ANTIEPILEPTIC ACTIVITY AND NEUROPHARMACOLOGICAL SCREENING OF METHANOLIC EXTRACT OF *LEPTADENIA RETICULATA* AGAINST DIFFERENT EXPERIMENTAL MODELS

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Abstract

Epilepsy is a chronic neurological disorder characterized by recurrent unprovoked seizures resulting from abnormal and excessive neuronal activity in the brain. Although several synthetic antiepileptic drugs are available, a considerable proportion of patients continue to experience inadequate seizure control or adverse effects, creating interest in plant-derived compounds with potential neuropharmacological activity. *Leptadenia reticulata* (Retz.) Wight & Arn., commonly known as Jivanti, is a medicinal plant traditionally used in South Asian systems of medicine and contains a variety of phytoconstituents including flavonoids, sterols, triterpenoids, phenolic compounds, and related secondary metabolites. The purpose of this study is to evaluate the reported antiepileptic potential and neuropharmacological profile of the methanolic extract of *L. reticulata* using established experimental models and to discuss possible mechanisms of action. A literature-based experimental analysis was conducted with emphasis on maximal electroshock, pentylenetetrazol, lithium–pilocarpine status epilepticus, and neurobehavioral screening approaches. Previous experimental work has reported that methanolic extract of *L. reticulata* demonstrated meaningful protection in maximal electroshock- and pentylenetetrazol-induced seizure models, whereas its activity was less pronounced in lithium–pilocarpine-induced status epilepticus [1,2]. These findings suggest that the extract may influence mechanisms associated with seizure propagation and inhibitory neurotransmission. The presence of flavonoids such as apigenin, rutin, luteolin-related compounds, and other bioactive constituents may contribute to these effects through antioxidant, neuroprotective, or neurotransmitter-modulating mechanisms. However, the currently available evidence remains primarily preclinical. Further studies are required to isolate active compounds, define molecular targets, establish dose–response relationships, and evaluate long-term safety before therapeutic conclusions can be drawn.

Keywords: *Leptadenia reticulata*, antiepileptic activity, methanolic extract, neuropharmacology, maximal electroshock, pentylenetetrazol, status epilepticus, medicinal plants.

Introduction

Epilepsy is one of the most common chronic neurological disorders and is characterized by a persistent tendency toward recurrent seizures. Seizures develop when the normal balance between excitatory and inhibitory neuronal activity becomes disturbed, producing excessive synchronized electrical discharges within neuronal networks.

The mechanisms underlying epilepsy are complex and may involve altered ion-channel function, excessive glutamatergic excitation, impaired gamma-aminobutyric acid-mediated inhibition, inflammatory signaling, oxidative stress, mitochondrial dysfunction, and structural neuronal abnormalities.

Conventional antiepileptic drugs act through several mechanisms, including enhancement of GABAergic neurotransmission, inhibition of voltage-gated sodium or calcium channels, modulation of synaptic vesicle proteins, and reduction of excitatory neurotransmission.

Despite the availability of multiple pharmacological options, not all patients achieve adequate seizure control. Adverse effects such as sedation, cognitive impairment, dizziness, behavioral changes, hepatotoxicity, and drug interactions can also complicate long-term treatment.

These limitations have encouraged continued investigation of medicinal plants as potential sources of novel anticonvulsant agents.

Leptadenia reticulata is a perennial climbing plant belonging to the family Apocynaceae and is widely known in traditional Ayurvedic medicine as Jivanti. It has historically been used for several conditions and is recognized for its rejuvenating and medicinal properties [2,3].

Phytochemical investigations have identified numerous compounds in the plant, including β-sitosterol, γ-sitosterol, phytol, α-amyrin, β-amyrin, apigenin, rutin, diosmetin, reticulin, deniculatin, and leptaculatin [3].

More recent phytochemical studies have confirmed that *L. reticulata* possesses a chemically diverse metabolite profile, which may help explain its wide range of experimentally reported biological activities.

Among its pharmacological properties, antiepileptic activity has received particular attention.

Pushpa et al. evaluated the methanolic extract of *L. reticulata* in several experimental seizure and neuropharmacological models and reported notable activity in maximal electroshock and pentylenetetrazol models, while activity was weaker in lithium–pilocarpine-induced status epilepticus [1]. This experimental finding has subsequently been summarized in broader pharmacological reviews of the plant.

The purpose of this article is to analyze the antiepileptic and neuropharmacological potential of the methanolic extract of *L. reticulata*, with emphasis on the interpretation of different seizure models and possible biochemical mechanisms responsible for the observed effects.

Materials and Methods

This article was prepared as a literature-based experimental analysis of the reported neuropharmacological activity of methanolic *L. reticulata* extract.

Published studies and comprehensive reviews concerning the phytochemistry, pharmacology, and antiepileptic effects of *L. reticulata* were analyzed.

The principal experimental models considered were maximal electroshock-induced seizures, pentylenetetrazol-induced seizures, lithium–pilocarpine-induced status epilepticus, and general neuropharmacological screening.

These models were selected because they represent different mechanisms of seizure induction and can therefore provide complementary information regarding possible anticonvulsant action.

The maximal electroshock model is commonly used to evaluate the ability of a test compound to inhibit seizure spread and generalized tonic extension.

The pentylenetetrazol model is particularly useful for identifying substances that increase seizure threshold and may influence inhibitory neurotransmission.

Lithium–pilocarpine-induced status epilepticus represents a more complex model involving prolonged seizure activity and extensive cholinergic excitation.

The available experimental literature was interpreted together with known phytochemical constituents of *L. reticulata* to identify plausible relationships between extract composition and observed neuropharmacological effects.

Results

The available evidence indicates that methanolic extract of *L. reticulata* possesses measurable anticonvulsant activity in selected experimental models.

One of the most important findings concerns the maximal electroshock model.

In the reported experimental study, the maximal electroshock stimulus was applied at an intensity of approximately 150 mA for 0.2 seconds. Methanolic extract of *L. reticulata* demonstrated significant protection against electroshock-induced seizures [1].

The maximal electroshock model is particularly associated with generalized tonic–clonic seizure activity and seizure propagation.

Substances that reduce tonic hind-limb extension in this model are generally considered capable of limiting the spread of abnormal neuronal discharges.

Therefore, the activity of *L. reticulata* in this model suggests a possible influence on neuronal excitability or ion-channel-dependent seizure propagation.

The extract was also evaluated against pentylenetetrazol-induced seizures.

Pentylenetetrazol is a chemoconvulsant that reduces inhibitory GABAergic activity and produces generalized seizures at sufficiently high doses.

The reported study used approximately 70 mg/kg pentylenetetrazol administered intraperitoneally and found that methanolic *L. reticulata* extract produced a significant anticonvulsant effect [1,2].

This finding is pharmacologically important.

Protective activity in the pentylenetetrazol model may indicate that the extract increases seizure threshold, supports inhibitory neurotransmission, or interferes with mechanisms that facilitate chemically induced convulsions.

In contrast, the extract showed comparatively limited effectiveness in lithium–pilocarpine-induced status epilepticus [1].

The lithium–pilocarpine model produces prolonged and severe seizures through complex cholinergic and downstream excitatory mechanisms.

Reduced activity in this model suggests that the methanolic extract does not provide equal protection against all forms of experimental seizure activity.

This difference between models is an important finding rather than a weakness.

Antiepileptic agents frequently show different levels of effectiveness depending on the mechanism responsible for seizure generation.

The available literature also indicates that the extract was not strongly effective in haloperidol-induced catalepsy, supporting the view that its central nervous system activity may be relatively selective rather than producing broad nonspecific motor suppression [2].

Phytochemical Basis of the Observed Activity

The neuropharmacological activity of *L. reticulata* may be associated with its complex phytochemical composition.

The plant contains flavonoids and related polyphenolic compounds, together with sterols and triterpenoids.

Reported constituents include apigenin, rutin, diosmetin, β-sitosterol, stigmasterol, α-amyrin, β-amyrin, and several species-specific compounds [2,3].

Phytochemical analysis of *L. reticulata* extracts has also demonstrated the presence of flavonoids, including quercetin-related compounds [4].

Flavonoids are particularly relevant to neuropharmacology.

Several flavonoids have been investigated experimentally for effects on GABAergic neurotransmission, oxidative stress, neuroinflammation, and neuronal excitability.

These mechanisms may theoretically contribute to anticonvulsant effects.

However, the precise active compound responsible for the effects of *L. reticulata* has not yet been established.

The methanolic extract represents a mixture of numerous chemical constituents.

Consequently, the observed activity may result from a single dominant compound or from synergistic interactions between several phytochemicals.

Recent metabolomic work has further demonstrated the chemical complexity of methanolic *L. reticulata* extract, with more than one hundred compounds detected in advanced LC–MS-based analyses.

This complexity supports the need for fractionation and activity-guided isolation studies.

Possible GABAergic Mechanism

The activity of the extract in the pentylenetetrazol model suggests that GABAergic mechanisms may be involved.

GABA is the principal inhibitory neurotransmitter in the mammalian central nervous system.

Activation of GABA receptors decreases neuronal excitability and contributes to suppression of excessive electrical activity.

Pentylenetetrazol promotes seizure activity partly by interfering with inhibitory neurotransmission.

Therefore, compounds that increase GABAergic signaling often delay or prevent pentylenetetrazol-induced seizures.

If phytoconstituents in *L. reticulata* enhance GABA receptor function or increase GABA availability, this could explain at least part of the observed anticonvulsant activity.

However, direct receptor-binding or neurochemical studies are required before such a mechanism can be confirmed.

Possible Ion-Channel Effects

The significant effect observed in the maximal electroshock model may indicate a second mechanism involving ion-channel regulation.

Propagation of generalized seizures depends strongly on repetitive neuronal firing.

Voltage-gated sodium channels play an essential role in this process.

Several established antiepileptic drugs suppress sustained high-frequency neuronal firing by stabilizing the inactivated state of sodium channels.

Calcium channels and potassium channels also contribute to regulation of neuronal excitability.

The activity of *L. reticulata* in the maximal electroshock model therefore raises the possibility that some of its constituents may influence membrane excitability.

At present, this remains a pharmacological hypothesis rather than a demonstrated molecular mechanism.

Electrophysiological studies would be necessary to identify direct effects on ion-channel function.

Oxidative Stress and Neuroprotection

Oxidative stress is increasingly recognized as an important component of seizure-induced neuronal damage.

During prolonged seizure activity, mitochondrial metabolism increases and large quantities of reactive oxygen species may be generated.

Excessive oxidative stress can damage lipids, proteins, and nucleic acids.

It may also contribute to mitochondrial dysfunction and neuroinflammation.

L. reticulata has been reported to contain compounds with antioxidant properties, including flavonoids and phenolic constituents [3,4].

These antioxidant effects could theoretically contribute to neuroprotection during seizure activity.

The mechanism may be particularly relevant after repeated or prolonged seizures, where secondary neuronal injury becomes important.

However, antioxidant activity alone cannot fully explain anticonvulsant effects.

It is more likely to represent a complementary mechanism alongside direct effects on neuronal signaling.

Neuropharmacological Screening

Neuropharmacological screening is important when evaluating a medicinal plant extract because apparent anticonvulsant activity can sometimes result from general motor impairment or profound sedation.

For example, a substance that severely reduces locomotor activity may appear to suppress some behavioral manifestations of seizures without having true antiepileptic activity.

Therefore, evaluation of motor coordination, spontaneous activity, sedation, muscle relaxation, catalepsy, and behavioral responses can help distinguish specific anticonvulsant effects from generalized central nervous system depression.

The reported neuropharmacological screening of methanolic *L. reticulata* extract suggested that its effects were not identical across all central nervous system models [1].

This selective response strengthens the need for more detailed mechanistic studies.

Discussion

The available evidence suggests that methanolic extract of *L. reticulata* possesses genuine anticonvulsant potential, particularly in maximal electroshock and pentylenetetrazol models.

These two models represent different seizure mechanisms.

Activity in both may suggest that the extract affects more than one neuropharmacological pathway.

The maximal electroshock result is consistent with inhibition of seizure propagation.

The pentylenetetrazol result suggests an influence on seizure threshold or inhibitory neurotransmission.

The comparatively weak activity in lithium–pilocarpine-induced status epilepticus indicates that the extract may not effectively suppress severe prolonged cholinergic seizure activity.

This difference highlights the importance of using multiple experimental models when evaluating potential antiepileptic substances.

A compound that is effective in one model cannot automatically be considered broadly effective against all seizure types.

The phytochemical composition of *L. reticulata* provides several plausible explanations for its pharmacological activity.

A modern review published in *Natural Product Research* identified multiple biologically active constituents, including apigenin, rutin, diosmetin, phytol, β-sitosterol, α-amyrin, and β-amyrin [3].

Some of these chemical classes have recognized antioxidant, anti-inflammatory, and neuroactive properties.

The combined presence of these constituents may produce a multitarget effect.

This is a common characteristic of medicinal plant extracts.

Unlike conventional drugs that frequently act through one dominant molecular target, crude extracts contain multiple compounds capable of interacting with different pathways simultaneously.

Such complexity may provide pharmacological advantages but also creates major challenges.

Standardization becomes difficult because phytochemical composition may vary according to plant age, geographical origin, season, plant part, extraction method, and storage conditions.

Methanolic extraction may also yield a different chemical profile compared with aqueous, ethanolic, or hydroalcoholic extraction.

Any future development of *L. reticulata* as a standardized neuropharmacological preparation would therefore require chemical fingerprinting and identification of marker compounds.

The existing evidence also needs to be interpreted cautiously.

The key antiepileptic study cited in major reviews was published in 2010 [1], and despite repeated citation, there remains limited independent experimental replication.

The 2017 comprehensive botanical and pharmacological review explicitly noted that much of the biological evidence for *L. reticulata* is based on crude extracts and that many active compounds still require identification [2].

A more recent 2024 review likewise emphasizes the broad phytochemical and pharmacological potential of the plant but does not establish clinical efficacy for epilepsy.

Therefore, the present evidence should be regarded as promising but preliminary.

Future Research Directions

Further investigation should begin with reproducible extraction and standardization.

The methanolic extract should be chemically profiled using techniques such as HPLC, LC–MS/MS, and high-resolution mass spectrometry.

Activity-guided fractionation should then be used to determine which fractions retain anticonvulsant effects.

Isolated compounds should be tested individually and in combination.

Mechanistic studies should evaluate GABA levels, GABA receptor interactions, glutamatergic signaling, voltage-gated ion channels, inflammatory markers, oxidative stress biomarkers, and mitochondrial function.

Additional seizure models could also provide valuable information.

Chronic epilepsy models may be more informative than single acute seizure tests because human epilepsy is a long-term disorder.

Long-term toxicity is another major requirement.

A plant extract that reduces seizures acutely may not necessarily be suitable for chronic administration.

Repeated-dose studies should evaluate hepatic, renal, hematological, neurological, and behavioral safety.

Pharmacokinetic studies are also needed to determine whether active constituents reach the central nervous system at pharmacologically relevant concentrations.

Only after these stages would clinical evaluation become scientifically justified.

Limitations

The main limitation of the current evidence is that the antiepileptic activity of *L. reticulata* is supported primarily by preclinical animal studies.

There is insufficient information on the exact active constituent, molecular target, pharmacokinetics, brain penetration, long-term toxicity, and chronic anticonvulsant effectiveness.

Another limitation is the use of crude methanolic extract.

Different phytochemicals may produce synergistic, additive, or antagonistic effects, making it difficult to assign activity to a specific molecule.

Differences in plant material and extraction procedures may also reduce reproducibility between laboratories.

Finally, experimental seizure models reproduce only selected aspects of human epilepsy.

Positive results in animals should therefore not be interpreted as evidence that *L. reticulata* is an established treatment for epilepsy in humans.

Conclusion

Methanolic extract of *Leptadenia reticulata* demonstrates promising antiepileptic and neuropharmacological activity in experimental seizure models.

The strongest reported effects have been observed in maximal electroshock- and pentylenetetrazol-induced seizures, whereas activity against lithium–pilocarpine-induced status epilepticus appears less pronounced [1,2].

These findings suggest that the extract may interfere with seizure propagation and may also influence inhibitory neurotransmission.

The phytochemical profile of *L. reticulata*, particularly its flavonoids, phenolic compounds, sterols, and triterpenoids, provides a plausible chemical basis for neuroprotective and anticonvulsant activity.

Nevertheless, the evidence remains preclinical.

Further research should isolate the active constituents, determine molecular mechanisms, standardize the extract, evaluate chronic toxicity, and investigate pharmacokinetic behavior.

Therefore, *L. reticulata* should currently be regarded as a promising source of potential neuropharmacological lead compounds rather than as a clinically established antiepileptic therapy.

References

1. Pushpa KB, Mahipal RR, Manasa VB, Mohan BT, Ranganayakulu D. Antiepileptic activity and neuropharmacological screening of methanolic

extract of *Leptadenia reticulata* against different experimental models. *Journal of Advanced Drug Research*. 2010;1:1–8.

2. Swamy MK, Sinniah UR, Ghasemzadeh A. *Leptadenia reticulata* (Retz.) Wight & Arn. (Jivanti): Botanical, agronomical, phytochemical, pharmacological, and biotechnological aspects. *Molecules*. 2017;22(6):1019. doi:10.3390/molecules22061019.
3. Kumari S, Saini R, Bhatnagar A, Mishra A. A comprehensive review on Ayurvedic herb *Leptadenia reticulata* (Jeevanti): A phytochemistry and pharmacological perspective. *Natural Product Research*. 2024;38(23):4234–4260. doi:10.1080/14786419.2023.2282119.
4. Patel RV, Patel VR, Patel MG. Phytochemical evaluation of dried aqueous extract of Jivanti [*Leptadenia reticulata* (Retz.) Wt. et Arn.]. *Ayu*. 2012;33:412–415.
5. Löscher W. Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs. *Seizure*. 2011;20(5):359–368.
6. Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma. *Epilepsia*. 2011;52(4):657–678.
7. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. *Nature Reviews Neuroscience*. 2004;5:553–564.
8. Kandeda AK, Taiwe GS, Moto FCO, et al. Antiepileptogenic and neuroprotective effects of medicinal plant-derived compounds in experimental seizure models. *Frontiers in Pharmacology*. 2021.
9. Halliwell B, Gutteridge JMC. *Free Radicals in Biology and Medicine*. 5th ed. Oxford University Press; 2015.
10. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475–482.