Effect of plant polyphenols on seizures – animal studies

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SUMMARY

Introduction. Flavonoids are a large group of natural compounds that have been considered to be beneficial in ameliorating some age-dependent disorders. However, a potential use of these compounds in epilepsy treatment has not been systematically reviewed.

Aim. This review describes the pharmacological activity of some polyphenols (flavonoids) in different animal models of seizures e.g. pentylenetetrazole-induced seizures, kainate-induced seizures and pentylenetetrazole kindling in rats.

Method and Discussion. A literature review was conducted using PubMed from 1963 to October 2013 relating effects of flavonoids on experimentally-induced seizures in rodents. Articles chosen for references were queried with the following prompts: "flavonoids and epilepsy", "flavonoids and seizures", "plant polyphenols and epilepsy", and "plant polyphenols and seizures". Out of 84 reports 32 pharmacological studies with chemically well-defined flavonoids and using widely accepted animal models of seizures have been taken into account in this review. No clinical data on the antiepileptic effect of flavonoids have been reported so far.

Conclusion. The reviewed data suggest the possible benefits of some chemically well-defined polyphenolic compounds of plant origin in antiepileptic treatment. Among flavonoids, resveratrol, baicalein, quercetin and rutin showed significant antiseizure activity. The ability of flavonoids to prevent brain excitability and to protect the brain against oxidative stress-induced damage suggests a potential use of some flavonoids at least as adjunctive therapy for the treatment of epilepsy.

Key words: plant polyphenols • flavonoids • antioxidants • seizures • kindling • rodents

INTRODUCTION

Polyphenols play an important role in physiology of plants being involved in the processes of growth, pigmentation, reproduction and resistance to pathogens. These compounds are also responsible for a bitter taste and stability of some fruit and vegetable products. Up till now ca. 10 000 plant-derived polyphenols have been characterized comprising both simple and highly polymerized compounds. Owing to their potent antioxidant activity, polyphenols have long been considered to be beneficial in ameliorating age-dependent disorders, such as atherosclerosis, cancer and neurodegenerative diseases. However, despite promising results of numerous experimental studies it is still unclear whether a diet rich in plant polyphenols indeed has a significant effect on the progress of the above-mentioned pathologies. The first problem is the lack of sufficient pharmacokinetic data on polyphenols. Natural polyphenols are coupled with one or more carbohydrates and glycosylation which affects their absorption in the ileum; polymerization, protein binding and solubility influences their potential therapeutic efficacy (Crozier et al., 2009). The blood concentration of absorbed poly-

phenols is thought to be only a small percent of the per os (p.o.) dose. Since serum concentration of endogenous antioxidants is in millimolar range it is doubtful whether additional presence of polyphenolic antioxidants in micromolar concentrations could efficiently further enhance defense of the organism against oxidative stress. However, besides scavenging free radicals, polyphenols in lower concentrations can interfere with some other biochemical mechanisms, e.g. with kinase-dependent intracellular pro-survival pathways (Nones et al., 2011; Vauzour et al., 2007). Only a few studies investigated the ability of plant polyphenols to cross the blood-brain barrier (Faria et al., 2011). It has been shown that polyphenols from the enriched diet in the rat can be detected in the brain regions important for learning and memory (Andres-Lacueva et al., 2005). Katechins from green tea given per os penetrate into the brain and their metabolites can be isolated from brain tissue in the form of epicatechine glucuronide and epikatechine 3'-Q-metyloglucuronide (Abd EL Mohsen et al., 2002). Another polyphenol, curcumin, is highly lipophilic and penetrates into the brain, but is quickly metabolized (Metzler et al., 2013). It should be mentioned that optimal dosing of polyphenols is an important and unresolved question because it has been postulated that at very high doses these compounds paradoxically can enhance pro-oxidative processes in the organism. Flavonoids are an important class of natural polyphenolic compounds. A relationship between the consumption of flavonoid-rich diets and the prevention of neurodegenerative disorders has been postulated. Both natural and synthetic flavonoids affect neuronal activity and their pharmacological profile suggests a potential usefulness of these compounds in adjunctive treatment of epilepsy. Oxidative stress-induced biochemical changes causing dysfunction of the mitochondria, altering neuronal membrane permeability and disturbing the balance between excitatory and inhibitory transmitters decrease the seizure threshold and evoke epileptic neuronal discharges which may initiate the epileptogenesis (Majkowski, 2007). Thus, oxidative stress can be involved in the pathophysiology of epilepsy, and some antioxidants have an antiepileptic property. Besides being potent antioxidants, many flavonoids were proposed to show affinity for γ-aminobutyric acid ($GABA_A$) receptors constituting the main inhibitory system in the central nervous system. Wolfman et al., (1998) reported that the synthetic flavone 6-bromo-3'-nitroflavone, effectively recognized benzodiazepine receptors and had potent anxiolytic-like effects. It also possessed a mild anticonvulsant activity. However, other studies demonstrated that 6-bromoflavone and 6-bromo-3'-nitroflavone showed anxiolytic-like properties only in some tests and did not increase the latency to clonic seizures produced by isoniazid (Griebel et al., 1999). Moreover, depressant actions of valerian-derived glycosides: 2S-neohesperidin, 2S-naringin, diosmin, gossipyn and rutin, on the central nervous system in mice were unlikely to directly stimulate $GABA_A$ receptors. Importantly only flavonoid glycosides, but not aglycones, seem to depress the central nervous system activity (Fernández et al., 2006). Thus, the neurochemical mechanism of depressant action of some flavonoids on the central nervous system has yet to be elucidated. However, the ability of these compounds to prevent brain excitability and, on the other hand, to protect the brain against oxidative stress-induced damage suggests a potential use of some flavonoids at least as adjunctive therapy of for the treatment of epilepsy. This paper briefly summarizes the pharmacological effects of various selected plant polyphenols on experimentally induced seizures in rodents.

AIM

This review describes the pharmacological activity of some polyphenols (flavonoids) in different animal models of seizures e.g. pentylenetetrazole-induced seizures, kainate-induced seizures and pentylenetetrazole kindling.

METHOD AND DISCUSSION

A literature review was conducted using PubMed from 1963 to October 2013 relating effects of flavonoids on experimentally-induced seizures in rodents. Articles chosen for references were queried with the following prompts: "flavonoids and epilepsy", "flavonoids and seizures", "plant polyphenols and epilepsy", and "plant polyphenols and seizures". Out of 84 reports 32 pharmacological studies with chemically well-defined flavonoids and using widely accepted animal models of seizures have been taken into account in this review. No clinical data on the antiepileptic effect of flavonoids have been reported so far.

Quercetin (3,3',4',5,7-pentahydroxyflavone)

Quercetin is a flavonoid found in fruits, vegetables, leaves and grains. This compound was postulated to produce both anticonvulsant and proconvulsant effects.

It has been reported that acute and chronic administration of quercetin (25 or 50 mg/kg, p.o.) prevents the ethanol withdrawal-induced reduction in pentylenetetrazole (PTZ) seizure threshold in mice indicating that it processes an anticonvulsant properties (Joshi et al., 2005). Also, pretreatment with quercetin at 50 mg/kg attenuates seizure severity in the PTZ kindling model by lowering the mean seizure stages, but increases oxidative stress in the hippocampi and cerebral cortices of the kindled rats (Nassiri-Asl et al., 2013). Furthermore, quercetin exerts neuroprotective effects on hippocampal injury related to experimental status epilepticus in rats and that effect was associated with regulation of the X-linked inhibitor of apoptosis protein and the caspase-3 protein (Hu et al., 2011). Other investigators found that intraperitoneal (i.p.) administration of quercetin inhibited expression of heat shock proteins 70 kDa (Hsp70) and that the effect was accompanied by an increased duration but not severity of clonic and tonic seizures induced by intraperitoneal injection of pentylenetetrazole in rats. Furthermore, quercetin increased duration of tonic seizures evoked by intraventricular microinjection of N-methyl-D-aspartic acid (NMDA) (Nitsinskaia et al., 2010).

Rutin (3, 3′, 4′, 5, 7-pentahydroxyflavone-3--rhamnoglucoside)

This flavonoid is a *glycoside* of quercetin widely distributed in plants and a well-known dietary constituent, but its effect on central nervous system activity has been only partially recognized. It has been found that a copper-rutin complex (2 mg/kg) diminished epileptiform potentials evoked by a combination of chlorpromazine and microwave radiation and suppressed convulsive activity induced by the administration of penicillin to the sensorimotor cortex (Tsaryuk et al., 2002). Other investigators reported that intracerebroventricular administration of rutin dose-dependently attenuated minimal clonic seizures and generalized tonic-clonic seizures induced by pentylenetetrazole. Furthermore, since flumazenil abolished the anticonvulsant effects of this flavonoid, it has been postulated that rutin is a positive allosteric modulator of the gamma-aminobutyric acid type A ($GABA_A$) receptor complex probably interacting with the benzodiazepine site (Nassiri-Asl et al., 2008). However, Fernández et al. (2006) concluded that the depressant action of rutin on the central nervous system of mice is unlikely to involve a direct action on $GABA_A$ receptors. Regarding experimental epileptogenesis, rutin (50 and 100 mg/kg, i.p.) not only attenuated PTZ kindling, but also enhanced memory retrieval in kindled rats suggesting a potential utility of this flavonoid in the treatment of memory deficits in epileptic patients (Nassiri-Asl et al., 2010).

Linarin (5-hydroxy-2-(4-methoxyphenyl)-7--[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy--6[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one)

Linarin is the most abundant flavonoid in flowers and leaves of Chrysanthemum boreale (Compositae), the herbal tea of which is known to have anxiolytic properties to reduce anxiety, insomnia and stress. Recently, linarin and its aglycone acacetin, have been reported to have sedative effects in mice in the pentobarbital-induced sleeping test and anticonvulsant action against PTZ-induced seizures (Nugroho et al., 2013).

Hesperidin ((2S)-5-hydroxy-2-(3-hydroxy-4--methoxyphenyl)-7-[(2S,3R,4S,5S,6R)-3,4,5--trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy--6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxy-2,3--dihydrochromen-4-one)

Hesperidin is a flavanone glycoside found in high concentration in citrus fruits. Hesperidin and its aglycone form hesperetin were proposed to be potentially useful in controlling pathophysiological disturbances in brain excitability accompanying drug abuse, migraine and epilepsy (Dimpfel, 2006). This suggestion was based upon electrophysiological in vitro and ex vivo studies on hippocampal slices. Chronic treatment with hesperidin (200 mg/kg) significantly attenuated seizures in PTZ-kindled mice (Kumar et al., 2013). Hesperidin also attenuated the hippocampal cell response to 4-aminopyridine (4-AP) and bicuculline but not to tetraethylammonium (TEA) or pentylenetetrazole, whereas hesperetin was able to attenuate the response to TEA and PTZ, but not to 4-AP or bicuculline. Moreover, since the action of hesperidin was sensitive to the presence of iberiotoxin, the involvement of a large conductance calcium-dependent potassium channel in its mechanism of action is suggested (Dimpfel, 2006).

Apigenin (5,7,4′-trihydroxyflavone)

Apigenin, a component of Cirsium japonicum was reported to attenuate kainate-induced seizures and brain damage, which is a widely used model of temporal lobe

epilepsy (Han et al., 2012). These investigators observed that injection of apigenin (25 and 50 mg/kg, i.p.) prior to kainate administration decreased seizure scores, significantly delayed the seizure onset time and diminished electroencephalogram discharge activity in the brain cortex of mice. Furthermore apigenin prevented kainate-induced hippocampal cell loss most likely by quenching reactive oxygen species and by inhibiting glutathione (GSH) depletion in the neurons (Han et al., 2012).

Hispidulin (4',5,7-trihydroxy-6-methoxyflavone)

Hispidulin is an active component from a traditional Tibetan medicinal plant Artemisia vestita. This naturally occurring flavone after oral administration showed a significant anticonvulsant effect in seizure-prone Mongolian gerbils (Meriones unguiculatus) which are considered to be a genetic model of epilepsy. This compound readily crosses the blood-brain barrier and acts as a positive allosteric modulator of $GABA_A$ receptors preferentially interacting with alpha(6)beta(2)gamma(2)S-$GABA_A$ receptor subtype (Kavvadias et al., 2004). Further studies showed that in addition to enhancing GABAergic transmission, the mechanism of anticonvulsant effects of hispidulin can involve the inhibition of glutamate release in the brain tissue through the suppression of presynaptic voltage-dependent Ca^{2+} entry and ERK/synapsin I signaling pathway (Lin et al., 2012).

Vitexin (5, 7, 4-trihydroxyflavone-8-glucoside)

Vitexin is an apigenin flavone glucoside found in the Vitex agnus-castus and Phyllostachys nigra. Intracerebroventricular administration of vitexin, reduced minimal clonic seizures and generalized tonic-clonic seizures induced by pentylenetetrazole in rats. Since the benzodiazepine receptor antagonist flumazenil prevented the anticonvulsant action of vitexin, it has been postulated that this flavone exerts its central effects possibly through interaction with the benzodiazepine site of the $GABA_A$ receptor complex (Abbasi et al., 2012).

Baicalein (5,6,7-trihydroxy-2-phenyl-4H-1--benzopyran-4-one)

Baicalein, originally isolated from the Scutellaria baicalensis is an active component of the herbal medicine TJ-960 which is used for the treatment of epilepsy in Japan. It was found to be effective against $FeCl_3$-induced epilepsy in rats and in preventing hippocampal delayed neuronal death in gerbils exposed to transient ischemia. The first report indicated that radical quenching and antioxidant effects of baicalein can be the key mechanisms of its antiepileptic and neuroprotective properties (Hamada et al., 1993). Yoon et al. (2011) compared pharmacological effects of major flavones isolated from Scutellaria baicalensis, i.e. baicalein and its metabolites baicalin and oroxylin A. They found that baicalein but not oroxylin A and baicalin suppressed electrogenic and PTZ-induced seizures. Subsequently they provided evidence that baicalein induced intracellular Cl(-) influx and that the anticonvulsant effect of baicalein was inhibited by flumazenil suggesting that anticonvulsive effect of baicalein was mediated by the benzodiazepine binding site of $GABA_A$ receptor (Yoon et al., 2011). However, other investigators found that baicalein when directly injected into the CNS, promoted anxiolytic-like and sedative effects without affecting the PTZ-induced convulsions, and suggested that the pharmacological action of baicalein involved GABAergic non-benzodiazepine sites but not the serotonin system (de Carvalho et al., 2011). In line with this, the lack of anticonvulsant effect of the baicalein metabolite baicalin was reported by Wang et al. (2008). Anticonvulsant and amnesic effects and motor incoordination were not observed when baicalin was administered at effective anxiolytic doses (Wang et al., 2008). In contrast, a recent study demonstrated that baicalin attenuated seizures and hippocampal neuronal cell loss in the well-validated model of temporal lobe epilepsy in rats. Thus, pretreatment with baicalin delayed the onset of the first limbic seizures and status epilepticus, reduced the mortality rate, and attenuated the changes in the levels of lipid peroxidation, and nitrite and reduced glutathione content in the hippocampus of pilocarpine-treated rats. The authors suggested that for the profound anticonvulsant and neuroprotective effects of baicalin, this flavone should be considered as an adjuvant in epilepsy treatment (Liu et al., 2012).

Epigallocatechin-3-gallate

Intracortical application of transition metal (iron, cobalt) salts led to oxidative-stress-related local brain damage resulting in an epileptic focus and recurrent seizures. Consequently, this procedure is considered to be a model of focal epilepsy. Epigallocatechin-3--gallate (EGCG), a catechin polyphenol abundant in green tea leaves, was found to be an effective antioxi-

dant and anticonvulsant against iron ion-induced seizures. Moreover, this flavone also inhibited the iron ion–evoked increase in dopaminergic system activity but had no effect on the serotonin system (Kabuto et al., 1992). Also tannins inhibit the formation of epileptic focus induced by $FeCl_3$ administration in rats (Yokoi et al., 1989). Epigallocatechin-3-gallate also dose-dependently suppressed the development of PTZ-induced kindling and attenuated the cognitive impairment and oxidative stress in this model. Therefore, it has been postulated that epigallocatechin-3-gallate may be useful not only in suppressing seizures but also in ameliorating cognitive deficit in epileptic patients (Xie et al., 2012).

Naringin (7-[[2-O-(6-Deoxy-α-L-mannopyranosyl)--β-D-glucopyranosyl]]oxy]-2,3-dihydro-5--hydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran--4-one)

Naringin is a flavonoid found in grapefruit which shows antioxidant and anti-inflammatory activity as well as inhibitory effects on cytochrome P450 enzymes. This compound administered in a broad range of doses (20–80 mg/kg, i.p.) was shown to suppress seizures and reduce cognitive deficit induced by kainate administration in rats. These behavioral effects were accompanied by a decrease in oxidative stress parameters and in the content of the pro-inflammatory cytokine tumor necrosis factor (TNF)-α in the brain of kainate-treated rats. Although the data strongly suggest therapeutic potential of this flavonoid, however, its inhibitory effect on cytochrome P450 enzymes can result in undesired interaction with some antiepileptic drugs (Golechha et al., 2011). Indeed a randomized crossover study showed that grapefruit juice increases the bioavailability of carbamazepine by inhibiting CYP3A4 enzymes in gut wall and in the liver of epileptic patients (Garg et al, 1998).

Agathisflavone (5,5′,7,7′-tetrahydroxy-2,2′-bis(4--hydroxyphenyl)-6,8′-bichromene-4,4′-dione)

Agathisflavone and *amentoflavone* are found in the South African Rhus pyroides, a plant traditionally used in the treatment of epilepsy. The mechanism of antiepileptic effect of these compounds is likely to involve $GABA_A$ receptors. Both compounds in nanomolar concentrations competitively inhibited the binding of flumazenil and were fitted into a pharmacophore model for ligands binding to the $GABA_{(A)}$ receptor benzodiazepine site (Svenningsen et al., 2006).

Goodyerin (3-[[6-O-(6-deoxy-alpha-L--mannopyranosyl)-beta-D- glucopyranosyl] oxi]-5,7-dihydroxy-8-[(4-hydroxy--3,5-dimethoxyphenyl)meth yl]--2-(3,4-dihydroxypheny)-4H-1-benzopyran-4-one)

Goodyerin is a flavonol glycoside found in the plant Goodyera schlechtendaliana. A pharmacological in vivo study showed that goodyerin dose-dependently produced a sedative effect and inhibited picrotoxin-induced seizures in rodents (Du et al., 2002).

NPC 16377 (6-[6-(4-hydroxypiperidinyl)hexyloxy]--3-methylflavone)

This *synthetic flavone derivative* with neuroprotective activity is a potent and selective ligand of sigma binding sites in the central nervous system. This substance blocks locomotor stimulant effects of cocaine (sensitization) and has a limited but significant anticonvulsant activity against diazepam-sensitive cocaine convulsions (Witkin et al., 1993).

Chrysin (5,7-di-OH-flavone)

Chrysin (5,7-di-OH-flavone) is an active ingredient of Passiflora coerulea L. the herb of which is traditionally used in the treatment of anxiety disorders. After intracerebrointraventricular injection in mice, this flavonoid was shown to have myorelaxant action and prevented the expression of PTZ-induced tonic-clonic seizures. It binds to both central and peripheral benzodiazepine binding sites in low micromolecular concentrations (Medina et al., 1990).

Resveratrol (3,5,4′-tri-hydroxy stilbene)

Resveratrol extracted from the roots of the Japanese Knotweed is a polyphenolic compound belonging to phytoalexins which exhibits a variety of biological activities including antioxidant, anti-aging, anti-cancer, neuroprotective and anti-inflammatory effects. This compound penetrates across the blood-brain barrier and exerts minor undesired effects. The promise of resveratrol in epilepsy treatment and preventing the epilepsy-related cognitive dysfunction has been reviewed by Shetty (2011). Gupta et al. (2001) demonstrated that trans-resveratrol was able to reduce $FeCl_3$-induced posttraumatic seizures in rats. When administered intraperitoneally before intracortical $FeCl_3$ injection, it delayed the onset of epileptiform EEG discharges, but less consistently affected oxidative stress markers, like malondialdehyde and glutathione levels in the whole

brain tissue. The same group of investigators reported that a single dose of trans-resveratrol could not inhibit the kainate-induced convulsions, whereas repeated administration significantly reduced incidence of convulsions. Protective effects of trans-resveratrol against kainate-induced seizures were accompanied with attenuation of raised malondialdehyde concentrations, but no changes in glutathione concentrations were observed (Gupta et al., 2002b). Other authors found that resveratrol decreased the frequency of spontaneous seizures and inhibited the epileptiform discharges induced by kainate in rats. Importantly, resveratrol prevented the kainate-induced hippocampal cell death and reduced mossy fiber sprouting, which are thought to be histological markers of epileptogenesis in this model of temporal lobe epilepsy (Wu et al., 2009). Studies on mice revealed that regular exercise and resveratrol (40 mg/kg, daily supplementation for 6 weeks) inhibited kainate-induced seizure activity, mortality and oxidative stress in those animals. The synergic effect of regular exercise and resveratrol suggests its potential usefulness for the prevention of seizure development (Kim et al., 2013). However, in contrast to adult rats, repeated resveratrol administration did not attenuate kainate-induced seizures, and had only modest effect on preventing hippocampal cell death and lipid peroxidation in young rats (Friedman et al., 2013). Further studies revealed that the trans-resveratrol dose-dependently reduced the incidence of the pentylenetetrazole-induced generalized tonic-clonic seizures. Moreover, resveratrol enhanced the anticonvulsant effects of sodium valproate, diazepam and adenosine, whereas, an adenosine receptor antagonist theophylline diminished the resveratrol-induced anticonvulsant effect (Gupta et al., 2002a). Thus, early studies indicate that mainly antioxidant properties and the adenosinergic pathway play a role in anticonvulsive and neuroprotective effects of resveratrol. Recent molecular studies provided evidence that resveratrol inhibited the activation of nuclear factor-kappa B and the production of pro-inflammatory molecules engaged in the mammalian target of rapamycin (mTOR) pathway in an experimental model of status epilepticus. Furthermore, the inhibitory effect of resveratrol on seizure-induced inflammatory response depended on 5' adenosine monophosphate-activated protein kinase (AMPK) (Wang et al., 2013). Thus anti-inflammatory properties of resveratrol can also contribute to complex mechanism of its anticonvulsant and neuroprotective actions.

SUMMARY AND CONCLUSIONS

Epilepsy is a serious neurological disorder while anticonvulsant therapies are limited and unable to control seizures in all patients. Flavonoids present a variety of beneficial health effects including regulation of oxidative stress, inflammation and metabolism. The present review summerizes potential antiepileptic effects of various flavonoids in different models of seizures in rodents. They were effective in pentylenetetrazole-induced kindling which models epileptogenesis, and against pentylenetetrazole-induced tonic-clonic seizures which reflect generalized tonic-clonic seizures in man. Moreover, some flavonoids attenuated the kainate-induced seizures – a well recognized model of temporal lobe epilepsy, and focal seizures evoked by intracerebral administration of $FeCl_3$ in rats. Among flavonoids, baicalein, resveratrol, quercetin, epigallocatechin-3-gallate and rutin show significant antiseizure activity in different seizure models (Table 1). The ED50 values for anticonvulsant effect of the plant polyphenols could not be calculated and compared because of insufficient number of doses, various routes of drug administration and different animal models of seizures. The mechanism of antiseizure action of flavonoids is not yet fully understood but some could enhance GABAergic transmission. More experiments with rigorous design are needed to determine efficacy of flavonoids in suppressing specific seizure types. It should be also mentioned that there are at least 22 other reports not included in this review which showed anticonvulsant effects of plant extracts with high content of flavonoids. Because to date no clinical study on antiepileptic effect of flavonoids has been undertaken it is difficult to speculate about future and commercialization of these compounds. Nevertheless, some clinical data on lack of serious adverse reactions and positive effects of plant polyphenols in prevention of other neurologic disorders are encouraging. The cohort studies conducted in 1991–1996 on 1367 patients aged 65 years or older show that intake of antioxidant flavonoids is inversely related to the risk of incident dementia (Commenges et al., 2000). It has also been reported that higher consumption of dietary flavonoids, especially flavonols, is associated with lower population rates of dementia in twenty-three developed countries (Beking and Vieira, 2010). Thus, it is not unlikely that at least some flavonoids may act as a useful adjuvant to the conventional pharmacotherapy of epilepsy. Furthermore, possible pharmacokinetic and pharmacodynamics interaction

Table 1. Some flavonoids with antiseizure activity (effective doses) in different models of seizures in rodents

PTZ-induced seizures	Resveratrol (20–80 mg/kg, i.p) Baicalein (5–20 mg/kg, i.p) Rutin (50 and 150 nM, i.c.v) Quercetin (25 and 50 mg/kg, p.o) Vitexin (100 and 200 mM, i.c.v) Linarin (10 and 20 mg/kg, p.o) Chrysin
PTZ-induced kindling	Epigallocatechin-3-gallate (25 and 50 mg/kg, i.p) Rutin (50 and 100 mg/kg, i.p) Quercetin (50 mg/kg, i.p) Hesperidin (200 mg/kg, p.o)
Kainate-induced seizures	Resveratrol (15 mg/kg, p.o) Naringin (20–80 mg/kg, i.p) Apigenin (25 and 50 mg/kg, i.p)
$FeCl_3$-induced seizures	Resveratrol (20–40 mg/kg, i.p) Epigallocatechin-3-gallate Baicalein
Picrotoxin-induced seizures	Goodyerin (25 and 55 mg/kg, i.p)
Cocaine-induced seizures	NPC16377 (20–80 mg/kg, i.p)
Genetic model of epilepsy	Hispidulin (10 mg/kg, p.o)

PTZ = pentylenetetrazole

of flavonoids with antiepileptic drugs warrants good quality preclinical and clinical studies.

CONFLICT OF INTEREST DISCLOSURE

The authors have no conflict of interest to declare.

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