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Review Article

PHYTOFLAVONOIDS: ANTIEPILEPTICS FOR THE FUTURE

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ABSTRACT

Epilepsy has become second most common neurological disorder affecting 70 million people worldwide. Several shortcomings appeared with the use of conventional antiepileptic drugs (AEDs) like, inadequate seizure control, side effects, cost, potentiation of epilepsy-induced co-morbidities, etc., which limit their use as comprehensive therapy. Phytoflavonoids in this regard have been observed to be promising AEDs which can interact with most of the possible targets involved in the pathogenesis of epilepsy. They show modulatory effect on voltage gated sodium channels, calcium channels, potassium channels, GABAergic system, opioid receptors, NMDA receptors and posses a strong antioxidant effects through modulation of nitric oxide pathway, xanthine oxidase system and through leukocytic immobilization. Along with antiepileptic effect, flavanoids have also been observed to ameliorate memory deficit and mood disorders commonly associated with AEDs treatment. Based on the vast literature reports, an attempt has been made to collate the fragmented information available on flavonoids, to access there potential as antiepileptics for future. From this review it is cleared that, flavonoids open new encouraging perspectives for the antiepileptic treatment. A prospective randomized trial of flavonoids may be justified in humans.

Keywords: Flavonoids, Epilepsy, Epilepsy-induced comorbidities, Flavonoidal plants.

INTRODUCTION

The name epilepsy is derived from a Greek word "epilambanein", which means "to seize upon", "to attack". Epilepsy is characterized as a chronic brain disorder in which there is tendency of the patient to experience periodic, unpredictable recurring seizures with or without characteristic body movements, called convulsions [1]. Epilepsy is the second most common neurological disorder affecting around 70 million people worldwide, out of which approximately 80 % are in developing countries [2].

Around 60-70% of the total patients with epilepsy depend on the medical treatment with antiepileptic drugs (AEDs) to achieve control of their epileptic seizures. These AEDs are targeted on supressing an abnormal epileptic discharge, acting generally via one or more mechanism(s) through inactivation of Na^+(hydantoins, etc) and Ca^{2+} channels (ethosuximide, etc), increasing GABA-mediated inhibitory functions (barbiturates, benzodiazepines, etc), inhibition of glutamate-mediated excitation (felbamate, etc), activation of K^+ channels (retigabine) [3-5].

Despite, decades of advancements in AEDs, there are a lot of shortcomings associated with their use. One-third of the epileptic patients treated with the available AEDs do not obtain satisfactory seizure control. Moreover, chronic use of these AEDs is associated with several systemic and central nervous system adverse effects like, fatigue, agressivity, anxiety, headache, hair loss, skin reactions, diplopia or blurred vision, dyspepsia, gingival hypertrophy or bleeding, tremors, weight gain, dizziness, somnolence, memory impairment, sleep disturbance, lack of concentration, lack of libido, difficulty of erection in men [6, 7].

A majority of epileptic patients suffer from one or more psychiatric or somatic comorbid conditions, whose nature and prevalence vary with age and sociodemographic factors, these comorbid conditions include cognitive deficit, mood disorders, anxiety, etc [8]. In the developed countries where drugs are easily available only 70 % patients with epilepsy responds to antiepileptic drug therapy. However, in developing countries 75% of people with epilepsy do not receive the treatment they need and their epilepsy remains uncontrolled, rendering the patient unproductive in all spheres of life. All these issues direct a large proportion of the patients to move on to traditional healers and medicinal plants [9].

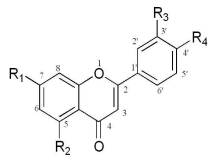
Traditional herbs due to presence of large amount of bioactive active ingredients have a great potential to treat epilepsy. Among all, phytoflavonoids are the most important bioactive product isolated from traditional herbs used in the treatment of epilepsy. "Phyto" is a Greek word that means plant, so phtoflavonoids means the flavonoids obtained from natural plant resources. Many of the traditional plants containing flavonoids have been experimentally explored for their anticonvulsant effect. Studies have shown that flavonoids possess remarkable anticonvulsant activity which can be exploited for the development of comprehensive AEDs of future [10-12]. Isolated phytoflavonoids like, hispidulin, rutin, hesperetin, naringenin, eriodictyol, chrysin, gossypin, apigenin, kaempferol, myricetin, quercetin, hyperoside etc. posses GABAergic agonism, sodiumchannels blockade, calciumchannels blockade, glutamate receptors antagonism and antioxidant etc., thereby act as anticonvulsants [13].

Flavonoids also had been found to ameliorate cognition deficit and depression, both of which occur in epileptic patient as comorbidities. It has also been found that herbal antioxidant like, curcumin have synergistic antiepileptic effect with standard AEDS like phenytoin [14]. Curcumin when co-administered with the subeffective doses of phenytoin, increased the latency to myoclonic jerks and protected against seizures, which was absent in animals treated *per se* with the same dose of phenytoin. Thus, flavonoids are turning out to be very useful and indispensable in the struggle for seizure management and future AEDs development. The present review focuses on antiepileptic flavonoids, their mechanisms, toxicology and their possible efficacy in epilepsy-induced comorbidities.

FLAVONOIDS

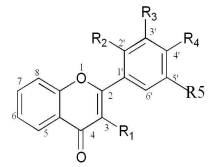
Flavonoids, also known as Vitamin P, are a class of secondary metabolites that provide UV protection and color to the plant. Nijveldt *et al.* [15] revealed their protective effect on brain stroke and cardiovascular system diseases.

Chemically, flavonoids are polyphenolic components containing a core of 15 carbon atoms; two benzene rings joined by a linear three carbon chain. Based upon the position present on basic parent moiety flavonoids are generally classified into 6 subclasses flavones, flavonols, isoflavones, flavonones, flavon-3-ols and anthocyanidin (Fig. 1). Biologically they are synthesised via acetate and shikimic acid pathway into a C_6 - C_3 - C_6 system [17, 18].



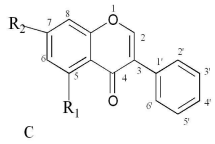
A

Flavones	R1	R2	R3	R4
Apigenin	OH	OH	H	OH
Luteolin	OH	OH	OH	OH
Chrysin	OH	OH	H	H
Diosmetin	OH	OH	OH	O-Me
Techtochrysin	OH	O-Me	H	H



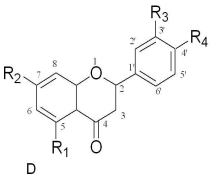
B

Flavonols	R1	R2	R3	R4	R5
Kaempferol	OH	H	H	OH	H
Rutin	O-Alk	OH	H	OH	H
Morin	OH	OH	H	OH	H
Myricetin	OH	H	OH	H	OH
Quercetin	OH	H	OH	OH	H
Kaempferide	OH	H	H	O-Me	H
Galangin	OH	H	H	H	H



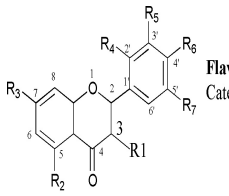
C

Isoflavones	R1	R2
Genistein	OH	OH
Daidzin	H	O-Glu



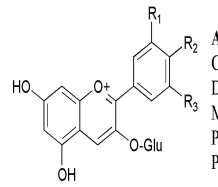
D

Flavonones	R1	R2	R3	R4
Hesperitin	OH	OH	OH	O-Me
Naringin	OH	O-Alk	H	OH
Naringenin	OH	OH	H	OH
Eriodictyol	OH	OH	OH	OH
Likvirtin	H	OH	H	O-Glu
Hesperidin	OH	O-Me	OH	O-Me



E

Flavan-3-ols	R1	R2	R3	R4	R5	R6	R7
Catechin	OH	OH	OH	H	OH	OH	H



F

Anthocyanidins	R1	R2	R3
Cyanidin 3-O-glycoside	OH	OH	H
Delphinidin 3-O-glycoside	OH	OH	OH
Malvidin 3-O-glycoside	OCH3	OH	OCH3
Peonidin 3-O-glycoside	OCH3	OH	H
Petunidin 3-O-glycoside	OH	OH	OCH3

A- Flavones, B- Flavonols, C- Isoflavones, D- Flavonones, E- Flavan-3-ols, F- Anthocyanidins

-O-Me= Methoxy, -O-Glu= Glucosyl, -Alkoxy= Alkoxy

Fig. 1: It shows the comprehensive list of all the chemical structures for the main classes of flavonoids.

Antiepileptic mechanisms of flavonoids

Flavonoids have been found to inhibit almost all the mechanisms involved in seizures generation in epilepsy. They have been found to modulate neuronal Na^+ channels, Ca^{2+} channels, GABA ergic pathway, glutamatergic pathway and opioid pathway (Fig. 2).

1. Inhibition of voltage gated Na^+channels resulting in decrease sodium ion influx into the neuronal cell
2. Activation of Ca^+activated K^+channels resulting in increased potassium ion outflow from thr neuronal cell
3. Activation of inhibitory GABAergic receptors through direct action on GABA or through benzodiazepine receptor resulting in increased chloride ion influx causing neuronal hyperpolarisation
4. Inhibition of opioid receptors leading to proconvulsant or anticonvulsant effects
5. Antioxidant effects of flavonoids leading to increased seizure threshold.
6. Inhibition of NMDA receptor, resulting in decrease entry of calcium into the neuronal cell

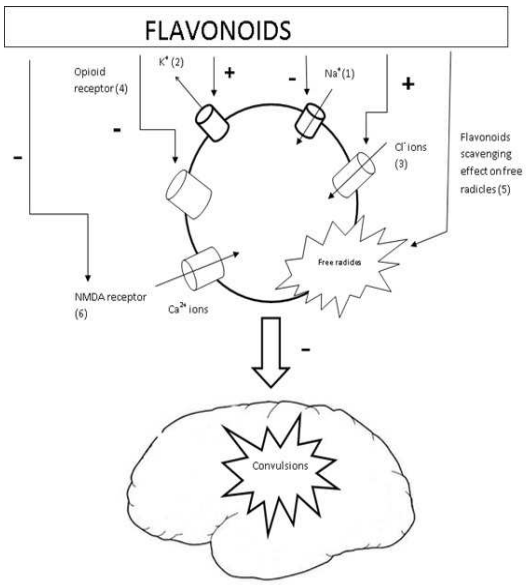


Fig. 2: Schematic antiepileptic mechanism of flavonoids.

Inhibition of voltage gated sodium channels

Abnormal increase in intracellular Na^+ causes high neuronal excitability leading to excessive depolarization leading to seizures. Several clinically used drugs like, Phenytoin, Carbamazepine, Valproic acid, etc. act via blockade of sodium channels, inhibiting abnormal depolarization. Flavonoids such as quercetin and pinostrobin have been found to act through similar mechanism [19]. Quercetin also decreases the amplitudes of sodium currents at different membrane potentials in rat hippocampal CA1 pyramidal neurons [20].

Activation of Ca^+activated K^+ channels

Repetitive ictal and interictal activity causes increase in extracellular K^+, leading to increased neuronal excitability. Neurons are very sensitive to changes in membrane K^+ currents, e.g. pyramidal cells in CA1 region of the hippocampus. Mutation in these voltage-gated K^+ channel causes benign familial neonatal convulsions [21]. Retigabin is a clinically used antiepileptic drug and act by opening K^+ channels. Flavonoids like quercetin have been reported to activate Ca^{2+}-activated K^+ channels and decreases extracellular K^+ leading to hyperpolarization amelioration of seizures [22].

GABAergic inhibition

GABA (γ-aminobutyric acid) is the principal inhibitory neurotransmitter in the mammalian CNS. GABA elicits inhibitory response in the brain via three classes of receptors, $GABA_A$, $GABA_B$ and $GABA_C$. $GABA_A$ is a GABA gated chloride channel which allows influx of chloride ions resulting in decrease excitatory stimulus [23].

The $GABA_B$ receptor is a G-protein coupled metabotropic receptor which interacts with G_i to inhibit adenylyl cyclase, activate K^+ channels and reduce Ca^{2+} conductance. The $GABA_C$ receptor is a transmitter-gated Cl^- channel and is less widely distributed than the A and B subtypes [24].

The GABA hypothesis of epilepsy implies that a reduction of GABA-ergic inhibition results in epilepsy, whereas an enhancement of GABA-ergic functions results in an antiepileptic effect. Modulation of ionotropic GABA receptors by a group of natural and synthetic flavonoids has been extensively studied in several experimental studies. Literature survey showed that, quercetin, apigenin, morine, chrysin and flavone inhibit ionic currents mediated by $GABA_A$ and $GABA_C$ receptors expressed in *Xenopus laevis* oocytes leading to suppression of abnormal depolarization [21, 25]. Flavonoids like apigenin and (-) epigallocatechin gallate potentiates the therapeutic effect of diazepam [26], indicating their efficacious role in combined therapy. This synergistic effect of flavonoids is due to their binding affinity with $GABA_A$ receptor through high-affinity flumazenil-sensitive site or low-affinity, flumazenil-insensitive site [25].

Benzodiazepines (BDZ) also play a vital role in ameliorating epilepsy and act by enhancing GABAergic functions leading to reduction in sustained repetitive firing. But because of their depressant nature they show several side effects. Whereas, flavones like, 6,3-dinitroflavone act by similar GABAergic action as that of BDZ sites but devoid of side effects like, ataxia, amnesia, etc [21, 27].

Opioid receptor interactions

Opioid receptors are found in various brain regions and spinal medulla, as well as in intramural nerve plexuses. These receptors are classified as μ, δ and κ, they mediate their physiological functions through G-protein coupled mechanism. Activation of these receptors causes increase in K^+ conductance, decrease in Ca^{2+}influx into nerve terminal leading hyperpolarization, decreased release of excitatory neurotransmitters and decreased synaptic activity**.** Depending on the cell population affected, the synaptic inhibition translates into depressant or excitatory effects. Studies have shown that opioids and opioid peptides had both convulsant and anticonvulsant properties. Several flavonoids have been evaluated for their opioid receptor modulatory effects. Amentoflavone and hyperoside present in *H. perforatum* have κ antagonist activity *in vitro* [21]. Katavic [28] also suggested flavonoid core as a future new scaffold for the development of opioid receptor ligands.

Inhibition of NMDA receptors

Excessive activation of glutamatergic N-Methyl-D-aspartate (NMDA) receptor leads to neuronal degeneration and death, due to increased Ca^{2+} concentration in the postsynaptic neurons leading to abnormal neuronal depolarisation. Binding of $Ca^{2+}$to calmodulin also activates nitric oxide synthase, thereby increasing the formation of nitric oxide (NO) that contributes to the neurotoxic effects. Moreover, activation of NMDA receptors also leads to increased production of superoxide radicals, leading to the generation of hydroxyl radicals causing oxidative damage which is responsible for worsening of epileptic condition and initiates its associated comorbidites. NMDA receptor antagonists are powerful anticonvulsant and are clinically used. They are responsible for the inhibition of calcium influx into the neurons thereby preventing abnormal excitation. Several flavonoids like, morin, kaemferol, myricetin, quercetin, anghyperoside have been reported to block glutamatergic excitation mediated through NMDA receptors. Morin provides neuroprotection by inhibiting excessive activation of NMDA receptors, NMDA receptor mediated neurotoxicity [29]. Thus, flavonoids like morin can be helpful in developing NMDA antagonists which can be effectively used for the treatment of epilepsy and its associated comorbidities in future.

Antioxidant potential

Free radicals play a crucial role in the pathogenesis of epilepsy. Increase in number of free radicals is coupled with low level of antioxidants, which results in the neuronal damage. It has been reported that free radical generation induces seizure activity by inactivation of glutamine synthase, leading to an abnormal build-up of excitatory neurotransmitter, glutamate or by decreasing glutamate decarboxylase, thus causing decrease in GABA turnover [13]. Flavonoids in this regard prove out to be a bioactive metabolite of choice for the treatment of oxidative stress induced diseases like, epilepsy. Traditionally also plants containing flavonoids have been experimentally explored for their anticonvulsant effect [10-12]. Flavonoids possess high antioxidant activity and low IC_{50} in *in vitro* antioxidant tests like 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay [30]. IC_{50} is the concentration at which the substance shows 50% inhibitory activity. Ishige *et al.* [31] found three distinct mechanisms of antioxidant protection like, increasing intracellular GSH, directly lowering levels of ROS, and preventing the influx of Ca^{2+} despite high levels of ROS.

Not all flavonoids have equal antioxidant potential. Flavonols were found to be best antioxidants when compared with anthocyanidins, flavone and flavanone and other type of flavonoids [32, 33]. Flavonols like goodyerin, quercetin, rutin can be used to effectively control epilepsy [11, 34-36]. Flavonols like quercetin and kaempferol are also reported for reversing oxidative stress induced-decrease of hippocampal BDNF and pCREB expression and leading to hippocampal neurogenesis and thus, ameliorating depression and cognitive deficit [37, 38].

Direct radical scavenging

Flavonoids have a highly reactive hydroxyl group in their structure. It reacts with free radical resulting into more stable less-reactive radical, thus providing direct radical scavenging activity [30]. Hanasaki *et al.* [40] studied the abilities of 15 flavonoids as a scavenger of active oxygens (hydroxyl radical and superoxide anion). Hydroxyl radical (·OH) which was generated by the Fenton system, and assayed by the amount of methanesulfinic acid (MSA) formed from the reaction of dimethyl sulfoxide (DMSO) with. OH (+)-Catechin, epicatechin, 7,8-dihydroxy flavone, and rutin showed the. OH scavenging effect almost 100-300 times superior to that of mannitol, a typical. OH scavenger.

Modulation of nitric oxide pathway

Increased levels of nitric-oxide synthase in macrophages enhance the production of both nitric oxide and superoxide anions. Nitric oxide when reacts with free radicals causes production of peroxinitrite, which are highly damaging to the cell. Flavonoids like silibin have been found to scavenge nitric oxide and free radicals directly (Fig. 3) [41, 42].

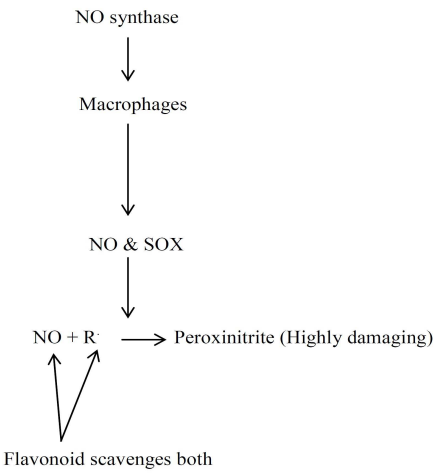


Fig. 3: It shows the pathway exhibited by flavonoids in scavenging action on nitric oxide radical; NO means nitric oxide, SOX means superoxide and R·means free radical.

Xanthine oxidase

During oxidative injury to tissues xanthine dehydrogenase gets configurationally changed to xanthine oxidase which is an important source of oxygen free radicals. Flavonoids such as quercetin, silibin, luteolin etc. inhibit xanthine oxidase activity, thereby resulting in decreased oxidative damage [44, 44]. Luteolin (3,4_5,7- tetrahydroxyflavone) have been found to be the most potent inhibitor of xanthine oxidase [45].

Leukocyte immobilization

Oxidative endothelium damage, as a consequence of ischaemia results in generate of endothelium derived mediators and complement factors, which cause adhesion of leukocytes to the endothelial wall and stimulating degranulation of neutrophils. As a result, oxidants and inflammatory mediators are released, resulting in tissue injury. Flavonoids due to modulation of receptor-directed Ca^{2+} channels in the plasma membrane [46] have been found to decrease the generation of various mediators and ameliorate oxidative stress [47, 48].

A majority of the above mentioned studies have been carried out in in vitro assay. In future the antioxidant effect of flavonoids can be further studied in the *in vivo* models of epilepsy to further understand and explore the mechanism involved in their anticonvulsant action.

Effect of flavonoids on epilepsy-induced comorbidities

Majority of epileptic patients suffer from one or more psychiatric or somatic comorbid conditions, whose nature and prevalence vary with age and sociodemographic factors, the most common comorbid conditions include, cognitive deficit and mood disorder. In these patients, comorbid conditions have a major adverse effect on overall health and quality of life and substantially increase health care costs [8]. Moreover, majority of antiepileptic drugs are consumed life long, concomitant administration predisposes to high risk of adverse-effects and drug interaction. Treatment with these conventional AEDs is associated with the brain dysfunction such as hippocampal atrophy causing memory disorders and mood disorders with a cascade of pervasive psychosocial problems. Phenobarbital and topiramate has the greatest potential to affect cognitive defect while levetiracetam, topiramate, zonisamide and phenobarbital has potential to cause behavioral adverse-effects [7]. Therefore, satisfactory treatment of epilepsy not only demands the suppression of abnormal neuronal discharge but also control of epileptic comorbidities associated with it.

During seizures the blood flow to the brain increases due to immediate increase in the diameter of pial arterioles and major resistance vessels of the brain that determine the cerebral blood flow. This increased cerebral blood flow is required to match increased oxygen and other metabolic demands of the activated neurons during the epileptic seizures [49]. This increased blood flow increases the metabolic load on the brain causing abnormal generation of free radicals. Excessive generation of free radicals like reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the key factors that react with endogenous substrates like, fatty acids, proteins and DNA, causing oxidative damage [50-52]. Oxidative and nitrosative stress also activates neutrophils and monocytes that cause nitration and nitrosylation of proteins to generate inactive autoepitopes to neoantigens which acquire immunogenicity and causes autoimmune responses [53]. It also induces decrease in hippocampal BDNF and pCREB expression leading to hippocampal cells degeneration. These pathways in turn generate neurodegenerative process mainly responsible for the induction of comorbid conditions. Oxidative stress is also established in the genesis of cognitive deficit associated with epilepsy via interaction with several pathways like, CREB, PI3K, PKG, ERK1/2 etc [54-58]. Flavonoids, due to their antiepileptic and neuroprotective effects have been found to ameliorate the comorbities. They interact with critical protein and lipid kinase signaling cascades, such as phosphatidylinositol-3 kinase (PI3K)/Akt, protein kinase C and mitogen-activated protein kinase in the brain, leading to inhibition of apoptosis triggered by neurotoxic species and promote neuronal survival and synaptic plasticity. Secondly, flavonoids induce beneficial effects on the vascular system leading to changes in cerebrovascular blood flow capable of causing angiogenesis, neurogenesis and changes in neuronal morphology [59].

Flavonoids and memory deficit

Flavonoids due to their remarkable antioxidant activity act to ameliorate cognitive deficit mainly by three common processes. Firstly, they interact with critical protein and lipid kinase signaling cascades such as phosphatidylinositol-3 kinase (PI3K)/Akt, protein kinase C and mitogen-activated protein kinase in the brain, leading to an inhibition of apoptosis triggered by neurotoxic species and to promote neuronal survival and synaptic plasticity. Secondly, flavonoids induce beneficial effects on the vascular system by decreasing reactive oxygen species and increasing nitric oxide bioavailability. It leads to changes in cerebrovascular blood flow capable of causing angiogenesis, neurogenesis and changes in neuronal morphology by activating PI3 kinase-Akt-eNOS system. Angiogenesis is followed by neurogenesis. Thirdly, flavonoid activate ERK and Akt pathway leading to activation of CREB pathway causing the release of neurotrophins such as BDNF and activate PI3 kinase-mTOR cascade and Arc/Arg3.1 which results in changes in synaptic plasticity and Long Term Potentiation(LTP) [59, 60]. Flavonoids such as flavonols, anthocyanins and flavonones have much better potential to ameliorate cognitive process. Isoflavone supplementation has been observed to have a favorable effect on verbal memory and on postmenopausal women. Isoflavones have been to mimic the actions and functions of oestrogens in the brain. Pure flavonols such as quercetin, rutin or fisetin have provided further evidence that dietary flavonoids are beneficial in reversing the course of neuronal and behavioural aging. The flavonoid-rich plant extract, *Ginkgo Biloba* has also been shown to induce positive effects on memory, learning and concentration. Fisetin, a flavonoid isolated from strawberries, has been shown to improve long-term potentiation and to enhance object recognition in mice.

The central cholinergic system plays an important role in learning and memory [61-62]. AChE (acetylcholinesterase), the main enzyme that hydrolyses acetylcholine, increases in the experimental and clinical epilepsy [63-65] and elevated AChE level has been suggested as pathogenic factor for memory deficit [66]. Acetylcholinesterase inhibitors have been shown to function by increasing the level of acetylcholine within the synaptic region, thereby restoring deficient cholinergic neurotransmission [69]. It has been reported that flavonoids like flavonols galangin, kaempferol, quercetin, myricetin, fisetin; flavons – apigenin, luteolin, and flavonol-glycoside quercetin-3-rutinoside (rutin) inhibits human AChE thereby effects memory functions. It has been found that AChE inhibition potency increase from rutin < apigenin < fisetin < kaempferol < galangin < luteolin < quercetin ≤ myricetin. It seems that larger number of OH groups on the side phenyl ring would result in the more pronounced AChE inhibition like in case of flavonols; quercetin and myricetin [67].

Since majority of aforesaid flavonoids have shown antiepileptic effects, their memory enhancing effect indicate that these flavonoids can be used for the treatment of epilepsy without the risk of memory impairment, provided their memory enhancing effect during epileptic condition is studied in future.

Flavonoids and mood disorders

Flavonoids extracted from plants are known to exert antidepressant like effects in animal models of depression [68, 69]. Naringenin a dietary flavonoid possessing neuroprotective actions in various central pathophysiological conditions including depression [70]. Xiaobuxin-Tang (XBXT), a traditional Chinese herbal decoction, has been used for the treatment of depressive disorder for centuries in China. It is reported to contain a large amount of flavonoids which on treatment reversed behavioral alterations including depression [37]. Similarly flavonoid-rich extract of *Hypericum perforatum* mainly containing quercetin and hyperoside flavonols [71] and flavonoids of *Scutellariae radix* were found to be responsible for antidepressant action [72]. Flavonoids, mainly flavonols like, quercetin and kaempferol are responsible to revert the oxidative stress induced-decrease of hippocampal BDNF and pCREB expression, leading to hippocampal neurogenesis and thus, ameliorating depression [37, 38]. These antidepressant effects of flavonoids can be further studied in epilepsy-induced depression to further expand their therapeutic potential in epilepsy.

Flavonoidal plants as antiepileptic

In several previous studies flavonoidal plants have been studied for their anticonvulsant activity in different animal models of convulsions. In this section, we have tried to summarize and discussed about the plants containing flavonoids that have been screened for their anticonvulsant activity (also summarized in Table 1). These

plants can be further explored in future as in majority of cases the information regarding the particular type of flavonoid involved for the anticonvulsant activity, exact mechanism of action, safety, etc. is lacking.

***Anisomeles malabarica* (L) R. Br**

Anisomeles malabarica is an herbaceous Australian plant belonging to family Lamiaceae, it is a plant of immense use and utility in folk medicine. It has been used for the treatment of epilepsy. Choudhary *et al.* [73] studied the anticonvulsant effect of flavonoidal-rich fraction from the leaves of *A. malabarica*. In the study the ethyl acetate fraction containing flavonoid showed antiepileptic activity against pentylenetetrazole (PTZ) and maximal electroshock (MES)-induced convulsions in wistar rats. Chronic treatment with the fraction at doses of 6.25 and 12.5 mg/kg *i.p.* for 1 week has showed significant anticonvulsant effect without any signs of neurotoxicity. Further research is required to determine the active responsible flavonoid(s) and their exact mechanism of action.

***Glychrrhiza glabra* L.**

G. glabra (Febaceae) also known as liquorice is native to southern Europe and parts of Asia. It is commonly known as "Mulaithi" in Northen India. It has been found to contain antioxidant substances like, ascorbic acid (0.58 g %) and flavonoids (0.926 g %) such as glabridin (an isoflavan) and isoliquiritigenin (a flavonoid) [74]. Ambawade *et al.* [75] studied its anticonvulsant activity using MES, PTZ and lithium-pilocarpine-induced convulsion mice models. Its ethanolic extract of roots and rhizomes containing flavonoids at 10, 30, 100 and 500 mg/kg *i.p.* doses inhibited PTZ and lithium-pilocarpine-induced convulsions, but was found to be ineffective against MES-induced convulsions. The extract was found to be safe up to 1g/kg *i.p.* dose in mice. Since it is rich in flavonoids, hence it is expected that the observed anticonvulsant effect can be due to their presence, however more studies are required to fulfill these expectations.

***Passiflora incarnate* L.**

P. incarnate commonly known as passion flower/maypop/apricot vine belongs to family Passifloraceae. It was discovered in 1569 by Spanish explorers in Peru. The local Indians used it to soothe their nerves and topically as a poultice, the crushed leaves being used on cuts and bruises [76]. Phytochemical research carried out on *Passiflora incarnata* had lead to the isolation of several flavonoids like, chrysin, apigenin, homoorientin, vitexin, luteolin, quercetin, kaempferol, isovitexin, orientin, isoorientin, etc. The anticonvulsant effect of the hydroethanolic extract of its aerial parts has been extensively explored and has been suggested to be due to presence of flavonoids like chrysin that act by agonizing benzodiazepine receptor [27, 77, 78].

***Scutellaria lateriflora* L.**

It belongs to family Lamiaceae and is commonly known as American Skullcap. *S. lateriflora* has been used for the treatment of epilepsy and several other neurological disorders in traditional medicine. Zhang *et al.* [79] isolated and identified 10 flavonoids, viscidulin III-2-O-β-D-glucopyranoside, chryin-6-C-α-L-arabionopyranosyl-8-C-β-D-glucopyranoside, trans-verbascoside, viscidulin III, baicalin, trans-martynoside, oroxylin A-7-O-β-D-glucopyranoside, wogonoside, baicalein, wogonin from whole extract of skull cap. In the same study, the anticonvulsant effect of the hydroalcoholic extract of whole skullcap at 90 mg/kg *i.p.* showed significant protection against PTZ-induced convulsions. The flavonoids present in the extract like wogonin which is known to have anticonvulsant activity [80] may be the active ingredients responsible for the anticonvulsant activity of American skullcap as they show high affinity for the benzodiazepine binding site at $GABA_A$ receptor [81] and have antioxidant effects [82, 83].

***Drosera burmanni* Vahl**

The genus *Drosera* is popularly known as Sundew and is the largest genus of carnivorous plants with over 105 species belonging to the family Droseraceae. Flavonoids like kaempferol, myricetin, quercetin and hyperoside have been isolated from *D. burmanni* [84]. Hema *et al.* [85] studied the anticonvulsant activity of the alcoholic extract of whole plant at a dose of 500 *mg/kg p.o.* The extract significantly delayed the onset of PTZ-induced convulsions in swiss albino mice. This anticonvulsant activity may be attributed because of flavonoids as the flavonoids like quercetin and kaempferol are known to be responsible for anticonvulsant activity [86] and kaempferol, myricetin, quercetin are also reported to have neuroprotective effects [87]. Flavonoids due to reduction of T-type calcium currents, enhancement of $GABA_A$-BZD receptor activity and blocking of glutametargic excitation mediated by NMDA receptors can effectively inhibit PTZ-induced convulsions.

***Cleome viscose* L.**

C. viscose also known as Dog mustard belongs to family Capparidaceae. Its fresh juice of crushed seeds has been used for treatment of infantile convulsions and other mental disorders. In a recent study, the anticonvulsant activity of its ethanol and aqueous seed extract containing flavonoids has been studied [88]. The extracts at 200, 400 and 600 *mg/kg p.o.* doses prevented MES and PTZ-induced convulsions in mice. The anticonvulsive effect might be because of flavonoids attributed due to inhibitory effect on voltage dependent sodium channels or due to blockage of glutaminergic excitation. However further studies are required to find out the exact role and types of flavonoids responsible for the activity.

***Caesalpinia bonducella* (L.) Roxb.**

It is a prickly shrub belonging to family Caesalpiniaceae and is commonly known as Nata Karanja. It is found throughout the hot regions of India, Myanmar and Sri Lanka. Ali *et al.* [89] investigated the anticonvulsant activity of the petroleum ether extract of its seed kernel. Phytochemical screening showed the presence of flavonoids like homoisoflavone (bonducillin) in the petroleum ether extract. The petroleum ether extract at chronic doses of 600 and 800 *mg/kg p.o.* for 8 days prevented PTZ, MES, strychnine and picrotoxin-induced convulsions in swiss albino mice. Anticonvulsant activity might be because of flavonoids, but still it is not clear that the effect of extract is due to flavonoids or some other bioactive metabolite, more studies are required in this area.

***Vitex negundo* L.**

V. negundu commonly known as five-leaved chaste tree or Monk's Pepper belongs to family Verbenaceae. It was used in Iranian ancient medical schools and Alkandi for the treatment of epilepsy and psychosis, in India it is also used as antiepileptic. Its methanolic leaf extract showed protection against strychnine and PTZ induced convulsions [90]. Tandon [91] reported the anticonvulsant activity of its petroleum and butanolic leaf extracts against MES-induced convulsion model. The extracts showed the presence of flavonoids like, flavones. In another study treatment with its ethanolic leaf extract not only showed anticonvulsant activity, but also potentiated the anticonvulsant effect of standard antiepileptic drugs when used in combination [92]. The study suggested that flavanoids can be used in combination with standard antiepileptic drugs to increase efficacy and mask side effects of latter, provided the safety of combined treatment is warrant in future research.

***Ocimum gratissimum* L.**

O. gratissimum also known as African Basil belongs to family Lamiaceae. Vieira *et al*. [93] reported the presence of Eugenol, thymol, and geraniol as the major volatile oil constituents and Xantomicrol and cirsimaritin as the major external flavones. Okoli *et al.* [94] studied the anticonvulsant activity of its leaves containing eugenol (volatile oil) and cirsimaritin (flavones) using PTZ model in mice. Methanolic and petroleum ether extract of leaves were administered at the doses of 200 and 400 mg/kg p.o. and was found to increase the latency of seizures and death and elicited 50% protection against mortality. As the studies aimed at isolating the anticonvulsant constituents of this plant are ongoing but still the role of flavonoids as anticonvulsant cannot be ruled out.

***Centella asiatica* (L.) Urban**

It is commonly known as Gotu Kola and belongs to family Umbelliferare. It has been used in Indian traditional medicine as a memory

enhancer, treatment of neurological disorders (insomnia, hysteria, insanity, epilepsy, etc) and skin diseases. Its leaves contain flavonoids like, 3-glucosylquercetin, 3-glucosylkaempferol and 7-glucosylkaempferol [95]. Visweswari *et al*. [96] studied the anticonvulsive activity of its *n*-hexane, chloroform, ethyl acetate, *n*-butanol leaf extracts. Treatment with all the extracts except aqueous extract at 200 mg/kg b.w. 1 week prior to dose of PTZ showed significant protection against PTZ-induced convulsions in male wistar rats. It was found that the activities of Na^+, K^+-ATPase, Mg^{2+}-ATPase, and Ca^{2+}-ATPase in brain (cerebral cortex, cerebellum, pons medulla and hippocampus) were significantly increased after treatment with different *C. asiatica* extracts which in general is decreased after PTZ induced epilepsy in all the above brain regions.

***Cissus sicyoides* L.**

C. sicyoides (Vitaceae) has been evaluated for its anticonvulsant activity. Phytochemical exploration had led to the isolation of two flavonoids, kaempferol 3-rhamnoside and quercetin 3-rhamnoside from its aerial parts [97]. De Almeida *et al.* [98] studied the anticonvulsant activity of the hydroalcoholic extract of the aerial parts of *C. sicyoides*. Treatment with the extract at 600 and 1000 mg/kg *i.p.* doses inhibited PTZ-induced convulsions in mice. Since, kaempferol and quercetin have been reported to have anticonvulsant activity, and kaempferol 3-rhamnoside and quercetin 3-rhamnoside are their flavano-glycosidic forms, hence the activity of the extract can be due to these metabolites. The glycosidic part conjugated with the flavonoid will increase solubility thus showing better pharmacokinetic property and increasing the anticonvulsant effects of these flavonoids. More studies are required to confirm the exact role of these flavano-glycosides for the observed anticonvulsant effect of *C. sicyoides* extract.

***Ficus hispida* L.**

F. hispida is a medicinally important member of family Moraceae. Dhanasekaran *et al.* [99] studied the anticonvulsant effect of its methanolic leaf extract containing flavonoids, using strychnine, picrotoxin, and PTZ mice models of convulsions. Treatment with the extract at 400 *mg/kg p.o.* dose completely abolished the seizures induced by picrotoxin and strychnine, but was found to be ineffective against PTZ-induced convulsions. Since, both PTZ and picrotoxin induces convulsions through similar mechanism, but the reason for the effectiveness of the extract in one model and not in other require more studies.

***Ficus sycomorus* L. Range**

F. sycomorus (Moraceae) is generally found in the Arabian peninsuala, tropical Africa to the east and Nigeria. Naturally, the tree is usually found in rich soils along rivers and in mixed woodlands. Ibrahim *et al.* [16] studied the anticonvulsant activity of the flavonoids-rich fraction of its ethanolic stem bark extract. Treatment with the flavonoids-rich fraction at 20 mg/kg *i.p.* dose significantly protected MES-induced convulsion in 30 day old white ranger cockerels and showed a weak anticonvulsant activity against PTZ-induced convulsions in mice. The flavonoids-rich fraction of the ethanolic stem bark extract of *F. sycomorus* can be further fractionated in future to get the bioactive flavonoid(s).

***Argyreia speciosa* (Burm.f.) Bojer**

Argyreia speciosa (Convolvulaceae) commonly known as *Vridha daraka* in Sanskrit and is one of the most important medicinal plant used in indigenous system of medicine. Its roots are regarded as an alternative tonic to cure nervine disorders. The major flavonoids isolated from the roots include, quercetin and kaempferol. Vyawahare *et al*. [100] studied the anticonvulsant activity of the hydroalcoholic extract of its roots in PTZ and MES mice models.

Treatment with the extract at 200 and 400 mg/kg doses significantly delayed the latency to the onset and reduced the duration of convulsion in PTZ and MES tests, respectively. Since the plant has also shown nootropic effects [101], as described memory deficit is a major complication in epilepsy, hence activity of the plant in both disorders indicate its possibility in suppression of epilepsy and associated memory impairment, which can be explored in future.

***Pongamia pinnata* (L.) Pierre.**

It belongs to family Febaceae and is commonly known as Karanj. Phytochemical studies revealed the presence of flavonoids in its leaves, pongol (flavone derivative), glabrachalone and isopongachromene in its seeds [102]. Manigauha *et al.* [103] reported the anticonvulsant activity of its ethanolic leaf extract. The study showed that, treatment with the extract at 250 mg/kg, *i.p.* dose prevented PTZ induced convulsions in wistar albino rats. It also reported that flavonoids like quercetin, kaempferol present in *P. pinnata* are responsible for protection against PTZ induced convulsions by modulating GABAergic or glutamatergic receptor functions.

***Abutilon indicum* (L.) Sweet**

Abutilon indicum (Malvaceae) commonly known as Thuthi and Atibala in Ayurveda is widely used as medicine in Ayurveda for antifungal, antibacterial, immunomodulator and analgesic activities [104]. It rich in luteolin, chrysoseriol, luteolin-7-O-β glucopyranoside, chrysoseriol 7-O-β glucopyranoside, apigenin 7-O-β-gluco pyranoside, quercetin 3-O-β-gluco pyranoside, quercetin3-O-α rhamnopyranosyl, β-gluco pyranoside [105]. Golwala *et al.* [106] studied the ethanolic (AIE) and aqueous (AIA) leaf extracts for anticonvulsive properties at 100 mg/kg and 400 mg/kg p.o. against PTZ and MES induced convulsions. Both the extracts provided protection but AIE showed better significant protection than AIA against the PTZ and MES induced convulsions. This study also indicated flavonoids for its anticonvulsant effect which might be true as flavonoids are extracted in the alcoholic extract and this study have shown that AIE as better anticonvulsant than AIE.

***Hypericum perforatum* L**

H. perforatum commonly known as St. John's Wort, belongs to family Hypericaceae. It has been used for the treatment of epilepsy since antiquity. It contains high amount of flavonols (catechins) and flavonoids (hyperoside, quercetin, quercetrin, rutin, biapigenin, kaempferol) [107, 108]. Hosseinzadeh *et al.* [109] reported the anticonvulsant activity of its aqueous and ethanolic extracts of aerial part in PTZ and MES convulsion mice models. Both the extracts at 0.1-1g/kg *i.p.* dose were found to be effective in PTZ, but not in MES model. Further pretreatment with a nitric oxide synthase inhibitor reduced anticonvulsant effect of the extracts, indication the involvement of nitric oxide pathways for the activity of extracts. As the class of flavonoids present in *H. perforatum* have shown anticonvulsant activity in other previous studies, and the role of flavonoids in the modulation of nitric oxide pathway has been well established, therefore it can be correlated that the anticonvulsant activity of *H. perforatum* is due to flavonoids. However further studies are required to generate more scientific support for the safe clinical use of *H. perforatum* in epilepsy.

***Mimosa pudica* L**

M. pudica (Missociaceae) commonly known as Lajvanti has been used for the treatment of numerous diseases related to nervous system. Bum *et al.* [110] investigated the anticonvulsant activity of the decoction of *M. pudica* leaves. Treatment with the leaf decoction at 1000 and 4000 mg/kg *i.p.* protected mice against PTZ and strychnine-induced convulsions. Since the leaves of *M. pudica* contains an appreciable amount of flavonoids [111], hence it is expected that the anticonvulsant effect of the leaves can be due to flavonoids. Therefore further studies are required to validate the role of flavonoids for the anticonvulsant effect of the leaves of *M. pudica*.

***Butea monosperma* (Lam.) Taub.**

In the Ayurveda it is known as Bastard Teak, it belongs to family Fabaceae. Silambujanaki *et al*. [112] evaluated the anticonvulsant activity of the methanolic leaf extract of *B. monosperma* in mice. Preliminary phytochemical screening showed the presence of flavonoids. The extract at 100, 200, 400 mg/kg p.o. doses was used against MES, PTZ and strychnine induced seizure models. It was found that the extract at 400mg/kg dose was effective against MES and PTZ but not against strychnine induced seizures. The anticonvulsant activity exhibited by the extract might be due inhibitory effect on Na^+, t-type Ca^{2+} channels, NMDA receptors and excitatory

effect on GABA aminergic mechanism. The study also suggested that the extract might be effective due to the presence of flavonoids in the extract.

***Nauclea latifolia* Sm.**

It is commonly known as pin cushion tree belonging to family Rubiaceae. It has been experimentally studied for its anticonvulsant activity [113]. Aqueous extract of the bark of dried roots at 16, 40, 80, and 160 mg/kg *i.p.* was studied against MES, PTZ and Strychnine induced seizures in mice. Study concluded that the dose of 160 mg/kg provided significant protection against MES, PTZ and Strychnine induced seizures. Flavonoids present in the extract might be showing this activity through benzodiazepine, GABA receptors in the GABA receptor complex and probably by prolonging the inactivation of sodium channels.

***Sphaeranthus indicus* L.**

It is commonly known as Gorakhmundi, which is an herb widely distributed in wet places of India belonging to family Compositae. Galani *et al*. [114] investigated anticonvulsant property of the hydroalcoholic extract of whole plant using PTZ, MES models in rats. Preliminary phytochemical screening revealed the presence of flavonoids in the extract. Study concluded that the extract at 500 mg/kg, p.o. dose possess CNS depressant action in addition to anticonvulsant action. Flavonoids present in the extract might be responsible for anticonvulsant effects but needs further investigation.

***Solanum nigrum* L.**

S.nigrum commonly known as Black night shade in English and Kakamachi in Tamil belongs to family Solanaceae. Ravi *et al*. [115] investigated the anticonvulsant activity of aqueous and ethanolic extract prepared from shade dried berries powder in albino rats. Ethanolic extract at the doses of 100, 200, 300 mg/kg, p.o. was found to possess anticonvulsant activity against seizures induced by MES. Phytochemical studies have reported the presence of flavonoids in aqueous and ethanolic extract. Exact mechanism of the extract showing anticonvulsant activity is not known but anticonvulsant activity might be due to stimulatory effect on GABA mediated synaptic inhibition which might be due to presence of flavonoids.

***Aegle marmelos* (L.) Corr.**

It is commonly known as Bael belonging to family Rutaceae. Sankari *et al*. [116] investigated the anticonvulsant effects of the ethanolic leaf extract using MES and PTZ induced seizure model in mice. It was found that the administration of the extract at 200 mg/kg p.o. significantly increased the onset, decreased the duration of MES induced tonic hind limb extension. The onset of tonic convulsion produced by PTZ was also significantly delayed. As the phytochemical estimations revealed the presence of flavonoids, the anticonvulsant effect might be due to their enhancing action on GABA-mediated inhibition in the brain which needs further studies.

***Vitex agnus castus* L.**

V. agnus commonly known as Vitagnus or Chaste tree belongs to family Lamiaceae. This plant has been used to treat epilepsy and psychosis in 1200 A.D. and is known as 'Black remedy'. Saberi *et al*. [117] investigated the hydroethanolic extract from the fruits containing flavonoid such as casticin, vitexin and orientin [118] for its possible anticonvulsant activity in electrical kindling model of epilepsy in male albino wistar rats. The extract at 60, 120 or 180 mg/kg *i.p.* doses showed anticonvulsant property indicated by increment in after discharge threshold, reduction in after discharge duration and seizure severity in a dose dependent manner. Anticonvulsant activity might be due to flavonoids having agonist action on kappa opioid receptors.

Ginkgo biloba

G. biloba belonging to family Ginkgoaceae has various uses in traditional medicine and neurodegenerative diseases including the formation of kindling epilepsy & epileptic discharge. Many flavonoids have been isolated from ginkgo leaves like monomer flavonoids (quercetin and kaempferol), dimer flavonoids (biflavone, ginkgetin, sciadopitysin and bilobetin). *G. biloba* extract can be used to prevent the development of epilepsy due to ischemic attacks. This is probably due to Bilobalides which appear to act at sites in the chloride channel of $GABA_A$ receptor and is thus a negative allosteric modulators [119, 120] and due to flavonoids from *G. biloba* extract, for which it has been established that they perform modulation of ionic currents mediated by GABA receptors [121].

Another experimental study reported by Ivetic *et al.* [122] showed an opposite effect of *G. biloba.* The experimental study reported that, administration of the extract had pro-epileptogenic effect, probably by conditioning the depolarization shift of the stimulated neurons of the hippocampus. They also established that some constituents of the extract have pro-epileptogenic effect and decrease the effect of antiepileptic (valproate and carbamazepine).These fully opposite observations, epileptogenic and anti-epileptogenic effects of *G. biloba* extract are mostly explained by the change of the GABA content, NMDA receptors, beta receptors etc. in various parts of the brain. These variations might be due to variation in experimental models, dose levels and difficulties in precise monitoring of epileptogenic effect, especially when the results of clinical studies are analyzed. Thus, whether the *G. biloba* has antiepileptic effect due to presence of flavonoids or it has pro-epileptogenic effect, it needs further investigation to establish the right connection and mechanism involved in epilepsy.

***Albizia lebbeck* (L.) Benth.**

It is commonly known as woman's tongue belonging to family Fabaceae. Its ethanolic leaf extract has been reported to protect the mice from MES and PTZ induced convulsions [108] which contain flavonoids kaempferol and quercetin 3-O-alpha-rhamnopyranosyl(1-->6)-beta-glucopyranosyl(1-->6)-beta- galactopyranosides. Thus the anticonvulsant activity might be due to presence of flavonoids which needs further investigation.

***Tanacetum parthenium* (L.) Sch. Bip.**

T. parthenium commonly known as Feverfew belongs to family Asteraceae. It is a traditional medicinal herb found in many old gardens. The extracts of *T. parthenium* have been used in Danish folk medicine for the treatment of epilepsy. Studies have shown that the ethanolic extract contain flavonoid apigenin which might be showing anticonvulsant effect due to its high affinity for the $GABA_A$-benzodiazepine site [18]. Thus flavonoids could be the active ingredient in the extract for its anticonvulsant activity.

Brahmi ghrita

Brahmi ghrita, one of the panchgavya formulation clamed as antiepileptic in ayurveda contains *Bacopa moneri. Acorus calamus, Evolves alsinoids, Sausserea lappa* out of which *Bacopa moneri* and *Acorus calamus* contain flavonoids which might be responsible for their anticonvulsant effects.

***Bacopa monniera* L. Pennell**

It is commonly known as brahmi belongs to family Scrophulariaceae. It is used to provide relief to patients with anxiety or epileptic disorders. Alcoholic leaf extract of *B. monniera* contains large amount of flavonoids [108, 123]. Kaushik *et al.* [124] studied the anticonvulsant activity of ethanolic leaf extract against PTZ, MES, strychnine, hypoxic stress and lithium pilocarpine induced convulsions in albino mice and wistar rats. It was found that the extract at 55 and 50 mg/kg p.o. doses to mice and rats respectively was effective against all the models of epilepsy. Mathewa *et al.* [125] also reported its use in epilepsy associated comorbities such as learning and memory impairment.

***Acorus calamus* L.**

Also known as *Acorus odoratus* and commonly known as Sweet Flag belongs to the family Adoraceae. It contains flavonoid Galangin (5,7-dihdroxyflavonol) [126]. Jayaraman *et al.* [127] evaluated the anticonvulsant activity of this plant using methanolic root extract at 100 and 200 mg/kg p.o. doses against PTZ model of convulsion in swiss albino mice. It was found that the extract significantly increased the latency period and reduced the duration of seizures. The flavonoids

present might be responsible for the above action by exhibiting potentiating effect on $GABA_A$ receptors.

Origanum vulgare

O. vulgare commonly known as Oregano is an erectly spreading plant having strong aromatic characteristics in leaves belongs to family Lamiaceae. Its leaves contain flavonoids in addition to triterpenoids, sterols, vitamin C, and vitamin A. In India, leaves are used traditionally for epilepsy, bronchitis, asthma, diarrhea, nephrocystolithiasi, fever, indigestion and cough [128]. Flavonoids present in Oregano might be responsible for their anticonvulsant action but further studies in this area need to be done to support this evidence.

Moringa oleifera

Moringa oleifera commonly known as Drumstick belongs to family Moringaceae. It contains flavonoids in addition to alkaloids, tannins, carbohydrates, amino acids, glycosides. It is reported to provide significant protection against strychnine and PTZ induced convulsions [108, 129, 130]. The exact mechanism of its anticonvulsant activity is not known which needs further investigation.

Nyctanthes arbortristis

Commonly known as Night Jasmine or Coral Jasmine belonging to family Oleaceae, it is an indigenous plant native of India. The ethanolic and aqueous leaf extract have shown to provide protected effect against MES and PTZ induced convulsions in mice [108, 131]. Phytochemical screening showed that the extract contain flavonoids & phenolic compounds. Flavonoids present in the extract might be responsible for anticonvulsant action but it needs further investigation.

***Artemesia vulgaris* L.**

vulgaris commonly known as Mugwort belonging to family Asteraceae has a long history of medicinal use as a traditional herbal remedy for epilepsy. It contains twenty known flavonoids which were isolated and identified as tricine, jaceosidine, eupafolin, chrysoeriol, diosmetin, homoeriodictyol, isorhamnetin, apigenin, eriodictyol, luteolin, luteolin 7-glucoside, kaempferol 3-glucoside, kaempferol 7-glucoside, kaempferol 3-rhamnoside, kaempferol 3-rutinoside, quercetin 3-glucoside, quercetin 3-galactoside, quercetrin, rutin, and vitexin [132]. The presence of large amount of flavonoids together with anticonvulsant properties highlights the involvement of flavonoids in anticonvulsant action, which needs further investigations.

***Abrus precatorius* L.**

A.precatorius commonly known as Rosary Pea belonging to family Fabaceae is famous for its beautiful but deadly seeds containing toxin abrin. The chloroform soluble fraction of the concentrated 80% methanolic extract of the seeds contains flavonol glycosides which are reported to possess anticonvulsant activity [133]. Flavonol glycoside has been reported to be present in this plant [134]. Thus flavonol glycoside might be responsible for its anticonvulsant action but more studies need to be done to support this evidence.

***Citrus aurantium* L.**

It is commonly known as sour orange belonging to family Rutaceae. It is one of the medicinal plants which have been grown all over the world because of its high medicinal values and as a traditional drug in Islamic medicine. The flowers of this plant have been used to control seizures. Electrospray mass spectrometer (HPLC–ES-MS) analyzed eight flavonoids i.e. isonaringin, naringin, hesperidin, neohesperidin, naringenin, hesperitin, nobiletin and tangeritin from the ethanolic extract of fruits showing anticonvulsant effects [135]. Hesperetin is able to ameliorate the response to tetraethylammonium and PTZ. These flavonoids might be responsible for anticonvulsant action through activation of large conductance calcium dependent potassium channels [136] or agonistic effect on benzodiazepine receptor [137].

Astragalus centralpinus

It is commonly known as milk-vetch which belongs to family Papilionaceae. It contain various flavonoids like 5,7,4'-trihydroxy3,3'-dimethoxy flavone, 3,5,7,3'-tetramethoxy-4'-hydroxyflavone, 3,7-dihydro-flavone and 4,5-dimethoxy-7- hydroxyflavan-7-ol. These flavonoids are reported to be effective against reversed convulsive action of barium chloride [9].

***Hibiscus vitifolius* L.**

H. vitifolius (Malvaceae) has been reported to contain a bioflavonoid, gossypin. Rasilingam *et al.* [138] studied the anticonvulsant activity of gossypin using PTZ, strychnine and MES-induced convulsion models in mice. Treatment with gossypin (10 and 20 *mg/kg p.o.*) significantly increased the latency to PTZ-induced convulsion. Moreover, treatment with gossypin at 20 mg/kg dose showed significant protection against strychnine and MES-induced convulsions. However more studies are required to understand the exact anticonvulsant mechanism of gossypin.

Table 1: It shows the comprehensive list of some herbal plants with anticonvulsant activity.

Plant	Family	Reported flavonoid(s)	Plant part	Type(s) of extract	Dose/ evaluating model(s)/ animal used	Inference	Reference
Abrus precatorius L.	Fabaceae	Flavonol glycosides are present. A new flavonol glycoside 7,3',5'-trimethoxy-4'-hydroxy flavone-3- O - β- d - galactosyl-(1 →4)- α- l -xyloside has been reported to be present in this plant.	Seeds	Chloroform soluble fraction of the concentrated 80% methanolic extract.	TNA	Flavonol glycoside might be responsible for its anticonvulsant action but more studies need to be done to support this evidence.	[133, 134].
*Abutilon indiciu m (*L.) Sweet.	Malvaceae	Luteolin, chrysoseriol, luteolin-7-O-β gluco pyranoside, chrysoseriol 7-O-β gluco pyranoside, apigenin 7-O-β-gluco pyrano side, Quercetin 3-O-β-g luco pyranoside, Quercetin 3-O-α rhamnopyranosyl, β-gluco pyranoside.	Leaves	Ethanolic and aqueous extracts.	100 mg/kg and 400 mg/kg p.o./ PTZ and MES model/ wistar rats.	Ethanolic extract showed better protection than aqueous extract. Ethanolic extract gave significant protection against the PTZ and MES induced convulsions.	[104-106]
Acorus	Adoraceae	Galangin (5,7-	Roots	Methanolicex-	100 and 200	Extract significantly in-	[126,

calamus L.		dihdroxyflavonol).		tract	mg/kg p.o./ PTZ/ swiss albino mice.	creased the latency period and reduced the duration of seizures. The flavonoids present might be responsible for the above action by exhibiting potentiating effect on $GABA_A$ receptors.	127]
Aegle marmelos (L.) Corr.	Rutaceae	Uncharacterized flavonoids.	Leaves	Ethanolic extract.	100, 200 mg/kg p.o./ MES and PTZ models/ mice.	Dose of 200 mg/kg p.o. was found to be effective. The anticonvulsant activity might be due to GABA inhibitory action in the brain.	[116]
Albizia lebbeck (L.) Benth.	Fabaceae	Kaempferol and quercetin 3-O-alpha-rhamnopyranosyl(1-->6)-beta-glucopyranosyl(1-->6)-beta- galactopyranosides.	Leaves	Ethanolic extract	MES and PTZ model/ mice.	It have been shown to protect the mice from MES, PTZ induced convulsions.	[108]
Anisomeles malabarica (L.) R. Br	Lamiaceae	Uncharacterized flavonoids	Leaves	Ethyl acetate.	6.25 and 12.5 mg/kg *i.p.* for 1 week/ PTZ and MES model/ wistar rats.	Ethyl acetate extract rich in flavonoids ameliorate epilepsy in chronic treatment without causing any neurotoxicity.	[73]
Argyreia speciosa (Burm.f.) Bojer	Convolvulaceae	Quercetin and kaempferol.	Roots	Hydroalcoholic extrct.	100, 200, 400 mg/kg p.o./ PTZ and MES model/ mice.	The extract significantly delayed the latency to the onset of convulsions, reduced the duration, death in both the models of convulsion and prevented cognitive deficit in convulsions.	[100, 101]
Artemesia vulgaris L.	Asteraceae	Twenty known flavonoids- tricine, jaceosidine, eupafolin, chrysoeriol, diosmetin, homoeriodictyol, isorhamnetin, apigenin, eriodictyol, luteolin, luteolin 7-glucoside, kaempferol 3-glucoside, kaempferol 7-glucoside, kaempferol 3-rhamnoside, kaempferol 3-rutinoside, quercetin 3-glucoside, quercetin 3-galactoside, quercetrin, rutin, and vitexin.	Aerial parts of the plant.	TNA	Further research on this topic need to be done.	TNA	[132]
Bacopa monniera L. Pennell	Scrophulariaceae	Uncharacterized flavonoids	Leaves	Ethanolic extract	55 and 50 mg/kg p.o. / PTZ, MES, strychnine, hypoxic stress and lithium pilocarpine induced convulsions/ albino mice and wistar rats respectively.	Ethanolic extract is effective against all the models epilepsy as well as in epilepsy associated comorbities such as learning and memory impairment.	[108, 123-125]
Butea monosperma (Lam.) Taub.	Fabaceae	Uncharacterized flavonoids.	Leaves	Methanolic extract.	100, 200, 400 mg/kg p.o. / MES, PTZ and strychnine model/ mice.	400 mg/kg dose was effective against MES and PTZ but not against strychnine induced seizures.	[112]
Caesalpinia bonducella (L.) Roxb.	Caesalpiniaceae	Homoisoflavone (bonducillin)	Seed kernels	Petroleum ether, ethanol, methanol and	600, 800 mg/kg p.o. for 8 days/ PTZ, MES,	The action might be due glycine inhibitory action or through activation of GABA	[89]

				aqueous extract.	strychnine and picrotoxin convulsion model/ mice.	channels.	
*Centella asiatica (*L.) Urban.	Umbelliferare	3-glucosylquercetin, 3-glucosylkaempferol and 7-glucosylkaempferol	Leaves	N-hexane, chloroform, ethyl acetate, n-butanol.	200 mg/kg b.w. 1 week prior to dose of PTZ/ PTZ model/ male wistar rats.	It was found that the activity levels of Na+, K+-ATPase, Mg2+-ATPase, and Ca2+-ATPase which were decreased in PTZ-induced epilepsy were significantly increased on pre-treatment with different CA extracts.	[95, 96]
Cissus sicyoides L.	Vitaceae	Kaempferol 3-rhamnoside and quercetin 3-rhamnoside.	Aerial parts of the plant.	Hydroalcoholic extract.	300, 600, and 1000 mg/kg *i.p.*/ PTZ model/ mice.	Extract showed significant action in protection against PTZ model. The flavanoglucosides present shows better pharmacokinetic property the anticonvulsant effects than flavonoids.	[97, 98]
Citrus aurantium L.	Rutaceae	Isonaringin, naringin, hesperidin, neohesperidin, naringenin, hesperitin, nobiletin and tangeritin.	Fruits	Ethanolic extract.	Tetraethylammonium (TEA) and PTZ model.	Flavonoids might be responsible for anticonvulsant action through activation of large conductance calcium dependent potassium channels or agonistic effect on benzodiazepine receptor.	[135-137]
Cleome viscosa L.	Capparidaceae	Uncharacterized flavonoids.	Seeds	Alcoholic and aqueous extract.	200, 400 and 600mg/kg p.o./ MES and PTZ models/ swiss albino mice.	The anticonvulsive effect might be because of flavonoids attributed due to inhibitory effect on voltage dependent sodium channels or due to blockage of glutaminergic excitation.	[88]
Drosera burmanni Vahl	Droseraceae	Kaempferol, myricetin, quercetin and hyperoside.	Entire plant	Alcoholic extract	500 mg/kg p.o./ PTZ model/ swiss albino mice.	Anticonvulsant activity may be attributed due to flavonoids causing reduction of T-type calcium currents, enhancement of $GABA_A$-BZD receptor activity and blocking of glutametargic excitation mediated by NMDA receptors.	[84-87]
Ficus Hispida L.	Moraceae	Uncharacterized flavonoids.	Leaves	Methnolic extract	200 and 400 mg/kg p.o./ Strychnine, picrotoxin, and PTZ models/ mice.	400mg/kg dose completely abolished the seizures induced by picrotoxin and strychnine but not with PTZ.	[99]
Ficus sycomorus L. Range	Moraceae	Uncharacterized flavonoids	Stem, bark	Crude flavonoid rich fraction partitioned from Ethanolic extract	5, 10 and 20 mg/kg *i.p.*/ PTZ and MES models/ mice and chicks respectively	Crude flavonoid rich extract revealed a significant activity in MES test and a weak anticonvulsant activity in the subcutaneous PTZ test.	[16]
Glychrrhiza glabra L.	Febaceae	Glabridin (an isoflavan) and isoliquiritigenin (a flavonoid)	Roots and rhizomes.	Ethanolic extract	10, 30, 100 and 500 mg/kg *i.p.*/ PTZ, MES and lithium and pilocarpine models/ mice.	G. glabra might be active against petitmal or absence seizure but not against generalised tonic-clonic seizures.	[74, 75]
Hibiscus vitifolius L.	Malvaceae	Gossypin	Flowers	Gossypin	10, 20 mg/kg p.o./ PTZ, strychnine and MES models/ mice.	It shows anticonvulsant activity probably by enhancing GABA transmission and has glycine inhibitory activity.	[138]

Hypericum perforatum L.	Hypericaceae	Catechin, hyperoside, quercetin, quercetrin, rutin, biapigenin, kaempferol.	Aerial parts	Aqueous and ethanolic extract	.1-1g/kg *i.p.*/ PTZ and MES models/ mice.	Extract is effective against petit mal convulsions.	[107-109]
Mimosa pudica L.	Missociaceae	Uncharacterized flavonoids	Leaves	Decoction	1000–4000 mg/kg *i.p.*/ PTZ and strychnine-model/ mice	The decoction showed protected effect in mice against PTZ and strychnine-induced seizures.	[110, 11]
Moringa oleifera	Moringaceae	Uncharacterized flavonoids	TNA	TNA	TNA	It is reported to provide significant protection against strychnine and PTZ induced convulsions.	[108, 129, 130]
Nauclea latifolia Sm.	*Rubiaceae*	Uncharacterized flavonoids	Bark of dried roots	Aqueous extract of the bark of dried roots	16, 40, 80, and 160 mg/kg *i.p.*/ MES, PTZ and strychnine models/ mice.	Flavonoids present in the extract might be showing activity against MES, PTZ and Strychnine induced seizures through benzodiazepine, GABA or by prolonging the inactivation of sodium channels.	[113]
Nyctanthes arbortristis	Oleaceae	Uncharacterized flavonoids	TNA	Ethanolic and aqueous extract of leaves.	TNA	Flavonoids present in the extract might be responsible for anticonvulsant action.	[108, 131]
Ocimum gratissimum L.	Lamiaceae	Cirsimaritin (flavone)	Leaves	Methanolic and petroleum ether extracts.	200 and 400 mg/kg p.o./ PTZ model/ mice.	Extracts increased the latency of seizures and death and elicited 50% protection against mortality.	[93, 94]
Passiflora incarnata L.	Passifloraceae	Chrysin	Leaves	Hydo-alcoholic extract.	0.05, 0.1, 0.2, 0.4 mg/kg *i.p.* / PTZ model/ mice.	The active constituent can be flavonoid chrysin which might be acting as a partial agonist at benzodiazepine receptor with micromolar affinity or through opioid receptors. But it still remains controversial whether chrysin is actually that active component or not.	[27, 76-78]
Pongamia pinnata (L.) Pierre.	Febaceae	Flavonoids in its leaves. Flavone derivative 'pongol', glabrachalone and isopongachromene from its seeds.	Leaves	Ethanolic extract	250 mg/kg *i.p.*/ PTZ model/ wistar albino rats.	Anticonvulsant action might be by modulating the function of GABA or glutamate receptors.	[102, 103]
Scutellaria lateriflora L.	Lamiaceae	Viscidulin III-2-O-β-D-glucopyranoside, chryin-6-C-α-L-arabionopyranosyl-8-C-β-D-glucopyranoside, trans-verbascoside, viscidulin III, baicalin, trans-martynoside, oroxylin A-7-O-β-D-glucopyranoside, wogonoside, baicalein, wogonin.	Above ground parts.	Hydroalcoholic fraction	30, 60, 90, and 150 mg/kg *i.p.* / Pilocarpine and PTZ model/ rats	Anticonvulsant effect might be due to high affinity for the benzodiazepine binding site of $GABA_A$ receptor.	[79-83]
Solanum nigrum L.	Solanaceae	Uncharacterized flavonoids.	Berries	Aqueous and ethanolic extract	100, 200, 300 mg/kg p.o./ MES model/ albino rats.	Ethanolic extract was found to be effective at all the doses. Anticonvulsant activity present might be due to stimulatory effect on GABA mediated synaptic inhibition.	[115]

Sphaeranthus indicus L.	Compositae	Uncharacterized flavonoids	Whole plant extract	Hydroalcoholic extract	100, 200 and 500 mg/kg p.o./ PTZ and MES model/ rats.	500 mg/kg p.o. possesses CNS depressant action in addition to anticonvulsant action.	[114]
Tanacetum parthenium (L.) Sch. Bip.	Asteraceae	Apigenin	Finely grounded aerial parts.	TNA	Further research on this topic need to be done.	Anticonvulsant effect might be due to high affinity of apigenin for the $GABA_A$-benzodiazepine site.	[18]
Vitex agnus castus L.	Lamiaceae	Flavonoids such as casticin, vitexin and orientin are present.	Fruits	Hydroalcoholic extrct	60, 120 or 180 mg/kg *i.p.*/ MES model/ male albino wistar rats	Extract showed increment in after discharge threshold, reduction in after discharge duration and stage 5 duration in a dose dependent manner.	[117, 118]
Vitex negundo L.	Lamiaceae	Flavonoids like flavones	Leaves	Petroleum, butanol and methanol leaf extracts	MES, Strychnine and PTZ models	*V. negundu* leaf extracts are not just anticonvulsant but also have synergistic activity with standard anticonvulsants.	[90-92]

TNA- Text Not Available

CONCLUSION

Flavonoids emerged as a very valuable class of secondary metabolite having potential for the comprehensive treatment of epilepsy. As future investigations continue, this class may prove to be a rich source of new molecules for the development of new therapeutic agents for the treatment of epilepsy. During our literature review we observed the modulatory role of flavonoids in almost all the neuronal pathways involved in the pathogenesis of epilepsy. Studies carried out till date suggests that flavonoids inhibit voltage gated sodium channels, activate Ca^+activated K^+ channels, stimulate GABAergic inhibition, interact with opioid receptors, inhibit NMDA receptors and exhibit antioxidant actions via modulation of nitric oxide and xanthine oxidase pathways and by leukocytic immobilization, one or more of these mechanisms are involved in suppression of epileptic seizures. Hispidulin, rutin, hesperetin, naringenin, eriodictyol, chrysin, gossypin, apigenin, kaempferol, myricetin, quercetin, hoslundin, hoslundal, hoslunddiol, morine, amentoflavone, hyperoside, anghyperoside, epicatechin, rutin, silibin and luteolin are some of the important flavonoids that possess one or more of the above mentioned mechanisms.

Copious studies pertaining to the anticonvulsant potential crude extracts containing flavonoids and flavonoids-rich fraction containing uncharacterized flavonoids have been carried out. Thus, it is difficult to reproduce the results of these studies and pinpoint the bioactive flavonoids. Hence, there is a need of phytochemical standardization and bioactivity-guided identification of bioactive flavonoids. Moreover it is expected that bioactivity-guided fractionation of the extracts and the rich fractions will yield new flavonoidal molecules. In several instances even where the active anticonvulsant flavonoids is known, their mechanism of action is missing, which needs further studies.

Since oxidative injury play a vital role in the initiation and progression of epilepsy, current treatment strategies are aimed on reducing oxidative stress to ameliorate tissue damage and to alter the clinical course of the disease [13, 139]. It has been reported that free radical generation induces seizure activity by inactivation of glutamine synthase, thereby permitting an abnormal build-up of excitatory neurotransmitter, glutamate [140] or by inhibition of glutamate decarboxylase, leading to decrease in GABA turnover in turn facilitating abnormal excitation [141]. Oxidative stress also plays an important role in the etiology of seizure induced neuronal death [142]. Since flavonoids shows a strong antioxidant effects as they have a highly reactive hydroxyl group in their structure, therefore provide a direct radical scavenging activity [39], hence ameliorate epileptic condition [13]. In several studies the antioxidant effect of the active flavonoids, flavonoids-rich fraction and flavonoids containing crude extracts was studied in *in vitro* studies, therefore further *in vivo* studies are required to further explore their clinical effectiveness and therapeutic potential.

Treatment of epilepsy includes the use of multiple dose regimens for prolonged periods, making the side and adverse effects inevitable to the patients. It has been suggested that these ill effects can be decreased by reducing the dose of antiepileptics and/or prescribing substances that can potentiate the effect of former and decrease unwanted effects [143]. Some studies depicted the synergistic antiepileptic effect of flavonoids with clinically used antiepileptic drugs. For example, apigenin and (-) epigallocatechin potentiates the therapeutic effect of diazepam [26]. As flavonoids are devoid of side effects which are commonly associated with clinically used antiepileptic drugs like, ataxia, amnesia, etc, therefore in future these flavonoids can be supplemented antiepileptic drugs to reduce the dose of later to limit side effects. Flavonoids not only suppress epilepsy but also found to be effective against epilepsy-induced comorbidities. Activation of ERK and CREB pathway helps in treating amnesia, while its antioxidant property helps to mitigate depression (Fig. 4). Flavonoids extracted from plants are known to exert antidepressant like effects in animal models of depression [68, 69].

Flavonoids, mainly flavonols like quercetin and kaempferol are responsible for reversing oxidative stress induced-decrease of hippocampal BDNF and pCREB expression leading to hippocampal neurogenesis and thus, ameliorating depression [37, 38]. Similar improvement is also reported in the learning and memory with the use of flavonoids possibly via prohibiting oxidative stress [144-146].

With few exceptions, in majority of studies flavonoids have been found to cross blood brain barrier, indicated by there observed neurological effects. Youdim *et al*. [147] studied citrus flavonoids, hesperetin, naringenin and their relevant *in vivo* metabolites, as well as the dietary anthocyanins and *in vivo* forms, cyanidin-3-rutinoside and pelargonidin-3-glucoside *in vitro* models (brain endothelial cell lines from mouse (b.END5), rat (RBE4) and ECV304 monolayerscocultured with C6 glioma cells). The study reported that flavonoids and its metabolites are able to travel through the blood brain barrier which is consistent with compound lipophilicity.

However, there are reports of toxic flavonoid-drug interactions, liver failure, contact dermatitis, hemolytic anemia, and estrogenic-related concerns such as male reproductive health and breast cancer associated with dietary flavonoid consumption [148]. Controlled clinical trials of flavonoids and their potential for toxicity is an understudied aspect till now, therefore it needs due attention and research before it gets too late. It is expected that systematic, preclinical and clinical studies will be undertaken in future in the above mentioned areas, so that the great potential of flavonoids to assist people living with epilepsy and other related ailments can be explored.

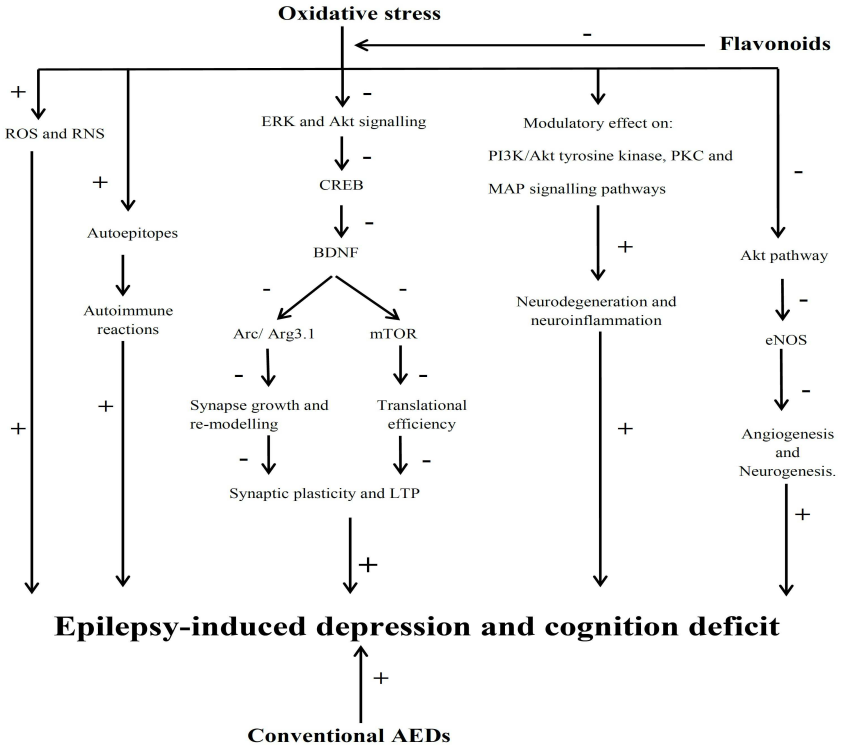


Fig. 4: Role of flavonoids in treating epilepsy-induced depression and cognition deficit via ameliorating oxidative stress.

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