Future Journal of Pharmaceutical Sciences

RESEARCH

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Protective effect of *Spondias mombin* leaf extracts against aluminum chloride-induced brain oxidative stress, inflammation and apoptosis in rats

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Abstract

Background Aluminum is recognized for its toxicity in humans and animals. This study investigates the protective effects of *Spondias mombin* leaf extracts against oxidative stress, inflammation, and apoptosis in male Wistar rats. Rats were divided into nine groups, receiving 100 mg/kg $AlCl_3$ for 3 weeks, followed by a 2-week treatment with *Spondias mombin* leaf extract (SME) or its fraction (SMF) at 100 and 200 mg/kg. Brain tissues were analyzed using biochemical, molecular, and histopathological techniques.

Results Phytochemical analysis confirmed the presence of tannins, phenols, terpenoids, flavonoids and steroids, while HPLC analysis identified kaempferol and other polyphenols, in the *Spondias mombin* extracts. Aluminum exposure led to increased oxidative and inflammatory damage in brain tissue as revealed by decreased glutathione concentrations and antioxidant enzyme activities, along with elevated levels of tumor necrosis factor-alpha, nitric oxide, myeloperoxidase, xanthine oxidase, and lactate dehydrogenase. Caspase-3, and BCL2 associated X (Bax) levels were also increased in $AlCl_3$-exposed rats. Both SME and SMF mitigated $AlCl_3$-induced redox imbalance, proinflammatory events, and neuronal cell death by enhancing levels of reduced glutathione and antioxidant enzyme activities, reducing the levels of inflammatory biomarkers, and preserving hippocampal formation and neuronal cell organization.

Conclusions These findings highlight the therapeutic potential of *Spondias mombin* leaf extracts against aluminum-induced neurotoxic effects through their antioxidant, anti-inflammatory, and antiapoptotic properties.

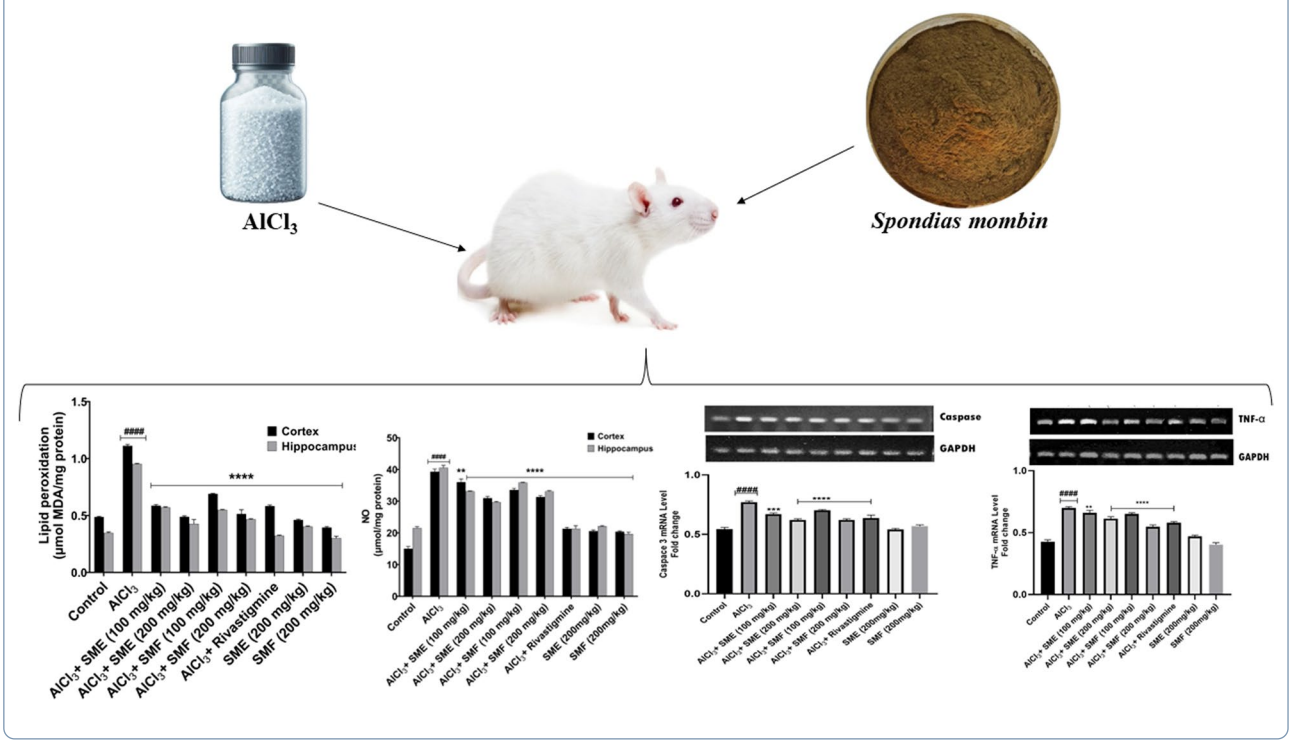
Keywords Aluminum neurotoxicity, Antioxidant activity, Anti-inflammatory effect, Anti-Apoptosis, *Spondias mombin*

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Graphical abstract



Background

Aluminum (Al) is a ubiquitous environmental element that poses a potential risk of toxicity to both humans and animals. Its presence in the body is inevitable and can occur through various routes such as skin exposure, inhalation of aerosols, ingestion of medications, beverages and food, immunizations, as well as through hemodialysis equipment [1]. Extensive research has indicated that the average weekly intake of Al ranges from 70 to 140 mg. Despite its limited absorption rate of more than 1% from the gastrointestinal system, Al has the ability to build up in different tissues, including the brain, liver, and kidneys, thereby leading to neurotoxic and other toxic effects over time. The implications of Al exposure encompass inflammation, metabolic disturbances, oxidative damage, genotoxicity, immune system alterations, as well as necrosis and cell death. Several studies have documented these negative impacts [2, 3]. On exposure to this metal, inflammation, metabolic imbalance, oxidative damage, genotoxicity, immunological alterations, necrosis and apoptosis will occur [4, 5]. Researchers have observed that Al has the capability to disrupt the blood–brain barrier (BBB) due to its inherent ability to access the regular physiological functioning of the central nervous system and its propensity to accumulate in the brain [5, 6]. Notably, the buildup of aluminum in the brain has been linked to oxidative stress, neuroinflammation, and other neurodegenerative changes that participate in the onset of Alzheimer's illness [7].

Oxidative stress and neuroinflammation are increasingly recognized as contributing factors to the etiology of multiple brain disorders [8]. Oxidative stress refers to continuous damage inflicted on cells due to an imbalance between reactive oxygen species and defensive systems. These reactive oxygen metabolites are generated during cellular metabolism [9]. Aluminum has been demonstrated to induce inflammation systemically. It has been suggested that portal inflammation is associated with metal exposure and might contribute to the onset of Alzheimer's illness, with the duration and amount of aluminum exposure being key factors. This is corroborated by findings of higher aluminum levels in both the brain and liver of individuals with the disorder. However, some studies have contradicted this, proposing that aluminum, once within the brain, might trigger a comparable inflammatory reaction [10, 11].

Plant-based antioxidants have recently gained popularity due to their potential to disrupt free radical chain reactions [12]. The natural antioxidant properties of medicinal extracts suggest that restoring oxidative

balance could be a key mechanism through which therapeutic herbs guard against aging and cognitive impairment. This antioxidant capacity of plants may be attributed to the existence of polyphenolic substances such as flavonoids and phenolic acids [7, 13].

Medicinal plant remedies are an integral part of the history and culture of people in various countries where they are widely used to cover basic health care needs [14]. They have been shown to contain many bioactive phytochemicals which positions them as promising candidates for neuroprotection against Alzheimer's disease (AD) [15, 16]. Polyphenolic compounds have shown neuroprotective characteristics in animal models of AD, stroke, and Parkinson's disease, as well as influencing normal cognitive function [17]. Traditional medicinal plants, such as *Ginkgo biloba*, contain flavonoids and terpenoids that exhibit neuroprotective effects by reducing Aβ deposition and enhancing cerebral blood flow [18]. Medicinal herbs with significant antioxidant and anti-inflammatory capabilities may consequently give benefits in the therapy of Al poisoning.

Spondias mombin, a member of the Anacardiaceae family, holds cultural significance with names such as Iyeye, ngulungu, and isadaa in Yoruba, Igbo, and Hausa languages. Commonly known as hog plum, true yellow mombin, golden apple, and java plum, this plant thrives in tropical regions across Asia, America, Brazil, and Africa [19–21]. Recognized for its multifaceted utility, the utilization of different elements ranging from the dense corky bark to the leaves, flowers, and fruits is documented in the literature [22]. Traditional uses include memory enhancement and anti-aging practices involving *S. mombin* leaves.

The Yoruba community in South West Nigeria particularly associates the fruit, referred to as"iyeye,"with the"ability to confer longevity,"linking it to notions of memory and intelligence. Extensive research has highlighted the plant's antioxidant, antibacterial, cardioprotective, antiepileptic, and antipsychotic properties [22–26]. The present study's objective was to assess the defensive efficacy of methanol extract and fraction of *Spondias mombin* against oxidative stress and inflammatory indicators in Aluminum toxicity.

Methods

Chemicals

Thiobarbituric acid (TBA), trichloroacetic acid (TCA), Ellman's reagent (DTNB), *N*-(1-Naphthyl) ethylenediamine dihydrochloride, neocuproine, 2,4,6-Tris(2-pyridyl)-s-triazine (TPTZ), 2,2-diphenyl-1-picryl-hydrazyl (DPPH), acetylthiocholine iodide, and quercetin, were obtained from Sigma-Aldrich, USA. Methanol was sourced from Merck (Darmstadt, Germany). All other chemicals and reagents used in this study were obtained from standard suppliers.

Extraction of plant leaves

The leaves of *Spondias mombin* were collected from the Federal University of Technology, Akure, Southwest Nigeria (Latitude 7° 18' 15.372" N and Longitude 5° 8' 13.247" E). Voucher samples were placed in the herbarium of the university. Following authentication, the leaves were air-dried at room temperature, pulverized using a blender, and extracted with 80% methanol by maceration for 48 h. The resulting extract was then evaporated using a rotary evaporator, followed by lyophilization to remove solvent content, ensuring preservation for subsequent use.

Preparation of fraction of *Spondias mombin* (SMF)

In a tiny flask, 3 g of the initial extract was dispersed in 20 ml of 1% (v/v) H_2SO_4. The mixture was heated for 30 min at 60 °C in a water bath to cause hydrolysis. To precipitate the flavonoid aglycones, the heated mixture was then chilled on ice for fifteen minutes. The flavonoid aglycone mixture was extracted from the cooled solution by filtration, and the filtrate was subsequently dissolved in 50 ml of warm (50 °C) 95% ethanol. Once more filtering the mixture into a 100-ml volumetric flask, 95% ethanol was added to bring it to volume. Thereafter, the filtrate was dried by evaporation, the fraction (SMF) was obtained.

Phytochemical screening of SME and SMF

The qualitative phytochemical tests were carried out utilizing established protocols to examine the classes of phytochemicals in the plant's methanolic extract (SME) and its fraction (SMF). To ascertain whether anthraquinones, tannins, alkaloids, and saponins are present, the methods outlined by Trease et al. (1989) were employed. Sofowora's (1996) procedure was utilized to test for flavonoids. Moreover, the steroid test was conducted in compliance with Harborne's guidelines (1973).

HPLC–DAD analysis

HPLC analysis with UV detection was carried out using a Shimadzu NexeraMX system. Inverse phase chromatographic analyses were conducted with uBONDAPAK C18 column, measuring 100 mm in length, 4.6 mm in diameter, and 7 mm in thickness, employing a mobile phase consisting of 70% acetonitrile and 30% water. The 10 mg sample, extracted with acetonitrile and stabilized using ethyl acetate, was prepared in a 25 mL standard flask and adjusted accordingly. Initially, the standard analyte profile was introduced into the HPLC system, generating a chromatogram displaying specific peak areas and shapes, which served as a baseline for analyzing the test

specimen. The specimen flow rate was set at 2 mL/min, and substances were detected using a UV sensor (Diode Array Sensor, DAD) at 254 nm.

Evaluation of the in vitro antioxidant activity and radical scavenging potentials of SME and SMF

DPPH radical scavenging activity of SME and SMF were evaluated as demonstrated [27]. Superoxide radical scavenging activity was evaluated using [28] method. Nitric Oxide Radical Scavenging Capacity was established as stated [29]. 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonate) ($ABTS^{\cdot+}$) radical scavenging activity was determined according to [30]. Reducing Power activity was determined according to [31]. Fe^{2+} Chelation Capacity was evaluated using the method of [32]. Lipid peroxidation activity of SME and SMF was evaluated according to [33]. Acetylcholinesterase activity of SME and SMF was evaluated according to [34].

Animal grouping and treatment

Wistar rat (males), averaging 200 ± 20 g in weight was acquired from an animal housing facility in Osun State, Nigeria. After that, these rats were kept in closely monitored laboratory settings in the Animal House of the Department of Biochemistry, at the Federal University of Technology, (Akure), Nigeria. Throughout the experiment, the rats were fed regular animal pellets and allowed unrestricted access to water. The research received ethical approval from FUTA's animal research ethics committee (Approval No: FUTA/ETH/21/04), adhering to the 2011 NIH Guide for the Care and Use of Laboratory Animals. The rats were then organized into nine groups, each consisting of ten rats. Over a span of three weeks, toxicity was induced in the rats by daily oral administration of $AlCl_3$ at a dosage of 100 mg/kg body weight [35]. Subsequently, treatments were administered for 14 days, involving both a standard drug and various doses of the plant extracts. Group 1 (Control) was received vehicle (water) while Group 2 was administered 100 mg/kh $AlCl_3$. Groups 3 and 4: received $AlCl_3$ + 100 and 200 mg/kg of *Spondias mombin* methanol extract (SME), respectively. Groups 5 and 6 were administered $AlCl_3$ + 100 and 200 mg/kg of *Spondias mombin* fraction (SMF), respectively. Group 7 received $AlCl_3$ + reference standard drug (0.3 mg/kg rivastigmine). Groups 8 and 9 were administered 200 mg/kg of SME and 200 mg/kg of SMF, respectively. The sample size per group (10 rats) was chosen based on similar studies that have demonstrated sufficient power to detect meaningful differences with this number of animals per group. Pilot data and previous research in similar experiments suggest that 10 rats per group is sufficient to detect differences in outcome measures related to the effect of plant extract on AD symptoms.

Following the last treatment, the animals were euthanized to dissect their cortices and hippocampi. The harvested tissues were then processed for biochemical evaluations, following the methodology demonstrated in Akinmoladun et al. (2018).

Evaluation of oxidative stress markers

Determination of lipid peroxidation level

The level of lipid peroxidation was measured by detecting the production of thiobarbituric acid reactive substances (TBARS) using the Varshney and Kale technique (1990). The degree of lipid peroxidation was determined using a molar extinction coefficient of 1.56×10^5 M^{-1} cm^{-1} at 532 nm.

Glutathione peroxidase (GPx) activity

The GPx activity was evaluated using the methodology described by Rotruck et al. [36].

Reduced glutathione (GSH) level

The level of GSH was estimated using Beutler's 1963 method.

Estimation of superoxide dismutase (SOD) activity

SOD activity was evaluated according to the procedure delineated by Misra and Fridovich in 1972. A mixture of brain homogenate (0.2 ml), 0.3 mM epinephrine (0.3 ml), and 2.5 ml of carbonate buffer with a 0.05 M concentration and pH 10.2 along with distilled water was prepared. The spectrophotometer was set at 480 nm to monitor the absorbance at 30-s intervals over a total duration of 150 s.

Evaluation of catalase activity

Evaluation of catalase activity was performed following the procedure outlined by Sinha (1972). Brain homogenate (0.2 ml) was blended with 0.8 ml of distilled water to achieve a 1:5 dilution of the specimen. The assessment combination consisted of 2 ml of hydrogen peroxide (H_2O_2) solution (800 µmoles) and 2.5 ml of phosphate buffer in a test tube. The evaluation was carried out at ambient temperature. At 60-s intervals, 1 ml of the response blend was introduced to 2 ml of dichromate/acetic acid reagent, resulting in the generation of an unsteady blue precipitate of perchromic acid. Subsequently, the solution was subjected to heating for 10 min in a boiling water bath, inducing a shift in color to a steady green hue due to the development of chromic acetate. The optical density was gaged at 570 nm.

Evaluation of pro-inflammatory biomarkers

Nitrite level

Nitric oxide (NO) generation is commonly measured using estimates of nitrite and nitrate in biological material. According to Guevara et al. [37], the Griess reaction was used to calculate the amount of nitrite. The amount of nitrite in the tissue homogenate was measured in µmol/mg of protein using a calibration curve made from sodium nitrite.

Myeloperoxidase (MPO) activity

A previously reported protocol was used to measure myeloperoxidase activity (Eiserich et al. 1998). A tetramethylbenzidine (TMB, 1.2 mM) and H_2O_2 (100 mM) solution in NaH_2PO_4 (43 mM, pH 5.4) was mixed with the test sample (0.2 ml), and the absorbance was measured spectrophotometrically at 450 nm. The ability of MPO to oxidize TMB was used to measure its peroxidase activity.

Xanthine oxidase (XO) activity

XO activity was assessed following the method described by Prajda and Weber (1975).

Lactate dehydrogenase activity

Lactate dehydrogenase (LDH) activity was measured according to the 1973 Tienhaara procedure. Over the course of three minutes, measurements were made every minute at 340 nm to track the change in absorbance. The data were given in units of protein per milligram.

RNA preparation and RT-PCR

The extraction of total RNA from brain tissues was carried out using Trizol reagent (Thermofisher Scientific) in accordance with the manufacturer's instructions. The quantification and purity of the extracted RNA were validated through spectrophotometric measurements at 260 and 280 nm. The ProtoScript II First Strand cDNA Synthesis Kit (Biolabs, New England) was employed to convert RNA to complementary DNA, while the OneTaq® 2X Master Mix (NEB) was utilized for PCR amplification with the primer set listed in Table 1. The resulting PCR amplicons were subjected to electrophoresis in 1% agarose gels, and images depicting the relative density of DNA bands were captured using blue light-gel photography, as previously described [38]. The basal gene expression of each animal under investigation was monitored using glyceraldehyde 3-phosphate dehydrogenase (GAPDH).

Table 1 The primers used for PCR

GENES	PRIMERS (OLIGONUCLEOTIDES SEQUENCE)
TNF-α	Forward: CTCTTCTGCCTGCTGCACTTTG
	Reverse: ATGGGCTACAGGCTTGTCACTC
Cas-3	Forward: GGCCGACTTCCTGTATGCTT
	Reverse: TGACCCGTCCCTTGAATTTC
Bax	Forward: TCAAGGCCCTGTGCACTAAA
	Reverse: CCCGGAGGAAGTCCAGTGT

Statistical analysis

The experimental data were presented as mean values with standard deviations. One-way ANOVA was used to analyze the experimental data, and Tukey's multiple comparison test was then performed. A statistical significance threshold of $p < 0.05$ was applied to ascertain the results. GraphPad Prism version 8.02 (GraphPad Software Inc., CA, USA) was used for statistical analysis.

Results

Phytochemical constituents of *Spondias mombin* leaf extracts

Phytochemical screening of *Spondias mombin* methanol leaf extract (SME) showed the presence of saponins, phenols, flavonoids, tannins, terpenoids, cardiac glycosides and steroids while the fraction of *S. mombin* (SMF) tested positive for flavonoids.

The HPLC–DAD fingerprinting of the extracts revealed the presence of phenolic acids (chlorogenic acid, ellagic acid and gallic acid), flavonoids (rhamnetin, isorhamnetin, isoquercetin, quercetin, kaempferol, rutin, isoquercitrin and astragalin), terpenoids (humulene, lupeol and cadinene), and other compounds. Flavonoids were the preponderant phytochemicals in the extracts (Tables 2 and 3). The chromatograms have been supplied as supplementary files.

In vitro antioxidant activities

The antioxidant activities of SME and SMF were evaluated through various radical scavenging assays. Table 4 presents a comprehensive analysis of the extracts' and reference compounds' performance in the various tests, as indicated by their IC_{50} (inverse logarithmic method) values. At the maximum concentration (200 µg/ml), the extracts exhibited the strongest scavenging activity. The values were comparable to the reference standard compounds in most instances.

Effect of SME and SMF on oxidative stress markers

The administration of aluminum chloride ($AlCl_3$) induces oxidative damage in animals through depletion

Table 2 HPLC–DAD quantified compounds in methanol leaf extract of *Spondias mombin* (SME)

Compound	Standard retention time	SME leaf extract	
		Area (mUA)	(mg/g)
Chlorogenic acid	1.266	1699.3360	2.11
Ellagic acid	2.750	2818.3005	3.51
Gallic acid	4.450	943.3170	1.17
Rhamnetin	5.466	473.0410	0.59
Isorhamnetin	6.483	416.3200	0.51
Humulene	7.033	288.6240	0.36
B-sitosterol	7.950	170.0725	0.21
Isoquercetin	8.816	191.9900	0.24
Quercetin	11.050	10037.9580	12.49
Kaempferol	12.166	3824.3670	4.76
Rutin	13.700	3739.4150	4.65
Lupeol	16.250	188.4180	0.23
Cadinene	18.500	391.1870	0.49
Isoquercitrin	19.683	247.0720	0.31
Geraniin	20.500	170.8950	0.21
Astragalin	21.133	161.4540	0.20

Table 3 HPLC–DAD quantified compounds in fraction of *S. mombin* (SMF)

Standard compound	Standard retention time	SMF extract	
		Area (mUA)	Conc. (mg/g)
Chlorogenic acid	3.700	2532.3230	2.27
Ellagic acid	5.883	628.8510	0.65
Rhamnetin	7.233	44.5875	0.05
Isoquercitrin	7.966	712.0680	0.74
Quercetin	9.116	62.5550	0.07
Rutin	15.500	591.2300	0.61
Lutein	17.233	2199.0965	2.27
Rutinose	19.166	26.8600	0.03
Zeinoxanthine	19.400	27.1710	0.03

of cortical and hippocampal endogenous antioxidants in the brains of rats. The inhibitory effect of SME and SMF on the cortical and hippocampal MDA levels is illustrated in Fig. 1. The MDA level drastically increased ($p < 0.0001$) in the group administered$AlCl_3$ only relative to the control group. In the groups administered the extracts, the MDA level dramatically dropped. The result showed that SME, SMF and the Rivastigmine standard had remarkable inhibitory effects.

Decreased activities of Glutathione perioxidase (GPx), (Fig. 2) occasioned by $AlCl_3$ administration were ameliorated in rats treated with SME and SMF. The effectiveness of the extracts is in the order: SME (200 mg/kg) > SMF (200 mg/kg) > SME (100 mg/kg) > SMF (100 mg/kg).

Figure 3 shows that the reduction in GSH level occasioned by $AlCl_3$ administration was significantly alleviated in rats treated with rivastigmine, 200 mg/kg of SME and 200 mg/kg SMF. In the hippocampal region of the brain, 100 mg/kg of SME and SMF treated groups showed no discernible variations from the $AlCl_3$-administered group.

The effects of SME and SMF on SOD activity are illustrated Fig. 4. The SOD activity of rats administered $AlCl_3$ (Group II) was considerably lower ($p < 0.0001$) than rats in the control group (Group I). However, treatment with SME (200 mg/kg), SMF (200 mg/kg), and Rivastigmine (startard drug) increased the SOD enzyme activities compared to the rats in the $AlCl_3$ group (Group II). The investigation suggested that SME has a greater antioxidant effect than SMF in the $AlCl_3$-intoxicated rats.

In Fig. 5, the administration of SME and SMF solely did not influence catalase activities both in the hippocampus and the cortex when compared to the corresponding controls. Meanwhile, $AlCl_3$-intoxicated animals showed marked decrease in catalase activity than all other groups, however, the Rivastigmine, SME and SMF treated groups showed increase in catalase activities.

Table 4 IC_{50} values for the antioxidant activities of methanol leaf extracts of SME and SMF

Antioxidant Parameter	SME IC_{50} (µg/ml)	*SMF* IC_{50} (µg/ml)	Standards	IC_{50} (µg/ml)
2,2-diphenyl- 1-picrylhydrazyl (DPPH) radical scavenging capacity	44.75 ± 0.64^a	70.71 ± 0.11^b	Quercetin	37.92 ± 0.44
Superoxide radical scavenging activity	34.09 ± 0.33^a	57.56 ± 0.22^b	Quercetin	31.52 ± 0.50
Nitric oxide radical scavenging activity (NO)	63.16 ± 1.76^a	86.68 ± 1.87^b	Ascorbic acid	45.11 ± 1.58
Hydroxyl radical scavenging activity (OH)	54.72 ± 1.52^a	55.16 ± 2.11^b	Mannitol	52.38 ± 2.40
$ABTS^+$ radical scavenging activity	26.91 ± 1.47^a	35.67 ± 1.27^b	Trolox	22.56 ± 1.01
Reducing power	53.47 ± 1.60^a	58.67 ± 2.32^b	Ascorbic acid	36.71 ± 2.15
Iron chelating	39.17 ± 1.25^a	47.67 ± 1.51^b	EDTA	25.78 ± 1.34
Lipid peroxidation	56.28 ± 2.04^a	62.12 ± 1.92^b	Ascorbic acid	53.72 ± 1.00

Values are presented as mean ± SD (n = 3). Values with different superscripts in a row are significantly different ($^{a,b}p < 0.001$ vs. standard)

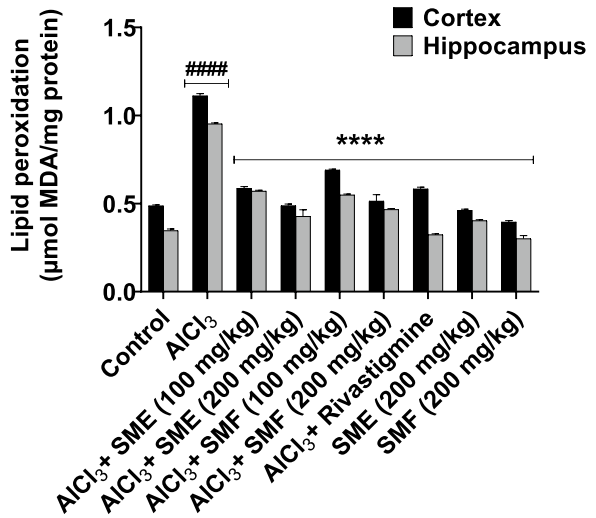


Fig. 1 Effect of *Spondias mombin* leaf extracts on lipid peroxidation in rats with $AlCl_3$-induced Alzheimer's disease. Each bar is represents mean ± SD (n = 8). $^{####}p < 0.0001$ vs control; $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

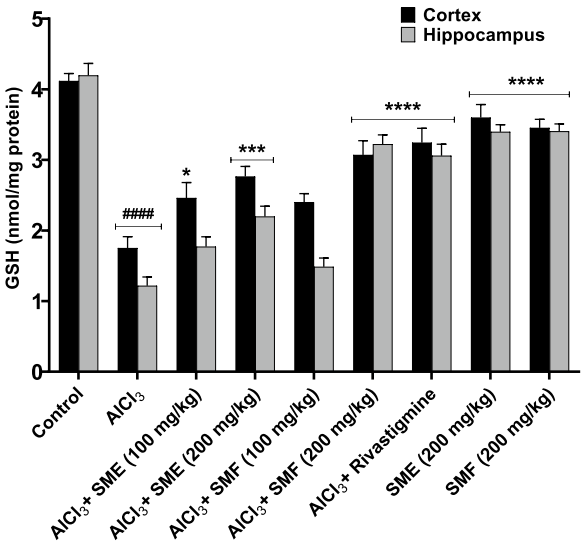


Fig. 3 Effect of *Spondias mombin* leaf extracts on reduced glutathione level in rats with $AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 3$). $^{####}p < 0.0001$ vs control; $^{*}p < 0.05$, $^{***}p < 0.001$ $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

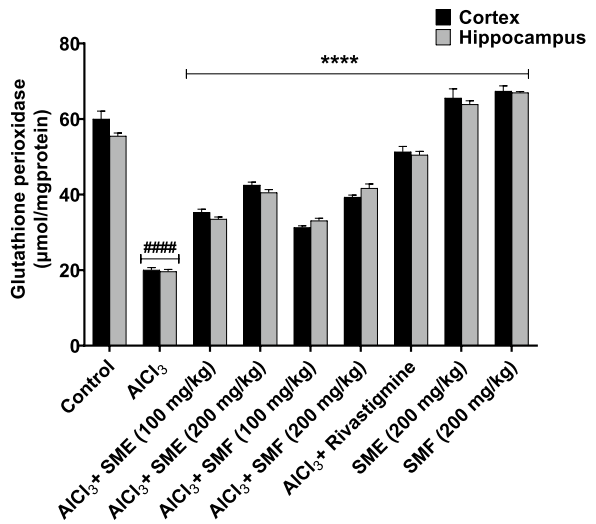


Fig. 2 Effect of *Spondias mombin* leaf extracts on glutathione perioxidase activity in rats with$AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 8$). $^{####}p < 0.0001$ vs control; $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

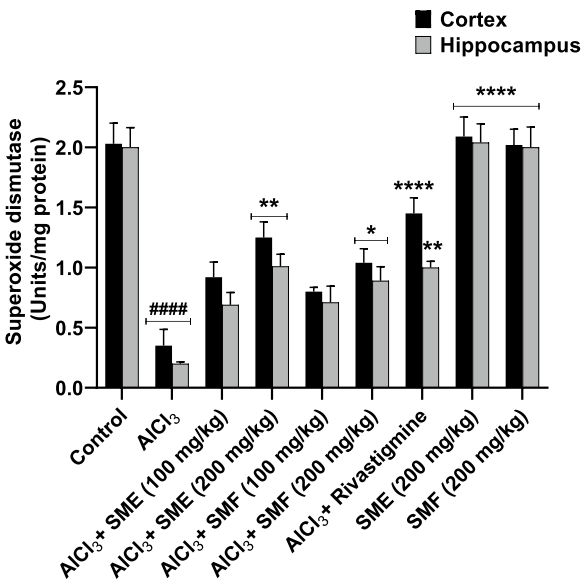


Fig. 4 Effect of *Spondias mombin* leaf extracts on Superoxide dismutase activity in rats with $AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 3$). $^{####}p < 0.0001$ vs control; $^{*}p < 0.05$ $^{**}p < 0.01$, $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

Effect of SME and SMF on pro-inflammatory and pro-apoptotic markers

The scavenging capacities of SME and SMF on cortical and hippocampal nitrite production are illustrated in Fig. 6. $AlCl_3$-administered animals showed considerably higher cortical and hippocampal nitrite levels than the control group ($p < 0.0001$); however, this was dramatically reduced in rats treated with SME, SMF, and rivastigmine ($p < 0.0001$).

Figure 7 demonstrates a substantial increase in MPO activity in brain cortical and hippocampal regions

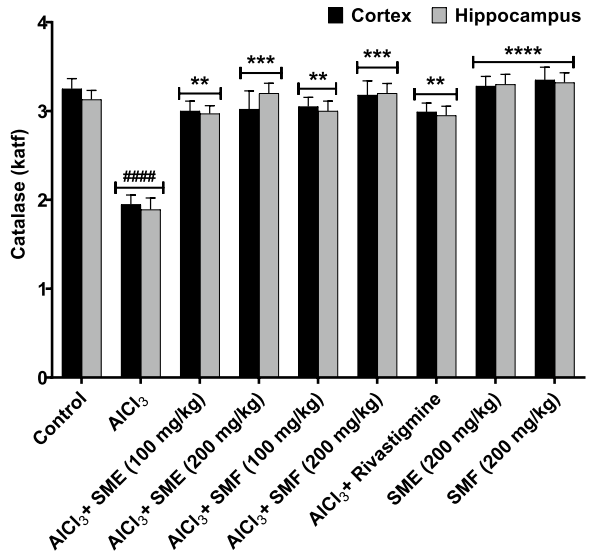


Fig. 5 Effect of *Spondias mombin* leaf extracts on Catalase activity in rats with aluminum chloride ($AlCl_3$)-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 3$). $^{\#\#\#\#}p < 0.0001$ vs control; $^{**}p < 0.01$ $^{***}p < 0.001$ $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

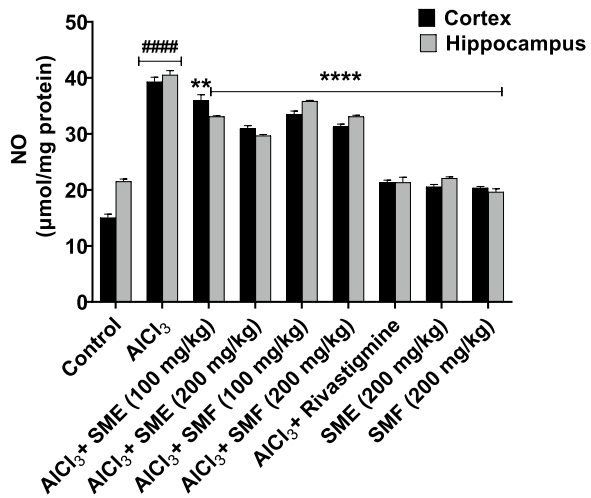


Fig. 6 Effect of *Spondias mombin* leaf extracts on Nitric oxide activity in rats subjected to $AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 8$). $^{\#\#\#\#}p < 0.0001$ vs control; $^{**}p < 0.01$, $^{****}p < 0.0001$vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

of $AlCl_3$-toxified rats ompared to the control group, which can be a sign of inflammation. However, there was significant reduction in MPO activity i rats treated with SME, SMF (100 mg/kg, 200 mg/kg), and 0.3 mg/kg rivastigmine ($p < 0.0001$).

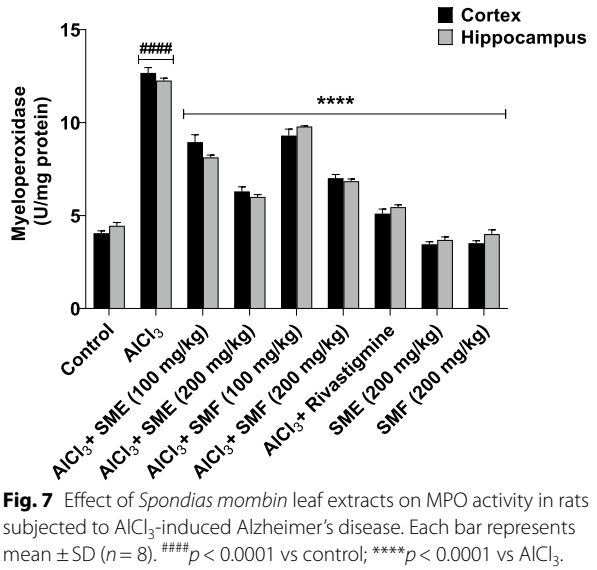


Fig. 7 Effect of *Spondias mombin* leaf extracts on MPO activity in rats subjected to $AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 8$). $^{\#\#\#\#}p < 0.0001$ vs control; $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

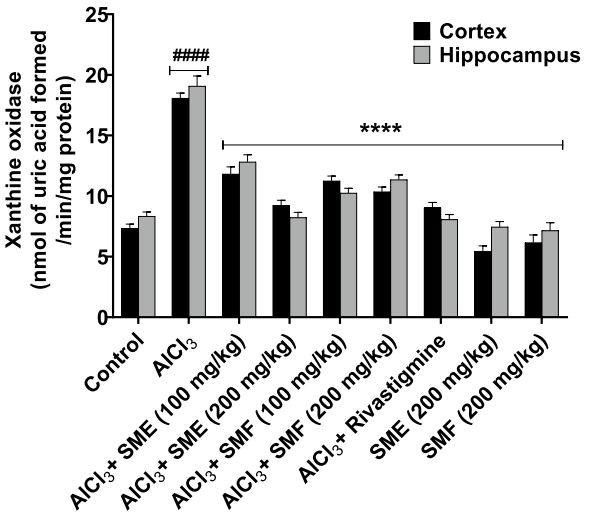


Fig. 8 Effect of *Spondias mombin* leaf extracts on Xanthine oxidase activity in rats subjected to $AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 8$). $^{\#\#\#\#}p < 0.0001$ vs control; $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride:

The inhibitory effect of SME and SMF on XO activity in the cortex and hippocampus is illustrated in Fig. 8. When compared to the control group, there was a significant increase in the activities of cortical and hippocampal XO in the aluminum chloride-administered group ($p < 0.0001$), but this was significantly ameliorated in rats treated with SME, SMF (100 mg/kg, 200 mg/kg), and 0.3 mg/kg rivastigmine ($p < 0.0001$).

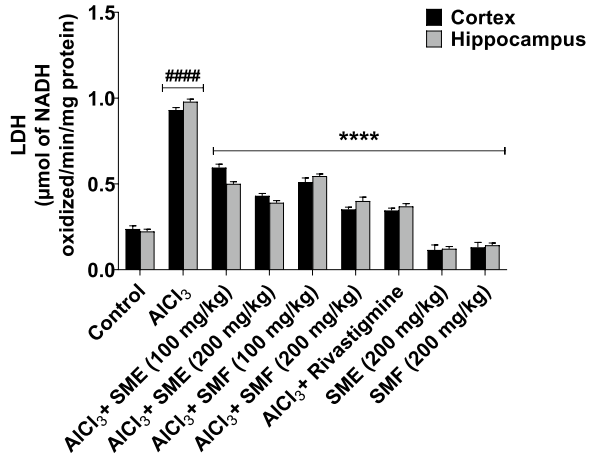


Fig. 9 Effect of *Spondias mombin* leaf extracts on LDH activity in rats subjected to $AlCl_3$-induced Alzheimer's disease. Each bar is represents mean ± SD ($n = 8$). $^{\#\#\#\#}p < 0.0001$ vs control; $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

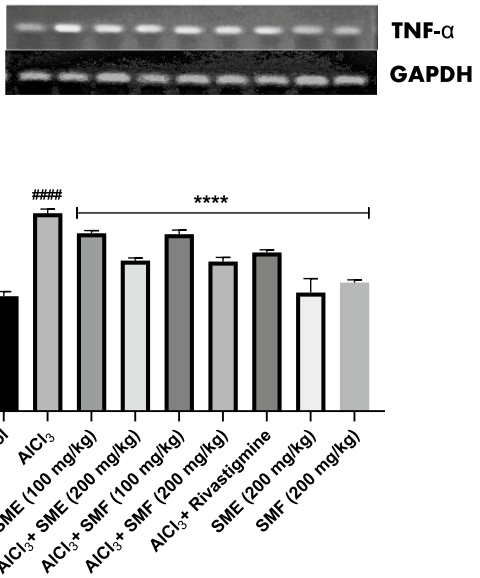


Fig. 10 Effect of *Spondias mombin* leaf extracts on tumor necrosis factor α (TNF-α) expression in the hippocampal tissue of rats subjected to $AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 3$). $^{\#\#\#\#}p < 0.0001$ vs control; $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

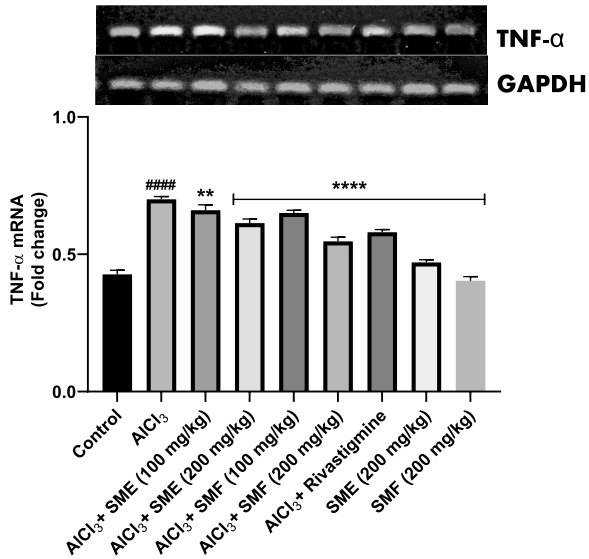


Fig. 11 Effect of *Spondias mombin* leaf extracts on tumor necrosis factor α (TNF-α) expression in the brain cortex of rats subjected to $AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 3$). $^{\#\#\#\#}p < 0.0001$ vs control; $^{**}p < 0.01$, $^{****}p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

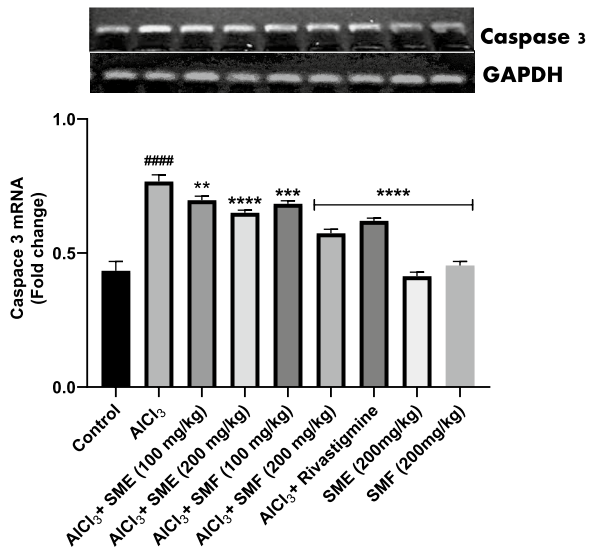


Fig. 12 Effect of *Spondias mombin* leaf extracts on caspace 3 expression in the brain cortex of rats subjected to$AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 3$). $^{\#\#\#\#}p < 0.0001$ vs control; $^{*}p < 0.05$ $^{**}p < 0.01$ $^{***}p < 0.001$ $^{****}p < 0.0001$) vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

Figure 9 reveals that, when compared to control rats, all brain regions of rats toxified with $AlCl_3$ had a significant increase ($p < 0.0001$) in LDH activity. Rats administered SME, SMF, and rivastigmine ameliorated the $AlCl_3$-induced increase in LDH activity ($p < 0.0001$).

The extracts caused some significant alterations in the molecular parameters (Figs. 10, 11, 12, 13). The $AlCl_3$-administered group showed a marked increase in

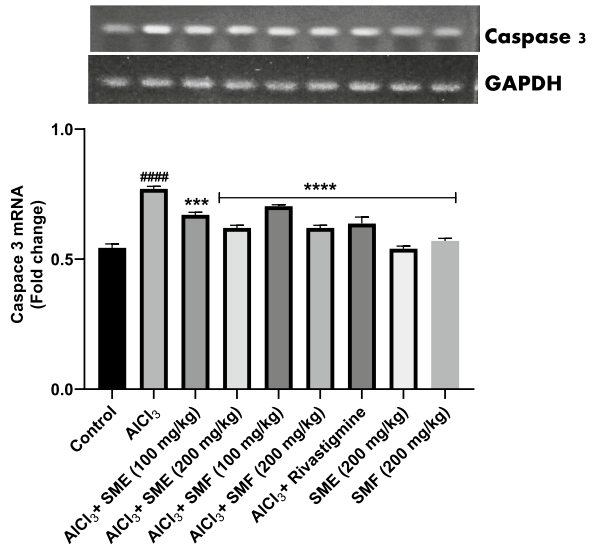


Fig. 13 Effect of *Spondias mombin* leaf extracts on caspace 3 expression in the hippocampal tissue of rats subjected to $AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 3$). $^{\#\#\#\#}p < 0.0001$ vs control; *** $p < 0.001$ **** $p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

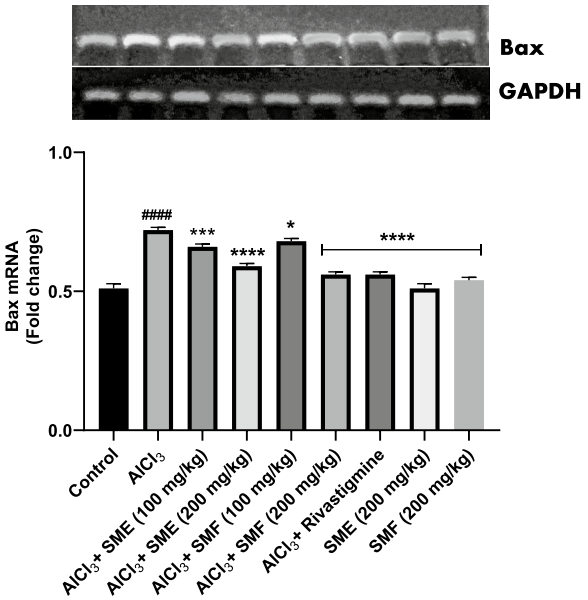


Fig. 14 Effect of *Spondias mombin* leaf extracts on BAX expression in the brain cortical tissue of rats subjected to aluminum chloride ($AlCl_3$)-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 3$). $^{\#\#\#\#}p < 0.0001$ vs control; *** $p < 0.001$, **** $p < 0.0001$) vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

the expression of TNF-α and caspase-3 (in both the hippocampus and cortex of the brain) compared to the control group. When compared to the $AlCl_3$-administered group, $AlCl_3$ toxified rats treated with rivastigmine showed an ameliorative effect by downregulating the expression of TNF-α and caspase-3. The $AlCl_3$-toxified group that received 200 mg/kg of extracts (SME and SMF) showed comparable outcomes to the rivastigmine-treated group, and a stronger response than the group that received the low dose (100 mg/kg) of extracts.

Induction of AD through $AlCl_3$ administration elevated the expression of pro-apoptotic Bax proteins significantly ($p < 0.0001$) when compared to a control cohort (Figs. 14 and 15). Bax expression was downregulated both in the cortical and hippocampal brain regions by the extracts. The two extracts (SME and SMF) downregulated the expression of Bax compared to the $AlCl_3$-induced group. The higher dose of the extracts (200 mg/kg) showed comparable effects to the reference drug rivastigmine.

Discussion

Medicinal plants have attracted a lot of interest as a hopeful choice in order to treat neurological conditions, primarily because of the presence of phytoconstituents with pharmacological activity, often with minimal side effects [39]. Numerous investigations have underscored the beneficial impacts of Medicinal plants,

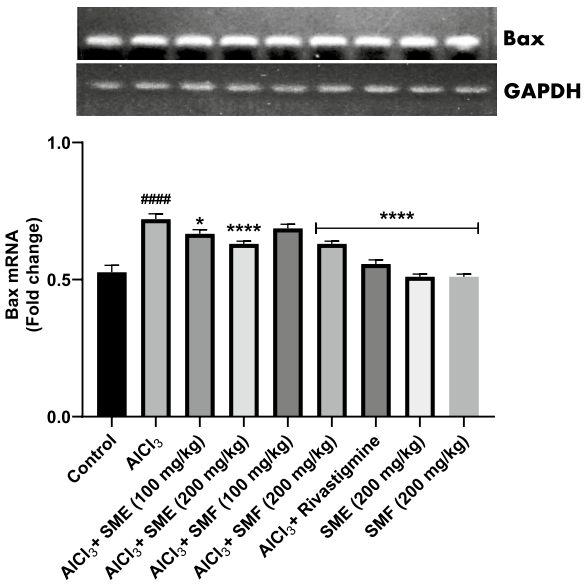


Fig. 15 Effect of *Spondias mombin* leaf extracts on BAX expression in the hippocampal tissue of rats subjected to $AlCl_3$-induced Alzheimer's disease. Each bar represents mean ± SD ($n = 3$). $^{\#\#\#\#}p < 0.0001$ vs control; * $p < 0.05$, **** $p < 0.0001$ vs $AlCl_3$. SMC: *Spondias mombin* methanol leaf extract; SMF: *Spondias mombin* fraction; $AlCl_3$; aluminum chloride

which possess multiple mechanisms of action, potentially offering enhanced protection against various pathological conditions. These plants also play a crucial function in preserving the neuronal chemistry by modulating the operations of diverse receptors through various mechanisms.

Various bioactive compounds have been discovered to possess a wide range of activities that could potentially aid in the prevention of neurodegenerative disease [40]. The phytochemical evaluation of *Spondias mombin* methanol leaf extract demonstrated the existence of numerous phytochemicals, which may be responsible for its diverse pharmacological effects, particularly in the management of Alzheimer's disease. The primary classes of phytochemicals identified in the methanol leaf extract of *Spondias mombin* include flavonoids, saponins, tannins, phenols and cardiac glycosides. The therapeutic effects of *S. mombin* are attributed to its secondary metabolites [41, 42].

The analysis of *S. mombin* methanol leaf extract and fraction using HPLC–DAD fingerprinting indicated the existence of various phytochemicals like phenolic acids (gallic acid, chlorogenic acid and ellagic acid), flavonoids (astragalin, isoquercetin, isorhamnetin, rutin, kaempferol, and quercetin), terpenoids (cadinene, humulene and lupeol), and other compounds. Flavonoids were the preponderant phytochemicals in the extracts. Previous studies also confirmed the presence of the aforementioned compounds in both *S. mombin* leaf and fruit extracts. The pharmacological benefits of phyto-compounds, such as their ability to reduce inflammation and inhibit oxidative stress, have drawn attention to them [19]. Furthermore, flavonoids such as kaempferol and quercetin undergo glycosylation into glycosidic derivatives, enhancing their ability to scavenge free radicals by donating electrons or hydrogen [43]. These antioxidant properties are crucial in the treatment of neurological illnesses [22].

Accumulating evidence suggests that phytochemicals such as kaempferol and quercetin exert significant effects on molecular pathways involved in antioxidant defense, apoptosis regulation, and inflammation. These bioactive compounds interact with various cellular mechanisms, positioning them as promising therapeutic agents for managing neurodegenerative disorders. Notably, these phytochemicals activate Sirtuin 1 (SIRT1), a key regulator that promotes antioxidant, anti-inflammatory, and antiapoptotic responses [44]. Kaempferol, in particular, mitigates inflammation by inhibiting tumor necrosis factor-alpha (TNF-α), a crucial pro-inflammatory cytokine [45]. Additionally, kaempferol has been shown to mitigate oxidative stress by increasing glutathione (GSH) levels. Its antiapoptotic effects are further evidenced by significant decreases in caspase-3 and caspase-9 activities, key mediators of apoptosis [46].

Assessing the in vitro antioxidant properties of phytoextracts can offer valuable insights into their potential in vivo biological effects. The medicinal value of plants is often associated with their antioxidative attributes [47, 48]. Various tests are used to assess the antioxidant mechanisms exhibited by phytochemicals. The antioxidant investigation of SME and SMF revealed substantial radical scavenging and antioxidative activities, particularly in countering the highly destructive hydroxyl radicals and lipid peroxidation. The latter, known for its role in the development of various pathologies, is a major contributor. The presence of polyphenolic compounds within SME and SMF is likely responsible for their noteworthy efficacy. These herbal extracts performed well across various antioxidant assays, each targeting distinct antioxidative mechanisms.

Antioxidants play a critical role in the human body, working to mitigate oxidative processes. Notably, the brain, with its elevated rate of metabolism and rich content of fats that are polyunsaturated, is particularly vulnerable to oxidative damage, largely stemming from lipid peroxidation [40, 49].

Antioxidants are essential for lowering the oxidation of proteins and mitigating the influence of lipid-derived carbonyls on proteins, which can, in turn, affect protein functionality [50]. These observations underscore their remarkable antioxidative potential. The impressive antioxidant capabilities demonstrated by SME and SMF are in line with their effectiveness in combating oxidative stress in in vivo experiments.

Aluminum (Al) intoxication, increases oxidative stress by elevating iron's pro-oxidant properties in the brain, stimulating neuroinflammatory cytokines NFTs and amyloidogenic fragments [51]. The results showed that the cortical and hippocampus tissues were subjected to oxidative stress due to $AlCl_3$ administration, as demonstrated by the increased LPO, activities of antioxidant enzymes, and decreased GSH content. These findings are consistent with those of prior investigations [35, 52, 53]. A major form of oxidative damage in neurodegenerative lesions is lipid peroxidation. Polyunsaturated fatty acids undergo non-enzymatic oxidation, leading to lipid peroxidation and the subsequent production of MDA. According to [54], the short lifespan of free radicals makes MDA measurement a simple way to assess lipid peroxidation and, consequently, oxidative stress in humans.

Antioxidative enzymes that protect cells from the damage inflicted by free radicals, including glutathione peroxidase (GPX), superoxide dismutase (SOD), catalase (CAT), and the antioxidant glutathione (GSH), are essential [35, 52, 53]. High quantities of reactive oxygen

species (ROS) arise from toxicity, which can induce lipid peroxidation and oxidative damage to proteins. The body's inherent antioxidants serve as the primary defense mechanism against oxidative stress, with CAT playing a crucial role in converting hydrogen peroxide into water and oxygen. Similarly, the SOD enzyme scavenges superoxide anions as part of the defense mechanism against oxidative stress [55].

An increasing amount of studies demonstrates the powerful antioxidant properties of *S. mombin* leaf extracts against nitrosative and/or oxidative stress in cells, which are also implicated in AD. In an Alzheimer's disease animal model, *S. mombin* leaf extracts increased antioxidant activity and removed damaging radical species caused by the heavy metal. It reduced the amounts of TBARS while stepping up the involvement of GPX, SOD, GSH, and CAT. *S. mombin* leaf extracts scavenge ROS/RNS and reduce the damage caused by oxidation via inhibiting the production of malondialdehyde and enhancing the activity of antioxidant enzymes.

Oxidative stress and inflammation exhibit a strongly intertwined pathophysiological relationship, wherein the initiation of one can readily provoke the other. Consequently, both mechanisms are simultaneously present in multiple disease states [52]. Nitric oxide (NO) is crucial in a wide array of inflammatory processes. The findings from our investigation reveal a notable surge in NO levels following $AlCl_3$ intoxication. This observed elevation of NO concentration aligns with the outcomes of prior studies, further substantiating the association between increased NO levels and Alzheime's disease (AD) [56]. According to well documeted recent research findings, the superoxide anion, generated by reactive oxygen species (ROS), readily engages with nitric oxide (NO) to form peroxynitrite, a molecule activated in inflammatory responses [57]. Elevated concentrations of peroxynitrite have neurotoxic effects, leading to DNA damage, lipid peroxidation, disruption of cellular communication, and mitochondrial malfunction [42]. However, recent insights highlight NO compensatory neuroprotective role, particularly in the early stages before cognitive decline becomes evident. NO has been shown to support synaptic function by enhancing neuronal excitability, promoting neuroplasticity, facilitating neuroprotection, and contributing to myelination [58, 59]. Additionally, its cytolytic activity helps mitigate inflammation [58]. Notably, *S. mombin* leaf extracts, known for their potent anti-inflammatory properties, effectively attenuated the elevated NO levels observed in our study, further reinforcing their therapeutic potential.

Myeloperoxidase (MPO) is a peroxidase that contains heme and is widely expressed in various inflammatory cells (neutrophils, activated microglia, monocytes/macrophage, astrocytes and neurons). According to several publications, AD pathogenesis is influenced by the activation of microglia, astrocytes, and neurons in the cortex and hippocampus, which results in neuronal sprouting and synaptic maturation [60, 61]. The observed impact of *S. mombin* leaf extracts on MPO activity supports their anti-inflammatory attributes, possibly attributable to the presence of phenols in the extract, as polyphenols are known for their anti-inflammatory properties in neurovascular and neurological diseases [62]. Akinmoladun et al. [40] have previously reported the anti-inflammatory properties of S. mombin leaf extract.

To further elucidate the toxicity of $AlCl_3$ on brain tissues, the study examined the activities of lactate dehydrogenase (LDH) and xanthine oxidase (XO). $AlCl_3$ intoxication significantly increased LDH and XO activities, with LDH release considered indicative of tissue injury. The elevation in LDH activity may be linked to excessive lactic acid production, impacting the Astrocyte-Neuron Lactate Shuttle and neuronal ATP production. *S. mombin* leaf extracts (SME and SMF) demonstrated a notable reduction in LDH levels, suggesting an inhibitory effect that preserves neuronal excitation.

XO, responsible for generating reactive oxygen species, exhibited heightened activity in the $AlCl_3$-treated group. SME and SMF were found to ameliorate the neurotoxic effects of $AlCl_3$ in the cortical and hippocampal regions, indicating a potential protective role against oxidative stress. $AlCl_3$ administration induced a robust inflammatory response, as evidenced by elevated proinflammatory cytokine (TNF-α) levels in the hippocampus and cortex. SME, SMF, and rivastigmine mitigated the inflammatory processes, demonstrating anti-inflammatory properties consistent with other markers in the study. The effects of SME and SMF align with the role of phytochemicals, which modulate molecular mechanisms by enhancing anti-inflammatory pathways, upregulating anti-inflammatory cytokines, or disrupting inflammatory pathways to reduce pro-inflammatory cytokine synthesis [63].

Apoptosis, a programmed cell death process, has been identified as a principal cause of neuronal death in AD [64]. In the current study, the focus was on understanding how SME and SMF, can mitigate aluminum chloride-induced apoptosis in brain homogenates. The mechanism explored involves the assessment of proapoptotic proteins, specifically Bax, and caspase-3 expressions in rat brain homogenates. Elevated levels of reactive oxygen species (ROS) can disrupt the mitochondrial membrane's permeability, leading to mitochondrial failure. An important factor in this process is the amount of the mitochondrial permeability transition pore (MPTP). Cytochrome C is released via the inner membrane of the mitochondria into the cytosol when MPTP is disrupted

[65]. Caspases are activated by cytochrome c after it is released, and caspase-9 functions as an upstream initiator to link apoptotic signals to downstream effector caspases, such caspase-3. Caspase-3 activation ultimately leads to cell death through the apoptotic pathway. In the context of the study, exposure to aluminum chloride ($AlCl_3$) resulted in increased expression of the proapoptotic Bax (Bcl-2 associated X) protein, indicating an increase in apoptosis. Bax controls the release of cytochrome c into the cytosol, triggering caspase-3 activation [65, 66]. However, treatment with SME and SMF attenuated apoptosis by reducing the activation of caspase-3 and Bax. This suggests a protective effect of SME and SMF against aluminum chloride-induced apoptosis, potentially through the regulation of key apoptotic proteins (Bax). The presence of identified chemical compounds, including flavonoids, phenols, and tannins, in the extracts may contribute to these anti-inflammatory effects, aligning with previous research on the neuroprotective properties of natural flavonoids [67].

Despite the promising findings of this study, several limitations are acknowledged. First, the short-term duration of the study may not fully capture the long-term effects of *Spondias mombin* extracts on oxidative stress, apoptosis, and inflammation. Additionally, while this study provides mechanistic insights based on controlled experimental conditions, its real-world applicability required further investigation. The physiological complexity of in vivo systems and potential interactions with other biomolecules may influence the efficacy of these compounds. Therefore, further investigations, including long-term in vivo studies and clinical trials, are necessary to validate these findings and explore their therapeutic potential in neurodegenerative disorders.

Conclusion

In conclusion, this study underscores the promising therapeutic efficacy of *Spondias mombin* leaf extracts in mitigating aluminum-induced neurotoxicity. The observed robust antioxidant and anti-inflammatory activities and protection against cell apoptosissuggest a potential avenue for developing novel interventions against neurotoxic effects. These outcomes provide important new information about the possible neuroprotective qualities of *S. mombin*, paving the way for further exploration and development of targeted treatments for conditions associated with aluminum-mediated neurotoxic effects. Future research should focus on in vivo studies using other neurotoxic agents, such as amyloid-beta, rotenone, or MPTP, to assess the broader neuroprotective potential of S. mombin across different models of neurodegeneration. Additionally, synergistic studies with established pharmacological agents to explore potential combinatory therapeutic applications are deserving of consideration. Finally, clinical trials assessing its safety and efficacy in human populations are essential to validate these findings and facilitate translational applications.

Abbreviations

ABTS	2,2′-Azino-bis-(3-ethylbenzothiazoline-6-sulphonic acid)
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ATCI	Acetylthiocholine iodide
ROS	Reactive oxygen species
FRAP	Ferric reducing antioxidant power
NO	Nitric oxide
NMDA	*N*-Methyl-D-aspartate
DPPH	1,1-Diphenyl-2-picrylhydrazyl
HPLC-DAD	High-performance liquid chromatography diode-array detector
CUPRAC	Cupric ion reducing antioxidant capacity

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43094-025-00803-9.

Additional file 1.

Acknowledgements
Not applicable.

Author contributions
AR: Investigation, Data curation, Formal analysis, Writing—original draft. SO: Project administration, Supervision. AC: Conceptualization, Supervision, Validation, Writing—review *and* editing. AA: Project administration, Resources.

Funding
The authors did not receive support from any organization for the submitted work.

Availability of data and materials
All data generated or analyzed during this study are included in this article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Consent for publication
The authors declare no conflict of interest.

Competing interests
The authors declare that they have no competing interests.

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Received: 12 November 2024 Accepted: 28 March 2025
Published online: 23 April 2025

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