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ORIGINAL ARTICLE

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Abstract

Background: **Epilepsy is a common neurological disorder characterized by recurrent seizures. Simvastatin was recognized as a new candidate that exhibits a variety of neuroprotective effects, including antioxidant and anti-inflammatory effects that have the ability to inhibit neuronal hyperexcitability and seizure susceptibility.**

Aim: **The purpose of this study is to assess the possible anticonvulsant action of simvastatin in the mouse seizure model.**

Material and methods: **The eighteen adult albino mice (25−30 g) were allotted randomly to three groups (n = 6). Thirty minutes before the induction of convulsion, the groups received different intraperitoneal pretreatments: Group 1: Distilled water (0.1 ml), Group 2: Diazepam (1 mg/kg), Group 3: Simvastatin (10 mg/kg). Convulsions were induced in all the mice through intraperitoneal administration of lidocaine hydrochloride (75 mg/kg). The animals exhibited drowsiness, ataxia, loss of righting reflex, convulsions and incipient convulsive periods.**

Results: **Results show that simvastatin significantly delayed the onset of convulsions compared to the induction group and reduced their duration compared to the induction and diazepam groups. Compared to the induction and diazepam groups, it delayed the onset of drowsiness, ataxia and loss of righting reflex.**

Conclusions: **Simvastatin displayed an anticonvulsant effects in this experimental model, and thus it might have a beneficial influence on hyperlipidemic patients suffering from epilepsy.**

Keywords: Epilepsy, Antiepileptic, Anticonvulsant, Lidocaine and simvastatin

Introduction

Epilepsy refers to a chronic neurological disease that impacts around 1 % of the world's population. It is also termed as unprovoked, repeated seizures that can result in serious disability and reduced life expectancy (Tayal et al., 2025).

Epilepsy may be induced by more than a single etiology that distorts the physical and chemical balance of the brain, such as redox imbalance, cytokine expression, dysfunction of neurogenesis pathway, imbalance of gamma-aminobutyric acid (GABA) and glutamate receptors, neuroinflammation, reactive oxygen species (ROS) increase, and finally, oxidative stress (OS) (Ciltas et al., 2023; Parsons et al., 2022). Clinically, such changes could present as transient loss of consciousness, compelled motor activity, abnormal behaviors or sensory disturbances (Rahimi-Tesiye et al.,2025).

Despite the abundance of antiepileptic drugs (AEDs); controlling epilepsy is still challenging due to etiological and pathophysiologic heterogeneity. Therefore, efforts are placed on finding more effective and less toxic compounds (Sultana et al.,2021).

As per the recent literature, preclinical and clinical evidence suggest that statins can produce neuroprotection and antiepileptogenic effects. These effects are attributed to their anti-inflammatory, antioxidant and endothelial function− improving

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properties (Kamath et al., 2023; Zivkovic et al.,2023). Simvastatin, a widely prescribed HMG-CoA reductase inhibitor, has shown beneficial effects in various neurological conditions, including stroke, traumatic brain injury, neurodegenerative diseases, Alzheimer's disease and Parkinson's disease making it a candidate for evaluation in epilepsy models (Susanto et al.,2023; Tayal et al., 2025).

Materials and methods

Animals

Eighteen healthy male albino mice (25–30 g) were kept under standard laboratory conditions (12 h light/dark cycle, controlled temperature) with unlimited access to water and standard diet.

Preparation of injectable simvastatin

The injectable simvastatin solution was prepared fresh under aseptic conditions by dissolving the required amount of simvastatin in a suitable solvent (dimethyl sulfoxide with distilled water). The solution was then sterilized through filtration and stored until administration (Tan et al.,2015).

Study design

Mice were randomly divided into three groups (n = 6) and pretreated with a single intraperitoneal dose of distilled water, diazepam or simvastatin 30 min before lidocaine injection as follows

Group 1 (Induction group): Received distilled water (0.1 ml/I.P.) 30 min before administration of lidocaine.

Group 2 (Diazepam group): Received diazepam (1 mg/kg/I.P.) 30 min before lidocaine administration (Tehewel & Shihab, 2020).

Group 3 (Simvastatin group): Received simvastatin (10 mg/kg/I.P.) 30 min before lidocaine administration (Kamath et al., 2023).

Subsequently, all groups of mice were injected with 2 % lidocaine hydrochloride (75 mg/kg/I.P.) to perform the induction of convulsions. Following lidocaine administration, the onset of drowsiness, ataxia, loss of righting reflex, convulsions, and duration of convulsions were monitored.

Statistical analysis

Results were expressed as mean ± SEM and analyzed using one-way ANOVA followed by Tukey's post hoc test. Results A p-value of ≤ 0.05 was considered as significant.

Results

In the present study, intraperitoneal administration of lidocaine induced generalized tonic-clonic convulsions after approximately 424.4 s, accompanied by drowsiness, ataxia, and loss of the righting reflex as central nervous system effects, without any lethal impact on the mice.

Diazepam significantly delayed convulsion onset and reduced their duration compared to the induction group. It also significantly delayed the onset of ataxia and loss of righting reflex, but did not significantly delay the onset of drowsiness.

Simvastatin, when administered to mice exhibited anticonvulsant and neuroprotective effects against epileptic seizures induced by lidocaine. This was evidenced by a significant delay in the onset of convulsions compared with induction group, and a non-significant delay compared to the diazepam group. Additionally, it significantly reduced the duration of convulsions compared to both the induction and diazepam groups. Furthermore, simvastatin significantly delayed the onset of drowsiness, ataxia, and loss of the righting reflex compared to both the induction and diazepam groups (Table 1; Figs. 1–5).

Discussion

Epilepsy is a chronic neurological disorder characterized by repeated seizures resulting from abnormal, excessive, and synchronized neuronal electrical activity.

In this study, administration of lidocaine induced generalized tonic–clonic seizures within approximately 7 min. This observation is consistent with previous reports indicating that lidocaine provokes seizures by increasing intracellular calcium levels in neurons, a mechanism that may underlie its neurotoxic effects. In addition, lidocaine is thought to suppress GABA activity by binding to specific recognition sites on the GABA-ionophore receptor complex, as well as enhancing excitatory glutamatergic signaling through both NMDA and non-NMDA receptors. Furthermore, its impact on the redox balance and antioxidant defense systems contributes to oxidative stress in hippocampus and amygdala of brain (Zhu et al., 2014; Santos et al., 2021; Aminiahidashti et al., 2015).

In this study, simvastatin showed remarkable anticonvulsant activity, as evidenced by a significant delay in the onset of convulsions and a reduction in their duration. These findings align with previous studies showing that statins may have anticonvulsant effects by reducing neuroinflammation through

Table 1. Effect of simvastatin against epileptic seizures induced by lidocaine.

Groups	Parameters				
	Onset of Drowsiness (Seconds) M ± S.E.M	Onset of Ataxia (Seconds) M ± S.E.M	Onset of Loss of righting reflex (Seconds) M ± S.E.M	Onset of Convulsion (Seconds) M ± S.E.M	Duration of Convulsion (Seconds) M ± S.E.M
Induction	71.86 ± 0.44	168.9 ± 0.98	337.1 ± 0.79	424.4 ± 1.02	121.5 ± 0.92
Diazepam	52.08 ± 0.54	94.68 ± 0.34 a*	737.04 ± 0.39 a*	802.68 ± 0.4 a*	69.5 ± 0.28 a*
Simvastatin	141 ± 0.30 a*, b*	319 ± 0.39 a*, b*	511.2 ± 0.44 a*, b*	750 ± 0.26 a*	47 ± 0.54 a*, b*

* = Significant ($P \leq 0.05$), a = as compared to induction group, b = as compared to diazepam group.

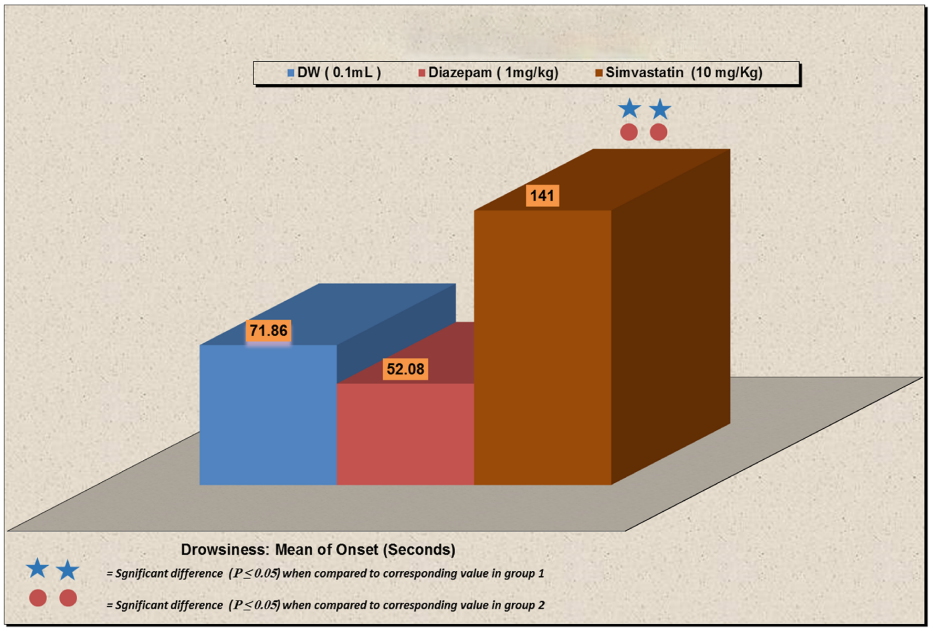

Fig. 1. Effect of simvastatin on mean onset of drowsiness (seconds).

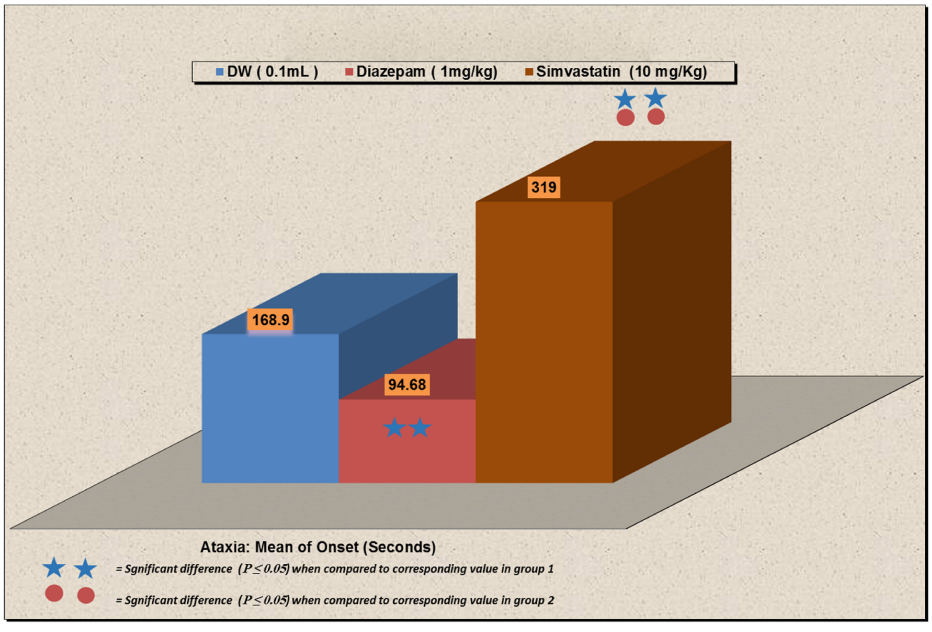

Fig. 2. Effect of simvastatin on mean onset of ataxia (seconds).

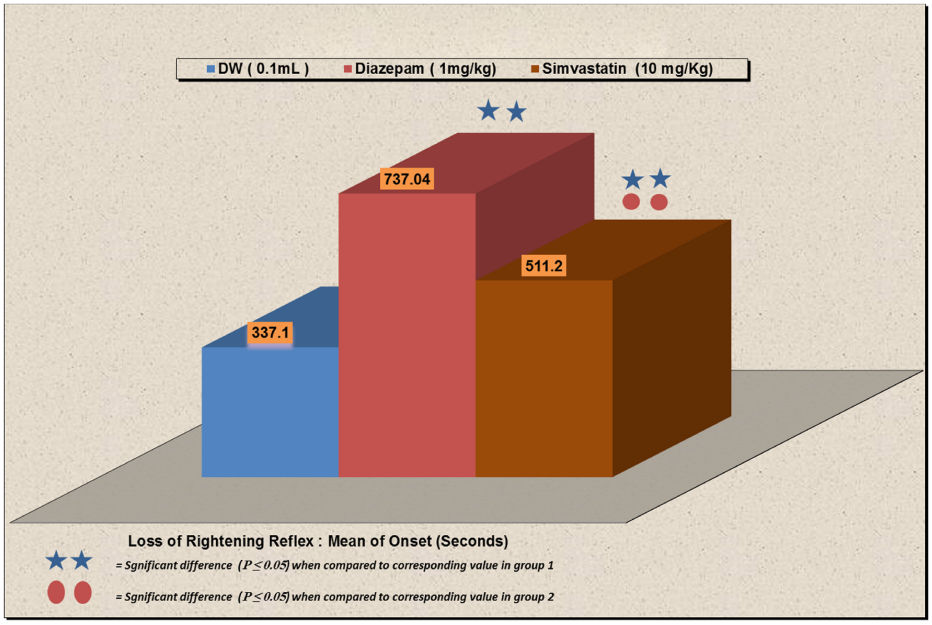

Fig. 3. Effect of simvastatin on mean onset of loss of rightening reflex (seconds).

downregulation of pro-inflammatory gene expression and reduced release of proconvulsant cytokines, including IL-1β, TNF-α, and IL-6, alongside increased production of the anti-inflammatory cytokine IL-10. Furthermore, simvastatin might influence the synthesis of neurosteroid via an immediate, neurosteroidal effect that is involved in neuromodulation ensuring balance between excitatory and inhibitory neurotransmission, which may also contribute to the improvement of its antiepileptic effects. This dual mechanism of reduced inflammation and altered neurosteroidogenesis is neuroprotective, suppressing the seizure threshold (Lin et al., 2018; Reddy, 2013; Scicchitano et al., 2015).

Further data also support that simvastatin has NMDA receptor antagonist-like effects. Specifically, this may support its anticonvulsant and neuroprotective properties by reducing glutamate-

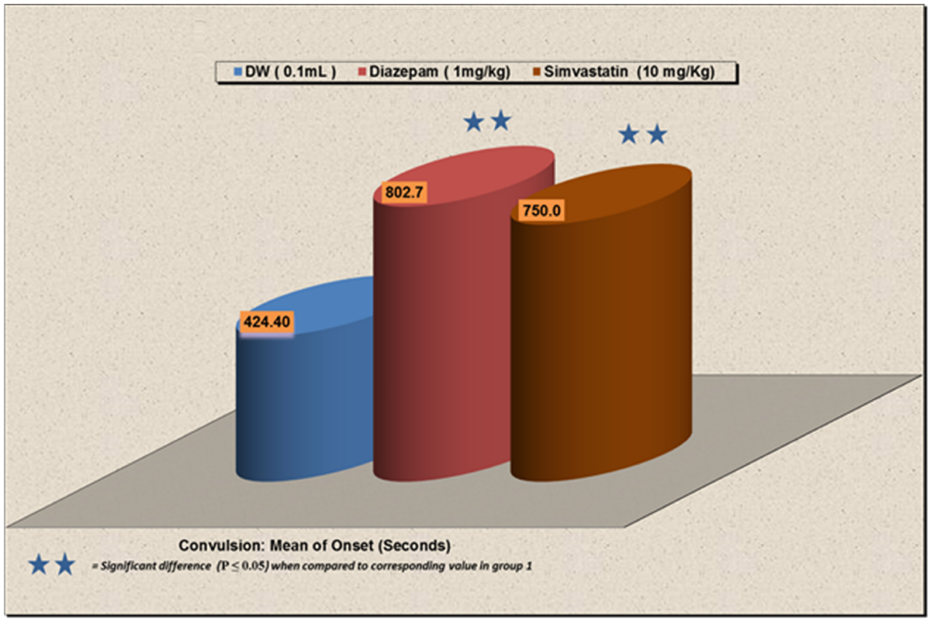

Fig. 4. Effect of simvastatin on mean onset of convulsion (seconds).

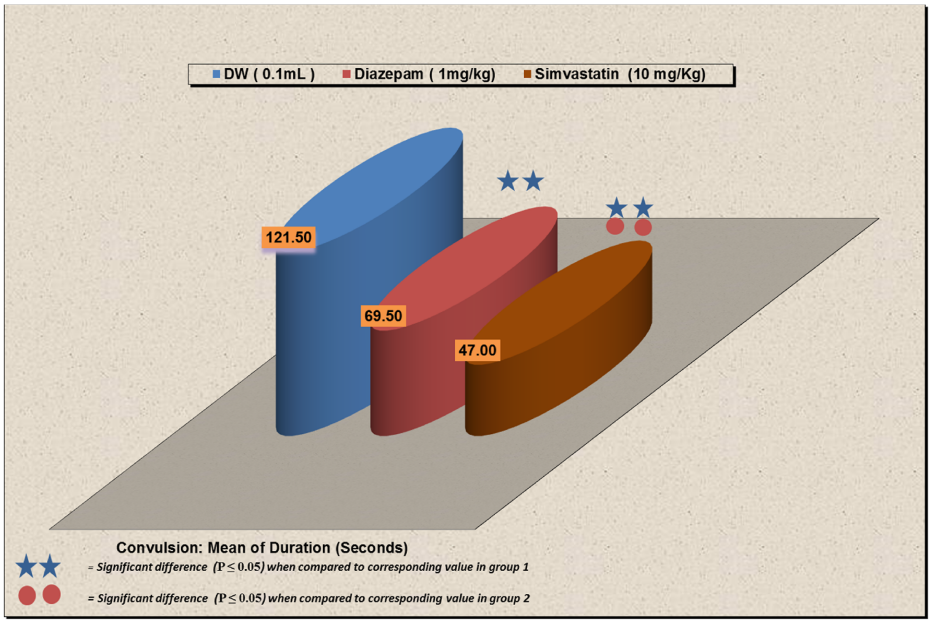

Fig. 5. Effect of simvastatin on mean duration of convulsion (seconds).

stimulated calcium influx and modulating NMDA receptor function. Simvastatin may also protect cortical neurons from damage induced by excitotoxic glutamate (Lin et al., 2018; Xie et al., 2011).

The neuroprotective and anticonvulsant effects of statins may be attributed to other proposed mechanisms include suppression of reactive astrogliosis associated with seizure-induced neuroinflammation, enhancement of GABAergic transmission, inhibition of glutamatergic overactivity, inhibition of the glycogen synthase kinase-3β signaling pathway. Involves modulation and reduction of monocyte infiltration which is implicated in hippocampal neuronal loss (Hanin et al., 2023; Quintana-Pájaro et al., 2018).

Several studies also highlight that control of brain cholesterol homeostasis through lipid-lowering agents such as simvastatin can reduce excitotoxicity and prevent the development of seizures. Cholesterol plays an important role in controlling the activity of voltage-gated and ligand-gated ion channels; Thus, excessive neuronal cholesterol accumulation can be excitotoxic, promoting neuronal death and spontaneous hippocampal seizures (Hanin et al., 2021, 2023).

Additionally, simvastatin has been shown to upregulate endothelial nitric oxide synthase (eNOS) expression in cerebral vascular endothelium, thereby increasing nitric oxide production. This in turn increases vasodilation and cerebral blood flow, potentially stabilizing neuronal activity, improving oxygenation and ensuring an adequate supply of nutrient to the brain, thereby collectively reducing seizure susceptibility (Amanlou et al., 2023; Gorabi et al., 2019).

In conclusion, simvastatin shows promising anticonvulsant and neuroprotective effects in experimental epilepsy models. Further research is needed to explore its potential as an adjunct therapy, especially for patients with concomitant dyslipidemia and epilepsy.

Ethics information

This study received approval from the Scientific and Ethical Committee of Al-Ameed University.

Author contribution

All authors worked together to choose the research topic and contributed collectively to writing, reviewing, and improving the manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

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