ANTI EPILEPTIC ACTIVITY OF POLYHERBAL EXTRACTS OF *MENTHA PIPERITA* AND *OCIMUM SANCTUM* AGAINST PTZ INDUCED EPILEPSY IN MICE MODEL

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ABSTRACT :

The present study was designed to investigate the anti-epileptic activity of ethanolic extract of Mentha piperita and Ocimum sanctum against the pentylenetetrazole (PTZ) induced epilepsy in Swiss albino mice. The ethanolic extracts of Mentha piperita and Ocimum sanctum were screened for its antiepileptic activity against Pentylenetetrazole (PTZ) induced epilepsy. The extracts were given orally at the doses of 200 mg/kg and 400mg/kg for the induction of seizures. Behavioral paradigms evaluated the protection action against PTZ induced seizures. In Pentyletetrazole induced epilepsy model, the treatment with ethanolic extracts of Mentha piperita and Ocimum sanctum at 200mg/kg and 400mg/kg showed a significant increase in onset of action and decrease in death latency. No of convulsions, No. of Straub's tail, duration of convulsions, jerking, Tonic, Clonic and duration of stupor in mice model. In conclusion present study shows potent antiepileptic activity role of ethanolic extract of Mentha piperita and Ocimum sanctum on Swiss albino mice with significant changes in behavioral paradigm. Further studies are required for elucidation of the potent action of MP and OS on treatment of epilepsy.

Key words: Mentha piperita and Ocimum sanctum Pentylenetetrazole, Antiepilepsy

I. INTRODUCTION

Need for the study: Antiepileptic activity

Epilepsy is a heterogenous symptom complex, a chronic disorder characterized by recurrent seizures affecting approximately 1% of the world's population and second most common neurological disorder after stroke. Seizure is defined as abnormal, disordered discharges of brain nerve cells resulting in a temporary disturbances of sensory, motor/mental function.[1]

There is compelling evidence of an imbalance between excitatory and inhibitory neurotransmitters in epilepsy. The amino acid transmitter GABA (inhibitory), glutamate (excitatory) and possibly aspertate the neuromodulator involved in the mechanisms of the epileptic seizures. The concentration of this amino acid has been shown to change during epileptic activity in human brain perturbing the balance between excitation and inhibition i.e, decrease inhibitory and increase excitatory amino acid transmitter have been thought to play pivotal role in causing epilepsy.[2]

TYPES OF SEIZURES

Epilepsy is not characterized by one type of seizure. The kind of seizure depends on which part and how much of the brain is affected. Seizures can be classified into generalized seizures, focal seizures, non-epileptic seizures and status epilepticus.

1. **Generalized seizures**

With generalized seizures both cerebral hemispheres are affected. They originate at some point within, and rapidly engage, bilaterally distributed networks. The bilateral networks can include cortical and sub-cortical structures, but do not necessarily include the entire cortex. They are characterized by loss of consciousness and can be categorized into six types. The first is the most common type, the grand mal seizures, also known as the tonic-clonic seizures. They begin with stiffening of the limbs (tonic phase), followed by jerking of the limbs (clonic phase). The second category consists of the myoclonic seizures. These are characterized by rapid, short contractions of the muscles, which usually occur synchronously on both sides of the body. Third are the absence seizures, also known as petit mal seizures which are lapses of awareness. They begin and end abruptly and only last a few

seconds. They are more common in children than in adults. The fourth and fifth types are clonic seizures and tonic seizures, respectively. The sixth type is atonic seizures which occur as a sudden loss of muscle tone.

2. **Focal seizures**

Focal seizures originate within networks limited to one hemisphere. For each seizure type the ictal onset is consistent from one seizure to another. These seizures are the most common type, accounting for about 60% of people with epilepsy. Focal seizures can occur with or without impairment of consciousness or awareness.

3. **Non-epileptic seizures**

Non-epileptic seizures are episodes that change a person's behavior for a short time and look like epileptic seizures. An important difference between the two is that non-epileptic seizures are not caused by abnormal electrical activity in the brain. Non-epileptic seizures can be classified into two groups according to the cause of the seizures. Physiologic non-epileptic seizures are caused by a metabolic disturbance in the brain. Medical causes can be cardiac arrhythmia, syncopal episodes or hypoglycemia. Psychogenic non-epileptic seizures appear to be caused by stressful psychological experiences or emotional trauma.

4. **Status epilepticus**

Status epilepticus means a continuous state of seizure. The mortality rate of status epilepticus is very high (at least 20%), especially if treatment is not initiated quickly. Status epilepticus often occurs in people who do not have epilepsy, but can be triggered by brain tumors or infections, cerebrovascular disease or ingestion of cocaine or other drugs.[3]

The recently approved WHO Intersectarial global Action plan for Epilepsies and other Neurological Disorders Calls for a multi-stakeholder approach driven at the national and local level to reduce the treatment gap, Stigma, and aim for 70% of the people with epilepsy to be seizure free.

The overall prevalence of epilepsy in India has been estimated to be 5.59-10 per 1000. About 65 million people worldwide have epilepsy and nearly 80% of people with epilepsy live in developing countries, where annual new cases occur between 40 to 70 per 1,00,000 people in general population.

Aside from the disease's dismal prognosis numerous issues (motor problems, anxiety, cognitive deficiencies, depression and social impairment) also lead to decreased quality of life, several anticonvulsant medicines are accessible for the pharmacological medication of epilepsy cases across the globe, such as (Brivaracetam, Carbamazepine, Clobazam, Lamotrigine, Phenobarbital and Divalproex.) However, seizures remain resistant in over 20% of cases. In addition to failing to control seizures in certain individuals, the existing antiepileptic medicines also have significant side effects.[4] Further, a large number of drug interactions seen with almost all current antiepileptic drugs make it more difficult to attain easy control on seizure and also treatment of co-morbidities.

Many antiepileptic drugs, for example, have a depressant action on the central nervous system (CNS) which can be additive or even show reciprocal potentiation when these agents are used together.[5]

People with epilepsy around the world have tried many alternative and complimentary therapies; however, few of these therapies have been rigorously tested against the scientific standards used to assess the effectiveness and safety of much alternative therapy. Non-vitamin, non-mineral natural products and especially herbal extracts were found to be safer and efficient. In countries like China and India well developed medical systems, such as traditional Chinese medicine and Ayurveda are often the basis for treating patients with epilepsy.[6] Natural products and plants for that matter used in traditional medicine can be an invaluable source for search of novel antiepileptic compounds, as large section of world's population relies on traditional medicine not only because of their lesser side effect, least drug interaction but also because of their cost effective treatment and easy access. This creates a worldwide trend to undertake research activities to search for safer, efficient and cheaper remedies for epilepsy.[7]

Pentylenetetrazol (PTZ) is a central and respiratory stimulant, similar to doxapram hydrochloride. It is an antagonist of the gamma-amino butyric acid (GABA) A receptor and is anxiogenic. PTZ induces oxidative stress, increases cortical malondialdehyde content and affects the hippocampus, resulting in seizures. PTZ is used to produce a model of chemical induced epilepsy. PTZ induced seizures are characterized as a model of generalized seizures among all animals seizures and epilepsy model. It causes petit mal-like/ myoclonic seizures.[4]

PLANT PROFILE[8,9,10,11,12]

SI. NO	DISCRIPTION	PLANT-I (MENTHA PIPERTIA)	PLANT – II (OCIMUM SANCTUM L)
01	Synonym	Mint	Krishna Tulsi
02	Habitaite	Mentha is extensively dispersed in Europe, Africa, Asia, Australia and North America.[9]	Tulsi, originating in India, ha a widespread distribution in tropical and subtropical region, including southeast Asia, Central Asia and parts of Africa.[11]
03	Chemical Constituents	Menthone and Methyl acetate almost 1.2-3.9%	The leaves of OS contain 0.7% volatile oil comprising about 71% eugenol and 20% methyl eugenol.
04	Uses	* a medicinal herb to treat gastrointestinal pain and chest pain * irritable bowel syndrome and aromatherapy	cure of many illness likecold, headache, cough, flu, earache, fever, colic pain, sore throat, bronchitis, asthma, hepatic diseases, malaria fever, as an antidote for snake bite and scorpion sting, flatulence, migraine headaches, fatigue, skin diseases, wound, insomnia, arthritis, digestive disorders, night blindness, diarrhea and influenza, Chewing of Tulsi leaves also cures ulcers and infections of mouth.[12]
05	Medicinal Properties:	* Treating cough and bronchitis along with oral mucosal and throat inflammation. * to overcome the problems, such as flatulence, diarrhea, nausea, vomiting, indigestion, anorexia and morning sickness.	* Basil is antispasmodic, appetizer, carminative, galactagogue, and stomachic * It is used for stomach cramps, gastric catarrh, vomiting, intestinal catarrh, constipation and enteritis. * Tulsi has antioxidant properties and reduces blood glucose levels. Thus it is useful for cardiac disease patients.
06	Pharmacological Actions	Anti-oxidant activity, Anti-microbial activity, Insecticidal, Anti-cancerous activity, Anti-epileptic activity.[9]	Antimicrobial activity, Anti-oxidant activity, Anti-diabetic activity, Cardiac activity, Anti-fertility activity, Anti-cancer activity, Larvicidal activity, Nootropic activity.[13]

II. MATERIAL AND METHODS

Chemicals:

Pentylenetetrazole (PTZ), Ethanol, Diazepam.

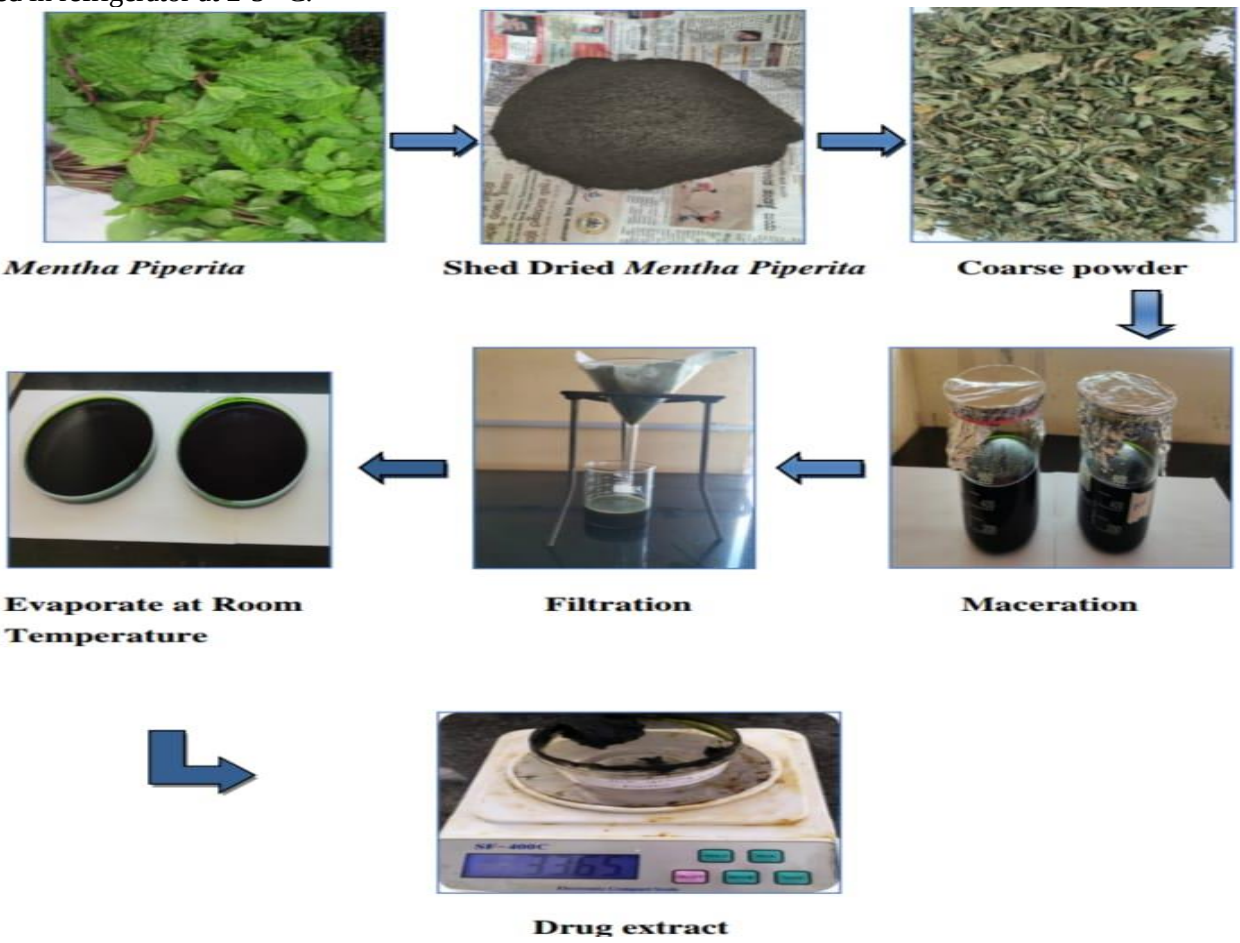
COLLECTION PLANT MATERIAL:

The *Mentha piperita and Ocimum sanctum* are widely grown in most parts of India. The fresh dried leaves of *Ocimum sanctum* were collected from the regional area of Hubballi, Karnataka. The fresh Roots of *Mentha piperita* were collected from the nursery of Haveri, Karnataka.

PREPARATION OF PLANT EXTRACT:

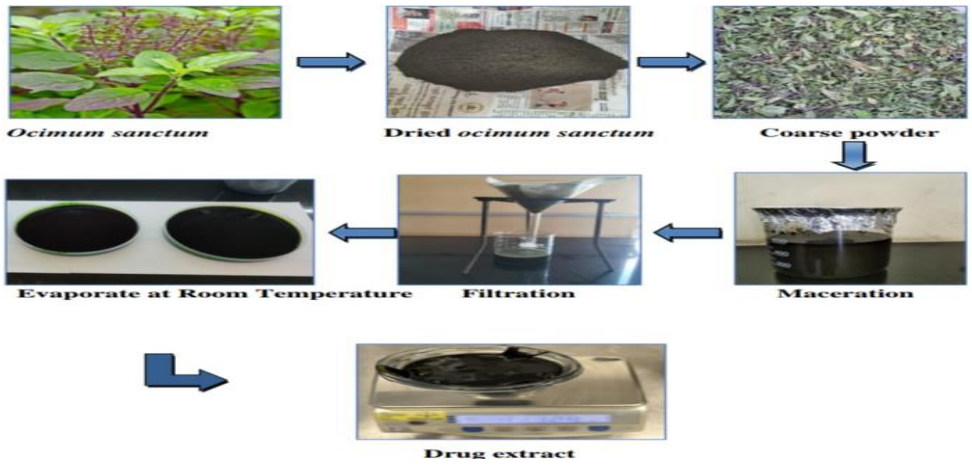
Extraction of *Mentha piperita*

A leaves were chopped into and small pieces allowed to shed dry. The dried leaves were subjected to coarse powder. The collected coarse powder was allowed to macerate with ethanol up to 8 days with occasional stirring. The macerated solution is allowed to filter and evaporate at room temperature and extracted drug was stored in refrigerator at 2-5 ^{0}C.[13]



Extraction of *Ocimum Sanctum*

The whole plants were washed thoroughly with water and leaves were chopped into small pieces and allowed to shed dry. The dried leaves were subjected to coarse powder. The collected coarse powder was allowed to macerate with ethanol up to 3 days with occasional stirring. The macerated solution is allowed to filter and evaporate at room temperature and extracted drug was stored in refrigerator at 2-5^0 C.[14]



ANIMAL GROUPING:

Group I: Control group received PTZ 95mg/kg, (n=6).

Group II: Standard group received diazepam 10mg/kg, (n=6).

Group III: Received PTZ and 200mg/kg polyherbal extract of *Mentha piperita* and *Ocimum sanctum*, (n=6).

Group IV: Received PTZ and 400mg/kg ployherbal extract of *Mentha piperita* and *Ocimum sanctum*, (n=6).

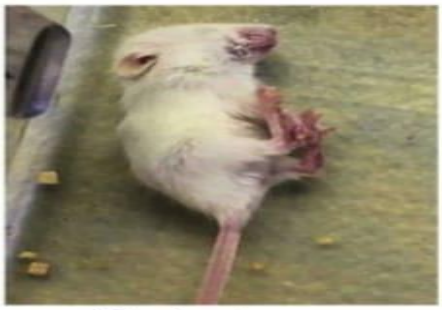
ANIMALS:

Young Swiss albino mice of both sex (18-25gm) were procured from the Central Animal House of H.S.K College of Pharmacy Bagalkote. Animals were acclimatized to laboratory condition at room temperature prior to experimentation. Animals were kept under standard conditions of a 12-hour light/ 12-hour dark cycle with food and water ad-libitum in groups of plastic cages with soft binding. The protocol was approved by the Institutional Animal Ethics Committee of H.S.K. College of Pharmacy, Bagalkote. And carried out in accordance with the CPCSEA Guidelines for the use and care of laboratory animals.

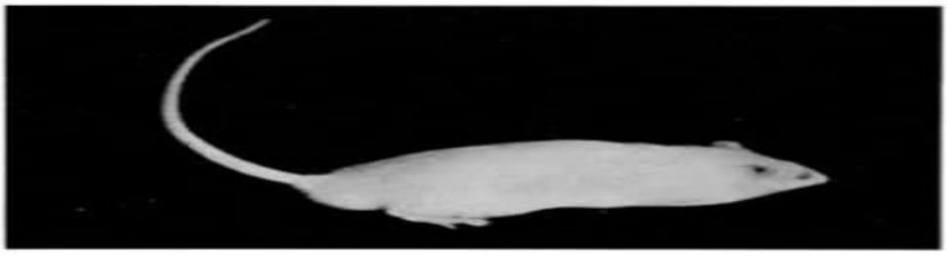
PENTYLENETETRAZOLE INDUCED MODEL:

Healthy Swiss albino mice were selected and weighed between 18-25gm of either sex chosen for in vivo study.[3] 24 mice were divided into IV groups of Six animals.[4] Group I received PTZ intraperitonially (The prevention of seizures induced by PTZ in laboratory animals is the principal protocol used to characterize a potential anticonvulsant drug[5]), group II received standard drug (diazepam 10mg/kg) orally and Group III and IV received polyherbal extracts of *Mentha piperita* and *Ocimum sanctum* at different doses (200mg/kg and 400 mg/kg) oral respectively. All treatment and standard groups were statistically compared with control group. Then after 30min injected with PTZ (95mg /kg).[6] After mice were observed for (1) Onset of action, (2) Death latency, (3) No.of convulsion, (4) No. of Straub's tail, (5) Duration of convulsion, (6) Jerking, (7) Tonic, (8) Clonic, (9) Stuper, (10) Straub's tail.[7]

Tonic seizures



Clonic seizures



Straub's tail

III. RESULTS

Effect of ethanolic extract of *Mentha piperita* and *ocimum sanctum* on PTZ induced epilepsy in mice.

The Effect of Ethanolic extract *Mentha piperita* and *Ocimum sanctum* on PTZ induced epilepsy (Onset of Action and Death latency) in mice represented in Table 1 and Fig 1. In treatment group, it shows significant increase in Onset of Action and decrease in Death latency as compared to Control group. The Effect of Ethanolic extract of *Mentha piperita* and *Ocimum sanctum* on PTZ induced epilepsy (No. of Convulsion and No. of Straub's tail) in mice represented in Table 2 and Fig 2. In treatment group, it shows significant decrease in No. of Convulsion and No. of Straub's tail as compared to Control group.The Effect of Ethanolic extract of *Mentha piperita* and *Ocimum sanctum* on PTZ induced epilepsy (Duration of Convulsion, Jerking, Tonic, Clonic, Stuper and Straub's tail) in mice represented in Table 3 and Fig 3. In treatment group, it shows significant decrease in Duration of Convulsion, Jerking, Tonic, Clonic, Stuper and Straub's tail as compared to Control group.

Table No.1 The effect of Ethanol extract of *Mentha piperita* and *Ocimum sanctum* on PTZ induced epilepsy (Onset of Action and Death Latency) in mice.

Groups	Time in minutes	
	Onset of Action(Convulsion)	Death Latency
Control	3.24±0.084	6.85±0.242
Standard	0.0±0.0***	0.0±0.0***
MPOS (200mg/kg)	4.79±0.130***	0.0±0.0***
MPOS (400mg/kg)	5.04±0.098***	0.0±0.0***

All values are expressed as mean ± SEM, n=6, One way Analysis variance(ANOVA) followed by multiple comparisons Dunnett's test.The value significant $^{c}p < 0.05$, $^{b}p < 0.01$, $^{a}p < 0.001$ as compared to normal group and $^{*}p< 0.05$, $^{**}p <0.01$, $^{***}p < 0.001$ as compared to control group

Fig.1. The Effect of Ethanol extract of *Mentha piperita* and *Ocimum sanctum* on PTZ induced epilepsy (Onset of Action and Death Latency) in mice

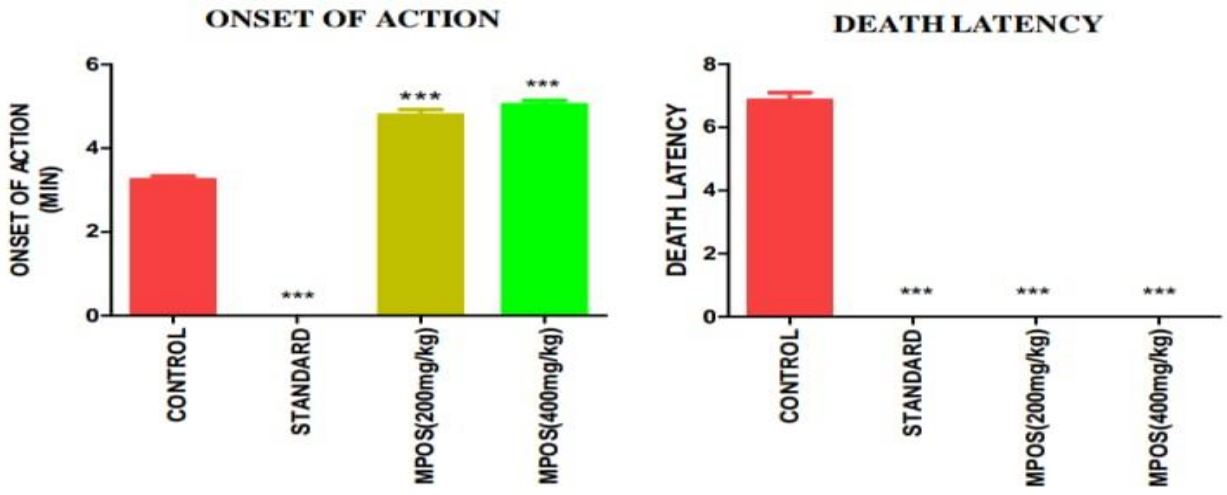


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Table No.2 The effect of Ethanol extract of *Mentha piperita* and *Ocimum sanctum* PTZ induced epilepsy (No. of convulsion and No.of Straub's tail) in mice.

Groups	No.of Convulsion	No.of Straub's tail
Control	1.833±0.307	4.00±6.365
Standard	0.0±0.0***	0.0±0.0***
MPOS (200mg/kg)	6.66±0.210***	2.667±0.33**
MPOS (400mg/kg)	0.33±0.210***	1.500±0.223***

All values are expressed as mean± SEM,n=6, One way Analysis of Variance (ANOVA) followed by multiple comparisons Dunnett's test. The value significant $^{c}p < 0.05$, $^{b}p < 0.01$, $^{a}p < 0.001$ as compared to normal groups and $^{*}p< 0.05$, $^{**}p <0.01$, $^{***}p < 0.001$ as compare to control group**.**

Fig.2. The Effect of Ethanol extract of *Mentha piperita* and *Ocimum sanctum* on PTZ induced epilepsy (No. of Convulsion and No. of Straub's tail) in mice.

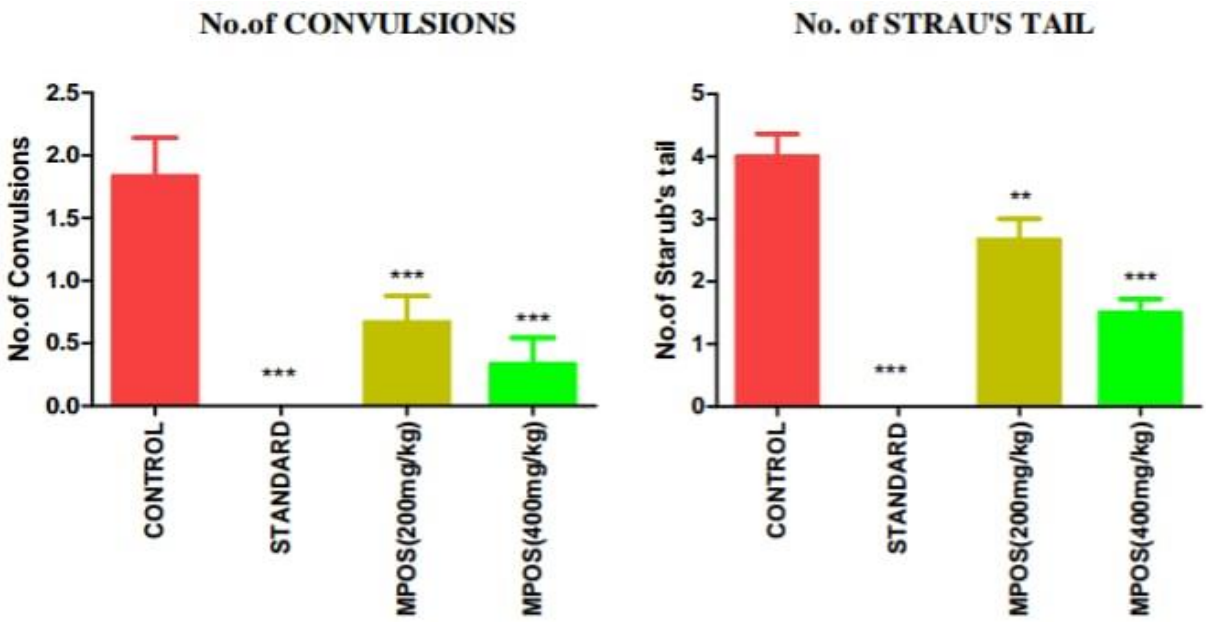

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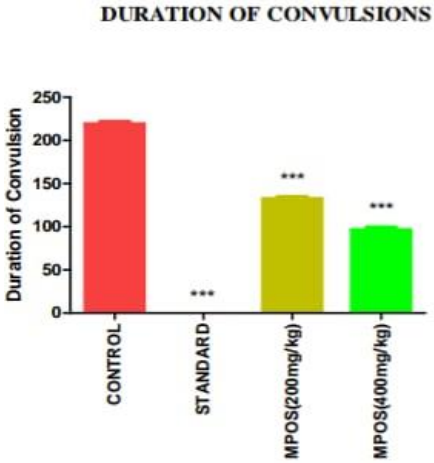
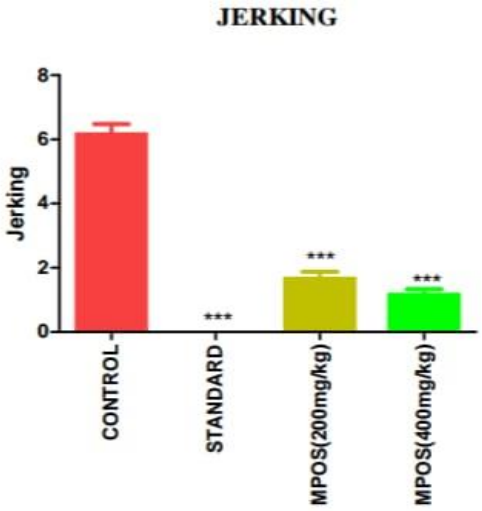
TABLE NO.3 THE EFFECT OF ETHANOL EXTRACT OF *MENTHA PIPERITA* AND *OCIMUM SANCTUM* ON PTZ INDUCED EPILEPSY (DURATION OFCONVULSION,JERKING,TONIC,CLONIC,STUPER,STRAUB'S TAIL) IN MICE.

Groups	Time in seconds					
	Duration of Convulsion	Jerking	Tonic	Clonic	Stuper	Straub's tail
Control	219.2±2.786	6.167±0.307	15.00±1.211	4.33±0.33	154.7±2.565	28.0±1.065
Standard	0.0±0.0***	0.0±0.0***	0.0±0.0***	0.0±0.0***	0.0±0.0***	0.0±0.0***
MPOS (200mg/kg)	132.7±2.186***	1.667±0.210***	0.33±0.210***	0.166±0.166***	109.7±2.45***	7.16±0.30***
MPOS (400mg/kg)	96.67±2.728***	1.167±1.66***	0.0±0.0***	0.0±0.0***	60.50±2.262***	4.667±0.42***

All values are expressed as mean ± SEM, n=6, One way Analysis of Variance (ANOVA) followed by multiple comparisions Dunnett's test.The value significant $^{c}p < 0.05$, $^{b}p < 0.01$, $^{a}p < 0.001$ as compared to normal group and $^{*}p< 0.05$, $^{**}p <0.01$, $^{***}p < 0.001$ as compared to control group.

FIG.3 THE EFFECT OF ETHANOL EXTRACT OF MENTHA PIPERITA AND OCIMUM SANCTUM ON PTZ INDUCED EPILEPSY (DURATION OF CONVULSION, JERKING,TONIC, CLONIC, STUPER,STRAUB'S TAIL) IN MICE.





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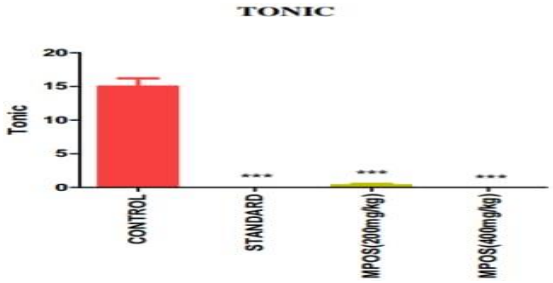

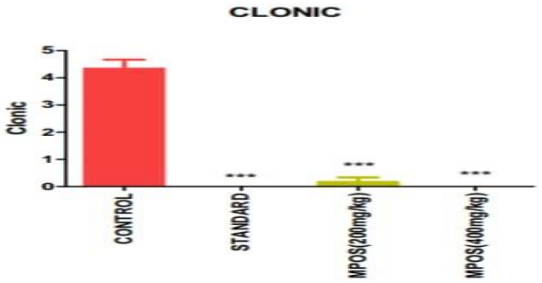

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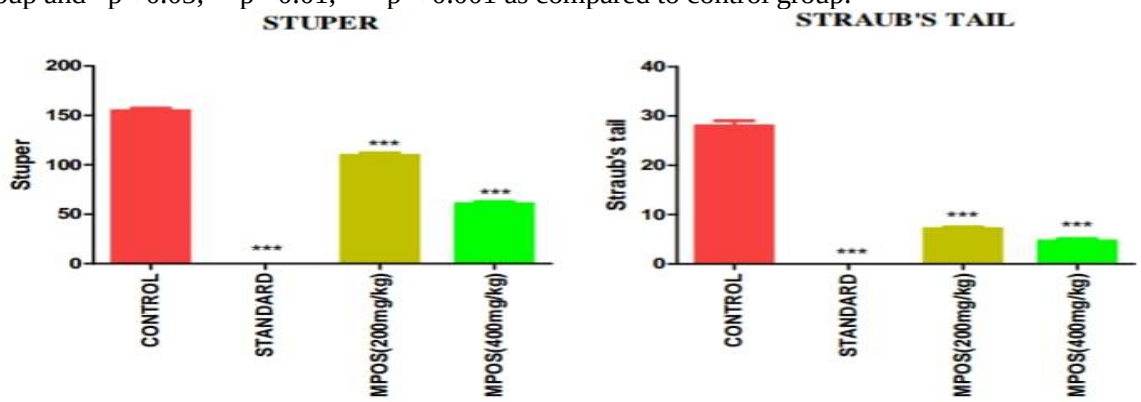

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IV. DISCUSSION

Epilepsy is a condition of the central nervous system featured by frequent seizures caused by the coordinated firing of neuronal networks in the brain. Animal models of epilepsy are exhaustively described to comprehend the illness's neurobiology and identify new antiepileptic compounds.

The most prevalent seizure models are produced by pharmacological administration of convulsant drugs (pentylenetetrazol and pilocarpine) or electrical stimulation of specific brain areas at their threshold levels.

Several studies indicated that seizures cause the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the brain, which is an organ susceptible to oxidative stress.

ROS generation increases cytoplasmic Ca2+ concentrations, directly impacting GABA A receptor function, boosting neuronal hyperexcitability, and modifying neuronal membrane possibility.

Oxidative stress causes mitochondrial failure, and this dysfunction may induce epileptic seizures via decreased ATP synthesis and altered Na+ /K+ ATPase activity in the cell membrane. Thus, compounds with antioxidant activity. may aid in treating epilepsy by lowering oxidative stress in the brain.

Epilepsy is a very common disorder affecting 1% of the world's population. The incidence in India is around 20- 50 cases/lakh population. GABA potentiating drugs like diazepam, benzodiazepine, barbiturate, valproate etc have been adopted to treat epilepsy. However, prolonged use of such drugs develops tolerance and dependence.

The present study is planned to demonstrate the anti-epileptic activity of poly-herbal extract of *Ocimum sanctum* and *Mentha piperita* against PTZ induced seizures in mice. In continuation of such search the field survey was carried out and whole plant of *Ocimum Sanctum* and *Mentha piperita* contains several phytochemicals, namely terpenoids, phenols, flavonoids, glycosides, and propenyl phenols.

PTZ tests are the best-validated method for assessment of AED {automated external defebrillator} in human generalized tonic–clonic seizures and absence seizures, respectively, among the tests used for evaluation of anticonvulsant activity.

Moreover, it also contains vitamin C, A, and minerals such as zinc, iron, and calcium. The protein content in *O. sanctum* is 4.2 g, then 0.5 g fat, 25 mg carbohydrates, 287 mg phosphorus, 25 mg calcium, vitamin C per 100 g, and 15.1 mg iron.

In the first phase of the present study the plant material was collected, authenticated and the ethanol extract of *Ocimum sanctum* and *Mentha piperita was* prepared.

The chemical constituents like triterpenes, terpenoids, phenolic, flavonoids, glycosides, phenolic compounds and essential oils for the antiepileptic activity which is highly soluble in ethanol due to their organic and moderately polar nature. So extraction was carried out in ethanol.

Recent research has found that the PTZ paradigm is widely used to evaluate a drug's anticonvulsant potential. There is conclusive evidence that PTZ harms neural membranes.

PTZ regulates potassium and calcium channels and triggers the release of calcium ion repertoires from within cells. Chloride permeability caused by neurotransmitters is also reduced by PTZ.

Because drugs that work against PTZ-induced seizures are also very helpful in treating mild to no epilepsy. So, Poly-herbals of *Ocimum sanctum and Mentha piperita* extract has shown promise in preventing PTZ-induced epilepsies and could be helpful Poly-herbals of *Ocimum sanctum and Mentha piperita* leaf in the management of absence seizures.

Medical plants can be applied because of their structural diversity and wide spectrum of pharmacological effects in contrast to common synthetic antiepileptic drugs.

V. CONCLUSION

The present study was an attempt to evaluate the anti-epileptic activity of polyherbal extract of *Ocimum sanctum* and *Mentha piperita* against pentylenetetrazole induced seizure in mice.

The polyherbal extract of whole plant of *Ocimum sanctum* and *Mentha piperita* with a dose of 200mg/kg and 400mg/kg orally were evaluated for anti-epileptic activity. A dose of 200mg/kg and 400mg/kg has shown anti-epileptic activity in pentylenetetrazole induced seizures in mice.

This anticonvulsant activity of poly-herbal extract of *MP* and *OS* 200mg/kg and 400 mg/kg evidenced by decrease in the various phases stupor of convulsion in PTZ model and significant increase in onset in duration of seizure, decrease in duration of the seizure and reduced mortality rate in PTZ model in a dose dependent manner.

In the PTZ model the effect shown by poly-herbal extract of *MP* and *OS* is similar to standard drug because of reduction in the facilitation of Na+ ions to the neuronal area of the brain. So this may be the reason for shortening in time of both the phases and delay in firing of neurons**.**

The effect of poly-herbal extract *MP* and *OS* produced anti-convulsant activity in PTZ induced seizure model resembles diazepam in onset and duration of convulsion in mice.

The probable mechanism associated by the extract may due to GABA mediated occupational theory with the receptors there by augmenting inhibitory neurotransmission there by depressing neuronal brain parts.

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