

The chemical structures of some potent flavonoids are shown (In Figure 3). The discovery that quercetin and structurally linked compounds significantly improved neuronal survival during an oxidative stress model while scavenging antioxidants (vitamin E, boldine) failed to protect cells against oxidative stress indicates that all of these molecules have specific cell long-term viability effects. Several flavonoids’ cytoprotective activities may be associated with their capability to stimulate the release of some intracellular biomolecules (gene regulators, protein kinase, and phosphatases), which convert to serve as molecules of neuronal cascades, enhancing the expression of the survival signaling.

Luteolin, [3,4,5,7-tetrahydroxyflavone] is a dietary flavonoid found in a wide variety of fruits, vegetables, and plant species. According to prior research, Pre-treatment by luteolin (50 and 100 mg/kg/d via oral delivery for 5 weeks) decreased onset of convulsion, regularity, then intensity after pentylentetrazol (PTZ) dose. Researchers discovered that luteolin decreased malondialdehyde (MDA) levels, restored decreased GSH levels, and prevented kindling behaviour triggered by PTZ treatment.

Apigenin, [5,7,4-trihydroxy-flavone] is a nutritional flavonoid present in high concentrations in a variety of vegetables as well as in fruits. Furthermore, apigenin pre-treatment significantly reduced significant rises in GSH level in a nerve cell of the hippocampus following Kainic-acid induced seizures. Apigenin (25 or 50 mg/kg, intraperitoneal injection) significantly decreased the onset duration of seizure in the picrotoxin-induced convulsion model in rats.
### Table 2: Experimental animal studies of selected flavonoids with their potential efficacy on acute models of epilepsy

<table>
<thead>
<tr>
<th>Flavonoids</th>
<th>Natural source/Family/Plant part</th>
<th>Study models</th>
<th>Animals</th>
<th>Dosage</th>
<th>Pharmacological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteolin</td>
<td>Abutilon indicum m (L.) Sweet. Malvaceae /Leaves</td>
<td>PTZ-model</td>
<td>Mice/Rats</td>
<td>50 or 100 mg/kg/d, p.o.</td>
<td>Onset delayed in myoclonic jerks; onset delayed in clonic seizures and develop hind limb extension; Protection against mortality neuroprotective effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PILO model</td>
<td>Mice</td>
<td>5, 10, 20 mg/kg, i.p.</td>
<td>Delayed the initiation of seizure and shortened the period of clonic seizures; Cognitive function improvements</td>
</tr>
<tr>
<td>Apigenin</td>
<td>Artemisia vulgaris L./ Asteraceae/Aerial parts</td>
<td>Picrotoxin-induced seizures</td>
<td>Mice</td>
<td>Pre-treatment with 25, 50 mg/kg, i.p.</td>
<td>Onset of seizures significantly delayed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KA-model</td>
<td>Mice</td>
<td>25, 50 mg/kg, i.p.</td>
<td>Reduction of the number of seizures</td>
</tr>
<tr>
<td>Baicalin</td>
<td>Oroxylum indicum L./Bignoniaceae /Leaves</td>
<td>PILO-model</td>
<td>Rats</td>
<td>Pre-treatment, 100 mg/kg, i.p., 30 min before pilocarpine administration</td>
<td>Significant delay in seizures; Reduced neuronal death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KA-model</td>
<td>Mice</td>
<td>100 mg/kg, i.p. twice at 1-8 h after KA administration</td>
<td>Neuroprotective effect</td>
</tr>
<tr>
<td>Hesperidin</td>
<td>Citrus aurantium L./ Rutaceae/ Fruits</td>
<td>PTZ-model</td>
<td>Mice</td>
<td>100, 200 mg/kg, p.o. for 7 d before onset of seizure</td>
<td>Increased anti-seizure effect alone or in combination with diazepam; Neuroprotective effect</td>
</tr>
<tr>
<td>Rutin</td>
<td>Hypericum perforatum L./ Hypericaceae/ Aerial parts</td>
<td>PTZ model</td>
<td>Rat</td>
<td>50, 100 mg/kg/d, i.p. administration for 14 d</td>
<td>Reduced the frequency of seizure behaviours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KA-induced model</td>
<td>Mice</td>
<td>100, 200 mg/kg/d, i.p. administration for 7 d</td>
<td>Reduced the frequency of epilepsy behaviours; Anti-oxidant effect</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Argyreia speciosa (Burm.f.) Bojer/ Convolulaceae/ Roots</td>
<td>PTZ model</td>
<td>Rat</td>
<td>50 mg/kg/day, i.p. 30 min before PTZ administration</td>
<td>Improvement of cognitive function; Antiepileptic effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KA induced model</td>
<td>Rat</td>
<td>50, 100 mg/kg/d, i.p. administration</td>
<td>Inhibition in the expression of the GABA&lt;sub&gt;3&lt;/sub&gt; in mRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Picrotoxin model</td>
<td>Rat</td>
<td>10, 20 mg/kg, i.p. 30 min before onset of convulsions</td>
<td>Anticonvulsant effects</td>
</tr>
<tr>
<td>Vitexin</td>
<td>Vitex agnus castus L./ Lamiaceae/ Fruits</td>
<td>PTZ- model</td>
<td>Rat</td>
<td>100, 200 mg/kg, i.p. 30 min before PTZ administration</td>
<td>GABA level alteration and anticonvulsant effects; Receptor modulation</td>
</tr>
<tr>
<td>Wogonin</td>
<td>Scutellaria lateriflora L./ Lamiaceae/ Above ground parts</td>
<td>MES induced convulsion</td>
<td>Mice</td>
<td>5 or 10 mg/kg b/w, i.p.</td>
<td>Anticonvulsant effect; Inhibited the CI influx; Effect on GABAergic neuron</td>
</tr>
<tr>
<td>Morin</td>
<td>Fragaria - ananassa L./ Rosaceae/Fruits</td>
<td>PTZ-induced model</td>
<td>Mice</td>
<td>20, 40 mg/kg, i.p. 45 min before onset of seizure</td>
<td>Enhance GABA and dopamine regulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KA-induced model</td>
<td>Mice</td>
<td>80 mg/kg, p.o. 1 d and 1 hr before KA administration</td>
<td>Anti-inflammatory and Anti-apoptotic effects</td>
</tr>
<tr>
<td>Hispidulin</td>
<td>Artemisia abrotanum L./ Asteraceae/Leaves</td>
<td>KA-induced model</td>
<td>Rat</td>
<td>(10 or 50 mg/kg, i.p.) 30 min before kainic acid injection.</td>
<td>Anticonvulsive activity; Neuroprotective effect; Anti-inflammatory effects</td>
</tr>
<tr>
<td>Naringenin</td>
<td>Citrus aurantium L./ Rutaceae/ Fruits</td>
<td>Pilocarpine-induced Model</td>
<td>Mice</td>
<td>20, 30 mg/kg, p.o. for 14 d before seizure onset</td>
<td>Antioxidant properties</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MES and PTZ-induced model</td>
<td>Mice</td>
<td>200 mg/kg, i.p. (30 min) before onset of convolution</td>
<td>Anticonvulsant effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KA-induced model</td>
<td>Mice</td>
<td>Pre-treatment, 100 mg/kg/d i.p. (for 8 days)</td>
<td>Anti-inflammatory activity and Decrease of granule cell dispersion effects</td>
</tr>
</tbody>
</table>

Baicalin [7-glucuronic acid, 5,6-dihydroxy flavone] is the primary flavonoid constituent found in ayurvedic medicine prepared from leaves extract of Oroxylum Indicum. According to previous studies, Baicalin (100 mg/kg, i.p. injection administered twice at 1 to 8 hours after onset of seizure) effectively diminished cleavage caspase-3 expression and enhanced B cell lymphoma development<sup>[32-33]</sup>.  

Hesperidin is a natural flavone found primarily in citrus fruits in excess amounts. hesperidin chemical name is [3,5,7 trihydroxy-4-methoxy-flavanone], have already been reported to be effective in the prevention of seizures. Researchers have previously shown that hesperidin (20 mg/kg/d, oral administration 1 day before Kainic acid (KA) treatment and 7 days after onset of convulsion) corrects basic functional and structural alterations in the hippocampus region of KA-treated mice, involving GCD and mTORC1 reactivation<sup>[34]</sup>.  

Rutin[3,3’,4’,5,7-Penta-hydroxy-flavone-rhamnoglucone] is a flavonoid that belongs to the Flavonols category and is mainly found in some foods and plant-based products. In their research, they showed the anti-seizure properties of rutin in a PTZ-induced model.
on rats. It is used to cure autism and also to protect the skin from sun damage.[35]

Quercetin [3,3',4',5,7-Penta-hydroxy flavone] plays as an important flavonoid found in plants and fruits. Much research has indicated that quercetin possesses anticonvulsant and antioxidant properties in PTZ-induced epilepsy models in rats and mice. Quercetin (given an intraperitoneal injection for 15 days and up to 30 minutes before PTZ administration on 25, 50, or 100 mg/kg/day) showed anticonvulsant effects[36].

Vitexin [5, 7, 4-tri-hydroxy flavone-8-glucoside] is a flavone found in Passiflora sp., bamboo leaves, and pigeon pea leaves. It was investigated for its neuroprotective potential in PTZ-induced models on rats[37].

Wogonin [5,7-Dihydroxy-8-methoxy, 2-phenyl-4-H-benzopyran-4 one]. When the influx was reduced by flumazenil, a flavonoid component of S. baicalensis may have increased Cl− influx via IMR32 cells (neuroblastoma cells). Further research is required to establish all the relationships between such a flavonoid and the GABAA subunits[38].

Morin is a yellowish chemical compound [2-(2,4-dihydroxy phenyl)-3-5-7-trihydroxy-4H-benzopyran-4-one] extracted from the plant of Maclura tinctoria (old fustic), Maclura pumifera (Osage orange), Psidium guajava leaves (guava). Morin possesses antiepileptic properties in PTZ-induced seizure mouse models, according to recent studies. Morin (at 20 and 40 mg/kg, i.p. 45 minutes before PTZ administration) significantly prevent or decreased seizure activity and enhanced PTZ-induced locomotive impairments[39].

Hispidulin is a flavone present in plants that also has antiseizure properties in rats and gerbils. It is obtained from plants such as Grindelia argentina, Arrabidaea chica, and Saussurea involucrata. Mast cell-mediated allergy reactions reduce the risk of inflammation. Naringenin, [5,7-Dihydroxy-2-[4-hydroxyphenyl]-2,3-dihydro-4H-benzopyran] is a flavonoid that belongs to the flavanone’s family. It is found in a variety of citrus fruits, bergamot, tomatoes, and other fruits, as well as also found in some glycosides[40].

Pre-clinical investigation of specific flavonoids on experimental models of epilepsy

The potential of flavonoids to suppress the action of several enzymatic reactions may trigger basic survival transmissions, resulting in a total indirect antioxidant-specific response in terms of direct scavenging from oxidative stress. So, it is also worthwhile to note that similar effects of quercetin and some bioactive flavonoids are observed at the critical level of glia and small blood vessels in the human brain. Antioxidant and anti-inflammation agents would be combined to induce vasodilation at the micro-vessel level, enhancing blood flow and continuing to work to inhibit the ischemic phase. Although the specific description of quercetin’s pharmacological action on the human brain has only recently initiated to be explored, many problems remain unresolved, but flavonoids may act as a leading chemical in the production of a new generation of biomolecules for their clinical efficacy and experimental animal studies of selected flavonoids on various epilepsy model as shown in table below[41-46].

<table>
<thead>
<tr>
<th>Pharmacological effects</th>
<th>Efficacy of Flavonoids</th>
<th>Efficacy of Flavonoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant effects</td>
<td>Apigenin, Baicalin</td>
<td>Luteolin, Morin, Ruin</td>
</tr>
<tr>
<td>GABA receptor antagonism</td>
<td>Apigenin, Baicalin</td>
<td>Luteolin, Morin, Ruin</td>
</tr>
<tr>
<td>Anticonvulsant effects</td>
<td>Vitexin, Quercetin, Wogonin</td>
<td>Hesperidin, Ruin</td>
</tr>
<tr>
<td>GABA Receptor modulation</td>
<td>Vitexin</td>
<td>Hesperidin, Ruin</td>
</tr>
<tr>
<td>Reduction of glutamate release</td>
<td>Hesperidin</td>
<td>Vitexin</td>
</tr>
<tr>
<td>Protection against memory impairment</td>
<td>Quercetin</td>
<td>Luteolin, Morin</td>
</tr>
<tr>
<td>Inhibition of GCD formation via mTORC1 inhibition</td>
<td>Naringenin</td>
<td>Morin</td>
</tr>
<tr>
<td>Inhibition of kindling behaviour</td>
<td>Vitexin</td>
<td>Luteolin</td>
</tr>
<tr>
<td>Inhibits mast cell-mediated allergic Inflammation</td>
<td>Naringenin</td>
<td>Hesperidin</td>
</tr>
<tr>
<td>Inhibit the production of TNFα and IL-1β, delaying the onset of seizures</td>
<td>Naringenin</td>
<td>Hesperidin</td>
</tr>
</tbody>
</table>

CONCLUSIONS

According to preclinical research, various specific flavonoids have more potent therapeutic value for the treatment of epileptic disorders. In addition, quercetin may have moderate therapeutic efficacy in an amygdala kindling model, it is also used to treat refractory epilepsy. While AEDs are beneficial for controlling seizures in epilepsy, 30 to 40% of individual patients with epilepsy do not respond effectively with conventional AED treatment after resistance to the drug. Furthermore, modern AEDs have limited therapeutic potential because of several complications, including dose-related neurotoxicity and altered circulatory processes. Certain flavonoids possess significant synergistic effects and can be taken with particular AEDs to reduce the possibility of drug resistance [47]. As a result, alternative treatments for seizures that are both effective and safe are extremely desirable. Recent research has found that flavonoids, specifically Temporal lobe epilepsy, can help with epilepsy by reducing neuronal cell death, cytotoxic inflammation, and adaptable mRNA expression in the hippocampus. The particular chemical processes that inhibit structural modifications and mossy fiber sprouting in the hippocampus are still unknown. Furthermore, there is a lack of clinical trial data on the curative and negative effects of flavonoids. However, many flavonoid positive effects have recently been reported, indicating that flavonoids may have the neuroprotective potential to become safe and active alternative.
therapies. Some specific flavonoids could be impactful in the examination of new therapeutic approaches for the treatment of acute and chronic epilepsy.

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DECLARATIONS
Conflict of interest
The authors declare that there is no conflict of interest.

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