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Anticonvulsant effects of medicinal plants with emphasis on mechanisms of action

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ABSTRACT

Epilepsy is a disorder in brain in which clusters of nerve cells, or neurons, occasionally signal abnormally and cause strange emotions, sensations, and behavior, or sometimes muscle spasms, convulsions, and loss of consciousness. Neurotransmitters in central nervous system greatly affect and play a very important part in neuronal excitability. Traditional treatments are still a component of health care system in many communities despite the fact that well-established alternatives are available. In this review article, we addressed epilepsy and its treatments with emphasis on medical plants and introduction of antiepileptic plants and their action mechanisms. Relevant articles published since 2010 were retrieved using the search terms including epileptic seizure, anticonvulsant, medicinal plants, and oxidative stress. Most plants/herbal preparations that are ethnomedically used to treat epilepsy or those which have been tested for anticonvulsant activity were reported. Overall, the results of the published articles show that the symptoms of epilepsy seizure can be inhibited or treated by active ingredients derived from medicinal plants.

1. Introduction

Epileptic seizure syndromes can be due to a wide variety of causes, including genetic, developmental, or acquired ones. Seizures mainly occur suddenly without warning, have short duration (a few seconds or minutes), and stop by themselves [1]. Epileptic seizures are considered to be the most common neurologic symptoms in different human populations and remain the most common neurological condition involving people at any age. At any time, fifty million worldwide are estimated to have a diagnosis of epilepsy [2].

Epileptic seizures are seizure events that occur due to excessive, abnormally synchronized, localized, or widely distributed neuronal electrical discharges [3].

An epileptic seizure is an episode of neurologic dysfunction due to abnormal neuronal firing obviously occurring clinically via changes in sensory perception, motor control, behavior, or autonomic function [4].

2. Types of epileptic seizures

Seizures have two main types, *i.e.* focal or partial seizures and generalized seizures. In focal seizures, only one part of the brain, occasionally called the 'focus' of the seizures, is affected. Focal seizure may affect a large part of one hemisphere or only a small area of a lobe but generalized seizures occur when seizure activity is widespread in the brain's left and right hemispheres and the affected people become unconscious (except in myoclonic seizures), though for a few seconds [5].

3. Basic mechanisms of epilepsy

Seizure initiation is characterized by two parallel conditions: 1) high-frequency bursts of action potentials, and 2) hyper synchronization of a neuronal population [6].

The bursting activity due to the neuronal membrane's relatively prolonged depolarization occurs because of influx of extracellular Ca^{++}, which results in influx of Na^{+}, opening of voltage-dependent Na^{+} channels, and generation of repetitive action potentials. The hyperpolarizing potential is mediated by Cl^{-} influx and gamma-aminobutyric acid (GABA) receptors, or by K^{+} efflux, according to the cell type [7]. GABA is a type of the brain's inhibitory neurotransmitter, which effectively prevents the brain from sending messages [7].

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GABA interneurons may result in paradoxical facilitation of certain types of epileptic discharges in some models. Drugs that cause increase in synaptic GABA by inhibition of GABA catabolism or reuptake, are considered effective anticonvulsants, including benzodiazepines, which improve GABA binding to the GABA receptor, leading to increased frequency of chloride channel openings [8]. Some GABA synthesis inhibitors are able to cause seizures, including thiosemicarbazide, 4-deoxypyridoxine, isoniazid, and L-allyglycine [8].

GABA, the major inhibitory neurotransmitter, interacts with two key subtypes of receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are found postsynaptically, but $GABA_B$ receptors are found presynaptically and can therefore modulate synaptic release. $GABA_A$ receptors are permeable to Cl^- ions in the brain in adulthood; Cl^- influx, upon activation, hyperpolarizes the membrane and inhibits action potentials. Therefore, $GABA_A$ receptor agonists, including barbiturates and benzodiazepines, suppress seizure activity. $GABA_B$ receptors are related to second messenger systems but not Cl^- channels, and result in attenuation of transmitter release because of their presynaptic location [8].

Glutamate is a type of amino acid and a major excitatory neurotransmitter in the brain. Glutamate released from synapses is taken up by astrocytes under normal conditions, and is rapidly converted to the non-excitotoxic amino acid glutamine by glutamine synthetase [9].

The ionotropic *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/kainate, and metabotropic glutamate receptor-mediated mechanisms are involved in epileptic seizures [9].

Excitatory glutamatergic mechanisms are involved in acute, transient, evoked seizures as well as long-term, adaptive cellular plasticity related to epileptogenesis in chronic epilepsy models. Glutamate exerts its excitatory effects through ligand-gated ion channels (NMDA and non-NMDA receptors) in order to increase sodium and calcium conductance [10].

Neuronal (EAAC1) and glial glutamate transporters facilitate reuptake of glutamate and aspartate after synaptic release. Down-regulation of glutamate transporters can be compatible with enhanced excitatory activity [11].

4. Epilepsy and oxidative stress

Oxidative stress leads to cellular damage and functional cellular disruption and can subsequently cause cell death through oxidation of biomolecules such as lipids, proteins, and nucleotides [12].

Seizure generation can be associated with the homeostatic imbalance between antioxidants and oxidants. Oxidative stress has been described as an imbalance between generation and elimination of reactive oxygen species (ROS) and reactive nitrogen species [13].

ROS levels are relatively well regulated to do significant functions including autophagy, cell division, chemical signaling, and mitogen-activated protein kinase signaling and apoptosis. Because of the highly reactive nature of this molecule, the ROS is tightly regulated. ROS-induced mitochondrial dysfunction is frequently seen following seizures throughout epileptogenesis [14].

Epileptic seizure causes initiation of remarkable influx of calcium through voltage-gated and NMDA-dependent ion channels that escalate intracellular ions and bring about biochemical cascades. High levels of intracellular calcium can induce ROS [15]. ROS may be scavenged by certain enzymatic antioxidant defense systems such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and peroxiredoxins and non-enzymatic ones such as vitamin C, vitamin E, and reduced glutathione (GSH) [12]. Antioxidant therapies to reduce oxidative stress have attracted much attention in treatment for epilepsy.

5. Epilepsy and inflammation

Experimental findings in rodents have indicated that seizures cause inflammatory mediators to increase in brain regions involved in generating epileptic activity [16]. Direct anti-inflammatory treatments have been found to suppress some types of epileptic seizures. Inflammatory processes may occur prior to the onset of epilepsy in humans, potentially contributing etiopathogenetically to incidence of spontaneous seizures. A rapid-onset inflammatory response is triggered in glia by seizures that have been induced by chemoconvulsants or electrical stimulation [17].

The over-expressing cytokines, *e.g.* interleukin-6 (IL-6) and tumor necrosis factor-α, inside astrocytes have been reported to cause age-dependent neurological dysfunctions such as decreased seizure threshold and spontaneous seizure frequency [18].

Inflammatory cytokines such as IL-1β and high-mobility group box 1, activate IL-1 receptor type I and Toll-like receptor 4, respectively. IL-1 receptor/Toll-like receptor signaling can regulate neuronal excitability, including inhibition of Ca^{2+} channels outward current, alteration of synaptic transmission, and decrease in GABA production [19].

6. Antiepileptic drugs

Most epileptic seizures are controlled by drug therapy, especially anticonvulsants. Treatments for seizures are based on anticonvulsant medication, although there are various choices of anticonvulsant drugs with different seizure types and epileptic syndromes [20]. Patients with newly diagnosed epilepsy who need treatment can start treatment with standard anticonvulsants including carbamazepine, valproic acid/valproate semisodium, phenytoin, phenobarbital, or more recently with gabapentin, oxcarbazepine, lamotrigine, or topiramate [21].

The type of prescribed treatment depends on different factors including the severity and frequency of the seizures as well as age, overall health, and medical history. Accurate diagnosis of epilepsy type is essential to choose the best treatment [21].

Conventional antiepileptic drugs may block sodium channels or improve GABA function. Different antiepileptic drugs have multiple or uncertain mechanisms of action [22]. Next to the voltage-gated sodium channels and components of the GABA system, their targets include $GABA_A$ receptors, the GABA transporter 1, and GABA transaminase. Other targets include voltage-gated calcium channels, SV2A, and $\alpha_2\delta$ [23].

Through blocking sodium or calcium channels, antiepileptic drugs decrease the release of excitatory glutamate, which increases in epilepsy, and also GABA [23]. This is possibly a side effect or the actual action mechanism of some of the antiepileptic drugs, because GABA can directly or indirectly act proconvulsively [24].

Most of the drugs currently being used have unpleasant side effects and unpredictable pharmacological actions; therefore, it

is necessary to search for newer drugs with fewer or no side effects and predictable pharmacological action because treatment of epilepsy is a long-term process and drug taking is discontinued gradually for about six months [25].

Nature is a rich source of biological and chemical varieties. The peerless and complicated structures of natural products cannot be figured out easily by chemical synthesis [26]. Medicinal plants play an important role in treating neurological disease such as Alzheimer's disease [27–31], brain ischemia, reperfusion [32–35], and other degenerative diseases [36–38].

In reality, current interest in traditional medicine has resulted in quick development and investigation of many remedies applied in various ethnic groups across the world. The data on the type of extract, essential oil and active components, mechanisms of action, methods and reference related to the plants which have been tested or reported for anticonvulsant properties are summarized in Table 1.

Table 1
Antiepileptic medicinal plants or compounds of plant origin.

Compounds	Methods (induced seizures)	Mechanism of action	Reference
Withania somnifera methanolic extract	Unilateral hippocampal injection of kainite (1 mg/kg) in male rats	Ameliorated spatial memory deficit in Y-maze	[39]
Trichosanthes dioica Roxb fruits aqueous extract	Delivering electroshock (50 mA) for 0.2 s through a pair of ear clip electrodes, PTZ (80 mg/kg) *i.p.* injection induces tonic-clonic convulsions in mice	Activity against generalized tonic-clonic and cortical focal seizures	[40]
Ficus platyphylla methanol extract	PTZ (37.5 mg/kg) *i.p.* for a total of 13 convulsant injections in mice, learning performance was tested in a two-way shuttle-box	Affinity for undifferentiated glutamate receptors, affinity for the 3H-GABA binding assay, decrease the K^+-stimulated glutamate release from rat hippocampal slices	[40]
Feretia apodanthera Del lyophilized aqueous extract	Administered PTZ (30 mg/kg; *i.p.*) 22nd injection in mice, behavioral tests include elevated plus-maze and T-maze tests	Decreased brain MDA levels, increased brain GSH levels, increase of AChE and BChE activity in brain	[41]
Nigella sativa oil	Electroshock and PTZ in mice	Potent antioxidant actions	[42]
Psidium guajava (guava) leaves ethanolic extract	Delivering electroshock (50 mA) for 0.2 s through a pair of ear clip electrodes and PTZ (70 mg/kg) *i.p.* injection induces tonic-clonic convulsions in mice	Selectively inhibit NMDA receptor	[43]
Trachyspermum ammi (L.) methanol extract	Strychnine (4 mg/kg) *i.p.* injection-induced seizure in rats	Excite GABA responses mainly by stimulating human $GABA_A$ receptors and increasing the chloride ion channel opening	[44]
Zingiber officinale (ginger) rhizomes hydroethanolic extract	Administrated PTZ into the tail vein	Antioxidant activity, inhibit NO production, reduce inducible nitric oxide synthase	[45]
Anacyclus pyrethrum root hydroalcoholic extract	Administrated *i.p.* injection of PTZ (60 mg/kg), behavioral tests include elevated plus-maze and passive avoidance tests	Increase in GSH levels of brain, decreased MDA levels of brain, increased AChE and BChE activity in brain	[46]
Valeriana officinalis root aqueous extract	Amygdala-kindled rats	Existence of adenosine ligand(s) in the valerian aqueous extract and activation of A1 adenosine system, binding to GABA receptors	[47]
Panax ginseng root butanol extract	Seizures were induced by administration of 40 mg/kg pilocarpine hydrochloride, magnetic resonance imaging study of the rat brain	Increased hippocampal volume, increase in T_2 relaxation time in rat hippocampus, entorhinal cortex, piriform cortex, amygdala, thalamus	[48]
Pimpinella anisum essential oil	Administrated PTZ (120 mg/kg) in rat	Inhibited production of dark neurons, inhibited induction of long-term potentiation in hippocampal slices	[49]
Cyperus rotundus Linn. essential oil	MES induced convulsion in rats	Inhibit voltage-dependant Na^+ channels, block glutamatergic excitation mediated by the NMDA receptor	[50]
Zhumeria majdae essential oil and methanolic extract	PTZ (110 mg/kg) and MES models in mice	Inhibit voltage-dependent Na^+ channels, block glutamatergic excitation mediated by the NMDA receptor	[51]
Angelica archangelica Linn. roots essential oil	PTZ (80 mg/kg) and MES models in mice	Block glutamatergic excitation	[52]
Cymbopogon winterianus Jowitt essential oils	Pilocarpine-induced convulsions (350 mg/kg *i.p.*) administrated PTZ in mice	GABAergic mechanisms, deteriorated autoregulation of glutamate release	[53]
Rosmarinus officinalis essential oils	Administrated PTZ (80 mg/kg) in mice	Elevate GABA levels in the midbrain region	[54]
Ocimum basilicum essential oils	Administrated PTZ (80 mg/kg) in mice	Modulate glutamate activation expression, reduction of the ACh-evoked release, direct interaction with the NMDA receptor complex	[54]
Mentha spicata essential oils	Administrated PTZ (80 mg/kg) in mice	GABAergic mechanisms	[54]

Table 1 (*continued*)

Compounds	Methods (induced seizures)	Mechanism of action	Reference
Lavandula angustifolia essential oils	Administrated PTZ (80 mg/kg) in mice	Modulate glutamate activation expression, reduction of the ACh-evoked release, direct interaction with the NMDA receptor complex	[54]
Mentha piperita essential oils	Administrated PTZ (80 mg/kg) in mice	GABAergic mechanisms	[54]
Origanum dictamnus essential oils	Administrated PTZ (80 mg/kg) in mice	GABAergic mechanisms	[54]
Origanum vulgare essential oils	Administrated PTZ (80 mg/kg) in mice	GABAergic mechanisms	[54]
Mentha pulegium essential oils	Administrated PTZ (80 mg/kg) in mice	GABAergic mechanisms	[54]
Turmeric methanolic extract	40 mmol/L PTZ in zebrafish larvae, PTZ (50, 100 mg/kg) infusion in tail vein in mice	Higher lipophilicity and easily cross the blood–brain barrier, suppress oxidative DNA damage and lipid peroxidation	[55]
α-Asarone	MES seizure test in mice, pilocarpine administered *i.p.* (320 and 350 mg/kg), pentylenetetrazole administered (85 mg/kg)	Inhibited pyrogallol auto-oxidation, α-asarone displays 5 units of superoxide dismutase-like activity, inhibit the hydroperoxide dependent oxidation of glutathione	[56]
Acorus calamus Linn aqueous extract	PTZ (80 mg/kg) and MES models in mice	Block NMDA receptors	[57]
Bunium persicum essential oil and methanolic extract	PTZ (110 mg/kg) induced convulsion in NMRI male mice, MES models	GABAergic mechanisms	[58]
Phytol (a constituent of chlorophyll)	Pilocarpine hydrochloride (400 mg/kg *i.p.*) in mice	Muscarinic activation and alterations in AChE activity in hippocampus	[59]
Soy extract	Administrated PTZ (40 mg/kg *i.p.*) for 14 days or a single injection of a high dose of PTZ (90 mg/kg in ovariectomized rat)	Phytoestrogens of soy affect seizure severity	[60]
Zizyphus jujuba hydroalcoholic extract	Administrated PTZ (60 mg/kg *i.p.*), MES in rat	Increase in brain GSH, decreased brain MDA levels, increased brain AChE and BChE activity	[61]
Emblica officinalis hydroalcoholic extract	Administrated PTZ (60 mg/kg) in rat	Decreased brain MDA levels, increase in brain GSH levels	[62]
Naringin (bioflavonoid present in the grapefruit)	Administrated PTZ (60 mg/kg) in rat	Increased brain GSH levels, decreased levels of MDA, attenuated the high brain levels of tumor necrosis factor-α	[63]
Anisomeles malabarica (flavonoids fraction from the leaves)	MES, administrated PTZ (50 mg/kg) in rat	Decreased tonic hindlimb extension phase and extensor/flexion ratio in MES model	[64]
Curcumol (from *Rhizoma Curcumae*)	Hippocampal neurons in culture	Facilitation of $GABA_A$ Rs by curcumol in hippocampal neurons, facilitation of recombinant $GABA_A$ Rs, enhancement of phasic GABAergic inhibition by curcumol in hippocampal slices, enhancement of tonic GABAergic inhibition by curcumol in hippocampal slices	[65]
Hydroalcoholic extract of citrus flower	Administrated PTZ (90 mg/kg) in rat	Increase in minimal clonic seizure	[66]
Vitexin (a flavonoid)	Vitexin administered intracerebroventricularly, administered PTZ (90 mg/kg *i.p.*)	Vitexin is a ligand for benzodiazepine receptors, exerts anticonvulsant effects through a $GABA_A$ benzodiazepine receptor	[67]
Quercetin (a flavonoid)	Administration of PTZ every other day (35 mg/kg *i.p.*, 15 injections in total)	Decreased brain MDA levels, increased sulfhydryl in brain	[68]
Centella asiatica (gotu kola)	Injection of pentylenetetrazol (60 mg/kg *i.p.*)	Increased AChE activity, elevated levels of ACh	[69]
Curcumin	Administration of PTZ (35 mg/kg) in mice	Increased brain norepinephrine level, reduced total nitrite levels of brain, reduced AChE activity	[70]
Nigella sativa oil	Injection of a single dose of pilocarpine (380 mg/kg *i.p.*)	Attenuate the increased NO levels resulting from pilocarpine, attenuate the decrease in hippocampal Na^+, K^+ ATPase activity, increase the AchE enzyme	[71]

PTZ: Pentylentetrazole; MES: Maximal electroshock; MDA: Malondialdehyde; AChE: Acetylcholinesterase; BChE: Butyrylcholinesterase; ACh: Acetylcholine.

7. Discussion

Epilepsy is the second leading neurological disorder after stroke, involving at least 50 million worldwide [72]. Cognitive impairment, dose-related neurotoxicity, and a spectrum of systemic side effects are the main side effects due to antiepileptic drugs [20].

The PTZ kindling model is a commonly used screening model to test anticonvulsive compounds. It exerts action mainly through the *t*-butyl-bicyclo-phosphorothionate/picrotoxin site of the $GABA_A$ receptor. PTZ is a blocker of choice for the $GABA_A$ receptor chloride ionophore complex [73]. It has convulsant effects after repeated or single administration and affects several neurotransmitter systems, such as adenosinergic, GABAergic,

and glutamatergic systems [74]. After PTZ-induced seizures, significant decreases in GSH, cysteine, glutathione disulfide, and protein thiols as well as increases in the protein disulfides and protein carbonyl levels were observed in the mouse cerebral cortex [75].

The MES seizure test, in which tonic hindlimb seizures are induced by bilateral corneal or transauricular electrical stimulation, is believed to predict effectiveness of anticonvulsant drug against generalized tonic-clonic seizures [76]. Local or systemic administration with pilocarpine and kainate in rodents has led to a pattern of repetitive limbic seizures and status epilepticus, lasting for several hours [77].

The drugs used to treat epilepsy may cause certain side effects. The occurrence of side effects depends on the dose of the drug taken, duration of treatment, and type of medication. The side effects are more likely to occur due to taking higher doses of the drugs but tend to mitigate over time because of the body's adjustment to the medication [78]. Natural products and their derivatives comprise over 50% of all the drugs used in clinical settings worldwide [79].

Medical plants can be applied because of their structural diversity and wide spectrum of pharmacological effects in contrast to common synthetic antiepileptic drugs. Available evidence suggests that many herbal medicines may cause adverse effects in people suffering from seizure [79].

It can be concluded that studies on active compounds in the plant-based extracts may be important to identify chemical compounds for development of antiepileptic drugs in the future.

Conflict of interest statement

I declare that I have no conflict of interest.

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