

Iranian Medicinal Plants and Intractable Epilepsy in Childhood (A narrative review)

Abstract:

Epilepsy, which is one of the major neurological disorders, can happen in all ages including children. Approximately 20% of epileptic children are drug resistant. Uncontrolled seizure poses variable risks to patients such as higher rates of mortality, trauma, cognitive and psychiatric problems. So, effective treatment to control attacks is essential. Although currently, there are many antiepileptic drugs available for clinical treatments, clinicians are still awaiting the discovery of safer drugs which have improved antiepileptic effects and have less side effects. Traditional medicine provides a strong ground for the modern medicine. It has been shown that use of some plants can either reduce or prevent further progression of seizures.

The present review attempts to discuss the efficacy of some medicinal plants on children with intractable epilepsy.

Online literature review was conducted using Iran Medex, Scopus, Medline, and Google Scholar to identify studies which discuss the use of plants in children with intractable epilepsy. Searches for this review were also done by going through the files of authors in the reference list and bibliographies of those related papers.

Overall, researches have shown that herbal therapies have the potential to yield new treatment options for children with intractable epilepsy. Using herbs may represent an inexpensive way of treatment in these children which is culturally acceptable to their families as well.

Key words: Epilepsy, Seizure, Children, Plants

Introduction:

Epilepsy is a type of neurological disorder which is characterized by unprovoked seizures that are recurring and disrupt brain activity and even can impair mental as well as physical function. Epilepsy is not a single disorder but rather it includes a group of problems that are developed as a result of some abnormal electrical activity in the brain. Worldwide, there are almost 50 million people who are having epilepsy while approximately 50% of them are children. (1) Although many antiepileptic drugs (AEDs) are currently available, nearly 25% of patients who have epilepsy continue to have seizures and the same proportion experience side effects as a result of AEDs. New antiepileptic drugs are getting discovered that compared to the administration of the AEDs in human volunteers, currently yield better efficacy and safety during the preclinical employment of animal models. (2)

The development of anticonvulsant drugs in 20th century has witnessed considerable progress. The major drugs in clinical use (for example phenytoin, valproate, carbamazepine, benzodiazepines, ethosuximide, primidone, and phenobarbital) which are considered as “old drugs” were developed and introduced between 1910 and 1970. However, there are several newly-developed drugs introduced as more recent anticonvulsants (like vigabatrin, felbamate, gabapentin, lamotrigine, tiagabine, oxcarbazepine, and topiramate) and are considered as “new drugs”, which are currently in preclinical trials and will be called the “new generation” of drugs. Although 70% of children with epilepsy can be seizure-free using current antiepileptic drugs, over 25% of epileptic children remain intractable although they are taking two or three antiepileptic drugs. (3)

Historically, alternative therapies especially plant-based therapies have captivated human beings. The WHO has reported that in developing countries, about 80% of people for their health care needs rely largely on plant based drugs. (4)

Many researches established a scientific basis for explanation of efficacy of most herbs. Neurological disorders such as epilepsy, Parkinson disease, anxiety and depression have been studied extensively. (5, 6)

The present study aims to investigate Iranian plants or their extracts with anticonvulsant activity on children who suffer of intractable epilepsy.

In this literature, we have reviewed the available trial researches, using Iran Medex, Medline, Google Scholar, and Scopus to identify all studies about Iranian medicinal plants with antiepileptic effects. Searches were also performed by going through the authors' files as well as by looking at bibliographies of all identified papers. No time or language limitation was posed to the literature.

Literature review:

Nigella sativa

Black cumin seed (botanical name is *Nigella Sativa*) has been cultivated in the Mediterranean region as well as several other locations in the world. It plays important roles such as an antihypertensive, hypoglycemic, antihistaminic, and diuretic agent. (7) In ancient Islamic societies, it was known to be an anticonvulsant. (8)

Nigella Saliva oil has shown antiepileptic effects against PTZ- kindling seizure in mice. The mechanism for this effect seems to be due to antioxidant effect. (9)

Akhondian and colleagues used the water extract collected from black cumin seeds (its major constituent is thymoquinone) as syrup (included 60% sucrose solution) with a placebo as an add-on in a study based on double-blinded, placebo-controlled, randomized, cross-over protocol. (6) In this study, 20 patients were enrolled. All patients received the extract or placebo (40 mg/k/q8h) as add-on for one month with a two-week period in between during which they received only conventional anti-epileptic drugs. Participant patients reported that the frequency of their seizures decreased during treatment with the extract and the change

between the mean seizure frequencies was statistically significant. Constipation and maculopapular rash reported in two patients as side-effects. (6)

Most of the efficacy of Sativa and its derivatives are attributed to thymoquinone (9). Studies show that thymoquinone has several therapeutic effects while not presenting evidence of side effects. (9, 10)

The effects of thymoquinone on intractable pediatric seizures were reported in one double-blinded, cross-over pilot study. Study authors enrolled 22 patients (1-14 years old) who were suffering from intractable epilepsy. Thymoquinone was administered with the dose of 0.5 mg/kg/q12h. Eventually, 54.5% of patients who were using thymoquinone showed a 50% reduction in weekly seizure frequency relative to their baseline compared to a 13.6% reduction in weekly seizure frequency for the patients who were using the placebo. The reported side effects were nausea and somnolence. Since the base of the drugs was alcohol, alcohol may be responsible for these adverse effects. (11)

Rosa Damascena:

In the 15th century, cultivation of Rosa Damascena began and the Turkish province began producing rose oil. The rose petals contain very little oil crops (oil content = 0.03% of rose petals). (12)

In Persian, this plant is named "Gol-e-Mohammadi". Its essential oil content and composition include citronella, geraniol, nerol, linalool, phenylethyl alcohol, monoterpene alcohols. The effects of anti-HIV, antioxidant activities, antibacterial, hypnotic, antitussive, antidiabetic, and relaxant effects on tracheal chains have been reported. (13) In another study, Rosa Damascena extract when induced by acetaminophen in rats, showed the hepatoprotective activities and these data suggest it may prevent toxicity through its antioxidant's effects. (14, 15)

Rakhshandeh et al. also investigated the effects of Rosa Damascena essential oil in rats and found that the oil can significantly retard development of seizures induced by amygdala kindling in rats. (16) In a similar study, Rosa essential was shown to be able to attenuate the latent periods of initiating, and the degree of severity of pentylenetetrazol (PTZ) -induced seizures in rats. (17)

The effects of aqueous, ethanolic and chloroformic extracts on Rosa damascena on PTZ induced seizures in mice showed ethanolic extract of Rosa damascena can increase latency of seizure development in mice compared with normal saline. (18)

Ataei et al. showed that the Rosa damascena can significantly decrease the frequency of epileptic attacks in children with intractable e study was found in children with intractable epilepsy. (19) In this placebo-controlled, double-blind study enrolled 16 patients between the ages of 3 and 12 years. They received Rosa oil (from the Nader factory, which was prepared a 10% extract with MCT oil) and placebo (0.05 cc/kg/dose) in 3 divided dose administered with their antiepileptic drugs as an add-on therapy. The first drug or placebo administered during the days 1-10, classic antiepileptic drugs were administered days 11-20, and for the third 10-days placebo or drug were administered. 56.3% of patients experienced several types of seizure (myoclonic, tonic, tonic-clonic, and partial) and 42.8% experienced only one type of seizure. Rosa oil had significant effects on reducing the frequency of seizures but did not affect the duration of seizures. The study did not report any side effects. (19)

Curcumin

Curcumin, which is the main biological component of the common spice used in cooking called turmeric, has been studied recently. Molecular investigations revealed which; this agent has anti-inflammatory, antimicrobial, anti-hepatotoxic, and anti-hyperlipidemic effects. It is useful for thrombotic events and psoriasis. (20)

Recent studies suggest that curcumin has a neuro-protective role as well.

There are several theories about its effects. Some studies show that it can eliminate oxidative stress and cytokine release, which are activated during seizures. (20) Other evidence suggests that it plays a protective role in hippocampal neuronal loss, prevents mitochondrial malfunction, and rescue the hepatotoxic effect of antiepileptic drugs. Curcumin can also act as an inhibitor of amyloid- β formation and prevent transcription of nuclear factor kappa B (which is an inflammatory cytokine). (21)

Since curcumin has low molecular weight and polar structure, it can penetrate the blood brain barrier effectively. Experimental study showed that the curcumin causes an increase in the number of the newly generated cells in the dentate gyrus region of hippocampus and can amplify the hippocampus neurogenesis process. Also, curcumin is a potent inhibitor of the expression of reactive astrocytes. This prevents hippocampal cell death caused by kainic acid. (20, 21)

The protective effects of curcumin have been shown in several studies in experimental models when electro shocks have induced seizures in mice. Curcumin also shows antidepressant activity that has been reported in animal models which were inflicted by depression. Another promising use of curcumin is in the treatment of diabetic neuropathy. Curcumin has been used in animal models during treatment of tardive dyskinesia as pretreatment method that can reduce side effects of haloperidol. (21)

Akhondian et al. in their study in children with myoclonic epilepsy investigated the effects of curcumin. . In their double-blinded and placebo controlled trial, 33 patients, with the ages from 3 months old to 14 years old were evaluated. Patients in that study received either nano-curcumin capsules or placebo capsules for a period of 4 weeks. At the end of this period placebo was replaced with the drug. Duration of that study was 10 weeks that included the

washout period as well. At the end of that study, 24.2% of participant children were seizure free when none of them experienced any side effects. (22)

Conclusion:

Currently, most reviews of treatments for epilepsy concentrate on the pharmacological agents. However, at the present time, drugs used to cure epilepsy not only fail to control seizure activities in some of children, but they have many side effects and harmful drug interactions. In addition, high expenses of treatments, especially in long term therapy regiments, are other limitations of synthetic antiepileptic drugs. Traditional medicine which is popular practice among developing countries, where up to 80% of the populations rely on methods of traditional medicines for their primary health care needs, may be utilized as an alternative method for the treatment of epilepsy. Medicinal plants may constitute an important source of new chemical substances that have potential therapeutic effects. The present review highlights studies of different Iranian plants that are used in the treatment of epilepsy in children and it can be concluded that medical plants possessed multiple effects on epilepsy. They can be future drugs for the treatment of epilepsy.

Acknowledgements:

We would like to thank all patients who with their participation provided the means for these researches toward finding better results for future treatments.

Conflict of interest:

The authors declare no conflict of interest.

Reference:

- 1 -Samleti AS, Sharma N, Tambole RD, Dhobale SK. Traditional herbs used in treatment of epileptic seizures. IJPCS 2012 3:1411-1416.
- 2-Schachter SC. Botanicals and herbs: a traditional approach to treating epilepsy. Neurotherapeutics 2009 6:416-420.

- 3-Quintan LJ, Almeida J, Lima JT, Nunes XP, Siqueira JS, Oliveira LEG, Ameida RN, Athayde Filho PF, Batbosa Filho JM. Plants with anticonvulsant properties- a review. *Rev.Bras.Farmacogen* 2008 5:798-819.
- 4-Hishe M, Asfaw Z, Giday M. Review on value chain analysis of medicinal plants and the associated challenges. *Jour of Med Plan Stu* 2016 4(3):45-55.
- 5- Sahranavard S, Ghafari S, Mosaddegh M. Medicinal plants used in Iranian traditional medicine to treat epilepsy. *Seizures* 2014 23:328-332.
- 6-Das MK, Mazumder PM, Das S. Antiepileptic activity of methanol extract of *Bultea monosperma kuntz* and its isolated bioactive compound in experimentally induced convulsion in Swiss albino mice. *Int J Drug Dev & Res* 2016 8:18-22.
- 7-Ilhan A, Gurel A, Armutcu F: Antiepileptogenic and antioxidant effect of *Nigella sativa* oil against pentylentetrazole-induced kindling in mice. *Neuropharmacology*, 2005 49(4): 456–64
- 8- Akhondian J1 Parsa A, Rakhshandeh H. The effect of *Nigella sativa* L. (black cumin seed) on intractable pediatric seizures. *Med Sci Monit* 2007 13(12):555-559.
- 9-Khader M, Eckl PM. Thymoquinone: an emerging natural drug with a wide range of medical applications. *Iran J Basic Med Sci.* 2014 17:950-975.
- 10- Sedaghat R, Roghani M, Khalili M. Neuroprotective effect of thymoquinone, the *Nigella Sativa* bioactive compound, in 6-hydroxydopamine-induced hemi-parkinsonian rat model. *IJPR* 2014 13(1):227-234.
- 11- Akhondian J, Kianifar HR, Raoofziaee M, Moayedpour M, Beiraghi Toosi M, Khajedaluae M. The effect of thymoquinone on intractable pediatric seizures (pilot study). *Epilepsyres* 2011 39:39-43.
- 12- Baydar H, Baydar NG. The effects of harvest date, fermentation duration and Tween 20 treatment on essential oil content and composition of industrial oil rose (*Rosa damascena* Mill.) *indcrop* 2005 21:255-251-255.

- 13- Boskabadi MH, Shafei MN, Sabery Z, Amini S. Pharmacologicology effects of rosa damascene. IJBMS 2011 14:295-307.
- 14- Achuthan, C R, Babu B H, Padikkala J. Antioxidant and hepatoprotective effects of Rosa damascene. Pharmaceutical Biology 2003 41:357-361.
- 15- Sexena M, Shakya AK, Sharma N, Shirvastava S, Shukla S. Therapeutic efficacy of rosa damascene mill on acetaminophen induced oxidative stress in albino rats. J Environ Path Toxicol Onco 2012 31(3):193-201.
- 16- Ramezani A, Moghimi A, Rakhshandeh H, Ejtehad H, Kheirabadi M. The effect of rosa damascene essential oil on the amygdale electrical kindling seizures in rat. PJBS 2008 11(5):746-751.
- 17- Hosseini M, ghasemzadeh Rahbardar M, Sadeghnia HR, Rakhshandeh H. Effects of different extract of Rosa damascene on PTZ induced seizures in mice. Zhong Xi Yi He Xue Bao 2012 10(12):1328-1335.
- 18- Kheirabadi M, Moghimi A, Rakhshandeh H, Rassoli MB. Evaluation of the anticonvulsant activities of Rosa damascene on the PTZ induced seizures in Wister rats. J Biol Sci 2008 8(2):426-430.
- 19- Ataei AA, Mirhaghjoo SF, Abdollapour, N, Ardakani SA, Ashrafzadeh F. The assessment of rose essence in treating intractable phamacoresistant epilepsy in children between 3-12 years. AJPCR 2015 3(4):117-123.
- 20- Kulkarni SK, Dhir A. An overview of curcumin in neurological disorders. Indian J. Pharm. Sci., 2010, 72 (2): 149-154.
- 21- Mehla J, Reeta KH, Gupta P, Gupta YK. Protective effect of curcumin against seizures and cognitive impairment in a pentylenetetrazole-kindled epileptic rat model. Life Sciences 2010 87:596–603.

22- Akhondian J, Ashrafzadeh F, beiraghi Tossi M, Hasanpor K. evaluation of therapeutic effects of active ingredient of tumeric (curcumin) on children with myoclonic epilepsy.

Underprint.

Uncorrected Proof