ejpmr, 2020,7(4), 147-152

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON ANTIEPILEPTIC ACTIVITY OF CENTELLA ASIATICA

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Article Received on 06/02/2020 **Article Revised on 26/02/2020** **Article Accepted on 16/03/2020**

ABSTRACT

This present review on antiepileptic activity on centella asiatica focused on various experiments to demonstrate its antiepileptic activity compared to other antiepileptic drugs. Centella asiatica, commonly known as “gotu kola, Asiatic pennywort, Indian pennywort, wild violet, and tiger herb” a tropical plant, cultivated successfully due to its medical importance in some countries including turkey, and it has a utilization in ayurvedic and Chinese traditional medicines since centuries. From the various experiments, It is found that aqueous extract of centella asiatica contain constituents like triterpeniods, vitamins, aminoacids, Asiatic, asiaticoside, centellic, centoic and pectic acids which is responsible for antiepileptic activity. Centella asiatica also used different diseases like asthma, skin disorders, kidney troubles and elephantiasis etc. Since centella asiatica is important in epilepsy because of its longer duration of action and less adverse effect that compared to other antiepileptic drugs.

KEYWORDS: Antiepileptic drugs, Centella asiatica, Maximal Electro Shock, Pentylenetetrazole, Tonic hind limb extension.

INTRODUCTION

Many herbal medicines have been employed in various medical systems for the treatment and management of different diseases.[1] The medicinal properties of the plant is due to the presence of secondary metabolites like alkaloids, cardiac glycoside, tannins, vitamins, aminoacids, Asiatic, asiaticoside, centellic, centoic and pectic acids.[2]

India has a rich culture of medicinal herbs and spices, which includes more than 2000 species and has a vast geographical area with high potential abilities for Ayurvedic, Unani, Siddha traditional medicines but only very few have been studied chemically and pharmacologically with their potential medicinal value.[3]

Herbal medicine is based on the premise that plants contain natural substances that promote health and alleviate illness. There are many herbs, which are predominantly used to treat cardiovascular problems, liver disorders, central nervous system, digestive and metabolic disorders. Plants also have the capability to safeguard the body from oxidative damage by scavenging the free radicals and inhibiting peroxidation and radical mediated process.[4]

Centella asiatica is a perennial, creeper, faintly aromatic and a valuable medicinal herb. it is widely distributed throughout tropical and subtropical regions. The use of centella in food and Beverages has Increased over the years basically due to beneficial functional properties. Centella asiatica belonging to Apiaceae family native to South East Asian countries such as India, Srilanaka, China, Indonesia and Malayesia as well as South Africa and Madagascar. Centella asiatica had been used as a medicinal herb for thousands of years in India, china, Srilanka, Nepal. Centella asiatica is one of the precious herbs for revatalizing the nerves and brain cells, hence primarily it is known as a "Brain food".[5] In India, Centella asiatica is valued as an ethnomedicine as well as in Ayurveda and Unani, the traditional Indian medicinal systems for thousands of years for different ailments like asthma, skin disorders, ulcers and body aches, in treatment of dropsy, elephantiasis, gastric catarrh, kidney troubles, leprosy, leucorhea, in maternal health care, in treatment of stomach disorders and also as a vegetable.[6]

PLANT PROFILE

Centella asiatica, commonly known as “gotu kola, Asiatic pennywort, Indian pennywort, wild violet, and tiger herb” in English, is a tropical plant, cultivated successfully due to its medical importance in some countries including turkey, and it has a utilization in ayurvedic and Chinese traditional medicines since centuries.

CLASSIFICATION
Kingdom: Plantae
Subkindom: Tracheobionta
Division: Magnoliphyta
Class: Magnoliopsida
Subclass: Rosidae
Order: Apiales
Family: Apiaceae
Genus: Centella
Species: asiatica.[7]

Description: It is a slender trailing herb, rooting at the nodes. It has long, reddish, prostate stem emerging from the leaf axils of a vertical root stock. Leaves are orbicular, reniform, entire, crenate, glaborous, 1.3-7 cm in diameter. Flowers are sessile, white or reddish, covered by bracts and 3-6 flowers are arranged in an umbel. Fruits are small, compressed, 8mm long, mericarps are curved, rounded at the top, broad and 7-9 ridged. Seeds are compressed laterally. This has a characteristic of greyish green colour and bittersweet taste.[8] Fruits are borne in the growing season in approx 2 inches long, oblong, globular in shape and strongly thickened pericarp. Centella asiatica is found through out tropical and subtropical regions of India up to an altitude of 600m. The plant is indigenous to South East Asia, India, china, Madagascar.[9]

Pharmacognostic studies

- **Organoleptic properties**

Colour : Greyish green;
Odour : characteristic;
Taste : Acrid, bitter, sweet
Nature: Cool natured.

Macroscopic characteristics
Centella asiatica (L.) is a prostate, faintlyaromatic, stoloniferous, perennial, attains up to an altitude of 1800 m. It flourishes extensively in shady, marshy, damp and wet places such as paddy fields, river banks forming a dense green carpet.
• Seeds are solitary in each mericarp, pendulous embryo, laterally compressed.
• Stem is glabrous, striated emerging from the leaf-axils of a vertical rootstock, filiform, with long internodes and rooting at nodes.
• Leaves are cordate or hastate, 1-3 from each node of stems, long petioled, 2-6 cm long and 1.5-5 cm wide, orbicular-reniform, sheathing leaf base, crenate margins, leaf blades are dendate, crenate with thick radiate veins.
• Flowers are small, sessile and dark pink in colour, arise as simple umbels of 3-6 flowers at the ends of slender peduncles arising from axils of leaves and much shorter than petioles. Each flower bears five stamens and two styles.
• Fruits are clusted at joints, Carpels oblong, sub-cylindric curved and less in length much laterally compressed, readily separating into 2 indehiscent halves(mericarps) United by a very narrow plane of junction.

Microscopic characteristics
Greyish green with stomata on both surfaces of the leaf, 30 by 28 micrometer, mostly rubiaceous type. Palisade cells differentiated into 2 layers of cells, 45 by 25 micrometer. Spongy parenchyma of about 3 layers of cells with many intercellular spaces, some with rosette crystals of calcium oxalate. Hairs are absent; Midrib region shows 2 or 3 layers of parenchymatous cells without chloroplastids; Petiole shows epidermis with thickened inner walls; collenchyma of 2 or 3 layers of cells; a broad zone of parenchyma; 7 vascular bundles within parenchymatous zone, 2 in projecting arms and 5 forming the central strand; vessels 15-23micrometer in diameter. Some parenchymatous cells contain crystals of calcium oxalate.[10]

EPILEPSY
Epilepsy, a common chronic Nervous system disorder with Repeated Seizures affects 1-3% population world wide.[11] Cellular and Molecular Mechanisms responsible for various epileptiform phenomena such as a) Imbalance between excitatory and inhibitory neurotransmission, b) Alterations in neurotransmitter expression and function, c) Channelopathies, and d) Aberrant neuronal synchronization.purine nucleotides in addition to serving as precursors of Nucleic acids, play an Critical role in diverse physiological function such as energy metabolism, protein synthesis, Regulation of enzyme activity, and signal transduction.[12] ATPase play an Important role in the maintenance of ionic gradient by Coupling ATP hydrolysis with energy processes.[13] Na+-k+ ATPase is a membrane bound enzyme and inactivation of this enzyme is a important factor in epileptization of Neurons.[14] Several studies have reported significant inhibition of ATPase activity in the brain during different types of epileptic seizures.[15] Studies have also Shown alterations in the activities of ATPase in different model of Epilepsy and modulation of ATP hydrolysis by Antiepileptic drug treatment.[16]

- **Causes of Epilepsy**

Epilepsy can be caused by chemical abnormalities, brain injury or brain tumour, alocohol or drug effects, or the existence of inherited condition. In most of the cases cause is unclear. Epilepsy occurs in higher frequency in those people with developmental disabilities and is often more severe and more difficult to control than in the other people. Infections, menstruation, alcohol, stress or lack of sleep may trigger a seizure in people with a tendency to have seizure.

- **Types of Epilepsy**

Seizure may be partial when the abnormal electrical activity occurs in one specific area of brain, or generalized, where the whole brain becomes involved. Partial seizure may be simple, complex. Some seizures may start as partial then become generalized. There are several types of generalized seizures Absence, atonic, tonic, myoclonic and tonic-clonic. Accurate diagnosis of the type of seizure is important in determining which

medication is most likely to be effective, and for prognosis and lifestyle advice.

- **Treatment of epilepsy**

About two thirds of people with epilepsy will be controlled with anti-epileptic drug(AEDs) and some will go into remission and be able to come off medication. Most people with epilepsy will need some degree of specialist overview of their management, but the general practitioner is well placed to play a major role in coordinating both diagnosis and treatment.

- **Diagnosis of Epilepsy**

Diagnosis is based on an accurate description by those who have observed what happens, the circumstances, and frequency. It is confirmed by electroencephalogram(EEG) but absence of characteristics abnormalities does not exclude a diagnosis of an epilepsy if the eclinical evidence is strong. Some people with developmental disabilities will be resistant to having an EEG and may need desensitization or sedation. EEG under GA is rarely useful due to effects of the anaesthetic medication on brain activity. EEG combined with video monitoring and neuroimaging (MRI, CT scan) can provide additional informational where the diagnosis is unclear.[17] In recent years considerable progress has been made in identifying active factors from indigenous medicinal plants that can be used to prevent different human ailments. Centella asiatica is a great multipurpose miracle herb which is used in oriental medicine; it has also been used in ayurvedic preparations for the treatment of mental fatigue and anxiety. Mohandas Rao demonstrated that the constituents of centella asiatica fresh leaf extract markedly stimulate neuronal dendritic growth in hippocampal CA3 neurons. Centella asiatica extracts also been used to improve general mental ability in children with learning difficulties and in people with cognitive disorders.[18]

DISCUSSION

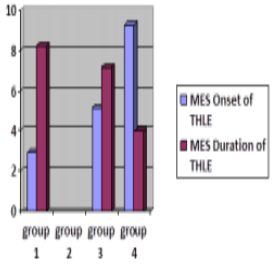
Herbal medicines generally have broad spectrum because they are an assortment of bioactive compounds. Most of the extracts tested were chosen based on the knowledge that they are traditionally used against other ailments or as antiepileptics by traditional herbalists. Although herbs have been used for years and tested in animal trials, there is a lack of standardization and safety and efficacy studies. For a substance to be an effective anticonvulsant, it must cross the blood-brain barrier. Selecting the appropriate model is a key factor in AED screening in the case of false positive or false-negative results as different models could simulate dissimilar kinds of epilepsy. The processes underlying epileptogenesis differ among models. Maximal electroshock (MES) and subcutaneous pentylenetetrazol (PTZ) are the two most widely used models in screening compounds for antiepileptic activity. Other less commonly used models exist, each modelling a particular form of epilepsy. Positive results in either model suggest that the test compound, or its metabolite crossed the blood–brain barrier and exerted its effect in the central nervous system. In this review, all experiments consisted initially of phenotypic screens in rodents using predominantly PTZ, MES and pilocarpine seizure models. A few researchers dared to test their extracts in more than one phenotypic screening models There is considerable concern among AED researchers that the limited models being used only identify me-too drugs that act by the same old physiological mechanisms, thus limiting chances of discovering novel therapies with different targets especially compounds with efficacy against drug resistant seizures. Novel potential targets for the treatment of epilepsy have been described. Time is more ripe now than never before for the diversification and adoption of more screening animal models. Besides, testing a substance in different models gives a more holistic idea of the substance's efficacy as each model models a different form of epilepsy and thus a different mechanism of action of the test extract. It is evident that herbal extracts have potential to be a rich source for safer and more effective, low-cost and culturally acceptable antiepileptic agents especially in resource poor regions. In most experiments, the tested extracts prolonged the time to onset of seizures and decreased their duration.[19] Seizure is a characteristic feature in epilepsy and rhythmic high frequency discharge of impulses by a group of neurons in the brain.[28] In the present study aqueous extract of leaves of Centella asiatica was evaluated for the anticonvulsant activity against seizure induced by maximal electro shock and Pentylenetetrazole. The MES test predicts activity against generalized tonic-clonic seizures and the PTZ test predicts against absence seizure. MES induced seizures are abolished by the drugs that blocks voltage gated sodium channels like Phenytoin and Carbamazepine and by the drugs that block NMDA receptors like Felbamate. Whereas the drugs that block T type Ca2+ current in thalamus like Sodium valproate, Ethosuximide prevents PTZ induced convulsions and the drugs like Diazepam, Clonazepam, which increases the duration of opening of GABA-Chloride channels prevents MES and PTZ induced convulsions. ALECA increased the time of onset of MES induced seizures and also decreased the duration of THLE, so it increases the threshold of MES induced seizures. ALECA showed 67% of protection at the dose of 400mg/kg. The abolition of MES induced THLE by the aqueous extract of leaves of C asiatica may be due to voltage gated sodium channel blockade or NMDA antagonistic activity. PTZ diminishes brain GABA (Gama Amino Butyricacid) level at sub-convulsive dose of 50mg/kg. The aqueous extract of leaves of C asiatica increased the threshold of PTZ-induced convulsion in rats. It showed 33% of protection at 200mg/kg and 67% protection at 400mg/kg. Many plants having anticonvulsant activity are known to inhibit GABA transaminase activity thereby increasing the GABA level in the brain. The anticonvulsant activity of Centella asiatica in PTZ induced convulsion may be due to increase in the the GABA level by inhibiting GABA

transaminase or increases the frequency of opening of GABA-Chloride channel. MES induced seizure and PTZ induced seizures are also associated with oxidative stress to the brain. Centella asiatica is proved to have antioxidant property which may also contributes to its anticonvulsant activity against MES and PTZ induced convulsions. Long term administration of Centella asiatica prevents scopolamine induced cognitive impairment and associated oxidative stress. Schulz et al., found out that there is increase in free radicals and decreased glutathione level during the process of combating oxidative stress. YK Gupta et al., found out that aqueous extract of whole plant of Centella asiatica induces malondialdehyde levels which is the marker of lipid peroxidation and increases the glutathione level which may also be the reason for antiepileptic activity. Praveen et al., found out that aqueous extract of whole plant of C. asiatica at the dose of 100mg/kg suppressed THLE in 3 out of 6 mice and all the 6 animals at the dose of 300mg/kg in MES seizures. The convulsion induced by PTZ 80mg/kg was suppressed at the dose of 300mg/kg butnotat100mg/kg. S. Sudha et al., used crude drug and methanolic extract of whole plant of C. asiatica. They concluded that both at the dose of 1000mg/kg showed 50% reduction in THLE. In PTZ (70mg/kg) induced convulsion both does not afford any protection, 100% mortality was seen in rats and mice. De Lucia et al., usd the leaves of C asiatica & showed the crude extract has moderate activity. In our study Centella asiatica suppressed the PTZ induced seizures even in low dose (200mg/kg) compared to MES induced seizures which was suppressed only in high dose (400mg/kg) which may be reasoned by the use of sub-convulsive dose of PTZ. In the study of Evaluation of Antiepileptic Activity of Aqueous Leaf Extract of Centella asiatica in Wister Albino Rats they performed the experiments using aqueous leaf extract of centella asiatica to prove the antiepileptic activity of the same. In this study MES seizures are induced with the intensity of 150mA, 50Hz for 0.2 sec duration through ear electrodes. the results of the study is shown in the following Table.1.

Table 1; Maximal Electro Shock (MES) induced convulsion;

Sl.no	Group	Drug	Onset of THLE(sec)	Duration of THLE(sec)	Number of animals convulsed	Percentage(%) of protection
1	Group 1	Normal saline 0.5 ml	2.9 ± 0.18	8.25 ± 0.7	6/6	0%
2	Group II	Phenytoin 25 mg/kg b.w.	0***	0 ***	0/6	100%
3	Group III	ALECA 200mg/Kg b.w.	5.17 ± 0.2***	7.14 ± 0.53	6/6	0%
4	4 Group IV	ALECA 400mg/Kg b.w.	9.26 1.96***	3.98 ± 0.31***	2/6	67%

Graph 1;Maximal Electro Shock Induced Convulsion

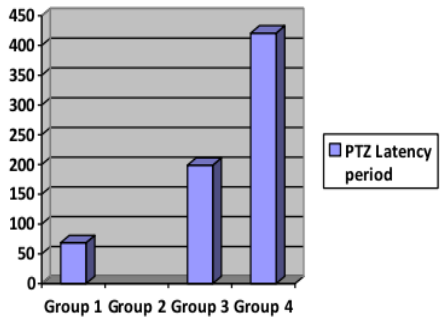


The similar study was carried out in pentylenetetrazole (PTZ) induced seizures.The results are shown in the following Table. 2

Table 2:Pentylenetetrazole induced convulsion :

Sl.no	Group	Drugs	Latency period(sec)	Number of animals convulsed	Percentage(%) of protection
1	Group1	Normal saline	68.7±3.4	6/6	0%
2	Group 2	Diazepam(4mg/kg)	0***	0/6	100%
3	Group 3	ALECA(200mg/kg)	199.08±3.1**	4/6	33%
4	Group 4	ALECA(400mg/kg)	420.96±1.06***	2/6	67%

Graph 2:Pentylenetetrazole induced convulsion



Comparing the activity of Aqueous extract of centella asiatica in MES induced seizuers and Pentylenetetrazole induced seizures, In MES induced seizures aqueous extract of Centella asiatica increased the time onset and decreased the duration of Tonic Hind Limb Extension. ALECA also increases the latency period of PTZ induced seizures. So the aqueous extract showed the anticonvulsant effect in both the MES & PTZ Induced

seizures. The anticonvulsant action of aqueous extract of C.asiatica was screened by PTZ method. The anticonvulsant action was compared with sodium valproate, which is considered as the standard drug for PTZ-induced seizures model. PTZ model is useful in screening of drugs effective in absence seizures. In this study, the aqueous extract of C. asiatica at both doses (100 mg/kg and 300 mg/kg) has exhibited anticonvulsant action in the PTZ induced seizure model. The anticonvulsant action of aqueous extract of C. asiatica at a dose of 300 mg/kg is comparable to sodium valproate. Hence, the aqueous extract of C. asiatica may play a role in the treatment of absence seizures. Many studies have reported the anticonvulsant action of C. asiatica in other models of epilepsy. In a study by Gupta et al. the cognitive impairment and the oxidative stress induced by PTZ kindling was attenuated by C. asiatica. Katare and Ganachari reported that C. asiatica has antilipid peroxidative and antiepileptic actions in the lithium–pilocarpine model of status epilepticus.[20] Visweswari et al. found that one of the facets of anticonvulsant action of C. asiatica was by causing perceptible changes in the cholinergic system. In another study by Visweswari et al., there was a decrease in Na+, K +-ATPase, Mg2+-ATPase, and Ca2+-ATPase activities in brain during PTZ-induced epilepsy. The levels of these ATPases were increased in brain by pretreatment with C. asiatica extracts except with aqueous extract. PTZ induces seizures by antagonizing the inhibitory gamma-amino butyric acid (GABA)ergic neurotransmission. Terpinoids, particularly triterpinoids and flavonoids, present in various plant extracts are reported to show anticonvulsant action in various epilepsy models such as PTZ model.[21] The phytochemical screening of aqueous extract of C. asiatica has revealed that it contains triterpines and flavonoids. Hence, the anticonvulsant action of aqueous extract of C. asiatica is probably owing to the triterpines and flavonoids present in it.

- Group 1- control animals
- Group 2-animals which are protected by sodium valproate
- Group 3-animals which receive 100mg/kg of aqueous extract of Centella asiatica
- Group 4-animals which receive 300mg/kg of aqueous extract of Centella asiatica

Table 3:Comparison of mean duration (in seconds) of different parameters in PTZ method

NS- not significant

Parameters(duration of action)	Group 1	Group 2	Group 3	Group 4
Latency of seizure	330±10.8	0	410±8.73***	0
Tonic hind limb flexion	1.5±0.23	0	1.5±0.23^{NS}	0
Tonic hind limb extension	10.66±0.61	0	10.66±0.43^{NS}	0
Clonic seizure	5.5±0.44	0	3.5±0.44**	0
Postictal depression	340.16±3.78	0	189.16±1.15***	0

Table 4:Percentage protection from clonic seizures in PTZ method

Group	% protection
Group 1	0
Group 2	100
Group 3	0
Group 4	100

All animals in the control group (group I) developed seizures. All animals in standard group (group II) were protected by sodium valproate and did not develop seizures. Group III animals, which received 100 mg/kg of aqueous extract of C. asiatica, exhibited significant delay in the onset of seizures (p o 0.001) and suppression of clonic seizure (p o 0.01) when compared with control, and it was statistically significant [Table 1]. The aqueous extract of C. asiatica at a dose of 300 mg/kg (group IV) has exhibited complete suppression of seizures, and its anticonvulsant activity is comparable to sodium valproate [Table 3]. Sodium valproate (group II) and aqueous extract of C. asiatica at a dose of 300 mg/kg (group IV) afford 100% protection from PTZ-induced seizures [Table 4]. Aqueous extract of C. asiatica at a dose 100 mg/kg (group III) has significantly increased the latency of seizure when compared with control group [Table 3].

The Another study described Above concludes that the aqueous extract of Centella asiatica exhibits anticonvulsant action comparable to sodium valproate in PTZ-induced seizures.[22]

CONCLUSION

In conclusion, from the overall studies of antiepileptic activity of Centella asiatica inferred that the extracts of Centella asiatica showed the antiepileptic activity. They are strongly recommended in the herbal treatment of neurological disorder. They afford maximum neuro protective mechanisms comparable to the standard drugs like sodium valproate in PTZ- induced seizures. The medicinal properties of the plant is due to the presence of secondary metabolites like flavonoids, saponins, tannins and other polyphenolic compounds.

A wide spectrum of the treatment of modalities is available for epilepsy. The present review reveals the effect of Centella asiatica in the treatment of epilepsy.

ACKNOWLEDGEMENT

The authors duly acknowledge the support and cooperation of the management of Jamia Salafiya Pharmacy College in permitting us to conduct our work.

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