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Iranian Medicinal Plants and Intractable Epilepsy in Childhood: A Narrative Review

Farah Ashrafzadeh (MD)*[1], Hadi Tohidi (MD)[2], Elnaz Faraji (MD)[2], Alireza Ataei Nakhaei (MD)[1]

[1]*Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad, Iran.*
[2]*Mashhad University of Medical Sciences, Mashhad, Iran.*

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ABSTRACT

Epilepsy is a major neurological disorder, which may occur in all age groups, including children. Approximately 20% of epileptic children are drug-resistant. Uncontrolled seizures pose variable risks to patients, such as increased mortality rate, trauma, and cognitive and psychiatric disorders. Therefore, effective treatment is essential to controlling seizure attacks. Although many antiepileptic drugs are currently available for clinical treatments, clinicians are concerned with the discovery of safer drugs with enhanced antiepileptic effects and fewer side-effects. Traditional medicine provides strong grounds for modern medicine. Use of some medicinal plants has been shown to reduce or prevent the further progression of epileptic seizures. The present review aimed to discuss the effectiveness of some medicinal plants in the treatment of children with intractable epilepsy. An online literature review was conducted in databases such as IranMedex, Scopus, Medline, and Google Scholar to identify the studies investigating the use of medicinal plants in children with intractable epilepsy. In addition, the files of the authors were reviewed in the reference lists and bibliographies of the retrieved articles. According to the results, herbal therapies could potentially yield new treatment options for children with intractable epilepsy. Using medicinal herbs could be a cost-efficient treatment method in these patients as a culturally acceptable option to their families.

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Introduction

Epilepsy is a neurological disorder characterized by unprovoked, recurrent seizures that disrupt brain activity and may impair mental and physical function. Epilepsy is not a single disorder, but rather a combination of disorders that develop due to the abnormal electrical activities in the brain. Approximately 50 million individuals are diagnosed with epilepsy across the world, 50% of whom are children (1).

Although many antiepileptic drugs (AEDs) are currently available, nearly 25% of epileptic patients continue to have seizures, and the same proportion experience the side-effects of AEDs. New AEDs have been discovered with higher efficacy and safety in animal models compared to the AEDs administered in human volunteers (2).

Development of anticonvulsant drugs in the 20th century has witnessed considerable progress. Major AEDs with clinical use (e.g., phenytoin, valproate, carbamazepine, benzodiazepines, ethosuximide, primidone, and phenobarbital) are among the 'old drugs', which were developed and introduced during 1910-1970. However, several newly-developed drugs have been introduced as anticonvulsants (e.g., vigabatrin, felbamate, gabapentin, lamotrigine, tiagabine, oxcarbazepine, and topiramate), which are currently used in preclinical trials as the new generation of AEDs.

***Corresponding author:** Farah Ashrafzadeh.*
Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad, Iran.
***E-mail:** ashrafzadehf@mums.ac.ir*
***Tel:**+985138012469*

Although 70% of the children with epilepsy could become seizure-free with new-generation AEDs, more than 25% of epileptic children remain intractable despite the use of 2-3 AEDs (3).

Historically, alternative therapies have captivated the attention of researchers, especially plant-based therapies. According to the World Health Organization (WHO), approximately 80% of the population in developing countries largely relies on plant-based medicines to meet their healthcare needs (4). Several studies have established a scientific basis to elucidate the effectiveness of medicinal herbs. In this regard, extensive research has been focused on neurological disorders, such as epilepsy, Parkinson's disease, anxiety, and depression (5,6).

The present study aimed to investigate the anticonvulsant effects of Iranian medicinal plants and their extracts on children with intractable epilepsy. Review of the literature for trials was performed via searching in databases such as IranMedex, Medline, Google Scholar, and Scopus to identify the studies investigating the Iranian medicinal plants with antiepileptic properties. Furthermore, the files of authors were reviewed in the reference lists and bibliographies of the retrieved articles without language or time limitations.

Literature Review

Nigella sativa

Black cumin seed (botanical name: Nigella sativa) is cultivated in the Mediterranean region, as well as several other locations in the world. This medicinal herb has significant antihypertensive, hypoglycemic, antihistaminic, and diuretic properties (7). In ancient Islamic communities, Nigella sativa was known as an anticonvulsant (8). In addition, the essential oil of Nigella sativa has been shown to have antiepileptic effects against pentylenetetrazole (PTZ)-kindling seizure models in mice. The mechanism of this effect seems to be associated with the antioxidant properties of the plant (9).

In a study, Akhondian et al. used the aqueous extract of black cumin seeds, which contained thymoquinone, in the form of a syrup (with 60% sucrose solution) and a placebo as an add-on therapy based on a double-blinded, placebo-controlled, randomized, cross-over protocol (6). The mentioned research was conducted on 20 patients who received the herbal extract or placebo (40 mg/k/q8h) for one month during two weeks. In the treatment course, the patients only received conventional AEDs. According to the self-report of the patients, the frequency of seizures decreased as a result of the treatment with the herbal extract, and the change in the mean seizure frequency was statistically significant. However, constipation and maculopapular rash were reported to be the side-effects in two patients (6).

The benefits of Nigella sativa and its derivatives are attributed to thymoquinone (9). According to the literature, thymoquinone has several therapeutic effects, and no evidence suggests any side-effects (9,10). The effects of thymoquinone on intractable pediatric seizures were reported in a double-blinded, cross-over, pilot study, which was performed on 22 patients (age range: 1-14 years) with intractable epilepsy. In the mentioned study, thymoquinone was administered at the dose of 0.5 mg/kg/q12h. Eventually, weekly seizure frequency reduced by 50% in 54.5% of the patients receiving thymoquinone compared to baseline. Furthermore, weekly seizure frequency decreased by 13.6% in the patients of the placebo group. The reported side-effects included nausea and somnolence, which could be caused by the alcohol content of the administered drugs (11).

Rosa Damascena

Cultivation of Rosa damascena began in the 15th century, and the production of rose essential oil was initiated in the Turkish province. Rose petals contain small amounts of oil crops (0.03%) (12). In Persia, this plant is called 'Gol-e-Mohammadi', and its essential oil contains citronella, geraniol, nerol, linalool, phenylethyl alcohol, and monoterpene alcohols.

Some of the main benefits of Rosa damascena have been reported to be anti-HIV effects, antioxidant properties, and antibacterial, hypnotic, antitussive, antidiabetic, and relaxant effects on tracheal chains (13). In a study in this regard, Rosa damascena extract was administered to rats with acetaminophen, and the findings indicated hepatoprotective effects. Therefore, it could be inferred that the antioxidant properties of Rosa damascena could prevent toxicity (14,15).

In another research, Rakhshandeh et al. investigated the effects of Rosa damascena essential oil on rats and reported that the herbal essential oil could significantly delay the seizures induced by amygdale kindling in the animals (16). Similarly, findings of another study showed that Rosa damascena essential oil could attenuate the latent initiation and severity of PTZ-induced seizures in rats (17).

Evaluation of the effects of the aqueous, ethanolic, and chloroformic extracts of Rosa damascena on PTZ-induced seizures in mice has shown that the ethanolic extract of Rosa damascena could increase the latency of seizure development in mice compared to normal saline (18).

According to the study by Ataei et al., Rosa damascena significantly decreased the frequency of epileptic attacks in children with intractable epilepsy (19). The mentioned study was placebo-controlled and double-blinded with a sample population of 16 patients aged 3-12 years. The subjects were administered with Rosa damascena oil (10% extract with MCT oil purchased from Nader Factory) and placebo (0.05 cc/kg/dose) at three separate doses, along with AEDs as an add-on therapy. The first drug/placebo was administered on days 1-10, while conventional AEDs were administered on days 11-20, and placebo/drug was administered on the last 10 days. According to the results, 56.3% of the patients experienced several seizure types (myoclonic, tonic, tonic-clonic, and partial), while 42.8% experienced only one seizure type. Therefore, it was concluded that Rosa damascena oil had significant effects on reducing the frequency of seizures although it did not affect the duration of the seizures. It is notable that no side-effects were reported in the studied patients (19).

Curcumin

Curcumin is the main biological component of turmeric, which is a spice commonly used in cooking. Recent molecular investigations have indicated that curcumin has anti-inflammatory, antimicrobial, anti-hepatotoxic, and anti-hyperlipidemic properties. Moreover, this compound has beneficial effects on thrombotic events and psoriasis (20).

Recent studies have suggested that curcumin plays a neuroprotective role as well, and

several theories have confirmed these effects. On the other hand, some studies have shown that curcumin could eliminate oxidative stress and cytokine release, which are often activated during seizures (20). Evidence suggests that curcumin plays a protective role in hippocampal neuronal loss, prevents mitochondrial malfunction, and relieves the hepatotoxic effects of AEDs. Curcumin could also inhibit amyloid-b formation and prevent the 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 studies have shown that curcumin increases the number of newly generated cells in the dentate gyrus region of the hippocampus, thereby amplifying the hippocampal neurogenesis process. Moreover, curcumin is a potent inhibitor of the expression of reactive astrocytes, preventing the hippocampal cell death caused by kainic acid (20,21).

The protective effects of curcumin have been elucidated in several studies on experimental models, in which electro shocks have been used to induce seizures in mice. Furthermore, curcumin has been reported to exert antidepressant effects on the animal models inflicted with depression. Another major benefit of curcumin is in the treatment of diabetic neuropathy. Curcumin has also been used in animal models during the treatment of tardive dyskinesia as the pretreatment method to reduce the side-effects of haloperidol (21).

In their study, Akhondian et al. evaluated children with myoclonic epilepsy to investigate the therapeutic effects of curcumin. In this double-blinded, placebo-controlled trial, 33 patients aged 3 months-14 years were examined, who received nano-curcumin capsules or placebo capsules for four weeks. After the treatment, the placebo agent was replaced with a drug. Study duration was 10 weeks, which consisted of a washout period as well. According to the obtained results, 24.2% of the children were seizure-free, and none of the subjects experienced side-effects (22).

Conclusion

Currently, most of the reviews regarding the treatments for epilepsy focus on the use of pharmacological agents. However, these agents have not only failed to control epileptic seizures in some children, but they also have caused numerous side-effects and harmful drug interactions. Another limitation of synthetic AEDs is the high treatment costs, especially in long-term therapies.

Traditional medicine is a common practice in developing countries, where up to 80% of the population relies on traditional medicine remedies to meet their primary healthcare needs. Traditional medicine could be a proper alternative for the treatment of epilepsy. Medicinal plants are abundant sources of new chemical substances with potential therapeutic effects. The present review aimed to highlight the studies focusing on various Iranian medicinal plants that could be beneficial in the treatment of epilepsy in children. According to the results, medical plants could exert multiple effects on epilepsy, which makes them a viable option for the effective treatment of epilepsy in the future.

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Conflict of Interest

The authors declare no conflict of interest.

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