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Research

Evaluation Of Anti-Epileptic Properties From Flowers Of Mussaenda Philippica In Isoniazid-Induced Convulsions In Wistar Rats

Afreen Begum*, Musarrath Mubeen[1], Priyanka.K[2], K. Sreevani[3], Rangam Chariitha[4], Teelavath Mangilal

Smt.Sarojini Ramulamma College Of Pharmacy, Seshadrinagar, Mahabubnagar, Telangana-509001

*Author for Correspondence: Afreen Begum
Email: teelavath@gmail.com

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Abstract

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, often associated with excessive neuronal activity. Current antiepileptic drugs have limitations due to side effects and lack of efficacy in some patients, prompting the need for alternative therapies. This study investigates the antiepileptic potential of ethanolic extract of *Mussaenda philippica* (EEMP) flowers using maximal electroshock (MES) and isoniazid (INH)-induced convulsion models in Wistar rats. Preliminary phytochemical analysis revealed the presence of alkaloids, flavonoids, phenols, glycosides, saponins, and terpenoids. In the MES model, EEMP significantly reduced seizure parameters including flexion, extension, clonus, stupor, and recovery time. It also improved percentage protection and increased gamma-aminobutyric acid (GABA) levels, indicating enhancement of inhibitory neurotransmission. In the INH-induced model, EEMP delayed seizure onset, reduced mortality, and demonstrated 100% protection in higher doses. Histopathological examination confirmed increased neuronal density and reduced brain damage. These effects are likely due to the flavonoid content and antioxidant properties of *M. philippica*, which may act by inhibiting GABA transaminase or promoting GABA synthesis. The results suggest that *Mussaenda philippica* possesses promising antiepileptic activity and may serve as a potential natural alternative for managing epilepsy.

Keywords: Mussaenda philippica, Epilepsy, GABA, Isoniazid-induced seizures, Maximal electroshock seizures, Antiepileptic activity.

INTRODUCTION

HERBAL MEDICINE

India possesses a wealth of documented and traditionally applied information about herbal therapy. Only a small number of commercially significant medicinal plants are absent from this nation. More than 3000 plants are recognized by the Indian government as having therapeutic properties. Over 6000 plants are thought to be

used in traditional, folk, and herbal medicine in India. In India, there are over 9,000 companies that produce traditional Ayurvedic medications. The potential medical usefulness of plant materials is currently being thoroughly investigated by major pharmaceutical corporations. The use of more than 340 medications derived from vegetables is documented in the Charaka Samhita (c. 1000 B.C). To satisfy the demands of the medical community, the majority of these are still collected from wild trousers. In 2002, Pulok K. et al.

Herbal medicines, often known as plant materials or herbalism, are used to cure wounds or illnesses by using complete plants or plant parts. The use of medicinal herbs to promote health and healing or to prevent and treat illnesses is known as herbal medicine. These are medications or plant-based preparations used for any of these uses. The earliest known medical treatment is herbal medicine. Numerous herbal remedies are available that claim to alleviate the symptoms of a wide range of issues, including depression, the flu, and the common cold. According to the World Health Organization (WHO), herbal pharmaceuticals are full, labeled medications that contain a variety of substances, including aerial or secretive plant parts, other plant material, or combinations of these. The World Health Organization has established clear standards for assessing the quality, safety, and effectiveness of herbal medications.

People have been using plants to heal for generations. Throughout history, people have employed plant-based ingredients in food or botanical powders and potions to treat and prevent illnesses, with differing degrees of effectiveness. When Friedrich Bayer and Co. brought synthetic acetyl salicylic acid (aspirin) to the globe in 1897, the long-standing connection between plants and human health started to weaken. Residents of both the New and Old worlds independently found aspirin as a treatment for fevers and aches. It is a safer synthetic version of salicylic acid, an active element of willow bark (Ilya Raskin and David M. Ribnicky, 2002).

In India, herbal medicine:

With over 45,000 plant species, India is one of the 12 mega biodiversity hubs. With 16 distinct agroclimatic zones, 10 vegetative zones, and 15 biotic provinces, it boasts unparalleled diversity. According to Drugs and Pharmaceuticals (1998), the nation is home to 15,000–18,000 flowering plants, 23,000 fungi, 2500 algae, 1600 lichens, 1800 bryophytes, and 30 million microorganisms.

Additionally, about three-quarters of India's land is in the ocean's exclusive economic zone, which is home to a wide range of plants and animals, many of which have medicinal qualities. Approximately 800 plants have been utilized in traditional medicine, while approximately 1500 plants with therapeutic properties have been documented in ancient writings.

EPILEPSY

Millions of individuals throughout the world suffer with epilepsy, a common and often debilitating illness. A brief change in behavior brought on by the disorganized, synchronized, and rhythmic firing of groups of brain neurons is referred to as a seizure. A condition of brain function known as epilepsy is typified by the sporadic and unpredictable occurrence of seizures. A common vernacular term for an epileptic episode is "fit." Involuntary, forceful, spasmodic, or prolonged contractions of the skeletal muscle are known as convulsions. Thus, epilepsy without convulsions can occur in a patient, and vice versa.

PROFILE OF THE PLANT

1. Recognition

Mussaenda philippica plant with bracts, leaves, and flowers (Fig. 1)

2. Classification by Science

Class: Asterids;
Division: Eudicots;
Order: Gentianales;
Family: Rubiaceae; Genus: Mussaenda;
Species: Mussaenda
Kingdom: Plantae;
Subkingdom: Tracheophytes;
Superdivision: Angiosperms. The Philippines

3. Synonyms

Tamil: Kattu mantharai;
Telugu: Kommu mandaara;
Malayalam: Nagamulla;
Kannada: Rajamanthara;
Bengali: Raktamandaara;
English: Tropical Dogwood, Virgin's Tree;
Sanskrit: Kapithika;

Hindi: Kanchan phool

4. Distribution

Although Mussaenda philippica is indigenous to the Philippines, it is grown extensively in tropical and subtropical areas, such as Africa, India, and Southeast Asia. In parks and gardens, the plant is frequently planted as an ornamental. Commonly found in Indian states like Kerala, Tamil Nadu, and West Bengal, it flourishes in warm, humid weather.

5. Conditions of Cultivation

Warm settings with temperatures between 20 and 35 degrees Celsius are ideal for Mussaenda philippica growth. It needs fertile, well-drained soils with a pH of 6.0 to 7.5, which is slightly acidic to neutral. Although it may withstand little shade, the plant prefers full light. Frequent pruning and watering promote robust development and copious blooms. Cuttings are usually used for propagation.

6. Description of Botany

Mussaenda philippica is a tiny tree or evergreen shrub that grows quickly, reaching a height of two to three meters. The dark green, oval, simple leaves have a slightly rough feel. The enormous, vividly colored bracts, which can be pink, white, or red, encircle the petite, tubular, yellow to orange blooms. People frequently confuse these bracts for flowers. Under ideal circumstances, the plant blooms all year round. The fruit is a tiny, seed-containing capsule-like structure.

7. The study of phytochemistry

Numerous bioactive substances are present in Mussaenda philippica, including:
Flavonoids: quercetin and kaempferol
Alkaloids, such as Mussaendine
Iridoids and Terpenoids
Triterpenoid saponins are saponins.
Additional substances include glycosides and phenolic acids, which have hepatoprotective, antibacterial, anti-inflammatory, and antioxidant qualities.

8. Conventional Applications

Traditional medical systems have employed Mussaenda philippica for a number of medicinal uses.
Ayurveda: Used to treat respiratory disorders, skin disorders, and fevers.
Folk Medicine: Wounds, boils, and sores are treated using leaves and flowers. Root decoctions are used as a general tonic and for gastrointestinal problems.
Southeast Asian medicine: used as an anti-inflammatory and detoxifying agent.

9. Important Scientific Records

1. Anti-Inflammatory Properties

Mussaenda philippica's flavonoids and iridoids are responsible for its strong anti-inflammatory properties. By blocking pro-inflammatory mediators including cytokines and prostaglandins, these substances lessen inflammation. Mussaenda philippica extracts have been shown in animal experiments to lessen redness, discomfort, and swelling in inflammatory models. Its antioxidant qualities also lend credence to its use in the treatment of long-term inflammatory diseases. (Rao and others, 2019)

2. Activity of Antioxidants

Mussaenda philippica has potent antioxidant qualities due to its abundance of flavonoids and phenolic substances. These substances shield cells from oxidative stress, neutralize free radicals, and increase the activity of natural antioxidant enzymes like catalase and superoxide dismutase. It has been shown to have promise in reducing oxidative damage linked to aging and chronic illnesses like neurodegeneration and cardiovascular problems. (Sharma and others, 2020)

3. Antimicrobial Action

Mussaenda philippica exhibits strong antibacterial and antifungal qualities. Research indicates that it works well against fungi like Candida albicans and bacteria like Staphylococcus aureus and Escherichia coli, both gram-positive and gram-negative. Bioactive substances including flavonoids and saponins, which damage microbial cell membranes and stop growth, are connected to its antibacterial properties. (Mishra and others, 2018)

4. Hepatoprotective Action

Experimental investigations have demonstrated the hepatoprotective properties of Mussaenda philippica. The bioactive components of the plant, especially flavonoids and phenolic acids, shield liver cells from harm brought on by poisons like alcohol and paracetamol. Studies using mice treated with extracts from Mussaenda

philippica have shown better antioxidant defense mechanisms and liver enzyme profiles. In 2022, Venugopal et al.

5. Activity for Wound Healing

Mussaenda philippica's antibacterial, anti-inflammatory, and collagen-promoting qualities all assist its capacity to heal wounds. According to studies, its extracts enhance tissue regeneration, hasten wound closure, and lower the incidence of subsequent infections. The plant is a useful natural treatment for skin injuries because of its capacity to promote angiogenesis and collagen formation. Singh and colleagues (2017)

6. Anti-Diabetic Action

Extracts from Mussaenda philippica may help control blood sugar levels, according to preclinical research. The plant's bioactive substances increase cell absorption of glucose and insulin sensitivity. Its antioxidant qualities also lower the incidence of diabetes complications by shielding pancreatic β-cells from oxidative stress. Mussaenda philippica shows potential as a supplemental treatment for diabetes when used regularly in herbal preparations. (Kumar and others, 2021).

10. Clinical Research

Clinical research confirms Mussaenda philippica's safety and effectiveness in treating skin injuries, liver diseases, and inflammation. At dosages of 250–500 mg per day, standardized extracts have demonstrated therapeutic advantages with little adverse effects. Long-term use of the plant is usually well tolerated.

RESULTS

Preliminary Phytochemical analysis of Ethanolic extract of Mussaenda philippica (EEMP)

The result of preliminary phytochemical analysis of Ethanolic extract of Mussaenda philippica showed presence of various phytochemical constituents such as phenols, Flavonoids, steroids, alkaloids, glycoside protein, tannins, terpenes and saponins with absence of CARBOHYDATES, sterol, gums and mucilage.

Table 1: Preliminary Phytochemical analysis of Ethanolic extract of *Centella asiatica*

S.No	Phytochemicalconstituents	Presence/Absence
1	Alkaloids	*Present*
2	Carbohydrates	*absent*
3	Steroids	*Present*
4	Proteins	*Present*
5	Tannins	*Present*
6	Phenol	*Present*
7	Flavonoids	*Present*
8	Gums and mucilage	*Absent*
9	Glycoside	*Present*
10	Saponins	*Present*
11	Terpene	*Present*
12	Sterols	*Absent*

EFFECT OF EEMP ON MES INDUCED EPILEPSY IN WISTAR RATS

Table 2: Effect of EEMP on Flexion in MES induced epilepsy in wistar rats.

GROUPS	FLEXION (SEC)
Group I	0
Group II	24.68 ± 3.64 a****
Group III	7.64 ± 3.26 a ^{ns} b****
Group IV	15.45± 5.79 a**** b****C**
Group V	4.26± 1.85 a*b****C ^{ns}

Values are expressed as mean ± SEM of 6 animals. Comparisons ere made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' est. Where * (p< 0.05), **(p< 0.01), *** (p<0.001), ****(p<0.0001) and ns- nonsignificant.

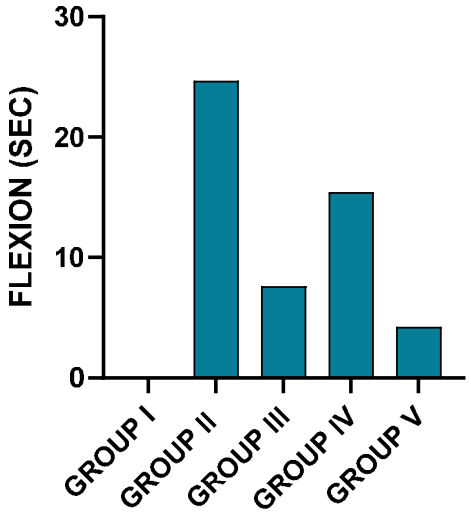

Fig 1: Effect of EEMP on Flexion in MES induced epilepsy in wistar rats.

Flexion in MES induced epilepsy in wistar rats

- The Flexion phase in Group II, IV (p<0.0001), V (p< 0.05) was significantly increased when compared with Group I (vehicle treated) and Group V was nonsignificant when compared with Group I
- The Flexion phase in Group II was significantly increased when compared with group IV (p<0.001).
- The Flexion phase in Group V was significantly decreased when compared with Group IV (p< 0.01), and nonsignificant with Group III

Table 3: Effect of EEMP on Extensor in MES induced epilepsy in wistar rats.

GROUPS	EXTENSOR (SEC)
Group I	0
Group II	24.57 ± 1.44a****
Group III	48.21 ± 1.78 a ^{ns} b****
Group IV	7.24 ± 2.75 a****b***C**
Group V	6.73 ± 1.18 a^{ns} b **** C^{ns}

Values are expressed as mean ± SEM of 6 animals. Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * (p< 0.05), **(p< 0.01), *** (p<0.001), ****(p<0.0001)
ns- nonsignificant.

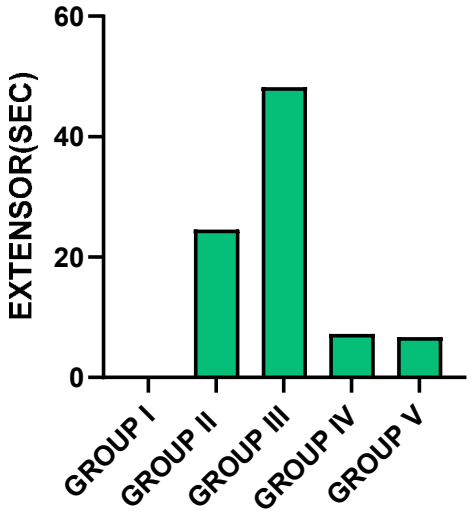

Fig 2: Effect of EEMP on Extensor in MES induced epilepsy in wistar rats.

Extensor in MES induced epilepsy in wistar rats.

- The Extensor phase in Group II and III($p<0.0001$) was significantly increased when compared with Group I (vehicle treated) and Group IV and V was nonsignificant when compared with Group I
- The Extensor phase in Group III was significantly increased when compared with group II, IV ($p<0.0001$) and IV ($p<0.001$).
- The Extensor phase in Group V was significantly decreased when compared with group III ($p< 0.01$) and non-significant with group IV.

Table 4: Effect of EEMP on Clonus in MES induced epilepsy in wistar rats.

GROUPS	CLONUS (SEC)
Group I	0
Group II	13.56 ± 1.56 a****
Group III	4.67 ± 1.34 a*b****
Group IV	7.45 ± 1.39a****b****C****
Group V	9.59 ± 1.32 a****b****C***

Values are expressed as mean ± SEM of 6 animals.
Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * ($p< 0.05$), **($p< 0.01$), *** ($p<0.001$), ****($p<0.0001$) ns- nonsignificant.

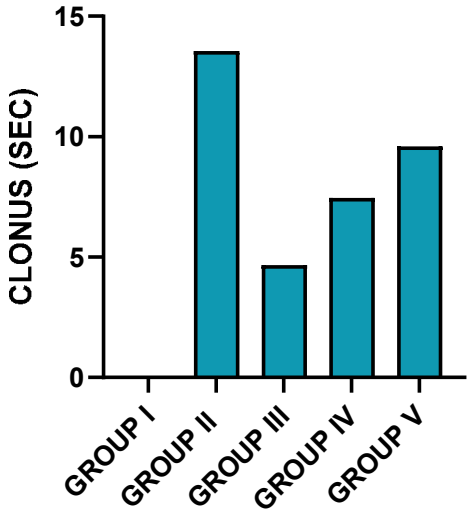

Fig 3: Effect of EEMP on Clonus in MES induced epilepsy in wistar rats.

Clonus in MES induced epilepsy in wistar rats.

- The Clonus phase in Group II, IV, V ($p<0.0001$) and III ($P<0.05$) was significantly increased when compared with Group I (vehicle treated)
- The Clonus phase in Group II was significantly increased when compared with group III, IV and V ($p<0.0001$).
- The Clonus phase in Group III was significantly decreased when compared with group II and V ($p<0.0001$).

Table 5: Effect of EEMP on Stupor in MES induced epilepsy in wistar rats.

GROUPS	STUPOR (SEC)
Group I	0
Group II	7.64± 1.46 a ****
Group III	2.61 ± 1.33 a^{ns} b****
Group IV	1.57 ± 1.28 a***b***C**
Group V	7..02± 1.03 a ^{ns} b**** c ^{ns}

Values are expressed as mean ± SEM of 6 animals. Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * ($p< 0.05$), **($p< 0.01$), *** ($p<0.001$), ****($p<0.0001$)
ns- nonsignificant.

Stupor in MES induced epilepsy in wistar rats.

- The Stupor phase in Group III ($p<0.0001$) and V ($p<0.001$) was significantly increased when compared with Group I (vehicle treated).
  Group II and V was nonsignificant when compared with Group I
- The Stupor phase in Group III was significantly increased when compared with Group IV, V ($p<0.0001$) and II ($p<0.001$)
- The Stupor phase in Group V was significantly decreased when compared with group III ($p< 0.01$) and non-significant with group II.

Table 6: Effect of EEMP on Recovery in MES induced epilepsy in wistar rats.:

GROUPS	RECOVERY (SEC)
Group I	0
Group II	15.45 ± 3.67a****
Group III	71.56 ± 6.34 a ^{ns} b****
Group IV	36.94 ± 3.88 a****b****C***
Group V	13.58 ±2.14 a****b****C**

Values are expressed as mean ± SEM of 6 animals. Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * ($p< 0.05$), **($p< 0.01$), *** ($p<0.001$), ****($p<0.0001$)
ns- nonsignificant.

Recovery time in MES induced epilepsy in wistar rats.

- The Recovery time in Group III, IV &II ($p<0.0001$) was significantly increased when compared with Group I (vehicle treated)
  Group III was nonsignificant when compared with Group I
- The Recovery time in Group III was significantly increased when compared with Group IV, II and V ($p<0.0001$).
- The Recovery time in Group V was significantly decreased when compared with Group III ($p<0.001$) and V ($p< 0.01$).

Table 7: Effect of EEMP on Percentage protection in MES induced epilepsy in wistar rats.

GROUPS	PERCENTAGE ROTECTION
Group I	NIL
Group II	98%
Group III	82%
Group IV	0%
Group V	74%

Values are expressed as Percentage
Percentage protection in MES induced epilepsy in wistar rats.,

- The percentage protection in Group III was significantly abolished when compared with group II, IV and V.
- The percentage protection in Group II was significantly increased when compared with group IV and V.

EFFECT OF EEMP ON ISONIAZID (INH) INDUCED EPILEPSY IN WISTAR RATS.

Table 8: Effect of EEMP on Latency in INH induced epilepsy in wistar rats.

GROUPS	LATENCY (onset epileptic seizure in sec)
Group I	NIL
Group II	146 ± 4.79
Group III	110 ±2.4 a****b****
Group IV	NIL
Group V	107± 6.31 a****b****

Values are expressed as mean ± SEM of 6 animals. Comparisons were made between the following:

- Group II compared with Group III, IV and V was considered as a
- Group III compared with Group IV and V was considered as b

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * ($p< 0.05$), **($p< 0.01$), *** ($p<0.001$), ****($p<0.0001$) ns- nonsignificant.

Latency in INH induced epilepsy in wistar rats.

- The Latency in Group III was significantly decreased compared with group II, IV and V ($p<0.0001$).
- The Latency in Group IV was significantly abolished when compared with group II and V ($p<0.0001$).

Table 9: Effect of EEMP on Mortality after 30 minutes in INH induced epilepsy in wistar rats.

GROUPS	Mortality after 30 min (No of animal alive)
Group I	NIL
Group II	5
Group III	3
Group IV	4
Group V	2

Values are expressed in Numbers

Mortality in INH induced epilepsy in wistar rats at 30 min interval.

- No mortality in Group I (vehicle treated)
- The Number of animals in Group III was significantly decreased when compared with group II, IV and V.
- The Number of animals in INH treated Group IV was significantly increased when compared with Group II and V.

Table 10: Effect of EEMP on Mortality after 24 Hours in INH induced epilepsy in wistar rats

GROUPS	Mortality after 24 Hours (No of animal alive)
Group I	NIL
Group II	6
Group III	4
Group IV	3
Group V	5

Values are expressed in Numbers

Mortality in INH induced epilepsy in wistar rats after 24 hours.

- No mortality in Group I (vehicle treated).
- The Number of animals in Group V was significantly decreased when compared with group II, III and IV.
- The Number of animals in Group II was significantly increased when compared with Group III and IV.

Table 11: Effect of EEMP on Percentage protection in INH induced epilepsy in wistar rats.

Groups	Percentage protection
Group I	NIL
Group II	84 %
Group III	67%
Group IV	85%
Group V	100%

Values are expressed in Percentage.

The percentage protection in INH induced epilepsy in wistar rats

- The percentage protection in Group V was significantly decreased when compared with group II, III and IV.
- The percentage protection in Group IV was significantly increased when compared with group II and III.

IN VITRO-EFFECT OF EEMP ON ESTIMATION OF GABA IN MES INDUCED EPILEPSY IN WISTAR RATS

Table 12: Effect of EEMP on estimation of GABA in MES induced epilepsy in wistar rats

Groups	GABA (ng/mg tissue)
Group I	406.38 ± 1.57
Group II	286.46 ±2.37a****
Group III	353.28 ± 1.84 a****b****
Group IV	264.44 ± 1.98 a****b****c****
Group V	307.57 ±1.48 a****b****c****

Values are expressed as mean ± SEM of 6 animals. Comparisons were made between the following:

- Group I compared with Group II, III, IV and V was considered as a
- Group II compared with Group III, IV and V was considered as b
- Group III compared with Group IV and V was considered as c

Statistical Significance test for comparison was done by one way ANOVA followed by Dunnets't' test. Where * ($p< 0.05$), **($p< 0.01$), *** ($p<0.001$), ****($p<0.0001$)

Estimation of GABA in MES induced epilepsy in wistar rats

- The Concentration of GABA in Group I (Vehicle Control) was significantly increased when compared with Group II, III, IV and V ($p<0.0001$).
- The Concentration of GABA in Group II was significantly decreased when compared with Group III, IV and V ($p<0.0001$).
- The Concentration of GABA in Group III was significantly increased when compared with Group IV and V ($p<0.0001$).

DISCUSSIONS

According to WHO, Epilepsy is a chronic non communicable disease of the brain that affects around 50 million people worldwide. It is characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function.[1] Seizure episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Seizures can vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions. Seizures can also vary in frequency, from less than 1 per year to several per day. A seizure has a clear beginning, middle, and end. Epilepsy was one of the first brain disorders to be Described. Epileptic seizures

are manifested by an abnormal, excessive, and hyper synchronous electrical discharge of neurons in the brain. Each distinct form of epilepsy has its own natural history and response to treatment [89]. This diversity probably reflects the many different underlying causes of epilepsy and the variety of epilepsy syndromes in which the clinical and pathological characteristics are distinctive and suggest a specific under lying etiologic mechanism. [90]

The International League against Epilepsy (ILAE) published a modified version of the International Classification of Epileptic Seizures (ICES), which has continued to be a very useful system. This system is based on the clinical features of seizures and associated EEG findings. The etiology or cellular substrate is not considered. There are three main types of seizures: partial, generalized, and unclassified. There are many kinds of seizures, each with characteristic behavioral changes and electrophysiological disturbances that can usually be detected in scalp electroencephalographic recordings. A seizure is a transient epileptic event, indicating a disturbance in brain function. Having a single seizure does not necessarily mean that a person has epilepsy. Ten percent of adults experience a seizure sometime during their lifetime. [91]

Globally, an estimated 2.4 million people are diagnosed with epilepsy each year. In high income countries, annual new cases are between 30 and 50 per 100000 people in the general population. In low and middle-income countries, this figure can be up to two times higher. In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination. Epileptic seizures arise from an excessively synchronous and sustained discharge of a group of neurons. The single feature of all epileptic syndromes is a persistent increase of neuronal excitability. Abnormal cellular discharges may be associated with a variety of causative factors such as trauma, oxygen deprivation, tumours, infection, and metabolic derangements. However, no specific causative factors are found in about half of the patients suffering from epilepsy. Underlying causes and pathophysiological mechanisms are (partially) understood for some forms of epilepsy, e.g., epilepsies caused by disorders of neuronal migration and monogenic epilepsies. For several other types of epilepsy, current knowledge is only fragmentary. Both neurotransmitter systems and ion channels play a crucial role in neuronal Excitability [28]. The major developmental disorders giving rise to epilepsy are disorders of neuronal migration that may have genetic or intrauterine causes. Abnormal patterns of neuronal migration lead to various forms of agyria or pachygyria whereas lesser degrees of failure of neuronal migration induce neuronal heterotopia in the subcortical white matter.

Recent experimental data suggest that cortical malformations can both form epileptogenic foci and alter brain development in a manner that diffuse hyperexcitability of the cortical network occurs. Other studies revealed increases in postsynaptic glutamate receptors and decreases in gamma aminobutyric acid receptors in microgyric cortex which could promote epileptogenesis.[2] The GABA hypothesis of epilepsy implies that a reduction of GABA-ergic inhibition results in epilepsy whereas an enhancement of GABA-ergic inhibition results in an anti-epileptic effect. Inhibitory postsynaptic potentials (IPSPs) gradually decrease in amplitude during repetitive activation of cortical circuits. This phenomenon might be caused by decreases in GABA release from terminals, desensitization of GABA receptors that are coupled to increases in Cl^- conductance or alterations in the ionic gradient because of intracellular accumulation of Cl^- In case of intracellular accumulation of Cl^- passive redistribution is ineffective.[93] Moreover, $Cl^- K^+$ co-transport becomes less effective during seizures as it depends on the K^+ gradient. As $Cl^- K^+$ co-transport depends on metabolic processes, its effectiveness may be affected by hypoxia or ischemia as well. These mechanisms may play a critical role in ictogenesis and interictal- ictal transition. Several studies have shown that GABA is involved in pathophysiology of epilepsy in both animal models and patients suffering from epilepsy.

Glutamatergic synapses play a critical role in all epileptic phenomena. Activation of both ionotropic and metabotropic postsynaptic glutamate receptors is proconvulsant. Antagonists of N-methyl-D aspartate (NMDA) receptors are powerful anti-convulsant in many animal models of epilepsy. Abnormalities of CNS catecholamines have been reported in several genetic models of epilepsy. In spontaneous epileptic rat, dopamine was decreased in the nucleus caudatus whereas noradrenaline was increased in midbrain and brainstem. Decreased levels of dopamine have been found in epileptic foci of epilepsy patients. In animal models of absence epilepsy, seizures are exacerbated by dopamine antagonists while fits are alleviated by dopamine agonists. These results suggest that decreased dopamine facilitates appearance of seizures by lowering the threshold triggering such seizures. Affected females present with epilepsy whereas affected males die embryonically. However Recently, a male patient with bilateral periventricular and subcortical heterotopia was described which raises the possibility of a novel gene involved in brain formation. X-linked lissencephaly and double cortex syndrome is another disorder of neuronal migration.

Although various epileptic syndromes were shown to differ pathophysiologically, they apparently share common ictogenesis-related characteristics such as increased neuronal excitability and synchronicity. Emerging insights point to alterations of synaptic functions and intrinsic properties of neurons as common mechanisms underlying hyper excitability. Progress in the field of molecular genetics revealed arguments in favor of this hypothesis as mutations of genes encoding ion channels were recently discovered in some forms of human

epilepsy. Antiepileptic drugs that are presently in clinical use include phenytoin, carbamazepine, ethosuximide, phenobarbitone, tiagabine, vigabatrin, gabapentin and clonazepam are the major drugs used for the treatment of epilepsy. The drug anti-epileptic drug phenytoin acts by blockade of voltage dependent sodium channels and stabilizes the neuronal membrane. It inhibits the generation of repetitive action potentials. Voltage dependent Na+ channels enter an inactivated state and delay the recovery of these channels from inactivation. AEDs have prominent side effects and fail to alter the course of epileptic complications. Dyskinesia, gingival hypertrophy, macrocytic anaemia, dermatitis, thyroiditis, taste disturbance, loss of appetite, dizziness, headache, flushing, increased urine output, gastrointestinal disturbance, skin rashes, drowsiness, overgrowth of hair, acne, hair loss, constipation, diarrhoea, double vision, insomnia, attention difficulties, visual disturbance, cough, weight changes, abdominal pain are the adverse effect produced, which make more disturbance in medication periods of patients.

In the present study the EEMP was evaluated for its anti-epileptic activity in experimental Rats. The Leaves of Mussaenda philippica has been used extensively in traditional medicines for various ailments. The leaves contain high levels of polyphenols such as anthocyanins and phenolic acids and are a good source of vitamins A, B and C, iron, calcium and phosphorus. Mussaenda philippica has been reported to possess antioxidant, anti-diabetic, wound healing, anti-ulcer, anti-bacterial, and anti-mutagenic activities. It is also used as an immune booster and for relief of gastrointestinal and upper respiratory symptoms. [61]

Maximal electroshock (MES) induced epilepsy in wistar rats:

Flexion is the first stage in convulsive epilepsy, where the bending of joints, limbs occur.

At this stage the rapid onset of a rigid posture with head flexed forwards, elevation of both arms, and flexion of the trunk forwards at the thigh. Convulsion induced by MES treated with EEMP for 21 days shows significant reduction in flexion phase, which elicits antiepileptic effect.

Extensor is the next stage followed by flexion, where limb extension occurs. Both flexion and extensor occur at very short duration. Convulsion induced by MES treated with EEMP for 21 days shows significant reduction in **Extensor** phase, which elicits antiepileptic effect.

Clonus stage in seizures consist of bilaterally synchronous involuntary muscle jerks that results in singly or in a brief salvo of repeated jerks. **Stupor** is characterized by impaired reaction to external stimuli, stuporous state is rigid, mute and only appear to be conscious, as the eyes are open. Convulsion induced by MES treated with EEMP for 21 days shows significant reduction in Clonus and Stupor phase

Recovery- Convulsion induced by MES treated with EEMP for 21 days shows significant reduction in **Recovery** period which elicits antiepileptic effect.

The Maximal electroshock induced seizures produce repetitive stimulation of high frequency action potentials thus opening of Na^{+} channels and increasing Ca^{2+} intracellularly leading depolarisation of cell. It has been found out that treatment of Rats with Mussaenda philippica. showed significant decrease in the hind limb extensor period. Animal models of seizures induced by electrical stimulation convey the advantage of reproducing epileptogenic features in the intact brain with low mortality and high reproducibility. Moreover, unlike chemical-induced seizures, postictal alterations from electrical stimulation can be investigated when the epileptogenic cause is no longer present. However, seizure modelling by electrical stimulation does not provide cell-type specificity in the brain. In addition, stimulation protocols can be costly and laborious when used for chronic studies [115]

GABA is an inhibitory neurotransmitter and glutamate is an excitatory neurotransmitter which is responsible for the production of excitation of neurons thus plays an important role in the generation of seizures. The Maximal Electroshock (MES) induced seizure showed significant decreased levels of GABA in brain, thus showing that GABA plays an important role in the inhibition of seizures i.e., The percentage protection in MES induced seizure, treated with EEMP is significantly increased when compared to MES alone induced seizure groups. GABA level in MES induced seizure, treated with EEMP is significantly increased when compared to MES alone induced seizure group.

CONCLUSION

The leaves of Mussaenda philippica. showed reduction in the flexion, extensor, clonus and stupor duration in MES induced epilepsy model. Which shows the antiepileptic activity of EEMP Hence the Ethanolic extract of Mussaenda philippica can be used in Grandmal epilepsy. The leaves of Mussaenda philippica. showed reduction in morbidity and mortality of animals in INH induced epilepsy model, which shows the antiepileptic activity of EEMP. Hence the Ethanolic extract of Mussaenda philippica can be used in TLE (Temporal Lobe Epilepsy. The Histopathology of brain showed normal architecture and there is increased neuronal density which is comparable with phenytoin. GABA level is increased in EEMP treated group, so the drug may probably act by GABA mechanism by Inhibiting the GABA transaminase enzyme or by increasing the synthesis of GABA.

The Standard drug Diazepam acts by GABA mediated mechanism. Hence it is used in the treatment of Epilepsy. As like Diazepam, the EEMP also shows increase in GABA level as it contain the active constituent GABA in it. Hence it is used in treatment of epilepsy. Thus, it may be concluded that Mussaenda philippica produces significant Anti-Epileptic activity in both MES and INH induced epilepsy in Wistar Rats, which is comparable with that of Phenytoin and Diazepam. Further work is necessary to elucidate the mechanism of action involved in the antiepileptic activity of Mussaenda philippica with special reference to Phytochemical constituents.

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