

Review

Treating Epilepsy with Natural Products: Nonsense or Possibility?

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Abstract: Epilepsy is a neurological disease characterized by recurrent seizures that can lead to uncontrollable muscle twitching, changes in sensitivity to sensory perceptions, and disorders of consciousness. Although modern medicine has effective antiepileptic drugs, the need for accessible and cost-effective medication is urgent, and products derived from plants could offer a solution. For this review, we have focused on natural compounds that have shown anticonvulsant activity in *in vivo* models of epilepsy at relevant doses. In some cases, the effects have been confirmed by clinical data. The results of our search are summarized in tables according to their molecular targets. We have critically evaluated the data we present, identified the most promising therapeutic candidates, and discussed these in the text. Their perspectives are supported by both pharmacokinetic properties and potential interactions. This review is intended to serve as a basis for future research into epilepsy and related disorders.

Keywords: epilepsy; anticonvulsant; natural products; GABA; AMPA; NMDA



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1. Introduction

Epilepsy, one of the most common neurological diseases, affects over 70 million people worldwide [1]. The International League Against Epilepsy (ILAE) offers the following practical clinical definition of epilepsy: (1) at least two unprovoked (or reflex) seizures occurring more than 24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and (3) the diagnosis of an epilepsy syndrome [2]. Recurrent seizures significantly worsen quality of life and contribute to epilepsy-related causes of death, such as sudden unexpected death in epilepsy (SUDEP), status epilepticus, accident, drowning, or suicide [1,3]. Although relatively effective pharmacotherapy is currently available, treatment with antiseizure medications is frequently associated with side effects like drowsiness, headaches, or uncontrollable shaking. Furthermore, in some cases, even appropriately chosen antiseizure drugs do not control seizures. This drug-resistant epilepsy is currently treated using surgery or neurostimulatory intervention [1]. It is worth mentioning that mortality caused by epilepsy is generally higher in low-income countries than in high-income countries, probably due to a lack of access to medical facilities and therapy, including antiepileptic drugs (AEDs) [4]. The affordability of AEDs is also a burning question due to the fact that total epilepsy costs were estimated to be USD 119.27 billion per year in 2019 [5]. With populations growing rapidly, especially in developing countries, the search for cost-effective and accessible medicines is like that for the Holy Grail. Additionally, exactly here, plant-derived products could be of priceless assistance as they may offer multiple mechanisms of action, thus overcoming resistance and giving fewer side effects. In addition, they could also be used in combination with conventional drugs to

increase their effectiveness. Numerous scientific reports have described the potent anticonvulsant activity of plant extracts and the essential oils of various plants in different animal models of seizures and epilepsy. Unfortunately, a purified form of cannabidiol (CBD, Epidiolex/Epidyolex; >99% CBD) used to treat two rare epilepsies, Lennox–Gastaut syndrome and Dravet syndrome, is the only plant-derived product approved for medical use [6], although many other natural compounds exert significant anticonvulsant activity in vivo. This raises the question of why these active substances have not been further investigated. Can we find more effective anticonvulsants in the plant kingdom than those already used in clinical practice? Could we reduce the total cost of epilepsy using plant-derived products? Moreover, many phytoconstituents possess anti-inflammatory or neuroprotective activity that might also be beneficial. They could, potentially, be administered as adjuvants in the therapy of epilepsy. Although the antiepileptic activity of natural compounds has been reviewed several times from different points of view, we have focused more on the most perspective phytoconstituents to point out their pharmacokinetic properties and where it is possible, the structure–activity relationships of various groups of compounds are also mentioned. We have therefore summarized the characteristics of potent natural anticonvulsants in this review in order to arouse interest, consider their use in clinical trials, and evaluate their potential use in clinical practice.

2. Data Collection Process

This review results from an in-depth search for scientific papers containing the terms “epilepsy”, “antiepileptic”, “anticonvulsant”, “antiseizure”, and “seizure”, alone and subsequently also their combinations with the keywords “natural compounds”, “natural products”, “flavonoid”, “terpene”, “terpenoid”, “coumarin”, “phenolic”, or “alkaloid” using Boolean operator AND. The scientific databases Science Direct, Web of Science, and Google Scholar were used to collect scientific papers, as was the US database clinicaltrials.gov, which deals with ongoing clinical trials. Only pure and structurally characterized compounds have been included in this review. Plant extracts, essential oils, and mixtures of compounds were excluded as these were often not well-defined, and it is difficult to determine whether the components would be active alone or synergy plays a crucial role which hinders their potential standardization. We included in the text only compounds affecting molecular targets and excluded those possessing antioxidant and anti-inflammatory properties as this topic is large enough for a separate review. The anticonvulsant activity of many natural substances has been reported at doses too high to be applicable in clinical practice, and we therefore include only compounds reported to be active at doses equal to or lower than 100 mg/kg, which represents the application of a maximum of 7 g of a drug in an average 70 kg person.

3. Conventional Therapy

Modern pharmacotherapy of epilepsy is based on an individual-patient-oriented approach. The choice of AED is therefore based on the conditions of the individual patient, including demographic and physiological conditions, comorbidities, and psychosocial environment. Generally, monotherapy with the most appropriate drug is started. Polytherapy is initiated only after three drugs, tried individually, have failed. Naturally, AEDs with diverse mechanisms of action are usually combined in the hope of achieving possible synergistic effects [7].

AEDs have traditionally been categorized based on their mode of action and especially the frequency and seriousness of any adverse effects. The first-generation drugs affect mostly the voltage-gated Na⁺ channels and escalate GABAergic transmission. Modern AEDs exhibit distinct mechanisms of action directed to specific receptors or specific receptor subunits. These unique mechanisms eliminate most of the side effects that occurred with the older generation AEDs. Based on their mechanism of action, we can divide AEDs into three main groups: (1) AEDs that reduce the presynaptic excitability and release of neurotransmitters by affecting voltage-gated Na⁺ channels (e.g., carbamazepine, phenytoin)

and Ca^{2+} channels (e.g., gabapentin, pregabalin) and acting on presynaptic vesicular SV2A protein (e.g., levetiracetam, brivaracetam); (2) AEDs that potentiate GABAergic transmission by prolonging or increasing the frequency of opening of the chloride channel of the GABA_A receptor, or by inhibiting the degradation or transport of GABA from the synapse (e.g., clonazepam, phenobarbital, tiagabine, vigabatrin); and (3) AEDs that reduce the postsynaptic excitability by affecting AMPA or NMDA receptors (e.g., perampanel). Some AEDs have multiple mechanisms of action (e.g., valproate, lamotrigine, topiramate), and for others, the exact mode of action is not fully understood [8,9].

New drugs are emerging. Although none provide better anticonvulsant potency than conventional therapy, they usually have fewer side effects and better pharmacokinetic profiles. Older generation AEDs (e.g., phenobarbital, primidone, and benzodiazepines) are characterized by a sedative effect ranging from mild drowsiness or tiredness to profound lethargy; severe idiosyncratic reactions may sometimes occur (e.g., carbamazepine, phenytoin), whereas modern AEDs are often associated with adverse psychiatric effects (e.g., topiramate, vigabatrin, zonisamide) [10]. As can be seen, no AEDs without adverse effects are known to exist, and the hunt for new medications should therefore be directed towards natural products which do not frequently exert adverse effects.

Studies available to date suggest that natural products show mechanisms of action similar to those of clinically used drugs. Some may also have multiple effects, including neuroprotective and anti-inflammatory activity. This complex activity along with having fewer side effects and interactions represents the main advantage of natural anticonvulsant drugs.

4. Molecular Targets of Natural Products and Experimental Models of Epilepsy

As mentioned above, the therapy of epilepsy involves a complex approach, and various AEDs affect distinct molecular targets. The same is true for natural substances. Based on the selected experimental model and seizure-inducing agent, we can predict the target protein (Figure 1). Currently, several animal models have become well-established for evaluating the anticonvulsant activity of plant-derived compounds.

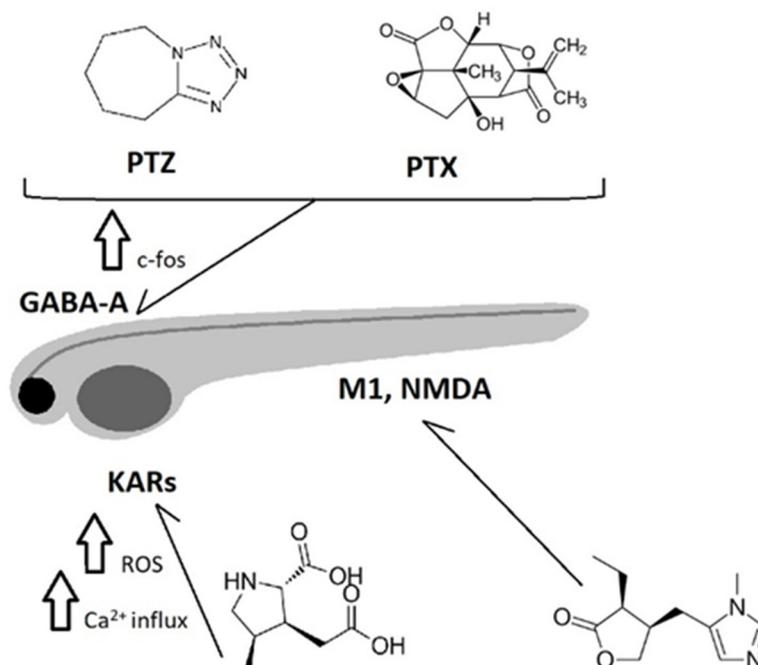


Figure 1. Seizure-inducing agents and proposed mechanisms of action. PTZ: pentylentetrazole; PTX: picrotoxin; GABA-A: γ -aminobutyric acid-A receptor; KARs: kainate receptors; M1: muscarinic receptor M1; NMDA: N-methyl-D-aspartate; ROS: reactive oxygen species; up arrow: increase.

Antiepileptic activity is tested primarily on mice and rats, where the inhibition of convulsions can be observed according to the seizure-inducing agent used. Neurons can also be removed from epileptic rodents and histopathological alterations studied *ex vivo*.

Several alternatives have been introduced into epilepsy research to replace mammalian models of seizures. The simplicity of the roundworm *Caenorhabditis elegans* enables it to serve as a basic model for understanding how genes specify the development of the nervous system. However, its small neural circuit limits comparison with humans [11,12]. Other non-mammalian models used in the study of epilepsy are *Xenopus laevis* oocytes and tadpoles. *Xenopus* oocytes represent a valuable tool to identify the types of ligand-gated ion channels present in different neuronal systems. Proteins can rapidly and easily be expressed and analyzed; thus, oocyte assays are predominantly used to identify GABA_A receptor subunits influenced by substances under study. However, the *Xenopus* oocytes model has disadvantages. Its membrane and intracellular organization differs from that of mammalian neurons and the optimum temperature (18–22 °C) maintained during the analysis of oocytes is approximately half the normal mammalian body temperature [12].

The zebrafish *Danio rerio* is currently widely recommended for testing neurobiological disorders because its genes are similar to human genes. Zebrafish have homologs for at least 85% of the recognized epilepsy genes found in humans. Furthermore, the larvae of zebrafish can develop rapidly *ex utero*, the fish are very fecund, and convulsant chemicals can easily be added directly into the water in which they swim. Together these features create a very powerful experimental model [11,12].

Seizures are commonly induced by various chemoconvulsants, but preliminary testing, performed by using the maximal electroshock (MES) test, has led to the discovery of many clinically effective AEDs. The MES test is a reasonable model of grand mal seizures (i.e., generalized tonic-clonic seizures) and was once considered to be nonselective with respect to molecular targets and mechanisms of action; however, nowadays, it is thought to be sensitive to drugs that block Na⁺ channels. In any case, because the MES test can produce false positive data, it is no longer recommended for any purpose [13]. Pentylentetrazole (PTZ), the chemoconvulsant most often used to induce acute seizures acts as a GABA_A antagonist. That the subcutaneous PTZ test is therefore most sensitive to GABA mimetic drugs limits its applicability because compounds with other mechanisms of action could be missed [14]. In addition to PTZ, other chemical GABA_A antagonists, such as picrotoxin (PTX) or bicuculline, possess the ability to induce absence-like seizures [12]. Kainic acid (a glutamate analog) and pilocarpine (a muscarinic agonist) are used as experimental models of status epilepticus or to produce chronic epilepsy with recurrent spontaneous seizures. Chronic models of epilepsy are used to predict clinical efficacy and adverse effects [15].

Aside from chemical models of epilepsy, genetic zebrafish models play an irreplaceable role in evaluating anticonvulsant activity. Genetic models are based on knocking out the genes responsible for an epilepsy-related disorder. Here, we briefly describe some of them. *Kcnj10a* is a model responsible for EAST syndrome (epilepsy, ataxia, sensorineural deafness, and renal tubulopathy), which causes seizures in infancy [16]. The *Scn1Lab* gene encodes the voltage-gated sodium channel Na_v1.1, the disruption of which causes Dravet syndrome [17]. *Stxbp1* (gene encoding syntaxin-binding protein 1) is a model for EIEE (early infantile epileptic encephalopathy), that is, childhood epilepsy. It plays a role in epilepsy and metabolic, physiological, and behavioral changes. Mutations of this protein are found in Dravet syndrome and Lennox–Gastaut syndrome [18]. *Gabra1* encodes GABA type A receptor subunit alpha 1. The knockdown of this gene revealed a reduced amount of GABA_A receptors in the brain, which causes epilepsy in juvenile zebrafish, and probably not only causes an imbalance between neuronal inhibition and excitation but also disrupts early development of the brain [19]. *Stx1b*—mutations in this gene cause epilepsy syndromes associated with fever. These seizures manifest ranging from febrile seizures to severe epileptiform encephalopathies. In zebrafish, it manifests as seizure-like behavior accompanied by epileptiform discharges resulting from hyperthermia [20].

Furthermore, an alteration in the expression of an epilepsy-related gene has also been observed when different methods of inducing convulsions were applied. Brain-derived neurotrophic factor (BDNF) plays an important role in epileptogenesis because its level is dramatically increased in both animal models and humans with epilepsy. The ability to regulate the neuronal morphology linked with neuroprotective effects is attributed to BDNF; it also reduces the excitability of neurons and prevents or slows seizures and seizure-induced neuronal damage. On the other hand, seizures induce the expression of BDNF, which then activates its receptor TrkB, and the consequent cascade can produce structural plasticities of the hippocampal dentate granule cells similar to those identified in the epileptic brain [21,22]. Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme for the synthesis of GABA. Its isoform GAD65 is related to epilepsy, and the family of these enzymes represents a promising target not only for potential antiepileptic drugs but also in the therapy of various autoimmune diseases [23,24]. The protooncogene *c-fos* is upregulated in response to such stress stimuli as seizures; therefore, natural compounds that reduce the expression of *c-fos* in experimental models are considered to be potential anticonvulsants [25]. In addition, many plant-derived products have been identified as neuroprotectants that can be used in the treatment of epilepsy. Examples, such as cytokines (TNF- α , IL-1 β , IL-6) or apoptotic proteins (Bax/Bcl-2), most often affect various signaling molecules linked to neurotoxicity and inflammation in the brain [26].

Modeling the different types of epilepsy that parallel human-type enabled the creation of a platform for the high-throughput screening of drugs that might be used to treat those epilepsies. Using this platform is not as complicated and time-consuming as would be the case for rodent models, so it might be perfect for generating new epilepsy models to choose drugs for further examination.

The small molecules isolated from plants have been summarized in Figure 2. They differ in their target structures, but all of them can influence the aforementioned proteins. We have therefore summarized the results of our search in tables that describe the mechanism of action according to the molecular target. The tables include the names of the compounds and their classification, the effective doses, animal models used, seizure-inducing agents, and proposed mechanisms of action. Natural anticonvulsants were administered as a treatment for several days (mentioned in tables in brackets). If this is not specified in the tables, each test substance was administered 10–90 min prior to the injection of the seizure-inducing agent. We describe in detail the interaction of phytoconstituents with voltage-gated ion channels (Table 1), GABA (Table 2), and AMPA and NMDA receptors (Table 3). Those natural products that affect diverse targets and thus relieve seizures are summarized in Table S1. Even more compounds exhibit anticonvulsant activity through mechanisms that are still unknown. These are identified in Table S2, but only those considered relevant receive mention in the text. Neuroprotective natural products are summarized in Table S3. We did not pay increased attention to the detailed description of neuroprotection in the text as this area has been reviewed extensively, e.g., by Brahmachari [26]. Furthermore, we discuss in the text only those natural compounds present in plants in significant amounts that could serve as a valuable source for effective isolation with considerable yields.

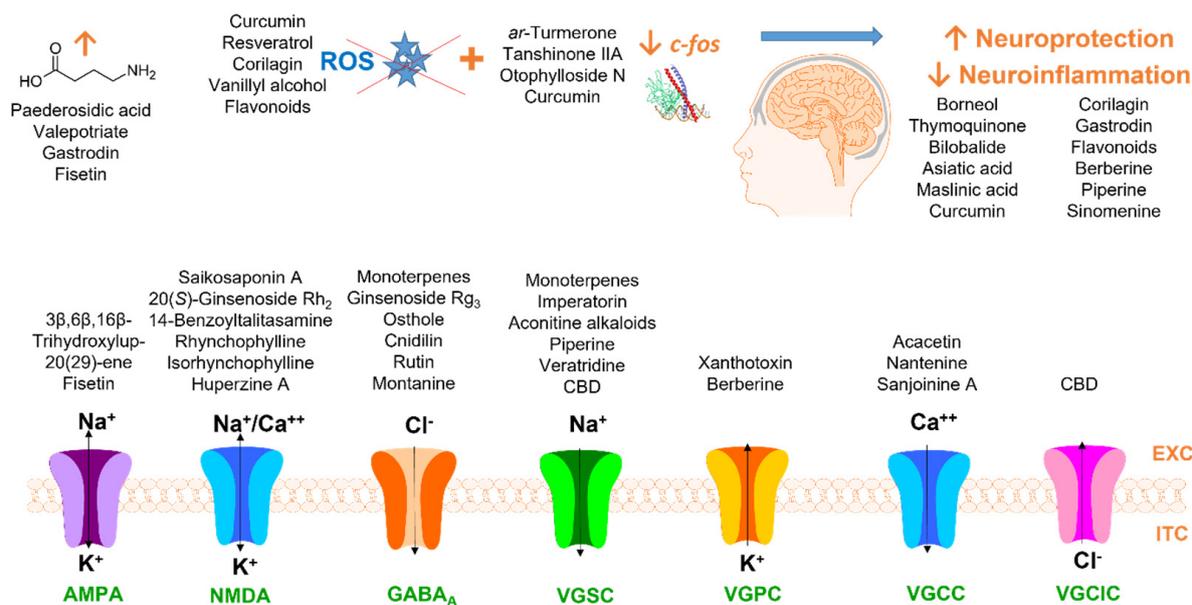


Figure 2. Natural products and their proposed targets of anticonvulsant activity. ROS: reactive oxygen species; CBD: cannabidiol; EXC: extracellular; ITC: intracellular; AMPA: α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid; NMDA: N-methyl-D-aspartate; GABA_A: γ -aminobutyric acid_A; VGSC: voltage-gated sodium channel; VGPC: voltage-gated potassium channel; VGCC: voltage-gated calcium channel; VGClC: voltage-gated chloride channel.

4.1. Natural Products That Affect Voltage-Gated Na⁺ and Ca²⁺ Channels

Voltage-gated sodium channels (VGSCs) initiate and conduct action potentials in excitable cells such as neurons or muscle cells, whereas voltage-gated calcium channels (VGCCs) are activated during action potentials, and they conduct the influx of Ca²⁺ into cells to initiate physiological processes, such as neurotransmission and muscle contraction [27]. Both channels represent molecular targets for drugs used in the treatment of epilepsy (see above).

Not many plant-derived compounds that affect VGSCs and VGCCs have been reported (Table 1). The effects of monoterpenes on various ion channels have been reviewed recently by Oz et al. [28], but most of the compounds mentioned exerted anticonvulsant effects only at doses too high to be implemented in clinical practice. Therefore, alkaloids and coumarins seem to have better prospects than monoterpenoids.

Several *Aconitum* alkaloids have been proven to interact with Na⁺ channels [29–34]. Unfortunately, these alkaloids have been isolated only from *Aconitum* species endemic to some regions of China. Furthermore, the isolation of these compounds is very tricky, with small yields. Because the total synthesis of aconitine-type alkaloids remains elusive, the prospects for *Aconitum* alkaloids are vague.

On the other hand, piperine, the major bioactive component in black pepper (*Piper nigrum*), significantly inhibited Na⁺ channel activity in mice [35]. Moreover, co-administration with carbamazepine (CBZ) or phenytoin decreased the elimination of these AEDs and enhanced their bioavailability [36]. The metabolism of piperine in the liver is limited, and its high blood–brain barrier permeability has been demonstrated in the Caco-2 monolayer model [37]. Its only limiting factor is poor solubility in water, and this can be improved, e.g., by a nanoprecipitation method leading to enhanced oral bioavailability and brain delivery of piperine after oral administration [38]. Altogether, piperine represents a very promising candidate for further evaluation in clinical trials, albeit with the caveat that increased attention must be paid to piperine-mediated drug interactions [39].

Similarly, the co-administration of coumarins significantly reduced the ED₅₀ values of AEDs in the MES test in mice, as observed for imperatorin (40 mg/kg, i.p.) in combination

with CBZ, phenobarbital, or phenytoin [40], and for xanthotoxin (50 and 100 mg/kg, i.p.) in combination with CBZ and valproate (VPA), respectively [41]. Additionally, xanthotoxin increased the total brain concentration of CBZ and VPA by about 84% and 46%, respectively, probably by inhibiting P-glycoprotein [41]. Therefore, co-administering natural compounds with conventional AEDs could be a way to increase the anticonvulsant activity of AEDs and thus improve the comfort of patients suffering from epilepsy.

Table 1. Natural products that affect VGSCs, VGCCs, or VGPCs.

| Compound | Effective Dose | Animal Model | Seizure-Inducing Agent | Mechanism | Source |
|--------------------------------------|---|--|---|---|--------|
| Paeoniflorin (monoterpene) | 100 mg/kg/day, p.o. (for 10 days) | Male immature Lewis rats | Hyperthermia | Suppression of $[Ca^{2+}]_i$ elevation via mGluR5 Possibly via positive modulation of GABA _A and voltage-dependent Na ⁺ channel blockade | [42] |
| Thymol (monoterpene) | 50 and 100 mg/kg, i.p. | Male Swiss mice Male Wistar rats | PTZ, MES, Strychnine, 4-AP | Inhibition of P-glycoprotein Inhibition of VGPC Modulation of calcium-dependent potassium channels Inhibition of glutamate release by decrease in voltage-dependent Ca ²⁺ entry | [43] |
| Iritectol G (triterpene) | 10 μM | Neocortical neurons of C57BL/6 mice | 4-AP | Interaction with inactivated state of VGSC | [44] |
| Imperatorin (coumarin) | 30–50 μM | NG108-15 cells | Voltage-clamp assay | Inhibition of VGSC | [45] |
| Xanthotoxin (coumarin) | 50 and 100 mg/kg, i.p. + CBZ 100 mg/kg, i.p. + VPA | Male Swiss mice | MES | Inhibition of P-glycoprotein Inhibition of VGPC Modulation of calcium-dependent potassium channels Inhibition of glutamate release by decrease in voltage-dependent Ca ²⁺ entry | [46] |
| Acacetin (flavonoid) | 10 and 50 mg/kg, i.p. | Male Sprague Dawley rats | KA | Inhibition of glutamate release by decrease in voltage-dependent Ca ²⁺ entry | [47] |
| Aconitine (alkaloid) | 1 μM | Hippocampal slices of male Wistar rats | Low Mg ²⁺ -ACSF | Modulation of Na ⁺ channels | [29] |
| 3-Acetylaconitine (alkaloid) | 0.01–1 μM | Hippocampal slices of male Wistar rats | Mg ²⁺ -free ACSF Bicuculline | Inactivation of Na ⁺ channels | [31] |
| Lappaconitine (alkaloid) | 1–100 μM | Hippocampal slices of male Wistar rats | Low Mg ²⁺ -ACSF Bicuculline | Blockade of Na ⁺ channels | [32] |
| N-desacetyl lappaconitine (alkaloid) | 1–100 μM | Hippocampal slices of male Wistar rats | Low Mg ²⁺ -ACSF Bicuculline | Blockade of Na ⁺ channels | [32] |
| 1-Benzoylnapelline (alkaloid) | 1–100 μM | Hippocampal slices of male Wistar rats | Low Mg ²⁺ -ACSF Bicuculline | Modulation of Na ⁺ channels | [33] |
| 6-Benzoylheteratisine (alkaloid) | 0.01–10 μM | Hippocampal slices of male Wistar rats | Bicuculline | Blockade of Na ⁺ channels | [34] |
| Nantenine (alkaloid) | 20–50 mg/kg, i.p. | Male albino mice | PTZ MES | Decrease in Ca ²⁺ -influx into the cell | [48] |
| Piperine (alkaloid) | 5, 10, and 20 mg/kg, i.p. | Male Swiss mice | PTZ, MES, NMDA, PTX, Bicuculline, BAYK-8644, Strychnine | Na ⁺ channel antagonist activity | [35] |
| Veratridine (alkaloid) | 1 μM | Hippocampal slices of male Wistar rats | Low Ca ²⁺ /high Mg ²⁺ -ACSF | Block of inactivation of Na ⁺ channels | [30] |

4.2. Natural Products That Affect the Gabaergic Transmission

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system (CNS). It is synthesized from glutamate by glutamic acid decarboxylase (GAD). GABA receptors can be divided into the ionotropic GABA_A receptors and the metabotropic GABA_B receptors. GABA_A receptors are ligand-gated ion channels that increase the flow of chloride ions into the cell and thus promote inhibitory effects in the brain [49]. The potentiation of GABAergic transmission is one of the main targets of the AEDs currently used in clinical practice (see above).

Whereas only a few natural products interact with VGSCs and VGCCs, phytoconstituents most often affect the modulation of GABA_A receptors (Table 2). The most significant anticonvulsant effects mediated by GABAergic transmission have been observed for terpenoids. Manayi et al. [50] have reviewed the ability of natural terpenoids to modulate

the GABAergic system, but most of the compounds identified exerted anticonvulsant effects only at doses too high to be implemented in clinical practice. We have therefore pointed out only those terpenes that exhibit notable activity at relevant doses.

Monoterpenes and sesquiterpenes are constituents of essential oils, and they have properties plausible for a potential application. Their low molecular weight and high lipophilicity allow them to penetrate membranes and interact with epilepsy-related proteins [51]. Thymoquinone, the dominant compound in black seed oil (*Nigella sativa*), has shown the most notable activity of all the monoterpenes found in this search, inhibiting convulsions in male BALB/c mice at the relatively low dose of 40 mg/kg [52]. Preclinical findings led to a pilot study in children with refractory epilepsy (see Section 5). The results demonstrated that thymoquinone was effective and well-tolerated [53]. Moreover, thymoquinone potentiated the antiepileptic properties of VPA [50] and phenytoin [54]. It also displayed a neuroprotective effect in Sprague Dawley rats by phosphorylating cAMP response element-binding protein (CREB) [55] and downregulating TNF- α and COX-2 [56]. Unfortunately, thymoquinone inhibits the activity of cytochrome P450 2C9 (CYP2C9), and this must be taken into account when thymoquinone is co-administered with phenytoin [57]. To sum up, its anticonvulsant and neuroprotective properties make thymoquinone a very promising substance that deserves further investigation with emphasis on an in-depth exploration of its pharmacokinetics and potential interactions.

Iridoids seem to be effective in the inhibition of convulsions as well, and especially the reports of the anticonvulsant activity of the extracts of *Valeriana* species are increasingly frequent. Pretreatment with valepotriate (5, 10, 20 mg/kg/day, i.p.) protected mice against MES and PTZ-induced convulsions, but it was far less effective than diazepam (4 mg/kg/day, i.p.) [58]. Significant anticonvulsant activity has also been reported for paederosidic acid, a rare sulfur-containing iridoid [59], but such compounds are, unfortunately, very unstable under acidic conditions, which makes their peroral administration difficult [60].

Bilobalide, the main sesquiterpene trilactone found in the leaves of *Ginkgo biloba*, must be included. Bilobalide (30 mg/kg, p.o., once a day for 4 days) elevated GABA levels in the hippocampus, cerebral cortex, and striatum of male ddY mice, possibly through the potentiation of the activity of GAD [61]. Also considering its neuroprotective effect [62], makes bilobalide seems very promising, although Ng et al. point out that bilobalide negatively modulated the action of GABA at $\alpha_1\beta_2\gamma_{2L}$ GABA_A receptors [63].

An even more promising natural product affecting GABA transmission has been found in huperzine A (HupA), a dietary supplement used in the USA as a memory enhancer. HupA is an acetylcholinesterase inhibitor isolated from the Chinese club moss *Huperzia serrata*. It also exerts anti-inflammatory and neuroprotective effects by activating nicotinic cholinergic receptors [64]. In addition, HupA has delivered seizure relief in a 6 Hz model, with an ED₅₀ value of 0.34 mg/kg in the 32 mA paradigm, being 57 times more potent than levetiracetam and 301 times more potent than VPA [65]. It also suppressed PTZ-induced seizures in rats by activating the cortical transmission of GABA [66]. These findings, together with the favorable pharmacokinetic properties of HupA in humans [67], have led to clinical testing (see Section 5).

Recently, several coumarins have been reported to effectively inhibit PTZ-induced seizures in the zebrafish larvae model of epilepsy at doses lower than those of the positive controls diazepam (10 mM) and VPA (1 mM), respectively [68,69]. Based on the seizure-inducing agent used (PTZ), it was postulated that the test coumarins interfered with the GABA transmission. Coumarins have previously been shown to inhibit the activity of GABA transaminase (GABA-T), the main degradative enzyme of GABA [70]. This hypothesis was supported by a molecular docking study of oxypeucedanin hydrate, the most active furanocoumarin, to the structural model of GABA-T. The results indicated that a bulky substituent at the C5 position is crucial for antiseizure activity, whereas an analogous bulky moiety substituted at the C8 position diminishes the activity [69]. Similar results have been reported by Singhuber et al. [71] in a study dealing with the modulation of

GABA-induced chloride currents by selected coumarin derivatives on recombinant $\alpha_1\beta_2\gamma_{2S}$ GABA_A receptors expressed in *Xenopus laevis* oocytes [71]. On the other hand, exactly the opposite results were found for the mice MES test. C5-substituted furanocoumarins were inactive, whereas C8-substituted furanocoumarins exerted strong anticonvulsant activity [72]. Hence, more studies are needed to clarify the structure–activity relationship with respect to the model of epilepsy used as well as to find out more about bioavailability. However, as coumarins are simple molecules, they are ideal for chemical synthesis and modifications to improve their pharmacodynamic and pharmacokinetic properties.

Table 2. Natural products with influence on GABAergic transmission.

| Compound | Effective Dose | Animal Model | Seizure-Inducing Agent | Mechanism | Source |
|---|---|--|---|---|--------|
| Thymol (monoterpene) | 50 and 100 mg/kg, i.p. | Male Swiss mice Male Wistar rats | PTZ, MES, Strychnine, 4-AP | Possibly via positive modulation of GABA _A and voltage-dependent Na ⁺ channel blockade | [43] |
| Thymoquinone (monoterpene) | 40 mg/kg/day, p.o. (for 7 days) | Sprague Dawley rats | PTZ | Activation of GABA _{B1} R/CaMKII/pCREB pathway | [55] |
| Paederosidic acid (iridoid) | 5–40 mg/kg, i.p. | Male ICR mice Sprague Dawley rats | MES PTZ | Upregulation of GAD65 | [59] |
| Valepotriate (iridoid) | 5–20 mg/kg/day, i.p. (for 3 weeks) | Male ICR mice Sprague Dawley rats | MES PTZ | Upregulation of GABA _A , GAD65, and Bcl-2 and downregulation of caspase-3 | [58] |
| Bilobalide (sesquiterpene) | 30 mg/kg/day, p.o. (for 4 days) | Hippocampus, cortex, and striatum of male ddY mice | INH | Elevation of GABA levels Potentiation of GAD activity | [61] |
| Curcumol (sesquiterpene) | 100 mg/kg/day, i.p. (for 3 days) | Male C57BL/6J mice | PTZ KA | Facilitation of GABAergic inhibition | [73] |
| (+)-Dehydrofukinone (sesquiterpene) | 10, 30, and 100 mg/kg, i.p. | Female Swiss mice | PTZ | Modulation of GABA _A receptors | [74] |
| Betulin (triterpene) | 50 and 100 mg/kg, i.p. | Male ICR mice | Bicuculline | Binding to the GABA _A receptor | [75] |
| Ginsenoside Rg ₃ (triterpene) | 100 μM | <i>Xenopus laevis</i> oocytes | Electrode voltage-clamp technique | GABA _A receptor activation via interaction with the γ_2 subunit | [76] |
| Ursolic acid stearyl glucoside (triterpene) | 50 mg/kg, i.p. | Wistar albino rats | MES INH | Possibly via GABA receptor stimulation | [77] |
| Embelin (benzoquinone) | 0.156–0.625 mg/kg, i.p. | Adult zebrafish | PTZ | Affinity toward GABA _A receptor | [78] |
| Cnidilin (coumarin) | 300 μM | <i>Xenopus</i> oocytes | Two-microelectrode voltage clamp assay | Modulation of GABA _A receptors of the subunit combination $\alpha_1\beta_2\gamma_{2S}$ | [79] |
| Osthole (coumarin) | 300 μM | <i>Xenopus</i> oocytes | Two-microelectrode voltage clamp assay | Modulation of GABA _A receptors of the subunit combination $\alpha_1\beta_2\gamma_{2S}$ | [79] |
| Lucidafuranocoumarin A (coumarin) | 10–16 μM | Zebrafish larvae | PTZ | Possibly via interaction with the GABA _A receptor | [68] |
| Oxypeucedanin (coumarin) | 10–40 μM | Zebrafish larvae | PTZ | Possibly via interaction with the GABA _A receptor | [69] |
| Oxypeucedanin hydrate (coumarin) | 20–50 μM | Zebrafish larvae | PTZ | Possibly via interaction with the GABA _A receptor | [69] |
| Notopterol (coumarin) | 0.25–2 μM | Zebrafish larvae | PTZ | Possibly via interaction with the GABA _A receptor | [69] |
| Pimpinellin (coumarin) | 20–80 μM | Zebrafish larvae | PTZ | Possibly via interaction with the GABA _A receptor | [69] |
| Hyuganin C (coumarin) | 2.5–20 μM | Zebrafish larvae | PTZ | Possibly via interaction with the GABA _A receptor | [69] |
| Rosmarinic acid (phenolic) | 30 mg/kg, i.p. | Female C57BL/6 mice | PTZ Pilocarpine | Probably activation of the GABAergic system | [80] |
| Chlorogenic acid (phenolic) | 5 mg/kg/day, p.o. (for 15 days) | Male Swiss albino mice | Pilocarpine | Suppressing glutamate receptors, neuroprotective effect | [81] |
| Gastrodin (phenolic) | 60 mg/kg/day, p.o. (for 7 days) | Mongolian gerbils | Genetic seizure model (seizure-sensitive gerbils) | Decrease in GABA degradation Decrease in GABA-T, SSADH, and SSAR immunoreactivities | [82] |
| Rutin (flavonoid) | 50 and 150 nM, i.c.v. | Male Wistar rats | PTZ | Positive allosteric modulation of the GABA _A receptor complex via interaction at the benzodiazepine site | [83] |
| Wogonin (flavonoid) | 5 and 10 mg/kg, i.p. | Male Sprague Dawley rats | MES PTZ | Potentiation of the activity of GABA | [84] |
| Vitexin (flavonoid) | 100 and 200 μM, i.c.v. | Male Wistar rats | PTZ | Interaction with GABA _A benzodiazepine receptor complex | [85] |
| | 10 mg/kg/day, p.o. (for 15 days) | Male Swiss albino mice | Pilocarpine | Suppressing glutamate receptors, neuroprotective effect | [81] |
| Nobiletin (flavonoid) | 12.5, 25, and 50 mg/kg/day, o.g. (for 6 days) | C57BL/6 mice | PTZ | Modulation GAD65/GABA _A expression, BDNF-TrkB, PI3K/Akt | [86] |

Table 2. Cont.

| Compound | Effective Dose | Animal Model | Seizure-Inducing Agent | Mechanism | Source |
|--|--------------------------------|--|----------------------------|--|--------|
| (+)-Erythravine (alkaloid) | 0.25–3 µg/µL, i.c.v. | Male Wistar rats | Bicuculline, NMDA, KA, PTZ | Probably modifying GABA neurotransmission | [87] |
| (+)-11- α -Hydroxy-erythravine (alkaloid) | 0.25–3 µg/µL, i.c.v. | Male Wistar rats | Bicuculline, NMDA, KA, PTZ | Probably modifying GABA neurotransmission | [87] |
| Huperzine A (alkaloid) | 0.6 mg/kg, i.p. | Male Sprague Dawley rats | PTZ | Activation of cortical GABA transmission | [66] |
| Lobeline (alkaloid) | 10, 20, 30 mg/kg, i.p. | Male Swiss mice | PTZ Strychnine | Enhancing the GABA release | [88] |
| Montanine (alkaloid) | 30 and 60 mg/kg, i.p. | Swiss mice and Wistar rats of either sex | PTZ | Modulation of several neurotransmitter receptor systems including GABA _A receptors | [89] |
| Piperine (alkaloid) | 2.5, 5, 10, and 20 mg/kg, i.p. | Male Swiss mice | Pilocarpine | Multiple anticonvulsant mechanisms, modulation of the GABA system, antioxidant, and anti-inflammatory activity | [90] |

4.3. Natural Products That Reduce Postsynaptic Excitability by Affecting AMPA or NMDA Receptors

Glutamate is the principal excitatory neurotransmitter in the brain, and therefore, glutamate receptor agonists, such as α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate, act as elicitors of seizures. Glutamate receptors can be divided into ionotropic glutamate receptors (ligand-gated ion channels) and metabotropic glutamate receptors (G-protein-coupled receptors) [91]. Among the ionotropic glutamate receptors, the AMPA-type and NMDA-type glutamate receptors are the most important, as certain AEDs affect these ionotropic receptors (e.g., perampanel and topiramate).

Interestingly, no reports of natural products interacting with AMPA receptors have been found during our search, except for one recent study describing the potent anti-convulsant activity of magnolol and honokiol in a model of therapy-resistant epilepsy. However, the authors postulate the involvement of not only AMPA receptors but also GABA_A and cannabinoid receptors [92]. Magnolol and honokiol, the main bioactive substances in the bark of *Magnolia officinalis*, are known for antioxidant, anti-inflammatory, and neuroprotective properties that make them promising for further research in the field of epilepsy, especially at a time when knowledge of their toxicity and bioavailability is accumulating [93].

Panax ginseng is well-known for its neuroprotective properties with ginsenosides as the main active constituents. Among the test ginsenosides, 20(S)-Rg₃ and 20(S)-Rh₂ inhibited NMDA receptors. However, 20(S)-Rg₃ interacted with the glycine site, while 20(S)-Rh₂ likely did so with the polyamine-binding site of NMDA receptors. (R)-isomers were inactive and the mono-glycosylated moiety at C-3 was found to be essential for binding to polyamine sites [94]. Further assays showed that 20(S)-Rg₃ regulated GABA_A receptor activity by interacting with the γ_2 subunit [76], demonstrating its multitarget mechanism of action. Nevertheless, the bioavailability of ginsenosides after oral administration is relatively poor. Low water solubility and easy degradation by gastric acid and gut microbiota are the crucial disadvantages. Therefore, their absorption needs to be enhanced by sophisticated formulation strategies [95].

Table 3. Natural products that affect AMPA or NMDA receptors.

| Compound | Effective Dose | Animal Model | Seizure-Inducing Agent | Mechanism | Source |
|---|------------------------------------|--|--|--|--------|
| 20(S)-Ginsenoside Rh ₂ (triterpene) | 10 μM | Hippocampal neurons of Sprague Dawley rats | NMDA, AMPA, KA, Glycine | Inhibition of NMDA receptors via the interaction with the polyamine-binding site | [94] |
| Saikosaponin A (triterpene) | 1 μM | Hippocampal neurons of Sprague Dawley rats | Kynurenic acid PTX | Inhibition of NMDA receptor current and persistent sodium current (<i>I_{NaP}</i>) | [96] |
| 3β,6β,16β-Trihydroxylup-20(29)-ene (triterpene) | 30 mg/kg, i.g. | Swiss mice | PTZ | Possibly via Na ⁺ , K ⁺ -ATPase activity maintenance | [97] |
| 6-Gingerol (phenolic) | 37.5 μM | Zebrafish larvae | PTZ | Inhibition of NMDA receptors via the interaction with the glutamate-binding site | [98] |
| Magnolol (neolignan) | 12.5 μM 30 mg/kg, i.p. | Adult zebrafish Male NMRI mice | PTZ, EKP 6-Hz test | Probably targeting GABA _A , cannabinoid, and AMPA receptors | [92] |
| Honokiol (neolignan) | 6.25 μM | Adult zebrafish | PTZ EKP | Probably targeting GABA _A , cannabinoid, and AMPA receptors | [92] |
| Huperzine A (alkaloid) | 1, 2, and 3 mg/kg, i.m. | Male Sprague Dawley rats | NMDA | NMDA antagonism | [99] |
| 14-Benzoyltalidasamine (alkaloid) | 0.3–10 μM | Hippocampal slices of male Wistar rats | Low Mg ²⁺ /high K ⁺ -ACSF | Modulation NMDA receptors | [100] |
| Ibogaine (alkaloid) | ED ₅₀ 31 mg/kg, i.p. | Male NIH Swiss mice | MES NMDA | Blockade of NMDA receptors | [101] |
| Rhynchophylline (alkaloid) | 30 μM | <i>Xenopus laevis</i> oocytes injected with total RNA from Male Wistar rat cortices or cerebelli | NMDA Glycine | Noncompetitive antagonist of the NMDA receptor | [102] |
| | 100 μM, i.c.v. | Male Sprague Dawley rats | Pilocarpine | Inhibition of the persistent sodium current <i>I_{NaP}</i> and NMDA receptor current | [103] |
| Isorhynchophylline (alkaloid) | 30 μM | <i>Xenopus laevis</i> oocytes injected with total RNA from Male Wistar rat cortices or cerebelli | NMDA Glycine | Noncompetitive antagonist of the NMDA receptor | [102] |

4.4. Natural Products with Multiple Mechanisms of Action: Cannabinoids

Cannabis sativa contains more than 100 compounds (lipophilic phytocannabinoids) with different therapeutic potentials and because phytocannabinoids affect diverse epilepsy-related targets [104], they have been given a separate section. Medicinal marijuana is applicable as a treatment option mainly for patients with chronic, autoimmune, inflammatory, degenerative, or oncological illnesses, and also for palliative care [105]. Multiple in vitro and in vivo preclinical trials have reported antiepileptic effects for several constituents of medical marijuana. Compounds of interest include psychoactive Δ⁹-tetrahydrocannabinol (Δ⁹-THC) and structurally similar cannabidiol (CBD), along with non-psychoactive Δ⁹-tetrahydrocannabivarin (Δ⁹-THCV), cannabidivarin (CBDV), and Δ⁹-tetrahydrocannabinolic acid (Δ⁹-THCA). Δ⁹-THC acts as a potent partial agonist on endocannabinoid receptor CB₁, influencing both GABAergic and glutamatergic synaptic transmission. The clinical use of medical marijuana is limited because the anticonvulsant effect of Δ⁹-THC is relatively unpredictable. It acts simultaneously on several receptor targets, such as the transient receptor potential (TRP) cation channels TRPA1, TRPV2, and TRPM8; the orphan G-coupled protein receptor GPR55; the 5-HT_{3A} receptor; the peroxisome proliferator-activated receptor gamma (PPARγ); the μ- and δ-opioid receptors, the β-adrenoreceptors; and some subtypes of Ca²⁺, K⁺, and Na⁺ channels. Interestingly, some experiments have shown medical marijuana to have no or even a pro-convulsant

effect [104]. Δ^9 -THCA is used to prevent seizures, e.g., in the USA. This metabolic precursor of Δ^9 -THC is more affordable and should have only minor psychoactive properties [106]. Experimental observations have demonstrated that it has anticonvulsant effects via the modulation of ion channels and enzymes crucial for the biosynthesis of the endocannabinoid 2-arachidonoylglycerol [104]. The mechanisms of anticonvulsant activity of Δ^9 -THCV and CBDV are not well understood. Both compounds probably exert their anticonvulsant effects via non-CB₁/CB₂ mechanisms. TRPV1, TRPV2, TRPA1, and TRPM8 channels are the likely molecular targets of Δ^9 -THCV and CBDV [107].

CBD is the most promising of these agents, with effects proved by several clinical trials, especially for the treatment of drug-resistant epilepsies (see Section 5. Clinical data). Recent studies have proposed that its anticonvulsant effect may involve agonistic activity at the TRPV1 channel, the blockade of human T-type VGCCs, the modulation of various receptors such as 5-HT_{1A}, 5-HT_{2A}, GPR55, adenosine A1 and A2, voltage-dependent anion-selective channel protein 1 (VDAC1), or an influence on the release of TNF- α [104].

Unlike other natural constituents mentioned in this review, the metabolism, pharmacokinetics, side effects, and interactions of the main phytocannabinoids have been and continue to be deeply studied. Smoked, inhaled, or vaporized Δ^9 -THC has a bioavailability in the range from ~10–35% in contrast to (~6%) by oral administration. CBD and CBDV are hardly soluble in water, and their bioavailability after oral administration is poor, but many trials have evaluated cannabinoids suspended in sesame oil or mixed with glycocholate to increase their bioavailability, and intranasal, sublingual, and transdermal applications are common. Unfortunately, because of their lipophilic properties, large amounts of cannabinoids accumulate in adipose and other tissues, especially with repeated administration. Negative interactions with other drugs metabolized by the cytochrome P450 system or isoenzymes CYP3A4, CYP2C19, CYP2C9, and CYP2D6 should be taken into account, especially in Europe, where the co-administration of CBD and clobazam has been approved as adjunctive treatment of Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS). The strong inhibition of CYP2C19 by CBD leads to a remarkable rise in clobazam concentration, which may contribute to side effects, including somnolence and sedation. Finally, potential pharmacodynamic interactions with conventional antiepileptics must be investigated as well [104,108].

5. Clinical Data

Although many natural compounds exert significant anticonvulsant activity *in vivo*, clinical data from human subjects are almost nonexistent. Some timid attempts have been made; but a robust, double-blind, placebo-controlled trial is missing in most cases.

We cannot begin a discussion of clinical data with anything other than medicinal cannabis. Many clinical trials have reported anticonvulsant effects of constituents isolated from *C. sativa* and medicinal cannabis itself. Although recent studies describe the safety and efficacy profiles of medicinal cannabis and CBD as comparable, the potential use of cannabis extract is not recommended because of adverse events related to THC, especially in long-term use [109]. Therefore, a highly purified CBD (Epidiolex[®]) remains the only cannabis-based product approved in 2018 by the Food and Drug Administration (FDA) for the treatment of drug-resistant epilepsies (LGS and DS). The European Medicine Agency (EMA) followed in 2019 by approving CBD (Epidyolex[®]) in combination with clobazam as adjuvant therapy for LGS and DS [108].

Epidiolex (100 mg/mL CBD solution in sesame oil) was approved based on results reported by Devinsky and coworkers. An open-label interventional trial including 214 patients (aged 1–30 years) with severe, intractable, childhood-onset, treatment-resistant epilepsy was undertaken at 11 epilepsy centers across the USA. CBD reduced seizure frequency and appeared to be an effective treatment option in highly treatment-resistant epilepsies, such as DS or LGS [110]. A double-blind, placebo-controlled trial on 225 participants (aged 2–55 years) investigated the effect of CBD on drop seizures in LGS. The administration of CBD at a dose of 10 or 20 mg/kg/day and added to a conventional therapy

decreased the frequency of seizures compared to a placebo [111]. Similarly, a reduction in convulsive seizure frequency was achieved in a randomized, double-blind, placebo-controlled study that evaluated the effect of CBD on 120 participants (aged 2–18 years) with DS [112]. Recently, an open-label extension trial showed that long-term use of add-on CBD had an acceptable safety profile and led to sustained reductions in seizure frequency in patients with treatment-resistant DS [113]. However, as the clinical impact of CBD is difficult to predict, the individual's response should be carefully observed [114].

Cannabidivarin (CBDV), a natural *n*-propyl analog of CBD, has been tested in a phase II clinical trial with a double-blind, randomized, placebo-controlled design, involving 162 adult patients (aged 18–65 years). The study was intended to evaluate the anticonvulsant effect of CBDV as add-on therapy in drug-resistant focal seizures [115], but the results of the study have not been published, and in 2018, GW Pharmaceuticals announced that the trial did not meet its primary endpoint, i.e., the percent change in focal seizure frequency from baseline to the end of treatment in subjects taking CBDV compared with a placebo [108,115].

Although in previous parts we have focused only on pure and structurally characterized compounds, black seed oil, the main product obtained from *Nigella sativa*, should not be omitted. A prospective, randomized, single-blinded, crossover pilot study has examined an adjuvant therapy with black seed oil on intractable pediatric seizures. Unfortunately, the administration of 40–80 mg/kg/day of black seed oil for a 4-week period showed a statistically non-significant effect on seizure frequency and serum levels of oxidative stress parameters [116]. Nevertheless, the preclinical findings of the significant anticonvulsant activity of thymoquinone, the major monoterpene of black seed oil, led to a pilot study that involved 22 juvenile patients with refractory epilepsy. After four weeks of administration of thymoquinone at a dose of 1 mg/kg/day, patients exhibited a significantly reduced frequency of seizures for thymoquinone compared with placebo groups. As most patients were taking other AEDs, the influence of thymoquinone on the blood levels of these drugs cannot be ruled out. Altogether, thymoquinone was generally well-tolerated with no serious adverse effects, such as nausea or somnolence [53].

Several alkaloids have also been tested in a clinical setup, with huperzine A (HupA) showing the most promising results. HupA is a well-known acetylcholinesterase (AChE) inhibitor that exerts anticonvulsant activity by activating cortical GABA transmission [66]. Although it has been demonstrated that naturally occurring (–)-HupA inhibited AChE 38-fold more potently than its synthetic (+)-isomer [117], (–)- and (+)-HupA both blocked the NMDA channel similarly [99]. Clinical testing of HupA has determined that the immediate-release formulation currently available is not adequate for clinical development as an antiseizure medication because its cholinergic side effects (nausea and vomiting) limit the acceptable dose. Attention was therefore focused on the development of an extended-release (ER) formulation of HupA to reduce dosing and side effects [118]. A phase I clinical trial to evaluate the bioavailability, safety, and tolerability of an ER formulation of HupA has recently been completed. The study was conducted on eight participants who were administered an initial dose of 0.5 mg twice daily (b.i.d.). The dose was increased every 2–3 days up to the maximum tolerated dose of 2.5 mg twice daily (b.i.d.) (NCT03156439). A clinical study (involving sixteen participants) is currently underway to evaluate an ER formulation of HupA for the treatment of adult focal impaired awareness seizures (NCT03474770). Since HupA is otherwise well-tolerated, shows no serious adverse effects, and has favorable pharmacokinetic properties [119], it is worth watching whether or not this substance will find application in clinical practice.

Reports of beneficial effects of quinidine in patients with *KCNT1* mutations are increasing dramatically, supporting the use of quinidine in the treatment of epilepsy of infancy with migrating focal seizures (EIMFS), which is also known as migrating partial seizures of infancy (MPSI). The *KCNT1* gene encodes the sodium-dependent potassium channel, with quinidine being a partial antagonist of the *KCNT1* channel [120]. Quinidine has been reported to decrease seizure frequency in one patient with the Y796H mutation in the

KCNT1 gene, but not in another patient with the K629N mutation in the same gene [121]. Other studies indicate that quinidine could be a candidate drug for the treatment of *KCNT1*-positive epilepsies [120,122,123] even though its efficacy has been demonstrated in only a small number of patients. Abdelnour et al. suggest that response may be age-dependent because, in their report, only the 3-month-old infant responded to quinidine, while two older children (9 and 13 years) did not [124]. On the other hand, quinidine did not show efficacy in six patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) due to *KCNT1* mutations in a single-center, inpatient, order-randomized, blinded, placebo-controlled, crossover trial [125]. Similarly, an observational study of 43 patients to evaluate the treatment responsiveness of patients with *KCNT1*-related epilepsy reported that quinidine was not utilized in any patients with an ADNFLE phenotype, whereas quinidine treatment was attempted in 17 patients with an EIMFS phenotype. Unfortunately, a reduction > 50% in seizures was seen in only four patients treated with quinidine [126]. Despite its controversial efficacy, quinidine deserves attention and should be evaluated further because too few cases have been studied.

6. Conclusions

This review describes the significant anticonvulsant effects of various natural products. Although their anticonvulsant activity is evident in *in vivo* models of epilepsy, and in most cases, their molecular targets are clearly recognized, not many plant-derived compounds have made the step up to evaluation by clinical trials. As summarized in Tables 1–3 and Tables S1–S3 [127–180], natural anticonvulsants can be found across the plant kingdom. They affect the same targets as conventional AEDs yet are still overlooked within drug development. An argument based purely on limited solubility and bioavailability becomes less and less acceptable in an era of nanocarriers and bioenhancers. Natural products can also serve as suitable templates for semisynthetic derivatives with better efficacy and pharmacokinetic properties. Moreover, plant-based therapy is usually well-tolerated, and in most cases, it is associated with no or only moderate adverse effects (if used sensibly). Plant-based therapy has a number of benefits. Given the multiple effects of many natural compounds, including neuroprotective and anti-inflammatory activity, plant-based therapy could become a powerful anticonvulsant tool and should not be overlooked. This review assumes that soon Epidiolex will not be the only plant-derived product approved for the treatment of epilepsy-related disorders.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ph16081061/s1>, Table S1: Natural products with other targets title; Table S2: Unknown targets; Table S3: Natural products with potential anti-epileptic activity via neuroprotection and anti-inflammatory action; References for Supplementary Material.

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References

1. Thijs, R.D.; Surges, R.; O'Brien, T.J.; Sander, J.W. Epilepsy in Adults. *Lancet* **2019**, *393*, 689–701. [[CrossRef](#)] [[PubMed](#)]
2. Fisher, R.S.; Acevedo, C.; Arzimanoglou, A.; Bogacz, A.; Cross, J.H.; Elger, C.E.; Engel, J.; Forsgren, L.; French, J.A.; Glynn, M.; et al. ILAE Official Report: A Practical Clinical Definition of Epilepsy. *Epilepsia* **2014**, *55*, 475–482. [[CrossRef](#)] [[PubMed](#)]
3. Devinsky, O.; Spruill, T.; Thurman, D.; Friedman, D. Recognizing and Preventing Epilepsy-Related Mortality: A Call for Action. *Neurology* **2016**, *86*, 779–786. [[CrossRef](#)]
4. Levira, F.; Thurman, D.J.; Sander, J.W.; Hauser, W.A.; Hesdorffer, D.C.; Masanja, H.; Odermatt, P.; Logroscino, G.; Newton, C.R. The Epidemiology Commission of the International League Against Epilepsy Premature Mortality of Epilepsy in Low- and Middle-Income Countries: A Systematic Review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia* **2017**, *58*, 6–16. [[CrossRef](#)] [[PubMed](#)]
5. Begley, C.; Wagner, R.G.; Abraham, A.; Beghi, E.; Newton, C.; Kwon, C.; Labiner, D.; Winkler, A.S. The Global Cost of Epilepsy: A Systematic Review and Extrapolation. *Epilepsia* **2022**, *63*, 892–903. [[CrossRef](#)] [[PubMed](#)]
6. Nabhout, R.; Thile, E.A. The Role of Cannabinoids in Epilepsy Treatment: A Critical Review of Efficacy Results from Clinical Trials. *Epileptic Disord.* **2020**, *22*, S23–S28. [[CrossRef](#)]
7. Lee, B.I.; Park, K.M.; Kim, S.E.; Heo, K. Clinical Opinion: Earlier Employment of Polytherapy in Sequential Pharmacotherapy of Epilepsy. *Epilepsy Res.* **2019**, *156*, 106165. [[CrossRef](#)] [[PubMed](#)]
8. Vajda, F.J.E. Pharmacotherapy of Epilepsy: New Armamentarium, New Issues. *J. Clin. Neurosci.* **2007**, *14*, 813–823. [[CrossRef](#)]
9. Brodie, M.J. Antiepileptic Drug Therapy the Story so Far. *Seizure* **2010**, *19*, 650–655. [[CrossRef](#)]
10. Perucca, P.; Gilliam, F.G. Adverse Effects of Antiepileptic Drugs. *Lancet Neurol.* **2012**, *11*, 792–802. [[CrossRef](#)]
11. Cunliffe, V.T.; Baines, R.A.; Giachello, C.N.G.; Lin, W.-H.; Morgan, A.; Reuber, M.; Russell, C.; Walker, M.C.; Williams, R.S.B. Epilepsy Research Methods Update: Understanding the Causes of Epileptic Seizures and Identifying New Treatments Using Non-Mammalian Model Organisms. *Seizure* **2015**, *24*, 44–51. [[CrossRef](#)]
12. Pitkänen, A.; Buckmaster, P.S.; Galanopoulou, A.S.; Moshé, S.L. *Models of Seizures and Epilepsy*, 2nd ed.; Elsevier: Amsterdam, The Netherlands; Academic Press: London, UK, 2017; ISBN 978-0-12-804067-6.
13. Sucher, N.J.; Carles, M.C. A Pharmacological Basis of Herbal Medicines for Epilepsy. *Epilepsy Behav.* **2015**, *52*, 308–318. [[CrossRef](#)] [[PubMed](#)]
14. Löscher, W.; Schmidt, D. Modern Antiepileptic Drug Development Has Failed to Deliver: Ways out of the Current Dilemma: Ways Out of the Current Dilemma with New AEDs. *Epilepsia* **2011**, *52*, 657–678. [[CrossRef](#)] [[PubMed](#)]
15. Löscher, W. Animal Models of Epilepsy for the Development of Antiepileptogenic and Disease-Modifying Drugs. A Comparison of the Pharmacology of Kindling and Post-Status Epilepticus Models of Temporal Lobe Epilepsy. *Epilepsy Res.* **2002**, *50*, 105–123. [[CrossRef](#)] [[PubMed](#)]
16. Mahmood, F.; Mozere, M.; Zdebik, A.A.; Stanescu, H.C.; Tobin, J.; Beales, P.L.; Kleta, R.; Bockenbauer, D.; Russell, C. Generation and Validation of a Zebrafish Model of EAST (Epilepsy, Ataxia, Sensorineural Deafness and Tubulopathy) Syndrome. *Dis. Model. Mech.* **2013**, *6*, 652–660. [[CrossRef](#)] [[PubMed](#)]
17. Baraban, S.C.; Dinday, M.T.; Hortopan, G.A. Drug Screening in Scn1a Zebrafish Mutant Identifies Clemizole as a Potential Dravet Syndrome Treatment. *Nat. Commun.* **2013**, *4*, 2410. [[CrossRef](#)]
18. Grone, B.P.; Marchese, M.; Hamling, K.R.; Kumar, M.G.; Krasniak, C.S.; Sicca, F.; Santorelli, F.M.; Patel, M.; Baraban, S.C. Epilepsy, Behavioral Abnormalities, and Physiological Comorbidities in Syntaxin-Binding Protein 1 (STXBP1) Mutant Zebrafish. *PLoS ONE* **2016**, *11*, e0151148. [[CrossRef](#)] [[PubMed](#)]
19. Samarut, É.; Swaminathan, A.; Riché, R.; Liao, M.; Hassan-Abdi, R.; Renault, S.; Allard, M.; Dufour, L.; Cossette, P.; Soussi-Yanicostas, N.; et al. γ -Aminobutyric Acid Receptor Alpha 1 Subunit Loss of Function Causes Genetic Generalized Epilepsy by Impairing Inhibitory Network Neurodevelopment. *Epilepsia* **2018**, *59*, 2061–2074. [[CrossRef](#)]
20. EuroEPINOMICS RES Consortium; Schubert, J.; Siekierska, A.; Langlois, M.; May, P.; Huneau, C.; Becker, F.; Muhle, H.; Suls, A.; Lemke, J.R.; et al. Mutations in STX1B, Encoding a Presynaptic Protein, Cause Fever-Associated Epilepsy Syndromes. *Nat. Genet.* **2014**, *46*, 1327–1332. [[CrossRef](#)]
21. Noebels, J.L.; Avoli, M.; Rogawski, M.A.; Olsen, R.W.; Antonio, V. *Jasper's Basic Mechanisms of the Epilepsies*, 4th ed.; NCBI Bookshelf Online Book Version; Wiley: New Jersey, NJ, USA, 2012. [[CrossRef](#)]
22. Yang, Z.-W.; Wu, F.; Zhang, S.-L. Effects of Ganoderic Acids on Epileptiform Discharge Hippocampal Neurons: Insights From alterations of BDNF, TRPC3 and Apoptosis. *Pharmazie* **2016**, *71*, 340–344. [[CrossRef](#)] [[PubMed](#)]
23. Daif, A.; Lukas, R.V.; Issa, N.P.; Javed, A.; VanHaerents, S.; Reder, A.T.; Tao, J.X.; Warnke, P.; Rose, S.; Towle, V.L.; et al. Antigliutamic Acid Decarboxylase 65 (GAD65) Antibody-Associated Epilepsy. *Epilepsy Behav.* **2018**, *80*, 331–336. [[CrossRef](#)] [[PubMed](#)]
24. McKeon, A.; Tracy, J.A. GAD65 Neurological Autoimmunity. *Muscle Nerve* **2017**, *56*, 15–27. [[CrossRef](#)] [[PubMed](#)]
25. De Melo, C.G.F.; Salgado, P.R.R.; Da Fonsêca, D.V.; Braga, R.M.; Filho, M.R.D.C.; De Farias, I.E.V.; De Luna Freire Pessôa, H.; Lima, E.M.; Do Amaral, I.P.G.; De Sousa, D.P.; et al. Anticonvulsive Activity of (1S)-(-)-Verbenone Involving RNA Expression of BDNF, COX-2, and c-Fos. *Naunyn-Schmiedebergs Arch. Pharmacol.* **2017**, *390*, 863–869. [[CrossRef](#)]
26. Brahmachari, G. *Neuroprotective Natural Products: Clinical Aspects and Mode of Action*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2017; ISBN 978-3-527-80378-1.

27. Catterall, W.A.; Lenaeus, M.J.; Gamal El-Din, T.M. Structure and Pharmacology of Voltage-Gated Sodium and Calcium Channels. *Annu. Rev. Pharmacol. Toxicol.* **2020**, *60*, 133–154. [[CrossRef](#)]
28. Oz, M.; Lozon, Y.; Sultan, A.; Yang, K.-H.S.; Galadari, S. Effects of Monoterpenes on Ion Channels of Excitable Cells. *Pharmacol. Ther.* **2015**, *152*, 83–97. [[CrossRef](#)]
29. Ameri, A.; Gleitz, J.; Peters, T. Inhibition of Neuronal Activity in Rat Hippocampal Slices by Aconitum Alkaloids. *Brain Res.* **1996**, *738*, 154–157. [[CrossRef](#)] [[PubMed](#)]
30. Ameri, A.; Shi, Q.; Aschoff, J.; Peters, T. Electrophysiological Effects of Aconitine in Rat Hippocampal Slices. *Neuropharmacology* **1996**, *35*, 13–22. [[CrossRef](#)]
31. Ameri, A. Inhibition of Rat Hippocampal Excitability by the Plant Alkaloid 3-Acetylaconitine Mediated by Interaction with Voltage-Dependent Sodium Channels. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1997**, *355*, 273–280. [[CrossRef](#)]
32. Ameri, A. Structure-Dependent Differences in the Effects of the Aconitum Alkaloids Lappaconitine, N-Desacetylappaconitine and Lappaconidine in Rat Hippocampal Slices. *Brain Res.* **1997**, *769*, 36–43. [[CrossRef](#)]
33. Ameri, A. Inhibition of Rat Hippocampal Excitability by the Aconitum Alkaloid, 1-Benzoylnapelline, but Not by Napelline. *Eur. J. Pharmacol.* **1997**, *335*, 145–152. [[CrossRef](#)]
34. Ameri, A. Effects of the Alkaloids 6-Benzoylheteratisine and Heteratisine on Neuronal Activity in Rat Hippocampal Slices. *Neuropharmacology* **1997**, *36*, 1039–1046. [[CrossRef](#)]
35. Mishra, A.; Punia, J.K.; Bladen, C.; Zamponi, G.W.; Goel, R.K. Anticonvulsant Mechanisms of Piperine, a Piperidine Alkaloid. *Channels* **2015**, *9*, 317–323. [[CrossRef](#)]
36. Tiwari, A.; Mahadik, K.R.; Gabhe, S.Y. Piperine: A Comprehensive Review of Methods of Isolation, Purification, and Biological Properties. *Med. Drug Discov.* **2020**, *7*, 100027. [[CrossRef](#)]
37. Ren, T.; Wang, Q.; Li, C.; Yang, M.; Zuo, Z. Efficient Brain Uptake of Piperine and Its Pharmacokinetics Characterization after Oral Administration. *Xenobiotica* **2018**, *48*, 1249–1257. [[CrossRef](#)] [[PubMed](#)]
38. Ren, T.; Hu, M.; Cheng, Y.; Shek, T.L.; Xiao, M.; Ho, N.J.; Zhang, C.; Leung, S.S.Y.; Zuo, Z. Piperine-Loaded Nanoparticles with Enhanced Dissolution and Oral Bioavailability for Epilepsy Control. *Eur. J. Pharm. Sci.* **2019**, *137*, 104988. [[CrossRef](#)]
39. Lee, S.H.; Kim, H.Y.; Back, S.Y.; Han, H.-K. Piperine-Mediated Drug Interactions and Formulation Strategy for Piperine: Recent Advances and Future Perspectives. *Expert Opin. Drug Metab. Toxicol.* **2018**, *14*, 43–57. [[CrossRef](#)] [[PubMed](#)]
40. Luszczki, J.J.; Glowniak, K.; Czuczwar, S.J. Imperatorin Enhances the Protective Activity of Conventional Antiepileptic Drugs against Maximal Electroshock-Induced Seizures in Mice. *Eur. J. Pharmacol.* **2007**, *574*, 133–139. [[CrossRef](#)] [[PubMed](#)]
41. Zagaja, M.; Pyrka, D.; Skalicka-Wozniak, K.; Glowniak, K.; Florek-Luszczki, M.; Glensk, M.; Luszczki, J.J. Effect of Xanthotoxin (8-Methoxypsoralen) on the Anticonvulsant Activity of Classical Antiepileptic Drugs against Maximal Electroshock-Induced Seizures in Mice. *Fitoterapia* **2015**, *105*, 1–6. [[CrossRef](#)]
42. Hino, H.; Takahashi, H.; Suzuki, Y.; Tanaka, J.; Ishii, E.; Fukuda, M. Anticonvulsive Effect of Paeoniflorin on Experimental Febrile Seizures in Immature Rats: Possible Application for Febrile Seizures in Children. *PLoS ONE* **2012**, *7*, e42920. [[CrossRef](#)] [[PubMed](#)]
43. Sancheti, J.; Shaikh, M.F.; Chaudhari, R.; Somani, G.; Patil, S.; Jain, P.; Sathaye, S. Characterization of Anticonvulsant and Antiepileptogenic Potential of Thymol in Various Experimental Models. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2014**, *387*, 59–66. [[CrossRef](#)]
44. Zhang, C.; Chen, J.; Zhao, F.; Chen, R.; Yu, D.; Cao, Z. Iritectol G, a Novel Iridal-Type Triterpenoid from Iris Tectorum Displays Anti-Epileptic Activity in Vitro through Inhibition of Sodium Channels. *Fitoterapia* **2017**, *122*, 20–25. [[CrossRef](#)] [[PubMed](#)]
45. Wu, K.-C.; Chen, Y.-H.; Cheng, K.-S.; Kuo, Y.-H.; Yang, C.-T.; Wong, K.-L.; Tu, Y.-K.; Chan, P.; Leung, Y.-M. Suppression of Voltage-Gated Na⁺ Channels and Neuronal Excitability by Imperatorin. *Eur. J. Pharmacol.* **2013**, *721*, 49–55. [[CrossRef](#)]
46. Skalicka-Wozniak, K.; Orhan, I.E.; Cordell, G.A.; Nabavi, S.M.; Budzyńska, B. Implication of Coumarins towards Central Nervous System Disorders. *Pharmacol. Res.* **2016**, *103*, 188–203. [[CrossRef](#)] [[PubMed](#)]
47. Lin, T.-Y.; Huang, W.-J.; Wu, C.-C.; Lu, C.-W.; Wang, S.-J. Acacetin Inhibits Glutamate Release and Prevents Kainic Acid-Induced Neurotoxicity in Rats. *PLoS ONE* **2014**, *9*, e88644. [[CrossRef](#)] [[PubMed](#)]
48. Ribeiro, R.A.; Leite, J.R. Nantenine Alkaloid Presents Anticonvulsant Effect on Two Classical Animal Models. *Phytomedicine* **2003**, *10*, 563–568. [[CrossRef](#)]
49. Akyuz, E.; Polat, A.K.; Eroglu, E.; Kullu, I.; Angelopoulou, E.; Paudel, Y.N. Revisiting the Role of Neurotransmitters in Epilepsy: An Updated Review. *Life Sci.* **2021**, *265*, 118826. [[CrossRef](#)]
50. Manayi, A.; Nabavi, S.M.; Daglia, M.; Jafari, S. Natural Terpenoids as a Promising Source for Modulation of GABAergic System and Treatment of Neurological Diseases. *Pharmacol. Rep.* **2016**, *68*, 671–679. [[CrossRef](#)]
51. De Alvarenga, J.F.R.; Genaro, B.; Costa, B.L.; Purgatto, E.; Manach, C.; Fiamoncin, J. Monoterpenes: Current Knowledge on Food Source, Metabolism, and Health Effects. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 1352–1389. [[CrossRef](#)]
52. Hosseinzadeh, H.; Parvardeh, S. Anticonvulsant Effects of Thymoquinone, the Major Constituent of Nigella Sativa Seeds, in Mice. *Phytomedicine* **2004**, *11*, 56–64. [[CrossRef](#)]
53. Akhondian, J.; Kianifar, H.; Raofzai, M.; Moayedpour, A.; Toosi, M.B.; Khajedaluee, M. The Effect of Thymoquinone on Intractable Pediatric Seizures (Pilot Study). *Epilepsy Res.* **2011**, *93*, 39–43. [[CrossRef](#)]

54. Pottoo, F.H.; Salahuddin, M.; Khan, F.A.; Alomar, F.; Al Dhamen, M.A.; Alhashim, A.F.; Alqattan, H.H.; Gomaa, M.S.; Alomary, M.N. Thymoquinone Potentiates the Effect of Phenytoin against Electroshock-Induced Convulsions in Rats by Reducing the Hyperactivation of m-TOR Pathway and Neuroinflammation: Evidence from In Vivo, In Vitro and Computational Studies. *Pharmaceuticals* **2021**, *14*, 1132. [[CrossRef](#)] [[PubMed](#)]
55. Ullah, I.; Badshah, H.; Naseer, M.I.; Lee, H.Y.; Kim, M.O. Thymoquinone and Vitamin C Attenuates Pentylentetrazole-Induced Seizures Via Activation of GABAB1 Receptor in Adult Rats Cortex and Hippocampus. *Neuromol. Med.* **2015**, *17*, 35–46. [[CrossRef](#)] [[PubMed](#)]
56. Shao, Y.; Feng, Y.; Xie, Y.; Luo, Q.; Chen, L.; Li, B.; Chen, Y. Protective Effects of Thymoquinone Against Convulsant Activity Induced by Lithium-Pilocarpine in a Model of Status Epilepticus. *Neurochem. Res.* **2016**, *41*, 3399–3406. [[CrossRef](#)]
57. Wang, Z.; Wang, X.; Wang, Z.; Lv, X.; Yin, H.; Li, W.; Li, W.; Jiang, L.; Liu, Y. Potential Herb-Drug Interaction Risk of Thymoquinone and Phenytoin. *Chem. Biol. Interact.* **2022**, *353*, 109801. [[CrossRef](#)] [[PubMed](#)]
58. Wu, A.; Ye, X.; Huang, Q.; Dai, W.-M.; Zhang, J.-M. Anti-Epileptic Effects of Valepotriate Isolated from Valeriana Jatamansi Jones and Its Possible Mechanisms. *Phcog. Mag.* **2017**, *13*, 512. [[CrossRef](#)] [[PubMed](#)]
59. Yang, T.; Kong, B.; Gu, J.-W.; Kuang, Y.-Q.; Cheng, L.; Yang, W.-T.; Cheng, J.-M.; Ma, Y.; Yang, X.-K. Anticonvulsant and Sedative Effects of Paederosidic Acid Isolated from Paederia Scandens (Lour.) Merrill. in Mice and Rats. *Pharmacol. Biochem. Behav.* **2013**, *111*, 97–101. [[CrossRef](#)] [[PubMed](#)]
60. Ling, S.-K.; Tanaka, T.; Kouno, I. Effects of Iridoids on Lipoxygenase and Hyaluronidase Activities and Their Activation by β -Glucosidase in the Presence of Amino Acids. *Biol. Pharm. Bull.* **2003**, *26*, 352–356. [[CrossRef](#)]
61. Sasaki, K.; Hatta, S.; Haga, M.; Ohshika, H. Effects of Bilobalide on γ -Aminobutyric Acid Levels and Glutamic Acid Decarboxylase in Mouse Brain. *Eur. J. Pharmacol.* **1999**, *367*, 165–173. [[CrossRef](#)]
62. Jiang, M.; Li, J.; Peng, Q.; Liu, Y.; Liu, W.; Luo, C.; Peng, J.; Li, J.; Yung, K.K.L.; Mo, Z. Neuroprotective Effects of Bilobalide on Cerebral Ischemia and Reperfusion Injury Are Associated with Inhibition of Pro-Inflammatory Mediator Production and down-Regulation of JNK1/2 and P38 MAPK Activation. *J. Neuroinflammation* **2014**, *11*, 167. [[CrossRef](#)]
63. Ng, C.C.; Duke, R.K.; Hinton, T.; Johnston, G.A.R. Effects of Bilobalide, Ginkgolide B and Picrotoxinin on GABA_A Receptor Modulation by Structurally Diverse Positive Modulators. *Eur. J. Pharmacol.* **2017**, *806*, 83–90. [[CrossRef](#)]
64. Damar, U.; Gersner, R.; Johnstone, J.T.; Schachter, S.; Rotenberg, A. Huperzine A as a Neuroprotective and Antiepileptic Drug: A Review of Preclinical Research. *Expert Rev. Neurother.* **2016**, *16*, 671–680. [[CrossRef](#)] [[PubMed](#)]
65. Bialer, M.; Johannessen, S.I.; Levy, R.H.; Perucca, E.; Tomson, T.; White, H.S. Progress Report on New Antiepileptic Drugs: A Summary of the Twelfth Eilat Conference (EILAT XII). *Epilepsy Res.* **2015**, *111*, 85–141. [[CrossRef](#)]
66. Gersner, R.; Ekstein, D.; Dhamne, S.C.; Schachter, S.C.; Rotenberg, A. Huperzine A Prophylaxis against Pentylentetrazole-Induced Seizures in Rats Is Associated with Increased Cortical Inhibition. *Epilepsy Res.* **2015**, *117*, 97–103. [[CrossRef](#)]
67. Li, Y.X.; Zhang, R.Q.; Li, C.R.; Jiang, X.H. Pharmacokinetics of Huperzine a Following Oral Administration to Human Volunteers. *Eur. J. Drug Metabol. Pharmacokinet.* **2007**, *32*, 183–187. [[CrossRef](#)]
68. Koziół, E.; Deniz, F.S.S.; Orhan, I.E.; Marcourt, L.; Budzyńska, B.; Wolfender, J.-L.; Crawford, A.D.; Skalicka-Woźniak, K. High-Performance Counter-Current Chromatography Isolation and Initial Neuroactivity Characterization of Furanocoumarin Derivatives from Peucedanum Alsaticum L (Apiaceae). *Phytomedicine* **2019**, *54*, 259–264. [[CrossRef](#)] [[PubMed](#)]
69. Koziół, E.; Józwiak, K.; Budzyńska, B.; De Witte, P.A.M.; Copmans, D.; Skalicka-Woźniak, K. Comparative Antiseizure Analysis of Diverse Natural Coumarin Derivatives in Zebrafish. *Int. J. Mol. Sci.* **2021**, *22*, 11420. [[CrossRef](#)] [[PubMed](#)]
70. Choi, S.Y.; Ahn, E.-M.; Song, M.-C.; Kim, D.W.; Kang, J.H.; Kwon, O.-S.; Kang, T.-C.; Baek, N.-I. In Vitro GABA-Transaminase Inhibitory Compounds from the Root Of Angelica Dahurica. *Phytother. Res.* **2005**, *19*, 839–845. [[CrossRef](#)] [[PubMed](#)]
71. Singhuber, J.; Baburin, I.; Ecker, G.F.; Kopp, B.; Hering, S. Insights into Structure–Activity Relationship of GABA_A Receptor Modulating Coumarins and Furanocoumarins. *Eur. J. Pharmacol.* **2011**, *668*, 57–64. [[CrossRef](#)]
72. Luszczki, J.J.; Wojda, E.; Andres-Mach, M.; Cisowski, W.; Glensk, M.; Glowniak, K.; Czuczwar, S.J. Anticonvulsant and Acute Neurotoxic Effects of Imperatorin, Osthole and Valproate in the Maximal Electroshock Seizure and Chimney Tests in Mice: A Comparative Study. *Epilepsy Res.* **2009**, *85*, 293–299. [[CrossRef](#)]
73. Ding, J.; Wang, J.-J.; Huang, C.; Wang, L.; Deng, S.; Xu, T.-L.; Ge, W.-H.; Li, W.-G.; Li, F. Curcumol from Rhizoma Curcumae Suppresses Epileptic Seizure by Facilitation of GABA(A) Receptors. *Neuropharmacology* **2014**, *81*, 244–255. [[CrossRef](#)]
74. Garlet, Q.I.; Pires, L.D.C.; Milanese, L.H.; Marafija, J.R.; Baldisserotto, B.; Mello, C.F.; Heinzmann, B.M. (+)-Dehydrofukinone Modulates Membrane Potential and Delays Seizure Onset by GABA_A Receptor-Mediated Mechanism in Mice. *Toxicol. Appl. Pharmacol.* **2017**, *332*, 52–63. [[CrossRef](#)] [[PubMed](#)]
75. Muceniece, R.; Saleniece, K.; Rumaks, J.; Krigere, L.; Dzirkale, Z.; Mezhapuke, R.; Zharkova, O.; Klusa, V. Betulin Binds to γ -Aminobutyric Acid Receptors and Exerts Anticonvulsant Action in Mice. *Pharmacol. Biochem. Behav.* **2008**, *90*, 712–716. [[CrossRef](#)]
76. Lee, B.-H.; Kim, H.-J.; Chung, L.; Nah, S.-Y. Ginsenoside Rg3 Regulates GABA_A Receptor Channel Activity: Involvement of Interaction with the γ_2 Subunit. *Eur. J. Pharmacol.* **2013**, *705*, 119–125. [[CrossRef](#)] [[PubMed](#)]
77. Kazmi, I.; Afzal, M.; Gupta, G.; Anwar, F. Antiepileptic Potential of Ursolic Acid Stearoyl Glucoside by GABA Receptor Stimulation. *CNS Neurosci. Ther.* **2012**, *18*, 799–800. [[CrossRef](#)]

78. Kundap, U.P.; Choo, B.K.M.; Kumari, Y.; Ahmed, N.; Othman, I.B.; Shaikh, M.F. Embelin Protects Against Acute Pentylentetrazole-Induced Seizures and Positively Modulates Cognitive Function in Adult Zebrafish. *Front. Pharmacol.* **2019**, *10*, 1249. [[CrossRef](#)] [[PubMed](#)]
79. Zaugg, J.; Eickmeier, E.; Rueda, D.C.; Hering, S.; Hamburger, M. HPLC-Based Activity Profiling of Angelica Pubescens Roots for New Positive GABAA Receptor Modulators in Xenopus Oocytes. *Fitoterapia* **2011**, *82*, 434–440. [[CrossRef](#)]
80. Grigoletto, J.; Oliveira, C.V.D.; Grauncke, A.C.B.; Souza, T.L.D.; Souto, N.S.; Freitas, M.L.D.; Furian, A.F.; Santos, A.R.S.; Oliveira, M.S. Rosmarinic Acid Is Anticonvulsant against Seizures Induced by Pentylentetrazol and Pilocarpine in Mice. *Epilepsy Behav.* **2016**, *62*, 27–34. [[CrossRef](#)]
81. Aseervatham, G.S.B.; Suryakala, U.; Doulethunisha; Sundaram, S.; Bose, P.C.; Sivasudha, T. Expression Pattern of NMDA Receptors Reveals Antiepileptic Potential of Apigenin 8-C-Glucoside and Chlorogenic Acid in Pilocarpine Induced Epileptic Mice. *Biomed. Pharmacother.* **2016**, *82*, 54–64. [[CrossRef](#)]
82. An, S.-J.; Park, S.-K.; Hwang, I.K.; Choi, S.Y.; Kim, S.K.; Kwon, O.-S.; Jung, S.J.; Baek, N.-I.; Lee, H.Y.; Won, M.H.; et al. Gastrodin Decreases Immunoreactivities of Gamma-Aminobutyric Acid Shunt Enzymes in the Hippocampus of Seizure-Sensitive Gerbils. *J. Neurosci. Res.* **2003**, *71*, 534–543. [[CrossRef](#)]
83. Nassiri-Asl, M.; Shariati-Rad, S.; Zamansoltani, F. Anticonvulsive Effects of Intracerebroventricular Administration of Rutin in Rats. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2008**, *32*, 989–993. [[CrossRef](#)]
84. Park, H.G.; Yoon, S.Y.; Choi, J.Y.; Lee, G.S.; Choi, J.H.; Shin, C.Y.; Son, K.H.; Lee, Y.S.; Kim, W.K.; Ryu, J.H.; et al. Anticonvulsant Effect of Wogonin Isolated from Scutellaria Baicalensis. *Eur. J. Pharmacol.* **2007**, *574*, 112–119. [[CrossRef](#)]
85. Abbasi, E.; Nassiri-Asl, M.; Shafeei, M.; Sheikhi, M. Neuroprotective Effects of Vitexin, a Flavonoid, on Pentylentetrazole-Induced Seizure in Rats: Neuroprotective Effects of Vitexin. *Chem. Biol. Drug Des.* **2012**, *80*, 274–278. [[CrossRef](#)] [[PubMed](#)]
86. Yang, B.; Wang, J.; Zhang, N. Effect of Nobiletin on Experimental Model of Epilepsy. *Transl. Neurosci.* **2018**, *9*, 211–219. [[CrossRef](#)] [[PubMed](#)]
87. Faggion, S.A.; Cunha, A.O.S.; Fachim, H.A.; Gavin, A.S.; Dos Santos, W.F.; Pereira, A.M.S.; Belebony, R.O. Anticonvulsant Profile of the Alkaloids (+)-Erythravine and (+)-11- α -Hydroxy-Erythravine Isolated from the Flowers of Erythrina Mulungu Mart Ex Benth (Leguminosae–Papilionaceae). *Epilepsy Behav.* **2011**, *20*, 441–446. [[CrossRef](#)]
88. Tamboli, A.M.; Rub, R.A.; Ghosh, P.; Bodhankar, S. Antiepileptic Activity of Lobeline Isolated from the Leaf of Lobelia Nicotianae-folia and Its Effect on Brain GABA Level in Mice. *Asian Pac. J. Trop. Biomed.* **2012**, *2*, 537–542. [[CrossRef](#)]
89. Da Silva, A.; De Andrade, J.; Bevilaqua, L.; Desouza, M.; Izquierdo, I.; Henriques, A.; Zuanazzi, J. Anxiolytic-, Antidepressant- and Anticonvulsant-like Effects of the Alkaloid Montanine Isolated from Hippeastrum Vittatum. *Pharmacol. Biochem. Behav.* **2006**, *85*, 148–154. [[CrossRef](#)]
90. Da Cruz, G.M.P.; Felipe, C.F.B.; Scorza, F.A.; Da Costa, M.A.C.; Tavares, A.F.; Menezes, M.L.F.; De Andrade, G.M.; Leal, L.K.A.M.; Brito, G.A.C.; Da Graça Naffah-Mazzacoratti, M.; et al. Piperine Decreases Pilocarpine-Induced Convulsions by GABAergic Mechanisms. *Pharmacol. Biochem. Behav.* **2013**, *104*, 144–153. [[CrossRef](#)]
91. Hanada, T. Ionotropic Glutamate Receptors in Epilepsy: A Review Focusing on AMPA and NMDA Receptors. *Biomolecules* **2020**, *10*, 464. [[CrossRef](#)]
92. Li, J.; Copmans, D.; Partoens, M.; Hunyadi, B.; Luyten, W.; De Witte, P. Zebrafish-Based Screening of Antiseizure Plants Used in Traditional Chinese Medicine: *Magnolia officinalis* Extract and Its Constituents Magnolol and Honokiol Exhibit Potent Anticonvulsant Activity in a Therapy-Resistant Epilepsy Model. *ACS Chem. Neurosci.* **2020**, *11*, 730–742. [[CrossRef](#)]
93. Lin, Y.; Li, Y.; Zeng, Y.; Tian, B.; Qu, X.; Yuan, Q.; Song, Y. Pharmacology, Toxicity, Bioavailability, and Formulation of Magnolol: An Update. *Front. Pharmacol.* **2021**, *12*, 632767. [[CrossRef](#)] [[PubMed](#)]
94. Lee, E.; Kim, S.; Chul Chung, K.; Choo, M.-K.; Kim, D.-H.; Nam, G.; Rhim, H. 20(S)-Ginsenoside Rh2, a Newly Identified Active Ingredient of Ginseng, Inhibits NMDA Receptors in Cultured Rat Hippocampal Neurons. *Eur. J. Pharmacol.* **2006**, *536*, 69–77. [[CrossRef](#)] [[PubMed](#)]
95. Pan, W.; Xue, B.; Yang, C.; Miao, L.; Zhou, L.; Chen, Q.; Cai, Q.; Liu, Y.; Liu, D.; He, H.; et al. Biopharmaceutical Characters and Bioavailability Improving Strategies of Ginsenosides. *Fitoterapia* **2018**, *129*, 272–282. [[CrossRef](#)] [[PubMed](#)]
96. Yu, Y.-H.; Xie, W.; Bao, Y.; Li, H.-M.; Hu, S.-J.; Xing, J.-L. Saikosaponin a Mediates the Anticonvulsant Properties in the HNC Models of AE and SE by Inhibiting NMDA Receptor Current and Persistent Sodium Current. *PLoS ONE* **2012**, *7*, e50694. [[CrossRef](#)]
97. Della-Pace, I.D.; Rambo, L.M.; Ribeiro, L.R.; Saraiva, A.L.L.; De Oliveira, S.M.; Silva, C.R.; Villarinho, J.G.; Rossato, M.F.; Ferreira, J.; De Carvalho, L.M.; et al. Triterpene 3 β , 6 β , 16 β Trihidroxilup-20(29)-Ene Protects against Excitability and Oxidative Damage Induced by Pentylentetrazol: The Role of Na⁺, K⁺-ATPase Activity. *Neuropharmacology* **2013**, *67*, 455–464. [[CrossRef](#)] [[PubMed](#)]
98. Gawel, K.; Kukula-Koch, W.; Banono, N.S.; Nieoczym, D.; Targowska-Duda, K.M.; Czernicka, L.; Parada-Turska, J.; Esguerra, C.V. 6-Gingerol, a Major Constituent of Zingiber Officinale Rhizoma, Exerts Anticonvulsant Activity in the Pentylentetrazole-Induced Seizure Model in Larval Zebrafish. *Int. J. Mol. Sci.* **2021**, *22*, 7745. [[CrossRef](#)] [[PubMed](#)]
99. Coleman, B.R.; Ratcliffe, R.H.; Oguntayo, S.A.; Shi, X.; Doctor, B.P.; Gordon, R.K.; Nambiar, M.P. [+]-Huperzine A Treatment Protects against N-Methyl-d-Aspartate-Induced Seizure/Status Epilepticus in Rats. *Chem. Biol. Interact.* **2008**, *175*, 387–395. [[CrossRef](#)]
100. Ameri, A. Structure-Dependent Inhibitory Action of the Aconitum Alkaloids 14-Benzoyltalidasamine and Talidasamine in Rat Hippocampal Slices. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1998**, *357*, 585–592. [[CrossRef](#)]

101. Chen, K.; Kokate, T.G.; Donevan, S.D.; Carroll, F.I.; Rogawski, M.A. Ibogaine Block of the NMDA Receptor: In Vitro and in Vivo Studies. *Neuropharmacology* **1996**, *35*, 423–431. [[CrossRef](#)]
102. Kang, T.-H.; Murakami, Y.; Matsumoto, K.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. Rhynchophylline and Isorhynchophylline Inhibit NMDA Receptors Expressed in *Xenopus* Oocytes. *Eur. J. Pharmacol.* **2002**, *455*, 27–34. [[CrossRef](#)]
103. Shao, H.; Yang, Y.; Mi, Z.; Zhu, G.; Qi, A.; Ji, W.; Zhu, Z. Anticonvulsant Effect of Rhynchophylline Involved in the Inhibition of Persistent Sodium Current and NMDA Receptor Current in the Pilocarpine Rat Model of Temporal Lobe Epilepsy. *Neuroscience* **2016**, *337*, 355–369. [[CrossRef](#)]
104. Gaston, T.E.; Friedman, D. Pharmacology of Cannabinoids in the Treatment of Epilepsy. *Epilepsy Behav.* **2017**, *70*, 313–318. [[CrossRef](#)]
105. Mouhamed, Y.; Vishnyakov, A.; Qorri, B.; Sambhi, M.; Frank, S.S.; Nowierski, C.; Lamba, A.; Bhatti, U.; Szewczuk, M.R. Therapeutic potential of medicinal marijuana: An educational primer for health care professionals. *Drug Healthc. Patient Saf.* **2018**, *10*, 45–66. [[CrossRef](#)] [[PubMed](#)]
106. Perucca, E. Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last? *J. Epilepsy Res.* **2017**, *7*, 61–76. [[CrossRef](#)]
107. Devinsky, O.; Cilio, M.R.; Cross, H.; Fernandez-Ruiz, J.; French, J.; Hill, C.; Katz, R.; Di Marzo, V.; Jutras-Aswad, D.; Notcutt, W.G.; et al. Cannabidiol: Pharmacology and Potential Therapeutic Role in Epilepsy and Other Neuropsychiatric Disorders. *Epilepsia* **2014**, *55*, 791–802. [[CrossRef](#)] [[PubMed](#)]
108. Morano, A.; Fanella, M.; Albin, M.; Cifelli, P.; Palma, E.; Giallonardo, A.T.; Di Bonaventura, C. Cannabinoids in the Treatment of Epilepsy: Current Status and Future Prospects. *Neuropsychiatr. Dis. Treat.* **2020**, *16*, 381–396. [[CrossRef](#)]
109. De Carvalho Reis, R.; Almeida, K.J.; Da Silva Lopes, L.; De Melo Mendes, C.M.; Bor-Seng-Shu, E. Efficacy and Adverse Event Profile of Cannabidiol and Medicinal Cannabis for Treatment-Resistant Epilepsy: Systematic Review and Meta-Analysis. *Epilepsy Behav.* **2020**, *102*, 106635. [[CrossRef](#)] [[PubMed](#)]
110. Devinsky, O.; Marsh, E.; Friedman, D.; Thiele, E.; Laux, L.; Sullivan, J.; Miller, I.; Flamini, R.; Wilfong, A.; Filloux, F.; et al. Cannabidiol in Patients with Treatment-Resistant Epilepsy: An Open-Label Interventional Trial. *Lancet Neurol.* **2016**, *15*, 270–278. [[CrossRef](#)]
111. Devinsky, O.; Patel, A.D.; Cross, J.H.; Villanueva, V.; Wirrell, E.C.; Privitera, M.; Greenwood, S.M.; Roberts, C.; Checketts, D.; VanLandingham, K.E.; et al. Effect of Cannabidiol on Drop Seizures in the Lennox—Gastaut Syndrome. *N. Engl. J. Med.* **2018**, *378*, 1888–1897. [[CrossRef](#)]
112. Devinsky, O.; Cross, J.H.; Laux, L.; Marsh, E.; Miller, I.; Nabbut, R.; Scheffer, I.E.; Thiele, E.A.; Wright, S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N. Engl. J. Med.* **2017**, *376*, 2011–2020. [[CrossRef](#)]
113. Devinsky, O.; Nabbut, R.; Miller, I.; Laux, L.; Zolnowska, M.; Wright, S.; Roberts, C. Long-term Cannabidiol Treatment in Patients with Dravet Syndrome: An Open-label Extension Trial. *Epilepsia* **2019**, *60*, 294–302. [[CrossRef](#)]
114. Arzimanoglou, A.; Brandl, U.; Cross, J.H.; Gil-Nagel, A.; Lagae, L.; Landmark, C.J.; Specchio, N.; Nabbut, R.; Thiele, E.A.; Gubbay, O.; et al. Epilepsy and Cannabidiol: A Guide to Treatment. *Epileptic Disord.* **2020**, *22*, 1–14. [[CrossRef](#)]
115. Bialer, M.; Johannessen, S.I.; Levy, R.H.; Perucca, E.; Tomson, T.; White, H.S. Progress Report on New Antiepileptic Drugs: A Summary of the Thirteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIII). *Epilepsia* **2017**, *58*, 181–221. [[CrossRef](#)]
116. Shawki, M.; El Wakeel, L.; Shatla, R.; EL-Saeed, G.; Ibrahim, S.; Badary, O. The Clinical Outcome of Adjuvant Therapy with Black Seed Oil on Intractable Paediatric Seizures: A Pilot Study. *Epileptic Disord.* **2013**, *15*, 295–301. [[CrossRef](#)]
117. McKinney, M.; Miller, J.H.; Yamada, F.; Tuckmantel, W.; Kozikowski, A.P. Potencies and Stereoselectivities of Enantiomers of Huperzine A for Inhibition of Rat Cortical Acetylcholinesterase. *Eur. J. Pharmacol.* **1991**, *203*, 303–305. [[CrossRef](#)]
118. Bialer, M.; Johannessen, S.I.; Koepp, M.J.; Levy, R.H.; Perucca, E.; Tomson, T.; White, H.S. Progress Report on New Antiepileptic Drugs: A Summary of the Fourteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIV). I. Drugs in Preclinical and Early Clinical Development. *Epilepsia* **2018**, *59*, 1811–1841. [[CrossRef](#)]
119. Rafii, M.S.; Walsh, S.; Little, J.T.; Behan, K.; Reynolds, B.; Ward, C.; Jin, S.; Thomas, R.; Aisen, P.S. For the Alzheimer’s Disease Cooperative Study A Phase II Trial of Huperzine A in Mild to Moderate Alzheimer Disease. *Neurology* **2011**, *76*, 1389–1394. [[CrossRef](#)]
120. Fukuoka, M.; Kuki, I.; Kawawaki, H.; Okazaki, S.; Kim, K.; Hattori, Y.; Tsuji, H.; Nukui, M.; Inoue, T.; Yoshida, Y.; et al. Quinidine Therapy for West Syndrome with KCNT1 Mutation: A Case Report. *Brain Develop.* **2017**, *39*, 80–83. [[CrossRef](#)]
121. Mikati, M.A.; Jiang, Y.; Carboni, M.; Shashi, V.; Petrovski, S.; Spillmann, R.; Milligan, C.J.; Li, M.; Grefe, A.; McConkie, A.; et al. Quinidine in the Treatment of KCNT1-Positive Epilepsies: Quinidine in KCNT1 Epilepsies. *Ann. Neurol.* **2015**, *78*, 995–999. [[CrossRef](#)]
122. Bearden, D.; Strong, A.; Ehnnot, J.; DiGiovine, M.; Dlugos, D.; Goldberg, E.M. Targeted Treatment of Migrating Partial Seizures of Infancy with Quinidine: MPSI and Quinidine. *Ann. Neurol.* **2014**, *76*, 457–461. [[CrossRef](#)]
123. Yoshitomi, S.; Takahashi, Y.; Yamaguchi, T.; Oboshi, T.; Horino, A.; Ikeda, H.; Imai, K.; Okanishi, T.; Nakashima, M.; Saito, H.; et al. Quinidine Therapy and Therapeutic Drug Monitoring in Four Patients with KCNT1 Mutations. *Epileptic Disord.* **2019**, *21*, 48–54. [[CrossRef](#)]
124. Abdelnour, E.; Gallentine, W.; McDonald, M.; Sachdev, M.; Jiang, Y.-H.; Mikati, M.A. Does Age Affect Response to Quinidine in Patients with KCNT1 Mutations? Report of Three New Cases and Review of the Literature. *Seizure* **2018**, *55*, 1–3. [[CrossRef](#)]

125. Mullen, S.A.; Carney, P.W.; Roten, A.; Ching, M.; Lightfoot, P.A.; Churilov, L.; Nair, U.; Li, M.; Berkovic, S.F.; Petrou, S.; et al. Precision Therapy for Epilepsy Due to *KCNT1* Mutations: A Randomized Trial of Oral Quinidine. *Neurology* **2018**, *90*, e67–e72. [[CrossRef](#)]
126. Fitzgerald, M.P.; Fiannacca, M.; Smith, D.M.; Gertler, T.S.; Gunning, B.; Syrbe, S.; Verbeek, N.; Stamberger, H.; Weckhuysen, S.; Ceulemans, B.; et al. Treatment Responsiveness in *KCNT1*-Related Epilepsy. *Neurotherapeutics* **2019**, *16*, 848–857. [[CrossRef](#)]
127. Rahimi, N.; Delfan, B.; Motamed-Gorji, N.; Dehpour, A.R. Effects of Oleuropein on Pentylentetrazol-Induced Seizures in Mice: Involvement of Opioidergic and Nitroergic Systems. *J. Nat. Med.* **2017**, *71*, 389–396. [[CrossRef](#)]
128. Buenafe, O.E.; Orellana-Paucar, A.; Maes, J.; Huang, H.; Ying, X.; De Borggraeve, W.; Crawford, A.D.; Luyten, W.; Esguerra, C.V.; De Witte, P. Tanshinone IIA Exhibits Anticonvulsant Activity in Zebrafish and Mouse Seizure Models. *ACS Chem. Neurosci.* **2013**, *4*, 1479–1487. [[CrossRef](#)]
129. Sng, J.C.G.; Taniura, H.; Yoneda, Y. Histone Modifications in Kainate-Induced Status Epilepticus. *Eur. J. Neurosci.* **2006**, *23*, 1269–1282. [[CrossRef](#)]
130. Jyoti, A.; Sethi, P.; Sharma, D. Curcumin Protects against Electrobehavioral Progression of Seizures in the Iron-Induced Experimental Model of Epileptogenesis. *Epilepsy Behav.* **2009**, *14*, 300–308. [[CrossRef](#)]
131. Gupta, Y.K.; Chaudhary, G.; Srivastava, A.K. Protective Effect of Resveratrol against Pentylentetrazole-Induced Seizures and Its Modulation by an Adenosinergic System. *Pharmacology* **2002**, *65*, 170–174. [[CrossRef](#)]
132. Gao, F.; Gao, Y.; Liu, Y.; Wang, L.; Li, Y. Berberine Exerts an Anticonvulsant Effect and Ameliorates Memory Impairment and Oxidative Stress in a Pilocarpine-Induced Epilepsy Model in the Rat. *Neuropsychiatr. Dis. Treat.* **2014**, *10*, 2139. [[CrossRef](#)]
133. Bhutada, P.; Mundhada, Y.; Bansod, K.; Dixit, P.; Umathe, S.; Mundhada, D. Anticonvulsant Activity of Berberine, an Isoquinoline Alkaloid in Mice. *Epilepsy Behav.* **2010**, *18*, 207–210. [[CrossRef](#)]
134. Aricioglu, F. Effect of Harmane on the Convulsive Threshold in Epilepsy Models in Mice. *Ann. N. Y. Acad. Sci.* **2003**, *1009*, 190–195. [[CrossRef](#)]
135. Ameri, A. Inhibition of Stimulus-Triggered and Spontaneous Epileptiform Activity in Rat Hippocampal Slices by the Aconitum Alkaloid Mesaconitine. *Eur. J. Pharmacol.* **1998**, *342*, 183–191. [[CrossRef](#)]
136. Chen, C.-Y.; Li, W.; Qu, K.-P.; Chen, C.-R. Piperine Exerts Anti-Seizure Effects via the TRPV1 Receptor in Mice. *Eur. J. Pharmacol.* **2013**, *714*, 288–294. [[CrossRef](#)]
137. Nassiri-Asl, M.; Zamansoltani, F.; Torabinejad, B. Antiepileptic Effects of Quinine in the Pentylentetrazole Model of Seizure. *Seizure* **2009**, *18*, 129–132. [[CrossRef](#)]
138. Bostanci, M.Ö.; Bagirici, F. Anticonvulsive Effects of Quinine on Penicillin-Induced Epileptiform Activity: An in Vivo Study. *Seizure* **2007**, *16*, 166–172. [[CrossRef](#)] [[PubMed](#)]
139. Yoon, S.-R.; Jo, Y.-J.; Yang, S.; Kim, Y.-B.; Nam, S.-Y.; Kim, H.-C.; Hong, J.T.; Oh, K.-W. Sanjoinine a Isolated from Semen Zizyphi Spinosi Protects against Kainic Acid-Induced Convulsions. *Arch. Pharm. Res.* **2009**, *32*, 1515–1523. [[CrossRef](#)]
140. Chang, C.-K.; Lin, M.-T. DL-Tetrahydropalmatine May Act through Inhibition of Amygdaloid Release of Dopamine to Inhibit an Epileptic Attack in Rats. *Neurosci. Lett.* **2001**, *307*, 163–166. [[CrossRef](#)]
141. Oliveira, C.C.D.; Oliveira, C.V.D.; Grigoletto, J.; Ribeiro, L.R.; Funck, V.R.; Grauncke, A.C.B.; Souza, T.L.D.; Souto, N.S.; Furian, A.F.; Menezes, I.R.A.; et al. Anticonvulsant Activity of β -Caryophyllene against Pentylentetrazol-Induced Seizures. *Epilepsy Behav.* **2016**, *56*, 26–31. [[CrossRef](#)]
142. Tchekalarova, J.; Da Conceição Machado, K.; Gomes Júnior, A.L.; De Carvalho Melo Cavalcante, A.A.; Momchilova, A.; Tzoneva, R. Pharmacological Characterization of the Cannabinoid Receptor 2 Agonist, β -Caryophyllene on Seizure Models in Mice. *Seizure* **2018**, *57*, 22–26. [[CrossRef](#)]
143. Torres-Hernández, B.A.; Del Valle-Mojica, L.M.; Ortíz, J.G. Valerenic Acid and Valeriana Officinalis Extracts Delay Onset of Pentylentetrazole (PTZ)-Induced Seizures in Adult Danio Rerio (Zebrafish). *BMC Complement. Altern. Med.* **2015**, *15*, 228. [[CrossRef](#)]
144. Talevi, A.; Cravero, M.S.; Castro, E.A.; Bruno-Blanch, L.E. Discovery of Anticonvulsant Activity of Abietic Acid through Application of Linear Discriminant Analysis. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1684–1690. [[CrossRef](#)] [[PubMed](#)]
145. Costa, J.P.; Ferreira, P.B.; De Sousa, D.P.; Jordan, J.; Freitas, R.M. Anticonvulsant Effect of Phytol in a Pilocarpine Model in Mice. *Neurosci. Lett.* **2012**, *523*, 115–118. [[CrossRef](#)]
146. Li, X.; Zhang, M.; Xiang, C.; Li, B.-C.; Li, P. Antiepileptic C₂₁ Steroids from the Roots of *Cynanchum otophyllum*. *J. Asian Nat. Prod. Res.* **2015**, *17*, 724–732. [[CrossRef](#)]
147. Li, J.-L.; Gao, Z.-B.; Zhao, W.-M. Identification and Evaluation of Antiepileptic Activity of C₂₁ Steroidal Glycosides from the Roots of *Cynanchum wilfordii*. *J. Nat. Prod.* **2016**, *79*, 89–97. [[CrossRef](#)]
148. Li, J.-L.; Zhou, J.; Chen, Z.-H.; Guo, S.-Y.; Li, C.-Q.; Zhao, W.-M. Bioactive C₂₁ Steroidal Glycosides from the Roots of *Cynanchum Otophyllum* That Suppress the Seizure-like Locomotor Activity of Zebrafish Caused by Pentylentetrazole. *J. Nat. Prod.* **2015**, *78*, 1548–1555. [[CrossRef](#)]
149. Challal, S.; Buenafe, O.E.M.; Queiroz, E.F.; Maljevic, S.; Marcourt, L.; Bock, M.; Kloeti, W.; Dayrit, F.M.; Harvey, A.L.; Lerche, H.; et al. Zebrafish Bioassay-Guided Microfractionation Identifies Anticonvulsant Steroid Glycosides from the Philippine Medicinal Plant *Solanum torvum*. *ACS Chem. Neurosci.* **2014**, *5*, 993–1004. [[CrossRef](#)]
150. Taviano, M.F.; Miceli, N.; Monforte, M.T.; Tzakou, O.; Galati, E.M. Ursolic Acid Plays a Role In *Nepeta Sibthorpii* Benthams CNS Depressing Effects. *Phytother. Res.* **2007**, *21*, 382–385. [[CrossRef](#)]

151. Nieoczym, D.; Socała, K.; Raszewski, G.; Wlaź, P. Effect of Quercetin and Rutin in Some Acute Seizure Models in Mice. *Prog. Neuro-Psychopharmacol. Biol. Psychiatr.* **2014**, *54*, 50–58. [[CrossRef](#)]
152. Khan, I.; Karim, N.; Ahmad, W.; Abdelhalim, A.; Chebib, M. GABA-A Receptor Modulation and Anticonvulsant, Anxiolytic, and Antidepressant Activities of Constituents from *Artemisia Indica* Linn. *Evid.-Based Complement. Altern. Med.* **2016**, *2016*, 1215393. [[CrossRef](#)]
153. Lee, J.-K.; Jeong, J.W.; Jang, T.; Lee, G.-W.; Han, H.; Kang, J.-S.; Kim, I.-H. Decursin Attenuates Kainic Acid-Induced Seizures in Mice. *NeuroReport* **2014**, *25*, 1243–1249. [[CrossRef](#)]
154. Nugroho, A.; Lim, S.-C.; Choi, J.; Park, H.-J. Identification and Quantification of the Sedative and Anticonvulsant Flavone Glycoside from *Chrysanthemum Boreale*. *Arch. Pharm. Res.* **2013**, *36*, 51–60. [[CrossRef](#)] [[PubMed](#)]
155. Avallone, R.; Zanolli, P.; Puia, G.; Kleinschnitz, M.; Schreier, P.; Baraldi, M. Pharmacological Profile of Apigenin, a Flavonoid Isolated from *Matricaria Chamomilla*. *Biochem. Pharmacol.* **2000**, *59*, 1387–1394. [[CrossRef](#)] [[PubMed](#)]
156. Du, X.-M.; Sun, N.-Y.; Takizawa, N.; Guo, Y.-T.; Shoyama, Y. Sedative and Anticonvulsant Activities of Goodyerin, a Flavonol Glycoside from *Goodyera schlechtendaliana*. *Phytother. Res.* **2002**, *16*, 261–263. [[CrossRef](#)]
157. González-Trujano, M.E.; Domínguez, F.; Pérez-Ortega, G.; Aguillón, M.; Martínez-Vargas, D.; Almazán-Alvarado, S.; Martínez, A. Justicia Spicigera Schltdl. and Kaempferitrin as Potential Anticonvulsant Natural Products. *Biomed. Pharmacother.* **2017**, *92*, 240–248. [[CrossRef](#)] [[PubMed](#)]
158. Copmans, D.; Orellana-Paucar, A.M.; Steurs, G.; Zhang, Y.; Ny, A.; Foubert, K.; Exarchou, V.; Siekierska, A.; Kim, Y.; De Borggraeve, W.; et al. Methylated Flavonoids as Anti-Seizure Agents: Naringenin 4',7-Dimethyl Ether Attenuates Epileptic Seizures in Zebrafish and Mouse Models. *Neurochem. Int.* **2018**, *112*, 124–133. [[CrossRef](#)]
159. Santos Rosa, D.; Faggion, S.A.; Gavin, A.S.; Anderson De Souza, M.; Fachim, H.A.; Ferreira Dos Santos, W.; Soares Pereira, A.M.; Cunha, A.O.S.; Belebony, R.O. Erysothrine, an Alkaloid Extracted from Flowers of *Erythrina Mulungu* Mart. Ex Benth: Evaluating Its Anticonvulsant and Anxiolytic Potential. *Epilepsy Behav.* **2012**, *23*, 205–212. [[CrossRef](#)]
160. Copmans, D.; Kildgaard, S.; Rasmussen, S.A.; Ślęzak, M.; Dirx, N.; Partoens, M.; Esguerra, C.V.; Crawford, A.D.; Larsen, T.O.; De Witte, P.A.M. Zebrafish-Based Discovery of Antiseizure Compounds from the North Sea: Isoquinoline Alkaloids TMC-120A and TMC-120B. *Marine Drugs* **2019**, *17*, 607. [[CrossRef](#)]
161. Copmans, D.; Rateb, M.; Tabudravu, J.N.; Pérez-Bonilla, M.; Dirx, N.; Vallorani, R.; Diaz, C.; Pérez Del Palacio, J.; Smith, A.J.; Ebel, R.; et al. Zebrafish-Based Discovery of Antiseizure Compounds from the Red Sea: Pseurotin A₂ and Azaspirofurane A. *ACS Chem. Neurosci.* **2018**, *9*, 1652–1662. [[CrossRef](#)]
162. Tambe, R.; Jain, P.; Patil, S.; Ghumatkar, P.; Sathaye, S. Antiepileptogenic Effects of Borneol in Pentylentetrazole-Induced Kindling in Mice. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2016**, *389*, 467–475. [[CrossRef](#)]
163. Orellana-Paucar, A.M.; Afrikanova, T.; Thomas, J.; Aibuldinov, Y.K.; Dehaen, W.; De Witte, P.A.M.; Esguerra, C.V. Insights from Zebrafish and Mouse Models on the Activity and Safety of Ar-Turmerone as a Potential Drug Candidate for the Treatment of Epilepsy. *PLoS ONE* **2013**, *8*, e81634. [[CrossRef](#)]
164. Wang, Z.; Mong, M.; Yang, Y.; Yin, M. Asiatic Acid and Maslinic Acid Attenuated Kainic Acid-Induced Seizure through Decreasing Hippocampal Inflammatory and Oxidative Stress. *Epilepsy Res.* **2018**, *139*, 28–34. [[CrossRef](#)]
165. Lu, C.W.; Lin, T.Y.; Wang, S.J.; Huang, S.K. Asiatic Acid, an Active Substance of *Centella Asiatica*, Presynaptically Depresses Glutamate Release in the Rat Hippocampus. *Eur. J. Pharmacol.* **2019**, *865*, 172781. [[CrossRef](#)]
166. Sheng, F.; Chen, M.; Tan, Y.; Xiang, C.; Zhang, M.; Li, B.; Su, H.; He, C.; Wan, J.; Li, P. Protective Effects of Otophyllaside N on Pentylentetrazol-Induced Neuronal Injury In Vitro and In Vivo. *Front. Pharmacol.* **2016**, *7*, 224. [[CrossRef](#)]
167. Tu, W.; Qian, S. Anti-Epileptic Effect of 16-O-Acetyldigitoxigenin via Suppressing MTOR Signaling Pathway. *Cell Mol. Biol.* **2019**, *65*, 59–63. [[CrossRef](#)]
168. Yu, X.; Zhou, T.; Yu, H.; Chang, L.; Wei, L. Corilagin Reduces the Frequency of Seizures and Improves Cognitive Function in a Rat Model of Chronic Epilepsy. *Med. Sci. Monit.* **2018**, *24*, 2832–2840. [[CrossRef](#)]
169. Zhou, Z.; Lin, Y.; Zheng, H.; He, Y.; Xu, H.; Zhang, S.; Weng, W.; Li, W.; Zhu, L.; Yang, H. Anticonvulsive and Neuroprotective Effects of Synergetic Combination of Phenytoin and Gastrodin on the Convulsion Induced by Penicillin in Mice. *Fundam. Clin. Pharmacol.* **2015**, *29*, 371–381. [[CrossRef](#)] [[PubMed](#)]
170. Ahmadian, S.R.; Ghasemi-Kasman, M.; Pouramir, M.; Sadeghi, F. Arbutin Attenuates Cognitive Impairment and Inflammatory Response in Pentylentetrazol-Induced Kindling Model of Epilepsy. *Neuropharmacology* **2019**, *146*, 117–127. [[CrossRef](#)] [[PubMed](#)]
171. Hsieh, C.-L.; Chang, C.-H.; Chiang, S.-Y.; Li, T.-C.; Tang, N.-Y.; Pon, C.-Z.; Hsieh, C.-T.; Lin, J.-G. Anticonvulsive and Free Radical Scavenging Activities of Vanillyl Alcohol in Ferric Chloride-Induced Epileptic Seizures in Sprague-Dawley Rats. *Life Sci.* **2000**, *67*, 1185–1195. [[CrossRef](#)]
172. Gupta, Y.K.; Briyal, S.; Chaudhary, G. Protective Effect of Trans-Resveratrol against Kainic Acid-Induced Seizures and Oxidative Stress in Rats. *Pharmacol. Biochem. Behav.* **2002**, *71*, 245–249. [[CrossRef](#)] [[PubMed](#)]
173. Ethemoglu, M.S.; Seker, F.B.; Akkaya, H.; Kilic, E.; Aslan, I.; Erdogan, C.S.; Yilmaz, B. Anticonvulsant Activity of Resveratrol-Loaded Liposomes in Vivo. *Neuroscience* **2017**, *357*, 12–19. [[CrossRef](#)]
174. Liu, Y.-F.; Gao, F.; Li, X.-W.; Jia, R.-H.; Meng, X.-D.; Zhao, R.; Jing, Y.-Y.; Wang, Y.; Jiang, W. The Anticonvulsant and Neuroprotective Effects of Baicalin on Pilocarpine-Induced Epileptic Model in Rats. *Neurochem. Res.* **2012**, *37*, 1670–1680. [[CrossRef](#)] [[PubMed](#)]

175. Ha, S.K.; Moon, E.; Kim, S.Y. Chrysin Suppresses LPS-Stimulated Proinflammatory Responses by Blocking NF-KB and JNK Activations in Microglia Cells. *Neurosci. Lett.* **2010**, *485*, 143–147. [[CrossRef](#)] [[PubMed](#)]
176. Raygude, K.S.; Kandhare, A.D.; Ghosh, P.; Bodhankar, S.L. Anticonvulsant Effect of Fisetin by Modulation of Endogenous Biomarkers. *Biomed. Prevent. Nutr.* **2012**, *2*, 215–222. [[CrossRef](#)]
177. Das, J.; Singh, R.; Sharma, D. Antiepileptic Effect of Fisetin in Iron-Induced Experimental Model of Traumatic Epilepsy in Rats in the Light of Electrophysiological, Biochemical, and Behavioral Observations. *Nutr. Neurosci.* **2017**, *20*, 255–264. [[CrossRef](#)]
178. Tambe, R.; Patil, A.; Jain, P.; Sancheti, J.; Somani, G.; Sathaye, S. Assessment of Luteolin Isolated from Eclipta Alba Leaves in Animal Models of Epilepsy. *Pharm. Biol.* **2017**, *55*, 264–268. [[CrossRef](#)] [[PubMed](#)]
179. Golechha, M.; Chaudhry, U.; Bhatia, J.; Saluja, D.; Arya, D.S. Naringin Protects against Kainic Acid-Induced Status Epilepticus in Rats: Evidence for an Antioxidant, Anti-Inflammatory and Neuroprotective Intervention. *Biol. Pharm. Bull.* **2011**, *34*, 360–365. [[CrossRef](#)]
180. Gao, B.; Wu, Y.; Yang, Y.-J.; Li, W.-Z.; Dong, K.; Zhou, J.; Yin, Y.-Y.; Huang, D.-K.; Wu, W.-N. Sinomenine Exerts Anticonvulsant Profile and Neuroprotective Activity in Pentylentetrazole Kindled Rats: Involvement of Inhibition of NLRP1 Inflammasome. *J. Neuroinflamm.* **2018**, *15*, 152. [[CrossRef](#)]

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