A pharmacological basis of herbal medicines for epilepsy

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A B S T R A C T

Epilepsy is the most common chronic neurological disease, affecting about 1% of the world’s population during their lifetime. Most people with epilepsy can attain a seizure-free life upon treatment with antiepileptic drugs (AEDs). Unfortunately, seizures in up to 30% do not respond to treatment. It is estimated that 90% of people with epilepsy live in developing countries, and most of them receive no drug treatment for the disease. This treatment gap has motivated investigations into the effects of plants that have been used by traditional healers all over the world to treat seizures. Extracts of hundreds of plants have been shown to exhibit anticonvulsant activity in phenotypic screens performed in experimental animals. Some of those extracts appear to exhibit anticonvulsant efficacy similar to that of synthetic AEDs. Dozens of plant-derived chemical compounds have similarly been shown to act as anticonvulsants in various in vivo and in vitro assays. To a significant degree, anticonvulsant effects of plant extracts can be attributed to widely distributed flavonoids, (furan)coumarins, phenylpropanoids, and terpenoids. Flavonoids and coumarins have been shown to interact with the benzodiazepine site of the GABA_A receptor and various voltage-gated ion channels, which are targets of synthetic AEDs. Modulation of the activity of ligand-gated and voltage-gated ion channels provides an explanatory basis of the anticonvulsant effects of plant secondary metabolites. Many complex extracts and single plant-derived compounds exhibit anti-inflammatory, neuroprotective, and cognition-enhancing activities that may be beneficial in the treatment of epilepsy. Thus, botanicals provide a base for target-oriented antiepileptic drug discovery and development. In the future, preclinical work should focus on the characterization of the effects of plant extracts and plant-derived compounds on well-defined targets rather than on phenotypic screening using in vivo animal models of acute seizures. At the same time, available data provide ample justification for clinical studies with selected standardized botanical extracts and plant-derived compounds.

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1. Introduction

Epilepsy is the most common chronic neurological disease worldwide with the burden of lifetime epilepsy affecting approximately 70 million people [1,2]. Almost 90% of people with epilepsy are thought to live in developing countries [1]. Epilepsy was first described in written texts around 2000 BCE [3]. The disease is still often considered a divine punishment or a consequence of witchcraft. Since antiquity, however, a possible familial propensity for the disease has been recognized [3,4]. As early as 600 BCE, Indian and Greek doctors considered epilepsy to be a disorder of the brain [3].

1.1. Definition of epilepsy

According to the most recent definition released by the International League Against Epilepsy (ILAE), epilepsy is a disease of the brain defined by any of the following conditions: (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) seizures occurring as symptoms of a known epilepsy syndrome. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [5].

The ILAE has also recently updated the terminology and concepts used for the classification of seizures and forms of epilepsy [6]. Roughly speaking, seizures are classified as either generalized or focal. Generalized epileptic seizures originate at a single point but rapidly engage bilaterally distributed networks in the central nervous system. The
affected bilateral networks can include cortical and subcortical structures but do not necessarily involve the entire cortex. Although the points of onset of individual seizures can appear localized, the location and lateralization can change from one seizure to another. Focal epileptic seizures originate within networks of only one hemisphere and may be discretely localized or more widely distributed. Focal seizures may also originate in subcortical structures. Overall, various forms of epilepsy are classified into 1) electroclinical syndromes, 2) epilepsies associated with structural or metabolic conditions, and 3) epilepsies of unknown cause. The electroclinical syndromes can be further classified according to age of onset.

1.2. Drug treatment of epilepsy

Treatment for epilepsy has historically included punishment, incantations, amulets, special diets and living arrangements; mineral, animal and plant products; X-ray irradiation, surgery; and, only since the second decade of the 20th century, synthetic drugs [3, 7]. Today, people with epilepsy are first treated with synthetic AEDs. In cases when drugs are not successful, a special diet, alternative and complementary medicine based therapy, vagus nerve stimulation, direct brain stimulation, or epilepsy surgery may be indicated [8].

The first synthetic AED was phenobarbital, which was introduced in 1912 by Hauptmann [9]. The drug was considered superior to bromide drugs (in use since 1857) and preceded the introduction of phenytoin (diphenylhydantoin) in 1939. Phenytoin is still one of the most widely used drugs globally and remains a drug of choice in the emergency treatment of seizures and in status epilepticus [10]. The 1960s saw the introduction of the “second generation” AEDs carbamazepine and valproate (first prepared in 1882, but its anticonvulsant effects were only serendipitously discovered in 1962) followed by another wave of new (“third generation”) AEDs in the 1990s [11–13]. Third generation AEDs are not more effective than the older drugs, but they appear to exert fewer pharmacokinetic interactions with other drugs and exhibit fewer adverse effects [14]. Importantly, all AEDs act as anticonvulsants, i.e., they prevent or shorten the occurrence of seizures, but not as antiepileptogenics (i.e., they do not prevent the development of epilepsy in humans such as after traumatic brain injury) [15] even though levetiracetam and ethosuximide have done so in animal models of genetic epilepsy [16]. Overall, 70% to 80% of the treated patients can lead seizure-free lives with appropriate medication; seizures in the remainder are considered pharmacoresistant or “treatment resistant” [17]. Nonetheless, it is estimated that, globally, 80% of patients with epilepsy (mostly residing in developing countries) receive no drug treatment for the disease at all [18, 19]. In order to overcome this treatment gap, the World Health Organization (WHO), ILAE, and International Bureau for Epilepsy (IBE) have united in a global campaign against epilepsy in Africa [20]. This partnership advocates the use of phenobarbital as a first-line drug for all patients with epilepsy. It has been estimated that phenobarbital may cost as little as $5 to $10 per patient/year in sub-Saharan Africa but up to six times more in many developing Asian countries [21].

Availability and cost of drugs are, however, two obstacles hindering the treatment of epilepsy. In sub-Saharan Africa, for example, the large majority of the rural population has virtually no access to modern healthcare facilities, and patients often must travel long distances to seek medical attention. Furthermore, epilepsy is often associated with tremendous stigma. Patients, therefore, may not be able to get the psychological, logistical, and financial support needed to obtain care in far-off medical facilities [22]. In this context, traditional healers often provide the first and only source of therapy. Reportedly, most of the traditional healers in Tanzania, for example, clearly recognize the symptoms of the disease, but many believe that epilepsy is caused by witchcraft or heredity (although head injury and malaria were also recognized as potential causative factors) [23]. Even when AEDs and health care facilities are available, more than 90% of patients receive parallel treatment from traditional healers [24]. While it is viewed that most of the people with epilepsy living in developing countries who do not receive treatment could be treated with existing drugs, the problem of drug-resistant epilepsy continues to motivate the search for new AEDs. Discovery and development of synthetic antiepileptic drugs, however, has come to a crossroads, and “new avenues for anti-epileptic drug discovery and development” have been proposed [12, 14].

Uncertainty creates opportunities and openings for previously underappreciated modes of discovery and treatment. One of the oldest and most widely used forms of antiepileptic treatment makes use of botanicals. For example, herbal medicine is the most common mode of treatment administered by traditional healers in sub-Saharan Africa [4, 23–25]. Herbal medicines are also used for epilepsy in Asia and Central and South America and were the only available form of antiepileptic drug treatment in Europe until the mid-19th century [26]. In fact, herbal medicine is the direct progenitor of modern pharmacotherapy, and some of the most important and successful drugs are derived from natural products [27, 28].

There is a large body of literature reporting research on the anticonvulsant effects of plants. To date, this knowledge has not had a major influence on mainstream antiepileptic drug development and treatment. Interestingly, however, three plant-derived compounds cannaabidiol and cannabidiavarin (from Cannabis sativa) and huperzine A (from Huperzia serrata) are currently under development as antiepileptic drugs [29]. In this article, the literature on anticonvulsant and antiepileptic effects of botanicals is reviewed and discussed. There is a particular focus on pharmacological effects on “established” molecular targets as well as a discussion on the activity of plant-derived compounds on emerging targets of AEDs. Concise summaries of the literature of anticonvulsant plant extracts and single plant-derived compounds underpinning this review are presented in Supplementary Tables 1 and 2, respectively.

2. Preclinical research on botanicals for epilepsy

2.1. Animal models

The anticonvulsant effects of phenobarbital were discovered serendipitously in 1912, the year of its synthesis, when the German physician Hauptmann gave the drug to patients with epilepsy as a tranquilizer and noticed a pronounced effect on their seizures [10]. The anticonvulsant activity of phenytoin was discovered when Merritt and Putnam used electroshock-induced seizures in cats to systematically screen for compounds with anticonvulsant activity almost 30 years after its synthesis by the German chemist Heinrich Blitz in 1908 [10, 13, 30]. Ever since, the search and discovery of AEDs has depended on the use of animal models [12]. For example, the Anticonvulsant Screening Project that was instigated by the National Institutes of Neurological Disorders and Stroke (NINDS) has used animal models to test over 25,000 investigational AEDs from academic and pharmaceutical chemists worldwide [30]. The two most widely used models are the maximal electroshock seizures (MES) and subcutaneous pentylentetrazol (PTZ) models in rodents [12, 30]. Positive results in either model suggest that the test compound likely penetrated the blood–brain barrier and exerted its effect in the central nervous system (CNS). Both models have clearly defined endpoints (e.g., time of onset and duration of seizures, death), and require only basic technical expertise [30], and appear to predict their effect in humans reasonably well [31].

Over the last decade the view of the most commonly used animal models in AED drug discovery has changed considerably [12, 32]. Contrary to the long prevalent view that both the MES and PTZ models were nonselective with respect to molecular targets and mechanisms of action [32], the MES model is now considered to be particularly sensitive to drugs blocking sodium channels, while the PTZ model is thought to be especially sensitive to GABA mimetic drugs [33]. The MES model has been blamed for producing false positive data. For
example, antagonists of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors exhibited very potent activity against tonic seizures in the MES test but not in patients with epilepsy [33].

Acute clonic seizures in animals can also be induced by the GABA<sub>B</sub> receptor antagonist allo chloride (from the North American plant *Dicentra cucullaria*) and the GABA<sub>B</sub> receptor Cl<sup>-</sup> channel-blocking alkaloid picrotoxin (from the Southeast Asian plant *Anamirta cocculus*). In order to differentiate investigational compounds from existing AEDs, the 6-Hz psychomotor seizure model in mice has been introduced [29]. This model is resistant to some of the old AEDs but similar to the MES and PTZ models, enabling the screening of a large number of compounds [12]. Overall, it appears that these acute seizure models fail to identify compounds with efficacy against drug-resistant seizures [12].

More recently, a number of alternative models have been introduced into epilepsy research including the unicellular social amoeba *Dicyostelium*, the fly *Drosophila melanogaster*, the roundworm *Caenorhabditis elegans*, and the zebrafish *Danio rerio* [34].

Chronic epilepsy models are used to study the processes leading from an initial insult to the brain (e.g., traumatic injury or status epilepticus) to the occurrence of spontaneous seizures, that is, the process of epileptogenesis [12,30,33,35]. Commonly used chronic models of epilepsy include electrical kindling of the amygdala or hippocampus via chronically implanted electrodes in the rat and temporal lobe epilepsy following pilocarpine or kainate induced status epilepticus [12,30,35].

2.2. Plant extracts with anticonvulsant activity

For this review, PubMed was searched and Google was used to search “the deep internet” for scientific papers containing various combinations of the terms “plant”, “herbal”, “epilepsy”, “seizure”, “anticonvulsant”, and “antiepileptic”. Data were compiled from relevant original research reports and several reviews on the subject [36–43] (Supplementary Table 1). Overall, data were analyzed from a total of 274 papers concerning the anticonvulsant effects of extracts prepared from 280 different species of plants in 216 genera and 93 families (Fig. 1A).

Investigators mostly chose plants based on traditional use from essentially all corners of the world — a significant fraction of this research was performed in Asia and Africa. The extracts were prepared from whole plants, aerial parts, leaves, stems, bark, wood, rhizomes, and roots (Fig. 1B) by a variety of polar and nonpolar extraction methods (aqueous, hydroalcoholic, methanolic, ethanolic, butanol, ethyl acetate, chloroform, hexane, ethyl ether, petroleum ether, or distillation for the preparation of essential oils) and administered either intraperitoneally or orally at doses of tens to hundreds of milligrams per kilogram of body weight (Fig. 1C). Virtually all experiments consisted of phenotypic screening in rodents (mice and rats; Fig. 1D). The large majority of investigators tested the plant extracts and essential oils using the MES and chemically induced seizure models (predominately PTZ but also bicuculline, kainate, NMDA, picrotoxin, and strychnine); a small number of plants were tested in electrical or chemical kindling models [44–66]. A GABA<sub>B</sub> receptor-binding assay was performed to screen plants used by traditional healers in South Africa in treating epilepsy [67,68]. Most plants have been tested in a single study, and most experiments have not been independently repeated.

In most experiments, the tested extracts prolonged the time to onset of seizures and decreased their duration or the seizure-related mortality. Only a few extracts were reported to afford complete protection from the experimentally induced seizures. For example, an *Emblica officinalis* extract was reported to have completely blocked seizures elicited by PTZ [69]. This plant has also been reported to exhibit antidepressant-like [70] and anxiolytic effects [71]. *Securidaca longepedunculata* was found to completely block PIC-induced, MES-induced, and PTZ-induced seizures and to exhibit anxiolytic, sedative [72], and antidepressant-like effects [73]. *Smilax zeylana* was reported to completely prevent seizure-related mortality [74]. *Paeonia lactiflora* root extract completely inhibited the EEG power spectrum changes as well as the extracellular calcium and potassium concentration changes related to seizure activity [75]. Administration of *P. lactiflora* root extract continued daily for 30 days prior to cobalt application completely inhibited EEG spike-wave discharges [76].

A few plant extracts were reported to have efficacy comparable to that of synthetic drugs. For example, *Aegle marmelos*, *Delphinium denudatum*, *Ficus religiosa*, and *Nymphaea alba* were reported to have an effect in the MES model similar to that of phenytoin [66,77–79]. *Aegle marmelos* was also reported to exhibit acetylcholinesterase inhibitory activity [80]. *Acorus calamus* reduced the duration of tonic hindlimb extension in MES-induced seizures comparable to valproate [81] and has been reported to exhibit neuroprotective activity [82]. *Delphinium denudatum* suppressed PTZ-induced threshold seizure and the loss of the righting reflex with tonic forelimb and hindlimb extension by 100%, similar to valproate [79]. *Casimiroa edulis* exhibited activity in the MES model similar to that of either phenytoin or phenobarbital [83]. The effects of *Nerium oleander* in both the MES and the PTZ models were reported to be comparable to those of phenytoin and diazepam [84]. *Vitex negundo* was found to potentiate the effect of phenytoin and valproate [85]. *Centranthus longiflorus* exhibited sedative and anticonvulsant effects similar to those produced by diazepam [86]. The anticonvulsant
effects of *Phyllanthus longiflorus* in the MES and PTZ models were comparable to diazepam [87].

Extracts of *Cleome cileata*, *Cynodon dactylon*, *Holarhena floribunda*, *Newbouldia leavis*, and *Tetrapleura tetraptera* were found to exhibit general CNS depressant activity [25]. *Cerbera odollam*, *F. religiosa*, *Hibiscus rosa-sinensis*, and *Magnolia grandiflora* potentiated the hypnotic effects of pentobarbital [53,78,88,89].

Only a small number of experimenters fully characterized the chemical composition of their extracts, and very few attempted the isolation and identification of active compounds. For example, an anticonvulsant extract prepared from the aerial parts of *Galium spurium* contained ten major compounds (phenolic and triterpenic acids, flavonoids, and iridoids); the authors speculatively attributed the anticonvulsant activity to the phenolic acids, flavonoids, and iridoids [90]. Guo and colleagues used ultra performance liquid chromatography–mass spectrometry (UPLC–MS) to determine the components of plant-derived compounds in the brains of rats treated with an ethanolic extract of *Abelmoschus manihot* [91]. They identified eight different flavonoids derived from five parent compounds including isouqueritin, hyperoside, hibifolin, quercetin 3′-O-glucoside, quercetin, and three of their metabolites. Flavonoids were also pinpointed as probable active ingredients in extracts of *Anisomeles malabrica*, *Tilia americana* (quercetin, rutin, and isouqueritin), and *Cissus sicyoides* (kaempferol 3-rhamnoside and quercetin 3-rhamnoside) [92–94]. The hydroxyxinnamic acids p-coumaric acid and caffeic acid were suggested to mediate the anticonvulsant activity of *Aster glehni* [95]. The phytosterols stigmasterol and stigmasteryl 3-O-(d-glucopyranoside and the triterpenoids oleanolic acid, ursolic acid, and betulinic acid were reported to be the main constituents of an anticonvulsant extract of *Cnestis ferruginea* [96]. Anticonvulsant activity of *Curcuma longa* was attributed to the terpenoids ar-turmerone: α,β-turmerone, and α-atlantone [97]. The flavonoid linarin and its aglycone, acacetin, were identified as the active components of a sedative and anticonvulsant extract of *Chrysanthemum boreale* [98]. Gallotannin (pentagalloylglucose) and the terpenoid alflobifolin accounted for the anticonvulsant effects of a *P. lactiflora* extract [75]. Bis(8-hydroxy-2-methylnaphthyl) phthalate was isolated as the anticonvulsant principle from a *Pyrenacantha staudtii* extract [99]. The anticonvulsant activity of *Cedrus deodara* extract was attributed to the compound 3,4-bis(3,4-dimethoxy-phenyl)furan-2,5-dione [100], which was also reported to have anxiolytic and antidepressant-like activities [101].

### 2.3. Plant-derived anticonvulsant compounds and their molecular targets

More than one hundred single, plant-derived compounds have been reported to exhibit anticonvulsant activity (Supplementary Table 2). A review of the literature on anticonvulsant essential oils listed 30 different active compounds, mostly monoterpenes or phenylpropanoids [43].

In recent years, an increasing number of molecular targets thought to play a role in epilepsy have been identified [102]. A large number of mutations in ion channel subunits have been linked to genetic and acquired forms of epilepsy [103]. Target-oriented drug development is seen not only as providing new opportunities for AED development but also as a sine qua non for progress in the field of epilepsy [12]. Currently used AEDs are thought to predominantly increase inhibitory activity in the CNS by either increasing the activation of γ-aminobutyric acid type A (GABA<sub>A</sub>) receptors (e.g., by phenobarbital and benzodiazepines) or decreasing the excitatory activity via inhibition of voltage-gated Na<sup>+</sup> channels (e.g., by phenytoin) and L-type, R-type, P/Q-type, N-type (e.g., by levetiracetam), and T-type voltage-gated Ca<sup>2+</sup> channels (e.g., by ethosuximide) [12,102,104]. Other targets of existing AEDs are the GABA transporter 1 (GAT-1; targeted by tiagabine), GABA transaminase (targeted by vigabatrin), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of glutamate receptors (targeted by perampanel), and the synaptic vesicle glycoprotein 2A (SV2A; targeted by levetiracetam) [32]. It is notable that essentially all of the currently used AEDs are thought to act on more than one target, while the relative importance of any specific target for their antiepileptic activity in vivo remains to be established.

Novel potential targets for the treatment of epilepsy include lactate dehydrogenase [105], cation chloride co-transporters [106,107], large-conductance Ca<sup>2+</sup>–activated potassium channels (BK<sub>Ca</sub>) [108,109], Kv<sub>7</sub> (M or KCNQ) potassium channels [109–111], P/Q-type Ca<sup>2+</sup> channels [110,112], hyperpolarization-activated cyclic nucleotide-gated channels (HCN) [110,113,114], transient receptor potential channels (TRP) [115,116], chloride channels (CLC family) [117], and gap junctions [118], as well as targets regulating inflammation and transcription [12]. Of increasing interest are targets involved in epilepsy accompanying comorbidities (e.g., depression, obsessive compulsive behavior, loss of motivation, decreased alertness and attention) such as the monoaminergic neuronal systems [12] and two-pore-domain background potassium (K<sub>2P</sub>) channels [119].

#### 2.3.1. The GABA<sub>A</sub> receptor complex

GABA<sub>A</sub> receptors are known to be targeted by a considerable number of plant-derived compounds including flavonoids (and their metabolites), terpenoids, (furan)coumarins, and a variety of other phenolic compounds [120,121]. Flavonoids interact with the benzodiazepine binding site of GABA<sub>A</sub> receptors and, thus, modulate the chloride flux through the chloride channel that is formed by the GABA<sub>A</sub> receptor complex [122]. It is of particular interest that some of the flavonoids thought to interact with the benzodiazepine site of the GABA<sub>A</sub> receptor complex appear to exhibit their anticonvulsant activity in the absence of sedative effects. For example, chrysin (5,7-dihydroxyflavone isolated from *Passiflora caerulea*) was reported to exhibit anticonvulsant effects [123]. It was also reported to be a specific benzodiazepine binding site ligand and to exhibit nearly equiportant anxiolytic effects comparable to those of diazepam but without its sedative and myorelaxant effects [124]. Similarly, wogonin (5,7-dihydroxy-8-methoxyflavone), baicalein (5,6,7-trihydroxyflavone), and baicalin (baicalein 7-O-glucuronide from *Scutellaria baicalensis* have all been reported to exhibit anxiolytic and anticonvulsant activities without accompanying sedation and myorelaxation [122,125,126]. Baicalin has been found to exert its in vivo anxiolytic-like effect mainly through the α2-containing and α3-containing subtypes of GABA<sub>A</sub> receptors [127].

#### 2.3.2. Other ion channels

A considerable number of extracts and single compounds have been shown to target ion channels (Table 1). Molecular effects of baicain and wogonin include activation of TREK-2 two-pore domain [128] and large-conductance Ca<sup>2+</sup>–activated potassium channels (BK<sub>Ca</sub>) [129], as well as inhibition of expression of TRPC1 channels [130]. Fisetin (2-(3,4-dihydroxyphenyl)-3,7-dihydroxyxchromen-4-one), which has been reported to exhibit anticonvulsant effects [131], was also found to potentiate the HCN2 channel [132]. Naringenin (5,7-dihydroxy-2-(4-hydroxyxphenyl)chromen-4-one) has been reported to be a BK<sub>Ca</sub> channel opener [133]. Hesperetin, the aglycone of hesperidin, and quercetin were reported to inhibit α-type Ca<sup>2+</sup> channels and increase voltage-gated K<sup>+</sup> channels [134,135]. Moreover, quercetin was found to inhibit Na<sup>+</sup> channels in hippocampal pyramidal neurons [136]. Quercetin and its dimer glycoside rutin were found to inhibit GABA<sub>A</sub> glycine, and 5-HT3A receptor channels [137,138].

The terpenoid tanshinone IIA from *Salvia miltiorrhiza*, which was reported to exhibit anticonvulsant effects [139], was also shown to enhance BK<sub>Ca</sub> channels [140,141], KCNQ1/KCNE1 K<sup>+</sup> channels [142], and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels [143], and to inhibit glutamate release from rat cortical synaptosomes via the inhibition of presynaptic Ca<sup>2+</sup> entry and inhibition of the mitogen-activated protein kinase (MEK) [144]. Ginsenosides have been shown to interact with a variety of ion channels, including the GABA<sub>A</sub> receptor (Rg<sub>3</sub>) [145], KCNQ1 K<sup>+</sup> channels (Rg<sub>3</sub>) [146], Na<sup>+</sup> channels (Rg<sub>3</sub>) [147], and L-type, N-type, P/Q-type, and T-type...
Ca\(^{2+}\) channels [148]. The ligand magnolol from *Magnolia officinalis* was reported to increase the probability of BK\(\alpha\) channel openings in a concentration-dependent manner with an EC\(_{50}\) value of 1.5 \(\mu\)M [149]. Isoxylitone from *D. denudatum* exhibited anticonvulsant activity, prevented kindling-induced seizures, and inhibited voltage-dependent Na\(^+\) currents at submicromolar concentrations [150]. The alkaloid berberine has anticonvulsant effects [151], and was reported to inhibit glutamate release from rat cortical synaptosomes via the suppression of presynaptic P-type Ca\(^{2+}\) channels and inhibition of extracellular ERK/synapsin I signaling cascade [152]. Berberine was also shown to inhibit KCNQ1 channels [153]. Mutations of KCNQ2 and KCNQ3, two genes encoding K\(^+\) channel proteins, have been found to underlie a rare inherited form of epilepsy known as benign familial neonatal convulsions [103]. The AED retigabine (ezogabine) is the first approved KCNQ2–5 channel opener [154]. Interestingly, KCNQ channel openers have also been shown to be neuroprotective in animal stroke models [155]. Berberine was also found to inhibit human cardiac HCN4 channel currents [156]. The phenylpropanoid α-asarone was found to inhibit both GABA\(_A\) receptors and the Na\(_V\)1.2 channel [157]. The terpenoid paeoniflorin was found to inhibit \(\alpha\)-type Ca\(^{2+}\) channels [158] and Na\(^+\) channels, but the physiological significance of the latter observation is questionable as the IC\(_{50}\) is 271 \(\mu\)M [159]. The compound exhibited neuroprotective activity via inhibition of microglia [160] and MAPKs/NF-κB-mediated inflammatory responses [161], and antidepressant-like effects [162]. The terpenoid β-eudesmol was found to activate TRPA1 channels [163]. Methylthionine from *Piper methysticum* (kava) was shown to inhibit Na\(^+\) channels in CA1 hippocampal neurons [164]. The alkaloid pipherine has been shown to both inhibit GABA\(_A\) receptors and activate transient receptor potential potential vanilloid 1 (TRPV1) receptors [165,166]. Eugenol was found to activate transient receptor potential ankyrin 1 in TRPA1 channels, though at a high EC\(_{50}\) of 261.5 \(\mu\)M [167], but inhibit the TRPL channels [168]. Carvacrol activates TRPV3 and TRPA1 channels and inhibits TRPC and TRPM channels [168,169]. Transient receptor potential ankyrin 1 has been found to reduce the intracellular Ca\(^{2+}\) concentration in astrocytes and, thus, decrease calcium-dependent trafficking of GABAA GABA transporters, which in turn leads to increased extracellular GABA concentrations and concomitant desensitization of GABA\(_A\) receptors leading to decreased GABA-mediated inhibition [116]. Another terpenoid found to activate TRPV3 channels is borneol [169], which has also been reported to have neuroprotective activity possibly via the inhibition of the hK-2/NS-F-β pathway [177]. The benzofuran lactone 3-n-butylphthalide from *Apium graveolens* (celery) is used in China for the treatment of ischemic stroke with apparently positive effects [170]. Long-term treatment of aged and chronically ischemic rats with this compound was found to attenuate cerebral hypoperfusion-induced learning dysfunction and brain damage [171,172]. The compound was recently reported to inhibit TLRK-1 K\(^+\) channels [173]. TREK-1 (TWIK-related potassium channel 1) is highly expressed in GABAergic neurons in some regions of the CNS, and inhibition of TREK-1 in these neurons might consequently lead to increased inhibitory activity [174]. Aconitine, a highly toxic (arrhythmogenic) alkaloid, was found to inhibit G protein-activated inwardly-rectifying potassium [163]. Methysticine from *Apium graveolens* was reported to increase the probability of BKCa channel openings in a concentration-dependent manner with an EC\(_{50}\) value of 1.5 \(\mu\)M [149]. Isoxylitone from *D. denudatum* exhibited anticonvulsant activity, prevented kindling-induced seizures, and inhibited voltage-dependent Na\(^+\) currents at submicromolar concentrations [150]. The alkaloid berberine has anticonvulsant effects [151], and was reported to inhibit glutamate release from rat cortical synaptosomes via the suppression of presynaptic P-type Ca\(^{2+}\) channels and inhibition of extracellular ERK/synapsin I signaling cascade [152]. Berberine was also shown to inhibit KCNQ1 channels [153]. Mutations of KCNQ2 and KCNQ3, two genes encoding K\(^+\) channel proteins, have been found to underlie a rare inherited form of epilepsy known as benign familial neonatal convulsions [103]. The AED retigabine (ezogabine) is the first approved KCNQ2–5 channel opener [154]. Interestingly, KCNQ channel openers have also been shown to be neuroprotective in animal stroke models [155]. Berberine was also found to inhibit human cardiac HCN4 channel currents [156]. The phenylpropanoid α-asarone was found to inhibit both GABA\(_A\) receptors and the Na\(_V\)1.2 channel [157]. The terpenoid paeoniflorin was found to inhibit \(\alpha\)-type Ca\(^{2+}\) channels [158] and Na\(^+\) channels, but the physiological significance of the latter observation is questionable as the IC\(_{50}\) is 271 \(\mu\)M [159]. The compound exhibited neuroprotective activity via inhibition of microglia [160] and MAPKs/NF-κB-mediated inflammatory responses [161], and antidepressant-like effects [162]. The terpenoid β-eudesmol was found to activate TRPA1 channels [163]. Methylthionine from *Piper methysticum* (kava) was shown to inhibit Na\(^+\) channels in CA1 hippocampal neurons [164]. The alkaloid pipherine has been shown to both inhibit GABA\(_A\) receptors and activate transient receptor potential potential vanilloid 1 (TRPV1) receptors [165,166]. Eugenol was found to activate transient receptor potential ankyrin 1 in TRPA1 channels, though at a high EC\(_{50}\) of 261.5 \(\mu\)M [167], but inhibit the TRPL channels [168]. Carvacrol activates TRPV3 and TRPA1 channels and inhibits TRPC and TRPM channels [168,169]. Transient receptor potential ankyrin 1 has been found to reduce the intracellular Ca\(^{2+}\) concentration in astrocytes and, thus, decrease calcium-dependent trafficking of GABAA GABA transporters, which in turn leads to increased extracellular GABA concentrations and concomitant desensitization of GABA\(_A\) receptors leading to decreased GABA-mediated inhibition [116]. Another terpenoid found to activate TRPV3 channels is borneol [169], which has also been reported to have neuroprotective activity possibly via the inhibition of the hK-2/NS-F-β pathway [177]. The benzofuran lactone 3-n-butylphthalide from *Apium graveolens* (celery) is used in China for the treatment of ischemic stroke with apparently positive effects [170]. Long-term treatment of aged and chronically ischemic rats with this compound was found to attenuate cerebral hypoperfusion-induced learning dysfunction and brain damage [171,172]. The compound was recently reported to inhibit TLRK-1 K\(^+\) channels [173]. TREK-1 (TWIK-related potassium channel 1) is highly expressed in GABAergic neurons in some regions of the CNS, and inhibition of TREK-1 in these neurons might consequently lead to increased inhibitory activity [174]. Aconitine, a highly toxic (arrhythmogenic) alkaloid, was found to inhibit G protein-activated inwardly-rectifying potassium (GIRK) channels [175] and moderately inhibit Na\(_V\)1.2 channels [176]. The antirhythmic alkaloid lappacontine was found to inhibit Na\(^+\) channels [177]. Caffeic acid esters were found to activate TREK-1 channels [178]. The anticonvulsant and psychoactive alkaloid ibogaine was found to be an open-channel blocker of NMDA- and indirect effects on ion channels of plant-derived anticonvulsant compounds remain a wide-open field of investigation.

It has been pointed out recently that “… epilepsy may be as much a disorder of cognition and behavior as it is of seizures, with cognitive and behavioral symptoms either preating seizures, or vice versa. Indeed, for some, the cognitive and behavioral symptoms may represent the most frequent and intrusive manifestation of the underlying disease, while seizures may be infrequent” [201]. If so, then the concept of AEDs will have to be expanded beyond the focus on anticonvulsant and antiepilepticogenic activities. In fact, many complex extracts and single plant-derived compounds exhibit antiinflammatory, neuroprotective,
and cognition-enhancing activities that may be beneficial in the treatment of epilepsy.

The recently discovered role of microglia in synaptic plasticity opens a whole new field of investigation. For example, it has been reported that activation of microglia facilitated excitatory synaptic transmission in the dorsal horn and, thus, might contribute to pain hypersensitivity in chronic pain states [202]. Even more intriguingly, it has been reported that microglia promote learning-dependent synapse formation in the CNS [203] but that peripheral inflammation can alter synaptic function and plasticity and that these changes are mediated by activated microglia [204]. If confirmed, these findings might suggest a connection between seizures and peripheral inflammation and provide an additional rationale for the use of antiepileptic botanical extract or compounds, which also exhibit antinflammatory activity. It is beyond the scope of our paper to review the extensive and rapidly growing literature on antinflammatory effects of microorganisms in microglia, but some of the compounds of interest in the context of this paper include, for example, baicalin, curcumin, resveratrol, tanshinone II A, wogonin, and ursolic acid, among many others [205–213]. Baicalin and wogonin have also been shown to exhibit a plethora of other pharmacological effects. Of particular interest to the epilepsy field is their reported neuroprotective activity [214–216] and antidepressant [217] and memory-enhancing effects [218]. Tanshinone II A has also been reported to have neuroprotective effects [214].

4. Looking to the future

Loscher and colleagues proposed in a recent review that “...future anti-epileptic drug development may be improved through a new joint endeavour between academia and the industry, through the identification and application of tools for new target-driven approaches, and through comparative preclinical proof-of-concept studies and innovative clinical trials design” [12]. We would like to add that this applies similarly to the field of botanicals for epilepsy. Considering the volume of data in the literature on botanicals for epilepsy, one cannot help but feel that it is to the detriment of patients and progress if drug development efforts ignore the potential of plant-derived compounds and complex extracts for the treatment and prevention of epilepsy. It is clear, however, that the need to protect the huge investment required for drug development by patents has traditionally prevented the pharmaceutical industry from considering patentable natural products or plant extracts for commercial development. Similarly, areas where a large number of generics are available and a high hurdle exists for the demonstration of a new drug that does in fact add value (i.e., has better efficacy) are being deserted by the pharmaceutical industry [12]. Without changes in regulatory, patent, and health insurance frameworks that will make it possible to profit from the development of botanicals for the treatment of any disease, it is unlikely that this situation will change.

4.1. Social network driven drug development

Calls for a consortium approach including academia, government, and pharmaceutical industry partnerships under the heading of translational medicine have previously been made to overcome the failure of neuroprotective treatments in acute ischemic stroke (reviewed in ref. [214]). On this background, we previously proposed the establishment of a web-based social network as a basis for community-driven drug development [214]. We envision that such a web-based network would bring together both academic-based and industry-based preclinical and clinical researchers as well as governmental and nongovernmental organizations with a vested interest in funding clinical or preclinical work. The network would serve as a forum for anyone with a stake in the development of AEDs including patient advocate groups. For example, investigators might register their interest in working on filling the

### Table 1

<table>
<thead>
<tr>
<th>Target Channel</th>
<th>Compound</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaV1.1 (L-type Ca2+ channels)</td>
<td>Iboigane, hesperetin, ginsenoside Rg3, paeoniflorin, quercetin</td>
<td>[148,181]</td>
</tr>
<tr>
<td>CaV2.1 (P-type Ca2+ channels)</td>
<td>Berberine, ginsenoside Rg3</td>
<td>[148]</td>
</tr>
<tr>
<td>CaV2.2 (N-type Ca2+ channels)</td>
<td>Ginsenoside Rg3</td>
<td>[148]</td>
</tr>
<tr>
<td>CaV3.3 (T-type Ca2+ channels)</td>
<td>Ginsenoside Rg3</td>
<td>[148]</td>
</tr>
<tr>
<td>Cl- channels</td>
<td>Quinine</td>
<td>[195,196]</td>
</tr>
<tr>
<td>Connexins Cx36, Cx50</td>
<td>Quinine</td>
<td>[186,187]</td>
</tr>
<tr>
<td>GABA A (γ-aminobutyric acid type A)</td>
<td>α-Asarone, apigenin, baicalin, bilobalide, borneol, chrysin, ginsenoside Rg3 and Rc, hesperidin, linarin, magnolol, pipereine, resveratrol, thymoquinone, wogonin</td>
<td>[120,122,127,148,157,165,219]</td>
</tr>
<tr>
<td>GABA A (γ-aminobutyric acid type C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>Rutin, quercetin</td>
<td>[137,138]</td>
</tr>
<tr>
<td>HCN (hyperpolarization-activated cyclic nucleotide-gated channels)</td>
<td>Berberine, fisetin, tanshinone II A</td>
<td>[132,143,156,221]</td>
</tr>
<tr>
<td>KCa1.3</td>
<td>Curcumin</td>
<td>[222]</td>
</tr>
<tr>
<td>KCa1.4</td>
<td>Curcumin</td>
<td>[223]</td>
</tr>
<tr>
<td>KCa2.10 (1 pore K+ channel TREK-2)</td>
<td>Baicalin, wogonin</td>
<td>[128]</td>
</tr>
<tr>
<td>KCa2.1 (2 pore K+ channel TREK-1)</td>
<td>3-n-Butylphthalide, caffeic acid esters, curcumin</td>
<td>[173,178,224]</td>
</tr>
<tr>
<td>KCa1.1 (big, Ca+2 activated K+ channel BKca)</td>
<td>Baicalin, magnolol, naringenin, resveratrol, tanshinone II A, wogonin, Acicontine</td>
<td>[175]</td>
</tr>
<tr>
<td>KCa3.1 (G protein-coupled inwardly-rectifying K+ channels)</td>
<td>Iboigane, curcumin</td>
<td>[180,225]</td>
</tr>
<tr>
<td>KCa11.1 (HERG)</td>
<td>Berberine, ginsenoside Rg3, tanshinone II A</td>
<td></td>
</tr>
<tr>
<td>KCa7.x (KCNQ1, KCNE1)</td>
<td>Iboigane, huperzine A</td>
<td>[179,182]</td>
</tr>
<tr>
<td>N-methyl-D-aspartic acid (NMDA subtype of ionotropic glutamate receptors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na+ channels</td>
<td>Ioxylitoline, ginsenoside Rg3, imperatorin, lappaconitine, methysticin, quercetin, quinine</td>
<td>[176,177,188] [183]</td>
</tr>
<tr>
<td>nAChR</td>
<td>Iboigane, quinine</td>
<td>[180] [194]</td>
</tr>
<tr>
<td>Na+1.2</td>
<td>Aconitine, α-asarone</td>
<td>[157]</td>
</tr>
<tr>
<td>Na+1.5</td>
<td>Iboigane</td>
<td>[181]</td>
</tr>
<tr>
<td>Q-type Ca2+ channels</td>
<td>Berberine, ginsenoside Rg3</td>
<td>[148]</td>
</tr>
<tr>
<td>Serotonin receptors (5-HT3, 5-HT4)</td>
<td>Cannabis, rutin, quercetin, quinine</td>
<td>[193,220]</td>
</tr>
<tr>
<td>TRPA1 (transient receptor potential channel ankyrin)</td>
<td>Carvacrol, curcumin, l- eudesmol, eugenol</td>
<td>[163,167,226]</td>
</tr>
<tr>
<td>TRPC (transient receptor potential channel canonical)</td>
<td>Carvacrol, resveratrol</td>
<td>[198]</td>
</tr>
<tr>
<td>TRPM (transient receptor potential channel melastatin)</td>
<td>Carvacrol, eugenol</td>
<td>[168]</td>
</tr>
<tr>
<td>TRPV1 (transient receptor potential channel vanilloid)</td>
<td>Cannabis, cannabidiol, imperatorin, pipereine,</td>
<td>[166,183,185]</td>
</tr>
<tr>
<td>TRPV2 (transient receptor potential channel vanilloid)</td>
<td>Borned, carvacrol</td>
<td>[169]</td>
</tr>
</tbody>
</table>
knowledge gaps in regard to a particular compound or extract, and national and international private and public funding agencies might announce calls for grant applications to fund such work. Results (both positive and negative) from this work would be published in peer-reviewed journals and updated on the web site so that progress could be publicly monitored.

5. Conclusions

Extracts of hundreds of plants have been reported to exhibit anticonvulsant activity in phenotypic screens in experimental animals. A few extracts appeared to exhibit anticonvulsant efficacy similar to that of synthetic AEDs. Dozens of plant-derived chemical compounds have similarly been shown to act as anticonvulsants in various in vivo and in vitro assays. To a significant degree, anticonvulsant effects of plant extracts can be attributed to widely distributed flavonoids, (furano)coumarins, and terpenoids. Anticonvulsant effects of plant essential oils have been attributed to the presence of certain monoterpenes and phenylpropanoids, which are common in many plants. Flavonoids and coumarins have been shown to interact with the benzodiazepine site of the GABA<sub>A</sub> receptor and various voltage-gated ion channels. Modulation of the activity of ligand-gated and voltage-gated ion channels provides an explanatory basis of the anticonvulsant effects of plant secondary metabolites. Many anticonvulsant complex extracts and single plant-derived compounds exhibit additional antiinflammatory, neuroprotective, and cognition-enhancing activities that may be beneficial in the treatment of epilepsy. The available preclinical research data provide an appropriate theoretical framework (the “mechanistic basis”) to justify further target-oriented preclinical research and, most importantly, clinical trials. It will be important to establish biomarkers that can more directly relate preclinical data to clinical effects and, thus, allow mechanism-based hypothesis testing. Clinical studies with selected standardized botanical extracts are urgently needed.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2015.05.012.

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Conflict of interest

The authors declare that they have no conflict of interests.

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