



Antiepileptic potential of the aqueous extract of *Crassocephalum bauchiense* (Hutch.) Milne-Redh. (Asteraceae) in a kainate induced mouse model of temporal lobe epilepsy

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ABSTRACT

Introduction: Temporal lobe epilepsy (TLE) is characterized by an imbalance between excitatory and inhibitory systems associated with neuroinflammation. These mechanisms contribute to therapeutic resistance and disease progression. *Crassocephalum bauchiense* (Hutch.) Milne-Redh. (Asteraceae) has traditionally been used in the management of convulsions and epilepsy. This study aimed to investigate the antiepileptic potential of *C. bauchiense* in a kainate-induced mouse model of TLE.

Methods: In this experimental study, a single intraperitoneal injection of kainate (15 mg/kg) was used to induce status epilepticus (SE). Over the following two weeks, mice received daily oral treatment with distilled water, sodium valproate (300 mg/kg), or *C. bauchiense* extract (280, 140, 70, and 28 mg/kg). Seizure susceptibility was tested with pentylenetetrazol (15 mg/kg, i.p.), and hippocampal gamma-aminobutyric acid (GABA), GABA aminotransferase (GABA-T), and cytokines were measured.

Results: The extract increased ($P < 0.001$) seizure latency by 58.9-175% (doses 70-280 mg/kg), reduced duration and frequency of recurrent seizures, and at 140-280 mg/kg showed effects comparable to sodium valproate. GABA rose by 49.32%, while GABA-T decreased by 57.64% at the highest dose, restoring inhibitory neurotransmission ($P < 0.001$). Interleukin 1 beta (IL-1 β), interleukin 6 (IL-6), interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) were suppressed in a dose-dependent fashion, with the strongest effects ($P < 0.001$) observed at the higher doses. Moreover, the dysregulated level of interleukin-10 (IL-10) was corrected by the treatment.

Conclusion: The antiepileptic effects were associated with restoration of GABAergic signaling and attenuation of neuroinflammatory markers. These results support the future development of *C. bauchiense* as a source of bioactive compounds with antiepileptic potential.

Implication for health policy/practice/research/medical education:

The study suggests that the aqueous extract of *Crassocephalum bauchiense* may possess antiepileptic potential against epilepsy, particularly temporal lobe epilepsy, and calls for the integration of scientifically validated traditional medicine into health policies to strengthen clinical practice and stimulate interdisciplinary research.

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Introduction

Epilepsy ranks among the widespread chronic neurological disorders, affecting an estimated 50 to 60 million people worldwide, with approximately 85% originating from low-resource countries (1,2). This condition is defined by recurrent and unpredictable seizures arising from abnormal, excessive, and synchronized neuronal activity in the brain (3,4). Among all types of epileptic syndromes, temporal lobe epilepsy (TLE) stands out as one of the most common and hardest-to-treat focal epilepsy types in adults (5). TLE has further been associated with a wide range of health complications, including cognitive impairments, psychiatric comorbidities, and, most importantly, a poor quality of life for patients (6). Despite the availability of approximately twenty antiepileptic drugs, seizures in about 30% of patients remain uncontrolled, defining pharmacoresistant epilepsy (7-9).

The pathophysiology of TLE is based on two fundamental and interconnected mechanisms. The first is the imbalance between excitatory neurotransmission, which is primarily mediated by glutamate, and inhibitory neurotransmission, which is mainly mediated by gamma-aminobutyric acid (GABA), the brain's main inhibitory transmitter and a key regulator of neuronal excitability (10). In TLE, the increased activity of GABA aminotransferase (GABA-T) significantly reduces hippocampal GABA levels. GABA-T is the enzyme responsible for GABA metabolism (11). Decreased GABA directly induces neuronal hyperexcitability and the manifestation of epileptic seizures (12). The second process involves chronic neuroinflammation, which has been identified as a key element in epileptogenic mechanisms and the progression of TLE (13). Recurrent seizures activate microglia and astrocytes, triggering abnormal release of pro-inflammatory cytokines such as interferon gamma (IFN- γ), interleukin 6 (IL-6), interleukin 1 beta (IL-1 β), and tumor necrosis factor alpha (TNF- α) (14,15). These processes further contribute to amplifying neuronal excitability by impairing the function of GABA_A receptors, increasing blood-brain barrier permeability and triggering neuronal death (16,17). Underlying this cascade is a disturbed balance between pro- and anti-inflammatory cytokines, characterized notably by reduced levels of IL-10, a major anti-inflammatory cytokine (18).

Current treatments for epilepsy primarily target specific mechanisms, such as sodium channels, GABA_A receptors, or calcium channels, without simultaneously addressing the inflammatory component of the pathology (19,20). This single-target strategy is one of the reasons for treatment failure in approximately one-third of patients. The use of current medications is associated with numerous side effects that compromise their long-term effectiveness (21). Underscoring the need for new therapeutic strategies capable of acting on both the GABAergic imbalance and the neuroinflammatory process at once, while offering a better safety profile.

In this context, medicinal plants represent a promising source of new antiepileptic molecules (22,23). Numerous plants traditionally employed in the medical treatment of convulsions have demonstrated neuroprotective (24), GABAergic, and anti-inflammatory properties, lending scientific support to their pharmacological investigation (25). Tannins, flavonoids and phenolic compounds, which are frequently present in these plants, are known to modulate GABA_A receptors, inhibit GABA-T, and suppress inflammatory pathways, positioning them as promising therapeutic candidates in epilepsy (26,27).

Crassocephalum bauchiense (Asteraceae) is a medicinal plant traditionally used in Africa to manage anxiety, convulsions and epilepsy (28,29). Its anticonvulsant properties have already been experimentally demonstrated, confirming its efficacy in reducing acute seizures (30). In contrast, its antiepileptic properties have not yet been subjected to rigorous scientific investigation, and the molecular mechanisms underlying its effects remain unclear. The potential richness of this plant in phenolic and flavonoid compounds, combined with its traditional use in convulsive disorders, provides a strong rationale for its pharmacological evaluation in an experimental model of TLE. The present study was therefore designed to assess the antiepileptic potential of *C. bauchiense* in a kainate-induced mouse model of TLE.

Materials and Methods

Plant material and extract preparation

Specimens of *C. bauchiense* (Hutch.) Milne-Redh. were harvested in Ngaoundere, Adamaoua region, Cameroon, during the rainy season (June). Species identity was confirmed at the National Herbarium of Cameroon (Yaoundé) through comparison with a previously deposited voucher specimen (registration number 7954/SRF/Cam), which has been added as the herbarium number for this plant material. The stems and leaves were thoroughly washed with water, air-dried in the shade at ambient temperature and reduced to a fine powder. The aqueous extract of *C. bauchiense* was prepared following traditional practices. Briefly, 10 g of the dried plant powder were added to 50 mL of distilled water in a beaker, and the mixture was heated to boiling at 100 °C for 20 minutes. Once cooled, the preparation was passed through Whatman No. 1 filter paper, giving 32 mL of filtrate which was then dried in an oven set at 50 °C. This yielded 0.9 g of dry extract (9% yield). From the stock solution of 28 mg/mL (equivalent to 280 mg/kg), the required experimental doses were obtained by serial dilution of the 280 mg/kg stock solution (1/2, 1/4, 1/10) provided the three lower experimental doses 140, 70, and 28 mg/kg administered orally.

Chemical products

Kainate, pentylenetetrazol (PTZ) and sodium valproate were obtained from Sigma Chemical Co (St. Louis, USA)

and diazepam from Roche, (Paris, France). All chemicals were dissolved in distilled water, with the exception of *C. bauchiense* extract. Kainate, sodium valproate and PTZ were administered intraperitoneally (i.p.), while distilled water and *C. bauchiense* extract were administered orally (10 mL/kg). For the determination of GABAergic transmission, the reagents used were sourced from Sigma Chemical, USA. The ELISA kits for neuroinflammation markers (IL-6, IL-1 β , TNF- α , IFN- γ , and IL-10) were sourced from Quantikine® Colorimetric ELISA Kits, USA.

Animals

The animals were raised at the University of Ngaoundéré in the laboratory of medicinal plants, health, and galenic formulation. Adult *Mus musculus* mice (18–29 g, 40 days old) were housed in plexiglass cages with unrestricted access to water and used for the pharmacological testing. All procedures complied with the NIH Guide for the Care and Use of Laboratory Animals (Publication No. 85-23, revised 1996), and ethical clearance was granted by the Institutional Animal Care and Use Committee of the University of Buea (UBIACUC No. 008/2019). Every effort has also been made to spare mice unnecessary suffering.

Determination of bioactive compounds of *Crassocephalum bauchiense* aqueous extract

Total phenolics were quantified using the Folin–Ciocalteu method as reported by Ramde-Tiendrebeogo et al (31). Flavonoid content was assessed with the aluminum chloride reagent following the procedure of Omer et al (32). Tannin content was measured using acidified vanillin as described by Kengne et al (33).

Assessment of antioxidant activity by the DPPH test

Free-radical scavenging capacity was evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method adapted from Athamena et al (34), which relies on antioxidants donating electrons that neutralize the DPPH radical, causing its violet color to fade. In practice, 0.5-mL aliquots of hydro-methanolic extract at eight increasing concentrations (0.025 to 100 mg/mL) were combined with 2 mL of 0.1 mM methanolic DPPH solution and left to react for 1 hour at room temperature in the dark. Absorbance was then read at 517 nm on a UV/visible spectrophotometer, and percentage inhibition calculated as:

$$\% \text{ Antioxidant activity} = \frac{(\text{Control absorbance} - \text{Sample absorbance})}{\text{Control absorbance}} \times 100$$

The percentage of inhibition was plotted against the logarithm of extract concentrations to construct a dose–response curve. From this curve, the IC₅₀ value ($\mu\text{g/mL}$ indicating 50% inhibition of DPPH), was determined. Ascorbic acid, tested over the same concentration range, served as the reference standard.

Evaluation of antioxidant activity by the FRAP assay

A second, complementary antioxidant assay was

performed following Pulido et al (35), with minor modifications. The ferric reducing antioxidant power (FRAP) reagent was freshly prepared by combining sodium acetate buffer (pH 3.6, 300 mM), TPTZ solution (2,4,6-tris(2-pyridyl) -1,3,5-triazine, 10 mM), and FeCl₃ solution in a 10:1:1 ratio. For each assay, 5 μL of sample (2 mg/mL) was added to 95 μL of FRAP reagent and the mixture incubated for 30 minutes at 37 °C in the dark. Absorbance was measured spectrophotometrically at 700 nm against a blank. Ascorbic acid was used as the positive control. Antioxidant capacity was expressed as $\mu\text{mol FeSO}_4$ equivalents per gram of sample, based on a calibration curve built from FeSO₄ standards (100–1000 μmol).

Induction and management of status epilepticus

To induce status epilepticus (SE), mice received a single intraperitoneal injection of kainate (15 mg/kg). Thirty minutes after kainate administration, mice displayed orofacial behaviors such as salivation, eye blinking, vibrissae twitching, and yawning. Between 30 and 80-minute post-injection, generalized tonic-clonic seizures culminating in SE were observed. Mice presenting recurrent seizures during a 2-hour observation period were selected and then divided into six groups, each consisting of six mice. In these animals, administration of diazepam at 10 mg/kg (i.p.) effectively controlled seizure recurrence. A seventh group of healthy mice was added and served as the normal control. Over the following 2 weeks, animals received once-daily oral treatment: distilled water (10 mL/kg) for the negative control group; aqueous extract of *C. bauchiense* (280, 140, 70, and 28 mg/kg) for the test groups; sodium valproate (300 mg/kg) for the positive control group; and for the normal control, distilled water (10 mL/kg) combined with a saline injection (0.9%). Following recovery from kainate-induced SE, seizure susceptibility was evaluated using a subconvulsive dose of PTZ. After the two-week treatment period, the mice received PTZ (15 mg/kg) to evaluate their susceptibility to seizures and to determine the antiepileptogenic properties of the extract (36–38). Subsequently, each mouse was confined in an acrylic cage and observed for 90 minutes to assess the latency to the first tonic-clonic seizure, as well as the duration and number of myoclonic and tonic-clonic seizures. Seizure intensity was graded using a validated seven-level behavioral scale (38,39), summarized below:

- Level zero: no response;
- Level one: ear and facial twitching;
- Level two: convulsive waves running axially through the body;
- Level three: myoclonic jerks;
- Level four: generalized clonic seizures, animal turning onto its side;
- Level five: generalized with tonic-clonic seizures progressing to SE;
- Level six: death.

Seizure scores were determined based on the latency to generalized tonic-clonic seizures. The seizure score is a quantitative index used to evaluate the effectiveness of a treatment or extract on seizure severity, based on the latency to seizure onset. This score was derived using the equation below (40): Seizure score = 1 – (latency of the negative control group / latency of the test groups or the positive control group).

Biochemical estimation

Preparation of homogenates

Mice were euthanized by cervical dislocation ninety minutes after the PTZ challenge. The cerebral cortex was dissected out without delay and rinsed in ice-cold saline (0.9%; w/v). For biochemical analysis, hippocampal tissue was processed separately: it was homogenized at a 10% (w/v) ratio in 0.1 M phosphate buffer (pH 7.4) and then centrifuged (3,000 rpm, 15 min, 4 °C). The resulting supernatants were aliquoted and stored at –20 °C until assayed for gamma aminobutyric acid (GABA) content, GABA-transaminase activity (GABA-T) and pro/anti-inflammatory markers.

Determination of GABA concentration and GABA-T enzymatic activity

GABA content was assessed colorimetrically (41), based on the reaction between ninhydrin and succinic semialdehyde, which forms a complex whose absorbance at 512 nm is proportional to GABA concentration. Sample values were read against GABA standards (50, 100, 150, 200, 250, 300, 350, and 400 µg), each combined with 1.5 mg of glutamate dissolved in 2 mL of TCA (10%).

The activity of GABA-T was evaluated using a colorimetric spectrophotometric method (42). The principle is based on the fact that when 12% FeCl₃ is present, succinic semialdehyde and 3-methyl-2-benzothiazolone-2-hydrazone (MBTH) form a colored complex. The spectrophotometer measured the intensity of the coloration, which was proportional to the enzymatic activity in the homogenate, at 610 nm, with readings taken at 30 s and 90 s against the blank. GABA-transaminase activity was estimated according to the Beer-Lambert law using the following equation: Activity (pg/min/mg tissue) = $(Am \times 10^3 \times Vt) / (\epsilon \times l \times t \times Ve \times m)$, where Am is the mean absorbance at 610 nm, ϵ is the molar extinction coefficient (40 M⁻¹·cm⁻¹), Vt is the total reaction volume, Ve is the homogenate volume, t is the reaction time (min), l is the optical path length (1 cm), and m is the tissue mass (43,44).

Determination of inflammation marker levels in the hippocampus

Hippocampal concentrations of IL-6, IL-1β, TNF-α, IFN-γ, and IL-10 were quantified by ELISA following the Quantikine® kit manufacturer's protocol, with results expressed in pg/mL (45).

Histological study

To assess structural integrity, hippocampal tissue encompassing the CA1, CA3, and dentate gyrus subfields was fixed, paraffin-embedded, and sectioned at 7-µm sections before hematoxylin-eosin staining. Microscopic observations were performed with a Scientico STM-50 optical microscope (Hallbergmoos, Germany) connected to a computer at magnifications (25×, 40×, 100×, and 250×). The resulting images were subsequently processed and analyzed.

Statistical analysis

All statistical processing and graphing relied on GraphPad Prism (version 8.0.1). Results were expressed as mean ± standard error of the mean (SEM) or as percentage. Values were compared using one-way ANOVA, and when significant differences were observed, Tukey's post hoc test was applied to highlight differences among groups. At $P < 0.05$, differences were considered significant.

Results

Phytochemical analysis of the aqueous extract of *Crassocephalum bauchiense*

The phytochemical analysis revealed that the extract contained 105.72 ± 0.28 mg equivalent of gallic acid (EAG/g) for total polyphenols, 35.51 ± 0.33 mg quercetin equivalent (QE/g) for flavonoids, and 22.63 ± 0.12 mg equivalent of tannic acid (EAT/g) (Table 1).

Antioxidant activity of the aqueous extract of *Crassocephalum bauchiense*: evaluation using DPPH and FRAP assays

The extract showed measurable antioxidant activity relative to the positive control (Table 2). Specifically, the activity rose from 37.42 ± 0.11 µg/mL in the positive control to 68.75 ± 1.23 µg/mL with the extract of *C. bauchiense*. The extract exhibited a lower reducing capacity than the

Table 1. Bioactive compound content of *Crassocephalum bauchiense* aqueous extract

Compounds	Value
Polyphenols (mg EAG/g)	105.72 ± 0.28
Flavonoids (mg QE/g)	35.51 ± 0.33
Tannins (mg EAT/g)	22.63 ± 0.12

EAG: Equivalent of gallic acid; QE: Quercetin equivalent; EAT: Equivalent of tannic acid.

Table 2. Effect of *Crassocephalum bauchiense* aqueous extract on the antioxidant activity

Compounds	DPPH test (IC ₅₀ (µg/mL))	FRAP method (µmol FeSO ₄ /g)
<i>C. bauchiense</i>	68.75 ± 1.23	32.16 ± 0.24
Vitamin C	37.42 ± 0.11	145.92 ± 0.72

DDPH: 2,2-Diphenyl-2-picrylhydrazyl; FRAP: Ferric reducing antioxidant power.

positive control, with values decreasing from 145.92 ± 0.72 $\mu\text{mol FeSO}_4/\text{g}$ in the positive control to 32.16 ± 0.24 $\mu\text{mol FeSO}_4/\text{g}$ in the aqueous extract of *C. bauchiense*.

Effect of *Crassocephalum bauchiense* on latency and score of kainate-induced generalized tonic-clonic seizures

Mice in the negative control group reached their first tonic-clonic seizure after 25.06 ± 1.15 min (Figure 1A). At the lowest dose tested (28 mg/kg), the extract lengthened this latency to 34.93 ± 5.05 min, 39.4% but the change was not statistically significant. Treatment with *C. bauchiense* at the other doses significantly increased [$F(6,35) = 139$, $P < 0.001$] the latency, reaching 68.91 ± 3.75 min (175%), 66.18 ± 1.43 min (164.2%) and 39.81 ± 6.40 min (58.9%) at doses of 280, 140 and 70 mg/kg, respectively (Figure 1A). Sodium valproate produced a comparable increase (70.25 ± 5.24 min; 180.4%) (Figure 1A).

Relative to the normal control, the untreated kainate group showed a markedly reduced seizure score (Figure 1B). The extract increased [$F(6, 35) = 12$, $P < 0.001$] the seizure score to 0.64 ± 0.04 (64%), 0.62 ± 0.06 (62%), 0.37 ± 0.01 (37%) and 0.28 ± 0.02 (28%) at doses of 280, 140, 70 mg/kg respectively (Figure 1B). Sodium valproate produced a similar reduction, to 0.64 ± 0.02 , (64%) (Figure 1B). The two highest extract doses (140 and 280 mg/kg) produced seizure scores ranging from 0.62 to 0.64, values very close to those obtained with sodium valproate (0.64). These findings indicate a comparable efficacy between the extract and the reference treatment.

Effects of *Crassocephalum bauchiense* extract on kainate-induced seizure duration and number

Relative to the normal group, the negative control exhibited significantly longer myoclonic seizure episodes (Figure 2A). Extract treatment shortened this duration in a dose-related fashion [$F(6, 35) = 63.3$, $P < 0.001$] bringing it down from 43.95 ± 3.44 s in untreated kainate-injected

mice to 14.02 ± 1.76 s (68.10%), 14.67 ± 4.66 s (66.62%), 24.87 ± 1.67 s (43.37%) and 31.07 ± 4.8 s (29.30%) at doses of 280, 140, 70 and 28 mg/kg respectively (Figure 2A). Sodium valproate reduced duration in similar fashion ($P < 0.001$) to 16.28 ± 3.43 s (62.96%) in extract-treated groups (Figure 2A).

Generalized tonic-clonic seizure duration likewise augmented ($P < 0.05$) in untreated kainate-injected mice (33.6 ± 2.14 s) compared to the normal group (Figure 2A). The duration of these seizures attenuated [$F(6,35) = 78.8$, $P < 0.001$] to 15.16 ± 2.23 s (54.88%), 18.24 ± 2.45 s (45.71%), 25.16 ± 2.07 s (25.12%) and 24.72 ± 2.88 s (26.42%) at doses 280, 140, 70 and 28 mg/kg of *Crassocephalum bauchiense* extract respectively (Figure 2A). The response resembled that of sodium valproate, which induced a significant reduction to 16.28 ± 1.15 s (51.55%) (Figure 2A).

In untreated kainate-injected mice (27.67 ± 2.66), the number of myoclonic episodes increased sharply relative to the normal group (Figure 2B). This increase was significantly attenuated by the extract [$F(6, 35) = 48.2$] which lowered episode counts to 5.83 ± 1.5 (78.93%, $P < 0.001$), 8.66 ± 1.66 (68.70%, $P < 0.001$) and 18.33 ± 4.66 (33.75%, $P < 0.01$) respectively, in mice dosed at 280, 140 and 70 mg/kg compared to the untreated kainate-injected mice (Figure 2B). Sodium valproate produced a 77.74% reduction ($P < 0.001$, down to 6.16 ± 1.83) over the same comparison (Figure 2B).

In untreated kainate-injected mice (negative control), generalized tonic-clonic seizure counts were significantly higher ($P < 0.001$; 23.30 ± 4.37) compared with the normal group (Figure 2B). The extract lowered this count [$F(6, 35) = 49.6$] to 7.73 ± 1.17 (66.82%, $P < 0.001$), 8.19 ± 0.95 (64.85%, $P < 0.001$), and 14.26 ± 3.06 (38.80%, $P < 0.001$) to 17.26 ± 1.66 (25.92%, $P < 0.01$) in mice treated with 280, 140, and 70 mg/kg respectively, compared with the untreated kainate-injected mice (Figure 2B). Sodium

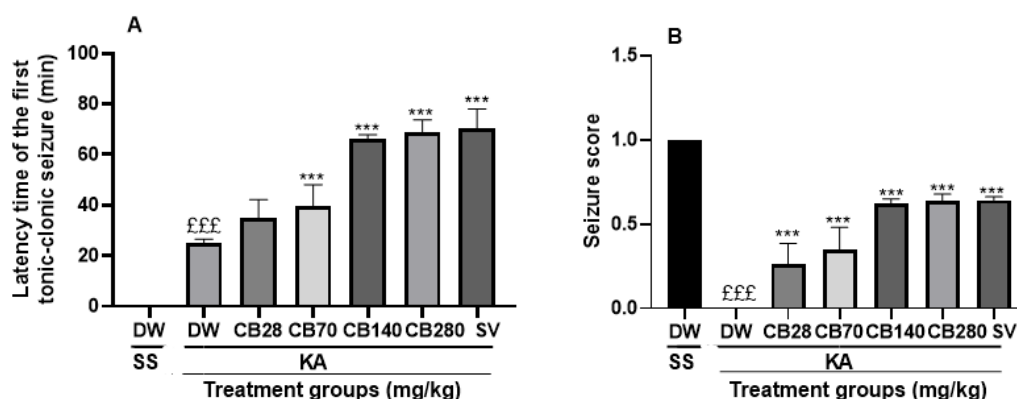


Figure 1. Effect of *Crassocephalum bauchiense* on latency to the first tonic-clonic seizure (A) and seizure score (B) in the kainate model. Mean $\pm$ SEM ($n = 6$) are shown; data analyzed by one-way ANOVA with Tukey's post hoc test. *** $P < 0.001$: significant difference compared to the negative control (DW/KA). $^{***}P < 0.001$; significant difference compared to the normal control (DW/SS); DW: Distilled water (10 mL/kg); SS: Saline solution (0.9%); KA: Kainate (15mg/kg); CB/KA: Groups treated with *Crassocephalum bauchiense* extract (28–280 mg/kg); SV/KA: Group treated with sodium valproate (300 mg/kg).

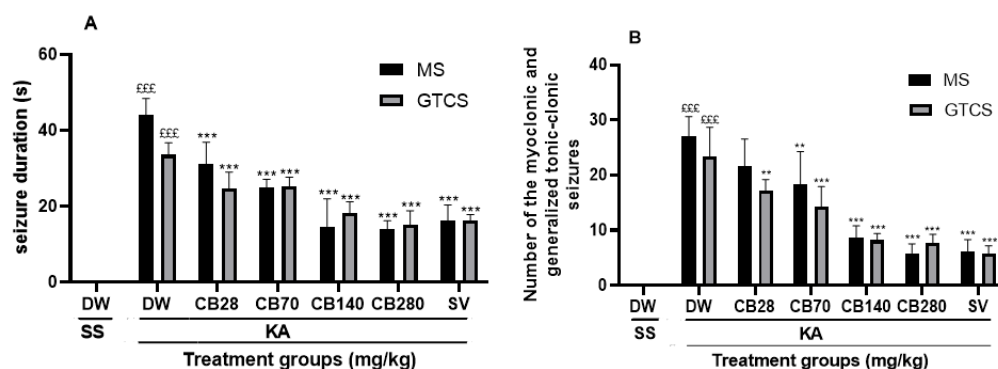


Figure 2. Effect of *Crassocephalum bauchiense* on the seizure duration (A) and the number of myoclonic and generalized tonic-clonic seizures (B) of kainate-induced seizures. Mean $\pm$ SEM (n = 6) are shown; data analyzed by one-way ANOVA with Tukey's post hoc test. ** $P < 0.01$; *** $P < 0.001$: significant difference compared to the negative control (DW/KA). ^{EEE} $P < 0.001$; significant difference compared to the normal control (DW/SS). DW: Distilled water (10 mL/kg); SS: Saline solution (0.9%); KA: Kainate (15mg/kg); CB/KA: Groups treated with *Crassocephalum bauchiense* extract (28–280 mg/kg); SV/KA: Group treated with sodium valproate (300 mg/kg). GTCS: Generalized tonic-clonic seizures. MS: Myoclonic seizures.

valproate achieved a 74.98% reduction ($P < 0.001$), down to 5.83 ± 1.00 compared to the untreated kainate-injected mice (Figure 2B).

Effect of *Crassocephalum bauchiense* extract on the GABA metabolism in the hippocampus

Kainate administration lowered hippocampal GABA content in the untreated kainate-injected mice to 250.33 ± 6.67 $\mu\text{g/g}$ tissue or 34.24% ($P < 0.001$) reduction relative to the normal control (380.67 ± 1.33 $\mu\text{g/g}$ tissue) (Table 3). The *C. bauchiense* extract augmented [F (6, 35) = 194, $P < 0.001$] the GABA concentration by 373.83 ± 6.17 $\mu\text{g/g}$ tissue (49.32%), 356.67 ± 9.4 $\mu\text{g/g}$ tissue (42.47%) and 287.17 ± 7.16 $\mu\text{g/g}$ tissue (14.73%) respectively at doses of 280, 140 and 70 mg/kg (Table 3). There was also a significant increase effect with sodium valproate by 374.17 ± 7.78 $\mu\text{g/g}$ tissue (49.46 %).

GABA-transaminase activity showed a significant increase in untreated kainate-injected mice (123.71 ± 11.78 pg/min/mg of tissue or 126.1%) compared to the normal control (54.72 pg/min/mg of tissue) (Table 3). The extract suppressed this enzymatic activity in a dose-dependent

fashion [F (6, 35) = 32.7, $P < 0.001$] bringing it down by 52.38 ± 5.17 pg/min/mg ($P < 0.001$) (57.64%), 81.05 ± 5.17 pg/min/mg ($P < 0.001$) (34.50%) and 99.88 ± 18.33 pg/min/mg ($P < 0.05$) (19.29%) in mice treated with 280, 140, and 70 mg/kg (Table 3). Sodium valproate reduced GABA-T activity by 53.05 ± 1.83 pg/min/mg tissue ($P < 0.001$) (57.12%) a magnitude closely matching that of the highest extract dose (Table 3).

Effect of *Crassocephalum bauchiense* extract on hippocampal pro- and anti-inflammatory markers

Administration of kainate amplified the level of pro-inflammatory markers (Figure 3). The levels of TNF- α , IFN- γ , IL-1 β and IL-6 amplified ($P < 0.001$) to 138.92 ± 22.5 pg/mL, 151.83 ± 11.62 pg/mL, 141.46 ± 7.27 pg/mL, and 303.11 ± 7.15 pg/mL in the normal control group to 136% (327.78 ± 12.58 pg/mL, Figure 3A), 151.7% (382.15 ± 6.54 pg/mL, Figure 3B), 130.2% (325.60 ± 20.43 pg/mL, Figure 3C), and 55.8% (472.26 ± 11.47 pg/mL, Figure 3D) in the untreated kainate-injected mice respectively (Figure 3).

The extract of *C. bauchiense* suppressed [F (6, 35) = 48, $P < 0.001$] the concentration of TNF- α to 147.90 ± 13.61

Table 3. Effect of *Crassocephalum bauchiense* extract on the GABA metabolism in the hippocampus

Treatment	Doses (mg/kg)	GABA ($\mu\text{g/g}$)	Significant % increase	GABA-T activity (pg/min/mg)	Significant% Decrease
DW/SS	--+--	380.67 ± 1.33	0	54.72 ± 0.94	0
DW/KA	--+ 15	250.33 ± 6.67 ^{EEE}	0	123.72 ± 11.78 ^{EEE}	0
CB28/KA	28+15	262.83 ± 8.5	0	120.21 ± 17.67	0
CB70/KA	70+15	287.17 ± 7.17 ^{***}	14.73%	99.88 ± 18.33 [*]	19.29%
CB140/KA	140+15	356.67 ± 9.44 ^{***}	42.47%	81.04 ± 5.17 ^{***}	34.50%
CB280/KA	280+15	373.83 ± 6.17 ^{***}	49.32%	52.38 ± 5.17 ^{***}	57.64%
SV/KA	300+15	374.17 ± 7.78 ^{***}	49.46%	54.04 ± 1.83 ^{***}	57.12%

Mean $\pm$ SEM (n = 6) are shown; data analyzed by one-way ANOVA with Tukey's post hoc test. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$: significant difference compared to the negative control (DW/KA). ^{EEE} $P < 0.001$; significant difference compared to the normal control (DW/SS). DW: Distilled water (10 mL/kg); SS: Saline solution (0.9%); KA: Kainate (15mg/kg); CB/KA: Groups treated with *Crassocephalum bauchiense* extract (28–280 mg/kg); SV/KA: Group treated with sodium valproate (300 mg/kg); --+--: Distilled water (10 mL/kg) and saline solution (0.9%); --+15: Distilled water (10 mL/kg) and kainate (15 mg/kg).

pg/mL (54.9%), 142.35 ± 13.26 pg/mL (56.6%), 204.68 ± 26.31 pg/mL (37.6%), and 246.57 ± 25.66 pg/mL (24.8%) at doses 280, 140, 70 and 28 mg/kg, respectively (Figure 3A). It also suppressed [F (6, 35) = 10, $P < 0.001$] the level of IFN- γ to 152.76 ± 18.23 pg/mL (60.02%), 165.17 ± 19.15 pg/mL (56.8%), 239.54 ± 15.20 pg/mL (37.32%), and 300.91 ± 27.20 pg/mL (21.3%) at doses 280, 140, 70 and 28 mg/kg, respectively (Figure 3B). It also suppressed [F (6, 35) = 39] the level of IL-1 β to 145.79 ± 14.37 pg/mL (55.22%, $P < 0.001$), 177.26 ± 14.25 pg/mL (45.6%, $P < 0.001$), 149.92 ± 44.11 pg/mL (53.95%, $P < 0.001$), and 270.14 ± 14.79 pg/mL (17.03%, $P < 0.05$) at dose 280, 140, 70 and 28 mg/kg, respectively (Figure 3C). Finally, it suppressed [F (6, 35) = 95, $P < 0.001$] the level of IL-6 to 301.92 ± 4.01 pg/mL (36.06%), 317.79 ± 11.12 pg/mL (32.70%), 327.01 ± 18.63 pg/mL (30.75%), and 376.01 ± 15.38 pg/mL (20.4%) at doses 280, 140, 70, and 28 mg/kg, respectively (Figure 3D).

Sodium valproate produced comparable reductions across all four cytokines ($P < 0.001$) to 136.83 ± 7.12 pg/mL (58.25%), 158.99 ± 12.99 pg/mL (58.4%), 140.26 ± 8.17 pg/mL (56.92%), and 300.83 ± 4.5 pg/mL (36.3%) for TNF- α , IFN- γ , IL-1 β , and IL-6 levels, respectively (Figure 3).

The level of IL-10 amplified from 136.48 ± 7.65 pg/mL in normal control group to 307.12 ± 28.21 pg/mL (125.02%) in the untreated kainate-injected mice (Figure 3E). *C. bauchiense* suppressed [F (6, 35) = 50] the concentration of IL-10 to 137.60 ± 12.49 pg/mL (55.19%, $P < 0.001$), 152.66 ± 18.49 pg/mL (50.29%, $P < 0.001$), 166.98 ± 26.06 pg/mL (45.64%, $P < 0.001$), and 251.71 ± 16.67 pg/mL (18.03%, $P < 0.01$) at doses 280, 140, 70, and 28 mg/kg,

respectively (Figure 3E). Sodium valproate suppressed ($P < 0.001$) the concentration of IL-10 (Figure 3E) to 134.50 ± 7.28 pg/mL (56.20%).

Effect of *Crassocephalum bauchiense* extract on the hippocampal neuronal damage

Hematoxylin and eosin staining showed that neurons in the CA1, CA3, and dentate gyrus regions were normal and densely packed in the normal control group (DW/SS) (Figure 4). The negative control (DW/KA) displayed hallmark features of hippocampal sclerosis: thinning of the CA1 and CA3 pyramidal layers alongside a marked drop in neuronal cell density (Figure 4). Kainate administration resulted in neuronal loss and disorganization of the pyramidal layer, accompanied by reactive gliosis in the CA3 region, as well as pyramidal cell degeneration with decreased neuronal density in the CA1 region and granule cell dispersion in the dentate gyrus (Figure 4). In mice treated with *C. bauchiense* extract (140 and 280 mg/kg), preservation of the CA1, CA3, and dentate gyrus layers was observed. Furthermore, in mice receiving sodium valproate, neurons in the CA1 layer were better preserved than those in the CA3 layer (Figure 4).

Discussion

TLE is characterized by an imbalance between excitatory and inhibitory systems, together with chronic neuroinflammation that contributes both to disease progression and to therapeutic resistance (16,17). In this context, identifying molecules capable of targeting both mechanisms simultaneously remains a major therapeutic

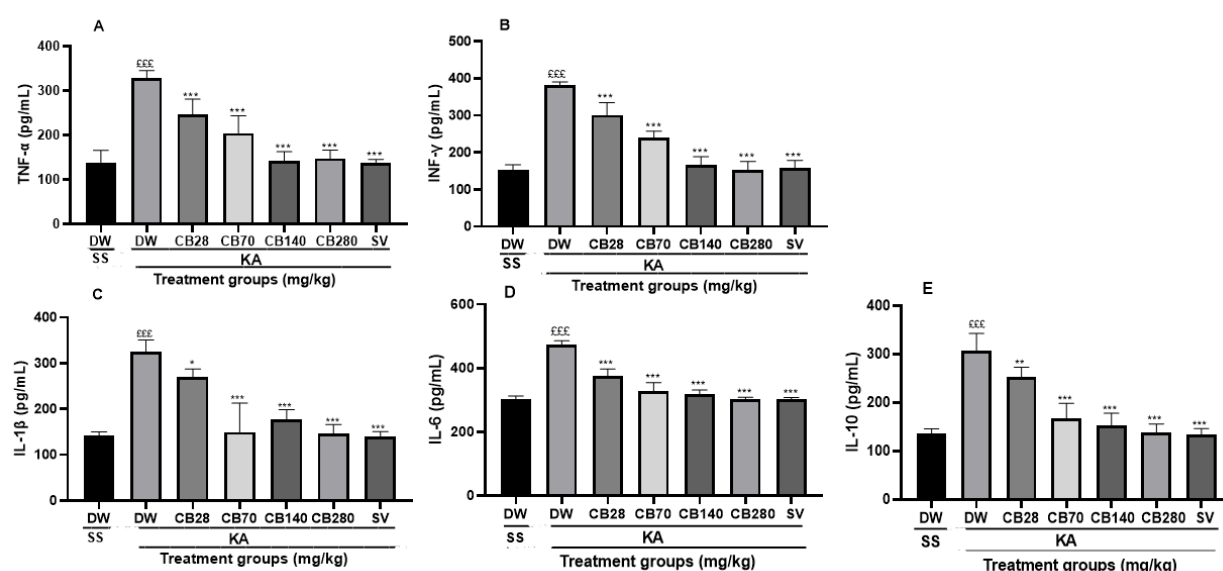


Figure 3. Effects of the aqueous extract of *Crassocephalum bauchiense* on hippocampal concentrations of pro- (A, B, C, D) and anti-inflammatory (E) markers. Mean $\pm$ SEM (n = 6) are shown; data analyzed by one-way ANOVA with Tukey's post hoc test. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$: significant difference compared to the negative control (DW/KA). ### $P < 0.001$: significant difference compared to the normal control (DW/SS). DW: Distilled water (10 mL/kg); SS: Saline solution (0.9%); KA: Kainate (15 mg/kg); CB/KA: Groups treated with *Crassocephalum bauchiense* extract (28–280 mg/kg); SV/KA: Group treated with sodium valproate (300 mg/kg); IL-1 β : interleukin 1 β ; IL-6: interleukin 6; TNF- α : tumor necrosis factor- α ; IFN- γ : interferon- γ ; IL-10: interleukin 10.

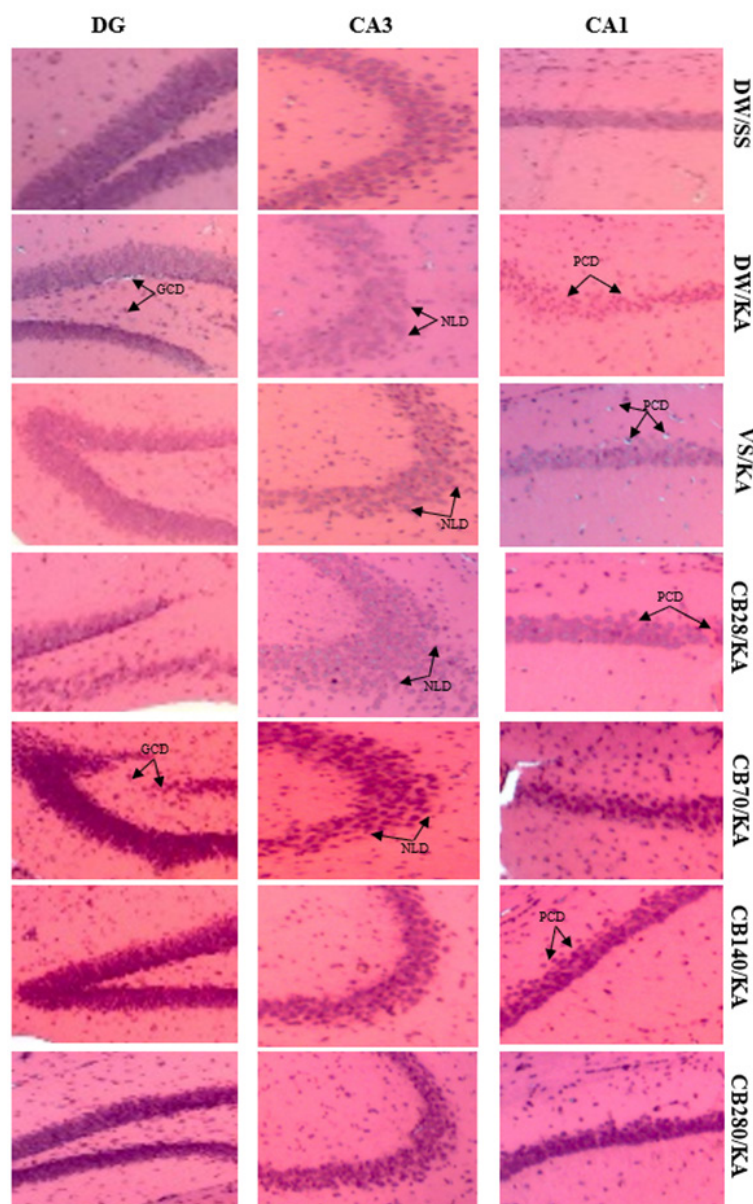


Figure 4. Hippocampal microphotographs (H&E, $\times 250$) illustrating kainate-induced damage and the neuroprotective action of the aqueous extract of *Crassocephalum bauchiense*. (DW/SS): normal control. (DW/KA): negative control. DW: Distilled Water (10 mL/kg); SS: Saline solution (0.9%); KA: Kainate (15mg/kg); CB/KA: groups treated with *Crassocephalum bauchiense* extract (28–280 mg/kg); SV/KA: Group treated with sodium valproate (300 mg/kg); DG: dentate gyrus; CA1: Cornu Ammonis 1; CA3: Cornu Ammonis 3; H&E: Hematoxylin and eosin; GCD: Granule cell dispersion; NLD: Neuronal loss and disorganization of the pyramidal layer, with reactive gliosis; PCD: Pyramidal cell degeneration, with reduced neuronal density.

challenge (25). The present findings show that the extract exerts significant antiepileptic effects in a kainate-induced mouse model of TLE by restoring GABAergic neurotransmission and modulating cytokine-mediated neuroinflammation. The kainate model is widely employed to reproduce both the symptoms and the pharmacological profile of human TLE (46).

Treatment with the extract lengthened the latency to seizure onset in a dose-dependent manner, with increases ranging from roughly 58.9% to 175% ($P < 0.001$), while also curbing both the frequency and the duration of subsequent seizures. These results may demonstrate a significant anticonvulsant effect. At the two highest

doses of 140 and 280 mg/kg, the observed effects were equivalent to those of sodium valproate (300 mg/kg), the reference antiepileptic drug whose mechanism of action is partly mediated through the elevation of cerebral GABA concentrations (47). This comparability with a well-established reference treatment reinforces the therapeutic relevance of *C. bauchiense* and suggests that both interventions may share convergent mechanisms of action. The PTZ (15 mg/kg) model employed to assess seizure susceptibility following treatment is a validated and widely used pharmacological tool for evaluating the convulsive threshold (48), which supports the reliability of these observations. These results corroborate our previous

work, which demonstrated the efficacy of *C. bauchiense* in reducing acute seizures induced by pilocarpine (30).

Among the most notable findings is the 58% reduction in hippocampal GABA-T activity observed in extract-treated animals. GABA-T catalyzes the conversion of GABA into succinic semialdehyde (49). Inhibition of this enzyme represents a well-established pharmacological strategy to enhance synaptic GABA availability and elevate the seizure threshold (50,51). Yasir et al (52) provided a detailed description of the molecular basis of GABA-T inhibition, emphasizing that this enzyme constitutes a particularly attractive therapeutic target in refractory epilepsy. Our results support this viewpoint, indicating that *C. bauchiense* may exert its antiepileptic effect by inhibiting GABA-T, similar to vigabatrin, the standard irreversible inhibitor. However, unlike vigabatrin, whose clinical use is limited by the risk of irreversible visual deficits (52), the extract of *C. bauchiense* may present a more favorable tolerance profile, although long-term toxicity studies are required to confirm this hypothesis. This reduction in GABA-T activity was accompanied by a 49% increase in hippocampal GABA levels. The hippocampus represents the central brain structure in the pathophysiology of TLE (53), and restoration of GABAergic inhibition at this site is of particular importance. The most likely explanation is that reduced enzymatic catabolism allows GABA to accumulate within the synaptic cleft (50). It cannot be excluded that the extract also acts by stimulating glutamate decarboxylase, the enzyme that synthesizes GABA from glutamate (54,55). This hypothesis warrants further investigation in subsequent studies to fully elucidate the molecular pathways involved in the GABAergic modulation induced by *C. bauchiense*.

Phytochemical screening revealed substantial concentrations of phenols, flavonoids, and tannins associated with strong in vitro antioxidant activity. These phytochemical data are consistent with the pharmacological effects observed. Several flavonoids have been described in the literature as modulators of GABA_A receptors, acting in a manner similar to benzodiazepines by potentiating inhibitory transmission (26). Certain phenolic compounds have also been shown to inhibit GABA-T directly, providing a plausible molecular basis for the effects observed (56,57). The identification and isolation of the active principles responsible for these effects represent a priority research perspective for future studies.

The extract treatment substantially suppressed hippocampal levels of TNF- α , IL-1 β , IL-6, and IFN- γ . These pro-inflammatory cytokines are known to amplify neuronal excitability through several mechanisms (13,58). IL-1 β and TNF- α impair GABA_A receptor function by reducing their membrane expression and altering their phosphorylation, weakening GABAergic inhibition (59,60). In contrast, IL-6 and IFN- γ contribute to chronic

microglial activation and disruption of the blood–brain barrier, promoting epileptogenic progression (61). The simultaneous reduction of these four inflammatory mediators suggests that *C. bauchiense* exerts a broad, non-selective anti-neuroinflammatory effect, targeting multiple arms of the cerebral inflammatory response. Beyond the suppression of pro-inflammatory cytokines, the normalization of IL-10 levels observed in our study deserves particular attention. IL-10 is a major anti-inflammatory cytokine whose production is often impaired under conditions of chronic epilepsy, contributing to the persistence of the inflammatory state (62). Restoration of IL-10 levels by *C. bauchiense* treatment suggests an active rebalancing of the pro-/anti-inflammatory axis, rather than a mere global suppression of the immune response. This immunological modulation profile favorably distinguishes the *C. bauchiense* extract from non-specific anti-inflammatory agents and highlights its capacity to restore cerebral immune homeostasis.

Together, these results may support the existence of a bidirectional interaction between neuroinflammation and the GABAergic signaling in TLE (63). Pro-inflammatory cytokines reduce GABA_A receptor expression and function, deepening the inhibitory deficit and facilitating seizure occurrence (60,64), while recurrent seizures in turn sustain microglial activation and cytokine release, perpetuating the cycle (14). By simultaneously targeting these two mechanisms, *C. bauchiense* may disrupt this vicious cycle, offering a potential therapeutic advantage over conventional antiepileptic drugs, which generally act on only one of these pathways (20).

Regarding antioxidant capacity, the DPPH assay is considered a reference method for evaluating antioxidant potential (65). It measures the ability of compounds to neutralize free radicals, a role in which tannins and flavonoids are particularly effective (66). Flavonoids exhibit strong antioxidant properties due to their conjugated aromatic structures and the presence of hydroxyl groups. They are particularly involved in scavenging superoxide, singlet oxygen, and peroxidized lipids, while stabilizing free radicals through hydrogenation reactions or complexation with oxidative species (67). In general, polyphenolic antioxidants such as flavonoids and tannins reduce and decolorize DPPH by donating hydrogen atoms (68). These constituents present in the aqueous extract are presumed to account for its antioxidant effect. Tannins and flavonoids enhance ferric reducing power, primarily through metal ion chelation and partial inhibition of the Fenton reaction (67). The hydroxyl groups of phenolic compounds present in the *C. bauchiense* extract further explain its ability to act as electron donors.

Results from this study demonstrated that kainate administration in mice induced a neuro-inflammatory response within the hippocampal regions CA1, CA3, and the dentate gyrus, reflecting an ongoing neurodegenerative

process. In contrast, treatment with the extract limited neuronal loss and reduced the disorganization of cellular architecture in these regions. These observations are corroborated by prior investigations that have highlighted the antioxidant and immunomodulatory properties of this plant (69,70).

On the basis of these findings, an integrated mechanism of action can be proposed for the aqueous extract of *C. bauchiense* in TLE. The phenolic and flavonoid compounds it contains likely act, on one hand by inhibiting hippocampal GABA-T activity, reducing GABA catabolism and increasing its synaptic availability (26,52). In parallel, the phenolic and flavonoid constituents act by curbing pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, IFN- γ) and normalizing IL-10 levels (61–63). These two convergent effects mutually reinforce each other to restore the excitation/inhibition balance in the hippocampus, elevate the seizure threshold, and reduce both their frequency and duration. This dual mechanism of action represents the major originality of *C. bauchiense* compared with conventional antiepileptic treatments that typically target a single pathway.

Several limitations temper the interpretation these results. First, the researchers conducted this study in a murine animal model, and they have yet to demonstrate the translatability of the findings to humans (71). Second, the extract used was a crude aqueous preparation containing multiple compounds, and the active principles responsible for the observed effects have not yet been individually isolated and characterized. Third, this study has not elucidated the precise mechanism of GABA-T inhibition, particularly whether it is reversible or irreversible (52). Fourth, the upstream molecular signaling pathways, including NF- κ B, mTOR, and MAP kinase cascades, which may mediate the observed anti-inflammatory effects, remain to be investigated (72). Finally, the absence of chronic toxicity and pharmacokinetic data represents a major limitation before any therapeutic development can be envisioned.

Conclusion

The results of this study provide scientific validation for the antiepileptic properties of *C. bauchiense*, a plant traditionally used to treat convulsions and epilepsy. The richness of the extract in phenolic compounds, flavonoids, and tannins, together with its strong antioxidant activity, provides a plausible phytochemical basis for the pharmacological mechanisms identified. The antiepileptic effects were associated with restoration of GABAergic signaling and attenuation of neuroinflammatory markers. These results indicate that the aqueous extract of *C. bauchiense* may possess therapeutic potential within traditional medicine for the management of epilepsy.

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Authors' contribution

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Formal analysis: Wangbara Alkali Tchang, Joseph Ngaibi and Taiwe Sotoing Germain.

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Conflict of interests

The authors declare no conflict of interest

Ethics considerations

All procedures complied with the NIH Guide for the Care and Use of Laboratory Animals (Publication No. 85-23, revised 1996), and ethical clearance was granted by the Institutional Animal Care and Use Committee of the University of Buea (UBIACUC No. 008/2019).

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