



Review

Medicinal plants used in Iranian traditional medicine to treat epilepsy

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ABSTRACT

Antiepileptic drugs used to treat epilepsy can cause severe, life threatening side effects. In Iranian traditional medicine, herbal remedies have been used for centuries to treat seizures. In this study, the five most important herbals in Iranian traditional medicine, namely Canon, al-Hawi, al-Abniah 'an Haqaeq al Adwia, Tuhfat al-Mu'minin, and Makhzan ul-Adwia, were searched for the term "sar-e", which means epilepsy, to identify the herbs used for treatment in ancient times. We also searched scientific literature for pharmacological evidence of their effectiveness.

Twenty-five plants were identified as herbal remedies to treat epilepsy. Pharmacological data related to the antiepileptic activity of eleven of these plants exists. A large number of these plants which have not been investigated pharmacologically for antiepileptic activity would be good candidates for study in exploring new herbal anticonvulsant remedies.

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1. Introduction

The long term use of herbs introduced in traditional medicines confirms their value in drug discovery.^{1,2} Based on historical evidence, herbal therapies were used to treat convulsive seizures for centuries.³ Medicine has always played a significant role in Iranian culture and civilization. Thousands of years of history and hundreds of books have placed Iranian traditional medicine among the oldest and richest alternative medicines.^{4,5}

Epilepsy is an important issue in the field of traditional Persian neuroscience. Iranian scientists such as Avicenna (Ibn Sina) and Rhazes (Zakariya al-Razi) defined epilepsy, described its signs and symptoms, and gave different approaches to prevent and treat it.⁶

It cannot be claimed with one hundred percent certainty that what was described in Iranian traditional medicine as epilepsy (sar-e) matches the same illness in conventional medicine, because of the lack of diagnostic equipment in that time. However, some signs and symptoms in both sar-e and epilepsy such as unconsciousness and seizure indicate that there is a resemblance and make the assumption more reasonable.

In this study, we investigated remedies listed in the most famous Iranian traditional medicine books as treatments for sar-e, and we selected those which were used most and were effective in managing the condition.

2. Material and method

The five books mentioned above were among the most important Iranian herbals dating from between the 10th and 18th centuries. In all the reviewed references, the term denoting epilepsy is 'sar-e'; therefore, it was the main keyword searched in the texts.

First the Canon of Avicenna was searched, as it is the most celebrated book in medicine. Thereafter, the plant names were searched in other books to find their usage as anticonvulsant remedies. Then these herbal medicines were scored based on the frequency of their mention in order to recognize the most valuable herbal drugs used to treat epilepsy through hundreds of years.

The plants used to treat epilepsy in Iranian traditional medicine were identified by matching their names with scientific names using different comprehensive glossaries including comparative descriptions of old medicinal plants.^{7,8}

A substantial search of scientific databases such as "Google Scholar" and "Medline" for the plant names in combination with the terms 'epilepsy' and 'anticonvulsant' was performed to find the plants' possible anticonvulsive activities.

3. Literature sources

3.1. The Canon of Avicenna

The Canon, which means "The Law", was the most significant contribution made by the most famous Persian physician, Ibn Sina, known as Avicenna in the western world (980–1037 AD). It is the most influential textbook ever written. For six centuries, it

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dominated the medical schools of Asia and Europe. The Canon surpassed other similar books on medicine and is considered the biggest medical encyclopedia of its time.⁹

Avicenna was the first person in medical history to use the term 'epilepsy', which means "being possessed by an outside force" in Latin. Ibn al-Nafis, a great Arab physician and scientist of his time, systematically described the symptoms and recovery of "head sick", which is a synopsis of the Canon written 250 years earlier.^{10–12}

The Canon consists of five books. The first book is about general principles of medicine; the second book comprises the *materia medica*, which lists about 800 mineral, herbal, and animal-based medicinal materials; the third book is on therapy; the fourth book discusses those diseases that affect the body and are not restricted to a single part of the body, such as fevers; the final book presents recipes for compound drugs.^{13,14}

Avicenna assigned a chapter of the Canon to epilepsy under the title 'Head and Brain Disorders'. From his point of view, there are two types of epilepsy: one that occurs suddenly and is over quickly, and one that is intense and continuous and may lead to death. In his opinion, epilepsy is a type of seizure which affects the brain.

Avicenna described symptoms of epilepsy as being weakness, forgetfulness, depression, nightmare, yellow tongue, tongue paresthesia, anger, and distress. He described an epileptic attack as follows: "The patient feels agitated and becomes unconscious, turns red, and stares with eyes distorted; respiration is impaired and the patient becomes cyanotic". Muscle contractions, dizziness, salivation, and teeth gnashing are other symptoms and signs.⁶

Avicenna theorized that the blockage of humors, especially phlegm and black bile, was a possible mechanism of epileptic convulsions.¹⁵ In the Canon, he classifies epilepsy based on age (children, adults) and the organ in which the attack starts (liver, stomach, spleen, or uterus). He explains that some precipitating factors (environmental temperature, direct solar radiation, bathing or training with a full stomach, overwhelming anger, fear or sorrow, and dyspepsia) provoke epileptic attacks.

Avicenna explains the general recommendation (to avoid excessive heat or cold, excess sexual intercourse, swimming, and postprandial exercise) and states that therapy is based on the specific condition of the patient.

Plant-based antiepileptic therapy constitutes a great part of the treatments described in the Canon and other Iranian traditional medicine references.¹⁶

3.2. Al-Abnih 'an Haqaeq al Adwia

The oldest preserved Persian text on *materia medica* (10th century), al-Abnih 'an Haqaeq al Adwia (principles of the attributes of plants) written by Abu Mansur Movafiq ibn Ali al-Heravi, is an introductory treatise on medicine and pharmacy. The book deals with 584 mineral, herbal, and animal-based drugs. Each monograph includes the name of the drug and its synonyms in Greek, Indian, and local Persian dialects, its therapeutic effects, methods of countering the side effects, and the dosage of the drug.^{17,18}

3.3. Al-Hawi fi al-Tibb

Before Avicenna's Canon, the best written work on medicine was al-Hawi fi al-Tibb (The Comprehensive Book of Medicine). It was written by Abu Bakr Mohammad ibn Zakariya Razi, known as Rhazes (865–925 A.D.), a renowned Iranian physician, philosopher, and chemist who wrote about 250 books and treatises. Al-Hawi is Rhazes' most important and complete book in which he surveyed Greek, Syrian, and early Arabic medicine, as well as some Indian medical knowledge. Throughout his work, he added his own considered judgment and his own medical experience as commentary. It was repeatedly printed in Europe during the

15th and 16th centuries under the title "Liber Continens", and it had a major influence on the development of medical practices in Europe.^{19–21}

3.4. Tuhfat al-Mu'minin

This work is also known as Tuhfeh-ye Hakim Mu'min (1669 AD). It is a medical treatise written by Mir Muhammad Mu'min Husaini Tonekaboni, known as Hakim Mu'min, the physician and pharmacist to the court of the Safavid Shah Sulayman in Persia. It contains 5570 entries, of which 940 concern plants or products derived from plants.²²

3.5. Makhzan ul-Adwia

Makhzan ul-Adwia (Drug Treasure) is an outstanding work about traditional medicine and medical terminology in 1772 AD. It was written in Persian by Mohammad Hossein Aghili Alavi Khorasani, a famous and expert physician. The book has 14 chapters and covers poisons and antidotes, temperaments, food as medicine, expiration and strengths of medicines. In it, 1744 simple drugs of plant or animal origin used in traditional medicine are described in detail.²³

4. Results

The sources consulted in this work pointed out that 25 *materia medica* were used in Iranian traditional medicine to treat epilepsy. Table 1 shows their names, parts used, administration, and the references in which they are mentioned.

In the following section, the results of tests performed on 11 plants have been summarized; attention was focused on their anticonvulsant activity.

4.1. Paeonia officinalis L.

The root extract of *P. officinalis* (peony root) was identified as a potent in vitro inhibitor of neuron damage in the CA1 area of the hippocampus in rats. Data indicated that peony root extract has excellent protective effects on damaged neurons in addition to anticonvulsant action when administered orally.²⁴

4.2. Bryonia alba L.

Ethanol extract of the aerial parts of *B. alba* showed moderate affinity to the benzodiazepine-site of the GABA receptor. The GABA_A-benzodiazepine site is a primary target in the treatment of epilepsy that enhances the sensitivity of the GABA_A receptor for endogenous GABA. After binding GABA to the receptor, the cell is inhibited and an anticonvulsant activity is achieved. Conversely, administration of the aqueous extracts showed no affinity for the GABA-benzodiazepine receptors.²⁵

4.3. Ferula persica Willd.

The effects of ethanol extract of the aerial parts of *F. persica* on epilepsy have been evaluated in mice.²⁶ Results indicated that a dose of 300 mg/kg (i.p.) of ethanol extracts cannot prevent pentylenetetrazole (PTZ)-induced seizures; therefore, it does not possess anticonvulsant effects compared with the untreated animals at the used dose.

4.4. Lavandula stoechas L.

The effects of the aqueous-methanolic extract of *L. stoechas* flowers on epilepsy and spasm were evaluated in mice. Results

Table 1
Plants found in the Iranian ancient herbals, Al-Abnihah 'an Haqaeq al Adwia (Abn), Canon (Ca), al-Hawi (Haw), Makhzan ul-Adwia (Mak) and Tuhfat al-Mu'minin (Tuhf) to treat epilepsy.

	Traditional name	Scientific name	Family	Used part	Herbals
1	Aftimoon	<i>Cuscuta epithimum</i> Murray	Convolvulaceae	Steam	Ca, Haw, Mak
2	Azan-ol-far	<i>Parietaria cretica</i> L.	Urticaceae	Whole part	Ca, Mak, Tuhf
3	Bandogh Hendi	<i>Caesalpinia bonducella</i> (L.) Roxb.	Caesalpiniaceae	Fruit	Ca, Mak, Tuhf
4	Balasan	<i>Commiphora opobalsamum</i> Engl. <i>Balsamodendron myrrha</i> kaunth <i>Myroxylon balsamum</i> L. <i>Myroxylon pereirae</i> Klotzsch	Burseraceae Fabaceae	Seed, gum	Abn, Ca
5	Divdar	<i>Cedrus deodara</i> Loudon	Pinaceae	Steam	Ca, Mak, Tuhf
6	Eshghil	<i>Urginea maritima</i> Baker	Hyacinthaceae	Root	Abn, Ca, Mak, Tuhf
7	Fasherā	<i>Bryonia dioica</i> Jacq.	Cucurbitaceae	Fruit, leave	Abn, Ca, Haw, Mak, Tuhf
8	Fasherestin	<i>Bryonia alba</i> L.	Cucurbitaceae	Fruit, leave	Ca, Haw, Mak, Tuhf
9	Fāvania	<i>Paonia officinalis</i> L.	Paeoniaceae	Fruit, root	Abn, Ca, Haw, Mak, Tuhf
10	Gheradmānā	<i>Lagoecia cuminoides</i> L.	Apiaceae	Fruit	Ca, Haw, Tuhf
11	Handaghughi	<i>Trigonella caerulea</i> (L.) Ser. <i>Trigonella hamosa</i> L. <i>Melilotus</i> sp.	Fabaceae	Leave, seed	Ca, Mak, Tuhf
12	Heltit	<i>Ferula asa-foetida</i> L.	Apiaceae	Gum	Ca, Haw, Mak, Tuhf
13	Hoor	<i>Populus nigra</i> L.	Salicaceae	Fruit	Ca, Haw, Mak, Tuhf
14	Jāvshir	<i>Opopanax chironium</i>	Apiaceae	Gum	Abn, Ca, Mak, Tuhf
15	Jawz Roomi	<i>Populus alba</i> L.	Salicaceae	Fruit	Ca
16	Kozborah	<i>Coriandrum sativum</i> L.	Apiaceae	Aerial part	Abn, Ca, Haw
17	Marzanjoosh	<i>Origanum majorana</i> L.	Lamiaceae	Leave	Ca, Mak, Tuhf
18	Moord Esfarom	<i>Ruscus aculeatus</i> L.	Ruscaceae	Leave, fruit	Abn, Ca, Mak, Tuhf
19	Ostokhodoss	<i>Lavandula stoechas</i> L.	Lamiaceae	Whole part	Abn, Ca, Haw, Mak, Tuhf
20	Qennah	<i>Ferula gummosa</i> Boiss.	Apiaceae	Gum	Ca, Mak, Tuhf
21	Sakbinaj	<i>Ferula persica</i> Willd.	Apiaceae	Gum	Abn, Ca, Haw, Mak, Tuhf
22	Shābābak	<i>Inula conyza</i> DC.	Asteraceae	Whole part	Abn, Ca, Mak, Tuhf
23	Sisalius	<i>Seseli tortuosum</i> L.	Apiaceae	Whole part	Abn, Ca, Haw, Mak, Tuhf
24	Zārāvand modahraj	<i>Aristolochia rotunda</i> L.	Aristolochiaceae	Root	Abn, Ca, Haw, Mak, Tuhf
25	Zārāvand tavil	<i>Aristolochia longa</i> L.	Aristolochiaceae	Root	Abn, Ca, Haw, Mak, Tuhf

showed that treatment with 600 mg/kg of extract significantly delayed first seizure onset, reduced convulsion severity, and prolonged the onset of lethality induced by PTZ. A prolongation in the time of sodium pentobarbital-induced hypnosis was also observed. Possible explanations of these results might be the role plant extract plays as a calcium channel blocker.²⁷

4.5. *Ferula asafoetida* L.

Bagheri et al. showed that the oleo-gum-resin of *F. assafoetida* (300 mg/kg, i.p.) could not prevent PTZ-induced seizures in mice. The latency of hind limb tonic extension was obtained within 2–3 min, and the percentage of mice mortality was 100% in the PTZ test. In the mentioned study, it was proposed that *F. assafoetida* could not prevent PTZ-induced seizure.²⁶

4.6. *Coriandrum sativum* L.

The aqueous and ethanolic seed extracts of *C. sativum* were investigated for their possible anticonvulsant effects using PTZ and (maximal electro shock) MES tests. The results indicated that both extracts have an anticonvulsant effect, and the maximum non-fatal dose of aqueous and ethanolic extracts, both of which exert activity, were 0.5 g/kg and 5 g/kg. It seems that the anti-seizure profile might be related in part to the coumarin compounds isolated from *C. sativum*.²⁸

4.7. *Caesalpinia bonducella* (L.) Roxb.

The antiepileptic activity of *C. bonducella* was investigated using MES-, PTZ-, and picrotoxin-induced convulsion models. Petroleum ether extract was active in all tests, and at the dose of 600 mg/kg, it increased the threshold for convulsions and delayed the onset of tonic convulsions. It can be concluded that the extract showed its effectiveness through possibly blocking the chloride ion channel linked to GABA receptors.²⁹

4.8. *Ferula gummosa* Boiss.

The effects of the seed acetone extract of *F. gummosa* on epilepsy and sedation were evaluated. Test results revealed that *F. gummosa* protected mice against tonic convulsions induced by MES and PTZ. It produced a more potent protective effect against seizures induced by PTZ (ED₅₀ = 55 mg/kg) than MES-induced seizures (ED₅₀ = 198.3 mg/kg). Neurotoxicity (sedation and motor deficit) of the acetone extract assessed by the rotarod test were obtained dose-dependently with a TD₅₀ value of 375.8 against MES- and PTZ-induced seizures.³⁰

In another study Sayyah et al. investigated the anticonvulsant effect of fruit essential oil of *F. gummosa*. The study revealed that the fruit essential oil of *F. gummosa* blocked PTZ-induced (though not MES-induced) seizures in mice. The LD₅₀ (2.62 ml/kg) value of neurotoxicity, however, was too close to the anticonvulsant dose (2.5 ml/kg).³¹

4.9. *Cuscuta epithimum* Murray

The anticonvulsant activity of hydro-alcoholic extract of *C. epithimum* was investigated using the PTZ test. Results showed that at a dose of 100 mg/kg, *C. epithimum* significantly increased seizure latency and percentage of survival, but no significant difference between convulsion duration with plant extract and the negative control was observed.³²

4.10. *Cedrus deodara* Loudon

Dhayabaran et al. investigated the alcoholic extract of heart wood of *C. deodara* (ALCD) for its anxiolytic effect in three experimental models, including elevated plus maze test, light dark model, and locomotor activity by actophotometer and anticonvulsant activity using PTZ- and MES-induced convulsions. The results showed that pretreatment with ALCD at doses of 100 and 200 mg/kg (po) significantly delayed the onset and duration of seizures

induced by PTZ and MES and exhibited significant anxiolytic activity by modulating GABA levels in the brain in a dose-dependent manner.³³

4.11. *Origanum majorana* L.

Deshmane et al. investigated the antiepileptic and sedative properties of different extracts of aerial parts of *O. majorana* using PTZ and MES tests. All the extracts delayed the onset and reduced the duration of seizures in the PTZ test and decreased the duration of seizures in the MES test. Chloroform extract exhibited the maximum reduction in the seizure duration (48.5% inhibition at 250 mg/mL). Bioassay-guided fractionation led to the identification of triterpenoic acid fraction containing substantial amounts of ursolic acid as the active principle, which have been identified as a major compound responsible for plant activity (55.6% inhibition at 250 mg/mL). The test extracts also decreased latency and increased the duration of total sleeping time significantly.³⁴

5. Discussion

Epilepsy continues to be one of the most common neurologic conditions encountered in children and adults. Hippocrates recognized epilepsy as an organic process of the brain; however, many ancient writers considered seizures to be the work of supernatural forces.³

Natural substances derived from plant, animal and mineral origins have provided a continuing source of medicines since ancient times, and their use has been perpetuated for centuries in traditional medicine.³⁵

In this study we reviewed the five most important books in Iranian traditional medicine, explored antiepileptic treatments, identified the plant species, and discussed what is known about their potential effectiveness.

Although all possible effort was taken to assign the correct scientific names to plants, in some cases the description of the plant was inadequate or different genus and specious matches were made with one explanation in ancient texts, which made corresponding them with their correct scientific and English names very difficult.

As one of the most important textbooks in medieval times, the Canon was the first reference searched for the remedies used for epilepsy in those times. In the Canon, 48 natural remedies for treating epilepsy with animal, herbal and mineral origin were identified, among which were 25 plants from different families. In Table 1, the names of plants based on information such as traditional name, which parts are used, and their administration are listed in alphabetical order. As shown in Table 1, the plants *Aristolochia longa* L., *Bryonia dioica* Jacq., *Ferula persica* Willd., *lavandula stoechas* L., and *Paeonia officinalis* L. are introduced in all of the books as treatments. This demonstrates their significance through hundreds of years. Seven plants, *Caesalpinia bonduc* (L.) Roxb., *Cedrus deodara* Loudon., *Ferula gummosa* Boiss., *Origanum majorana* L., *Parietaria cretica* L., *Populus alba* L., and *Trigonella caerulea* (L.) Ser. were introduced by Avicenna, and only three of them were not recommended after Avicenna for epilepsy treatment (*Populus alba* L., *Coriandrum sativum* L., and *Commiphora opobalsamum* Engl.).

As mentioned previously, one of the methods used to classify epilepsy in the Canon is based on age. There are also differences between epilepsy diagnosis and treatment in children and in adults in modern medicine.^{36,37} Among the plants listed, *Caesalpinia bonduc* (L.) Roxb., *Opopanax chironium*, and *Paeonia officinalis* L. have been prescribed for epilepsy in children.

Most of the administration routes of the plants found in the herbals was oral, but *Cedrus deodara* Loudon and *Origanum*

majorana L. were administered through inhalation. As mentioned above, most of those plants studied for possible anticonvulsant activity exerted an efficient antiepileptic ability. They either interacted with GABA receptors or had anxiolytic and sedative properties, although other pharmacological mechanisms, i.e., neuroprotective activity, might be involved.

Other plants have still not been investigated for their pharmacological effect in epilepsy, and they would be good candidates for future antiepileptic evaluation.

Surprisingly, a large number of these plants were traditionally used during the European Renaissance as antiepileptic treatments.³⁸

Overall, some plants from the list of plant species used in Iranian traditional medicine to treat epilepsy have been pharmacologically investigated for their antiepileptic activity and have shown anticonvulsant properties. Other plant species from that same list, especially *Aristolochia longa* L., *Aristolochia rotunda* L., and *Seseli tortuosum* L. which are mentioned in all herbals, remain to be investigated for their value as sources of antiepileptic treatments.

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