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ORIGINAL ARTICLE

An aqueous extract of *Syzygium cumini* protects against kainate-induced *status epilepticus* and amnesia: evidence for antioxidant and anti-inflammatory intervention

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Abstract

Temporal lobe epilepsy is the most common drug-resistant epilepsy. To cure epilepsy, drugs must target the mechanisms at the origin of seizures. Thus, the present investigation aimed to evaluate the antiepileptic- and anti-amnesic-like effects of an aqueous extract of *Syzygium cumini* against kainate-induced *status epilepticus* in mice, and possible mechanisms of action. Mice were divided into 7 groups and treated as follows: normal group or kainate group received *po* distilled water (10 mL/kg), four test groups received *Syzygium cumini* (28.8, 72, 144, and 288 mg/kg, *po*), and the positive control group treated intraperitoneally (ip) with sodium valproate (300 mg/kg). An extra group of normal mice was treated with piracetam (200 mg/kg, *po*). Treatments were administered 60 min before the induction of *status epilepticus* with kainate (15 mg/kg, ip), and continued daily throughout behavioral testing. Twenty-four hours after the induction, T-maze and Morris water maze tasks were successively performed. The animals were then sacrificed and some markers of oxidative stress and neuroinflammation were estimated in the hippocampus. The extract significantly prevented *status epilepticus* and mortality. In the T-maze, the aqueous extract markedly increased the time spent and the number of entries in the discriminated arm. In the Morris water maze, the extract significantly increased the time spent in the target quadrant during the retention phase. Furthermore, the aqueous extract induced a significant reduction of oxidative stress and neuroinflammation. These results suggest that the aqueous extract of *Syzygium cumini* has antiepileptic- and anti-amnesic-like effects, likely mediated in part by antioxidant and anti-inflammatory activities.

Keywords *Syzygium cumini* · Temporal lobe epilepsy · Anti-amnesic · Anti-inflammatory · Antioxidant

Introduction

Epilepsies are chronic neurological conditions defined by the recurrence of two or more paroxysmal seizures (Chin 2012; Weaver and Cromwell 2019; Zhu et al. 2020; Wagner et al. 2020). They manifest as brief episodes of involuntary tremors affecting part or all of the body, with or without the loss of consciousness (Fisher et al. 2014; Falco-Walter et al. 2018; Fisher and Bonner 2018; Pack 2019). These seizures result from hyperexcitability and hypersynchrony of neurons (Stafstrom 2010; Fisher et al. 2014; Falco-Walter et al. 2018; Fisher and Bonner 2018). Epilepsies affect approximately 50–70 million people worldwide with a morbidity of 0.5% (Kuate et al. 2015; Vezzani et al. 2016; Kwon et al. 2019). According to the review of Singh and Sander (2020), over 80% of deaths resulting from this disease occur in low- and middle-income countries. Epilepsy is also a major economic burden in Africa for epilepsy patients and their families (Chin 2012; Weaver and Cromwell 2019; Wagner et al. 2020). Of all types of epilepsy, TLE deserves special

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attention because it affects a specific area of the brain and accounts for 60% of epilepsies (Téllez-Zenteno 2012; Jaimes-Bautista et al. 2015; Taiwe et al. 2015; Mante et al. 2017). Primary precipitating injuries of the TLE include head trauma, prolonged febrile seizures, infections, or *status epilepticus (SE)* (Curia et al. 2014; Rusina et al. 2021). The latter is a seizure lasting more than 30 min without recovery of consciousness between seizure episodes (Cherian and Thomas 2009; Curia et al. 2014). TLE is often associated with neuropsychiatric comorbidities, including anxiety, depression, and amnesia (Ismail et al. 2017; Kandeda et al. 2021a, b, 2022a, b; Vinti et al. 2021). However, the complex mechanisms underlying epileptogenesis, the onset of spontaneous seizures, and the associated comorbidity are not readily understood in clinical studies (Butler and Zeman 2008; Kimiskidis and Valeta 2012; Kandratavicius et al. 2014; Lima et al. 2021). Also, the relationship between TLE and amnesia is poorly understood (Hubens et al. 2014; Mosbah et al. 2014; Madar et al. 2021). Amnesia is defined as the inability of individuals to learn and remember acquired information (Mosbah et al. 2014; Madar et al. 2021). This memory impairment is often associated with epilepsy since nearly 80% of epilepsy patients have episodic memory impairment (Butler and Zeman 2008; Jaimes-Bautista et al. 2015; Mosbah et al. 2014; Madar et al. 2021). This is due to the spread of seizures in the regions of the brain involved in the control of memory (Groticke et al. 2008; Kiasalari et al. 2016; Kandeda et al. 2022a). In addition, patients with drug-resistant TLE have a higher risk of developing short- and long-term memory impairment (Groticke et al. 2008; Holler and Trinka 2014; Kiasalari et al. 2016; Tramoni-Negre et al. 2017). Therefore, the use of animals and appropriate methods is in great experimental demand to understand these mechanisms, one of them being the kainate model of epilepsy. The first experiments using intraperitoneal injection of kainate were done in 1970 (Rusina et al. 2021). The findings revealed that administration of kainate (12 mg/kg) caused ‘’wet dog shaking” seizures between 30–90 min. These seizures then evolved into generalized tonic-clonic seizures in 88% of rats (Lévesque et al. 2016; Rusina et al. 2021). The kainate model of TLE has long been used to understand the molecular and cellular mechanisms underlying spontaneous seizures in rodents (Lévesque and Avoli. 2013; Lévesque et al. 2016). In fact, the systemic injection of kainate to rodents is associated with endoplasmic reticulum stress, excitotoxicity, oxidative stress, glial activation, and inflammation (Ojo et al. 2019; Ramazi et al. 2020; Kandeda et al. 2021b, 2022a, b). The kainate model also exhibits behavioral, cognitive, histological, pharmacological, and electroencephalographic characteristics of human TLE (Lévesque and Avoli 2013; Lévesque et al. 2016). Despite many and growing efforts of modern pharmacology, the treatment of epilepsies remains a mystery. Indeed, the antiepileptics currently available are symptomatic and can neither cure nor prevent epilepsy. Moreover, the majority of the world’s population does not benefit from this treatment, especially in Africa where over 60% of epilepsy patients do not receive any treatment (Chin 2012; Winkler 2012; Ba-Diop et al. 2014; Esterhuizen et al. 2018; Wagner et al. 2020). Numerous studies have shown that TLE is generally drug-resistant and requires surgical intervention (Lévesque and Avoli 2013; Lévesque et al. 2016). For millennia, humans have always used medicinal plants to solve their health problems (Petrovska 2012; Dibong et al. 2015). According to the World Health Organization, nearly 80% of the population in developing countries use traditional medicine and these drugs cause fewer side effects (Ekor 2014; Iwuoha et al. 2020; Wagner et al. 2020). *Syzygium cumini* Skeels (*S. cumini*) (Myrtaceae) is a plant used in traditional medicine to treat many conditions, including bronchitis, asthma, anxiety, epilepsy, memory impairment, diabetes, depression, dementia, obesity, dysentery, cough, and stomatitis (Ayyanar and Subash-Babu 2012; Pai et al. 2013; Chauhan and Intelli 2015; Hossain et al. 2017; Ulla et al. 2017; Ezhilarasan et al. 2019). According to previous literature, no precision was given on the type of epilepsy or memory impairment cured by this plant (Pai et al. 2013; Chauhan and Intelli 2015; Hossain et al. 2017; Ulla et al. 2017). However, in Cameroon, the plant is mostly prescribed by traditional healers against TLE and dementia (personal communication). This plant is mainly known for its antioxidant, cardioprotective, antimicrobial, anti-inflammatory, antiobesity, anticancer, antifungal, and antidiabetes properties (Chanudom et al. 2015; Akhtar et al. 2016; Hossain et al. 2017; Jagetia et al. 2008; Ezhilarasan et al. 2019). The plant extracts or fractions were also reported to possess sedative, anticonvulsant, and potent central nervous system depressant effects (Chanudom and Tangpong 2015; De Lima et al. 1998). The seeds of *S. cumini* have been found to possess an anti-amnesic effect on the Alzheimer’s disease model in rats (Hossein et al. 2017). The methanolic extract of *S. cumini* also revealed an anti-amnesic effect of the extract against scopolamine-induced spatial memory impairment in rats (Alikatte et al. 2012). In addition, the hydroethanolic extract of the leaves of the plant showed anticonvulsant effects that appear to be mediated by antioxidant and anti-inflammatory activities (De Lima et al. 1998). Previous phytochemical studies on *S. cumini* stem bark revealed the presence of alkaloids, flavonoids, anthocyanins, terpenoids, essential oils, tannins, and polyphenols (Srivastava and Chandra 2013; Jha 2017). Compounds isolated from stem bark decoction, using HPLC analysis, revealed mainly betulinic acid, ellagic acid, ß-sitosterol, friedeanol, anthocyanin di-glucosides, epifriedeanol, and

eugenin (Bijauliya et al. 2017; Abdin et al. 2020). This part of the plant equally contains ß-sitosterol-D-glucoside, kamepferol-3-0- glucoside, ellagitannins, quercetin, myricetin, friedelin, astragalin, and gallic acid (Ayyanar and Subash-Babu 2012; Srivastava and Chandra 2013; Bijauliya et al. 2017; Abdin et al. 2020). These compounds have shown various pharmacological effects, including antioxidant, antiulcer, antihyperlipidaemic, hepatoprotective, antiallergic, antiarthritic, anti-inflammatory, and antibacterial activities (Simões-Pires et al. 2009; Srivastava and Chandra 2013; Abdin et al. 2020). All of these allowed us to hypothesize that the plant extract could be endowed with antiepileptic- and anti-amnesic-like properties. The present study, therefore, aimed to evaluate the antiepileptic- and anti-amnesic-like effects of an aqueous extract of *S. cumini* in kainate-treated mice. Specifically, it was to determine the effects of the aqueous extract of *S. cumini* on some parameters of *SE*, amnesia, oxidative stress (GSH and MDA), and neuroinflammation (TNF, IL-6, and IL-1β).

Materials and methods

Plant material and identification

The bark of *S. cumini* was collected in July 2020, in the Adamawa region (Cameroon), Vina department, and precisely in the forest gallery (latitude 7.425, longitude 13.531, and altitude 1075.03 ± 11 m). This plant was identified by Professor Pierre Marie Mapongmetsem, botanist at the University of Ngaoundéré. The anatomical and morphological clues considered by the Professor are the follows:

- - the leaves, 5–13 cm long, were dark green, leathery, shiny, glabrous, coriaceous, and oblong in shape. The apex was round, short, and obtuse; the stalk was light yellow and slender with 1.2–2 cm long; the side veins were fine, parallel, close together with tiny gland dots;
- - the flowers, 6–13 mm long, were fragrant, numerous, white, greenish, or creamy. The calyx was 4 white, concave, and rounded petals of 3 mm; the pistil has an inferior ovary; the ovules were tiny, stout, and numerous; the style (5–8 mm long) was white;
- - the fruits, 1.5–3.8 cm long and 2 cm in diameter, were fleshy, elliptically shaped, ovoid-oblong, berries, crowded in clusters with a single brown central seed (1–2 cm long). The pulp of the fruits was yellow or pale violet.

The plant was then authenticated at the National Herbarium of Cameroon (Yaoundé) where a voucher specimen number 57 903 HNC exists. The plant name was also checked on plantlist.org.

Preparation of the aqueous extract of*S. cumini*.

The bark of *S. cumini* was cleaned, shade-dried, and then powdered. This crude powder was sieved and weighed, of which 50 g were placed in an aluminum container, containing 500 mL of distilled water. The whole was boiled for 15 min at 100 °C. After cooling at room temperature and filtration with Wattman No. 1 paper, a filtrate of 300 mL was obtained (Kandeda et al. 2017, 2022a). This filtrate was evaporated for 24 h, in an oven set at 45 °C. This operation allowed us to obtain 4.32 g of dry aqueous extract (dry mass), giving a yield of 8.64%. To prepare the different doses of the extract, 1.44 g of dry extract of *S. cumini* was weighed and introduced into a graduated cylinder. Then distilled water was added to the extract until a final volume of 50 mL was obtained. The mixture was stirred until complete dissolution to obtain a stock solution of 28.8 mg /mL concentration. The other three solutions were obtained by diluting the stock solution with distilled water in a ratio of 1/2, 1/4, and 1/10. Therefore, this gave solutions with concentrations of 14.4, 7.2, and 2.88 mg/mL, respectively. The doses administered to the animals were thus 28.8, 72, 144, and 288 mg/kg. The aqueous extract was administered *po* to the animals at a volume of 10 mL/kg body weight.

Chemicals

The following chemicals were purchased from Sigma Chemical, St. Louis (USA): kainate (cat no: 487-79-6), sodium valproate (cat no: 1069-66-5), piracetam (cat no: 7491-74-9), diazepam (cat no: 439-14-5), Ellman's reagent (cat no: 69-78-3), NaCl (cat no: 7647-14-5), Tris-HCl (cat no: 1185-53-1), trichloroacetic acid (TCA, cat no: 76-03-9), and thiobarbituric acid (TBA, cat no: 504-17-6).

Animals and ethics

The experiment was carried out in white mice, *Mus musculus* swiss, aged 10 ± 2 weeks and weighing 22 ± 4 g. These mice were provided by LANAVET (National Veterinary Laboratory of Garoua, Cameroon) and acclimatized to the animal biology laboratory (University of Ngaoundéré) for three days. Mice had free access to food and water, with 12 h /12 h in light and dark. The animals were kept 5 per cage (30 cm × 30 cm) at ambient temperature (24–26 °C) and relative humidity (52%). The study was conducted following the Cameroon National Ethical Committee (Ref No. FW-IRB00001954, 22 October 1987). Every effort was made to minimize the number of mice used and their

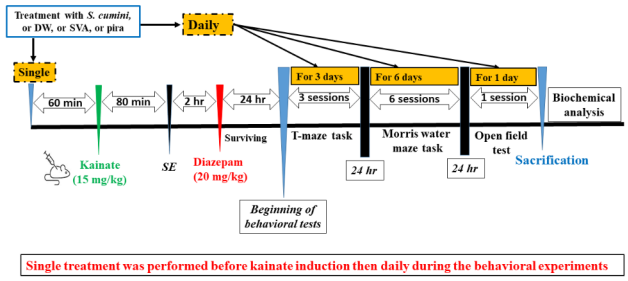

Fig. 1 Schematic diagram of the experimental procedure. *S. cumuni*: *Syzygium cumuni*; DW: distilled water; SVA: sodium valproate; pira: piracetam; hr: hour

suffering. All experiments were performed during the day (8:00 h – 17:00 h). Blinding and randomization procedures during experiments were accomplished according to ARRIVE 2.0 guidelines (https://arriveguidelines.org/arrive-guidelines). The sample size was determined based on previous laboratory estimation (Bertoglio et al. 2017; Khamse et al. 2015; Mohd et al. 2018; Zeng et al. 2009). We confirmed these numbers by using Power G software for size sample estimation (Lan et Lian2010) and the following formulae: sample size = (Z – score)2 * StdDev*(1 – StdDev) / (margin of error)2. Where Z: confident level; StdDev: standard deviation.

Grouping of animals and induction of*SE*by kainate.

To assess the effects of *S. cumini* on the development of *SE*, 63 mice were divided into 7 groups and treated as follows (Hsieh et al. 2011; Puttachary et al. 2015; Rusina et al. 2021):

- normal group of 6 mice was treated with distilled water (10 mL/kg, *po*);
- kainate group of 12 mice was treated with distilled water (10 mL/kg, *po*);
- test groups of 9 mice each were treated with the aqueous extract of *S. cumini* (28.8, 72, 144, and 288 mg/kg, *po*);
- positive control group of 9 mice was treated intraperitoneally (ip) with sodium valproate (SV group, 300 mg/kg).

An extra/additional group (pira group) of 9 mice was treated with piracetam (300 mg/kg, *po*), a standard anti-amnesic drug. This group was treated with piracetam, one hour before kainate administration, but not assessed for seizures as the above groups. However, this group was treated daily with piracetam during behavioral experiments. Indeed, significant memory impairment is usually observed in rodents after 24 h or days following kainate-induced *SE* (Maia et al. 2014; Kiasalari et al. 2016; Kandashvili et al. 2022; Kandeda et al. 2022a). Hence, it was relevant to study this group during behavioral experiments.

Based on previous laboratory findings, the injection of kainate is associated with high mortality in unprotected animals (Hsieh et al. 2011; Lévesque and Avoli 2013; Puttachary et al. 2015; Rusina et al. 2021). However, because of inter-individual variability, some animals are most susceptible to mortality than others (Lévesque and Avoli 2013; Puttachary et al. 2015; Bertoglio et al. 2017; Rusina et al. 2021). Therefore, the number of mice per group was ideally adjusted to 12 mice in the kainate group, and 9 mice in other experimental groups (Hsieh et al. 2011; Lévesque and Avoli 2013; Puttachary et al. 2015; Rusina et al. 2021). During the experimental procedure, a single administration of the different treatments was performed one hour before kainate injection. Thereafter, these treatments were administered daily for the duration of the behavioral experiments (Fig. 1).

Sixty minutes after the single administration of the above-mentioned treatments, each mouse was injected with kainate (15 mg/kg, ip), a glutamatergic agonist, used to induce epilepsy in rodents (Lévesque and Avoli 2013; Lévesque et al. 2016). However, the animals of the normal group were treated with distilled water (10 mL/kg, ip). Immediately after the injection of kainate or distilled water, each mouse was placed in a cage and their behavior was carefully observed for 80 min. Indeed, approximately 20 min after kainate injection, animals became hypoactive and displayed oro-facial movements, salivation, eye blinking, twitching of vibrissae, and yawning. A generalized tonic-clonic seizure, which marked the onset of *SE* was observed 40–80 min after kainate injection (Lévesque and Avoli 2013; Lévesque et al. 2016; Kandeda et al. 2022a, b). Thus, when the mouse developed tonic-clonic seizures, which marked the onset of *SE* (prolonged seizures, with or without loss of the righting reflex, lasting more than 30 min), the latency time and the duration of the *SE* were recorded. It is well known that stages 0–2 nonconvulsive seizures are observed approximately 14 min after kainate administration (Lévesque and Avoli 2013; Lévesque et al. 2016). These seizures are usually electroencephalogram seizures without behavioral signs. The first stage 3 seizure appeared after another additional 23 min, while the first convulsive seizure (stage 4 or 5) required a time interval of approximately 1 h. Stage 5 seizures only, occurred approximately 80 min after the treatment (Racine 1972; Lévesque et al. 2016; Sharma et al. 2018). The severity of seizures, referring to the most severe seizures exhibited by the mice, was assessed using the Racine scale (Racine 1972):

- Stage 0: indicates no response;
- Stage 1: indicates hyperactivity, vibrissae twitching, and chewing;

- Stage 2: indicates head nodding, head clonus, and myoclonic jerks;
- Stage 3: indicates unilateral forelimb clonus;
- Stage 4: indicates rearing with bilateral forelimb clonus;
- Stage 5: indicates generalized tonic-clonic seizures with loss of the righting reflex.

Furthermore, when *SE* was not observed during the above period, the animal was considered as protected against *SE* and the percentage of protection among alive mice was determined (Cherian and Thomas 2009; Lévesque et al. 2016; Sharma et al. 2018). The percentage of protection against death in mice that developed *SE* was also recorded during this period. At the end of observations, i.e. two hours following the onset of *SE*, diazepam (20 mg/kg, ip) was administered to the animals to terminate kainate-induced seizures or mortality (Fritsch et al. 2010; Qashu et al. 2010; Lévesque and Avoli 2013; Puttachary et al. 2015). Overall, the percentage of mice protected against the development of *SE* was calculated as follows: [(Number of mice that did not develop *SE*/ Number of alive mice used) * 100]. However, the percentage of mice death mice after *SE* was determined as follows: [(Number of dead mice after *SE*/ Number of mice that developed *SE*) * 100].

Twenty-four hours after *SE*, surviving mice were subjected to the T-maze task. One day later, i.e. 24 h after the 3-day T maze task protocol, the same mice were subjected to the Morris water maze task for 6 days. Twenty-four hours following the last session of the Morris water maze task, the open field test was performed for 1 day (Fig. 1). During behavioral assays, the above treatments were administered, once daily, until behavioral experiments were completed, i.e. 1 h before each session of the T-maze (3 sessions), Morris water maze (6 sessions), and the open field test (1 session). These mice were treated in this manner, once daily, at the same hours, until the end of the behavioral experiments (Fig. 1). Besides, the group receiving the piracetam (pira group), only used during behavioral experiments, served as the second positive control. Indeed, apart from evaluating the antiepileptic effect of the extract, the aim of this study was also to evaluate the anti-amnesic effect of the plant extract against memory impairment associated with seizures. It was, therefore, important to compare the anti-amnesic potential of the extract with a standard anti-amnesic drug such as piracetam. So, it is expected that animals receiving this treatment would show less memory impairment compared to the kainate group.

Behavioral tests

T-maze task

This test is based on the willingness of mice to explore a new arm rather than a familiar arm (Deacon and Rawlins 2006; Kandeda et al. 2017). The T-Maze is a "T" shaped device made of wood, black on the outside and white on the inside. It consists of a start compartment (starting arm), a central corridor, and two arrival corridors (arrival arms), perpendicular to the central corridor. The device has a wall of 20 cm high, 10 cm wide, and 30 cm long. An opaque guillotine door is placed at the exit of the departure compartment, as well as at the entrance to the arrival corridors. This makes it possible to control access to the different areas of the labyrinth. At the end of each arrival arm, there was a food reinforcer (a feeder) of 3 cm in diameter and 1 cm in height. This device was similar to that described by Kandeda et al. (2017). The T-maze test is used to detect drugs acting on working memory (Werk 2001; Deacon and Rawlins 2006; Yang and Mailman 2018). Working memory refers to a memory associated with the ability to remember a space or localization over a short period (Werk 2001; Deacon and Rawlins 2006). One day before the experiment (habituation phase), animals were individually placed in the starting arm for a 5-min exploration. When the animal entered the first one of the arrival arms, this arm was considered the preferred arm (opposite to discriminated arm). The next day, i.e. day 2 (acquisition phase), the animals were again placed in the T-maze for 5-min exploration. During this phase, the discriminated arm was closed, while the preferred arm was opened. Finally, during the retention phase, i.e. day 3 (retention phase), the animals were reintroduced to the T-maze for a 5-min testing period. On the new trial (both choice arms were opened), the animals were placed in a start arm and the number of entries and the time spent in the two arms were recorded. The device was cleaned with 70% ethanol to remove the odor left by the previous mouse.

Morris water maze task

The Morris water maze is an experimental device, designed by Richard Morris in 1980 (Morris et al. 1982). It is a circular device with 120 cm diameter and 75 cm height. It was divided into four virtual quadrants (north, south, east, and west). A stationary and transparent escape platform (30 cm in height and 5 cm diameter) was immersed at 3 cm below the surface of water. This platform was placed in an invariable frame (South-East). In addition, visual cues of various shapes were placed around the device and served as spatial cues for mice (Pahaye et al. 2017). The Morris water maze

provides both accurate and reproducible measures of spatial learning and memory. It is also a highly sensitive tool for assessing hippocampal damage (Wenk 2004; Broadbent et al. 2006). In this apparatus, two types of memory can be assessed mainly, reference memory (spatial long-term memory) and working memory (a type of short-term memory). On the first day of the assay, during the habituation phase, each rat was acclimated for 60 s without the platform. Each rat then performed sessions of three-block with 30 min intervals between sessions. Thus, each block consisted of four successive trials of 60 s each. On each trial, animals were randomly released into the water from one of four quadrants facing the maze wall. The acquisition phase began on day 2 with the refuge platform and continued for 3 days with three sessions per day. The water in the device was clouded by adding liquid milk so that the platform was invisible from the surface of the water. The session time for each mouse to find the platform was 120 s, and the interval of time between sessions was 5 min. Once the animal found the platform, it was allowed to stay on it for 15 s. During the acquisition phase sessions, the time taken to find the hidden platform was recorded for each animal. Learning efficiency was then assessed during the retention phase on day 6. During this phase, which lasted 120 s, the platform was removed from the maze. Thus, the time spent in the target quadrant was recorded for each animal.

Open field test

The open field is a square enclosure (40 cm x 40 cm), with raised edges of 45 cm high and illuminated in its center. The device used was similar to that described by Taiwe et al. (2015). The exploration area is divided into 17 squares of 10 cm x 10 cm each (16 squares divide the interior area and 1 central square) (Moto et al. 2018). Each mouse was placed in the center of the device and had 5 min to explore the field. Thus, all animal behaviors were carefully observed, and the parameters recorded were the time spent in the center, the number of groomings, the number of straightenings, and the number of lines crossed. This assay makes it possible to evaluate ambulatory behavior, as well as environmental and dietary neophobia (Belzung 1999). At the end of the experimental session, the device was cleaned with 70% ethanol to remove the odors of the previous mouse.

Sacrification and preparation of homogenates

Immediately after the open field test, the animals were sacrificed by cervical decapitation. All brains were collected and washed with 0.9% NaCl, cleaned and placed in dishes containing 0.9% NaCl, and frozen for 1 h. After solidification, these organs were dissected and kept cold to extract the hippocampus. For each animal, a fixed mass of the hippocampus thus removed was estimated using a digital analytical microbalance (U.S. Solid, USA). Homogenates were prepared at 20% with Tris buffer (50 mM HCl; 150 mM KCl; pH 7.4) and then centrifuged at 10,000 rpm for 15 min at 4 °C (Kandeda et al. 2017; Pahaye et al. 2017). Indeed, protein concentration in the homogenate was quantified in each sample by grinding an equal amount of tissue (measured with a microbalance) in a fixed volume of buffer. In this way, the concentration of proteins in each sample was determined as follows: fixed mass of brain tissue (mg)/fixed volume of buffer (mL) (Dieckmann-Schuppert and Schnittler 1997). The obtained supernatant was introduced into a labeled Eppendorf tube, which was then stored at -20 °C in a freezer for subsequent analysis of biochemical parameters.

Determination of the concentration of some oxidative stress parameters in the hippocampus

Reduced glutathione (GSH) assay

The concentration of GSH was performed according to the protocol described by Ellman (1959). One and a half microliters of Ellman's reagent were introduced into test tubes previously containing 100 µL of homogenate, while the blank tube contained 1 mL of Tris buffer (50 mM HCl; 150 KCl mM; pH 7.4). These mixtures were then incubated for 1 h at room temperature (24–26 °C). The absorbance was read by a spectrophotometer (Fisher Scientific; cat no: 108-88-3) at 412 nm.

Malondialdehyde (MDA) assay

Two hundred and fifty microliters of homogenate and Tris buffer (50 mM HCl; 150 mM KCl; pH 7.4) were introduced into the test tubes and the blank tube, respectively. In each of the aforementioned tubes, 125 µL of 20% TCA was then added, followed by 250 µL of 0.67% TBA. The tubes were closed with glass beads and incubated for 10 min at 90 °C in a water bath (MRC laboratory-instruments; cat no: WBO-100). Then, these tubes were cooled and centrifuged at 3000 rpm for 15 min at room temperature. The supernatant was pipetted and read on a spectrophotometer. The MDA reacts with TBA in a warm acidic medium to give a pink complex. This pink complex exhibits an absorption maximum at 530 nm (Wilbur et al. 1949). The intensity of

the coloration was proportional to the presence of MDA in the sample.

Determination of the concentration of some pro-inflammatory cytokines in the hippocampus

The determination of the concentration of tumor necrosis factor (TNF), interleukin 6 (IL-6), and interleukin 1 beta (IL-1β) was carried out by the ELISA technique (Enzyme-Linked Immunosorbent Assay) using Quantikine Kit for TNF (Minneapolis, USA; cat no: RTA00) or IL-6 (Minneapolis, USA; cat no: R6000B) or IL-1β (Minneapolis, USA; cat no: RLB00) (Zhu et al., 2020). Fifty microliters of dilution solutions (RD1-42 for TNF, RD1-21 for IL-1β, and RD1-54 for IL-6) were added to each well of an ELISA plate, respectively. Then 50 µL of standard, control, or sample was added to each well. The mixture was homogenized by gently tapping the frame plate for 1 min. The microplates were incubated for 2 h at 37 °C. After incubation, each well was washed 5 times with the washing buffer (400 µL). Then, the specific antibody for each protein conjugated to biotin was added to each well at a rate of 100 µL for each cytokine. The preparations were again incubated for 2 h at 37 °C and washed 5 times with the washing buffer (100 µL). After washing, 100 µL of substrate consisting of streptavidin coupled with peroxidase were added to each well, and the preparation was incubated for 30 min at room temperature and protected from light. The enzymatic reaction was stopped by adding 100 µL of stop solution (HCl). Absorbance was measured at 450 nm with a microplate reader. The ELISA technique allows the specific detection of antigens (proteins) by the use of two specific antibodies. The concentration of each pro-inflammatory cytokine, expressed in pg/mL, was determined from the standard calibration curve.

Statistical analysis

The data presented in this study are expressed as mean ± SD. However, the number of mice that developed *SE* or the number of dead mice is expressed in percentage (%). These data were analyzed using Graph Pad Prism software version 8.0.1. The normality data was evaluated using the Shapiro-Wilk and Kolmogorov-Smirnov tests, while variance homogeneity between experimental groups was assessed using the Brown-Forsythe test. When the assumption of variance homogeneity was established, one-way ANOVA (some behavioral and biochemical tests) or two-way ANOVA (Morris water maze test) was performed. Thus, when the difference between means of experimental groups existed, Tukey *post-hoc* test was performed. Furthermore, when the data do not assume Gaussian distribution, Kruskal Wallis test followed by Dunn's test *post-hoc* test was performed, and results were displayed as mean median and interquartile range. The difference between the number of mice that developed *SE* and the number of dead mice was determined using the Chi-square test (two-side) (Taiwe et al. 2015). For all analyses, the difference for which $p < 0.05$ was considered significant.

Results

The aqueous extract of *S. cumini* dose-dependently prevented the development of *SE* and protected mice against *SE*-induced mortality.

There is no available antiepileptic drug that can prevent *SE* in people at risk (Cherian and Thomas 2009; Kim et al. 2021). Therefore, a drug or extract with a preventive effect on the development of *SE* should be sought.

Compared to animals of the normal group, 91.67% ($p < 0.001$) of animals in the kainate group had *SE* [Chi^2 (1,11) = 4, $p < 0.001$] (Table 1 and supplement I.1). The aqueous extract of *S. cumini* at the dose of 72 mg/kg markedly ($p = 0.01$) prevented the development of *SE* in 57.14% ($p = 0.01$) of animals [Chi^2 (1,7) = 4, $p = 0.01$], compared to the kainate group (Table 1). This effect of the extract was comparable to that of sodium valproate, a reference antiepileptic drug, which protected 55.56% ($p = 0.01$) of mice from developing *SE* [Chi^2 (1,9) = 4, $p = 0.01$] (Table 1 and supplement I.1).

SE is known to cause sudden unexpected death in patients. Thus, a drug that can prevent *SE*-induced death is sought (Hsieh et al. 2011; Hockers 2019). In the present study, the preventive effect of the extract against *SE*-induced mortality was therefore evaluated.

In the kainate group, kainate caused 45.45% ($p = 0.01$) of death only between mice developing *SE*, unlike the normal group where no deaths were observed [Chi^2 (1,11) = 4, $p = 0.01$] (Table 1 and supplement I.2.). However, the aqueous extract of *S. cumini* (144 and 288 mg/kg) significantly protected 100% ($p < 0.001$) of the mice against death also between mice that developed *SE*, compared to the kainate group [Chi^2 (1,6) = 4, $p < 0.001$]. This protection was greater than that of sodium valproate, a standard antiepileptic drug that protected 25% ($p = 0.05$) of mice against death after *SE* [Chi^2 (1,4) = 4, $p = 0.05$] (Table 1 and supplement I.2.).

The aqueous extract of *S. cumini* extract increased the latency and reduced the duration of *SE*.

A drug may not prevent *SE*, but should at least delay its onset (Sharma et al. 2018; De Farias et al. 2022). The purpose of this trial was to test whether the extract could

Table 1 The aqueous extract *S. cumini* dose-dependently prevented the development of *SE* and protected mice against *SE*-induced mortality

Treatments	Total No of mice used	No of dead after kainate and before *SE*	No of mice that developed *SE*	Percentage of mice protected against *SE*	No of dead after *SE*	Percentage of mice protected from death after *SE*	No of surviving mice after *SE*
Normal	6	0	0	100	0	100	6
Kainate	12	0	11	8.33^{c}	6	45.45^{b}	6
S.c28.8	9	0	6	33.33*	3	50.00	6
S.c72	9	2	3	57.14**	1	66.67*	6
S.c144	9	3	4	33.33*	0	100**	6
S.c288	9	3	4	33.33*	0	100**	6
SV	9	0	4	55.56**	3	25.00*	6

Each value represents the percentage (%). c$p < 0.001$; b$p < 0.01$ compared to the normal group and ** $p < 0.01$; * $p < 0.05$ compared to the kainate group. Normal = normal group treated with distilled water only; Kainate = kainate group treated with distilled water; S.c28.8 – S.c288 = test groups treated with different doses of the aqueous extract of *S. cumini* (28.8, 72, 144, and 288 mg/kg, respectively); SV = positive control group treated with sodium valproate (300 mg/kg) ; % = percentage; No: number; SE = *status epilepticus*

delay the onset of kainate-induced *SE* in mice not protected against *SE*.

There were significant inter-group differences in the latency to the onset of *SE* [$F(6, 16) = 77.48$, $p < 0.0001$] (Supplement II.1.). Administration of kainate to the kainate group resulted in a decrease (2.88 ± 0.26 min, $p < 0.001$) in *SE* latency time compared to the normal group (Fig. 2 A). Compared to the kainate group, the aqueous extract of *S. cumini* (144 mg/kg) remarkably increased this time by 64.56% (7.99 ± 0.01 min, $p < 0.001$). The effects of the extract were more marked than those of sodium valproate. Indeed, sodium valproate increased this time by 56.39% (6.26 ± 0.04 min, $p = 0.0145$) (Fig. 2 A).

SE is a medical emergency associated with mortality in TLE patients (Hsieh et al. 2011; Gaínza-Lein et al. 2019; Kim et al. 2021). To improve quality of life and avoid unexpected death in patients, an antiepileptic drug must at least reduce the duration of *SE* (Hsieh et al. 2011; Gaínza-Lein et al. 2019; Kim et al. 2021). Thus, the effect of the extract on the duration of *SE* was assessed.

There were significant inter-group differences in the duration of *SE* [H (8) = 36.76, $p < 0.0001$] (Supplement II.2.). Administration of kainate to the kainate group resulted in a significant increase (17.14 ± 1.19 min, $p < 0.001$) in the duration of *SE* compared to the normal group (Fig. 2B). The extract (144 mg/kg) markedly decreased *SE* duration by 67.21% (5.82 ± 0.18 min, $p < 0.001$). The effects

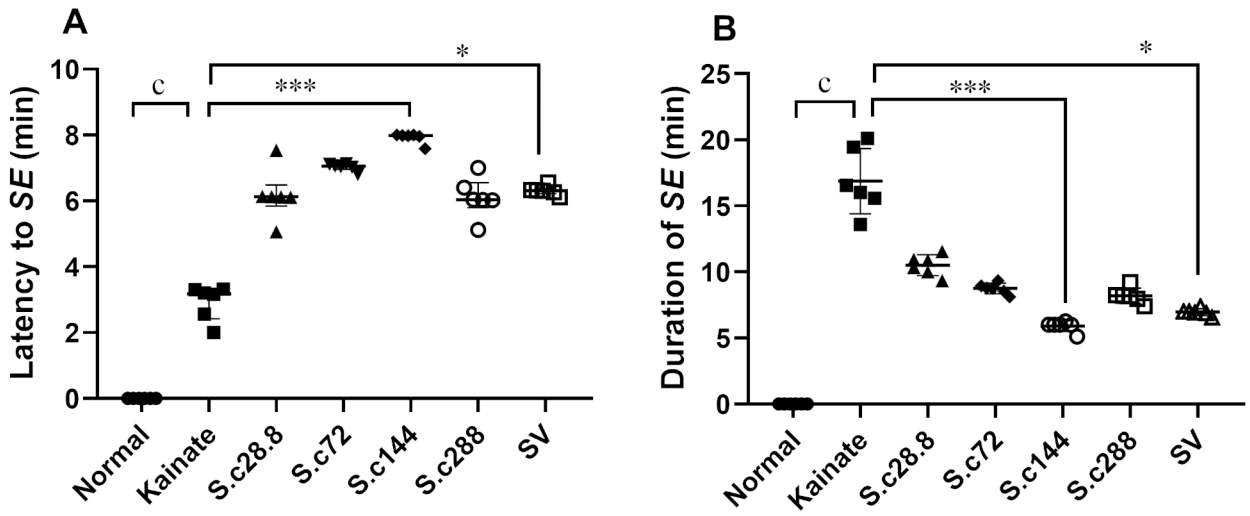

Fig. 2 The aqueous extract of *S. cumini* increased the latency (A) and decreased (B) duration of *SE*. Each value represents the mean ± SD (duration of *SE*) or mean with interquartile range (latency to onset of *SE*) of the group, n = 6. c$p < 0.001$; b$p < 0.01$ compared to the normal group and *** $p < 0.001$, * $p < 0.05$ compared to the kainate group. Normal = normal group treated with distilled water only ; Kainate = kainate group treated with distilled water; S.c28.8 – S.c288 = test groups treated with the different doses of the aqueous extract of *S. cumini* (28.8, 144, 72, and 288 mg/kg, respectively); SV = positive control group treated with sodium valproate (300 mg/kg) ; *SE* = *status epilepticus* ; min = minute

of the extract were similar to those of sodium valproate, which decreased this duration by 59.17% (6.88 ± 0.09 min, $p = 0.05$) (Fig. 2B).

The aqueous extract of *S. cumini* improved the working memory of mice in the T-maze.

A major complaint in TLE patients is impairment of working memory (Groticke et al. 2008; Kiasalari et al. 2016; Kandeda et al. 2022a). Indeed, hippocampal sclerosis and the spread of seizures to the prefrontal cortex could explain why working memory is the most impaired, as this structure plays a critical role in the memory process (Abrahams et al. 1999; Groticke et al. 2008; Kiasalari et al. 2016; Mosiashvili et al. 2017). Therefore, the effect of the extract on working memory was evaluated by studying spontaneous alternation in the T-maze.

There were significant inter-group differences in the latency to choose the preferred arm in the T-maze [H (8) = 29.95, $p < 0.001$] (Supplement III.1.). Mice in the normal group took a long time to regain the preferred arm, while those in the kainate group took a shorter time to regain this preferred arm ($p = 0.3098$) (Fig. 3 A). Compared to the kainate group, the extract at all doses increased this time, with a greater effect ($p < 0.001$) at the dose of 144 mg/kg. Piracetam (standard nootropic and anti-amnesic drug) ($p = 0.6638$) and sodium valproate (standard antiepileptic drug) ($p = 0.999$) induced a nonsignificant increase in this time (Fig. 3 A).

Significant inter-group differences were observed in the number of returns in the starting arm [F (7, 40) = 4.201, $p = 0.0015$] (Supplement III.2.). Mice from the normal group returned a few times in the starting arm, while those from the kainate group returned several times ($p = 0.05$) (Fig. 3B). Compared to the kainate group, the aqueous extract of *S. cumini* (144 mg/kg) markedly decreased the number of returns in the starting arm ($p = 0.01$). This decrease was more marked than that of piracetam ($p = 0.05$) (Fig. 3B).

Significant inter-group differences were observed in the time spent in the preferred arm [H (8) = 22.1, $p < 0.001$] or discriminated arm [H (8) = 23.6, $p < 0.001$] (Supplement III.3. and III.4.). Compared to the normal group, animals in

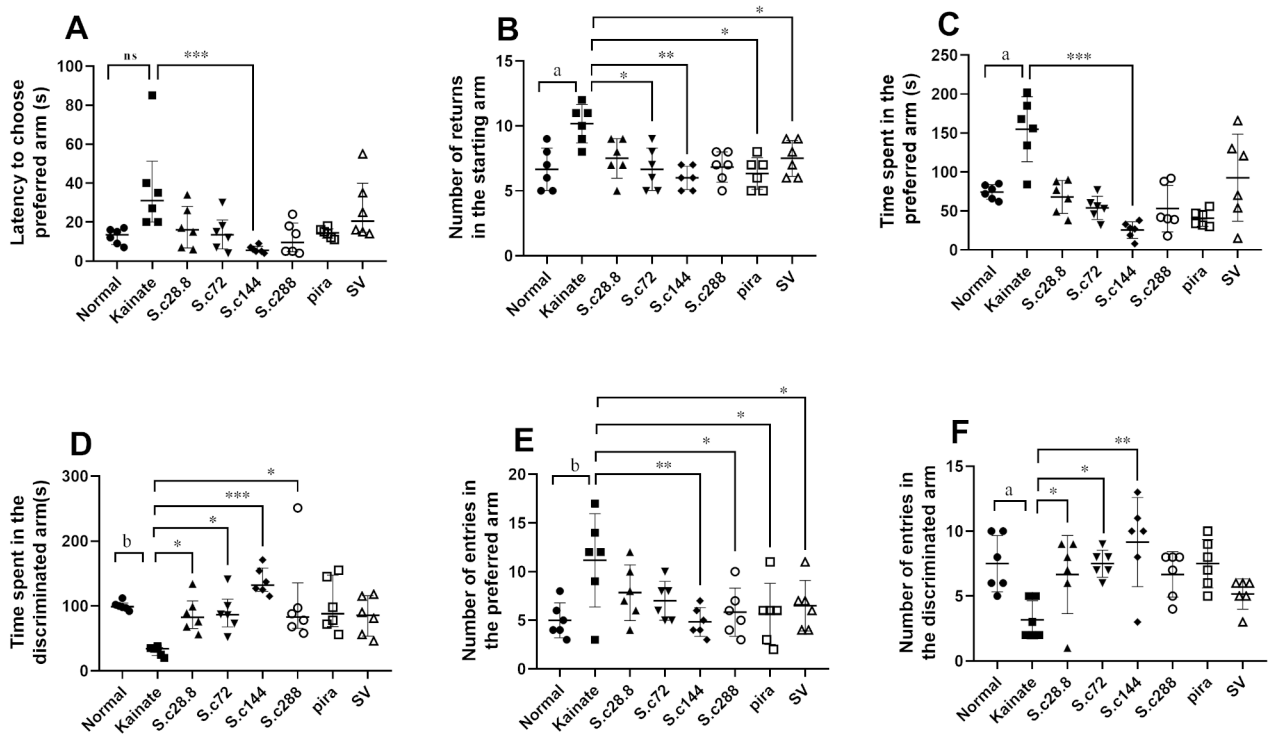

Fig. 3 The aqueous extract of *S. cumini* decreased the time taken to choose the preferred arm (A), decreased the number of returns in the starting arm (B), decreased the time spent in the preferred arm (C), increased the time spent in the discriminated arm (D), decreased the number of entries in the preferred arm (E), increased the number of entries in the discriminated arm (F). Each point represents the mean ± SD or mean with interquartile range (latency to choose preferred arm, and time spent in the preferred arm or discriminated), n = 6. *b*$p < 0.01$; *a*$p < 0.05$ compared to the normal group and *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ compared to the kainate group. Normal = normal group treated with distilled water; Kainate = kainate group treated with distilled water ; S.c28.8 – S.c288 = test groups treated with the different doses of the aqueous extract of *S. cumini* (28.8, 72, 144, and 288 mg/kg, respectively) ; pira = positive control group treated with piracetam (200 mg/kg) ; SV = positive control group treated with sodium valproate (300 mg/kg); ns = nonsignificant

the kainate group spent more time ($p=0.0209$) in the preferred arm (Fig. 3 C) and few times ($p=0.999$) in the discriminated arm (Fig. 3D). The aqueous extract of *S. cumini* (144 mg/kg) remarkably decreased ($p<0.001$) the time spent in the preferred arm (Fig. 3 C) and increased ($p<0.001$) this time in the discriminated arm (Fig. 3D), compared to the kainate group. piracetam induced a significant increase in the time spent in the discriminated arm ($p=0.481$) (Fig. 3 C and D).

Significant inter-group differences were observed in the number of entries in the preferred arm [F (7, 40) = 4.262, $p<0.0013$] or discriminated arm [F (7, 40) = 3.205, $p<0.0086$] (Supplement III.5. and III.6.). Animals from the normal group entered the preferred arm (Fig. 3E) less than the discriminated arm (Fig. 3 F). However, those in the kainate group entered the preferred arm more than the discriminated arm ($p=0.01$). Compared to the kainate group, the aqueous extract of *S. cumini* (144 mg/kg) remarkably decreased ($p=0.01$) the number of entries in the preferred arm (Fig. 3E) and increased ($p=0.01$) the number of entries in the discriminated arm (Fig. 3 F). The effects of the extract were greater than those of the positive control groups (piracetam and sodium valproate), which also increased this number in the discriminated arm ($p=0.05$) (Fig. 3E and F).

The aqueous extract of*S. cumini*reduced the long-term spatial memory of mice in the Morris water maze.

TLE is associated with impaired long-term spatial memory (Holler and Trinka 2014; Kiasalari et al. 2016; Tramoni-Negre et al. 2017). Therefore, an antiepileptic drug with ideally anti-amnesic effect against long-term memory is sought. The ability of the extract to prevent or reduce this memory impairment was evaluated in the Morris water maze.

Significant inter-group differences were observed in the time taken to find the hidden platform during the acquisition phase [F (7, 128) = 5.928, $p<0.0001$] (Supplement IV.1.). Compared to the normal group, animals from the kainate group took longer ($p=0.01$) to regain the platform during the last two days of the experiment (Fig. 4 A). The aqueous extract of *S. cumini* at all doses reduced ($p<0.001$) the time spent to find the platform on the fourth day of the experiment, compared to the kainate group (Fig. 4 A). The effects of the extract were similar to those of piracetam (an anti-amnesic drug) ($p<0.001$) (Fig. 4 A) and sodium valproate (an antiepileptic drug with GABA-enhancing effect) ($p<0.001$) (Fig. 4 A).

Significant inter-group differences were observed in the time spent in the target quadrant during the retention phase in the Morris water maze [H (8) = 24.4, $p<0.001$] (Supplement IV.2.). The animals of the kainate group spent less time in the target quadrant ($p=0.690$) as compared to the normal group (Fig. 4B). Compared to the kainate group, the animals treated with the extract (144 mg/kg) spent a greater time ($p<0.001$) in the target quadrant (Fig. 4B). The effects of the aqueous extract of *S. cumini* were more marked than those of piracetam, a nootropic and anti-amnesic drug, which failed to induce a significant decrease ($p=0.282$) (Fig. 4B).

The aqueous extract of*S. cumini*attenuated anxiety-like behavior in the open field.

Devices used to assess memory disorders are associated with anxiety, due to their anxiogenic environment (Rodgers and Dalvi 1997; Harrison et al. 2009). Therefore, performing such a test may lead to false-positive results, if a drug or extract is devoid of anxiolytic properties. To exclude the influence of anxiety on memory performance during testings, the anxiolytic effect of the extract was therefore determined.

Significant inter-group differences were observed in the time spent [H (8) = 29, $p<0.0001$] and the number of lines crossed [F (7, 38) = 5.511, $p<0.0004$] in the center of the open field (Supplement V.1 and V.2.). The animals in the kainate group crossed few lines ($p=0.01$) (Fig. 5 A) and spent few times ($p=0.01$) (Fig. 5B) in the center of the device, compared to the normal group. Compared to the kainate group, the aqueous extract of *S. cumini* (144 mg/kg) markedly increased the number of lines crossed ($p<0.001$) (Fig. 5 A) and the time spent ($p=0.01$) (Fig. 5B) in the center of the device. The effects of the extract were similar to those of piracetam, which increased the number of lines crossed ($p<0.001$) (Fig. 5 A) and the time spent ($p=0.05$) (Fig. 5B) in the center of the device.

Significant inter-group differences were observed in the number of straightenings [H (8) = 20.92, $p=0.0039$] and groomings [H (8) = 20.68, $p=0.0043$] in the open field (Supplement V.3. and V.4.). Animals in the kainate group performed few straightenings (Fig. 5 C) and more groomings ($p=0.0164$) (Fig. 5D), compared to the normal group. Compared to the kainate group, *S. cumini* extract (144 mg/kg) remarkably ($p<0.001$) increased the number of straightenings (Fig. 5 C) and decreased the number of groomings ($p=0.01$) (Fig. 5D). The effects of the extract were greater than those of the positive control groups, which failed to significantly increase the number of straightenings (Fig. 5 C) and decrease the number of groomings (Fig. 5 A).

The aqueous extract of*S. cumini*reduced the concentration of some oxidative stress parameters in the hippocampus.

Oxidative stress is the first event that follows the permanent activation of NMDA receptors during kainate-induced *SE* (Cheng et al. 2004; Liang et al. 2007; Shin et al. 2011). Thus, a drug or extract with antioxidant properties could help to prevent the development of epilepsy or its aggravation.

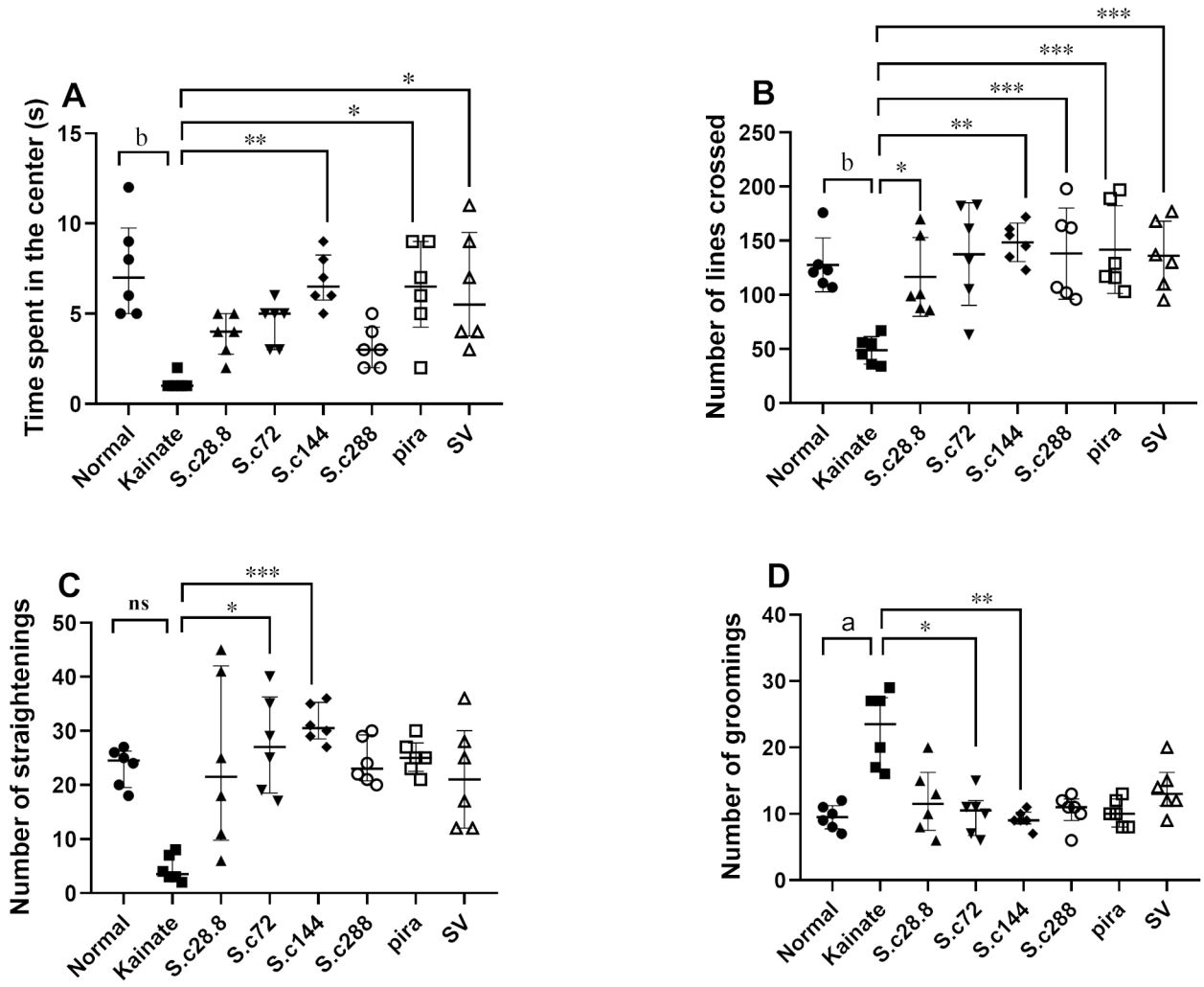

Fig. 4 The aqueous extract of *S. cumini* reduced the time taken to find the hidden platform during the acquisition phase (A) and increased the time spent in the target quadrant during the retention phase (B). Each point or curve represents the time performed by the animals in each group, and each point in the middle of each curve indicates the mean ± SD, n = 6. c$p < 0.001$; b$p < 0.01$ compared to the kainate group and *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ compared to the kainate group. Normal = normal group treated with distilled water ; Kainate = kainate group treated with distilled water ; S.c28.8 – S.c288 = test groups treated with the aqueous extract of *S. cumini* (28.8, 72, 144, and 288 mg/kg, respectively) ; pira = positive control group treated with piracetam (200 mg/kg) ; SV = positive control group treated with sodium valproate (300 mg/kg) ; s = second; D = day; ns = nonsignificant

Significant inter-group differences were observed in the concentration of MDA [F (7, 15) = 6.645, $p < 0.0011$] or GSH [F (7, 15) = 5.101, $p = 0.0040$] in the hippocampus (Supplement VI.1. and VI.2.). In the animals of the kainate group, kainate increased the concentration of MDA ($p = 0.01$) (Fig. 5 A) and decreased that of GSH ($p = 0.05$) (Fig. 6B), compared to the normal group. However, the extract decreased the concentration of MDA at the dose of 144 mg/kg ($p < 0.001$) (Fig. 6 A), while it increased that of GSH at the doses of 144 and 288 mg/kg ($p = 0.01$) (Fig. 6B), compared to the kainate group. The effects of the extract were greater than those of the positive control groups, which also decreased the concentration of MDA ($p = 0.01$) (Fig. 6 A) and increased that of GSH ($p = 0.01$) (Fig. 6B).

The aqueous extract of*S. cumini*reduced in a dose-dependent manner the concentration of some pro-inflammatory cytokines in the hippocampus.

During kainate-induced *SE*, inflammatory response contributes to accelerating or exacerbating the development of epilepsy (Oprica et al. 2003; Lee et al. 2008; Ramazi et al. 2020). Thus, a drug or extract with anti-inflammatory properties could prevent or reduce the development of epilepsy or its aggravation.

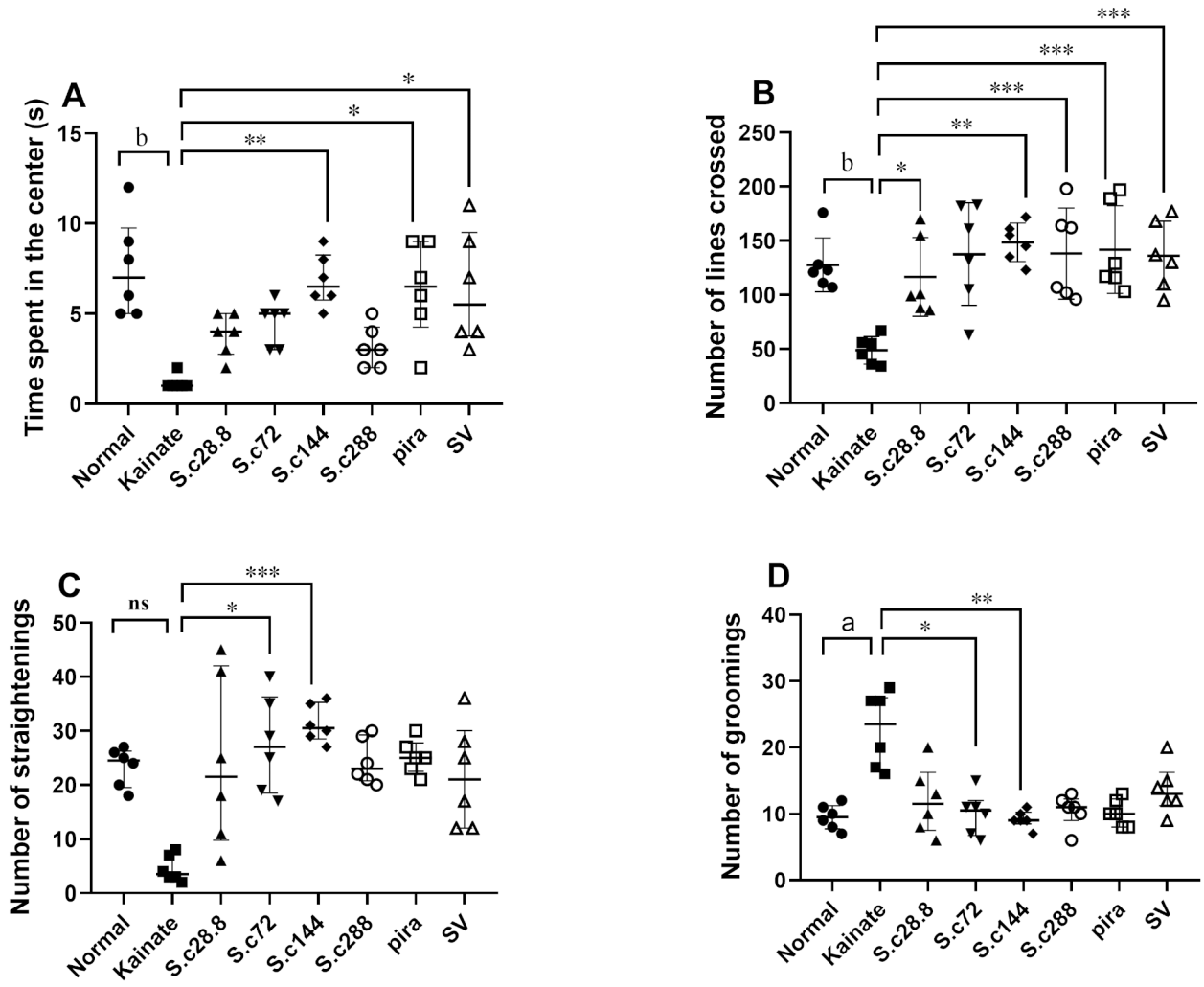

Fig. 5 The aqueous extract of *S. cumini* increased the time spent in the center (A), the number of lines crossed in the center (B), increased the number of straightenings (C), and reduced the number of groomings (D) in the open field. Each point represents the mean ± SD or mean with interquartile range (time spent in the center, number of straightenings, and number of groomings) of the group, n = 6. b$p < 0.01$; a$p < 0.05$ compared to the normal group and *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ compared to the kainate group. Normal = normal group treated only with distilled water; Kainate = kainate group treated with distilled water ; S.c28.8 – S.c288 = test groups treated with the different doses of the aqueous extract of *S. cumini* (28.8, 72, 144, and 288 mg/kg, respectively); pira = positive control group treated with piracetam (200 mg/kg) ; SV = positive control group treated with sodium valproate (300 mg/kg) ; s = seconds; ns = nonsignificant

Significant inter-group differences were observed in the concentration of TNF [F (7, 40) = 95.88, $p < 0.0001$], IL-6 [H (8) = 24.27, $p = 0.0010$], and IL-1β [H (8) = 42.36, $p < 0.0001$] in the hippocampus (Supplement VII.1, 2, and 3). Data show that there is an increase in the concentration of TNF ($p < 0.001$) (Fig. 7 A), IL-1β ($p < 0.001$) (Fig. 7B), and IL-6 (Fig. 7 C) in the animals of the kainate group compared to the normal group. Compared to animals in the kainate group, the aqueous extract at all doses and reference drugs lowered the concentration of TNF ($p < 0.001$) (Fig. 7 A). However, the effects of the extract (144 mg/kg) on the IL-6 and IL-1β concentrations were greater ($p < 0.001$) than those of the positive control groups (Fig. 7B and D).

Discussion

The objective of the present study was to assess the effects of an aqueous extract of *S. cumini* on *SE* and amnesia in mice treated with kainate. Thus, the aqueous extract of *S. cumini* significantly prevented the development of *SE* and protected mice from *SE*-induced mortality as compared to sodium valproate. In addition, the extract attenuated

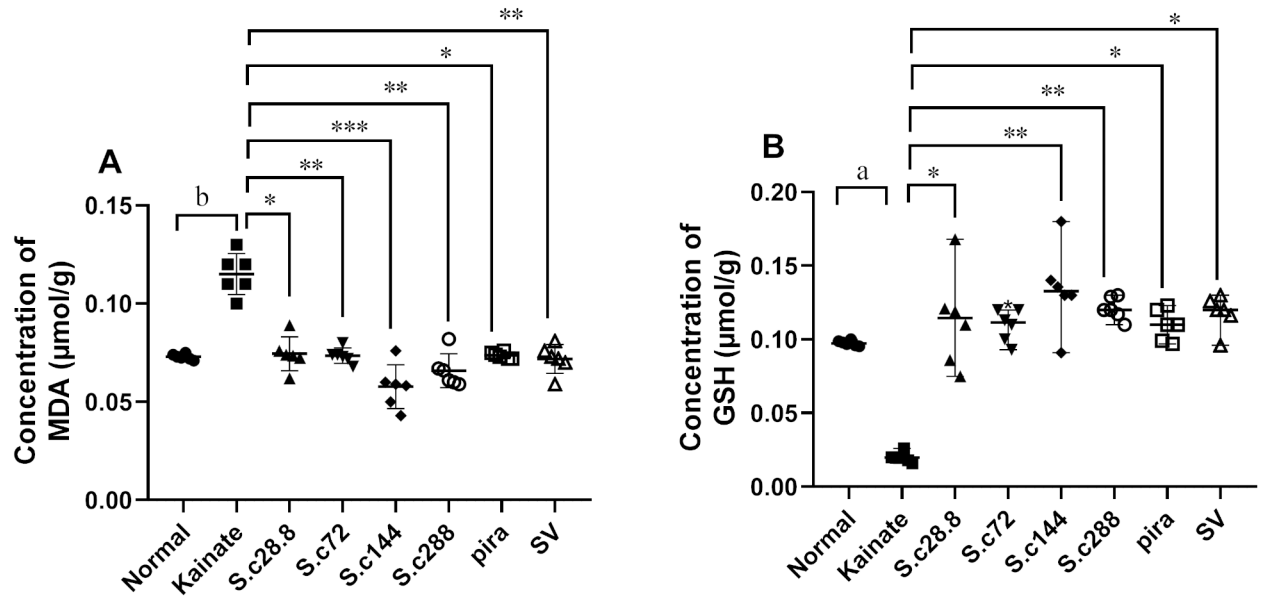

Fig. 6 The aqueous extract of *S. cumini* reduced the concentration of MDA (A) and increased that of GSH (B) in the hippocampus. Each point represents the mean ± SD of the group, n = 6. b$p < 0.01$; a$p < 0.05$ compared to the normal group and *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ compared to the kainate group. Normal = normal group treated only with distilled water ; Kainate = kainate group treated with distilled water ; S.c28.8-S.c288 = test groups treated with the different doses of the aqueous extract of *S. cumini* (28.8, 72, 144, and 288 mg/kg, respectively); pira = positive control group treated with piracetam (200 mg/kg) ; SV = positive control group treated with sodium valproate (300 mg/kg) ; MDA = malondialdehyde ; GSH = reduced glutathione

working memory impairment in the T-maze and long-term spatial memory in the Morris water maze as compared to piracetam. Neurochemical tests revealed that the aqueous extract significantly reduced oxidative stress and prevented inflammatory responses in the hippocampus.

TLE is a form of epilepsy characterized by the occurrence of partial complex seizures with secondary generalization (Golechha et al. 2011; Kandratavicius et al. 2014). This condition is due to excessive and hypersynchronous discharges that start in the temporal lobe and spread to the whole brain as secondarily generalized seizures (Golechha et al. 2011; Kandratavicius et al. 2014). The kainate model, developed by Ben-Ari in late 1970, is widely used to understand hippocampal hyperexcitability and epileptogenesis (Ben-Ari et al. 1979; Lévesque and Avoli 2013; Lévesque et al. 2016). Hence, the administration of kainate induces a severe and prolonged seizure called *SE*, which marks the starting point of the disease (Lévesque et al. 2016). *SE* is a prolonged or repeated seizure, that last at least 30 min, without a return to consciousness between seizures (Cherian and Thomas 2009; Curia et al. 2014; Moto et al. 2018). In the present study, kainate caused the development of *SE* in the kainate group. The administration of kainate also increased *SE*-induced mortality, increased the duration of *SE*, and reduced the latency to *SE*. These results corroborate those of Solomonia et al. (2010) and Hsieh et al. (2011) who induced TLE with kainate in mice and obtained similar results. Moreover, studies have pointed out the role of the kainate receptor complex in neuronal depolarization that causes hyperexcitability (Vincent and Mulle 2009; Falcon-Moya et al. 2018). The latter could be associated with a selective loss of inhibitory interneurons and major cells in the dentate gyrus, CA3, and CA1 regions (Tuunanen et al. 1996; Smith and Dudek 1997; Lévesque and Avoli 2013; Rattka et al. 2013; Holler et al. 2014). This hypothesis could therefore explain in part the development of *SE* and *SE*-induced mortality in mice (Cherian and Thomas 2009; Kim et al. 2021). It is well known that the interneurons in the dentate gyrus are generally GABA neurons. Since GABA neurons regulate the hyperexcitability of the pyramidal neurons in the dentate gyrus, the loss or alterations of these neurons could lead to *SE* or sudden unexpected death because of prolonged seizures (Wang et al. 2016; Dudek 2020). The aqueous extract of *S. cumini*, in a dose-dependent manner, significantly reduced the development of *SE*, with greater effect at the dose of 72 mg/kg. The extract at all doses protected mice against *SE*-induced mortality with complete protection at the doses of 72 and 144 mg/kg. In this study, we equally noticed that the highest doses of the extract (144 and 288 mg/kg) led to a high mortality rate, i.e. immediately after kainate injection.

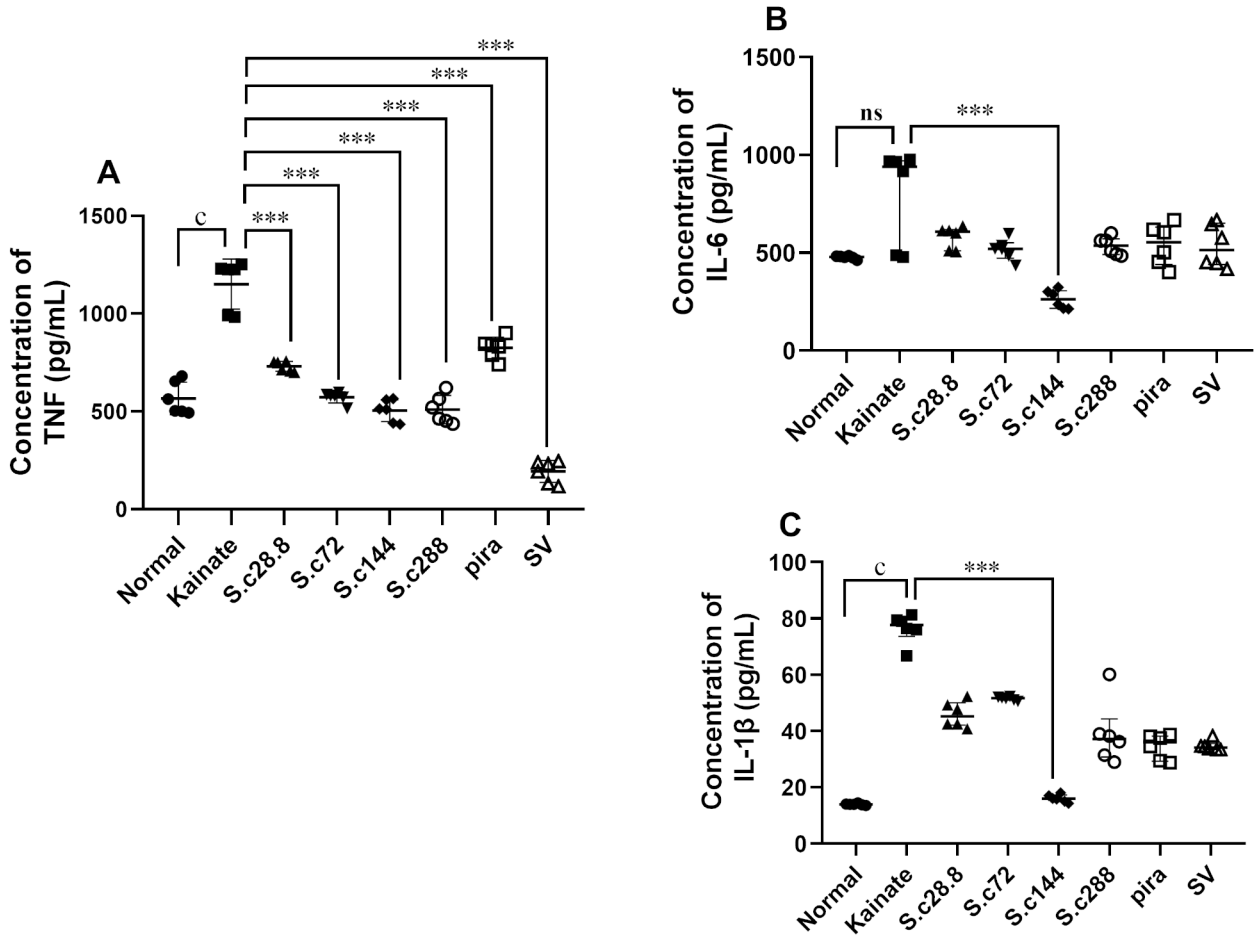

Fig. 7 The aqueous extract of *S. cumini* reduced in a dose-dependent manner the concentration of TNF (A), IL-6 (B), and IL-1β (C) in the hippocampus. Each point represents the mean ± SD or mean with interquartile range (concentration of IL-1β or IL-6), n = 6. c$p < 0.001$; b$p < 0.01$ compared to the normal group and *** $p < 0.001$; * $p < 0.05$ compared to the kainate group. Normal = normal group treated with distilled water only ; Kainate = kainate group treated with distilled water ; S.c28.8 – S.c288 = test groups treated with the different doses of the aqueous extract of *S. cumini* (28.8, 72, 144, and 288 mg/kg, respectively) ; pira = positive control group treated with piracetam (200 mg/kg) ; SV = positive control group treated with sodium valproate (300 mg/kg); TNF = tumor necrosis factor; IL-6 = interleukin six; IL-1β = interleukin 1 beta; ns = nonsignificant

Since the injection of kainate could lead to death in rodents (Kandeda et al. 2022a, b), the administration of high doses of the extract could also explain some death in mice in this study. Hence, the mortality observed in the present study could be the action of high doses of the extract alone rather than the random effect of kainate injection. In addition, the fact that a normal group treated only with the extract was not added in the present study, the results obtained make it difficult to attribute the mortality observed in mice to the only action of kainate. In future studies, a toxicity study of the high doses of the extract will be performed to exclude the possibility of a toxic effect of the extract. Furthermore, the extract (144 mg/kg) significantly increased the latency to *SE*. The extract also significantly reduced the duration of *SE* with a greater effect at the dose of 144 mg/kg. Given that the extract significantly protected mice against the development of *SE*, and increased the latency to *SE* or decreased the duration of *SE* in non-protected mice, these results suggest that the extract may possess antiepileptic-like properties (Hsieh et al. 2011; Mante et al. 2017; Hockers 2019; Wang et al. 2021). These findings also are corroborated by previous studies on the anticonvulsant and sedative effects of the plant in rats (Chanudom and Tangpong 2015; De Lima et al. 1998). The fact that the effect of the extract was comparable to that of sodium valproate (Mattson et al. 1992; Romoli et al. 2019), an antiepileptic drug widely prescribed against TLE, these results suggest the extract could be effective against partial complex seizures (Mattson et al. 1992; Romoli et al. 2019). Further studies using other models of temporal epilepsy should be performed to confirm the obtained results. Additionally, these properties of the extract could be related to the presence of kaempferol,

triterpenoids, and polyphenols, which are abundant in the extract. These compounds have been found to reduce the number and duration of seizures in electrical and chemical models of seizures in mice (De Lima et al. 1998; Luna et al. 2014; Taiwe et al. 2015). Also, studies reported beneficial effects of flavonoids and kaempferol on epilepsy, particularly in TLE (Kwon et al. 2019; Kandeda et al. 2021a, b).

TLE is often associated with memory disorders that affect short- and long-term memories (Abrahams et al. 1999; Groticke et al. 2008; Bonansco and Fuenzalida 2016; Kiasalari et al. 2016; Mosiashvili et al. 2017; Postnikova et al. 2017; Zhu et al. 2020).

Of all types of memory, working memory has gained much attention as evidenced by extensive literature. Working memory is the manipulation and retention of information for a short period in the prefrontal cortex or hippocampus (Zhao et al. 2014; Mosiashvili et al. 2017). Working memory impairment has clinical importance not only because it leads to altered quality of life, but also because of its relation to long-term memory (Abrahams et al. 1999; Groticke et al. 2008; Kiasalari et al. 2016; Mosiashvili et al. 2017). In the present study, the injection of kainate to the distilled water treated mice caused an increase in the number of entries and the time spent in the preferred arm of the T-maze. However, it decreased these parameters in the discriminated arm. These results are in agreement with those of Gorantla et al. (2016) and Kandeda et al. (2021b) who induced TLE with kainate in rodents and obtained similar results. The fact that the mice did not remember the first choice suggests an alteration of working memory (Wenk 2001; Lainiola et al. 2014; Prieur and Jadavji 2019; Kandeda et al. 2022a). Studies showed that epileptic patients are often subjected to working memory impairment (Abrahams et al. 1999; Kiasalari et al. 2016; Mosiashvili et al. 2017). Indeed, working memory amnesia is associated with a decrease in synaptic plasticity in the hippocampus (Rattka et al. 2013; Postnikova et al. 2017) and correlated dysfunction in the prefrontal cortex (Jin and Maren 2015; Mosiashvili et al. 2017). The aqueous extract of *S. cumini*, in a dose-dependant manner, with the greatest effect at the dose of 144 mg/kg, significantly increased the number of entries and time spent in the discriminated arm, indicating that the mice recall the preferred arm that they visited. These results suggest therefore anti-amnesic-like properties of the extract against working memory impairment (Hasselmo 2006; Vorhees and Williams 2014; Hussein et al. 2018; Kandeda et al. 2021b). These effects could be mediated by an interaction of the extract with the cholinergic neurotransmission. Indeed, several studies revealed the presence of major compounds such as betulinic acid, Beta-sitosterol, and kaempferol-3-0- glucoside in the extract. However, these compounds have been shown to modulate and interact with cholinergic neurotransmission (Ayaz et al. 2017; Rebas et al. 2020; Lee et al. 2021). Thus, further studies have to be performed to determine the direct action of the extract on the cholinergic neurotransmission. The anti-amnesic effect of the extract could be also mediated by the protective effect against the loss of the neurons involved in the working memory process (Abrahams et al. 1999; Hasselmo 2006; Groticke 2008; Kiasalari et al. 2016; Mosiashvili et al. 2017). Thus, further studies are needed to determine the exact mechanism of action by which the extract exerts its anti-amnesic effect. The fact that the seeds of the same plant have been shown to improve memory in Alzheimer's disease models in rats, these findings equally suggest the presence of bioactive molecules with anti-amnesic potential (Hossain et al. 2017). Furthermore, the anti-amnesic effect of the extract could be correlated to its antiepileptic-like activities. Indeed, limiting the excessive discharge and neuronal loss in the hippocampus has been shown to reduce memory impairment in rodents (Nygaard et al. 2015; Clossen and Reddy 2017).

Memory impairments are common in TLE patients, where memory-related brain regions are involved in the generation of epileptic discharge (Tramoni-Negre et al. 2017). Accumulating evidence suggested that TLE may also alter long-term memory. This condition generates therefore the loss of autobiographical information and an inability to store new information over a long period (Holler and Trinka 2014; Kiasalari et al. 2016). In this study, the Morris water maze test was used to assess long-term spatial memory deficit. The results of this test showed that kainate significantly increased the time taken to find the hidden platform during the acquisition phase in the kainate group. It equally decreased the time spent in the target quadrant during the retention phase in the same group. These data corroborate those of Zeng et al. (2013), Kandeda et al. et al. (2022a), and Kandashvili et al. (2022) who induced long-term spatial memory loss in the Morris water maze with kainate and made similar observations. Numerous studies showed that in rodents, an injury in the hippocampus (part of the brain involved in long-term memorization) leads to a deficit in the processes of spatial learning and memory (Shors et al. 1992; Luine et al. 1994; Tramoni-Negre et al. 2017; Voss et al. 2017). Treatment of mice with the aqueous extract of *S. cumini*, at the doses of 144 and 288 mg/kg, reversed these effects as compared to the kainate group. These effects were greater than those of piracetam, a nootropic and anti-amnesic drug (Chaudhry et al. 1992; Pohle et al. 1997; Fisher et al. 2004; Chaudhari et al. 2013). These data suggest therefore that the aqueous extract possesses anti-amnesic-like properties against long-term spatial memory (Bolanos et al. 1998; Hubens et al. 2014). Furthermore, the seeds or the methanolic extract of the same plant showed an anti-amnesic effect against long-term memory in an animal

model of Alzheimer's disease (Alikatte et al. 2012; Hossain et al. 2017). These observations also suggest the presence of bioactive molecules in the extract with an anti-amnesic effect against long-term spatial memory impairment (De Lima et al. 1998; Alikatte et al. 2012; Ayyanar and Subash-Babu 2012; Bijauliya et al. 2017; Hossain et al. 2017; Abdin et al. 2020). Further studies have to be performed in other models of long-term memory impairment to confirm the obtained results, and to unravel the mechanism of action of the extract.

Devices used to evaluate memory impairments are often associated with anxiety-like behavior, due to their anxiogenic configuration (Rodgers and Dalvi 1997; Harrison et al. 2009). Therefore, to exclude the influence of anxiety-like behavior on memory performance during testings, the anxiolytic effect of the extract was performed. In the present study, the locomotor activity of each animal was assessed in the open field. The results showed that kainate caused a significant decrease in the number of lines crossed, straightenings, and time spent in the center as compared to the kainate group. It also increased the number of groomings. These conditions demonstrated an increase in anxiety-like behavior in animals (Maia et al. 2014; Mohd et al. 2018; Kandeda et al. 2021). Kainate increases GABA-transaminase activity and decreases brain GABA concentration, as well as the density of GABA receptors in the striatum, frontal cortex, and hippocampus (Sperk et al. 2003; Ngo Bum et al. 2012; Kandeda et al. 2022a, b). This dysfunction is at the origin of the excitability of the brain, and consequently of the anxious state of animals (Maia et al. 2014; Mohd et al. 2018). Treatment of mice with the aqueous extract of *S. cumini*, with greater effect at the dose of 144 mg/kg, alleviated these alterations and induced opposite effects to those of the kainate group. These results suggest that the aqueous extract of *S. cumini* may contain compounds with anxiolytic-like properties (Ngo Bum et al. 2009; Beppe et al. 2015; Kandeda et al. 2022a). These findings are confirmed by the sedative effect of the extract demonstrated by Hossein et al. (2017). In addition, these results also suggest that the anti-amnesic-like effects of the extract are possibly favored by its anxiolytic effect. Indeed, anxiolytic drugs promote exploratory behavior in animals by reducing anxiety and stress caused by an anxiogenic device environment (Kilfoil et al. 1989; Cryan and Sweeny 2011). Hence, exploratory behavior is strongly associated with a memory-enhancing activity (Kilfoil et al. 1989; Cryan and Sweeny 2011).

Oxidative stress is an imbalance between the production of radical (or reactive) oxygen species and antioxidant cellular capacities (Hsieh et al. 2011; Aguiar et al. 2021; Pizzino et al. 2017). Oxidative stress participates in the pathogenesis of many neurodegenerative diseases (Wang et al. 2005; Shin et al. 2011; Ngo Bum et al. 2012; Cenini et al. 2019). In the present research, data revealed that kainate caused oxidative stress in the hippocampus of the kainate group. This was marked by an increase in the concentration of MDA. The kainate also decreased that of GSH. These results corroborate those of Huang et al. (2012) and Ramazi et al. (2020). It is well known that following the injection of kainate to rodents, this molecule activates kainate receptors and leads to increased glutamate concentration in the synaptic cleft. This in turn generates excitotoxicity associated with dysfunction of the mitochondrial respiratory chain, ROS or free radicals production, and subsequent neuronal damage (Cheng et al. 2004; Liang et al. 2007; Shin et al. 2011). With a reduced supply of GSH, free radicals or ROS react quickly with neighboring macromolecules such as (DNA, proteins, lipoproteins, and membrane phospholipids with MDA production) and damage them (Jacoby et al. 2015; Vezzani et al. 2016; Liu et al. 2017). Besides, the injection of kainate could increase the density of glutamatergic receptors and decrease the number of gabaergic receptors in the hippocampus. These dysfunctions also contribute to excitotoxicity, and subsequently to ROS production (Khamse et al. 2015; Taiwe et al. 2015; Lin et al. 2020). Administration of the aqueous extract of *S. cumini* (at all doses) is remarkably associated with a decrease in the concentration of MDA and an increase in that of GSH as compared to the kainate group. The brain possesses antioxidant systems including catalase, reduced glutathione, and superoxide dismutase. These proteins have been shown to alleviate oxidative stress-induced damage (Khamse et al. 2015). The fact that the extract reduced oxidative stress in treated mice, these results suggest an antioxidant-like property of *S. cumini* (Hsieh et al. 2011; Huang et al. 2012; Cheng et al. 2021). These results also confirm the abundant literature on the antioxidant-like properties of *S. cumini* (Katiyar et al. 2016; Santos et al. 2020). Otherwise, these properties of the extract could be related to their richness in alkaloids, anthocyanins, flavonoids triterpenoids, and flavonoids, whose neuroprotective-like properties are strongly correlated to their ability to eliminate free radicals or ROS (Adebesin et al. 2015; Foyet et al. 2015). Other studies have to be performed to unravel the antioxidant mechanisms of the extract.

Inflammation is considered to be one of the most important mechanisms contributing to the pathogenesis or recurrence of seizures (Renaud et al. 2015; Feng et al. 2016; Ramazi et al. 2020). In addition, excitotoxicity, inflammatory response, and oxidative stress are three processes involved in the development of so-called secondary lesions during the chronic phase of epilepsy (Renaud et al. 2015; Feng et al. 2016; Ramazi et al. 2020). Accumulating studies in rodents suggested the involvement of inflammatory processes in the pathogenesis of TLE (Golechha et al. 2011). Pro-inflammatory cytokines such as TNF, IL-1β, and IL-6

are overexpressed following the injection of chemoconvulsants such as kainate (Golechha et al. 2011). Thus, therapeutic strategies that target inflammatory pathways constitute a hope to find a cure against TLE. The pro-inflammatory cytokine assay in the present study showed that kainate markedly increased the concentration of all cytokines tested (TNF, IL-6, and IL-1β) in the hippocampus of the kainate group. These results are consistent with those of Hsieh et al. (2011), Ho et al. (2015), Vezzani et al. (2015), and Kandeda et al. (2021a) who reported that the injection of kainate to rodents is associated with a significant increase in the concentration of TNF, IL-6, and IL-1β. Indeed, the administration of kainate is highly associated with pro-inflammatory cytokine synthesis (Feng et al. 2016; Ojo et al. 2019; Lin et al. 2020). The inflammatory reaction after kainate-induced *SE* leads to the activation of nitric oxide synthase inducible (iNOS). This latter causes the synthesis of nitric oxide which reacts with ROS and exacerbates oxidative stress in kainate-induced *SE* (Lin et al. 2020). According to several studies, this synthesis is caused by the activation of microglia, macrophages, endothelial cells, and neutrophils (Mohd et al. 2015; Feng et al. 2016; Lin et al. 2020). Treatment of mice with the aqueous extract of *S. cumini*, in a dose-dependent manner, significantly decreased the concentration of all cytokines tested as compared to the kainate group. These results demonstrate that the aqueous extract of *S. cumini* is likely endowed with anti-inflammatory properties (Golechha et al. 2011; Mohd et al. 2015, 2018; Kandeda et al. 2021b). The results corroborate previous findings on the anti-inflammatory properties of *S. cumini* stem bark (Muruganandan et al. 2001). These activities could be related to the presence in this extract of phenolic compounds such as triterpenoids and flavonoids (Muruganandan et al. 2001; Lim 2012; Jagetia et al. 2008; Koepp et al. 2017). Triterpenoids have been shown to interact with intracellular neuronal or glial signaling pathways involved in inflammation (Luna et al. 2014). Also, flavonoids were revealed to reduce the expression of pro-inflammatory cytokines, as well as the activation of nuclear factor-κB (NFkB) in neurons (Khamse et al. 2015; Koepp et al. 2017). Regarding the implications of several factors in vivo assays, in vitro studies need to be performed for a better understanding of the exact molecular mechanisms of the extract.

Conclusions

The objective of the present investigation was to study the antiepileptic- and anti-amnesic-like effects of the aqueous extract of *S. cumini* on kainate-treated mice, and possible mechanisms of action. Compared to the normal control group, the administration of kainate caused *SE* in all mice of the kainate group and altered the working memory in these mice by increasing the time spent in the preferred arm. The injection of kainate equally altered the long-term memory in mice by increasing the time spent in the target quadrant during the retention phase. Treatment with the aqueous extract of *S. cumini*, as well as with sodium valproate (a widely prescribed antiepileptic drug), effectively protected the mice against kainate-induced *SE* or mortality. The aqueous extract of *S. cumini* also improved working memory and long-term memory in mice by increasing the time spent in the discriminated arm and the time spent in the target quadrant, respectively. Furthermore, the extract significantly increased the concentration of GSH and decreased that of MDA. The concentration of pro-inflammatory cytokines (TNF, IL-1β, and IL-6) in the hippocampus was also reduced following the administration of the aqueous extract of *S. cumini*. These results suggest that the aqueous extract of *S. cumini* possesses antiepileptic- and anti-amnesic-like effects. These effects are likely mediated in part by antioxidant and anti-inflammatory activities. Although the study of other parameters is essential to understanding the pharmacodynamic effects of this extract, these results validate the traditional use of the aqueous extract of *S. cumini* against epilepsy and associated comorbidities.

Abbreviations

S. cumini	*Syzygium cumini*.
SE	*status epilepticus*.
TLE	temporal lobe epilepsy.
MDA	malondialdehyde.
GSH	reduced glutathione.
TNF	tumor necrosis.
IL-6	interleukin six.
IL-1β	interleukin one beta.
SV	sodium valproate.
pira	piracetam.
SD	standard deviation.
ANOVA	analysis of variance.
ROS	reactive oxygen species.
i.p.	intraperitoneally.
po	*per os*.

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Authors' contributions AKK and SN designed the study, performed all behavioral studies, accomplished data analysis, and drafted the manuscript. AKK and SMT critically reviewed the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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Data Availability Data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval The study was conducted following the Cameroon National Ethical Committee guidelines (Ref No. FW-IRB00001954, 22 October 1987). All efforts were made to minimize the number of mice used and their suffering.

Competing Interests The authors have no relevant financial or nonfinancial interests to disclose.

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