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ORIGINAL ARTICLE

Anticonvulsant Activity of Aqueous Extract of *Andrographis paniculata* Leaves in Wistar Albino Rats

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Abstract

Background: The anticonvulsant effect of Aqueous Extract of *Andrographis paniculata* leaves (AEAP) and its synergistic action with Sodium valproate were evaluated in this research. **Methods:** Anticonvulsant activity of AEAP 500 mg/kg b.w. was evaluated in Wistar albino rats using the Maximal Electroshock Seizure (MES) model and the Pentylenetetrazol (PTZ) seizure model. **Results:** The Extract demonstrated significant anticonvulsant activity in both MES and PTZ seizure models. In the MES model, the anticonvulsant action of plant extract was comparable to that of the standard drug Sodium valproate 300 mg/kg in reducing the duration of Tonic hind limb extension (THLE). AEAP exhibited a synergistic effect with sodium valproate in both MES and PTZ seizure models, resulting in 100% protection. **Conclusion:** AEAP exhibits anticonvulsant action. Additional research is needed to elucidate the precise mechanisms through which *Andrographis paniculata* mediates its anticonvulsant activity.

Keywords: *Andrographis paniculata*, Anticonvulsant action, MES, PTZ

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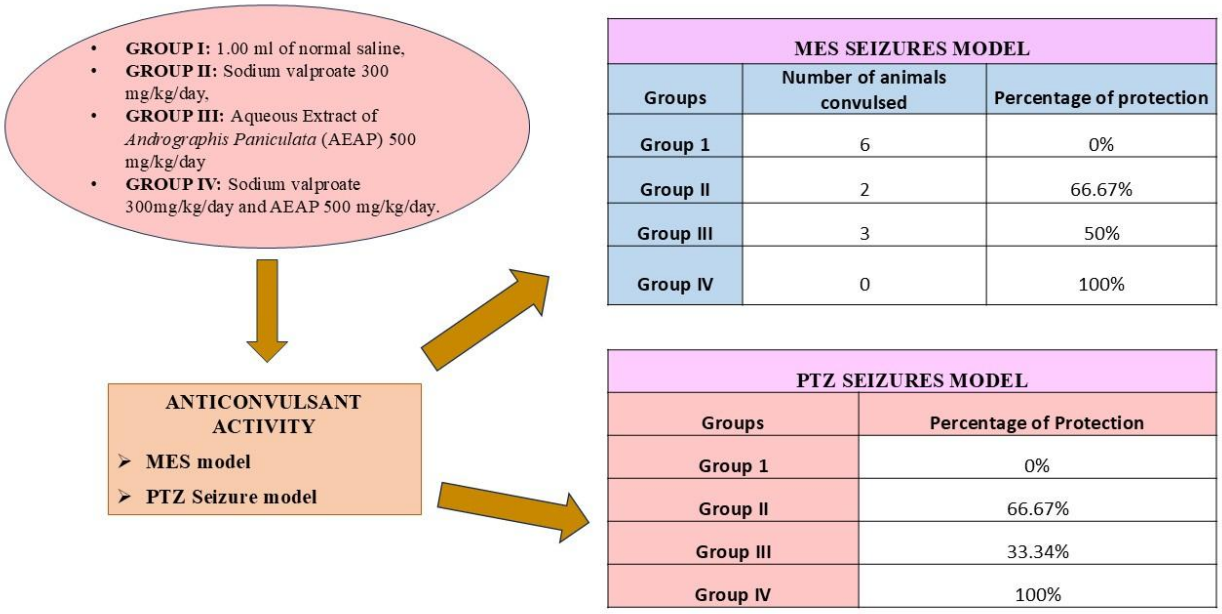
Graphical Abstract



MES SEIZURES MODEL		
Groups	Number of animals convulsed	Percentage of protection
Group 1	6	0%
Group II	2	66.67%
Group III	3	50%
Group IV	0	100%

PTZ SEIZURES MODEL	
Groups	Percentage of Protection
Group 1	0%
Group II	66.67%
Group III	33.34%
Group IV	100%

Introduction

A seizure is a paroxysmal event caused by abnormal, excessive, and asynchronous neuronal activity in the brain. Among the general population, 5-10% has experienced at least one seizure episode in their lifetime. The highest occurrence arises in early childhood and late adulthood. Epilepsy is a neurological condition involving recurrent, unprovoked seizures due to an underlying chronic disorder. The global prevalence of epilepsy is estimated to range from 5 to 10 cases per 1,000 individuals, with an incidence rate between 0.3% and 0.5%. According to the International League Against Epilepsy (ILAE) Commission, seizures are classified into three categories: focal seizures, generalized seizures, and seizures of unknown origin. Absence seizures and tonic-clonic seizures fall under generalized seizures, as they involve widespread electrical discharges throughout the brain [1].

Andrographis paniculata pertains to the family Acanthaceae [2]. It is commonly known as Nilavembu in Tamil and Kalmegh in Hindi. *Andrographis paniculata* and its major bioactive phytoconstituent Andrographolide, exhibit wide range of pharmacological activities. These include anti-inflammatory, analgesic, antipyretic, antimicrobial (active against bacteria, virus, retrovirus, malaria, larva), antidiabetic, hypolipidemic, anti-obesity, anticancer, hepatoprotective, immunomodulator, neuroprotective (effective in Parkinsonism, Alzheimer's, and ischemic conditions), and anti-fertility effects [3-5].

Andrographis paniculata is a widely recognized traditional medicinal plant in many countries, including India. Ethnobotanically, this herb has been used for the treatment of snake bite and bug bite [6,7].

Methanolic extracts of *Andrographis paniculata* leaves demonstrate immunostimulant, antioxidative and nootropic effects (improving cognitive function) in both normal and diabetic rat models [8].

The majority of routinely used anti-epileptic drugs do not prevent or reverse the underlying pathological changes that cause seizures, prompting continued research into newer antiepileptic therapies with improved efficacy and tolerance. 30–40% of patients develop into pharmaco-resistant or intractable epilepsy necessitating the search for alternative treatment options. Herbal medicine plays a vital role in the primary health care in many countries, including India, due to its wide availability and cultural acceptance. In the search for herbal medicines for epilepsy, some of the medicinal plants have potential as safe and effective alternatives [9]. Ajit Kumar Thakur et al. reported that, andrographolide, the active constituent of *Andrographis paniculata, exhibits* Benzodiazepine-like potentiation of pentobarbital induced hypnosis [6,10].

Based on the above considerations, the present study was conducted with the aim of investigating the anticonvulsant potential of the aqueous extract of *Andrographis paniculata* leaves in Wistar albino rats using Maximal Electroshock Seizure and Pentylenetetrazol seizure models, and to evaluate the synergistic effects of combining this extract with sodium valproate in these models.

Materials and Methods

Place and study duration

The study was conducted over a period of three months, from September 2023 to November 2023, at KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu. The study was carried out after obtaining approval from the Institutional Animal Ethics Committee (Approval number: 02/IAEC/2022) of KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu.

Animals

A total of 48 female Wistar albino rats, weighing between 200–220 g, were procured from the institutional animal house. The animals were housed in groups of six per cage under standard laboratory conditions, with a controlled room temperature of 25 ± 1°C. They were provided with free access to food and water *ad libitum*. On the day of the experiment, the animals were fasted for four hours, with no access to food or water prior to the procedure.

Preparation of extract

Fresh *Andrographis paniculata* leaves were collected locally from the Coimbatore district, Tamil Nadu, in September 2023. The aqueous extract was prepared using the maceration method. The collected leaves were shade dried and ground into a coarse powder. A total of 500 g of the coarse powder was boiled in hot water for 30 minutes and then allowed to cool. The decoction was filtered using cotton gauze. The filtrate was then poured into small Petri dishes and dried at room temperature to yield solid residues. The dried extract was stored in an airtight container at 4°C in a refrigerator. Fresh preparations were made from this stock as needed [11].

Drugs

For this study, pentylenetetrazol (PTZ) was obtained from Sigma (USA), and sodium valproate was sourced from Sanofi India Ltd. PTZ was administered intraperitoneally to induce seizures, while sodium valproate, served as the standard reference drug, was given orally. All drug solutions were freshly prepared using distilled water prior to administration.

Anticonvulsant activity:

Maximal Electroshock Seizures (MES) Model

This anticonvulsant model was employed to study grand mal (generalized tonic-clonic) seizures. In this model, electrical stimulation induces Tonic Hind Limb Extension (THLE), which serves as an indicator of seizure activity. A drug was considered to exhibit antiepileptic activity if it was able to abolish or significantly reduce THLE. Seizures were induced using ear electrodes delivering an electrical stimulus of 150 mA at 50 Hz for a duration of 0.2 seconds.

Twenty-four Wistar albino rats were randomly allocated to four groups, comprising six rats per group (n = 6). Group I (Control): Received 1.0 mL of 0.9% normal saline, Group II (Standard): Received sodium valproate at 300 mg/kg/day [12], Group III: Received the aqueous extract of *Andrographis paniculata* leaves (AEAP) at 500 mg/kg/day and Group IV: Received a combination of sodium valproate (300 mg/kg/day) and AEAP (500 mg/kg/day).

All treatments were given orally once daily for a duration of 15 days. On the day of experiment, MES seizures were evaluated by observing the time of onset and duration of THLE, along with the number of animals that experienced convulsions [13]. The percentage of protection was calculated [11] (Table 1 and Figure 1).

Table 1. Maximal electroshock seizure (MES) model

Groups	Name	Onset of THLE (Sec)	Duration of THLE (Sec)	Duration of PID (Sec)	Number of animals convulsed
I	Normal saline	3.79± 0.25	8.77±0.89	138.37±2.16	6
II	Sodium valproate	5.82±0.24***	1.25±0.83***	23.19±4.19***	2
III	*Andrographis paniculata*	6.08±0.2***	1.93±0.89***	29.51±2.16***	3
IV	Sodium valproate + *Andrographis paniculata*	0***	0***	7.3±1.14***	0

*p < 0.05, **p < 0.01, ***p < 0.001 (ANOVA followed by Dunnett's test); Results are stated as mean ± SEM
THLE: Tonic Hind Limb Extension, PID – Postictal depression

Pentylenetetrazol (PTZ) induced seizure

The pentylenetetrazol (PTZ)-induced seizure model is a well-established method for studying absence seizures [13]. Twenty-four Wistar albino rats were randomly assigned to four experimental groups, with six animals in each group (n = 6). Group I: received 1.00 mL of 0.9% normal saline, Group II: received sodium valproate at a dose of 300 mg/kg/day, Group III: received AEAP at 500 mg/kg/day, and Group IV: received a combination of sodium valproate (300 mg/kg/day) and AEAP (500 mg/kg/day). The standard and test drugs were administered orally for 15 consecutive days. Following a 12-hour fasting period, an intraperitoneal injection of PTZ (70 mg/kg body weight) was administered on the day of the experiment. Post-injection, the rats were observed for 30 minutes to record the latency to onset of the first forelimb clonus, the number of animals that exhibited convulsions, and mortality rates [11,14]. The percentage of protection was calculated [7] (Table 2 and Figure 1).

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Table 2. Pentylenetetrazol (PTZ) seizure model

Group	Drug	Latency (Sec)	Number of animals died
I	Normal saline	46.77 ± 4.18	6
II	Sodium valproate	82.155 ± 2.349***	2
III	*Andrographis paniculata*	75.291 ± 6.148**	4
IV	Sodium valproate + *Andrographis paniculata*	330.166 ± 22.928***	0

*P < 0.05, **p < 0.01, ***p < 0.001 (ANOVA followed by Dunnett's test)
Results are stated as mean ± SEM

Statistical analysis

Data were analysed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test, employing SPSS version 21. A p-value of <0.05 was considered statistically significant. Data are expressed as mean ± standard error of the mean (SEM) [15].

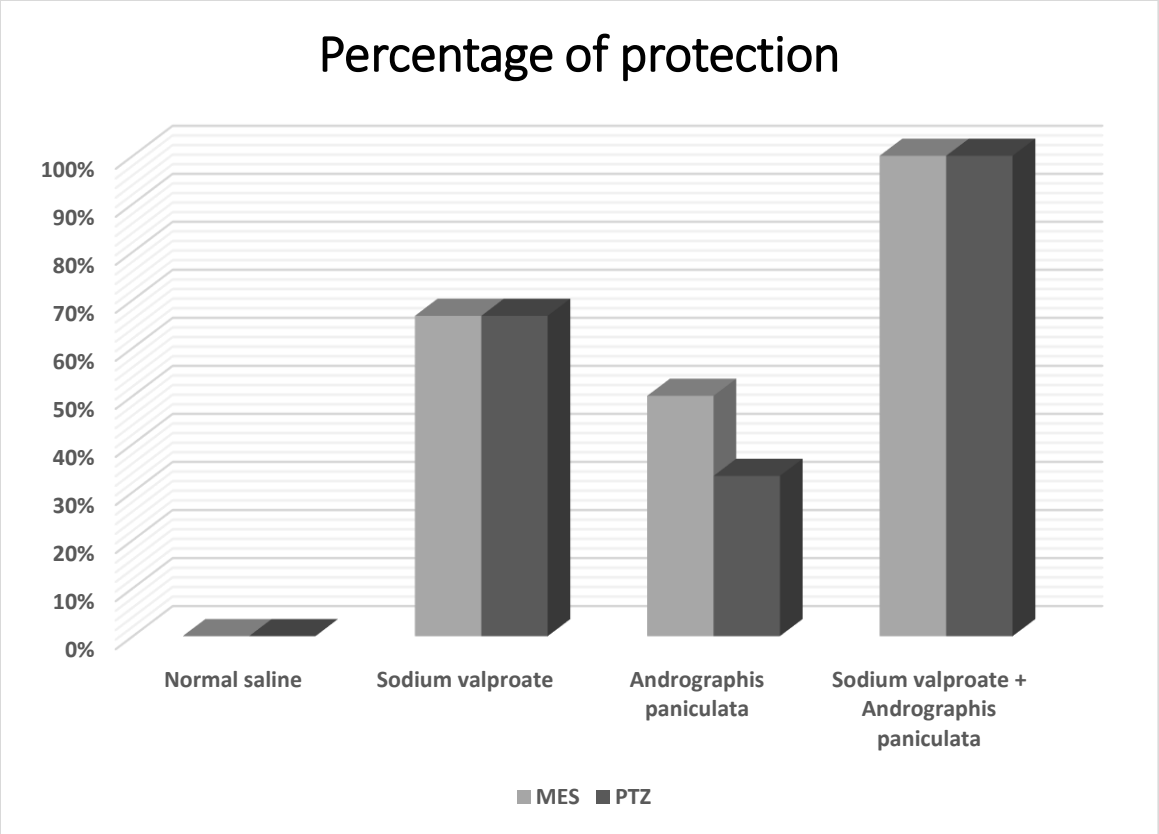

Figure 1. Percentage of Protection in MES and PTZ seizure models:

Discussion

The present study evaluated the anticonvulsant efficacy of AEAP and its potential synergistic action with sodium valproate. AEAP at a dose of 500 mg/kg body weight (Group III) demonstrated a statistically significant inhibition of THLE in the MES seizure model and a significant delay in the onset of clonic seizures in the PTZ-seizure model, which is comparable to the effects observed with sodium valproate at 300 mg/kg body weight (Group II). The combination treatment (Group IV), comprising sodium valproate (300 mg/kg) and AEAP (500 mg/kg), produced a highly significant inhibition of THLE in the MES model and further delayed the latency to PTZ seizures compared to Groups II & Group III. These findings suggest that *Andrographis paniculata* possesses notable anticonvulsant activity and potentiates the therapeutic efficacy of sodium valproate when used in combination.

The neuroprotective effects of andrographolide on the central nervous system were reviewed by Jiashu Lu et al., who concluded that andrographolide is capable of crossing the blood brain barrier and is distributed across various regions of the brain [16]. Sasi Kumar Murugan et al. conducted a toxicological safety assessment of *Andrographis paniculata* extract in rats, including both acute and 90-day repeated-dose sub-chronic toxicity studies. They

reported that the median lethal dose (LD_{50}) of AP-Bio® exceeded 5000 mg/kg of body weight, with no adverse effects observed at doses up to 900 mg/kg body weight [17]. Based on these findings, present study used an aqueous extract of *A. paniculata* leaves at a dose of 500 mg/kg body weight, administered for 15 days, assuming it to be within the no-observed-adverse-effect level for rats.

Ajit Kumar Thakur et al. conducted a preclinical study on the neuropsycho pharmacological effects of *Andrographis paniculata* extract in rodents and reported that oral administration of the extract was well tolerated at doses up to 800 mg/kg, with no observable behavioural alterations. A daily dose of 200 mg/kg body weight administered for 10 days potentiated pentobarbital-induced sleep and significantly antagonized seizures induced by both PTZ seizure and MES models. Additionally, anxiolytic, and antidepressant-like effects were observed following the 10-day dosing regimen. The study also documented suppression of central sensitivity to acute stressful stimuli and downregulation of central dopaminergic receptors after prolonged administration. The authors concluded that *A. paniculata* exhibits benzodiazepine-like anxiolytic and anticonvulsant properties when administered daily over an extended period [18].

Ramana et al. investigated the anti-kindling and antioxidant activities of *Andrographis paniculata* leaves and roots through both in silico and in vivo studies in rats, utilizing the bioactive compound andrographolide and its nano-formulation for enhanced delivery. The study employed a PTZ-induced kindling model, along with computational techniques such as network pharmacology and molecular docking, to explore the multi-target mechanisms underlying the antiepileptic effects of andrographolide. Their findings indicated that andrographolide exerts its antiepileptic action primarily by upregulating GABA levels. However, due to the compound's low bioavailability, the researchers opted to use andrographolide-loaded nanoparticles. In PTZ kindled rats, PTZ increased oxidative stress, as evidenced by elevated malondialdehyde levels and reduced levels of glutathione (GSH), superoxide dismutase (SOD), and GABA. Treatment with andrographolide effectively reduced these levels. The study concluded that andrographolide possesses significant antiepileptic potential, and its nano-formulated version may be a promising therapeutic strategy for managing kindled seizures [19].

Verma and Vinayak reported that the aqueous extract of *Andrographis paniculata* significantly elevated the levels of key antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione-S-transferase (GST), thereby contributing to its antioxidant potential [20]. In a longitudinal study conducted by Eduardo Beltrán-Sarmiento et al., the oxidant–antioxidant status of epileptic children prescribed on valproate monotherapy was evaluated in a Mexican cohort. The study found that, in comparison to healthy children, epileptic children exhibited decreased activity of antioxidant enzymes and elevated oxidative stress. However, valproic acid monotherapy significantly improved

antioxidant enzyme activities and reduced oxidative stress. The authors concluded that the antioxidant properties of valproic acid may contribute to its antiepileptic and neuroprotective effects, potentially through modulation of reactive oxygen species in a time-dependent manner [21].

Unhealthy gut microbiota can enhance the production of epilepsy-promoting metabolites and elevate inflammatory factors, leading to alteration in the GABA–glutamate ratio, which may contribute to the development of epilepsy. Chronic stress has also been identified as a potential trigger for this process [22].

Lerner-Natoli et al. observed an increased expression of Nuclear Factor kappa B (NF-κB) in the brain tissues of both animal models and epileptic patients. Similarly, Prasad et al. reported heightened NF-κB activity in hippocampal neurons of pentylenetetrazol (PTZ)-induced epilepsy models. Lerner-Natoli further demonstrated a significant upregulation of NF-κB expression in the hippocampus 24 hours after kainic acid injection, a response that may be linked to calcium influx mediated by N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPA) [24,25]. Andrographolide, a bioactive compound derived from *Andrographis paniculata*, has been shown to inhibit NF-κB activation by preventing the binding of NF-κB oligonucleotides to nuclear proteins [3,26].

Su Jing Chan et al. conducted an experimental study to evaluate the neuroprotective effects of andrographolide in a rat model of cerebral ischemia. Their findings demonstrated that andrographolide exerts neuroprotective actions by suppressing NF-κB activation and inhibiting microglial activation, thereby reducing the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and prostaglandin E2 (PGE2). Based on these results, the authors proposed that andrographolide may have therapeutic potential in the treatment of stroke [27].

Lerner-Natoli et al. work on the role of NF-κB in epilepsy suggests that the antiepileptic effects of *Andrographis paniculata* may, in part, be attributed to its ability to inhibit NF-κB in brain tissues [24].

According to Pradip Chauhan et al. (Chapter 2), brain regions specialized for learning and memory—particularly the neocortex and hippocampus regions—are more susceptible to seizures compared to other brain areas. Epilepsy is commonly associated with anatomical alterations in the hippocampus, amygdala, frontal cortex, temporal cortex, and olfactory cortex [28].

Eduitem Sunday Otong et al. investigated the neuroprotective effects of an aqueous extract of *Andrographis paniculata* against mercury chloride ($HgCl_2$)-induced oxidative damage in rat brain tissue. Their study demonstrated that $HgCl_2$ administration led to significant oxidative damage in the hippocampus and cerebellum, which was effectively mitigated by oral administration of *A. paniculata* extract at a dose of 500 mg/kg body weight for twenty eight days. Additionally, they observed that $HgCl_2$ exposure elevated glutamate concentrations in the brain, while treatment with *A. paniculata* significantly reduced these levels [29].

Eun-Ju Yang et al. investigated the neuroprotective effects of andrographolide

using a glutamate-induced HT22 mouse hippocampal neuronal cell death model. Their findings revealed that andrographolide significantly reduced apoptosis by inhibiting calcium influx, lipid peroxidation, and the formation of intracellular reactive oxygen species [30].

Meldrum et al. demonstrated, repeated electrical stimulation-induced 'kindling' limbic seizures is dependent on the activation of NMDA receptors, with enhanced function, observed particularly in the hippocampal region of kindled rats. Through micro-dialysis analysis, increased levels of extracellular glutamate and aspartate were detected in the brain both preceding and during seizure activity, suggesting a key role of excitatory neurotransmitters in seizure propagation. Anticonvulsant drugs such as lamotrigine have been shown to reduce ischemia-induced glutamate release [31,32]. Supporting this mechanism, studies by Eduitem Sunday Otong et al. and Eun-Ju Yang et al. demonstrated that *Andrographis paniculata* can reduce glutamate concentrations in the hippocampus—a brain region commonly affected in epilepsy [28-30].

Yan Pan et al. conducted an *in vitro* study to evaluate the effects of andrographolide and various extracts of *Andrographis paniculata* like aqueous, ethanolic, and methanolic extracts on human cDNA expressed hepatic cytochrome p450 (CYP450) enzymes. Specifically, they examined the enzymatic activity of CYP2C9, CYP2D6, and CYP3A4. The study concluded that *A. paniculata* extracts are significant inhibitors of CYP3A4 and CYP2C9, whereas andrographolide alone showed only weak inhibition of CYP3A4 activity [33].

Sodium valproate, the standard anticonvulsant used in this study, undergoes hepatic metabolism primarily through oxidation via cytochrome P450 enzymes, particularly CYP2C9 and CYP2C19 [31]. As reported by Yan Pan et al., *Andrographis paniculata* is a potent inhibitor of CYP2C9 activity [33]. Therefore, the observed potentiation of sodium valproate's anticonvulsant effect when combined with *A. paniculata* may be attributed to a pharmacokinetic interaction involving the inhibition of CYP2C9-mediated metabolism. However, this proposed mechanism warrants further investigation through comprehensive preclinical and clinical studies.

The anticonvulsant effect of the aqueous extract of *Andrographis paniculata* (AEAP) may be attributed to enhancement of GABAergic activity, antioxidant properties, inhibition of NF-κB signalling, as well as calcium and sodium channel blocking actions. These effects are likely mediated by its major bioactive compound, andrographolide. The observed potentiation of sodium valproate's anticonvulsant activity when combined with AEAP could be due to complementary GABA-enhancing effects, inhibition of CYP2C9-mediated metabolism, or other mechanisms. However, these possibilities require further detailed investigation through preclinical and clinical studies.

Limitations

The limitations of this study include the lack of evaluation of the proposed mechanisms of AEAP, its effects on pregnant

animals, its potential to potentiate other anticonvulsant drugs aside from sodium valproate, and its influence on CYP450 enzyme activity. These aspects warrant further investigation in future research.

Conclusion

Andrographis paniculata exhibits potent anticonvulsant activity. Its inhibition of the CYP2C9 enzyme may contribute to the potentiation of anticonvulsant effect of sodium valproate; however, this also raises concerns regarding potential pharmacokinetic drug interactions with chronic use. Therefore, further studies are needed to clarify its anticonvulsant mechanisms and to assess possible drug interactions.

Acknowledgment

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Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

No funding was received for conducting this study.

Data Availability Statement

The original data is available with the corresponding author

Statement of Informed Consent

This study did not involve human participants; therefore, informed consent was not applicable.

Ethics of Human and Animal Experimentation

This study was conducted following approval from the Institutional Animal Ethical Committee (IAEC approval number: 02/IAEC/2022) and adhered to the guidelines set forth by the Committee for the Control and Supervision of Experiments on Animals (CCSEA).

Authors Contribution

All authors contributed to the conceptualization and design of the study, data collection and analysis, manuscript revision, and gave final approval of the version to be published.

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