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Research Paper

LAGGERA AURITA LINN. LEAF EXTRACT: ANTIEPILEPTIC STUDIES IN ALBINO MICE AND RATS

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Abstract:
The plant Laggera aurita (Asteraceae) is a commonly utilized medicinal plant growing as a weed in African countries used in the treatment of many diseases. Besides, several phytochemical and pharmacological studies were conducted to check its phytocompounds and therapeutic potentials. However, there is unavailable information on the plant documenting its ethnomedicinal uses and medicinal properties. Therefore, the current research aims to provide updated information on the ethnomedicinal values, phytochemical compounds, and therapeutic potentials regarding anticonvulsant effects of Laggera aurita for further studies to develop noble bioactive molecules.

Keywords*: Epilepsy, Anticonvulsant studies, Laggera aurita linn, Albino mice, Wistar rats.*

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I. Introduction:

The use of plants as medicine is an ancient practice common to all societies especially the African society and this practice continues to exist in the developing nations. It is on this basis that researchers keep searching for medicinal plants in order to produce the best for physiological uses as medicines (Usman and Osuji, 2007). The medicinal value of plants lies in some chemical substances that produce a definite physiological action in the human body**.**

The most important of these bioactive compounds of plants are alkaloids, flavonoids, tannins and phenolic compounds (Edeoga et al.,2005). The use of medicinal plants as traditional medicines is well known in rural areas of many developing countries (Sandhu and Heinrich, 2005) and traditional healers claim that their medicine is cheaper, more effective and impart least side effects as compared to synthetic medicines**.**

Epilepsy:

Epilepsy is defined as a chronic disorder of the central nervous system of various etiologies characterized by recurrent seizures due to excessive discharge of cerebral neurons (Olubunmi, 2006). Seizure can be defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Malvi et al., 2011). International League Against Epilepsy (ILAE) and international Bureau for Epilepsy (IBE) in 2005 defined Epilepsy as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychologic, and social consequences of this condition (Fisher et al., 2005).

Etiology of Epilepsy:

Epileptic conditions are multifactorial disorders in which the action of more than one gene together with environmental factors contributes to the disease phenotype (Todorova et al., 1999). Epilepsy is characterized by abnormal synchronized discharge of neurons leading to alterations in electroencephalograph activity and behavior, it may result from long lasting phasic changes in the brain affecting neurotransmitter release and transport, the properties of receptors and channels, synaptic reorganization and astrocyte activity (Sierra et al., 2007).

Three important factors have been implicated in the etiology of epilepsy. The first factor is predisposition, or threshold. The ease with which a seizure can be provoked, or an epileptic condition can be induced, is referred to as a threshold. Individual differences in threshold are largely attributable to genetic

variations but could also be acquired via different means e.g. certain types of perinatal injuries which can alter threshold. Threshold is a dynamic phenomenon which varies throughout the day, and it also changes in relation to hormonal influences during the menstrual cycle in women (Omeret al., 2011). Patients with a high seizure threshold can experience severe epileptogenic brain injuries and precipitating factors but never have seizures, while those with low seizure thresholds can develop epilepsy with minimal insults and, in many, from precipitating factors alone (provoked seizures).Stimulant drugs lower seizure threshold and sedative drugs increase it but withdrawal from sedative drugs can lower threshold and provoke seizures, however, Antiepileptic drugs work by increasing seizure threshold (Fisher et al., 2005).

The second important factor for epilepsy is the epileptogenic abnormality itself which is attributable to identifiable brain defects including brain malformations, infections, vascular disturbances, neoplasms, scars from trauma, including strokes, and disorders of cerebral metabolism. Treatment for this abnormality is most effective if it is directed at the underlying cause and the most common type of epilepsy related is temporal lobe epilepsy (TLE), usually associated with a characteristic lesion called "hippocampal sclerosis". Hippocampal sclerosis appears to be caused by cerebral injury within the first few years of life in individuals with a genetic predisposition to this condition and it is relatively found among elderly people over the age of 85 years (Nelson et al., 2011). Some forms of epilepsy are unassociated with identifiable structural lesions or diseases and are usually unassociated with other neurological or mental deficits. These are genetically inherited, generally easily treated with medications without sequelae, and referred to as idiopathic epilepsies (Sheth and Hermann, 2007).

The third important factor is the precipitating condition, which determines when seizures occur. Common precipitating factors include fever for children with febrile seizures, alcohol and sedative drug withdrawal, hypoglycemia, anoxia sleep deprivation, stimulant drugs and in some patient's stress. Reflex seizures are precipitated by specific sensory stimuli. The most common are photosensitive seizures induced by flickering light, but some patients have very specific reflex epilepsy with seizures precipitated by such stimuli as being startled, particular types of music, certain visual patterns, reading (NINDS, 2003). Identification of precipitating factors is helpful if they 10 can be avoided, but in most patients specific precipitating factors are not apparent, and may not exist at all.

Classification of Seizures:

Optimum treatment of seizure disorders requires accurate classification of seizure type as well as appropriate choice and use of medication. The seizure classification used is based on the international classification of epileptic seizures (Dreifuss, 1989).

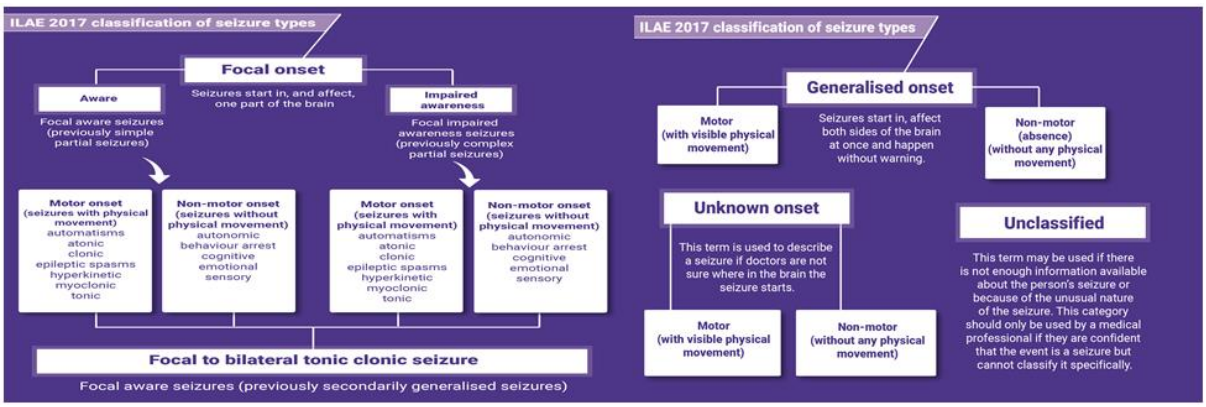


Fig.1 Classification of Seizures

Mechanism of Epileptogenesis:

Epileptogenesis is the process by which the previously normal brain is functionally altered and biased towards the generation of abnormal increase in electrical activity that subserves chronic seizures (Goldberg and Douglas, 2013). A widely accepted hypothesis holds that during the interval between brain injury and the appearance of clinically obvious seizures (latent period) which characterizes many (if not all) cases of epilepsy, there is a cascade of poorly understood changes that transform the non-epileptic brain into one that generates spontaneous recurrent seizures (Pitkanen and Lukasiuk, 2009). This insult-induced process, which is of variable length in different patients and ultimately leads to chronic epilepsy is called epileptogenesis.

Neurotransmitters and Epilepsy:

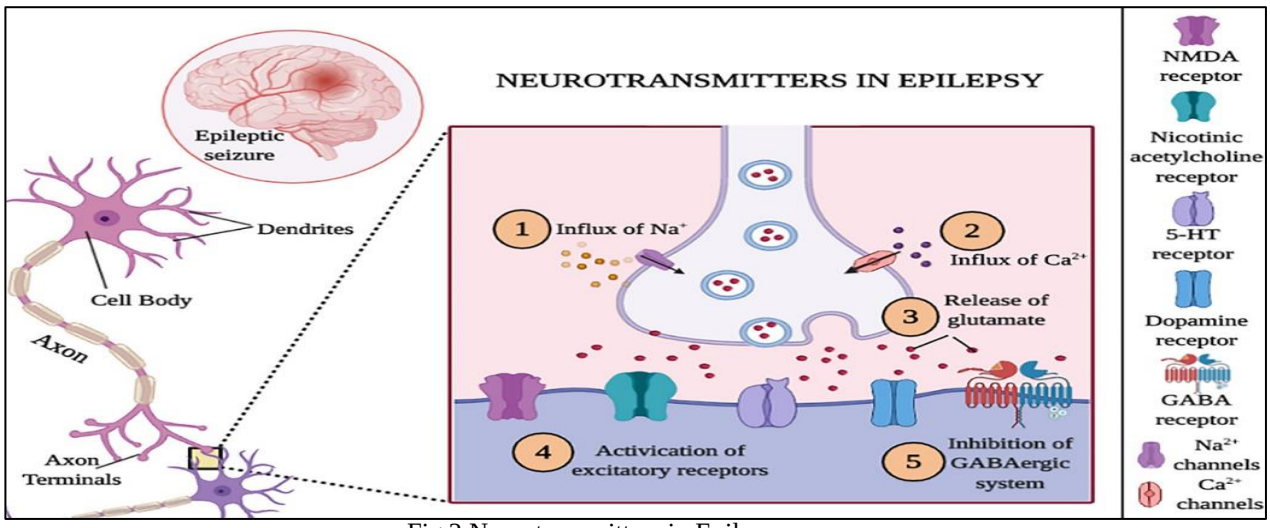


Fig.2 Neurotransmitters in Epilepsy

Diagnosis of Epilepsy:

Seizures can be confused with the symptoms of a number of other conditions. For this reason, four distinct methods are relied upon to properly diagnose epilepsy. These methods are; history, examination, electroencephalography (EEG) and magnetic resonance imaging (MRI).

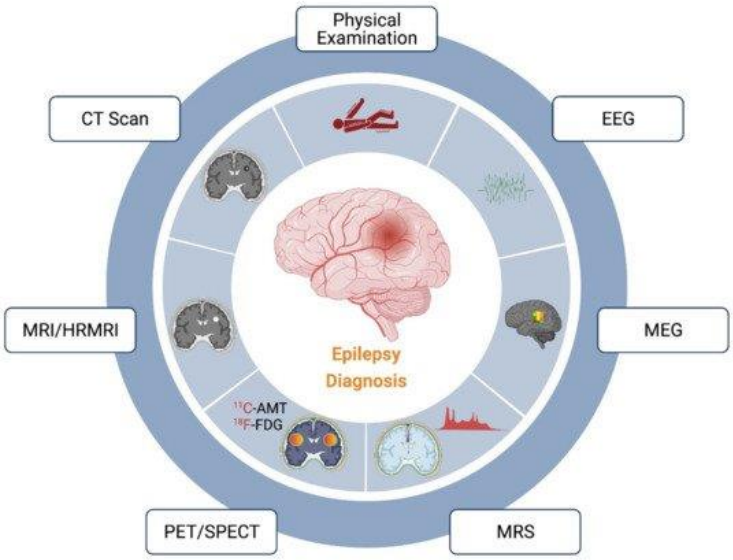


Fig.3 Diagnosis of Epilepsy

Treatment of Epilepsy:

Anticonvulsants, more accurately called antiepileptic drugs (AEDs) are a diverse group of drugs used in the treatment of epileptic seizures. They are sometimes referred to as anti-seizure drugs. For effective treatment of epileptic seizures, it is very important to choose appropriately anticonvulsant of maximal benefit with minimal adverse effects.

Chemical Class	Examples of antiepileptic drug
Barbiturates	Phenobarbitone, Mephobarbitone, Primidone
Hydantoins	Phonations, Mephenytoin
Iminostilbene	Carbamazepine
Oxazolidinedione	Trimethadione (Troxidone)
Succinimide	Ethosuximide
Aliphatic Carboxylic acid	Valproic acid (Sodium valproate)
Benzodiazepines	Clonazepam, Diazepam
Acetyl urea	Phenacemide
Newer drugs	Progabide, Vigabatrin, Gabapentin Lamotrigine, Felbamate, Topiramate, Tiagabine
Miscellaneous	Acetazolamide, Dexamphetamine

Drug Profile:
Plant Name: *Laggera aurita linn* (Asteraceae)
Description:
Laggera aurita Linneus (Asteraceae) also known as *Blumea aurita* is a viscid, crisped pubescent annual plant. The upper leaves are amplexicaul, while lower ones are spathulate, all with sharply dentate margins. Flowers are yellow, tubular, sometimes mixed with a few broad ligulate. *Laggera aurita Linneus* (Asteraceae) belongs to the family of Asteraceae and it is an annual herbaceous plant which is found growing as weeds in India, Nigeria and spread throughout the sub-Saharan Africa & Asian region.

Fig.4 *Laggera aurita linn*

Taxonomical Classification
Kingdom: *Plantae*
Phylum: *Magnoliophyta*
Class: *Magnoliopsida*
Order: *Asterales*
Family: *Asteraceae*
Genus: *Laggera*
Species: *Aurita*
Name: *Laggera aurita*

Phytochemical constituents of the plant:
Phytochemical analysis showed that sesquiterpenoids, monoterpenoids and some flavonoids with some bioactivities have been isolated from the whole plant of *Laggera aurita*. Recent study revealed the presence of tannins, saponins and carbohydrates.

Ethnomedicinal uses:
Ethnobotanical investigations in the central region have shown that *Laggera aurita* is widely used in traditional medicine to treat various kinds of diseases such as malaria, fever, pain, stomatitis, asthma, bronchitis and nasal congestion and has also antibacterial activity.
The plant has been reported for use in cereal grains preservation in Cameroon and in Nigeria as remedy for pediatric malaria. The plant has also acclaimed to have anticonvulsant activity. Previous studies have shown that *Laggera aurita* possesses antiviral, antibacterial and hepatoprotective properties. Essential oils from the leaves are used for the treatment of different diseases including cancer and cardiovascular diseases, in atherosclerosis and thrombosis. Anti-inflammatory and anti-norcitative properties of the plant has also been reported.

Fig.5 Flowers and leaves of *Laggera aurita linn* plant

II. Materials And Methods:

Experimental Animals

The pharmacological experiments were conducted using adult Swiss Albino mice of both sexes (20-26 g), Wister rats of both sexes(160-240g) obtained from Animal House, Department of Pharmacology and Therapeutics, Sardar Patel University. The animals were housed in a standard cage at room temperature and then allowed to acclimatize with the laboratory environment for at least five days prior to the commencement of the experiments. The animals were fed with standard pelletized feed and water was provided *ad libitum*. All experiments performed on laboratory animals were in accordance with the Sardar Patel University Research Policy Guidelines.

Plant Extraction

The leaves of *Laggera aurita* plant were air dried under shade. The leaves were then crushed into a coarse powder with the aid of a mortar and pestle. A portion (500g) of the powdered leaves was extracted with 1 Litre of absolute methanol for 8 hours using Soxhlet method of extraction. The solvent was collected in a round bottom flask where it was decanted into an evaporating dish and evaporated to dryness over water bath maintained at about 50˚C. The dried methanol leaf of *Laggera aurita* was stored in an airtight container. The solutions of the extract were always freshly prepared for each study by dissolution of the appropriate amount required in deionized water under standard laboratory conditions.

Preliminary phytochemical studies

Preliminary phytochemical screening of the methanol leaf extract of *Laggera aurita* was carried out according to the methods described by Trease and Evans, 2002. Like Carbohydrates, Alkaloids, Saponins, Tannins, Flavonoids, Steroids and Terpenoids.

Acute toxicity study (LD50 determination):

Median lethal dose (LD50) was investigated in rats and mice using the method of Lorke (1983). The study was divided into 2 phases. In the first phase, nine animals were divided into 3 groups of 3 animals per group. Group 1 received the extract at a dose of 10 mg/kg body weight while groups 2 and 3 received extract at doses of 100 and 1000 mg/kg body weight respectively. The animals were observed for signs and symptoms of toxicity including death within 24 hours after treatment. In the second phase, 4 groups each comprising of one mouse/rat was treated with the methanol extract of *Laggera aurita* using four specific doses of the extract which was dependent on the outcome of the first phase. The LD50 value was calculated as the square root of the product of the lowest lethal dose and the highest non-lethal dose i.e., the geometric mean of consecutive doses for which 0 and 100% survival was recorded.

Anticonvulsant Studies:

Pentylenetetrazole-induced seizure (Sc-PTZ) test in mice

The method of Swinyard et al (1952) was employed. Thirty mice were randomly divided into 5 groups of six mice each. The first group which served as negative control was treated with normal saline (i.p.), while groups 2 – 4 received graded doses of the aqueous ethanol extract reconstituted in water (600, 300 and 150 mg/kg, i.p. respectively). Group 5 which served as positive control was treated with 200 mg/kg i.p. sodium valproate. Thirty minutes later, 90 mg/kg of freshly prepared solution of pentylenetetrazole was administered subcutaneously to all the mice. The mice were observed for 30 minutes for onset and incidence of seizures. An episode of clonic spasm of at least 5seconds duration was considered as seizure. Lack of clonic spasm during 30 minutes of observation was regarded as protection. The number of mice protected was noted and the antiepileptic activity of the extract expressed as percentage protection.

Strychnine – induced seizure test in mice

The method described by Krall et al (1978) was adopted. Thirty mice were randomly divided into 5 groups of six mice each. Group 1 served as a negative control and received normal saline (10 ml/kg i.p.), while groups 2 – 4 received the extract at a dose of 600, 300 and 150 mg/kg (i.p.) respectively. Group 5 which served as the positive control received phenobarbitone (30 mg/kg i.p). Thirty minutes later, 1.0 mg/kg of 43 freshly prepared solution of strychnine was administered subcutaneously to all the mice. The mice were observed for presence or absence of tonic convulsion and latency to death within a 30 minutes period.

Picrotoxin – induced seizure test in mice

The method described by Swinyard et al (1989) was adopted. Thirty mice were randomly divided into 5 groups of six mice each. Group 1 served as a negative control and received normal saline (10 ml/kg i.p.), while groups 2 – 4 received the extract at a dose of 600, 300 and 150 mg/kg (i.p.) respectively. Group 5 which served as the positive control received Diazepam (10 mg/kg, i.p). Thirty minutes later, 4 mg/kg of freshly prepared solution of picrotoxin was administered subcutaneously to all the mice. The mice were observed for presence or absence of tonic hind limb extension within a 30 minutes period. Prolongation of the latency of tonic hind limb extension was also considered as indication of anticonvulsant activity.

Pentylenentetrazole – induced kindling model in rats

The method described by Gupta et al (2001); Dhir et al (2007) was employed. A sub – convulsive dose of 35 mg/kg of PTZ was injected i.p. every 48 hours (Zhang et al., 2003), for 20 days. Fourty rats were divided into five groups of eight rats each. Group 1 served as a negative control and received normal saline 1 ml/kg i.p, Groups (2 – 4) received the extract at a dose of (600, 300 and 150 mg/kg i.p.) respectively. Group 5 received Sodium Valproate (100 mg/kg i.p.). Thirty minutes post treatment, all the groups were administered pentylenetetrazole (PTZ) and the rats were observed for seizure intensities within a 20 minutes period and classified as follows: Stage 0: no 44 response, stage 1: ear and facial twitching, stage 2: convulsive waves throughout the body, stage3: myoclonic jerks, rearing, stage 4: turning over onto one side, stage 5: turning over onto the back, generalized tonic-clonic seizures (Wu et al., 2006).

III. Result:

Percentage Yield of the Plant Extract of *Laggera aurita*

The extraction of the powdered leaf of *Laggera aurita* with 90% methanol afforded a yield of 20.4% w/w.

Phytochemical Constituents of Methanol Leaf Extract of *Laggera aurita*

Preliminary phytochemical screening of the methanol leaf extract of *Laggera aurita* revealed the presence of alkaloids, flavonoids, saponins, steroids/terpenoids, and tannins (Table 1).

Sr. No.	Phyto-Constituents	Present/Absent
1	Alkaloids	++
2	Anthraquinones	-
3	Flavonoids	+
4	Saponins	++
5	Steroids/Terpenoids	+
6	Tannins	+
7	Cardiac glycosides	+

Table1: Preliminary phytochemical screening tests

Median Lethal Dose (LD50) Values of Methanol Leaf Extract of *Laggera aurita* in Mice and Rats

The intraperitoneal median lethal dose (LD50) values of the methanol leaf extract of *Laggera aurita* in both mice and rats was found to be 2154.05 mg/kg while the oral (LD50) value was found to be greater than 5000 (Table 2).

Species	Routes of administration	LD_{50} Values (mg/kg)
Mice	Intraperitoneal	2154.06
Mice	Oral	>5000
Rats	Intraperitoneal	2154.06
Rats	Oral	>5000

Table 2 Median lethal dose Values of Methanol Leaf Extract of *Laggera aurita* in Mice and Rats

Effect of Methanol Leaf Extract of *Laggera aurita* on Pentylenetetrazole induced Seizure in Mice

The methanol leaf extract of Laggera aurita offered protection against seizures induced by pentylenetetrazole (90 mg/kg).

Treatment (mg/kg)	Mean	Onset of Seizure (min)	% Protection against Seizure	% Protection against Mortality
N/S (10ml/kg)	6.83	±1.11	0.001	6.67
LAME (600)	15.67	15.67±1.67*5	0.006	6.67
LAME (300)	10.60	10.60±0.93	16.67	6.67
LAME (150)	11.17	11.17±0.87	0.005	0.00
SV (200)	13.50	13.50±1.50*6	6.67	100

Table 3 Effect of Methanol Leaf Extract of *Laggera aurita* on Pentylenetetrazole induced Seizure in Mice

Effect of Methanol Leaf Extract of *Laggera aurita* on Strychnine-Induced Seizure in Mice

The methanol leaf extract of Laggera aurita at 300 mg/kg offered 50% protection against strychnine-induced seizure.

Treatment (mg/kg)	Mean	Onset of Seizure (min)	% Protection against Seizure	% Protection against Mortality
N/S (10ml/kg)	5.17	±0.17	0.001	6.67
LAME (600)	12.00	12±1.00*1	16.67	33.33
LAME (300)	12.67	12.67±0.67*5	16.67	6.67
LAME (150)	12.20	12.20±1.071	0.003	3.33
PBT (30)	100	100±1.50*6	6.67	16.67

Table 4 Effect of Methanol Leaf Extract of Laggera aurita on Strychnine Induced Seizure in Mice

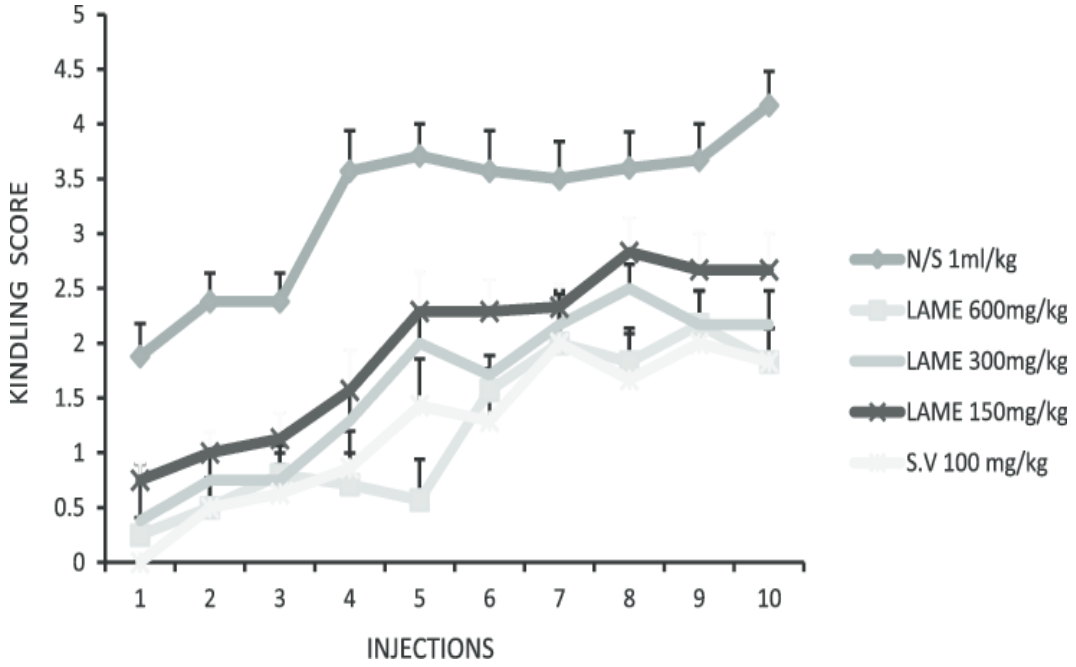
Effect of Methanol Leaf Extract of *Laggera aurita* on Picrotoxin Induced Seizure in Mice

Treatment (mg/kg)	Mean	Onset of Seizure (min)	% Protection against Seizure	% Protection against Mortality
N/S (10ml/kg)	9.33	±0.99	0.001	6.67
LAME (600)	20.50	20.50±1.44*3	3.33	33.33
LAME (300)	20.00	20.00±1.45*1	6.671	6.67
LAME (150)	15.00	15.00±1.15	0.001	6.67
DZP (10)	0.00	0.0	100	100

Data presented as Mean SEM and Percentage, n = 6; *p 0.05 (One-way ANOVA) followed by Posthoc test (Scheffe) for multiple comparison; N/S = Normal saline, DZP= Diazepam LAME = *Laggera aurita* Methanol Extract.

Effect of the Methanol Leaf Extract of *Laggera aurita* on Pentylenetetrazole Induced Kindling in Rats

The extract at all doses tested reduced the kindling scores induced by sub convulsive dose (35 mg/kg) of pentylenetetrazole. The reduction as recorded by seizure scoring model was generally statistically significant ($p<0.05$) throughout the treatment days.



Effect of the Methanol Leaf Extract of Laggera aurita on Pentylenetetrazole induced Kindling in Rats

LAME = Laggera aurita Methanol Extract, N/S = Normal Saline, S.V = Sodium Valproate.

IV. Discussion:

Recent research by Abdullah et al., (2013) established that *Laggera aurita* possesses triterpenes, flavonoids, saponin, coumarins, tannins and alkaloids as some of its active constituents. Phytochemical screening provides basic information about the different classes of secondary metabolites present in a plant and the medicinal importance of such plant (Shabbir et al., 2013). The preliminary phytochemical screening of the methanol leaf extract of *Laggera aurita* revealed the presence of alkaloids, flavonoids, saponins, tannins, steroids/terpenoids, glycosides, carbohydrates, and cardiac glycosides. Based on the results obtained from the phytochemical screening, it is not possible to attribute with certainty the observed anticonvulsant effect of *Laggera aurita* to one or several active principles amongst those detected in the phytochemical screening. However, triterpenic steroids and saponins have been reported to possess anticonvulsant activity in experimental seizure models such as MEST and Sc PTZ (Kasture et al., 2002; Chaunhan et al., 1988).

Some alkaloids and flavonoids have also been shown to exhibit protective effects against PTZ convulsions. Studies have revealed that flavonoids have neuroprotective effect against electrical kindling in rats (Tourandokht et al.,2010). The presence of these phytochemical constituents might be responsible for the observed pharmacological activities of the crude methanol leaf extract of *Laggera aurita* in the tests conducted. 64 Median lethal dose (LD50) determination is of importance because it is a valuable tool employed to compare toxicities of compounds relative to their therapeutic doses (Berkowitz, 2004). The extract at all doses was able to reduce the severity of the seizure by not allowing the seizure to reach the classical seizure stage and this suggest that the extract could have antiepileptogenic activity.

V. Conclusion:

The methanol leaf extract of *Laggera aurita* possesses significant anticonvulsant and has antiepileptogenic properties.

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