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SYSTEMATIC REVIEW ARTICLE

Fruits for Seizures? A Systematic Review on the Potential Anti-Convulsant Effects of Fruits and their Phytochemicals

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Abstract: Epilepsy is a devastating neurological disorder. Current anti-convulsant drugs are only effective in about 70% of patients, while the rest remain drug-resistant. Thus, alternative methods have been explored to control seizures in these drug-resistant patients. One such method may be through the utilization of fruit phytochemicals. These phytochemicals have been reported to have beneficial properties such as anti-convulsant, anti-oxidant, and anti-inflammatory activities. However, some fruits may also elicit harmful effects. This review aims to summarize and elucidate the anti- or pro-convulsant effects of fruits used in relation to seizures in hopes of providing a good therapeutic reference to epileptic patients and their carers. Three databases, SCOPUS, ScienceDirect, and PubMed, were utilized for the literature search. Based on the PRISMA guidelines, a total of 40 articles were selected for critical appraisal in this review. Overall, the extracts and phytochemicals of fruits managed to effectively reduce seizure activities in various preclinical seizure models, acting mainly through the activation of the inhibitory neurotransmission and blocking the excitatory neurotransmission. Only star fruit has been identified as a pro-convulsant fruit due to its caramboxin and oxalate compounds. Future studies should focus more on utilizing these fruits as possible treatment strategies for epilepsy.

Keywords: Epilepsy, drug-resistant, fruit extract, anti-seizure, pro-convulsant, anti-oxidant.

1. INTRODUCTION

Epilepsy is one of the most common, debilitating neurological illnesses in the world. Epilepsy is characterized as spontaneous recurrent seizures caused by excessive and synchronous neuronal activity in the brain [1]. More than 65 million people worldwide are suffering from epilepsy [2]. Epilepsy is often diagnosed in a person when two or more unprovoked seizures occur at least 24 hours apart, where these seizures are likely elicited in the absence of direct stimuli such as injury, brain tumor, renal and hepatic failure [1, 3]. In order to control these seizures, antiepileptic drugs (AEDs), or now known as anti-seizure drugs (ASD), are commonly first prescribed to patients. ASDs are prescribed as combination therapy or as a monotherapy, depending on the effectiveness and adverse effects they elicit on each patient. The effectiveness of ASDs may vary depending on family history, the extension of neurological abnormalities, and type of seizures [4]. Currently, there are three generations of ASDs. The first-generation of ASDs are more commonly used, and they include carbamazepine, phenytoin, valproic acid, and phenobarbital. The second-generation include topiramate, gabapentin, levetiracetam, and more [5], while the third-generation includes lacosamide, rufinamide, eslicarbazepine acetate, and more [6]. Although the newer ASDs may not exhibit any greater anticonvulsant effects than older ASDs, they may still be advantageous in terms of causing fewer drug-drug interactions [6, 7].

Nevertheless, current ASDs may only be capable of managing seizures in about 70% of patients. The remaining 30% of epileptic patients often may not respond well to any ASDs, thus categorizing their epilepsy as drug-resistant, refractory or intractable epilepsy. In fact, it was shown that if seizures were ineffective at being controlled even after the third ASD, trying anymore may just be fruitless [2, 8]. Since drug-resistant epilepsy occurs in nearly 7% to 20% of children and 30% to 40% of adults [9], efforts have been made to explore alternative ways to control seizures in these patients so that they may possess a good quality of life.

Recently, there has been a growing interest in studying the effects of fruit extracts and their compounds as an alternative therapeutic strategy to control seizures. Fruits are equipped with an abundance of bioflavonoids that possesses multiple beneficial properties such as anti-oxidant and anti-inflammatory activities that may be therapeutic against seizures [10]. Since previous literature had shown that flavonoids from digesting medicinal plants and herbs have anti-convulsant properties [11], it may be proposed that this beneficial effect may also extend to fruits. Similarly, alkaloids,

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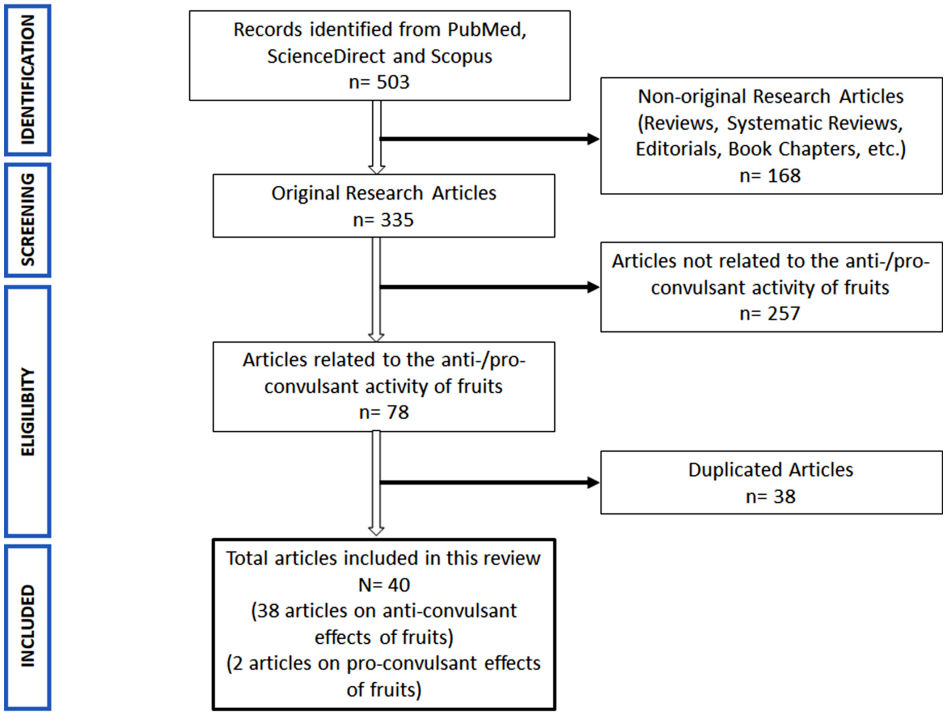

Fig. (1). PRISMA flowchart.

which may be found commonly in dietary plants and coffee seeds, have also been reported to have therapeutic effects on neurodegenerative diseases [12], and this effect may transgress towards epilepsy as well. In addition, cannabidiol found in marijuana has also exhibited anti-convulsant, antioxidant, and anti-inflammatory properties that may contribute to its neuroprotective action against epilepsy [13], but its commercial use is still with limitations, particularly due to its label as an illegal substance in many countries.

In more recent times, the ketogenic diet (KD) has been implemented as an alternative approach to treating epilepsy. In contrast, KD is shown to be effective in drug-resistant epileptic children and potential adults [14, 15]. The long-term compliance has been low, which limits KD usage [16, 17]. Low-fat dairy products have also been reported to reduce seizure threshold and reduce the latencies of pentylenetetrazol (PTZ)-induced clonic and myoclonic jerk [18], but its clinical effects have yet to be determined.

In contrast, some food may instead be more detrimental towards epileptic patients. For example, caffeine has been shown to lower the efficacy of several ASDs, particularly topiramate, and thus, to achieve and maintain seizure control, caffeine intake should be considered as a factor prior to ASD prescription [19].

Since diet intake may exhibit both pro-convulsant or anti-convulsant effects depending on the type of food, it is highly recommended that patients, caregivers, and health care providers understand and prioritize their diet regime when managing epilepsy. Fruits sit at the highest priority on the human food chain, and, therefore, their effects on seizures are of utmost importance. This review aims to summarize and elucidate the different types of fruits and their compounds, which have been reported to have anti-convulsant or pro-convulsant effects on seizures. This review will hopefully provide great guidance to epileptic patients and their caregivers to increase the effectiveness of their ASD and possibly even to revert their ineffectiveness in those who are drug-resistant.

2. METHODOLOGY

2.1. Literature Search

An extensive literature search was conducted to identify currently available research articles reporting the potential anti-/pro-convulsant effects of various fruits. Three databases have been utilized for the literature search, which include SCOPUS, ScienceDirect, and PubMed. The search terms used were ‘epilepsy’, ‘seizure’, ‘anti-convulsant’, and ‘pro-convulsant’, which were searched in combination with the search term ‘fruit.’

2.2. Literature Selection

The search results were subjected to the PRISMA guidelines [20] before arriving at the final number of articles selected for this systematic review (Fig. **1**). The inclusion criteria were articles published in the English language or those that had an English-translated version, were original research articles, and had evaluated the anti-convulsant or pro-convulsant effects of fruit extract, fruit origin-essential oil, fruit peels, and specific compounds in the fruit. The exclusion criteria were duplicated articles, non-original articles such as reviews, systematic reviews, book chapters, case reports, communications, conferences, symposiums, and editorials, articles that investigated other parts of the plant such as leaves, barks, and roots, and articles that did not investigate the anti-convulsant or pro-convulsant activity of fruits.

2.3. Quality Appraisal

The quality of the selected articles included in this systematic review was assessed using the Systematic Review Centre for Laboratory Animal Experimentation Risk of Bias (SYRCLE RoB tool) (File **S1**).

3. RESULTS AND DISCUSSION

A total of 503 articles were identified and retrieved from the three search databases (Fig. **1**). One hundred and sixty-eight non-original research articles and 257 articles that were not related to the anti-/pro-convulsant activity of fruits were excluded. The remaining 78 articles were further screened and 38 duplicated articles were removed. Thus, the total number of articles that were included in this review for critical appraisal was 40. These 40 articles have been evaluated for their investigations into the anti-convulsant (38 articles) and pro-convulsant (2 articles) properties of fruits and were categorized into four main groups: common fruits, local/regional fruits, rare fruits with anti-convulsant properties, and fruits with pro-convulsant properties.

3.1. Common Fruits with Anti-convulsant Effects

According to Table **1** [21-35], there were six phytochemicals, four crude extracts, one fruit peel extract, and one seed extract originating from common fruits, which were found to have potential anti-convulsant properties. Common fruits are categorized based on their easy availability and abundance in multiple continents of the world.

Naringin is a flavonoid that can be found in most citrus fruits, including grapefruits. It was found to exhibit anti-convulsant activity by significantly increasing the latency of seizures induced by kainic acid (KA). Other than that, naringin was also found to attenuate autophagic stress, neuronal cell death, and microglial activation [21], thus attributing it as a neuroprotective flavonoid. Naringin may exhibit its anti-convulsant and neuroprotective properties *via* the attenuation of KA-induced granule cell dispersion (GCD), which is achieved through the deactivation of mammalian target of rapamycin complex 1 (mTORC1) in the hippocampus [24]. The mTORC1 hyperactivity has been strongly related to the epileptogenesis pathway [36].

Similarly, naringenin, a major metabolite of naringin, has also shown promising anti-convulsion activity. Studies showed that naringenin was able to delay the onset of KA-induced seizures and attenuate KA-induced GCD through a similar pathway as naringin; deactivation of mTORC1 in the hippocampus [22]. It also managed to reduce the seizure severity in a pilocarpine model [23], which may be a more reliable model in the generation of spontaneous seizures, as seen in human temporal lobe epilepsy [37]. Temporal lobe epilepsy (TLE) is the most common type of epilepsy in adults, where granule cell dispersion (GCD) was seen as a common key pathological feature [38]. The mammalian target of rapamycin (mTOR) pathway plays an important role in the functional development of neurons. Overactivation of the mTOR pathway was shown to induce epilepsy in TLE rodent models, and rapamycin (mTOR inhibitor) was able to inhibit the epileptic seizures in these models [39, 40].

Besides its anti-convulsant activity, naringenin may also reduce the KA-induced production of pro-inflammatory cytokines and microglial activation [22]. In the pilocarpine model, naringenin showed an increase in anti-oxidant activity by reducing lipid peroxidation. Naringenin decreased the thiobarbituric acid reactive substances (TBARS) levels, which in turn reduced the free radical generation. In addition, glutathione reductase (GR), superoxide dismutase (SOD), and catalase (CAT) activity were also seen to be increased when naringenin was administered, which further proves its anti-oxidant properties [23]. These results suggest that naringenin and naringin, both of which have exhibited anti-convulsant, anti-inflammatory, and anti-oxidant properties, may help to curb the progression of epilepsy.

The common black pepper (*Piper genus*) has a major alkaloid called piperine. This alkaloid was shown to exhibit anti-convulsant activity by delaying the onset of PTZ- and picrotoxin (PIC)-induced seizures in mice models (Table **1**). The anti-convulsant activity may have been caused by the activation of the GABAergic pathways [25]. Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter, which acts as a ligand for the GABAA receptor, a ligand-gated chloride ion channel that is often targeted by many anti-convulsant drugs (AED/ASDs) [4, 41]. Besides the GABAergic pathway, piperine may also elicit its anti-convulsant activity through another inhibitory neurotransmission; the glycinergic signaling pathway [26]. The same study also suggested that the anti-convulsant effect of piperine in maximal electroshock (MES)-induced model may involve the inhibition of the sodium ion channel. This involvement was evidently demonstrated through a whole-cell patch-clamp technique. Moreover, piperine was also found to inhibit a non-selective cation channel called transient receptor potential vanilloid 1 (TRPV1), which has a high permeability towards calcium ions [26]. TRPV1 activation promotes glutamate release, which is the major excitatory neurotransmitter [4]. The imbalance of the excitatory and inhibitory neurotransmission results in seizures [1]. Thus, this supports that the inhibition of the TRPV1 receptor may contribute to the anti-convulsant activity of piperine. These findings suggest that piperine may have multiple therapeutic pathways for its anti-convulsant activity, thus lowering the chances of resistance development.

Rutin is a flavonoid found in many common plants ranging from apples to buckwheat. Rutin was found to elicit anti-convulsant and anti-oxidant activity towards KA-induced convulsions [27]. However, the mechanism of action has not been extensively explored and may leave room for future studies to investigate.

D-pinitol, a polyol that can be found in many legumes and beans of the Leguminosae or Fabaceae families, was also shown to have anti-convulsant activity. D-pinitol delayed the onset and reduced the duration of PTZ-induced seizures through the involvement of the GABAergic system [28]. Further studies may be needed to uncover other possible mechanisms of action of D-pinitol that encourage its anti-convulsant activity.

Morin, a bioflavonoid from fruits such as orange, guava, and old fustic, delayed the onset of convulsions by inhibiting the GCD and the mossy fiber sprouting (histopathological feature of neuronal loss), as well as inhibited the occurrence of spontaneous recurrent seizures through mTORC1

Table 1. List of common fruits identified to have anti-convulsant activity along with its major constituents and potential mechanism of action.

Fruit Scientific Name	Native Distribution	Major Active Constituent Studied (dose and route of administration)	Animal Model (animal strain and age)	Anti-Convulsant Activity	Mechanism of Action	Refs.
Citrus fruits	South Asia, East Asia, Southeast Asia, Melanesia, and Australia	Naringenin phytochemical (50mg/kg and 100mg/kg, I.P)	Kainic Acid Model (Male C57BL/6 mice, 8 weeks old)	> Decreased the severity and delayed the onset of KA-induced seizure activity. > Inhibited KA-induced GCD. > Reduced KA-induced neuroinflammation and lipid peroxidation.	* Increased GR, SOD, CAT activity. * Deactivation of mTORC1. * Inhibit the production of pro-inflammatory cytokines.	[22]
		Naringenin phytochemical (20mg/kg and 40mg/kg, oral)	Pilocarpine Model (Male and Female Swiss Albino mice, adult)	> Decreased in lipid peroxidation. > Decrease in severity of seizure.	* Recovery of antioxidant enzymes and glutathione content.	[23]
		Naringin phytochemical (80 mg/kg per day, I.P)	Kainic Acid Model (Male C57BL/6 mice, 8 weeks old)	> Delay onset of KA-induced seizures. > Decreased occurrence of chronic spontaneous recurrent seizures.	* Attenuate autophagic stress, neuronal cell death. * Attenuate the increase in TNF-α.	[21]
			Kainic Acid Model (Male C57BL/6 mice, 8 weeks old)	> Significantly reduce KA-induced GCD activation.	* Deactivation of mTORC1.	[24]
Pepper plants *Piper* genus	-	Piperine phytochemical (30, 50 and 70 mg/kg, I.P) PTZ and MES: 5, 10, 20 mg/kg, I.P NMDA, Strychnine, Picrotoxin, Bicuculline and BAYK-8644: 20 mg/kg, I.P	Pentylenetetrazol and Picrotoxin Model (Male mice, 20-30g)	> Significantly decrease onset of PTZ-, picrotoxin- and strychnine-induced convulsions.	* Unknown, possibly by GABAergic pathways.	[25]
			Pentylenetetrazol, NMDA, Maximal Electroshock, Bicuculline, Strychnine and BAYK-8644 Model (Male Swiss Albino mice, 22-28g)	> Reduced mortality in MES and PTZ model. > Delayed onset of tonic-clonic convulsion in PTZ, picrotoxin, strychnine and BAYK-8644 induced convulsions. > Complete protection and delayed onset of BAYK-8644 induced convulsions.	* Increase basal GABA and glycine levels. * Act as a Sodium channel antagonist.	[26]
Apple, passion flower, buckwheat and *Ginkgo biloba*	-	Rutin (quercetin-3-O-rutinoside) phytochemical (100 and 200 mg/kg, I.P)	Kainic Acid Model (Male BALB/c mice, 20-25g)	> Lower seizure scores of KA-induced seizures > Reduced the number of wet dog shakes (WDS).	* Prevent neuronal hyperactivity possibly *via* GABAergic system similar that of many flavonoids.	[27]
Beans, pea and legumes	-	D-pintol phytochemical (10, 50 and 100 mg/kg, I.P)	Pentylenetetrazol Model (BALB/c mice)	> Delayed onset of PTZ-induced convulsions. > Reduced duration of seizure.	* May involve the GABAergic system.	[28]
Osage orange *Maclura pomifera*, guava *Psidium guajava* and old fustic *Maclura tinctoria*	-	Morin phytochemical (20, 40 and 80 mg/10ml/kg per day, oral)	Kainic Acid Model (Male C57BL/6 mice, 8 weeks old, 22-23 g)	> Delay onset of KA-induced seizures. > Inhibits GCD activation. > Reduce pro-inflammatory mediators. > Reduce frequency of spontaneous recurrent seizures.	* Suppression of mTORC1 activation.	[29]

(Table 1) contd….

Fruit Scientific Name	Native Distribution	Major Active Constituent Studied (dose and route of administration)	Animal Model (animal strain and age)	Anti-Convulsant Activity	Mechanism of Action	Refs.
Spiny gourd *Momordica dioica*	India, Myanmar, Sri Lanka, Bangladesh, China, South East Asia, South America, Tropical Africa and Polynesia	Alcoholic crude extract (100 and 300 mg/kg, oral)	Pentylenetetrazol Model (Swiss albino mice, 20-25 g)	> Delay onset of PTZ-induced seizure reflexes. > Attenuated PTZ-induced oxidative stress.	* Decrease cholinesterase activity. * Decrease glutamate levels. * Increase GABA levels. * Lowered levels of MDA. * Increase GSH, SOD and catalase activity.	[30]
Sweet orange *Citrus sinensis*	-	Methanolic extract of citrus peel, naringin, and hesperidin (500 mg/kg bwt, oral)	Cyanide Poisoning Model (Adult male Wistar albino rats, 200-250 g)	> Increased latency to first seizures.	* Prevented the depletion of intracellular GSH, suppression of CAT and SOD activity, increase in LPO levels, and cellular damage.	[31]
Chayote *Sechium edule*	Australia, Brazil, Colombia, Ecuador, India, Nepal, Jamaica, Portugal and Philippines	Ethanolic fruit crude extract, ß-carotene, lutein and vitamin C (100 and 200 mg/kg, oral)	Maximum electroshock and Pentylenetetrazol Model (Male and Female Wister rats, 150-200 g)	> Significantly reduced duration of various phases of MES-induced convulsion. > Delayed onset of clonus and extensor in PTZ-induced convulsion.	* Unknown	[32]
Chinese red date *Zizyphus jujuba*	Subtropical regions of America, Asia, and the Mediterranean region	Hydroalcoholic crude extract (100, 250, 500 and 1000 mg/kg, oral)	Maximum electroshock and Pentylenetetrazol Model (Male Wister rats, 150-200 g)	> Significantly increased the latency of myoclonic jerks of PTZ-induced seizures. > Protection against MES-induced seizures. > Improve cognitive impairment > Attenuated PTZ- and MES-induced oxidative stress.	* Possibly by the inhibition of the overexcitation induced by glutamate or reduction in the synaptic release of glutamate or NMDA. * Significantly decreased MDA levels and increased GSH levels. * Increased AChE and BChE activity in PTZ- and MES-induced seizure.	[33]
Bottle gourd *Lagenaria siceraria*	Africa, tropical regions of Asia and America.	Aqueous crude extract (200, 400 and 800 mg/kg, oral)	Maximal Electroshock Model (Albino rats, 150-250 g)	> Reduction in hind limb extension phase (similar to phenytoin). > Protection against tonic extensor phase.	* Unknown.	[34]
Pomegranate *Punica granatum*	Himalayas, Iran, Mediterranean region, China, and USA	Ethanolic seed extract (150, 300 and 600 mg/kg, oral)	Strychnine and Pentylenetetrazol Model (NMRI male mice, 20-25 g)	> Increase seizure latency and duration in PTZ- and strychnine induced convulsions, but no protection was provided.	* Possibly by GABAergic neurotransmission enhancement or by glycinergic pathway.	[35]

Note: NA: not available; I.P: intraperitoneal injection; KA: kainic acid; GCD: granule cell dispersion; GR: glutathione reductase; SOD: superoxide-dismutase; CAT: catalase; mTORC1: mammalian target of rapamycin complex; PTZ: pentylenetetrazol; GABA: gamma-aminobutyric acid; AChE: acetylcholinesterase; BChE: butyrylcholinesterase; MDA: malondialdehyde; GSH: glutathione; MES: maximal electroshock seizure; NMDA: N-Methyl-D-aspartate; LPO: lipid peroxidation; TNF-α: tumor necrosis factor-alpha.

deactivation [29]. In addition, morin may also exhibit neuroprotective properties by reducing the apoptotic signaling molecules, and the pro-inflammatory mediators in the KA treated hippocampus [29]. This shows that morin possesses both anti-convulsant and anti-inflammatory properties. Its potential as an anti-oxidant should be explored in future studies, as this may help in the prevention of acquired epilepsy.

Besides phytochemicals found in fruits, the crude extract of fruits may also elicit therapeutic properties for epilepsy. Crude alcoholic extract of the spiny gourd (*Momordica dioi-*

ca) was found to portray its anti-convulsant activity mainly through the increase in GABA and the decrease in glutamate levels [30]. Besides that, the extract was also shown to reduce lipid peroxidation *via* the reduction in malondialdehyde (MDA) levels, as well as increase the glutathione, SOD, and CAT activity [30]. These results indicate that spiny gourd extract may also possess an anti-oxidant property, which may prevent epileptogenesis post-oxidative stress events (trauma, stroke, *etc.*). Another crude extract, known as Chayote (*Sechium edule*), which is commonly consumed in many countries, was found to reduce the duration of MES-induced seizures and prolonged the onset of PTZ-induced seizures in a dose-dependent manner [32]. However, unlike the previous crude extract, the mechanism of action of chayote has not been adequately explored.

The hydroalcoholic crude extract of the edible fruit, Chinese red date (*Zizyphus jujuba*), was also found to elicit anti-convulsant activity by increasing the latency to myoclonic jerks and providing protection against PTZ-induced convulsions in a dose-dependent manner [33]. The study showed that the highest concentration (1000 mg/kg) of the extract provided 100% convulsion protection and significantly increased its latency. The study also showed that chronic administration of *Z. jujuba* extract did not enhance the anti-convulsant effect, suggesting that this extract may be better recommended as an acute treatment strategy for epilepsy. Interestingly, the *Z. jujuba* extracts provided lower protection against the MES-induced group compared to the PTZ-induced group, which was also dose-dependent, suggesting that this extract may be more beneficial for absence seizure (PTZ) compared to generalized tonic-clonic seizure (MES) [42]. Pre-treatment of *Z. jujuba* extract was also shown to reduce MDA, increase glutathione levels and increase acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) levels in a dose-dependent manner [33], which may help to prevent epileptogenesis. It was also shown that *Z. jujuba* extract was able to enhance the effects of sub-therapeutic doses of phenytoin and phenobarbitone without altering their serum levels [43]. This suggests that *Z. jujuba* extract can be used as adjuvants for phenytoin and phenobarbitone by enhancing the anti-convulsant efficacy of these two drugs. Thus, a lower dosage of the drugs may be administrated together with the *Z. jujuba* extract, which may reduce the occurrence of unwanted side effects of anti-convulsant drugs.

Bottle gourd (*Lagenaria siceraria*) is a traditional medicinal plant, where its aqueous crude extract was reported to have an anti-convulsant effect similar to phenytoin. The extract reduces the tonic extension and the duration of the stupor onset in MES-induced convulsions [34]. Unfortunately, more studies are needed to determine its possible mechanism of action.

Interestingly, citrus fruit peels, usually treated as waste material, were found to have beneficial properties attributed to the flavonoids, such as naringin and hesperidin found in the peel extract. Methanolic extract of citrus fruit peels increased the latency of the first seizure, which may be enhanced through the increase in the duration of pre-treatment of the extract [31]. The extract was found to reduce oxidative stress and attenuate the decrease in neurotransmitters (dopamine, norepinephrine, and serotonin) brought upon by cyanide poisoning-induced seizures, indicating neuroprotective properties [31]. Similar to the anti-convulsant activity, the anti-oxidant and neuroprotective activity may also be enhanced through the increase in the duration of extract pre-treatment.

Pomegranate (*Punica granatum*) is a fruit widely used in the industrial production of juices, wine, vinegar, jellies, and syrup. The seed ethanolic extract of *P. granatum* was reported to increase seizure latency and its duration in PTZ-induced as well as in strychnine-induced convulsions, both in a dose-dependent manner [35]. It was suggested that the mechanism of action might involve the GABAergic and glycinergic pathway; however, further studies may be required for its verification.

Overall, this review found that naringenin, which has been investigated under KA and pilocarpine model, may display its anti-convulsant activity *via* multiple mechanisms. In contrast, piperine exhibited anti-convulsant activity with mechanisms similar to phenytoin (sodium channel antagonist) [44]. Hence, among the common fruits included in this review, naringenin, which is found in citrus fruits, and piperine, which is found in pepper plants, were the most promising therapeutic candidates for future clinical studies in humans for epilepsy.

3.2. Local Fruits with Anti-convulsant Effects

Altogether, there were 20 types of local fruits, extracts and phytochemicals, identified as possessing anti-convulsant properties (Table **2**) [46-65]. Local fruits are fruits that are easily available and locally grown in specific countries, with limited distribution in the rest of the world.

The phytochemical chrysin is a flavonoid found in many vegetables, fruits, and even mushrooms. Chrysin, in general, was reported to have multiple beneficial effects on the nervous system such as neuroprotective and neurotrophic effects, anti-neuroinflammation, anti-amyloidogenic, as well as potential anti-depression and anti-epileptic properties, as reviewed by Nabavi *et al.* (2015) [45]. In a more recent study, chrysin isolated from Himalayan pear (*Pyrus pashia*), a fruit regional to the Himalayans, evidently portrayed anti-convulsant activity, which had a similar therapeutic profile as diazepam in terms of delaying the onset of convulsions in the PTZ-induced model [46]. Chrysin was deemed to be safe due to the lack of sedative effects, which indicates the involvement of α2/α3 subunits of GABAA receptor in the anti-convulsant effect [46].

Garcinol, an anti-oxidant found in kokum (*Garcinia indica*) fruit which is native to India and South East Asia, was also reported to have anti-convulsant effect witnessed by reducing seizure scores and mortality rates [47]. It was suggested that garcinol's anti-convulsant activity was due to the downregulation of brain-derived neurotrophic factor (BDNF) signaling, which in turn inhibits the GABAergic neurotransmission. Besides that, garcinol also causes an upregulation of glutamic acid decarboxylase 65 (GAD65) and GABAA, which leads to glutamate/GABA neurotransmission balance restoration, thereby attenuating seizures. Moreover, garcinol also reduces the expression of caspase-3 and apoptotic proteins, which is increased by the PTZ-induced convulsions, thus indicating the presence of neuroprotective properties *via* apoptosis suppression [47].

Table 2. List of local fruits identified to have anti-convulsant activity along with its major constituents and potential mechanism of action.

Fruit *Scientific Name*	Native Distribution	Major Active Constituent Studied (Dose and Route of Administration)	Animal Model (Animal Strain and Age)	Anti-Convulsant Activity	Mechanism of Action	Refs.
Himalayan pear *Pyrus pashia*	Himalayans, Pakistan, Vietnam, southern China, northern India	Ethanolic extract (100, 200 and 400 mg/kg, oral); Isolated Chrysin (2.5, 5.0 and 10.0 mg/kg, oral)	Maximal Electroshock and Pentylenetetrazol Model (Inbred Charles Foster albino male rate, 180-220g)	> Ethanolic extract of *P. pashia* significantly decreased seizure duration of both MES- and PTZ-induced seizures. > Isolated chrysin significantly reduced seizure duration, reduced LPO and protein oxidation, increase in SOD and catalase activity and protein sulfhydryl.	*EPP may have $GABA_A$ and NMDA activity, block voltage-dependent sodium channel, and modulatory effect on monoaminergic system. *Chrysin may bind to α_2/ α_3 $GABA_A$ receptor.	[46]
Cornelian cherry *Cornus mas*	Europe, Peru, Iran, Asia, Armenia, Turkey and Caucasus	Crude extract (2.5, 5.0, and 10.0 mg/kg, I.P)	Penicillin-induced Epileptiform Model (Male Wistar rats, 8-12 weeks old, 225-260g)	> Significantly lowered mean frequency of epileptiform activity but has no change on amplitude of epileptiform activity.	* Reduce lipid peroxidation *via* MDA.	[50]
Red mulberry *Morus rubra*	Japan, China and Korea	Crude extract (2.5, 5.0, 10.0 and 20.0 mg/kg, I.P)	Penicillin-induced Epileptiform Model (Male Wistar rats, 8-12 weeks old, 225-260g)	> Significantly lowered mean frequency of epileptiform activity but has no change on amplitude of epileptiform activity.	* Reduce lipid peroxidation *via* reducing MDA levels.	[50]
Kokum *Garcinia indica*	India and South East Asia	Garcinol (50, 100 and 200 mg/kg, I.P)	Pentylenetetrazol Model (C57BL/6 mice, 4-6 weeks old, 20±2 g)	> Significantly reduced mortality rates and seizure scores. > Reduce neuronal cell loss.	* Prevent increase of apoptotic proteins and caspase-3. * Inhibit BDNF and TrkB expression.	[47]
Alsace harts wort *Peucedanum alsaticum*	Europe, Asia and Africa	Lucidafurano-coumarin A (10, 12, 14 and 16 µM)	Pentylenetetrazol Model (Zebrafish larvae (*Danio rerio*), AB strain	> Significant reduce average movement of zebrafish using locomotion evaluation.	*Unknown; May involve GABAergic system * Inhibition of BChE.	[48]
West African black pepper *Piper guineense*	African tropical forest	Essential oil, B-sesquiphellandrene (50, 100 and 200 mg/kg, I.P)	Pentylenetetrazol Model (Adult male and female albino mice, VOM strain, 18-25 g)	> Provide 100% protection against PTZ-induced convulsion (similar to diazepam).	* Possibly by inhibition of dopamine neurotransmission at D1/D2 receptor or enhancement of GABA neurotransmission at $GABA_A$-benzodiazepine receptor pathway or inhibition of dopamine neurotransmission at D1/D2 receptor.	[51]
Pepperfruit *Dennettia tripetala*	Tropical rain forest of West-African countries	Essential oil. 1-nitro-2-phenylethane (25, 50, 100 and 200 mg/kg, I.P)	Pentylenetetrazol and Strychnine Model (Male and female white albino mice, 20-30 g)	> 100% protection against PTZ-induced convulsions > Significant protection against strychnine-induced convulsions but less effective compared to PTZ-induced convulsions.	* Enhancement of $GABA_A$-BDZ receptor complex.	[52]
Sticky nightshade *Solanum sisymbriifolium*	South America and India	Solasodine (25, 50 and 100 mg/kg, I.P)	Pentylenetetrazol, Maximal Electroshock and Picrotoxin Model (Male and female Wister albino rats, age 4 months, 250-300 g)	> Reduce the duration of HLTE and provided 100% protection on MES-induced convulsions. > Delay latency of HLTE phase in PCT-induced convulsions.	* Possibly by the inhibition of voltage-dependent sodium ion channels.	[53]

(Table 2) contd….

Fruit *Scientific Name*	**Native Distribution**	**Major Active Constituent Studied (Dose and Route of Administration)**	**Animal Model (Animal Strain and Age)**	**Anti-Convulsant Activity**	**Mechanism of Action**	**Refs.**
Date palm *Phoenix dactylifera*	Middle East and North Africa	Hydroalcoholic crude extract (1000 mg/kg, oral)	Pentylenetetrazol Model (Male albino mice, 20-30g)	> Delay onset of PTZ- and MES-induced convulsions. > Reduce myoclonic convulsions strength. > Reduce lipid peroxidation.	* Possibly by enhancing the GABA levels in the brain. * Increase SOD and GPx levels. * Decrease MDA levels.	[54]
Black myrobalan *Terminalia chebula*	Middle East, China, India and Thailand	Hydroalcoholic crude extract (250, 500 and 1000 mg/kg, oral)	Pentylenetetrazol and Maximal electroshock Model (Male Wister rats, 200-225 g)	> Combination of extract with valproate and phenytoin was shown to have 100% protection against PTZ- and MES-induced seizures, respectively. > Produced anti-oxidant effect.	* Unknown; For anti-oxidant effect, extract alone and co-administration of extract and valproate significantly increase GSH levels and reduced MDA levels in PTZ- and MES-induced seizures.	[55]
Hawthorn *Crataegus oxyacantha*	Europe, Asia and North America	Ethanolic crude extract (50 mg/kg/day)	Penicillin-induced Epilepsy Model (Male Mongolian gerbils, 100-140 g)	> Fruit extract alone was able to delay the onset of first penicillin-induced epileptic activity as well as reduced spike frequency and amplitude of penicillin-induced epileptic activity. > Combination of exercise and extract administration was able to further delay the onset of first epileptic activity but was not able to reduce the spike frequency and amplitude of epileptic activity.	* Unknown.	[56]
Soap nut *Sapindus emerginatus*	India, Myanmar, Pakistan and Sri Lanka	Methanol crude extract (200 and 400 mg/kg, oral)	Pentylenetetrazol Model (Male albino Wistar rats, 180-220 g)	> Delayed onset and reduced duration of PTZ-induced seizures.	* Possibly by enhancing GABA-mediated inhibition, Inhibition of calcium ion currents and/or NMDA mediated glutamatergic neurotransmission. * Significantly increase GABA content. * Able to restore NA, DA and serotonin levels.	[57]
Lotus bulb *Nelumbo nucifera*	India, Pakistan, China, Thailand and Australia	Ethanolic crude extract (50, 100 and 200 mg/kg, oral)	Strychnine Model (Male Wister rats, no age and weight mentioned)	> Delayed onset of strychnine-induced convulsions. > Reduced intensity of convulsions and increased survival.	* Unknown.	[58]
Blue passion flower *Passiflora caerulea*	Argentina, Bolivia, Brazil, Chile, Uruguay and Paraguay	Aqueous crude extract, naringenin, hesperidin (100 and 200 mg/kg, oral)	Pilocarpine Model (Male Swiss albino mice, 23-25 g)	> Delayed onset of pilocarpine-induced seizure. > Reduced duration of clonic seizure.	* Significantly increased SOD, CAT and GSH levels. * Restored TBARS levels. * Reduced NO levels.	[59]
Garlic passion fruit *Passiflora tenuifila*	Brazil, Bolivia, Argentina, Chile, Uruguay and Paraguay	Crude extract (200 and 400 mg/kg, oral)	Pentylenetetrazol Model (Swiss mice, no age and weight mentioned)	> Significantly increase seizure and death latency. > Preventing death induced by PTZ.	* Unknown.	[60]
Japanese persimmon *Diospyros kaki*	China, Japan and Korea	Ethanolic crude extract (20 mg/kg, oral)	Penicillin-induced Epileptiform Model (Male Mongolian gerbils, 10 weeks old, 41±7 g)	> Fruit extract alone and combination of fruit extract and exercise significantly reduced spike frequency of penicillin-G-induced epileptiform.	* Unknown.	[61]

(Table 2) contd….

Fruit *Scientific Name*	**Native Distribution**	**Major Active Constituent Studied (Dose and Route of Administration)**	**Animal Model (Animal Strain and Age)**	**Anti-Convulsant Activity**	**Mechanism of Action**	**Refs.**
Wild colocynth *Adenopus breviflorus*	West African countries, predominantly Nigeria	Ethanolic crude extract (250, 500, 1000 and 2000 mg/kg, oral)	Pentylenetetrazol, Picrotoxin and Strychnine Model (Adult male albino mice, 20-25 g)	> Delayed onset of PTZ-, picrotoxin- and strychnine-induced convulsions and death time but has 100% mortality rate at all doses.	* Possibly by enhancing chloride ion flux through chloride ion channels at $GABA_A$ receptor which leads to enhanced GABAergic neurotransmission.	[62]
Amla *Emblica officinalis*	India and Middle East	Hydroalcoholic crude extract (300, 500 and 700 mg/kg, I.P)	Kainic Acid Model (Male Wistar rats, 150-200 g)	> Significantly increased latency of KA-induced convulsion. > Reduced oxidative stress.	* Significantly reduced TBARS levels. * Increased GSH levels. * Attenuated the elevation of TNF-α.	[63]
Longan *Dimocarpus Longan*	Southeast Asia, China, Taiwan, Thailand and Vietnam	Methanol fruit peel extract (1, 2 and 4 mg/kg, oral)	Kainic Acid Model (ICR male mice, 22-25 g and male Sprague-Dawley rats, 220-250 g)	> Reduced seizure severity score in KA-induced convulsions. > Attenuates neuronal cell death > Reduced electrical seizure activity. > Increased influx of chloride ions and prevent the increase in intracellular calcium ions.	* Possibly by blocking glutamate, calcium ion and calcium ion dependent channels. * It also could be stimulation of GABAergic system by transmission of chloride ion by $GABA_A$ receptors to produce hyperpolarization .	[64]
Ankola *Alangium salvifolium*	Extensively cultivated in India	Ethanolic seed extract (250 and 500 mg/kg, oral)	Maximal Electroshock Model (Male or female Wistar rats, 150-200 g and Swiss albino mice, 25-40 g)	> Significantly inhibit MES-induced convulsions. > Delayed onset of MES-induced seizure.	* Unknown.	[65]

Note: I.P: intraperitoneal injection; KA: kainic acid; SOD: superoxide-dismutase; CAT: catalase; PTZ: pentylenetetrazol; GABA: gamma-aminobutyric acid; BChE: butyrylcholinesterase; MDA: malondialdehyde; GSH: glutathione; MES: maximal electroshock seizure; NMDA: N-Methyl-D-aspartate; LPO: lipid peroxidation; TNF-α: tumor necrosis factor alpha; GPx: glutathione peroxidase; BDNF: brain-derived neurotrophic factor; TrkB: tropomyosin receptor kinase B; D1/D2: dopamine receptor; BDZ: benzodiazepine; HLTE: hind limb tonic extensor; DA: nopamine; NA: noradrenaline; TBARS: thiobarbituric acid reactive substances; NO: nitric oxide.

Lucidafurano-coumarin-A can be extracted from Alsace hartswort (*Peucedanum alsaticum*), which is a fruit native in Europe, Asia, and Africa. This phytochemical showed significant anti-convulsant activity by reducing the average movement of zebrafish larvae *via* the modulation of GABA activity, particularly through the interaction with GABAA subunits.

Similarly, the essential oil extracted from West African black pepper (*Piper guineense*) was also reported to exhibit anti-convulsant activity along with many other beneficial neurological effects. The essential oil provided 100% protection against PTZ-induced convulsions similar to diazepam, which may follow a similar mechanism of action, possibly through the enhancement of GABA neurotransmission at the GABAA-benzodiazepine receptor complex [51]. B-sesquiphellandrene was found to be the most abundant (20.9%) phytochemical in the *P.guineense* essential oil, but literature on its biological activity may be highly lacking. Another compound, linadol, which has a much lesser relative abundance (6.1%) in the essential oil, was reported to be the main compound driving the anti-convulsant activity [66]. Thus, this may explain the need for a higher dosage of the essential oil in order for the anti-convulsant effect to be noticed. In addition, this essential oil may also be a muscle relaxant and/or a sedative at the same dosage. Therefore these unwanted side effects should be taken into account before recommending this essential oil for epilepsy [51].

Another anti-convulsant fruit that is also found within the African region is the pepper fruit (*Dennettia tripetala*). This fruit was reported to have an abundance of 1-nitro-2-phenylethane (BPNE), which was shown to provide 100% protection against PTZ-induced convulsions even at low doses. The anti-convulsant activity was also significant against strychnine-induced seizures, but it was not as effective when compared to the PTZ model [52]. This difference in effectivity may be explained by the BPNE mechanism of action of enhancing the GABAA- benzodiazepine (BDZ) receptor activation [52]. The PTZ model mainly involves the disinhibition of the GABA neurotransmission and the activation of the NMDA receptor, while the strychnine model specifically inhibits the glycine receptors and the motor neuron feedback [67]. Thus, BPNE's action on GABA may result in its higher effectivity in the PTZ model.

Solasodine, an alkaloid isolated from sticky nightshade fruit (*Solanum sisymbriifolium*) that is native to South America, was reported to significantly delay the latency of hind limb tonic extensor (HLTE) phase as well as reduce its duration in picrotoxin (PCT)-induced convulsions, in a dose-dependent manner [53]. This alkaloid also provided 100% protection against MES-induced convulsions. It was suggested that the anti-convulsant activity of solasodine may be exhibited through the inhibition of voltage-dependent sodium ion channels or through the enhancement of the GA-

BAergic neurotransmission [53], suggesting multiple therapeutic pathways.

The fruit of date palm (*Pheonix dactylifera*) is a medicinal plant native to the Middle East and North Africa. Crude extract from this fruit was found to delay the onset of both PTZ- and MES-induced convulsions, suggesting the possession of an effective anti-convulsant property [54]. The hydroalcoholic extract of *P. dactylifera* was also reported to exhibit significant anti-oxidant properties. Both these properties may be elicited *via* the increment in GABA, SOD, and glutathione peroxidase (GPx) levels, as well as the decrement in MDA levels [54].

The hydroalcoholic crude extract of black myrobalan (*Terminalia chebula*) was reported to have a significant anti-convulsant effect as seen by its 83.33% and 66.66% protection against MES- and PTZ-induced convulsion, respectively [68]. The extract was also able to potentiate sub-therapeutic doses of phenytoin and valproate when co-administered with the extract, providing complete protection against PTZ- and MES-induced convulsions. In addition, the extract also exhibited an anti-oxidant effect by reducing the MDA levels and increasing the GSH levels in PTZ- and MES-induced convulsions [68]. Therefore, this extract may be highly efficient in providing a therapeutic effect against epilepsy.

A study by Tubaş *et al.* (2017) evaluated the anti-convulsant activity of crude extracts from both cornelian cherry (*Cornus mas*) and red mulberry (*Morus rubra*) [50]. They reported that both the extracts exhibited anti-convulsant activity by reducing the spike frequency of penicillin-induced epileptiform *via* reducing the MDA levels. It was also reported that the reduction of MDA by cornelian cherry was greater than red mulberry [50], indicating that cornelian cherry is more efficient in reducing lipid peroxidation and might be more neuroprotective against epilepsy.

Hawthorn (*Crataegus oxyacantha*), a plant native to the northern parts of Asia, Europe, and America, was reported to delay the onset of the first convulsion as well as reduce the spike frequency and amplitude of penicillin-induced epileptic activity [69]. Combination of exercise and extract administration was able to delay the onset of first epileptic activity even further, but it was not able to reduce the spike frequency and amplitude of the epileptic activity, suggesting a possible interference caused by exercise. Unfortunately, the anti-convulsant mechanism was not adequately explored in the study, but it was suggested that it could be due to the high anti-oxidant activity of hawthorn [69].

One study used penicillin-induced epileptiform to evaluate the anti-convulsant activity of Japanese persimmon (*Diospyrus kaki*), which are locally grown in China, Japan and Korea. The ethanolic crude extract of the fruit significantly reduced spike frequency of penicillin-G-induced epileptiform when combined with exercise [61], suggesting that this extract may be better suited for epileptic patients with an active lifestyle compared to extract from hawthorn. However, similar to the extract from hawthorn, the mechanism of action of the *D.kaki* was also not further explored. However, it was suggested that the phytochemicals such as proanthocyanidins, phenolic acid, catechin, and tannin may have contributed to the anti-convulsant activity of extract due to its anti-oxidant properties [61, 70, 71].

Soap nut (*Sapindus emerginatus*), a fruit native to East Asia, was reported to display its anti-convulsant activity by delaying the onset and duration of PTZ-induced convulsions [57]. Possible mechanisms of action may include the enhancement of GABA-mediated inhibition, inhibition of the calcium ion currents, and/or inhibition of the NMDA-mediated glutamatergic neurotransmission. Moreover, the extract of the soap nut was also able to restore the levels of dopamine, noradrenaline, and serotonin, which were reduced by PTZ [57]. This suggests that reduced levels of monoamines may cause an increase in susceptibility to seizures [72].

Lotus bulbs (*Nelumbo nucifera*) is a fruit native in Asia's tropical regions and Australia. The ethanolic crude extract of the lotus bulb was reported to delay the onset of convulsions, reduced the intensity of the seizures, and increased the survival-ability in the strychnine-induced model [58]. The survival rate of the extract (42.85%) was noteworthy as it was similar to diazepam (57.14%) and thus may follow a similar mechanism of action. It was suggested that the anti-convulsant activity of the extract was due to the rich content of alkaloids, flavonoids, terpenoids, and saponins as individually, these compounds were shown to have anti-convulsant properties [58, 73].

The fruit of blue passion flower (*Passiflora caerulea*), a plant native in South America, was also reported to have anti-convulsant activity by delaying the onset of convulsion, reduced the duration of seizures, and increased the survival in the pilocarpine-induced model in a dose-dependent manner [59]. The extract has also exhibited anti-oxidant activity by reducing the nitric oxide and TBARS levels and increasing the SOD, CAT, and GSH levels [59], which may contribute to its neuroprotective and anti-convulsant properties. The extract was also found to have compounds such as naringenin and hesperidin, which also have anti-convulsant activity. These compounds may also contribute to the anti-convulsant effect.

Another fruit from the *Passilora* genus is the garlic passion fruit (*Passilora tenuifila*), which is also native to South America. Its anti-convulsant activity was seen by the significant increase in seizure and death latency [60]. The highest dose of the crude extract at 400 mg/kg managed to prevent any mortality caused by PTZ. The crude extract also exhibited sedative activity but did not exhibit any muscle relaxant activity [60], suggesting caution should be taken prior to its recommendation to epileptic patients.

Wild colocynth (*Adenopus breviflorus*) is a plant native to West African countries. The ethanolic crude extract of the wild colocynth fruit was able to delay the onset of PTZ-, picrotoxin- and strychnine-induced convulsions. However, the extract did not manage to protect the mice from any of the drug-induced convulsions at any doses, which led to a 100% mortality [62]. It was suggested that the extract exhibited its anti-convulsant activity by enhancing the chloride ion flux through the chloride ion channels at the GABAA receptor [62], thus leading to enhanced GABAergic neurotransmission.

The Amla (*Emblica officinalis*) fruit, which is a native fruit in India and the Middle East, was found to increase the latency of KA-induced convulsions by reducing the TBARS levels and increasing the GSH levels while preventing the increase of TNF-α levels [63]. This suggests that the extract of Amla may also exhibit neuroprotective effects through the anti-inflammatory and anti-oxidant activity.

The methanol fruit peel extract of longan (*Dimocarpus logan*), a fruit widely grown in Southeast Asia, was reported to reduce the severity of seizures induced by KA, attenuate neuronal cell death, reduce electrical seizure activity in EEG, increase the influx of chloride ions and prevent the increase of intracellular calcium ions [64]. The extract may have also exhibited its anti-convulsant activity by blocking the glutamate and calcium ion, as well as by stimulating the GABAergic system through the transmission of chloride ions at the GABAA receptors [64].

The ethanolic seed extract of ankola (*Alangium salvifolium*), a fruit extensively cultivated in India, has significantly delayed and inhibited the onset of MES-induced convulsions in a dose-dependent manner [65]. The highest dose, 500 mg/kg, was able to provide 80.30% inhibition towards MES-induced convulsions, which is similar to that of diazepam with 83.01% [65]. The highest dose also delayed the onset of seizure with similar efficacy as diazepam, suggesting the potential of this extract as an anti-convulsant for epileptic patients. However, the mechanism of action was not adequately explored and may need further studies before recommending it for clinical use. Although, it may be noteworthy to know that the extract also exhibited anti-inflammatory activity, which may prevent acquired epilepsy.

Among the local fruits included in this review, the black myrobalan and the pepperfruit may be the most promising therapeutic candidates against epilepsy. The black myrobalan was able to potentiate the sub-therapeutic doses of anti-convulsant drugs, thereby increasing their effectiveness. In contrast, the pepperfruit displayed protection against PTZ-induced convulsions *via* the enhancement of $GABA_A$-BDZ receptor complex, a binding site of diazepam [74]. Therefore, this suggests that these fruits may be added into the epilepsy therapy regime, pending further studies.

3.3. Rare Fruits with Anti-convulsant Effects

Table **3** describes anti-convulsant properties exhibited by the crude extract and fruit juices extracted from rare fruits. Rare fruits are fruits that are not easily available and may be exclusively present in specific regions only due to unique preferences in weather and soil for growth.

Noni (*Morinda citrifolia*), a fruit plant found mainly in the Pacific, is commonly used as traditional medicine by societies living on the Pacific islands. The methanol crude extract of the fruit was seen to reduce the duration of MES-induced convulsions as well as reduce the recovery duration in animals in a dose-dependent manner [75]. It was believed that the extract inhibited monoamine oxidase (MAO), which led to regulation of brain monoamine levels, such as serotonin, dopamine, and noradrenaline. This is because the MAO enzyme is responsible for the breakdown of biogenic amines [76]. Similarly, prostaglandin inhibition also was shown to regulate the brain monoamine levels [75]. This restoration of certain brain monoamine levels may reduce seizures and modulate the seizure threshold [72].

Bitter apple (*Citrullus colocynthis*) is a fruit found only in the desert areas and is widely used as an Iranian traditional medicine. The hydroalcoholic extract of bitter apple fruit had delayed the onset of PTZ-induced convulsions in a dose-dependent manner (10, 25, and 50 mg/kg) but was ineffective at high doses of 100 mg/kg [77], suggesting a threshold on the therapeutic effect. Flumazenil was able to block the anti-convulsant activity of bitter apple extract, which suggests the mechanism of action of the extract may involve the GABA pathway, with some relation to the opioid receptors and benzodiazepine receptor activation [77].

Açaí is a fruit commonly found in the Amazon floodplains. The juice of Açaí fruit was reported to increase the latency to first generalized tonic-clonic seizure and its duration, as well as has shown to prevent the electrocortical alterations induced by PTZ by significantly reducing its amplitude and frequency [78]. In addition, another study on Açaí juice showed significant improvements in GABAergic neurotransmission caused by positive modulation of the benzodiazepine site and negative modulation of the picrotoxinin site [79]. These modulations may inhibit the exacerbation of the excitatory activity, as seen in antiseizure drugs [83]. The juice was also shown to inhibit GABA reuptake [79], which suggests that the juice was able to inhibit GABA transporters and promote GABA neurotransmission, thereby enhancing the inhibitory neurotransmission.

Among the rare fruits included in this review, Açaí juice may be the most promising candidate for epilepsy clinical trials, as the juice displayed an anti-convulsant activity as well as prevented lipid peroxidation. In addition, its mechanism of action in enhancing the inhibitory neurotransmission through the inhibition of GABA transporters may also support its possible therapeutic potential for epileptic patients.

3.4. Fruit with Pro-convulsant Effects

Interestingly, there was only one fruit that may elicit pro-convulsant effects and should not be recommended to epileptic patients or patients with renal failure (Table **4**). The extracts and phytochemicals from this fruit should, however, be studied in order to understand the pathological mechanism of the pro-convulsant molecules.

Multiple case reports have stated that star fruit (*Averrhoa carambola*) induces seizures when ingested by individuals with a pre-dialyzed stage of chronic renal failure [84-86]. A recent mini-review by Yasawardene *et al.* (2020) explored the possible mechanisms of neurotoxicity and nephrotoxicity induced by star fruit, which was attributed to a rich source of oxalate and caramboxin [87]. It was believed that patients with renal failure were unable to remove oxalate efficiently, leading to neurotoxicity and oxaleamia, as also demonstrated by Fang *et al.* (2007) with nephrectomised rats [81]. On the other hand, Garcia−Cairasco *et al.* (2013) believed that caramboxin, which has a similar structure with PTZ, may activate the NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/Kainate receptors [80], thereby causing hyperexcitability. The neuro-excitatory properties of caramboxin may also lead to the imbalance of excitatory/inhibitory neurotransmission, thus leading to

Table 3. List of rare fruits identified to have anti-convulsant activity along with its major constituents and potential mechanism of action.

Fruit *Scientific Name*	Native Distribution	Major Active Constituent Studied (Dose and Route of Administration)	Animal Model (Animal Strain and Age)	Anti-Convulsant Activity	Mechanism of Action	Refs.
Noni *Morinda Citrifolia*	Pacific Islands	Methanol crude extract (200 and 400 mg/kg, oral)	Maximal Electroshock Model (Male and Female Wistar albino rats, 200-250 g)	> Significantly reduced duration of various phases of MES-induced epileptic seizure. > Significantly increase noradrenaline, serotonin and dopamine levels in brain.	* Possibly by inhibition of monoamine oxidase and prostaglandin synthesis. * Reduce influx of calcium ions.	[75]
Bitter apple *Citrullus colocynthis*	Desert areas of the world	Hydroalcoholic crude extract (10, 25, 50 and 100 mg/kg, I.P)	Pentylenetetrazol Model (Male albino mice, 25-30 g)	> Delay onset and reduced the duration of PTZ-induced seizure.	* Possible involvement of GABA pathway, with relation to opioid receptor and benzodiazepine receptor activation.	[77]
*A*çaí *Euterpe oleracea*	Eastern Amazonian floodplains	Fruit juice (10 µL/g body weight) (1%, 5%, 10% and 25%)	Pentylenetetrazol Model (Male Swiss mice, 23-35 g)	> Significantly increased latency of both first generalized tonic-clonic seizure and first myoclonic jerk, decease duration of seizure induced by PTZ. > Prevented electrocortical alterations. > Prevent lipid peroxidation completely.	* Not explored.	[78]
			Primary cultures of neocortical neurons from 16-day-old NMRI mouse embryo	> Not explored (referred to previous study (78)).	* Enhance GABAergic inhibitory neurotransmission by blocking GABA transporters.	[79]

Note: I.P: intraperitoneal injection; PTZ: pentylenetetrazol; GABA: gamma-aminobutyric acid; MES: maximal electroshock seizure.

Table 4. List of fruits identified to have pro-convulsant activity along with its major constituents and potential mechanism of action.

Fruit *Scientific Name*	Native Distribution	Major Active Constituent Studied (Dose and Route of Administration)	Animal Model (Animal Strain and Age)	Pro-Convulsant Activity	Mechanism of Action	Refs.
Star fruit *Averrhoa carambola*	Malesia, Southeast Asia	Crude extract, (Homogenized in distilled water 4:1 (w/v); 5ml *via* intragastric catheter) (1.0 µL *via* cortical injection)	Electroencephalogram Epileptiform Model (Wistar rats, 159±1.45g)	> Animals displayed class 4 limbic seizures based on the Racine's scale. > Limbic seizures, generalized seizures and ataxic posture observed in cortical injection. > Seizure effects attenuated by diazepam treatment.	* Caramboxin has a similar structure with PTZ. * May activate NMDA and AMPA/Kainate receptors.	[80]
		Star fruit juice, (1.5 mL/100 g *via* a metal oral-gastric tube)	Nephrectomized Model (Sprague-Dawley rats, 8-10 weeks)	> Status epilepticus observed in nephrectomized animals given star fruit juice. > Oxalate and star fruit juice caused seizures and 50% mortality in nephrectomized animals but not in sham animals. > Inactivated star fruit juice showed no effect on nephrectomized animals.	* Oxalate in the juice specifically inhibits GABA binding in the central nervous system.	[81]

Note: PTZ: pentylenetetrazol; GABA: gamma-aminobutyric acid; NMDA: N-Methyl-D-aspartate; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

seizures. As caramboxin is excreted through the kidneys (80), the increased toxicity of caramboxin due to reduced excretion may explain the increased frequency of its neurotoxicity in renal impairment patients. The literature on pro-convulsant fruits may be lacking, as only star fruit has been identified as a pro-convulsant fruit thus far. Even though the pro-convulsant compounds of star fruit have been identified in previous studies, efforts into counteracting their effects have yet to be performed. Moreover, future studies on the absorption, metabolism and excretion of those compounds in humans should also be further explored.

CONCLUSION

This systematic review critically summarized and elucidated the anti-convulsant and pro-convulsant properties displayed by fruits across the world. Crude extracts and phytochemicals from fruits have significantly proven to reduce or dampen seizure activities across various preclinical seizure models. The majority of the extracts and phytochemicals displayed their anti-convulsant activity *via* the potentiation of the inhibitory neurotransmission (GABA) and the blocking of the excitatory neurotransmission (glutamate, calcium influx). Most of the fruits also displayed significant anti-oxidant and anti-inflammatory properties, which may help prevent epileptogenesis caused by environmental factors such as trauma and infection. There was only one fruit that was identified as a pro-convulsant in this review, which was attributed to its rich source of oxalate and caramboxin. This review hopes to provide patients, caregivers, and healthcare providers a reference on the fruits to be avoided or encouraged for epilepsy patients regardless of drug-resistant status. However, the studies reviewed were mainly based on preclinical animal models. Thus, further clinical trials may be needed to validate these effects on humans, especially to determine if dietary intake is sufficient for seizure suppression and improvement in the quality of life of epileptic patients.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines and methodologies have been followed in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

PRISMA checklist is available on the publisher's website along with the published article.

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