



ISSN: 2348-1900

Plant Science Today

<http://www.plantsciencetoday.online>

Review Article

Phytotherapy for seizure: An overview of the most important indigenous Iranian medicinal plants with anticonvulsant properties

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Article history

Received: 18 April 2019

Accepted: 19 May 2019

Published: 01 October 2019

Abstract

The statistics show that more than fifty million people worldwide suffer from seizure and epilepsy, and most of them are resistant to antiepileptic drugs. The causes of seizure attacks are different, including various diseases of the nervous system, infections, tumors, brain trauma, congenital diseases, fever, toxicity and metabolic factors. Currently, drugs such as phenytoin, phenobarbital, carbamazepine, valproic acid and diazepam are used to treat epileptic seizures, which in turn lead to side effects. Studies have shown that the use of natural and herbal antiseptic agents has beneficial and protective effects. In this review article, the most important indigenous Iranian medicinal plants used to treat seizures are reported. Information to conduct this review article has been obtained using the search terms *seizure*, *neurological lesion*, *phytotherapy*, *Iran*, *medicinal plants*, *extracts* and *essential oils* to retrieve articles indexed in databases such as *Scopus*, *Scientific Information Database*, *Magiran*, *Google Scholar* and other Persian databases. The relevant articles were further reviewed for medicinal plants with anticonvulsant properties. Based on the results, medicinal plants such as *Peganum harmala*, *Lavandula officinalis*, *Matricaria chamomilla*, *Tanacetum sonbolii*, *Launaea acanthodes*, *Ocimum basilicum*, *Salvia sahendica*, *Ruta graveolens*, *Elaeagnus angustifolia*, *Ziziphora tenuior*, *Heracleum persicum* and *Scrophularia striata* are among the most important medicinal plants in Iran with anticonvulsant effect.

Publisher

Horizon e-Publishing Group

Keywords: seizure; neural lung; medicinal plants; Iran

Citation: Farzan B, Shahsavari S, Abbaszadeh S, Hassan Teimouri H. Phytotherapy for seizure: An overview of the most important indigenous Iranian medicinal plants with anticonvulsant properties. *Plant Science Today* 2019; 6(4):367-372. <https://doi.org/10.14719/pst.2019.6.4.557>

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Indexing: Plant Science Today is covered by Scopus, Web of Science, BIOSIS Previews, ESCI, CAS, AGRIS, CABI, Google Scholar, etc. Full list at <http://www.plantsciencetoday.online>

Introduction

Epilepsy is a common neurological disorder characterized by unpredictable and periodic

seizures (1). The statistics show that more than fifty million people worldwide suffer from seizure and epilepsy, and most of them are resistant to antiepileptic drugs. (2). Seizure, which is a limited

event in the brain, results from abnormal firing of brain neurons (3). Major factors leading to seizure include brain trauma, cerebral ischemia, and brain infections (4, 5). Experiments conducted on animals, seizure-inducing materials act via different mechanisms, and it is argued that the glycine receptor acts as an inhibitory transmitter (6). The causes of seizure attacks are various, including different diseases of the nervous system, infections, tumors, brain trauma, congenital diseases, fever, toxicity and metabolic factors (7). The main point in treating seizure and epilepsy is the need for long-term treatment, which will further provide the conditions for the development of side effects of medications. Therefore, paying attention to traditional medicine and herbal drugs with the goal of achieving low-risk drugs with minimal side effects is becoming more apparent (8,9). Drugs such as phenytoin, phenobarbital, carbamazepine, valproic acid, and diazepam are commonly used to treat epileptic seizures, which, in turn, lead to certain side effects (10), including rash, jaundice, sore throat, fever, simple bleeding, bruising, and petechia bleeding (11-13). Medicinal plants have been used to control and treat diseases for centuries, and their appropriate therapeutic effects with less side effects have been proven over the years (14-19). Studies have shown that the use of anticonvulsants of natural and herbal origin has beneficial and protective effects (20).

Anti-epileptic drugs have side effects; while it is a known fact that medicinal herbs are safe and available in natural sources. In traditional medicine, for the formulation of a synthetic drug, chemical compounds in a single plant or those in different parts of several plants are utilized (16, 17). From ancient times, medicinal plants were fruitfully utilized with less complications and are found to be a suitable alternative for the treatment of diseases (16, 17). Therefore, the identification of medicinal herbs that can form as a remedial measure for the seizure can lead to the production of anticonvulsant herbal medicines. Hence, much attention have been paid to traditional medicine and herbal drugs that becomes more obvious in attaining low-risk drugs with minimal side effects. In this respect, the present review is focusing on the most important indigenous medicinal plants used in the treatment of seizures.

Methodology

Information to conduct this review article has been obtained using the search terms seizure, neurological lesion, phytotherapy, Iran, medicinal plants, extracts and herbs to retrieve articles indexed in databases such as Scopus, Scientific Information Database, Magiran, Google Scholar and other Persian databases. Altogether, 16 were obtained from the search, of which 4 were deleted due to ineffective results, invalid magazines, and

irrelevance. Finally, 12 articles were considered for review and the results were analysed. The relevant articles were further reviewed for medicinal plants with anticonvulsant properties.

Results

Based on the results, medicinal plants such as *Peganum harmala*, *Lavandula officinalis*, *Matricaria chamomilla*, *Tanacetum sonbolii*, *Launaea acanthodes*, *Ocimum basilicum*, *Salvia sahendica*, *Ruta graveolens*, *Elaeagnus angustifolia*, *Ziziphora tenuior*, *Heracleum persicum* and *Scrophularia striata* are among the most important medicinal plants in Iran with anticonvulsant effect. Additional information on the effects of these medicinal plants is as follows:

Peganum harmala L.

The results of one study showed that oral treatment with methanolic extract of *P. harmala* at 45 mg/kg for 15 days inhibited strychnine induced seizure, decreased the time at onset of seizure and its length, increased the duration of respiratory arrest pronouncedly. It was also observed that the extract of seed/phenytoin (21) decreased mortality in animals.

Lavandula officinalis Chaix

Lavandula officinalis extract at doses of 200, 400 and 800 mg/kg in NMRI mice could reduce the severity and duration of attacks. It also eliminated the fifth phase of seizures completely (22).

Matricaria chamomilla L.

The study revealed that the hydroalcoholic extract of *M. chamomilla* at doses of 800 and 1000 mg delayed the onset of tonic-clonic seizures compared to the control group (treated with saline). It also significantly reduced the 24-h mortality rate compared to the control group (23).

Tanacetum sonbolii Mozaff.

The tonic-clonic seizures in the groups receiving the *T. sonbolii* hydroalcoholic extract at 1200 mg were significantly reduced compared to the control group. Besides that, there was a statistically significant difference between the mean time of delay to onset of seizure between the groups receiving extract and the control group. Extract reduced the rate of mortality from seizure and prevented tonic-clonic seizures in several cases (24).

Launaea acanthodes (Boiss.) Kuntze

The results of one study showed that in the open box test, single dose of fraction caused a significant reduction in rearing, while such effect was not observed on motility. In addition, different doses of ethanolic extract (100, 200 and 300 mg) and the aqueous fraction inhibited seizure attacks by increasing the delayed periods to the onset of anterior limbs clonus and tonic-clonic attacks (25).

***Ocimum basilicum* L.**

Mice in the 100 mg/kg dose group showed the most epileptic seizures. Mice in the two groups in receiving 100 and 250 mg/kg showed the highest and the lowest myoclonic contractions in comparison with other groups, respectively. In the group receiving 250 mg/kg 65 minutes before injection of pentylenetetrazole, three factors, the number of seizures and mortality rate were significantly increased, decreased and decreased respectively (26).

***Salvia sahendica* Boiss. & Buhse**

The injection of hydroalcoholic extract of *S. sahendica* doze-dependently delayed the onset of clonic and tonic-clonic seizures. The doze of 600 mg/kg BW was the most effective doze on the quantity of seizure. Extract administration also reduced the time of tonic-clonic seizure in mice and also significantly reduced the mortality and the number of animals' sudden jumps during seizure (27).

***Ruta graveolens* L.**

The study in NMRI mice showed that the hydroalcoholic extract of *R. graveolens* in a doze-dependent manner, increased the delay in the onset of myoclonic seizures. Delay in myoclonic seizure was significant at dozes of 300, 500, 800 and 1000 mg/kg compared to the control group. Delay in tonic-clonic seizure was observed at the doze of 100, as well as in doses of 300, 500, 800 and 1000 mg/kg was significant compared to the control group (28).

***Elaeagnus angustifolia* L.**

The study on male mice showed that hydroalcoholic extract of *E. angustifolia* at 200 and 400 mg/kg increased the threshold of induced seizure significantly compared to control group of male mice (29).

***Ziziphora tenuior* L.**

The results of a study in a mouse model showed that injections of hydroalcoholic extract of *Z. tenuior* in a dose-dependent manner delayed the onset of clonic, tonic, and generalized tonic-clonic seizures, with the highest effects observed at 600 and 900 mg/kg of the extract. Besides, administration of hydroalcoholic *Z. tenuior* extract leaves caused a decrease in the average time of clonic, tonic and tonic-clonic seizure in animals. The extract also protected the animals against mortality and the number of sudden jerks, with the greatest effect observed at 600 and 900 mg/kg (30).

***Heracleum persicum* Desf. ex Fisch.**

Experiment with the mice showed that hydroalcoholic extract of *H. persicum* leaves at 300 and 600 mg/kg caused an increase in the tonic phase. In the tonic-clonic phase, the increase in seizure threshold was only significant at 600

mg/kg. The hydroalcoholic extract of *H. persicum* leaves significantly reduces the mean survival time in tonic and tonic-clonic seizures (31).

***Scrophularia striata* Boiss.**

The hydroalcoholic extract of *S. striata* in mice showed that at 300, 600 and 900 mg/kg delayed the onset of tonic, clonic and tonic-clonic seizures and also reduced the incidence of imbalance and jump in animals at birth. Injection of the hydroalcoholic extract of the plant resulted in the decrease of mortality rate to zero (32).

Discussion

Seizure is one of the most common and warning symptoms of brain diseases, which often informs the serious damage to the brain parenchyma. Accordingly, in Iran, medicinal plants such as *Peganum harmala*, *Lavandula officinalis*, *Matricaria chamomilla*, *Tanacetum sonbolii*, *Launaea acanthodes*, *Ocimum basilicum*, *Salvia sahendica*, *Ruta graveolens*, *Elaeagnus angustifolia*, *Ziziphora tenuior*, *Heracleum persicum* and *Scrophularia striata* are among the most important medicinal plants with anticonvulsant effect. The main alkaloid of this plant is a substance called harmalin (33). Various scientific studies have shown that the seeds of *P. harmala* have appetizing and diuretic properties and are involved in the treatment of neurological diseases (34, 35). Several studies on the effects of *L. officinalis* have reported the effects of the plant in reducing seizures and epileptic attacks (36-38). Compounds such as butyric acid, cinnamol, nerol, borneol, propionic acid, valeric acid, free linalool, tanin and flavonoids exist in *L. officinalis* (39). *T. sonbolii* is rich in antioxidants such as flavonoids, polyphenols and essential fatty oils, which have been shown to have antioxidant effects and to contribute to weakening the central nervous system (40). *T. sonbolii* contains certain compounds belonging to the sesquiterpenes, lactones and flavonoids (41).

In the recent studies, the possible effect of flavonoids on the central nervous system through binding benzodiazepine receptors as that of benzodiazepines has been reported. This argument has been raised according to evidence on the effect of flavonoids in creating sleepiness, removal of anxiety and control of seizure (42-44). Studies have shown that the activation of benzodiazepine receptors by stopping the epileptic seizures by strengthening the brain's gababaretic system (45). Polyphenols also have a positive effect on the treatment of many diseases such as cancers, cardiovascular diseases, and nervous system diseases (46). Since ancient times, gum derived from the stems of *L. acanthodes* has been used among the populations of desert areas as an effective herbal remedy for the treatment of many diseases, such as epilepsy, neurological diseases, local and joint pains (47). The basil has long been used as sedative,

analgesic and anticonvulsant in traditional medicine (48). The main constituents in *Ocimum basilicum* are 1, 8 cineoles, linalool and geraniol, which comprise 93% of essential oils (49). Compounds such as glycosides, coumarins, quinoline alkaloids, flavonoids and lignins are phytochemicals identified in *Ruta graveolens* (50). *Elaeagnus angustifolia* has analgesic, anti-inflammatory and restorative effects (51-55). The *Elaeagnus angustifolia* extract contains compounds such as cytosterol, cardiac glycosides, terpenoids and flavonoids (56). It has been shown that phytosterol and flavonoids have analgesic and anti-inflammatory effects (57). *Ziziphora tenuior* leaves are traditionally useful in improving seizures, respiratory diseases for sedative, antispasmodic and anticonvulsant, anti-smooth muscle spasm and anti-flatulence effects (58-60). The main compound of the leaf of *H. persicum* is trans-anthole (61). Medicinal plants can be effective in improving seizure symptoms due to their active and antioxidant ingredients and they can be used to produce effective drugs on seizure.

Acknowledgements

The authors are grateful to the Shahrekord University of Medical Sciences, Iran for financial assistance.

Authors' contributions

All the authors contributed equally to the work presented in this paper.

Competing Interests

The authors declared that they have no conflict of interest.

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