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Research Paper

Potential of *Khaya senegalensis* to mitigate epileptogenesis and cognitive dysfunction on kainate-induced post-*status epilepticus* model

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ABSTRACT

Background and aim: To date, there is no treatment to prevent the development of temporal lobe epilepsy, the most common form of drug-resistant epilepsy. A recent study revealed the antiepileptic-like effect of the aqueous extract of *Khaya senegalensis*. Given the potential of this extract, the antiepileptogenic- and learning and memory-facilitating-like effects of the aqueous extract of *Khaya senegalensis* were assessed using the kainate-induced post-*status epilepticus* model.

Methods: Epilepsy was induced by injecting a single dose of kainate (12 mg/kg, i.p.) in rats. Animals that developed 2 hours of *status-epilepticus* were randomized and treated as follows: a negative control group received distilled water (10 ml/kg, *p.o.*); two positive control groups received sodium valproate (300 mg/kg, *p.o.*) or phenobarbital (20 mg/kg, *p.o.*); and three test groups received the extract (50, 100, 200 mg/kg, *p.o.*). A sham group was added and received distilled water (10 ml/kg, *p.o.*). All treatments were performed twice daily until the occurrence of the first spontaneous seizure (stage 4 or 5) in the negative control group, on day 14. After the completion of treatments, memory impairment was assessed using the T-maze. Two weeks following behavioral analysis, the rats that received the most effective dose of the extract on spontaneous recurrent were challenged with pentylenetetrazole (30 mg/kg, i.p.). This is to assess their susceptibility to generalized tonic-clonic seizures (stage 5). Rats were finally euthanized, and pro-inflammatory cytokines, or neurogenesis markers were quantified in the hippocampus.

Results: The extract of *Khaya senegalensis* significantly prevented spontaneous recurrent seizures on day 14. It also reduced cognitive decline. Furthermore, it significantly decreased pro-inflammatory cytokines levels and increased those of neurotrophic factors.

Conclusions: These findings thus suggest that the extract is endowed with antiepileptogenic- and learning and memory-enhancing-like effects. These effects are likely mediated by anti-inflammatory and neurotrophic pathways. This justifies, therefore, its use to treat empirically epilepsy.

1. Introduction

Epilepsy is a neurological disorder characterized by an enduring predisposition to generate unprovoked seizures and by neurobiological, cognitive, psychological, and social consequences (Beghi, 2020). Approximately 70 million people worldwide suffer from epilepsy, and 90 % live in developing regions (Singh and Trevick, 2016). Indeed, studies carried out in developing and tropical countries showed a higher prevalence of epilepsy, ranging from 14 to 57 cases per 1000 persons (Singh and Trevick, 2016). Of all types of epilepsies, temporal lobe epilepsy (TLE) is the most common form of epilepsy in adults (Lévesque et al., 2013). TLE is a syndrome in which seizures originate in the temporal lobe (Lévesque et al., 2013). This syndrome is the most common intractable seizure disorder associated with hippocampal damage, including atrophy, neurogenesis alterations, and gliosis (Lévesque et al., 2013). TLE can be triggered by head trauma, infections, tumors, toxins, and uncontrolled seizures that last over 30 minutes, known as *status epilepticus*. Following these precipitating events (acute phase), the brain

Abbreviations: ANOVA, analysis of variance; DW, distilled water; I.p., intraperitoneally; *p.o.*, *per os*; *K. senegalensis*, *Khaya senegalensis*; *SE*, *Status epilepticus*; KA, Kainate; SVA, Sodium valproate; PhB, phenobarbital; SEM, standard error of the mean; TNF-α, Tumor necrosis factor-alpha; IL-β, Interleukin beta; IL-10, Interleukin 10; COX-2, Cyclooxygenase 2; BDNF, Brain-derived neurotrophic factor; FGF-2, Fibroblast growth factor 2; TLE, Temporal lobe epilepsy.

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undergoes a silent period, part of the epileptogenesis process that also includes the chronic phase of the disease characterized by recurrent spontaneous seizures (Kandeda et al., 2017). Thus, epileptogenesis is a dynamic molecular and cellular process in which a normal brain becomes epileptic (Pitkänen et al., 2015). To study this process, kainic acid (KA) model of TLE is used (Lévesque et al., 2013). Kainic acid is preferred to other chemoconvulsants (pilocarpine, 4-aminopyridine, and pentylenetetrazole) because it induces severe alterations or dysfunctions in limbic structures (amygdala, hippocampus, entorhinal cortex, subiculum, striatum) associated with severe inflammations. These changes or features are similar to those of human TLE. Systemic and intracerebral administrations of KA lead to similar brain damage, although systemic administration results in more extensive damage (Lévesque et al., 2013).

Several antiepileptic drugs such as sodium valproate, levetiracetam, lamotrigine, perampanel, lacosamide, vigabatrin, gabapentin, topiramate, carbamazepine, pentobarbital are used to treat TLE, however, these pharmacological treatments control seizures rather than the underlying causes of the disease (Smolensky et al., 2019). In addition, these treatments do not prevent or halt the development of epilepsy (epileptogenesis process) and associated cognitive comorbidities including learning and memory impairments, mood swings, attention deficits, and behavioral changes. Treatments that prevent or inhibit the development of TLE and associated learning and memory impairments are therefore necessary. Experimental evidence suggests a significant involvement of inflammation during the epileptogenesis process (Holtman et al., 2013). Equally, epileptic seizures can initiate the release of pro-inflammatory cytokines and activate immune responses (Vezzani et al., 2013a). These phenomena are largely correlated with the susceptibility of the brain to seizures, neurogenesis, and neuronal-like cell body preservation (Lee et al., 2010). Furthermore, epileptogenic alterations lead to aberrant hippocampal neurogenesis, including increased proliferation of neuronal progenitors, mossy fiber sprouting, neuronal hypertrophy, and persistence of hilar dendrites in adults (Cho et al., 2015). Past studies using nonspecific pharmacological agents suggest that blocking aberrant adult neurogenesis reduces seizures and associated memory impairment (Cho et al., 2015). Antiepileptogenic drugs with effects on learning and memory, anti-inflammatory and neurotrophic effects are therefore of great interest. Medicinal plants are a source of such discoveries. Among medicinal plants, *Khaya senegalensis,* a plant from the Meliaceae family, is endemic in many African countries (Djotan et al., 2018). *K. senegalensis* is a deciduous evergreen tree, 15–30 m high, up to 1 m in diameter, with a clean trunk of 8–16 m (Falodun and Obasuyi, 2009). This plant is used in African traditional medicine to treat rheumatoid arthritis, malaria, diarrhea, and cough. It is also used as an anthelmintic, emetic, and jaundice (Kubmarawa et al., 2008). In northern Cameroun, decoctions of stem bark, leaves, and seeds are used to treat epilepsy, anxiety, dementia, malaria, diarrhea, infections, inflammation, and pain. Pharmacology studies revealed that extract from the seeds, leaves, and stem bark are endowed with hepatoprotective, anti-inflammatory, anticancer, antiplasmodial, antioxidant, analgesic, sedative, and antihelmintic properties (Idu, 2012, Kubmarawa et al., 2008). The aqueous extract of the stem bark has been reported to possess antiepileptic-like effects on chemical models of epilepsy in mice (Ngo Bum et al., 2011). The phytochemical screening of the extract of roots' extract revealed the presence of tannins, saponins, alkaloids, phenols, cardiac glucosides, sterols, triterpenes, reduced sugars, and flavonoids (Kandeda et al., 2022). Overall, the stem bark extract showed the highest concentration of total phenolic (87.69 – 46.28 mg GAE/g), flavonols (3.60 –135.40 mg CAE/g), and phenolic acid (62.96 – 107.22 mg CE/g), while the leaf extract revealed significant concentration of total flavonoids (20.59–104.43 mg RE/g)(de la Luz Cádiz-Gurrea et al., 2021). Gas chromatography-mass spectrometry (GS-MS) chromatogram of the stem bark aqueous extract indicated the presence of 9, 12, 15-octadecatrienoic acid, n-Hexadecenoic acid, catechol khayandilobiride, limonoids, and oleic acid (Kandeda et al., 2022). Bioactive compounds such as Khasenegasin G and Seneganolide A, isolated from *K. senegalensis*, have been shown to protect neurons against L-glutamate-induced neurotoxicity *in vitro* (Kandeda et al., 2022). The seeds of this plant have been reported to contain around 67 % oil content by weight (Idu, 2012). This oil is quite rich in oleic acid (66 %) and is used in Cameroon for cooking as well as in cosmetics (Idu, 2012). In addition, phytochemical analysis revealed that limonoids, isolated from all parts of the plant, are the major secondary metabolite (Zhang et al., 2009). The limonoids found in this plant are the following: phragmalin limonoids named khayanolides-D and E, khayanosides, 2, 6-dihydrofissionolids; and two mexicanolide limonoids named khayanone and 2-hydroxyseneganolide (Nakatani et al., 2002). These limonoids possess a wide range of biological activities such as insect antifeeding, anticancer, antibacterial, and anthelminthic (Zhang et al., 2007). Acute administration of the stem bark extract of *K. senegalensis* is nontoxic with an LD_{50} greater than 5000 mg/kg, whereas long-term administration can be toxic, and this toxicity is organ-specific (Onu et al., 2013). Besides, the aqueous extract of the roots has been tested as safe at low doses in acute and subchronic toxicity studies (Folarin et al., 2023). Considering the potential of *K. senegalensis*, the antiepileptogenic- and learning and memory-enhancing-like effects of *K. senegalensis* aqueous extract were investigated on kainate-induced *SE* in rats. The role of anti-inflammatory and neurotrophic pathways was also explored.

2. Materials and methods

2.1. Plant collection and extract preparation

The roots of *K. senegalensis* were harvested in Ngaoundéré (Adamaoua region, Cameroon) in January 2018. The plant was authenticated at the National Herbarium of Cameroon (Cameroon forest research section) in comparison with the sample N°856470/HNC. The protocol for preparing the extract was that of a traditional healer. Indeed, the roots of *K. senegalensis* were peeled off, cut, dried, and ground. The obtained powder (50 g) was introduced into 750 ml of distilled water. The whole was boiled for 20 min. After cooling, the mixture was filtered with Whatman No. 1 paper, and the filtrate was evaporated at 45°C in an oven. The process allows us to obtain 7.4125 g of dry extract, i.e. a yield of 14.83 %. The stock solution (10 mg/ml) was framed by two solutions (5 and 20 mg/ml). The doses of extract administered *per os* (*p.o.*) to rats were therefore 50, 100, and 200 mg/kg.

2.2. Animals and ethics

Male Wistar rats of 10 weeks old and weighing approximately 200 g were used. These rats were raised in the animal facility of the Laboratory of Animal Physiology (University of Yaoundé I, Cameroon), and were kept three per cage under ambient temperature and a cycle of natural light. Animals had free access to tap water and diet. All studies were carried out following national (N° FWA-IRB00001954) and international (NHI, N°8023) ethics governing the use of laboratory animals. All animal experiments comply with the ARRIVE guidelines and are carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Research Council's Guide for the Care and Use of Laboratory Animals.

2.3. Chemicals and reagents

Kainate (KA) and pentylenetetrazole (PTZ) were provided by Sigma Aldrich Co., St. Louis (USA), phenobarbital (PhB) and sodium valproate (SVA) from Sanofi Winthrop Industries (France), diazepam from Roche (France), and Ethyl ether from Cooper Laboratory (France). Other chemicals and reagents used for biochemical assays were purchased from Sigma Aldrich Co., St. Louis (USA).

3. Methods

3.1. Induction of status-epilepticus and experimental design

On the first day of the experiment, rats were divided into two groups and treated once as follows:

- a sham group of 8 rats intraperitoneally (i.p.) received distilled water (10 ml/kg);
- a group of 72 rats received KA (12 mg/kg, i.p.).

During the induction procedure, 51 rats exhibited 2 hours of *status-epilepticus* (prolonged seizures). These animals were selected and immediately treated with diazepam (10 mg/kg, i.p.) to reduce mortality. In addition, out of 72 rats that received KA, 7 rats did not develop *status epilepticus,* while 14 died. These animals were therefore excluded from the study.

The selected animals (51 rats) were then randomized into 6 groups and treated as follows:

- a negative control group of 11 rats received distilled water (10 ml/kg, p.o.);
- two positive control groups of 8 rats each received SVA (300 mg/kg, p.o.) or phenobarbital (20 mg/kg, p.o.);
- three test groups of 8 rats each received the extract (50, 100, and 200 mg/kg, p.o.);

The above sham group was instead treated with distilled water (10 ml/kg, *p.o.*). The animals were treated twice daily (7:00 am and 6:00 pm) until the occurrence of the first spontaneous seizure (either stage 4 or 5) in the negative control group, on day 14. During the treatment period, rats were video-monitored for 14 hours per day (8: 00 am to 10: 00 pm). Furthermore, the severity of spontaneous seizures was determined according to the Racine scale (Phelan et al., 2015):

- stage 0: no response;
- stage 1: hyperactivity;
- stage 2: shaking of the head and myoclonic jerks;
- stage 3: unilateral clonus of the forelimbs;
- stage 4: rearing and bilateral clonus of the forelimbs;
- stage 5: tonic-clonic seizures with loss of the righting reflex.

An animal was considered protected against seizures when it did not develop seizures of stage 4 or 5. It is expected that all animals should reach stage 5 of seizures. However, because of individual variability, not all animals may reach this stage. Consequently, the stage 4 is considered. Twenty-four hours following the last treatment, rats were subjected to a T-maze test to assess learning and memory impairment. Two weeks later, the animals that received the most effective dose of the extract against spontaneous recurrent seizures were challenged with pentylenetetrazole (30 mg/kg, i.p.). The effect of this dose of the extract was compared to that of sodium valproate (300 mg/kg, *p.o.*), one of the standard drugs against TLE. The animals were then individually observed for 30 min for the occurrence of seizures (stages 1–5). The animal was considered protected when it did not exhibit seizures. The percentage of protection was determined as follows: **Percentage of protection = number of rats that did not develop a seizure/total number of rats in the group**. Furthermore, when the animals exhibited a seizure, the latency to the first stage 5 seizure (generalized tonic-clonic seizure) was recorded and converted into a seizure score. This score was calculated using the following relation (Mehla et al., 2010): **Seizure score = 1– (latency of the animal of negative control group /latency of the animal treated with the extract or standard).** Thus, when the seizure score is 1, the animal was considered protected against seizures. However, when this score is 0, the animal was considered unprotected (Mehla et al., 2010).

3.2. T-maze

The T-maze is used to assess cognitive ability in rodents (Deacon and Rawlins, 2006). It assesses spontaneous alternation based on intrinsic investigation and curiosity (Deacon and Rawlins, 2006). The T-maze consists of a starting arm, a central aisle, and two opposing end arms. The starting arm (A) (30 cm long × 10 cm wide × 20 cm high), as well as the arrival arms (B) (30 cm long × 10 cm wide × 20 cm high), are separated from the central aisle (C) by manually operated sliding doors. The experiment took place over three days: the habituation phase (first day); the acquisition phase (second day); and the retention phase (third day). The habituation phase consisted of familiarizing each rat with the maze for 5 min. A food enhancer was placed at the entry of each arrival arm to facilitate exploration. The rat was placed at the end of the starting arm. The experimenter opened all the sliding doors and the animal chose one of the arrival arms, thus indicating his preference. After 5 min of observation, the rat was returned to its cage, and the experimental device was cleaned with 50 % ethyl alcohol before the introduction of the next rat. The acquisition phase consisted of repeating the same experience, but the discriminated arm was blocked by a sliding door. The retention phase was carried out identically to the habituation phase, but the preferred arm was known beforehand. The behavioral parameters recorded during this phase were the number of entries in the arms (preferred, discriminated, and starting arms) and the time spent in the arms (preferred, discriminated, and starting arms).

3.3. Biochemical assays

3.3.1. Euthanasia and preparation of homogenates

Immediately after the challenge with PTZ, rats were euthanized by cervical dislocation under anesthesia with ethyl ether. The brains were then removed, washed in 0.9 % NaCl, and wrung out. The brains (n = 8) were dissected, and the hippocampi (n = 8) were removed. Of all hippocampi (n = 8) removed from the brains, five (05) hippocampi were used for biochemical analyses. For each animal, 0.1 g of hippocampus was homogenized in 1 ml of Tris buffer (50 mM HCl; 150 mM KCl; pH 7.4). The mixture was centrifuged at 10,000 rpm for 15 min. The obtained supernatant was collected and kept at −20°C for biochemical assays. Furthermore, the remaining hippocampi (n = 3) were fixed in 10 % formalin for subsequent histological analyses.

3.3.2. Determination of pro-inflammatory and neurogenesis marker concentrations

The concentrations of interleukin-1beta (IL-1β), interleukin 10 (IL-10), tumor necrosis factor-alpha (TNF-α), cyclooxygenase-2 (COX-2), brain-derived neurotrophic factors (BDNF), and fibroblast growth factor 2 (FGF-2) were determined using the Enzyme-Linked Immunosorbent Assay (ELISA). The kits were provided by Quantikine (Biotechne, Inc., Minneapolis, USA) and the assays were performed following the instructions of the supplier.

3.3.3. Histological analysis

Histological analysis included fixation, trimming, dehydration, embedding, cutting, staining, mounting, and observation. The brain tissues (n = 3) were cut, placed in labeled cassettes, and immersed for 1 hour in a 70 % ethanol bath. These tissues were cleaned of any traces of water before embedding in paraffin. For this purpose, they were left in ethanol baths of increasing concentration, i.e., 70 % ethanol (1 h), 95 % (1 h), 95 % (1 h 30 min), 100 % (1 h), 100 % (1 h 30), 100 % (2 h), respectively. The brain histomorphology was assessed from 5-µm sections of paraffin-embedded tissues after hematoxylin-eosin staining. Microscopic analysis of the structure of the hippocampus (CA1 and CA3 layers) was performed using the Zeiss equipment (Hallbermoos, Germany), consisting of a microscope (Axioskop 40) connected to a computer. The obtained image was edited and analyzed by Image J 1.52 software.

3.3.4. Statistical analysis

Statistical analysis of the obtained data was carried out using GraphPad Prism version 8.0 and Microsoft Office Excel 2013 version 15.0.4420.1017. The results were expressed as mean ± standard error or as percentage. Values were compared using the one-way or two-way analysis of variance (ANOVA). When differences existed, Tukey's multiple comparison test was performed. From $p < 0.05$, the differences were considered significant.

3.4. Quantitative phytochemical analysis of Khaya senegalensis aqueous extract

The concentrations of total phenols, total flavonoids, condensed tannins, total alkaloids, and saponins were determined as previously described by Djeuzong et al. [38].

4. Results

4.1. Effect of the extract of K. senegalensis on seizure stage

On day 14 of the treatments, kainate-induced *SE* led ($p < 0.01$) to stage 4 of seizures in the negative control group compared to the sham group (Fig. 1). The extract (50 mg/kg) and sodium valproate completely prevented ($p < 0.01$) these seizures compared to the negative control group.

4.2. Effect of K. senegalensis extract on the number of entries and time spent in the T-maze

In the negative control group, kainate-induced *SE* led to an increase in the number of entries in the preferred arm (3.12 ± 0.35; $p < 0.001$) compared to the sham group (Fig. 2A). The extract at all doses decreased this number. However, the extract at a dose of 50 mg/kg markedly reduced this number to 1.19 ± 0.18 ($p < 0.001$). Sodium valproate and phenobarbital also decreased this number to 1.88 ± 0.18 and 1.24 ± 0.15 ($p < 0.001$), respectively compared to the negative control group (Fig. 2A).

In the negative control group, Kainate-induced *SE* failed to significantly increase the number of entries in the discriminated arm compared to the sham group (Fig. 2A). The extract at all doses increased this number. However, the extract at a dose of 50 mg/kg markedly increased this number to 3.37 ± 0.56 ($p < 0.001$). Sodium valproate also increased this parameter, while phenobarbital failed to do so (Fig. 2A).

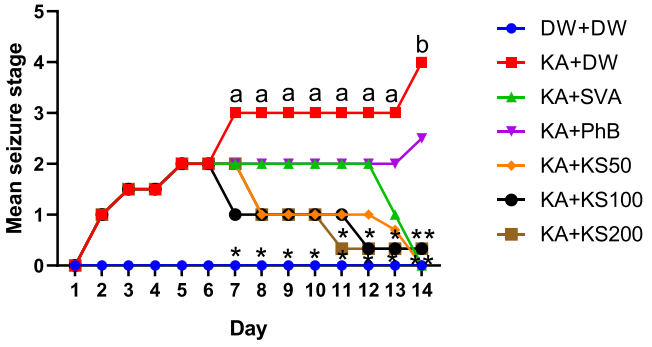

Fig. 1. Effect of the extract of *K. senegalensis* on seizure stage. Each symbol represents the mean ± SEM, n = 8. Data were analyzed by two-way ANOVA, followed by Tukey's test. a$p < 0.05$, b$p < 0.01$: significant difference compared to sham group (DW + DW); *$p < 0.05$, **$p < 0.01$: significant difference compared to the negative control group (KA + DW). DW + DW: sham group; KA + DW: negative control group; KA + SVA: positive control group treated with sodium valproate (300 mg/kg); KA + PhB: positive control treated with phenobarbital (20 mg/kg); KA + KS (50–200): test group treated with different doses of the extract (50, 100, and 200 mg/kg); DW: distilled water; SVA: sodium valproate; KA: kainate ; PhB: phenobarbital; KS: *Khaya senegalensis*.

No difference was observed in the number of returns in the starting arm between the negative control group and the sham group (Fig. 2A). The extract also failed to change this parameter. However, phenobarbital increased this number to 2.2 ± 0.14 ($p < 0.01$) compared to the negative control group (Fig. 2A).

Kainate-induced *SE* led to an increase in the time spent in the preferred arm (139.45 ± 0.55 s; $p < 0.05$) in the negative control group compared to the sham group (Fig. 2B). The extract at all doses failed to decrease this time. Sodium valproate and phenobarbital decreased this time to 52.88 ± 0.39 ($p < 0.01$) and 49.66 ± 0.42 s ($p < 0.01$), respectively, compared to the negative control group (Fig. 2B).

Kainate-induced *SE* failed to increase the time spent in the discriminated arm in the negative control group compared to the sham group (Fig. 2B). The extract at the doses of 50 and 100 mg/kg increased this time to 162.77 ± 0.33 ($p < 0.001$) and 187.84 ± 0.41 s ($p < 0.001$). Sodium valproate and phenobarbital increased this time to 173.61 ± 0.60 ($p < 0.001$) and 156.97 ± 0.54 ($p < 0.001$) s, respectively, compared to the negative control group (Fig. 2B).

No difference was observed in the time spent in the starting arm between the negative control group and the sham group (Fig. 2B). The extract at all doses as well as sodium valproate and phenobarbital failed to significantly increase this time compared to the negative control group (Fig. 2B).

4.3. Effect of the extract of K. senegalensis on the incidence and score of seizures induced by the challenge with PTZ

PTZ caused stages 1, 2, 3, and 4 of seizures in the negative control group compared to the sham group (Fig. 3A). The extract at a dose of 50 mg/kg protected 100 % ($p < 0.001$) of the animals against all seizure stages. Sodium valproate protected 100 % ($p < 0.001$) of rats against stages 2, 3, and 4 of seizures compared to the negative control group (Fig. 3A).

PTZ reduced the seizure score of all stages of seizures to 0 ± 0.0 in the negative control group compared to the sham group (Fig. 3B). The extract at the dose of 50 mg/kg increased this score to 1 ± 0.0 ($p < 0.001$) in all seizure stages. Sodium valproate increased this score to 1 ± 0.0 ($p < 0.001$) in stages 2, 3, and 4 of seizures compared to the negative control group (Fig. 3B).

4.4. Effect of the extract of K. senegalensis on the pro-inflammatory marker concentrations

In the negative control group, kainate-induced *SE* led to an increase in the level of IL-1β to 134.27 ± 1.26 pg/ml ($p < 0.001$) compared to the sham group (Fig. 4A). The extract at the doses of 50, 100, and 200 mg/kg decreased this level to 32.42 ± 0.33 pg/ml ($p < 0.001$), 34.62 ± 0.40 pg/ml ($p < 0.001$), and 52.47 ± 0.73 pg/ml ($p < 0.001$), respectively. Sodium valproate and phenobarbital caused a decrease in the concentration of IL-1β to 48.46 ± 0.81 pg/ml ($p < 0.001$) and 42.09 ± 0.34 pg/ml ($p < 0.001$), respectively compared to the negative control group (Fig. 4A).

Administration of kainate in the negative control group induced an increase in the level of TNF-α to 11.82 ± 1.65 pg/ml ($p < 0.001$) compared to the sham group (Fig. 4B). The extract at the doses of 50, 100, and 200 mg/kg decreased this concentration to 3.14 ± 0.72 pg/ml ($p < 0.001$), 6.91 ± 0.42 pg/ml ($p < 0.001$), and 1.24 ± 0.63 pg/ml ($p < 0.001$), respectively. Sodium valproate and phenobarbital caused a decrease in the concentration of TNF-α to 3.94 ± 1.93 pg/ml ($p < 0.001$) and 4.15 ± 0.39 pg/ml ($p < 0.001$), respectively, compared to the negative control group (Fig. 4B).

Administration of kainate in the negative control group led to an increase in the COX-2 activity to 1.97 ± 0.01 nmol/min/ml ($p < 0.001$) compared to the sham group (Fig. 4C). The extract at the doses of 50, 100, and 200 mg/kg decreased this activity to 0.86 ± 0.35 nmol/min/

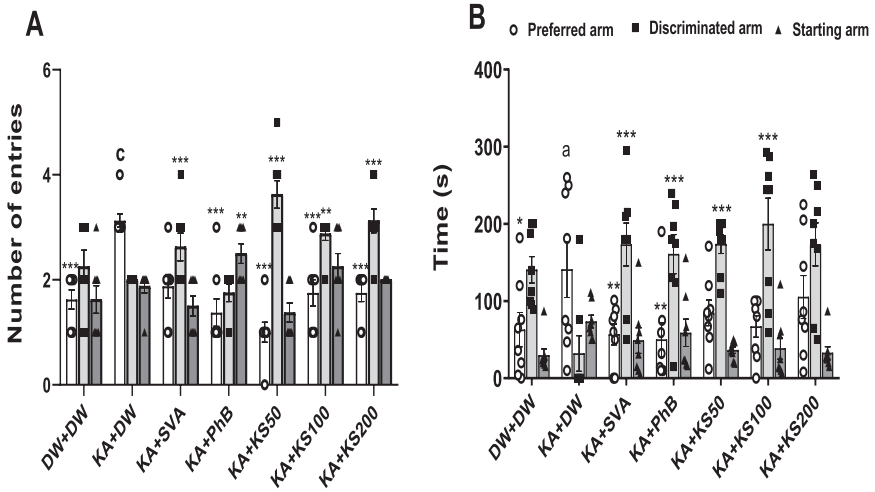

Fig. 2. Effect of the extract of *K. senegalensis* on the number of entries (A) and the time spent (B) in the different arms of the T-maze. Each bar represents the mean ± SEM, n = 8. Data were analyzed by two-way ANOVA, followed by Tukey's test. a$p < 0.05$, c$p < 0.001$: significant difference compared to sham group (DW + DW); *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$: significant difference compared to the negative control group (KA + DW). DW + DW: sham group treated with distilled water; KA + DW: negative control group treated with distilled water (10 ml/kg); KA + SVA: positive control treated with sodium valproate (300 mg/kg); KA + PhB: positive control treated with phenobarbital (20 mg/kg); KA + KS (50−200): test group treated with different doses of the extract (50, 100, and 200 mg/kg); DW: distilled water; SVA: sodium valproate; KA: kainate ; PhB: phenobarbital; KS: *Khaya senegalensis.*

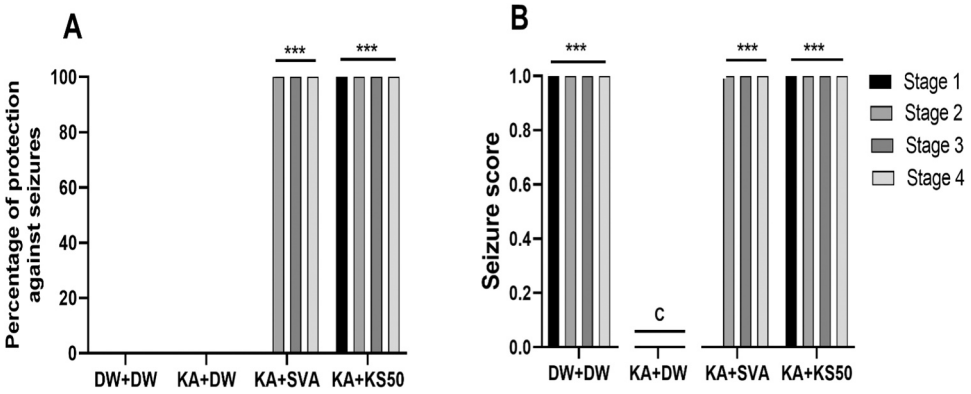

Fig. 3. Effects of the extract of *K. senegalensis* on the incidence (A) and score (B) of seizures induced by the challenge with PTZ. Each bar represents the percentage of protection, n = 8. Data were analyzed by two-way ANOVA, followed by Tukey's test. c$p < 0.001$: significant difference compared to the sham group (DW + DW); *** $p < 0.001$: significant difference compared to the negative control group (KA + ED). DW + DW: sham group treated with distilled water (10 ml/kg); KA + DW: negative control group treated with distilled water; KA + SVA: positive control treated with sodium valproate (300 mg/kg); KA + KS 50: test group treated with the most effective dose of the extract (50 mg/kg); DW: distilled water; SVA: sodium valproate; KA: kainate KS: *Khaya senegalensis.*

ml ($p < 0.001$), 0.18 ± 0.44 nmol/min/ml (p < 0.001), and 0.38 ± 0.57 nmol/min/ml ($p < 0.001$), respectively. Sodium valproate and phenobarbital caused a decrease in COX-2 activity to 0.96 ± 0.66 nmol/min/ml ($p < 0.001$) and 0.93 ± 0.60 nmol/min/ml ($p < 0.001$), respectively, compared to the negative control group (Fig. 4C).

Administration of kainate in the negative control group induced a decrease in the level of IL-10–240.36 ± 13.78 pg/ml ($p < 0.001$) compared to the sham group (Fig. 4D). The extract at the doses of 50, 100, and 200 mg/kg increased this level to 427.63 ± 0.70 ($p < 0.001$), 564.22 ± 12.17 ($p < 0.001$), 1210.40 ± 11.71 pg/ml ($p < 0.001$), respectively. Sodium valproate and phenobarbital caused an increase of this parameter to 443.60 ± 8.75 ($p < 0.001$) and to 456.86 ± 9.03 pg/ml ($p < 0.001$), respectively, compared to the negative control group (Fig. 4D).

4.5. Effect of extract of K. senegalensis on the neurogenesis marker concentrations

Administration of kainate to rats treated with distilled water caused a decrease in the concentration of BDNF to 174.55 ± 2.06 pg/ml ($p < 0.001$) compared to the sham group (Fig. 5A). The extract at the doses of 50, 100, and 200 mg/kg increased the concentration of BDNF to 479.44 ± 11.83 ($p < 0.001$), 493.22 ± 20.32 ($p < 0.001$), and 586.77 ± 11.70 pg/ml ($p < 0.001$), respectively. Sodium valproate and phenobarbital caused an increase in this concentration to 381.66 ± 10.48 pg/ml ($p < 0.001$) and 427.22 ± 11.83 pg/ml ($p < 0.001$), respectively, compared to the negative control group (Fig. 5A).

Administration of kainate to rats treated with distilled water caused a decrease in the concentration of FGF-2–96.10 ± 4.03 pg/ml ($p < 0.001$) compared to the sham group (Fig. 5B). The extract at the doses of 50, 100, and 200 mg/kg increased the concentration of FGF-2–332.18 ± 7.47 pg/ml ($p < 0.001$), 384.93 ± 3.07 pg/ml ($p < 0.001$) and 346.68 ± 5.92 pg/ml ($p < 0.001$), respectively. Sodium valproate and phenobarbital caused an increase in the concentration of FGF-2–264.43 ± 11.43 pg/ml ($p < 0.001$) and 392.43 ± 5.37 pg/ml ($p < 0.001$), respectively, compared to the negative control group (Fig. 5B).

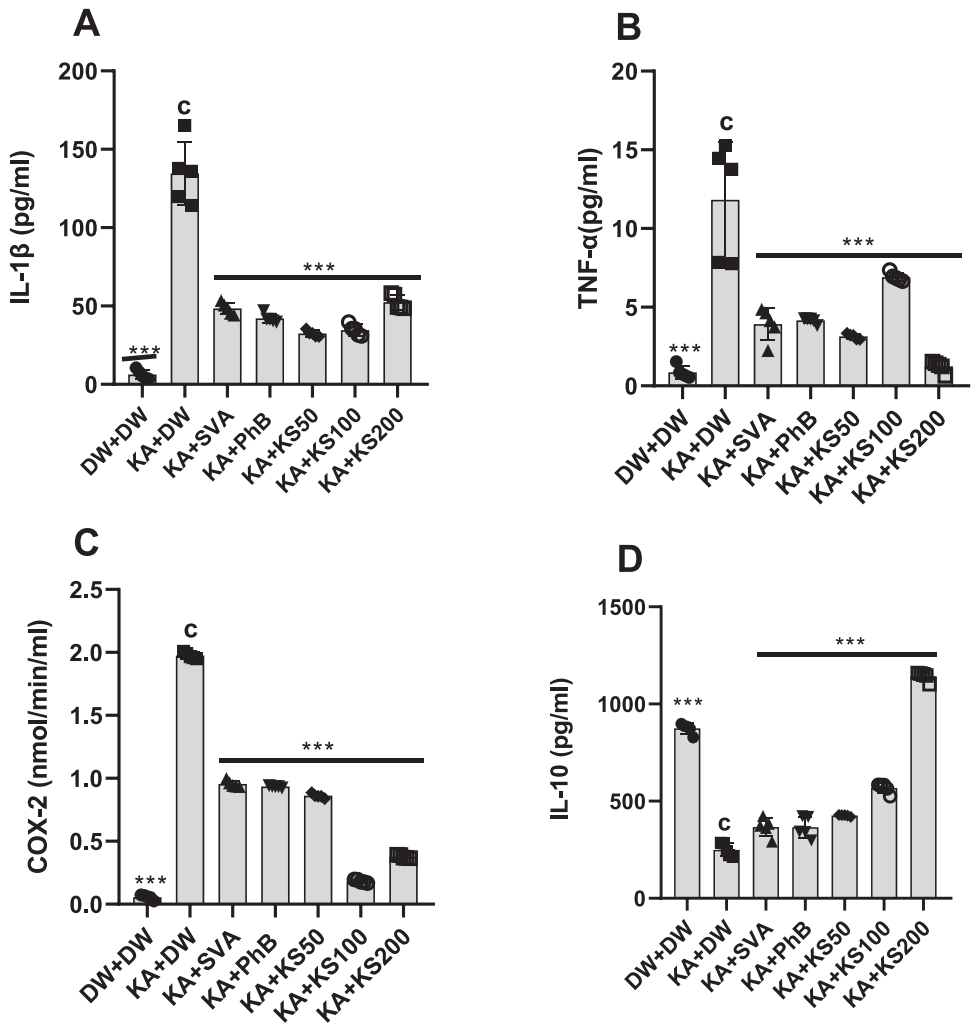

Fig. 4. Effect of extract of *K. senegalensis* on the concentrations of IL-1β (A), TNF-α (B), COX-2 (C), and IL-10 (D). Each bar represents the mean ± SEM, n = 8. Data were analyzed by two-way ANOVA, followed by Tukey's test. c$p < 0.001$: significant difference compared to sham group (DW + DW); *** $p < 0.001$: significant difference compared to the negative control group (KA + DW). DW + DW: sham group treated with distilled water (10 ml/kg); KA + DW: negative control group treated with distilled water; KA + SVA: positive control treated with sodium valproate (300 mg/kg); KA + PhB: positive control treated with phenobarbital (20 mg/kg); KA + KS (50−200): test group treated with different doses of the extract (50, 100, and 200 mg/kg); DW: distilled water; SVA: sodium valproate; KA: kainate ; PhB: phenobarbital; KS: *Khaya senegalensis*; IL-1β: interleukin beta; TNF-α: tumor necrosis factor-alpha; COX-2: cyclooxygenase 2; IL-10: interleukin 10.

4.6. Effect of K. senegalensis extract on the histological structure of the hippocampus

The microarchitecture of the hippocampus showed in the sham group an intact structure in the CA1 and CA3 layers of the hippocampus (Fig. 6A). The injection of kainate caused a reduction in the density of the neuronal-like cell bodies (Fig. 6B) (hippocampal sclerosis). In the negative control group, vacuolation in the cytoplasm, perivascular edema, and granulovascular degeneration were observed (Fig. 6B). In animals treated with aqueous extract at the doses of 50 and 200 mg/kg, CA1 and CA3 layers showed a structure comparable to that of the sham group (Fig. 6 E and G). The structure of the various layers of the hippocampus was less marked in the rats treated with valproate (Fig. 6D) and even in those treated with phenobarbital (Fig. 6C).

4.7. Quantitative phytochemical analysis of Khaya senegalensis aqueous extract

Total phenolic compounds (277.28 ± 0.51 mg gallic acid equivalent/ g), condensed tannins (103.44 ± 0.13 mg catechin equivalent/g) and flavonoids contents (87.66 ± 0.22 mg rutin equivalent/g) were abundant, while total alkaloids (9.45 ± 0.54 %) and saponins (6.68 ± 0.29 %) were less.

5. Discussion

The present study aimed to assess the antiepileptogenic- and learning and memory-facilitating-like effects of *K. senegalensis* aqueous extract using the kainate model of epilepsy in rats. The results of the present study showed that the extract at the most effective dose (50 mg/kg) protected animals from spontaneous recurrent seizures (seizures of stage 4) when compared to the negative control. This protection was comparable to that of sodium valproate, one of the best antiepileptic drugs against TLE in humans. It is well known that during the chronic phase of TLE, the epileptogenic process initiated during the silent period continues throughout the chronic phase of the disease (Löscher and Brandt, 2010). During this process, the lowering of the excitation threshold could lead to the onset of epileptic seizures (Lukasiuk and Becker, 2014). The fact that the aqueous extract prevented the occurrence of the seizures of stage 4, these results suggest an antiepileptogenic-like effect. Moreover, kainate injection is associated with total or partial impairment of learning and memory in rats. The fact that the extract reduces these impairments, these results suggest that the extract either protects

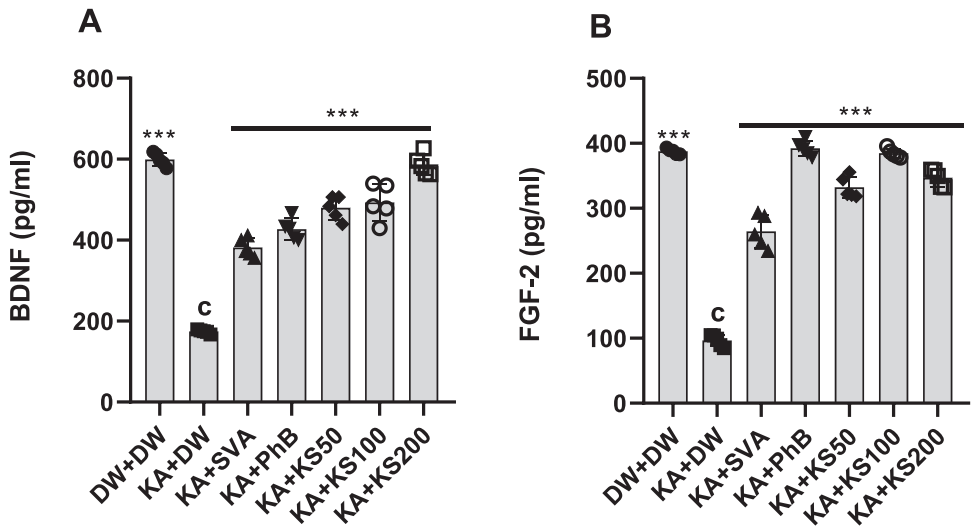

Fig. 5. Effect of *K. senegalensis* extract on the concentrations of BDNF(A) and FGF-2 (B). Each bar represents the mean ± SEM, n = 8. Data were analyzed by two-way ANOVA, followed by Tukey's test. *cp* < 0.001: significant difference compared to sham group (DW + DW); *** $p < 0.001$: significant difference compared to the negative control group (KA + DW). DW + DW: sham group treated with distilled water (10 ml/kg); KA + DW: negative control group treated with distilled water; KA + SVA: positive control treated with sodium valproate (300 mg/kg); KA + PhB: positive control treated with phenobarbital (20 mg/kg); KA + KS (50−200): test group treated with different doses of the extract (50, 100, and 200 mg/kg); DW: distilled water; SVA: sodium valproate; KA: kainate ; PhB: phenobarbital; KS: *Khaya senegalensis*; BDNF: brain-derived neurotrophic factor; FGF-2: fibroblast growth factor 2.

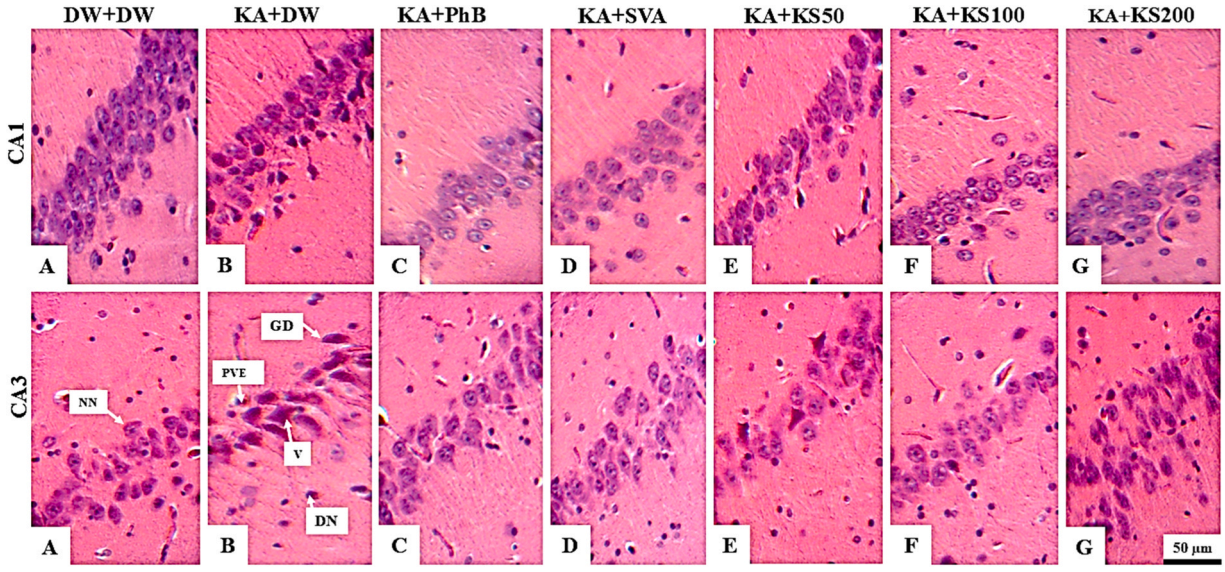

Fig. 6. Effect of the extract of *K. senegalensis* on kainate-induced hippocampal injury (Hematoxylin and eosin staining, ×100). Each panel represents a photomicrograph of the hippocampus. Panel A: DW + DW (sham group treated with distilled water; Panel B: KA + DW (negative control group treated with distilled water); Panel D: KA + PhB (positive control treated with phenobarbital at the dose of 20 mg/kg); Panel D: KA + SVA (positive control treated with sodium valproate at the dose of 300 mg/kg); Panels E, F, and G: KA + KS (50−200) (test groups treated with the extract at doses of 50, 100, and 200 mg/kg; respectively); DW: distilled water; SVA: sodium valproate; KA: kainate ; PhB: phenobarbital; KS: *Khaya senegalensis*; NN: normal neuron; V: vacuolization; PVE: perivascular edema; DN: Degenerated neuron; GD: granulovascular degeneration; CA1 and CA3: *Cornu Ammonis* regions 1 and 3.

neurons involved in the learning and memory process or enhances the learning and memory process by increasing the bioavailability of acetylcholine in the brain (mnemonic-like effect). The ameliorative effect of the extract on learning and memory impairments in the T-maze confirms this observation and suggests learning and memory-facilitating-like effects of the extract (Kandeda et al., 2017). According to the abundant literature, little is known about the exact physiopathological link between TLE and cognitive deficits. However, the loss or alteration of neurons in the hippocampus may be a cause or consequence of these dysfunctions (Smolensky et al., 2019).

To determine whether the effects of the extract were on the symptoms or underlying causes, a subconvulsive dose of PTZ, an antagonist of the $GABA_A$ receptor complex, was administered to animals. This chemoconvulsant was administered to assess the susceptibility of rats to seizures (Blanco et al., 2009). PTZ, at subconvulsive dose (between 1 and 40 mg/kg), is generally administered at the end of the silent period, which varies from 3 to 7 months in rodents, to test the animal's susceptibility to seizures. Indeed, during the silent period, i.e., after kainate-induced post-*SE*, animals are more prone to seizures, due to structural and biochemical alterations that lower the seizure threshold (Blanco et al., 2009). It is well known that the administration of PTZ at a subconvulsive dose is associated with a reduction in GABA

neurotransmission in the brain (Blanco et al., 2009). The PTZ therefore exerts its action by blocking $GABA_A$ receptors. N-methyl-D-aspartate (NMDA) is also known to play a major role in PTZ-induced seizures (Blanco et al., 2009). Thus, administering PTZ to an animal prone to seizures could lead to their onset.

The data showed that the administration of PTZ to distilled water-treated rats resulted in acute seizures at all stages. These findings are consistent with those of Blanco et al., (2009) who revealed that the administration of PTZ in rats pretreated with pilocarpine caused acute seizures in the animals by lowering the seizure threshold. The extract of *K. senegalensis* protected animals against all seizure stages. These results suggest that the extract acts on the underlying cause rather than the symptoms of the disease. These data also suggest that the extract protects animals from refractory-like seizures (Bankstahl et al., 2013). This hypothesis is confirmed by the fact that the structure of the CA1 and CA3 regions of the rats treated with the most effective dose (50 mg/kg) was comparable to that of the sham group.

The presence of injury in the hippocampus of patients with TLE is generally associated with the inflammatory process. Inflammation is one of the key events in the development of TLE or the epileptogenesis process (Vezzani et al., 2013b). The role of the anti-inflammatory mechanisms of the extract was therefore explored. In the present study, kainate-induced *SE* led to an increase in brain levels of pro-inflammatory cytokines (IL-1β, TNF-α, and COX-2) in the negative control group. It also led to a decrease in the level of anti-inflammatory cytokines (IL-10). These findings agree with those of Penkowa et al., (2001). The aqueous extract of *K. senegalensis* decreased the levels of pro-inflammatory cytokines and increased that of IL-10, coupled with a decrease in the activity of COX-2. Experimental studies showed that injection of KA in rats is associated with the production of COX-2, which catalyzes prostaglandins (Vezzani et al., 2013b). Nevertheless, the use of selective COX-2 inhibitors has been shown to have an antiepileptogenic or disease-modifying effect (Vezzani et al., 2013b). These results suggest that the aqueous extract of *K. senegalensis* possesses anti-inflammatory properties, probably through repression of COX-2 activity or synthesis (Vezzani et al., 2013a, 2013b). Additionally, KA-induced *SE* can activate a range of signal transduction pathways. These transcriptional responses control the production of several pro-inflammatory cytokines such as IL-1β and TNF-α. Inhibition of these pathways has been shown to alter epileptogenesis (Vezzani et al., 2013a, 2013b). The fact that the extract decreased the levels of pro-inflammatory cytokines, these findings also suggested anti-inflammatory properties likely through the repression of pro-inflammatory cytokines activity. Moreover, these properties could be linked to the presence of limonoids (Zhou et al., 2018) and phenolic compounds such as triterpenoids and flavonoids (Francis et al., 2002). Indeed, triterpenoids can interact with intracellular neuronal or glial signaling pathways involved in inflammation (Safayhi and Sailer, 1997), while flavonoids can reduce the expression of pro-inflammatory cytokines as well as inhibit nuclear factor-κB (Unger, 1998). Further, the *in vivo* anti-inflammatory activity of extract of *K. senegalensis* confirms its anti-inflammatory potential, which has been widely reported in the literature. Altogether, the antiepileptogenic properties of this extract may in part involve anti-inflammatory activity.

In parallel to the inflammatory process, neurogenesis has been found to significantly contribute to the pathogenesis of TLE. According to established evidence, altered neurogenesis may either hamper or aggravate epilepsy through neurotrophic factors such as BDNF and FGF-2 (Parent, 2002). Neurogenesis is the process in which neurons are generated from stem cells in adults (Braun and Jessberger, 2014). Neurogenesis can occur mainly during embryo formation and throughout adult life in the hippocampus (Ekdahl et al., 2009). This phenomenon also occurs following a brain insult due to inflammation or other dysregulations (Ekdahl et al., 2009). In the present study, KA-induced *SE* caused a decrease in the levels of BDNF and FGF-2 in the hippocampus. These findings suggest that neurons involved in the synthesis or release of these neurotrophic factors have been lost (Hu et al., 2019, Ma et al., 2012, Miranda et al., 2019). This decrease could be the consequence of neurotoxicity induced by glutamate hyperactivation in the neurons involved in the synthesis of neurotrophic factors (Almeida et al., 2005, Bathina and Das, 2015, Kume et al., 1997). Treatment with the aqueous extract induced a significant increase in BDNF and FGF-2 levels, suggesting therefore a beneficial neurotrophic effect. These results also indicate that the antiepileptogenic-like effect of the extract could be mediated in part by stimulation of neurogenesis. In fact, under specific conditions, neurotrophic factors could inhibit or alter epileptogenesis by reducing neuronal loss in the brain (Bovolenta et al., 2010). In some studies, BDNF is known to be neuroprotective, while in others it impairs or exacerbates neurotoxicity (Almeida et al., 2005, Bathina and Das, 2015, Kume et al., 1997). Given that the antiepileptogenic-like effect of the extract was associated with increased BDNF and FGF-2 levels, these results support the hypothesis on the neuroprotective effect or function of BDNF and FGF-2. Further studies are required to determine the exact mechanisms and factors contributing to these effects of the extract.

6. Conclusion

This study aimed to assess the antiepileptogenic- and learning and memory-facilitating-like effects of *K. senegalensis* aqueous extract using kainate-induced *SE* in rats. The aqueous extract *K. senegalensis* prevented the development of spontaneous recurrent seizures (stage 4) on day 14, suggesting an antiepileptogenic-like effect. This observation was confirmed by the learning and memory-facilitating-like effects of the extract. The analysis of possible mechanisms of action indicated the involvement of anti-inflammatory and neurotrophic pathways. These findings partly justify the empirical use of this herb in the treatment of epilepsy and related diseases. Further, this extract could be used as an adjunct to treat epilepsy associated with an inflammatory process.

Ethics approval

All procedures were performed according to the guidelines of the National Ethics Committee of Cameroon (Ref No. FW-IRB00001954, 22 October1987). All animal experiments comply with the ARRIVE guidelines and are carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Research Council's Guide for the Care and Use of Laboratory Animals.

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CRediT authorship contribution statement

Liliane Yimtsa Foutse: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Stéphanie Lewale:** Methodology, Formal analysis, Data curation, Conceptualization. **Théophile Dimo:** Writing – review & editing, Writing – original draft, Conceptualization. **Antoine Kavaye Kandeda:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that studies were conducted in the absence of any commercial, or academic, or financial relationships.

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References

Almeida, R., Manadas, B., Melo, C., Gomes, J., Mendes, C., Graos, M., Carvalho, R., Carvalho, A., Duarte, C., 2005. Neuroprotection by BDNF against glutamate-induced apoptotic cell death is mediated by ERK and PI3-kinase pathways. Cell Death Differ 12, 1329–1343.

Bankstahl, M., Bankstahl, J.P., Loscher, W., 2013. Pilocarpine-induced epilepsy in mice alters seizure thresholds and the efficacy of antiepileptic drugs in the 6-Hertz psychomotor seizure model. Epilepsy Res 107, 205–216. https://doi.org/10.1016/j.eplepsyres.2013.09.014.

Bathina, S., Das, U.N, 2015. Brain-derived neurotrophic factor and its clinical implications. Arch Med. Sci. 11, 1164.

Beghi, E., 2020. The Epidemiology of Epilepsy. Neuroepidemiology 54, 185–191. https://doi.org/10.1159/000503831.

Blanco, M.M., Dos Santos Jr., J.G., Perez-Mendes, P., Kohek, S.R., Cavarsan, C.F., Hummel, M., Albuquerque, C., Mello, L.E., 2009. Assessment of seizure susceptibility in pilocarpine epileptic and nonepileptic Wistar rats and of seizure reinduction with pentylenetetrazole and electroshock models. Epilepsia 50, 824–831. https://doi.org/10.1111/j.1528-1167.2008.01797.x.

Bovolenta, R., Zucchini, S., Paradiso, B., Rodi, D., Merigo, F., Navarro Mora, G., Osculati, F., Berto, E., Marconi, P., Marzola, A., Fabene, P., F.,Simonato, M., 2010. Hippocampal FGF-2 and BDNF overexpression attenuates epileptogenesis-associated neuroinflammation and reduces spontaneous recurrent seizures. J. Neuroinflamm. 7, 81. https://doi.org/10.1186/1742-2094-7-81.

Braun, S.M., Jessberger, S., 2014. Adult neurogenesis: mechanisms and functional significance. Development 141, 1983–1986. https://doi.org/10.1242/dev.104596.

Cho, K.O., Lybrand, Z.R., Ito, N., Brulet, R., Tafacory, F., Zhang, L., Good, L., Ure, K., Kernie, S.G., Birnbaum, S.G., Scharfman, H.E., Eisch, A.J., Hsieh, J., 2015. Aberrant hippocampal neurogenesis contributes to epilepsy and associated cognitive decline. Nat. Commun. 6, 6606. https://doi.org/10.1038/ncomms7606.

de la Luz Cádiz-Gurrea, M., Sinan, K.I., Zengin, G., Bene, K., Etienne, O.K., Leyva-Jiménez, F.J., Segura-Carretero, A., 2021. Bioactivity assays, chemical characterization, ADMET predictions and network analysis of Khaya senegalensis A. Juss (Meliaceae) extracts. Food Research International 139, 109970.

Deacon, R.M., Rawlins, J.N., 2006. T-maze alternation in the rodent. Nat. Protoc. 1, 7–12. https://doi.org/10.1038/nprot.2006.2.

Djotan, A.K.G., Aoudji, A.K.N., Tessi, D.R.Y., Kakpo, S.B., Gbetoho, A.J., Kourouma, K., Ganglo, J.C., 2018. Vulnerability of Khaya senegalensis Desr & Juss to climate change and to the invasion of Hypsipyla robusta Moore in Benin (West Africa). Int. J. Biol. Chem. Sci. 12, 24–42.

Ekdahl, C.T., Kokaia, Z., Lindvall, O., 2009. Brain inflammation and adult neurogenesis: the dual role of microglia. Neuroscience 158, 1021–1029. https://doi.org/10.1016/j.neuroscience.2008.06.052.

Falodun, A., Obasuyi, O.J., 2009. Phytochemical screening and evaluation of stem bark extract of Khaya senegalensis (meliaceae) on methicillin resistant staphyloccocus areus. Can. J. pure Appl. Sci. 925.

Folarin, R.O., Omirinde, J.O., Gilbert, T.T., Igbeneghu, C.J. a R., Biology, R.I., 2023. Acute and Sub-chronic Toxicity of Aqueous Extract of Roots of Khaya senegalensis (Desr.) A. Juss. in Mice and Rats Respectively, 38, 33–46.

Francis, G., Kerem, Z., Makkar, H.P., Becker, K., 2002. The biological action of saponins in animal systems: a review. Br. J. Nutr. 88, 587–605. https://doi.org/10.1079/BJN2002725.

Holtman, L., Van Vliet, E.A., Aronica, E., Wouters, D., Wadman, W.J., Gorter, J.A., 2013. Blood plasma inflammation markers during epileptogenesis in post–status epilepticus rat model for temporal lobe epilepsy. Epilepsia 54, 589–595.

Hu, W., Feng, Z., Xu, J., Jiang, Z., Feng, M., 2019. Brain-derived neurotrophic factor modified human umbilical cord mesenchymal stem cells-derived cholinergic-like neurons improve spatial learning and memory ability in Alzheimer's disease rats. Brain Res. 1710, 61–73.

Idu, M., 2012. Antimicrobial activity and phytochemistry of Khaya senegalensis ROOTS. Int. J. Ayurvedic Herb. Med. 2, 1.

Kandeda, A.K., Lewale, S., Djeuzong, E., Kouamouo, J., Dimo, T., 2022. An aqueous extract of Khaya senegalensis (Desv.) A. Juss.(Meliaceae) prevents seizures and reduces anxiety in kainate-treated rats: modulation of GABA neurotransmission, oxidative stress, and neuronal loss in the hippocampus. Heliyon 8 (5).

Kandeda, A.K., Taiwe, G.S., Moto, F.C.O., Ngoupaye, G.T., Nkantchoua, G.C.N., Njapdounke, J.S.K., Omam, J.P.O., Pale, S., Kouemou, N., Ngo Bum, E., 2017. Antiepileptogenic and neuroprotective effects of pergularia daemia on pilocarpine model of epilepsy. Front. Pharmacol. 8, 440. https://doi.org/10.3389/fphar.2017.00440.

Kubmarawa, D., Khan, M., Punah, A., Hassan, M., 2008. Phytochemical screening and antimicrobial efficacy of extracts from Khaya senegalensis against human pathogenic bacteria. Afr. J. Biotechnol. 7.

Kume, T., Kouchiyama, H., Kaneko, S., Maeda, T., Kaneko, S., Akaike, A., Shimohama, S., Kihara, T., Kimura, J., Wada, K.J., 1997. BDNF prevents NO mediated glutamate cytotoxicity in cultured cortical neurons. Brain Res. 756, 200–204.

Lee, J., Lim, E., Kim, Y., Li, E., Park, S., 2010. Ghrelin attenuates kainic acid-induced neuronal cell death in the mouse hippocampus. J. Endocrinol. 205, 263–270. https://doi.org/10.1677/JOE-10-0040.

Lévesque, M., Avoli, M.J.N., Reviews, B., 2013. The kainic acid model of temporal lobe epilepsy, 37, 2887–2899.

Löscher, W., Brandt, C., 2010. Prevention or modification of epileptogenesis after brain insults: experimental approaches and translational research. Pharm. Rev. 62, 668–700.

Lukasiuk, K., Becker, A.J., 2014. Molecular biomarkers of epileptogenesis. Neurotherapeutics 11, 319–323. https://doi.org/10.1007/s13311-014-0261-6.

Ma, H., Yu, B., Kong, L., Zhang, Y., Shi, Y., 2012. Neural stem cells over-expressing brain-derived neurotrophic factor (BDNF) stimulate synaptic protein expression and promote functional recovery following transplantation in rat model of traumatic brain injury. Neural Regen Res. 37, 69–83.

Mehla, J., Reeta, K., Gupta, P., Gupta, Y.K., 2010. Protective effect of curcumin against seizures and cognitive impairment in a pentylenetetrazole-kindled epileptic rat model. Life Sci. 87, 596–603.

Miranda, M., Morici, J.F., Zanoni, M.B., Bekinschtein, P., 2019. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. Front. Cell Neurosci. 13, 472800.

Nakatani, M., Abdelgaleil, S.A., Kassem, S.M., Takezaki, K., Okamura, H., Iwagawa, T., Doe, M., 2002. Three new modified limonoids from Khaya senegalensis. J. Nat. Prod. 65, 1219–1221. https://doi.org/10.1021/np020067v.

Ngo Bum, E., Taiwe, G., Moto, F., Ngoupaye, G., Vougat, R., Sakoue, V., Gwa, C., Ayissi, E., Dong, C., Rakotonirina, A., 2011. Antiepileptic medicinal plants used in traditional medicine to treat epilepsy. Clinical and Genetic Aspects of Epilepsy. IntechOpen.

Onu, A., Saidu, Y., Ladan, M., Bilbis, L.S., Aliero, A.A., Sahabi, S., 2013. Effect of aqueous stem bark extract of Khaya senegalensis on some biochemical, haematological, and histopathological parameters of rats. J. Toxicol. Environ. Health 2013.

Parent, J.M., 2002. The role of seizure-induced neurogenesis in epileptogenesis and brain repair. Epilepsy Res. 50, 179–189. https://doi.org/10.1016/s0920-1211(02)00078-5.

Penkowa, M., Molinero, A., Carrasco, J., Hidalgo, J., 2001. Interleukin-6 deficiency reduces the brain inflammatory response and increases oxidative stress and neurodegeneration after kainic acid-induced seizures. Neuroscience 102, 805–818. https://doi.org/10.1016/s0306-4522(00)00515-7.

Phelan, K.D., Shwe, U., Williams, D.K., Greenfield, L.J., Zheng, F., 2015. Pilocarpine-induced status epilepticus in mice: a comparison of spectral analysis of electroencephalogram and behavioral grading using the Racine scale. Epilepsy Res. 117, 90–96.

Pitkänen, A., Lukasiuk, K., Dudek, F.E., Staley, K.J., 2015. Epileptogenesis. Cold Spring Harb. Perspect. Med. 5, a022822.

Safayhi, H., Sailer, E.R., 1997. Anti-inflammatory actions of pentacyclic triterpenes. Planta Med. 63, 487–493. https://doi.org/10.1055/s-2006-957748.

Singh, A., Trevick, S., 2016. The epidemiology of global epilepsy. Neurol. Clin. 34, 837–847. https://doi.org/10.1016/j.ncl.2016.06.015.

Smolensky, I.V., Zubareva, O.E., Kalemenev, S.V., Lavrentyeva, V.V., Dyomina, A.V., Karepanov, A.A., Zaitsev, A.V., 2019. Impairments in cognitive functions and emotional and social behaviors in a rat lithium-pilocarpine model of temporal lobe epilepsy. Behav. Brain Res. 372, 112044. https://doi.org/10.1016/j.bbr.2019.112044.

Unger, J.W., 1998. Glial reaction in aging and Alzheimer's disease. Microsc. Res. Tech. 43, 24–28. https://doi.org/10.1002/(SICI)1097-0029(19981001)43:1< 24::AID-JEMT4> 3.0.CO;2-P.

Vezzani, A., Aronica, E., Mazarati, A., Pittman, Q.J., 2013a. Epilepsy and brain inflammation. Exp. Neurol. 244, 11–21. https://doi.org/10.1016/j.expneurol.2011.09.033.

Vezzani, A., Friedman, A., Dingledine, R.J., 2013b. The role of inflammation in epileptogenesis. Neuropharmacology 69, 16–24. https://doi.org/10.1016/j.neuropharm.2012.04.004.

Zhang, H., Tan, J., Vanderveer, D., Wang, X., Wargovich, M.J., Chen, F., 2009. Khayanolides from African mahogany Khaya senegalensis (Meliaceae): a revision. Phytochemistry 70, 294–299. https://doi.org/10.1016/j.phytochem.2008.12.004.

Zhang, H., Wang, X., Chen, F., Androulakis, X.M., Wargovich, M.J., 2007. Anticancer activity of limonoid from Khaya senegalensis. Phytother. Res. 21, 731–734.

Zhou, M.-M., Zhang, W.-Y., Li, R.-J., Guo, C., Wei, S.-S., Tian, X.-M., Luo, J.,Kong, L.-Y.J. P., 2018. Anti-inflammatory activity of Khayandirobilide A from Khaya senegalensis via NF-κB, AP-1 and p38 MAPK/Nrf2/HO-1 signaling pathways in lipopolysaccharide-stimulated RAW 264.7 and BV-2 cells. 42, 152-163.