

Application of Phytotherapy in Epilepsy: A Current Review

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ABSTRACT

Phytotherapy is the most commonly used method in “Traditional and Complementary Medicine” applications. It is based on scientific studies and clinical studies. It is known to treat with phytotherapy especially during the preventive medicine phase. Phytotherapy for the treatment of epilepsy is a traditional practical medical form in various cultures. Herbal medical traditions are reported in China, Iran, Europe and America. Phytotherapy is the prominent approach to complementary and alternative drugs that play a significant role in controlling epileptic seizures or complications caused by anti-epileptic drugs. Patients with epilepsy have access to herbal remedies in developing countries, their goals and attitudes are different from those in developed countries. Herbal medicines, which are the most commonly used and alternative drugs in developed countries; seizure control and anti-epileptic drugs are used to reduce the complications, caused by general health care. For this reason, a review of the phytotherapeutic agents used for epilepsy on all continents was prepared.

Keywords: Epilepsy, Phytotherapy, Herbal, Complementary medicine

INTRODUCTION

Phytotherapy, which can be defined as plant use in the prevention or treatment of diseases; medicinal and aromatic plants, various parts of the plants secreted by the gums, balsams, resins such as exudates, extracts, essential oils are defined as the help to the treatment [1]. Phytotherapy is not an alternative method of treatment but a complementary treatment. Phytotherapy is a rational, evidence-based, allopathic treatment method and it is determined which agent group is responsible for the biological effects [2].

Recent studies, experimental tests in most experimental studies, herbal medicines are reported to be used for epilepsy. However, there is no robust evidence for the efficacy and toxicity of most plants in epilepsy. Approximately 30% of epileptic patients receiving anti-epileptic drugs are still reported to have seizures [3].

In summary, phytotherapy studies are thought to provide a high degree of success to scientists in finding new molecular mechanisms and anti-epileptic drugs for epilepsy [4]. Therefore, a review of herbal medicines' efficacy on epilepsy is presented. The literature review is planned on the classification of phytotherapeutic agents according to use in all continents.

LITERATURE REVIEW

- 1996-2006

In a 1996 study, the inhibition of neuronal activity in hippocampal slices of epilepsy rats by Aconitum alkaloids was investigated. Accordingly, it was concluded that 10 wM lappaconitine, an extract of aconitum alkaloid, reduces epileptiform activity by maintaining normal neuronal activity [5].

In a 1997 study, the antiepileptic effect of nimodipine (NIM) on penicillin-induced seizures in rats was investigated. It has shown that NIM, a calcium antagonist, can significantly inhibit seizures and epileptic discharge. This supports NIM as a new type of anti-convulsant in clinical practice [6].

In 1999, *Hoslundia opposita* Vahl (Lamiaceae family) is a locally used medicinal plant for the treatment of epilepsy [7].

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In 1999, the proconvulsive effect of tea (*Camellia sinensis*) on mice was investigated. Tea extract (both black and green) significantly accelerated the onset of convulsions and increased the duration of convulsions and mortality in mice. Based on an earlier report that both black and green tea can be effective in the Ca^{2+} channels, since both extracts cannot alter the level of GABA in the brain, it is suggested that the observed proconvulsive effect of tea is mediated by Ca^{2+} channels, not through GABA [8].

Lavandula stoechas L. (Lamiaceae) has been used as anti-convulsant in traditional medicine. In a 2000 study, the anticonvulsant activity of Lamiaceae was evaluated ethnopharmacologically on mice. Plant extract shows anti-convulsant activity and it is also thought that calcium channel blockage may be associated with these activities [9]. In 2000, the anti-convulsant properties of the root source of *Afrormosia laxiotora* (Leguminosae) were investigated. Doses of 0-300 mg/kg of this extract significantly reduced the duration of convulsive symptoms and increased seizure latency in both picrotoxin and electroshock-induced seizures compared to controls. The results reveal the potential beneficial effects of plant root for epilepsy [10].

In a study published in 2001, the anti-convulsant properties of *Annona diversifolia* leaves of the palmiton were examined. The pharmacological profile of palmitone for the pentylene tetrazole (PTZ) model epilepsy suggests that this compound may be effective on the GABAergic inhibiting system [11].

Streblus asper Lour Moraceae is a small tree native to tropical countries such as India, Sri Lanka, Malaysia, the Philippines and Thailand. It was mentioned that *S. asper* root extract was recommended for use in epilepsy and cardiac disorders [12].

In a 2001 study, the protective role of *Bacopa monniera* in morphine-induced hepatotoxicity on rats was investigated. *Bacopa monniera*; is a small creeping plant that grows frequently in marshlands in India, known as brahmi in the ayurvedic medical system. It is used as a strong nerve tonic in the treatment of epilepsy [13].

In 2001, anticonvulsant activity of the ethanolic extract isolated from *Delphinium denudatum*, a popular folk medicine for the treatment of epilepsy in the traditional Unani medical system, was investigated. The results showed the presence of strong anti-convulsant compounds of *D. denudatum* [14].

Delphinium denudatum Wall. (Ranunculaceae) is a medicinal plant used in the treatment of epilepsy. In 2001, the anti-convulsant activity of the FS-1 subfraction isolated from the roots of ranunculaceae was studied. According to the results, the compounds of ranunculaceae in FS-1 show broad and strong anti-convulsant activity [15].

In a study conducted in 2001, the anti-convulsant properties of *Cyperus articulatus* (Cyperaceae) methanolic extract were investigated and results were found to have anti-convulsant properties for Cyperaceae rhizome used for epilepsy in Africa [16].

Considering the anti-convulsive benefits of plants carrying linalool by researchers of various conventional medical systems, the effects of linalool binding on cortical membranes in 2001 were studied. It is stated that the anti-convulsant mode of action of linalool involves a direct interaction with the NMDA receptor complex [17].

In a 2001 study, it was reported that *Indigofera tinctoria* Linn. plant was used for the treatment of epilepsy in the Indian medical system [18].

In 2002, the protective effect of *Acorus calamus* Linn (Araceae) plant against neurotoxicity due to acrylamide was investigated. According to the results, this plant shows the effect of seizure delay and decreasing mortality [19].

In a 2002 study, Goodyerin's anti-convulsant activity, a flavonol glycoside from *Goodyerin schlechtendalii*, was investigated. According to the results, Goodyerin showed a dose-dependent sedative and anti-convulsant effect [20].

In a 2002 study, four traditional Zulu medicinal plants (*Rhoicissus digitata*, *R. rhomboidea*, *R. tomentosa* and *R. tridentata*) were tested for anti-oxidant activity from their roots and leaves. All of these plants known under the name Zulu can be used in the treatment of epilepsy [21].

In 2002, the effect of St. John Wort (*Hypericum perforatum* L.) on rabbits was studied with kindling epilepsy model. The substances present in the butanol fraction of the yellow centaury suppress epileptic symptoms in 40% of epileptic animals, while lipid soluble components in the ether fraction increased epileptic activity [22].

Ferula gummosa Boiss (Apiaceae) is used as an anti-epileptic drug in traditional Iranian medicine. According to a study, Apiaceae's seed acetone extract was evaluated for anticonvulsant activity against seizures caused by PTZ and electroconvulsive shock in mice. The results showed that it had a protective effect against experimental seizures [23].

In a 1998 study, the effect of Coriaria Lactone (CL) on calcium homeostasis in the pyramidal neurons of the rat hippocampus was investigated. Since the opening of L-calcium channels plays an important role in epileptogenesis, it is thought that CL may play a role in activating calcium channels as one of the mechanisms of seizure triggering [24].

In 2002, anti-convulsant activity of *Sesbania grandis* leaves ora leaves in experimental animals was investigated. According to the results, it protected against pentylenetetrazole (PTZ) induced seizures. The benzene-

ethyl acetate fraction also showed anti-convulsive activity against PTZ-induced seizures [25].

Mistletoe is a semi-parasitic plant grown in dicotyledon trees. In a 2003 study, it was mentioned that mistletoe (*Loranthaceae*), it has been used as a traditional herb for centuries in the treatment of epilepsy [26].

In 2003, the effect of caffeinated beverages on seizure control was investigated. The case report showed an increased seizure frequency due to excessive tea intake. In this context, the authors suggest that patients with epilepsy should not take excessive caffeine [27].

Gastrodin is one of the natural compounds isolated from *Gastrodia elata* and has anti-convulsant effect. In a 2003 study, a study of the immuno-activity of aminobutyric acid shunt enzymes in the hippocampus of seizure-sensitive gerbils was performed and suggested that this might cause elevation of GABA concentration [28].

Gastrodia elata (GE), a medicinal plant, has traditionally been used in the treatment of convulsive diseases such as epilepsy in South Korea and has an essential place in traditional medicine. In 2003, the effect of GE on epilepsy was investigated and the low dose of GE did not alleviate the hippocampal neuronal damage in the CA1 region, but the high dose reduced the hippocampal neuronal damage in the same region [29].

In 2003, plants used in traditional medicine in South Africa were screened for genotoxic effects. In the results, the use of *Gardenia volkensii* and *Catunaregam spinosa* extracts in the Rubiaceae plant family were discussed in the treatment of epilepsy [30].

In a 2004 study, the acute effect of *Ambrosia paniculata* was investigated in epilepsy animal models. Findings show that *A. paniculata* acts by enhancing GABAergic neurotransmission, such as a few conventional anti-epileptic drugs [31].

In 2004, pilocarpine epilepsy model was induced in rats for herbal treatment after seizures. According to the data, no seizures developed in rats that received a solution of three herbal liquid extracts of *Scutellaria lat* (Skullcap), *Gelsemium sempervirens* (Gelsemium) and *Datura stramonium* (Jimson Weed). As a result, it is strongly suggested that the proper combination of herbal compounds may be helpful as additional interventions, although there is no evidence that herbal remedies can control limbic or temporal lobe epilepsy [32].

In a 2005 study, the effect of intracerebroventricular administration of thymoquinone, the main founder of the *Nigella sativa* seeds, on the epileptic seizures in rats was investigated. The results have shown that thymoquinone may have anti-convulsant activity, possibly mediated by an opioid receptor in the GABAergic tone [33].

In a 2005 review, plants used by the traditional researchers of Tanzania to treat epilepsy were investigated. It has demonstrated competence in the treatment of the disease and 60 commonly used plants are mentioned. *Abrus precatorius* L. (*Leguminosae*), *Clausena anisata* (Willd.) Oliv. (*Rutaceae*) and *Hoslundia opposita* Vahl (*Lamiaceae*) are among the mentioned plants and these plants have proven anti-convulsant activity. Several other species in the list have also been reported to be useful in the treatment of epilepsy [34].

In a study on the seed of *Heracleum persicum* in 2005, anti-convulsant activity was investigated in mice by PTZ and electroshock-induced seizures. According to the results of the experiment, a dose-dependent protective effect was shown for both seizure models [35].

In 2005, anti-convulsant properties of *Tetrapleura tetraptera* (*fabaceae*) fruit aqueous extract in mice were investigated. The findings provide pharmacological support for the use of the plant in painful, arthritic inflammatory conditions or in epilepsy and childhood convulsions in several tropical African countries [36].

In the study titled “Traditional Chinese Medicine Treatment of Epilepsy” published in 2006, three adult patients with epilepsy showing resistance to standard anti-epileptic drugs were studied. The frequency of seizures was reduced after all three were added to the traditional treatment (Bu-yanghuan-wu-tang treatment) [37].

In 2006, the reviewing of plants used in Danish folk medicine to treat epilepsy and convulsions was performed. The aqueous and ethanolic extracts of 42 plants were tested for affinity to the GABA_A-benzodiazepine receptor [38].

In 2006, the use of medicinal plants in South Africa was investigated. In the study, *Crassulaceae Cotyledon orbiculata* L. (kouterie, plakkie), *Euphorbiaceae Ricinus communis* L. (olieblare, castorolie boom), *Leonotis leonurus* (L.) R. Br. (klipdagga, wilde dagga) and *Ruta graveolens* L. (wynruit, rue) plants for the treatment of epilepsy traditional use is mentioned [39].

According to a study conducted in 2006, the anticonvulsant effect of *Annona diversifolia* saff. and palmitone on penicillin-induced convulsive activity was investigated. The results showed that *A. diversifolia* and palmitone plants were effective in reducing the severity of penicillin-induced seizures in rats [40].

The various morphological sections of *Persea americana* Mill (*Lauraceae*), i.e., avocadone, are widely used for the treatment, management and/or control of a variety of human diseases, including childhood convulsions and epilepsy, in African traditional drugs. In a 2006 study, anti-convulsant effect of avocado leaf aqueous extract was investigated in mice. Accordingly, it appears to produce anti-convulsant

effect by increasing GABAergic neurotransmission and/or action in the brain [41].

- **2007-To date**

Passion flower (*Passiflora incarnata*) is used in the treatment of epilepsy in the traditional medicine of Europe and South America. In 2007, the anti-convulsant effects of *Passiflora incarnata* extract were investigated in mice. The results were obtained that may be beneficial for the treatment of seizures and the effects on GABAergic and opioid systems [42].

In a 2007 study, the anti-convulsant activity of *Hypoxis hemerocallidea* and hypoxidacea aqueous extracts was investigated in mice. It has been shown that the aqueous extract of “African potato” has an anti-convulsive effect by increasing GABAergic neurotransmission and/or movement in the brain. The results provide a pharmacological assurance for the use of the plant [43].

In traditional medicine, *Nigella sativa* L. (black seed) has long been widely used as a natural medicine because of its anti-convulsant effects. In a study published in 2007, the effect of black seed on refractory pediatric seizures was investigated. The mean frequency of seizures in the children participating in the study decreased significantly during the extractive treatment. As a result, it was concluded that the extract of *Nigella sativa* L. has anti-epileptic effects in children with refractory seizures [44].

In 2007, a study on the binding activity of anti-plasmodial and GABA_A benzodiazepine receptor of a plant used in traditional medicine in Mali from West African countries was called the use of traditional treatment in epilepsy for medicinal plant “*Trichilia emetica* Vahl” [45].

In 2008, the effects of *Ginkgo biloba* (EGb 761) on the epileptic activity developed in rabbits were studied. The results show that the epileptogenesis process is affected by EGb 761 [46].

In a 2008 study, *Vitex agnus castus* extract was investigated for anti-epileptic activity in male rats over the kindling seizures in the amygdala. According to the results of the study, the appropriate dose of Vitex may help to prevent, prevent or reduce the epileptic activity [47].

The antioxidant activity of *Pimpinella anisum* L. (Anise) has been proven to have many biological effects. Probably, the candidate cellular mechanisms underlying hyperactivity produced by anise oil include increasing Ca²⁺ channel activity. This finding indicates that a certain attention is required as anise is used in the treatment of patients suffering from epilepsy [48].

In a study conducted in 2008, the anti-convulsant effect of *Rhus chirindensis* (Baker F.) (Anacardiaceae) root crust aqueous extract was investigated in mice. It has shown that childhood convulsions and epilepsy may be used as a natural

supplement in the management, control and/or treatment [49].

In 2009, the effects of Q'eqchi yeast antiepileptic plants on ethnopharmacology and GABAergic system were investigated. Q'eqchi yeast has a wide range of plants used to treat neurological disorders such as epilepsy. Within the results, information about the anti-epileptic activity of Q'eqchi is pharmacologically related [50].

In 2009, the anti-convulsant effect of flavonoid, linalool and α -tocopherol structures on the leaf extract of *Cissus sicyoides* L. was investigated. The results show that it has an anti-convulsant-like effect in mice, probably due to the effect of structures found in Vitaceae leaves [51]. In a 2009 study, the therapeutic role of cerebellar 5-HT_{2C} receptors and *Bacopa monnieri* extract in pilocarpine-induced epilepsy was investigated in rats. In the results, *B. monnieri* has been shown to have a neuroprotective effect by regulating the 5-HT_{2C} receptor in epileptic rats. This is of clinical importance for the treatment of epilepsy [52]. In a 2009 study, anti-convulsant properties of the extracts of *Randia nilotica* stapf were evaluated in mice. The results show the potential anti-convulsant activity of the root bark extract of *Randia nilotica* Stapf [53].

In a 2009 study, anti-convulsant activity of *Myristica fragrans* (small coconut oil) was investigated. It was shown that coconut oil prevented the spread of seizures in animal models. In this regard, it has been shown to be effective against large and partial seizures [54].

Excoecaria agallocha L. (Euphorbiaceae) is an essential mangrove species, mostly distributed in China, India, Philippines and Oceania. In a study conducted in 2009, Euphorbiaceae obtained from the bark of mangrove plants were studied. According to the information in this study, euphorbiaceae is traditionally used in the treatment of epilepsy [55].

In a 2009 study, *Searsia* species were reported to be used in the treatment of epilepsy in South Africa. *Searsia chirindensis* (Baker F.) Moffett, *Searsia dentata* (Thunb) F.A Barkley, *Searsia natalensis* (Bernh Ex Krauss) F.A. Barkley and *Searsia pyroides* (A. Rich) T.S. Yi, A.J. Mill and J. Wen (bazionym, *Rhus pyroides*) are given as examples. As a result, the ethanolic extract of *S. dentata* showed anticonvulsive properties in various epilepsy models [56].

In 2013, *Musa* sp., *Sapindus mukorossi* Gaertn. and *Trema orientalis* (L.) Blume plants have been used in the treatment of epilepsy [57].

In a 2011 study, *A. nilagarica* (Cl.) Pamp., *Cannabis sativa* L., *Iris kemaonensis* D. Don ex Royle and *Thymus linearis* Benth. Plants are reported to be involved in the treatment of epilepsy [58].

In a study conducted in 2004, *Passiflora incarnata* is considered anti-spasmodic, sedative and narcotic and it is reported to be beneficial in epilepsy [59].

In a study conducted in 2012, it draws attention to the use of *Passiflora incarnata* L. in the treatment of epilepsy. It is used for epilepsy in Turkey and among 500 species of the genus *Passiflora*, *P. incarnata* is the only species with a broad clinical practice worldwide [60].

In 2012, *Viscum album* L. is claimed to be useful in the treatment of epilepsy. The results of the study showed that *Viscum album* L. exhibited anti-epileptic activity in mice and rats [61].

In a 2012 study, turmeric obtained from *Curcuma longa* rhizomes is known to be used as a traditional medicine in the treatment of epilepsy in South Asia. To date, *in vivo* studies on anticonvulsant activity of turmericity have focused on curcuminoid curcumin [62].

In 2013, in some cases of epilepsy, the ineffectiveness of drugs and the serious side effects of antiepileptic drugs and chronic toxicity have led to the use of herbal treatment. The black fruit of *Terminalia chebula*, *Halile siah*, known as Agher Gherha, is used in the herbal treatment of epilepsy of *Anacyclus pyrethrum*, *Anisun*, *Origanum majorana*, *Ferula assafoetida* (Anghose), *Ruta graveolens* (Sodab) and *Lavandula stoechas* (Ostokhoddos) [57].

Experimental and clinical studies have shown that changes in brain serotonin may play an essential role in the pathophysiological changes of epilepsy. Accordingly, change of Piperin in serotonin levels indicate that it is related to the treatment of epilepsy [63].

In a study conducted in 2015, *Aloe vera* (Liliaceae) has been reported to be used for the treatment of epilepsy due to its antioxidant properties [64].

In this study conducted in 2015, the root stem of *Acorus tatarinowii* was investigated and plant-derived agents against epilepsy were discovered. The anticonvulsant and sedative effects of eudesmin isolated from *A. tatarinowii* were investigated and significant results were obtained [65].

In 2011, it was concluded that the use of *Passiflora incarnata* L. species in the treatment of epilepsy was determined [66].

In a 2017 study, it was described that the anti-microbial plant *Moringa olifera* is widely used for the treatment of epilepsy. The leaves, shell and seed of it have some anti-inflammatory and therapeutic properties. *M. olifera's* success in using extracts to control pathogens has been reported [67].

In 2017, the leaves of the *Laurus nobilis* plant were reported to be used for the treatment of epilepsy [68].

In a 2017 study, the role of *Caryocar coriaceum* Wittm in the treatment of epilepsy was investigated by evaluating the anticonvulsant effects [69].

It is known that Moriferin in mango shell and Morinin in *Maclura pomace* are natural antioxidants. In a study conducted in 2017, they might be used as herbal treatment in pathological conditions such as epilepsy with the characteristics of these plants [70].

In a study conducted in 2018, a detailed analysis of herbal medicine used for neurological conditions related to epilepsy in Asia, Africa and Latin America was conducted. As a result, *Acorus calamus* L. rhizomes and leaves of *Bacopa monnieri* (L.) Wettst, *Leonotis leonurus* (L.) R. leaves, *Uncaria rhynchophylla* (Miq.) Miq. ex Havil., *Calotropis gigantea* (L.) Dryand., *Ricinus communis* L., *Asparagus racemosus* Willd. and *Rauvolfia serpentina* (L.) Benth. It has been reported that ex Kurz may be used for treatment in epilepsy [71].

CONCLUSION

Despite all clinical and experimental studies, the fact that the treatment of epilepsy has not been elucidated led the investigator to alternative and complementary therapies. Throughout the world, dozens of plants have been shown to be used as a phytotherapeutic agent in epilepsy.

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