

Bridging Ethnomedicine and Evidence: A Systematic Review of the Anticonvulsant and Pharmacological Effects of *Waltheria indica* L.

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ABSTRACT

The world's leading source of raw materials for creating pharmaceutical medications that are safer, more effective, and more reasonably priced is medicinal plants. As a result of this expanding interest, more studies are being done on plants that may have therapeutic uses. A member of the Malvaceae family, *Waltheria indica* L. (syn. *Waltheria americana*) is indigenous to Tropical and Subtropical regions of the Americas and is used extensively in traditional medicine in South America, Hawaii, and Africa. Many parts of the plant are used to cure conditions like epilepsy, wounds, abscesses, conjunctivitis, discomfort, inflammation, convulsions, diarrhoea, and dysentery. This review focuses on the anticonvulsant potential of *Waltheria indica*, summarizing its phytochemical constituents, pharmacological properties, and toxicological data. Information was sourced from databases such as PubMed, Scopus, Google Scholar, and others. From around 100 reviewed articles, 50 were selected based on relevance and publication date, with 85% published between 2015 and 2024. Findings revealed anti-inflammatory, antioxidant, and anticonvulsant effects across various plant parts. The LD₅₀ values in rodents ranged from 300 to 5000 mg/kg, indicating a favorable safety profile, though high doses caused hepatotoxicity. Flavonoids, alkaloids, and saponins, especially phenolics, were identified as key anticonvulsant agents. *Waltheria indica* contains multiple bioactive compounds with promising therapeutic potential, particularly as an anticonvulsant. Further pharmacological and mechanistic studies are recommended.

KEYWORDS

Waltheria indica, phytoconstituents, toxicity profile, anticonvulsant, antioxidant, analgesic

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INTRODUCTION

A medical disorder known as convulsion occurs when muscles in the body contract and relax quickly and repeatedly. It is characterised by jerking or fitting and lasts for a few minutes when it occurs¹. Convulsion is commonly used as a synonym for seizure, but not all convulsions are brought on by epileptic seizures, and not all epileptic seizures induce convulsions². The threat of convulsions has been worldwide. There are more than 50 million people with epilepsy around the world. Globally, 70 million people suffer from epilepsy, with a high prevalence in developing countries, particularly Sub-Saharan African (SSA) countries.



The projected treatment gap for epilepsy, which affects over 10 million people in Africa, is 68.5%³. Over 13 million people's quality of life is thought to be impacted by epilepsy, and the condition is thought to be responsible for around 125,000 deaths and 5 million new cases diagnosed globally each year⁴. Between 4 and 10 out of every 1000 individuals with epilepsy require therapy at any given moment. According to estimates, eighty percent of epileptics reside in low- and middle-income countries. This condition may be brought on by endemic risk factors like malaria, neurocysticercosis, traffic accidents, birth trauma, inadequate medical facilities, subpar anti-seizure drugs, and other preventive healthcare initiatives⁵.

The International League against Epilepsy (ILAE) defines febrile convulsions (FC) as seizures that occur during infancy or youth (often between the ages of 3 months and 5 years) and are linked to temperatures above 38°C without any indication of an intracranial infection⁶. A prevalent childhood illness, especially in underprivileged areas, is febrile convulsions in children under five. compared to roughly 5% of all children in affluent nations. It is the most prevalent seizure disease among children in developing countries between the ages of 9 months and 5 years. Most mothers in rural communities in Ghana and Nigeria blame febrile convulsions FC on witchcraft, evil spirits, and fever. In Turkey, there are also reports of FC being attributed to supernatural entities. Family history of epilepsy and complex convulsions, which are recognised risk factors for FC, are also crucial. Feverish bewilderment, twitching, elevated body temperature, breath-holding episodes, and developing epilepsy syndrome are clinical and home diagnoses of FC. These symptoms can happen at any time of day and can be fatal if left untreated⁷.

Medication, surgery, nutritional therapy, acupuncture, moxibustion, and other methods have long been the mainstays of epilepsy treatment. Anticonvulsants are a broad class of pharmaceuticals for the treatment of epileptic seizures. They are sometimes referred to as antiepileptic drugs, antiseizure drugs, or anti-seizure meds (ASM)⁸. The global pharmaceutical market currently offers over fifty various antiepileptic medications (AEDs), such as carbamazepine, oxcarbazepine, sodium valproate, gabapentin, lamotrigine, topiramate, levetiracetam, lacosamide, pregabalin, stiripentol, and others⁸.

Anticonvulsants stop seizures from spreading across the brain and inhibit the excessively fast firing of neurons during seizures⁹. Numerous antiepileptic medications have several or unclear modes of action; some of their known targets include GABA transaminase, GABA A receptors, the GABA transporter type 1, voltage-gated sodium channels, and other elements of the GABA system¹⁰. Other targets include SV2A, $\alpha 2\delta$, and voltage-gated calcium channels. Antiepileptic medications decrease excitatory glutamate release, which is thought to be increased in epilepsy, as well as GABA release by blocking sodium or calcium channels. Lacosamide, pregabalin, gabapentin, carbamazepine, oxcarbazepine, ezogabine, phenytoin, and vigabatrin are examples of narrow-spectrum AEDs. The main purpose of narrow-spectrum AEDs is to treat partial or focal seizures¹¹.

As a first-line treatment, anticonvulsant medications like vigabatrin, an inhibitor of the gamma-aminobutyric acid A (GABA A) receptor or GABA transaminase, have been used and shown to be effective in resolving infant convulsions, particularly those linked to tuberous sclerosis. However, side effects of vigabatrin include encephalopathy, autism spectrum disorder, developmental delay, and the possibility of irreversible visual field (visual compromise). In addition to having undesirable side effects and significant drug interactions, vigabatrin treatment can last anywhere from 4 to 33 months. Just like vigabatrin, prolonged use of AEDs has been linked to negative side effects and the possibility of drug-drug interactions¹², which are also the main drawbacks of using AEDs in clinical settings.

Due to the various limitations of available treatments for epilepsy, phytotherapeutic treatment, also known as herbal medicines, has gained a lot of attention globally because of its low toxicity, safety, cost-effectiveness, ease of availability, and multitargeting ability to target different medicinal plants and their phytochemicals for epilepsy treatment. Furthermore, medicinal plants for epilepsy are frequently seen as

a gentle and secure substitute for chemical AEDs, and herbal medicine has been utilised globally as a supplemental or alternative therapy for the treatment of epilepsy. *Alum sativu*, *Telferia occidentalis*, *Cassy thafili*, *Zizyphus spina-christi*, and *Waltheria indica* are a few plants that are currently utilised locally as alternative treatments for convulsions¹³. Around the world, plant-based complementary and alternative medicines (CAMs) are frequently used to treat epilepsy, with varying degrees of efficacy¹⁴. In addition to the fact that not all of them have been assessed, they have helped herbalists succeed locally¹⁵. A variety of bioactive substances found in medicinal plants can be used to treat a wide range of illnesses, including epilepsy. Herbal medicine is now widely used as an alternative in the management of epilepsy and as a potential source of new drugs due to the high rate of untreated and uncontrolled seizures among individuals with epilepsy, inadequate access to quality anti-seizure medications, poor healthcare facilities, and a high death rate from epilepsy, particularly in countries with limited resources. Despite the availability of modern treatment and sophisticated healthcare delivery systems, they have gained international attention, especially in the developed world⁷. In Nigeria, residents in the North and Southwest employ a variety of medicinal plants, including *Waltheria indica*, *Xylopia aethiopica*, *Alstonia boonei*, and *Khaya grandifoliola*, to treat epilepsy¹⁶. Herbalists employ a decoction of *Waltheria indica* and various components of *Alstonia boonei* (stem bark) to treat convulsions. *Waltheria indica*'s pharmacological characteristics have been studied and recorded in a number of laboratories. *Waltheria indica*'s pharmacological properties, including sedative, analgesic, antibacterial, antiviral, antidiabetic, bronchorelaxant, antiparasitic, aphrodisiac, antidiabetic, antifungal, and anti-inflammatory properties, were documented in this research.

Waltheria indica (L.), is a common medicinal plant in many South American and African nations is Synonymous nomenclature of *Waltheria americana* (L.)¹⁷. They are little bushes that range in height from 0.5 to 1 m. Due to the influence of high winds, they develop numerous branches that spread near the ground when they live for a long time and grow separately. Their extensive and deep root system allows them to adapt to dry, dehydrated soil conditions¹⁷. It is an upright to spreading shrublet that may be pruned into a pretty, bushy, and sturdy pot plant. It is typically 300 mm to 1 m tall, with soft tiny yellow flowers and zigzag-edged leaves. The simple, star-shaped hairs cover the narrow stems and the remainder of the plant¹⁷. The objective of this review is to systematically evaluate and synthesize existing ethnomedicinal, pharmacological, and preclinical evidence on *Waltheria indica* L., with a specific focus on its anticonvulsant properties. This study aims to highlight its phytochemical constituents, therapeutic mechanisms, safety profile, and potential as a plant-based treatment for seizure disorders and related neurological conditions.

MATERIALS AND METHODS

To identify, document, and assess existing research on the Pharmacological and Toxicological properties of *Waltheria indica*, which inform its sedative and anticonvulsant effects, a literature review was conducted. The current review was created by searching databases including PubMed, Scopus, ResearchGate, and research.com for pertinent publications. Search for *Waltheria indica*, *Waltheria americana*, sedative and anticonvulsant activity, anti-inflammatory activity, antioxidant activity, anti-nociceptive action, and toxicity on Google Scholar and Science Direct. Fifty papers were carefully selected based on their relevance and year of publication, following a rigorous selection procedure that evaluated each article's relevance to the study questions, as determined by its title and abstract, after 100 articles were reviewed. Fifteen percent of the publications were published before 2015, and eighty-five percent were published between 2015 and 2024. The data gathered during the search was compiled and categorised in tables, and all of the chosen publications are original research and synthesis articles that are accessible online.

RESULTS

Phyto-constituents: *Waltheria indica*, commonly known as sleepy morning, is a widespread medicinal herb in tropical regions of the world. Nutrient elements such as sucrose, tannins, alkaloids, flavonoids, and caffeic acid (Table 1) found in whole plant extracts support medical usage. The existence of the plant's

Table 1: Phytochemical constituents in different parts of *Waltheria indica*

Part of the plant	Chemical group
Roots	Steroids, tannins, terpenoids, alkaloids, cardiac glycosides, and saponins ²¹
Leaves	Steroids, tannins, terpenoids, alkaloids, cardiac glycosides, phenolic acids, and saponins ²²
Leafy stems	Sterols, terpenes, alkaloids, flavonoids, coumarins, tannins, saponosides ²³
Aerial parts	Alkaloids, tannins, saponins, flavonoids, steroids, coumarins ¹⁶

Table 2: Compounds isolated from the biological and pharmacological activity of different *Waltheria indica* components

Plant part	Isolated compounds
Roots/hydroalcoholic extract	(-) -Epicatechin ²⁴
Whole plant/ethanolic extract	(-) -Epicatechin, quercetin, and tiliroside ⁵
Leaves/ethanolic extract	Tetradecane, hexadecane, squalene, 2,3-Dihydro-3,5-dihydroxy-6- Methyl-4H-pyran-4-one
Aerial parts/dichloromethane extract	Methyl (2R,3R)-3,4-dihydro-3,8-dihydroxy-2- methyl-(4-methylpent-3-en-1-yl)-2H-1-benzopyran-6-carboxylate; methyl (R)-2,3-dihydro-7-hydroxy-2-[(S)-2-hydroxy-6-methylhept-5-en-2-yl]-2H-1-benzofuran-5-carboxylate; methyl (R)-2,3-dihydro-7-hydroxy-2-[(2R,5S)-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]-2H-1-benzofuran-5-carboxylate(2S)- 16 2-[(1S)-1-(5,5-dimethyltetrahydrofuran-2-yl)-1-hydroxyethyl]-2,3-dihydro-2H-1-benzofuran-5-carboxylic acid; methyl (2S,4aR,10aS)-2,3,4,4a,10,10a-hexahydro-6-hydroxy-2-(2-hydroxypropan-2-yl)-4a-methylpyrano, benzopyran-8-carboxylate ²⁴

many bioactive components is necessary for its pharmacological activity. In animal models of epilepsy, a variety of phytochemicals derived from plants exhibit encouraging capacity to reach numerous pharmacological targets. Adouetin X, Y, Y1, and Z are among the known and named alkaloids found in *Waltheria indica* leaf and root extracts¹⁸. These alkaloids were believed to be the first cyclopeptide alkaloids in plants to be identified¹⁸.

Flavonoids, including epicatechin, kaempferol derivatives, tiliroside, and quercetin, were discovered to be present throughout the plant (Table 2)¹⁹. Despite the presence of 5,2,5-trihydroxy-3,7,4-trimethoxyflavone and 5,2 -dihydroxy-3,7,4,5 -tetramethoxyflavone in the leaves, 2,3-Dihydro-3,5-Dihydroxy-6-methyl-4h-pyran-4-one, tetradecane, tetracosane, nonadecane, squalene, and phytol are the primary bioactive compounds present in the ethanolic extracts of leaves¹⁹. Polyhydroxymethoxy flavonoids, including flindulatin, oxyanin A, chrysosplenol E, and 5-hydroxy-3,7,4-trimethoxyflavone, as well as quinolone alkaloids, including Waltheriones A, C, E-L, M-Q (2, 7, 8, 10, 11), and 5(R)-vanessine, were detected in the aerial sections of the dichloromethane extract¹⁹.

The identified phytochemicals can interact with a range of receptors in the central nervous system (CNS), including voltage-gated sodium, potassium, and calcium channels, N-methyl-D-aspartate receptors (NMDAR), Gamma-Aminobutyric Acid Receptors (GABAAR), and α -amino-3-hydroxy-5-methyl-4-Isoxazolepropionic Acid Receptors (AMPA), in addition to other enzymes and pathways that are essential in the onset and progression of epilepsy²⁰. Table 1, respectively, list the phytochemical groups found in various plant portions and the isolated chemicals found in *Waltheria indica* that were described in the several studies we reviewed. Methanol, ethanol, ethanol-water mixture, hexane, ethyl acetate, and water are among the extraction solvents utilised in the different investigations.

Toxicity profile of *Waltheria indica*: Six *in vivo* research on *Waltheria indica*'s toxicological effects were found in the database search. In these investigations, different plant parts, leaves, stems, and roots were used. Overall results from acute and subacute toxicity tests on rats and mice point to *Waltheria indica*'s low toxicity. Alkaloids, glycosides, proteins, and amino acids are among the many different types of chemical poisons that cause plant toxicity²⁵. After 21 days of continuous oral administration of *Waltheria indica*, mild toxicity (LD 50> 5000 mg/kg) was observed with certain vital enzymes and organs, indicating that the crude drug is safe to take orally²⁶. The sample also showed no effect on haematological or biochemical parameters²⁷.

Table 3: Summary of the reported toxicological effects of *W. indica*

Extraction methods/parts used	Model/type of study	Results
Methanol/leaves	Acute and subacute toxicity in rats	When taken orally, the LD ₅₀ was higher than 5000 mg/kg of body weight None of the biochemical markers showed any statistically significant variations Alkaline phosphate, AST/SGOT, and ALT/SGPT did not significantly change at 250 and 500 mg/kg, respectively ³⁰ . The blood cells were not significantly impacted When the liver, kidney, spleen, and heart were tested at 1000 mg/kg, histological analysis showed histopathological alterations in each of the organs ³¹
Ethanol/aerial parts	Subacute toxicity/albino Wistar rats	The 400 and 800 mg/kg/day doses did not cause any sub-acute toxicity Female rats given different extract dosages did not exhibit any appreciable changes in haematological parameters when compared to the control group ($p > 0.05$) ¹⁶ The MCH values of male rats given 1600 mg/kg for 28 days, however, significantly decreased ($p > 0.05$). Additionally, MCHC, MCH, and MCV were significantly reduced when high dosages of the extract (800 and 1600 mg/kg) were given over a 28-day period
Aqueous, water-ethanol/leafy stems	<i>In vivo</i> acute toxicity/mice	When administered orally, the LD ₅₀ was more than 5000 mg/kg of body weight ²³
Methanol/leaves	<i>In vivo</i> acute toxicity/rats	When taken orally, the LD ₅₀ was more than 5000 mg/kg of body weight ²³
Water/leafy stems	<i>In vivo</i> acute toxicity/mice	When taken orally, the LD ₅₀ was more than 5000 mg/kg of body weight
Hydroethanolic/roots	<i>In vivo</i> acute toxicity/rats	The LD ₅₀ was more than 2000 mg/kg of body weight when taken orally

In mice, the intraperitoneal lethal dose (LD₅₀) of *W. indica* root, stem, and leaf aqueous extracts was 141 mg/kg body weight¹⁶. In mice, the LD₅₀ for the aqueous ethanol extract from aerial parts was 875 mg/kg body weight. Adouetin Z sulfonate, a cyclopeptide alkaloid, also demonstrated a minimum fatal dose of 75 mg/mL and an intraperitoneal LD₅₀ of 52.5 mg/mL in mice²⁸. High dosages of the leaf extracts caused hepatotoxicity, which led to hydropic hepatocyte degeneration and caused cellular infiltration in the liver's periportal region²⁸. Although there is little information on toxicity and its effects on particular organs, the plant should be used carefully at high doses, particularly during pregnancy^{28,29} have previously compiled toxicological results of different plant parts and presented them in a table that is reproduced below as Table 3.

Biological and pharmacological properties that concern sedative properties of *W. indica*: In assessing the pharmacological activities related to the sedative potentials of *W. indica*, 18 research publications were found to be pertinent. The articles showed that different sections of *Waltheria indica* extracts had antioxidant, anti-inflammatory, and analgesic properties.

Sedative and anticonvulsant activity: Compared to traditional psychotropic medications, phytomedicine has been demonstrated to be a safer and more effective alternative for neurological illnesses. Certain flavonoids including caffeic acid, which is used to treat neuralgia and works as a medulla stimulant and central nervous system sedative, were found in *Waltheria indica* during earlier screening. Adouetin Z, which is extracted from *Waltheria indica* extracts, has been shown in a previous study to have a calming effect on mice by reducing their spontaneous motor activity. By preventing mice from experiencing convulsions brought on by leptazole, the plant's aqueous ethanol extract demonstrated sedative

and anti-convulsant properties. Different leaf extracts decreased the number of convulsions per minute and delayed the onset and death of convulsions in a dose-dependent manner. Additionally, methanolic extracts from *Waltheria americana* Linn's roots and cell suspension cultures have been shown to cause the release of GABA in mouse brain slices.

Antioxidant potentials of *Waltheria indica*: Researchers tested the antioxidant capacity of the aqueous extract of *Waltheria indica* stems and leaves by evaluating its ability to inhibit lipid peroxidation using the DPPH technique. Six of the twenty-three papers that documented pharmacological features related to sedative effects also noted *Waltheria indica*'s antioxidant qualities. The ethanolic extract of the entire plant showed a maximum superoxide anion scavenging activity of 587.66% at a concentration of 1000 µg/mL in an *in vitro* superoxide anion scavenging activity model, whereas quercetin (standard) showed a scavenging activity of 98.01% at the same concentration. The ethanolic extract of the entire plant exhibited a maximal DPPH radical scavenging activity of 48.40 percent at a dose of 1000 µg/mL in an *in vitro* DPPH radical inhibition model, whereas conventional rutin showed a scavenging activity of 69.83 percent at the same concentration. The rutin and ethanolic extract had respective IC₅₀ values of 1020 and 480 µg/mL.

The reference product, quercetin, has an IC₅₀ of 0.69 µg/mL, whereas the aqueous extract of stems with leaves *in vitro* DPPH radical inhibition model demonstrated an IC₅₀ value for the inhibition of 79.5 µg/mL of the DPPH radical. An *in vitro* suppression of lipid peroxidation (LPO) study found that a 400 mg/kg dose of methanol extract of the complete plant significantly reduced LPO in the liver and kidney tissues of rats with alloxan-induced diabetes.

In an *in vitro* model for scavenging cationic free radicals, methanol and aqueous stem extract of *W. indica* showed antiradical action³². The aqueous stem extract exhibits 100% antiradical activity at 25 µg/mL with an IC₅₀ of 2.5 µg/mL, while gallic acid reaches 100% antiradical activity at 0.84 µg/mL with an IC₅₀ of 0.35 µg/mL. Both extracts and gallic acid exhibit a linear increase with concentration. Similarly, the methanolic stem extract had 100% antiradical action at doses of 25 µg/mL or greater, with an IC₅₀ of 6 µg/mL³³. Ascorbic acid completely suppresses (100%) DPPH at a dosage of 0.5 mg/100 mL, while *Waltheria indica* methanol extract inhibits 65.71±2.32 percent at the same dose, per a study employing an *in vitro* DPPH free radical scavenging activity model³⁴.

Using the DPPH test, the whole plant inhibitory concentration (IC₅₀) of *W. indica* was determined in another investigation. With a lower IC₅₀ value of 87.19±0.005 µg/mL, *W. indica* showed better activity than the standard, ascorbic acid, indicating higher antioxidant capacity. As activity rose, IC₅₀ values decreased. In contrast, *W. indica* possesses 192.04±0.001, 0.0001 of ascorbic acid, which makes it a good antioxidant.

The findings of the study of Garba *et al.*³⁴ which reported strong radical scavenging activity in the root of *Waltheria indica*, align with the free radical scavenging properties of *W. indica* described by Veeramani *et al.*³⁵. A family of phenolic substances with antioxidant properties that may prevent the production of free radicals are flavonoids and tannins³⁶. Given that phenols are known to interact directly with activated oxygen species, *Waltheria indica*'s antioxidant activity may be caused by their presence^{37,38}.

Analgesic activities: Anti-inflammatory medicines, like NSAIDs, efficiently reduce pain and inflammation by blocking enzymes that create prostaglandins, which are responsible for pain and inflammation. However, these medicines are associated with side effects include gastrointestinal disorders as stomach upset, heartburn, and ulcers, as well as risk for headaches, dizziness, and in some cases, allergic responses³⁹. The cytopathological condition known as mitochondrial oxidative stress (MOS), which is brought on by the activation of damaging redox-active chain reactions, can be brought on by NSAIDs. It is characterized by severe mitochondrial damage, a severe bio-energetic crisis, and finally, cell death^{40,41}. They are also associated with pulmonary, brain, renal, hepatic, and cardiovascular issues⁴². Therefore, there is a pressing demand for analgesic medications that are safer and more effective. *Waltheria indica* is among the numerous potentially powerful anti-nociceptive plant-derived chemicals that have been found in the literature, according to our search.

Compared to stem extracts, the analgesic effect of *Waltheria indica* aqueous root extract considerably decreased the abdominal constrictions in Swiss albino mice generated by acetic acid writhes¹⁶. Wide-ranging pharmacological characteristics, including antioxidant, analgesic, sedative, anti-bacterial, anti-fungal, and anti-parasitic, were demonstrated by both crude extracts and purified chemicals from the entire plant and its parts in another study. Both the stem and leaf extracts of *Waltheria indica* have been shown to have analgesic effects in mice in an acetic acid-induced abdominal writhing model⁴³.

Anti-inflammatory activities: Numerous things, including microbial infections, chemical stimuli, and physical tissue damage, can trigger inflammation, a defence mechanism. Acute and chronic illnesses like hepatitis, arthritis, encephalitis, multiple sclerosis, and cancer may be exacerbated by excessive inflammation⁴⁴. Despite their effectiveness, the negative effects of nonsteroidal anti-inflammatory medications and synthetic versions of natural cortisol, known as glucocorticoids, are still a key worry when it comes to treating inflammatory illnesses⁴⁵. In many regions of the world, people have employed plants or formulations derived from plants to treat inflammatory diseases and related ailments. Among these plants is *Waltheria indica* (Malvaceae)⁴². Studies on humans as well as in animal and cell models verified quercetin's anti-inflammatory qualities. *Waltheria indica* extracts showed the plant's anti-inflammatory qualities by altering the expression of IL-1B, TNF- α , TNFRII, and NF- κ B in human macrophages.

Waltheria extracts were discovered to lower the mRNA and protein levels of TNF- α and its receptor, as well as to suppress important inflammatory cytokines and cytokine receptors, such as the protein levels of IL-1B, IL-1ra, IL-8, and IL-6. Targeted qRT-PCR and Inflammation Panels were used to evaluate the differential mRNA expression of two hundred immune-related genes in human macrophages challenged with LPS and TNF- α /IF- γ . TNF RII predicts decreased TNF- α -associated inflammatory signalling, which effectively inhibits the activities of various pro-inflammatory signalling pathways and mitigates critical processes in inflammatory illnesses, along with a considerable decrease in NF- κ B mRNA and protein.

Several additional chemicals that were extracted from *Waltheria indica*'s roots, including the anti-inflammatory Quinoline Alkaloids, showed significant anti-inflammatory properties. In addition to waltherione M(8b), 8 deoxoantidesmone (19), waltherione G(11), 9 waltherione H (12), 9 waltherione P(16), 8 antidesmone(18), 11 waltherioneE (20), 8 waltherioneA(22), 12 waltherione E2(23), 13 waltherioneC(24), 14 scutianeneL (25), 15 adouetin Y(26), 16 andamaiouine (27). One with IC₅₀ values ranging from 7.1 to 12.1 μ M, compounds 6, 8a, 9-11, 13, 21, and 24 specifically decreased TNF- α -induced NF- κ B activity. Significant No-inhibitory activity was demonstrated by compounds 6, 8a, 8b, and 11, with IC₅₀ values ranging from 11.0 to 12.8 μ M. According to these results, some chemicals derived from *Waltheria indica* roots show notable anti-inflammatory effects in an animal model at these concentrations⁴⁶.

DISCUSSION

By altering voltage-gated ion channels, strengthening GABA-mediated inhibition, and decreasing glutamate-mediated excitation, anticonvulsant or antiepileptic medications (AEDs) mainly target neuronal excitability and neurotransmission. Anticonvulsants stabilise neuronal activity and stop excessive electrical discharge by acting on a variety of molecular targets in the brain such as Gamma-Amino-Butyric Acid (GABA), a neurotransmitter that inhibits brain activity and thereby reduces excessive electrical firing, and other medications such as phenytoin, carbamazepine, and lamotrigine that block voltage-gated sodium channels to stops the spread of abnormal electrical impulses in the brain. In addition to having a calming effect, the cyclo-peptide adouetin Z, which was isolated from *Waltheria*, also had an impact on the GABAergic system by increasing GABA release.

Flavonoids from *Waltheria indica* have been shown to share structural similarities with benzodiazepines, which experimental data have shown convincingly to induce antiepileptic activity by altering the GABAA-Cl-channel complex. Numerous papers have revealed that *Waltheria indica* extracts are rich in flavonoids, which have been shown to be important for the plant's anti-inflammatory and antioxidant properties.

Thus, it is a potentially useful metabolite that may help with CNS conditions like epilepsy or convulsions. Because of their antioxidant properties, flavonoids are important in this respect. Thus, it is a potentially useful metabolite that could help with CNS conditions like epilepsy.

The systematic review points out a number of shortcomings in the corpus of existing *Waltheria indica* research. Its anticonvulsant and pharmacological actions in humans are not well supported by clinical data, despite encouraging preclinical results. The majority of current research is restricted to animal and *in vitro* models, which cannot fully represent human physiology. Furthermore, it is challenging to compare results or do meta-analyses due to methodological discrepancies among research, which include differences in experimental design, extraction methods, dosages, and outcome measures. Another issue is the caliber of reporting; many studies lack crucial components like blinding and randomization, which raises the possibility of bias. Furthermore, the ethnobotanical context is not well-represented, which may cause it to ignore a variety of traditional uses. The inconsistent identification and quantification of active phytochemicals further limit reproducibility and the formulation of standardized preparations.

Future studies should focus on planning and carrying out thorough, placebo-controlled clinical trials to assess *Waltheria indica*'s safety and effectiveness in humans in order to fill in these gaps. Findings will be more reliable and comparable if experimental procedures are standardised and reporting guidelines like ARRIVE are followed. While ethnobotanical partnerships may reveal traditional knowledge that improves medicinal application, in-depth phytochemical tests are required to isolate and comprehend bioactive ingredients. For a thorough grasp of the plant's potential, an interdisciplinary approach combining pharmacology, toxicology, and ethnomedicine is advised. Furthermore, in order to evaluate safety and facilitate its clinical translation, comprehensive toxicological profiling through long-term studies is necessary.

CONCLUSION

Waltheria indica L. is a promising therapeutic herb with strong pharmacological and anticonvulsant potential, according to this comprehensive study. Current scientific research backs up the ethnomedicinal uses of this substance, which has been utilized historically in many cultures to treat inflammatory and neurological disorders. Its antioxidant, anti-inflammatory, and neuroprotective properties are attributed to important phytochemicals such as flavonoids, alkaloids, and saponins. Although large dosages may be hepatotoxic, preclinical results show significant anticonvulsant effectiveness with a good safety profile. There are still gaps in clinical validation and mechanistic knowledge despite promising results. To fully realise the therapeutic potential of *Waltheria indica* in the management of seizure disorders and related neurological illnesses, future research should concentrate on identifying active chemicals, clarifying molecular pathways, and carrying out well-planned clinical studies.

SIGNIFICANCE STATEMENT

Waltheria indica L., a traditional medicinal herb widely used in Tropical, South American, and African Regions, demonstrates strong potential in modern pharmacology particularly for its anticonvulsant effects. This systematic review underscores the role of its diverse phytochemicals, notably flavonoids, alkaloids, and saponins, in contributing to its neuroprotective properties. Preclinical studies support its antioxidant, anti-inflammatory, and central nervous system activities, affirming its promise as a natural anticonvulsant agent. Although high doses may induce hepatotoxicity, toxicological data indicate a favorable safety profile at therapeutic levels. Further pharmacological, mechanistic, and clinical investigations are essential to validate *W. indica* as a viable plant-based treatment for seizure-related neurological disorders.

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