REVIEW ARTICLE

THE HERBAL CURE FOR EPILEPSY: AN OVERVIEW

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ABSTRACT

Plants have been used to cure epileptic seizures, since ancient times. Approximately 70 percent people living in developing countries still rely on complementary and alternative medicines (CAM) regardless of the improvement in conventional medicine. People, particularly living in rural and tribal areas, have faith in Hakeem's. According to them, alternative treatments do not have toxic effects and are more easily accessible, cost effective and have been used traditionally. Standard drugs therapies have several adverse effects; people become resistant and require a combination of treatments which may double the risk of adverse effects. Herbal agents could be a better alternative to conventional medicine; hence to prove the effectiveness and safety of medicinal plants, evidences-based researches are required from different parts of world. In order to prove the efficacy of herbal agents, different animal models of seizures are used to evaluate efficacy of plants and among all of them Maximum electroshock (MES) induced seizure model (a model of tonic-colonic seizure), is used as gate keeper to assess the anti-seizure efficacy of newly tested plants.

KEYWORDS: Ant seizure efficacy, epilepsy, herbal cure, alternative medicines.

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INTRODUCTION

Epilepsy is a neurological disorder specified by unprovoked and a continuing tendency to produce seizures. As stated by International League Against Epilepsy (ILEA), "two or more unprovoked seizures" can be entitled as epilepsy[1, 2] whereas a seizure is a brief episode of intense or synchronous neuronal discharge in the brain[2]. World Health Organization (WHO) estimated that epilepsy accounts for 0.75 percent, of global burden of disease and prevalent in 50 million people globally[3].

Prevalence of epilepsy in Pakistan is expected to be 10 per 1000 population. It is most common in younger individuals under 30 years of age and has a greater influence on people residing in rural regions [4]. A large number of conventional antiepileptic drugs are available to treat epilepsy; it is unfortunate that presently available antiepileptic drugs do not fulfill the criteria of perfect antiepileptic's [5].

Herbal agents could provide us a better alternative to conventional medicines, however sufficient data based on preclinical and clinical evidence with the implementation is mandatory to prove their effectiveness as well as safety[6]. This article is aimed to highlight the efficacy of medicinal plants in MES seizures model, according to documented researchers worldwide. The plants/herbs having antiepileptic efficacy is summarized in **Table 1**.

DISCUSSION

Perception regarding epilepsy in Pakistan

Epilepsy has association with humans since their existence[7]. Epilepsy has been identified as sacred illness [8, 9]. Population based surveys were conducted in Pakistan, where most of the cases have inherited origin, people believe that it could be due to fever, emotional disturbance or person is overcome by supernatural forces[10, 11]. Even with the passage of time and improvement in literacy rates, still people have their own myths related to epilepsy specifically in rural areas, where majority of people believe that epileptic patients are overcome by supernatural forces (jinnat)[10, 12]

Etiologies and symptoms of epilepsy
Epilepsy is multi-factorial, can be idiopathic or caused by traumatic brain injuries, infections of the brain, cerebrovascular disease, neurodegenerative ailments, brain tumors, developmental disabilities, prenatal and postnatal insults, side effect of certain drugs etc.[13, 14]. The symptoms of epilepsy depend on the site of origin of irregular neuronal firing in the brain[15]. Furthermore, epilepsy may also impair cognitive functions and cause psychological problems like depression and anxiety[3].

Pathophysiology of epileptic seizures
GABA and Glutamate, both of these neurotransmitters have been widely studied in relation to epilepsy. As GABA is an inhibitory neurotransmitter, it plays an important role in generating seizures[16]. A reduction in GABA-ergic transmission decreases chloride conductance and is accountable for generating epileptic seizures. Whereas increased levels of glutamate which is an excitatory neurotransmitter, may open sodium and potassium ion channels which prolongs depolarization state[17].

Current scenario
It is estimated that about 10 percent of epileptic patients may not achieve complete seizure control. Unfortunately, antiepileptic drugs have numerous adverse effects which include cognitive dysfunction, drowsiness, megaloblastic anemia, hepatotoxicity, aplastic anemia and teratogenicity etc[15]. Due to these significant adverse effects and lack of seizure control by conventional drugs, patients consider alternative treatment[18].

Plants are not only therapeutically effective but they also provide a variety of vitamins, minerals and antioxidants.[19], However, the adverse effects of phytochemicals need to be verified[20]. Several guidelines for screening of herbal medicines are available to test their toxicity or safety[21]. In the year 2015, WHO has developed a frame work for standardization of herbal drugs followed by many countries[22].

Evaluation of anti-seizure efficacy in MES (Maximal electroshock induced seizure) model
MES which is an acute seizure model is used as gold standard in initial phases of testing. It is apparently the ideal and validated method to evaluate the efficacy in generalized (tonic-colonic) seizures in preclinical testing[23, 24]. Other models of seizures are chemo-convulsants which include pentylenetetrazole, penicillin, lithium, lithium-pilocarpin, biculline, picorotxin etc.[25]. However, no solitary model of seizure can exactly replicate the diversity of human epilepsy. Furthermore, these models could not help in tracking the mechanisms of anti-seizure activity[23].

Botanicals Used in Epilepsy
Since centuries plants have been used to treat seizures in alternative or traditional system of medicine in Iran, China, India and even in Pakistan etc.[26-29]. In Pakistan, majority of people believe in alternative treatments and visit a Hakeem, since they have proved to be cost-effective and are easily accessible for lifelong serious ailments such as epilepsy[29].

Annacyclus Pyrethrum
It is commonly known as Aqar-qarha, the used of Anacyclus pyrethrum is documented in unani tibb for the management of epilepsy. Anti-seizure efficacy of ethanolic extract of Anacyclus pyrethrum roots has been shown at doses (200mg, 400mg, 600mg/kg., i.p) in a dose dependent fashion in MES induced seizures model. MES induced model displayed that the duration of HTLE decreased in a dose dependent manner, as compared to standard drug treatment[30, 31].

Sub-chronic toxicity of anacyclus pyrethrum was evaluated in rats after administration of ethanolic extract at the dose 1000 mg/kg per oral for 90 days, did not exhibit any dose related toxicity and mortality[32].

Brassica Nigra
Brassica nigra, generally called as black mustard in English, is the member of Brassicaceae family; the seeds of brassica nigra have been used to cure epilepsy. The methanolic extract of brassica nigra showed dose dependent effect in MES induced seizure model, two doses (200mg and 400mg/kg per oral) were selected to evaluate the anti-seizure activity in rats. At dose of 400mg/kg per oral, showed HLTE duration similar to standard drug [33, 34]. Acute oral toxicity test was conducted in animals and dose of 2000mg/kg per oral was administered to several groups of rats. Results showed that acute toxicity did not lead to any death or harmful sign[34].

Croccus Sativus
Crocus sativus(dried stigma), generally known as saffron, belonging to the Iridaceae family[35]. The ethanolic and aqueous extract of crocus sativus was administered to different groups of mice, in different doses. The doses of ethanolic and aqueous extract that were administered intraperitoneally to mice, were 0.2g/kg, 0.8g/kg, 1.4g/kg, 2.0g/kg and 0.08g/kg, 0.32g/kg, 0.56g/kg, 0.80g/kg respectively. In MES induced seizure models, both extracts showed dose dependent effects but showed better efficacy in the aqueous extract. However, neither extract protected animals from MES induced seizures[36].

Sub acute toxicity of ethanolic extract was carried out in rats, different doses (0.35, 0.70 and 1.05 g /kg) of extract, administered intraperitoneally for two weeks. The extract showed dose dependant effect, it decreased the levels of HCT, Hb, and total WBCs and significant increase in AST, ALT, urea and creatinine. Histological exam revealed that ethanolic

extract damaged the tissues of liver and kidney[37].

Delphinium Denudatum

Delphinium denudatum, belonging to the family Ranunculaceae, widely famous as Jadwar, its roots are used by traditional therapist in sub-continent. The ethanolic extract and aqueous fraction was used to assess the efficacy of Delphinium, the doses of ethanolic extract and aqueous fractions were 200, 400, 600mg/kg and 400, 600 and 800mg/kg respectively. Aqueous fraction greatly reduced the duration of HLTE in dose dependent manner[38].

Acute oral toxicity of aqueous root extract of delphinium denudatum was determined in different group of rats, in a manner that dose increased gradually (graded dose), doses up to 14,000mg/kg caused abnormal physical behavior for 6 hours along with CNS depression[39].

Myristica Fragrans

Myristica fragrans belongs to the family Myristicacea, used as herbal medicine. It is commonly known as "nutmeg" and also well known as jaiphal. The seeds of myristica fragrans in n-hexane fraction of acetone insoluble part of ether extract [10, 30] and 100mg/kg, exhibit anticonvulsant potential. Interestingly it showed anticonvulsant effect at low dose i-e 10mg/kg[40].

In a study, the ethanolic extract of myristica fragrans was given to rats by mouth, at doses of 100, 200, 400 and 500mg/kg, for the periods of 14 and 28 days in order to study hematological and biochemical parameters. Therefore myristica fragrans was considered to be safe with no significant adverse effects[41].

Terminalia Chebula

Terminalia chebula, which is commonly known as Halela, widely used in traditional system of medicine for epilepsy. For acute toxicity testing single oral dose (5000mg/kg) of terminalia was given and for chronic toxicity doses of 300, 600 and 1200 mg/kg were administered by mouth for 270 days. Result revealed that there were no mortality or evidence of behavioral alterations and histopathological changes in different animals' organs[42]. However anti seizure activity of ethanolic extract of terminalia fruits was revealed by another study conducted in MES model at doses 200 and 500 mg/kg given orally; was shown to protect animals against seizures in a dose dependent manner[43].

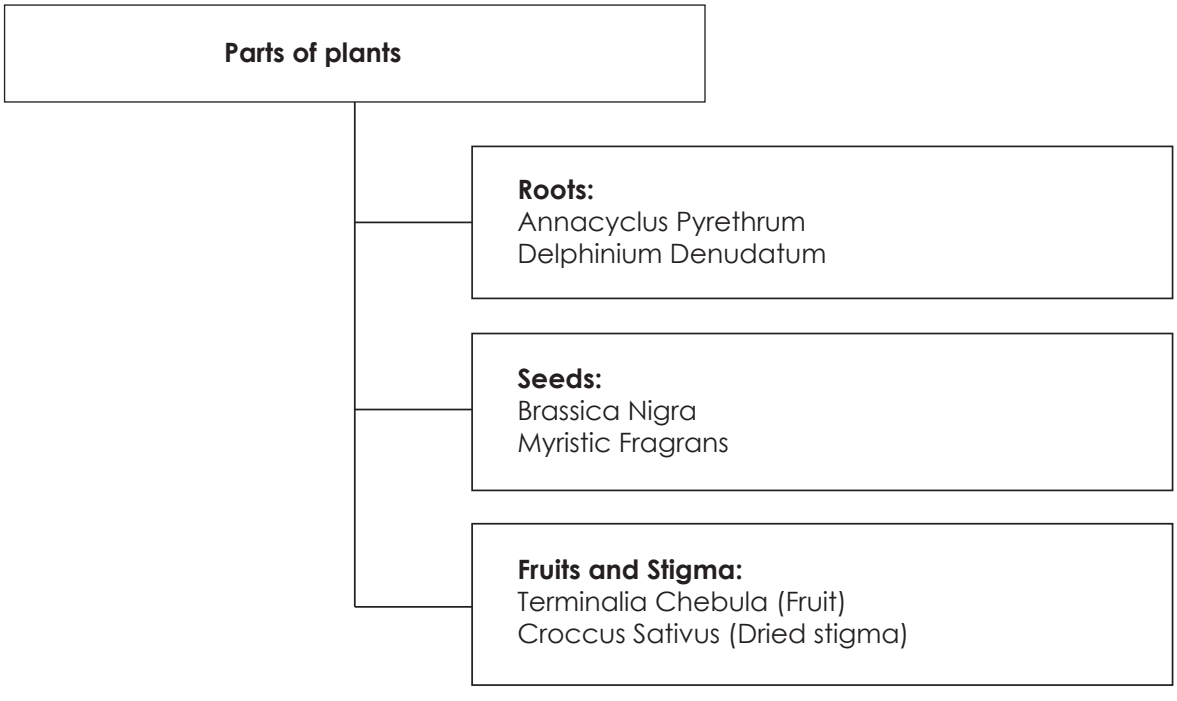

Figure 1: Parts of plants used to cure epilepsy

Table 1 : Commonly used Plants in Epilepsy

Plant (family)	Doses and routes of administration	Duration of HLTE (Sec) in MES at different does	Mortality percentage (%) at different doses	Toxicity test
Annacycleus Pyrethrum (Asteracase)	Ethanolic extract at doses 200, 400, 600 mg/kg., i.p	200mg/kg: 12.96+0.69 400mg/kg: 10.52+0.19 600mg/kg: 8.42+0.5	200mg/kg:0 400mg/kg:40 600mg/kg:0	Chronic toxicity test was proved to be safe at dose 1000mg/kg for 90 days.
Brassica Nigra (Brassicaceae)	Methanolic extract at does 200,400mg/kg., p.o	200mg/kg:5.8±0.86 400mg/kg: 0±0	200mg/kg:40 400mg/kg:0	Acute toxicity test did not show any sign of toxicity ie at 2000mg/kg.
Croccus Sativus (Iridaccac)	Ethanolic extract at doses 0.2g/kg, 0.8g/kg, 1.4g/kg, 2.0g/kg i.p, and Aqueous extract at doses 0.08g/kg, 0.32g/kg, 0.56g/kg, 0.80g/kg., i.p.	In ethnolic extract: 0.2g/kg: 22.8±0.5 0.8g/kg: 19.0±0.3 1.4g/kg: 17.5±1.1 2.0g/kg: 14.4±0.5 In aqueous extract: 0.08g/kg: 17.1±0.7 0.32g/kg: 17.0±1.4 0.56g/kg: 12.3±0.3 0.80g/kg: 10.5±0.5	In ethnolic extract: 0.2g/kg:0 0.8g/kg:0 1.4g/kg:0 2.0g/kg:0 In aqueous extract: 0.08g/kg:0 0.32g/kg:0 0.80g/kg:0	Sub acute toxicity was conducted at doses 0.35, 0.70 and 1.05g/kg, showed dose dependent toxicity.
Delphinium Denudatum (Ranunculaccae)	Ethanolic extract at doses: 200, 400 and 600mg/kg Aqueous fraction at: 400, 600 and 800mg/kg., SC	In ethanolic extract: 200mg/kg: 0±0 400mg//kg: 11.7±1.8 600mg/kg: 9.6±1.9 in aqueous extract: 400mg/kg: 8.3±0.9 600mg/kg: 6.4±0.7 800mg/kg: 5.1±0.6	Percentage protection was not mentioned.	In acute toxicity test at dose 14, 000mg/kg, abnormal behavior and CNS depression was seen
Myristica fragrans	Hexane fraction of acetone	10mg/kg:2.5±1.2 30mg/kg: 9.0±0.4	Percentage protection	In sub-acute toxicity test at
(Myristicaceae)	insoluble part of ether extract at doses: 10,30 and 100mg/kg., i.p.	100mg/kg: 8.0±1.0	was not mentioned.	doses 100, 200, 400 and 500mg/kg, did not show any toxic effects.
Terminalia chebula (Combretaccae)	Ethanolic extract at doses 200 and 500mg/kg., p.o	200mg/kg: 12.50±0.56 500mg/kg: 9.33±0.21	200mg/kg: 17 500mg/kg: 50	In chronic toxicity test, at doses 300, 600 and 120mg/kg, did not exhibit any toxicity.

HLTE=Hind limb tonic extension, MES= Maximal electroshock seizures, p.o = Per Oral, SC=Subcutaneous, i.p=Intraperitoneal

CONCLUSION

Since epilepsy is a chronic disorder; furthermore, the complex mechanism of epilepsy has made it difficult to treat with conventional medicines that have multiple adverse effects. The use of medicinal plants is as old as human existence. The herbs/plants discussed in this article are recommended by some of the Pakistani Hakeem's (as alternative medicine) in epileptic seizures either in combination or alone. However, their knowledge regarding the appropriate doses, dosage form, frequency and toxicity of the herb is insufficient. Therefore it is essential to confirm their efficacy and toxicity by research based evidences, as plants derived agents can be cost effective and safer alternatives. Funds should be provided to educational institutes to carry out animal based research which could open the doors for future clinical trials and validate the safer use of herbal derivatives in the cure of epilepsy.

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