RESEARCH ARTICLE

Neuroprotective effect of sesamol against aluminum nanoparticle-induced toxicity in rats

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Abstract

Alumina nanoparticles (ALNPs) are widely used causing neurobehavioral impairment in intoxicated animals and humans. Sesamol (SML) emerged as a natural phytochemical with potent antioxidant and anti-inflammatory properties. However, no study has directly tested the potential of SML to protect against AlNP-induced detrimental effects on the brain. AlNPs (100 mg/kg) were orally administered to rats by gavage with or without oral sesamol (100 mg/kg) for 28 days. In AlNP-intoxicated group, the brain AChE activity was elevated. The concentrations of MDA and 8-OHdG were increased suggesting lipid peroxidation and oxidative DNA damage. GSH depletion with inhibited activities of CAT and SOD were demonstrated. Serum levels of IL-1β and IL-6 were elevated. The expressions of GST, TNF-α, and caspase-3 genes in the brain were upregulated. Histopathologically, AlNPs induced hemorrhages, edema, neuronal necrosis, and/or apoptosis in medulla oblongata. The cerebellum showed loss of Purkinje cells, and the cerebrum showed perivascular edema, neuronal degeneration, necrosis, and neuronal apoptosis. However, concomitant administration of SML with AlNPs significantly ameliorated the toxic effects on the brain, reflecting antioxidant, anti-inflammatory, and anti-apoptotic effects of SML. Considering these results, sesamol could be a promising phytochemical with neuroprotective activity against AlNP-induced neurotoxicity.

Keywords Alumina nanoparticles · Sesamol · Neurotoxicity · Oxidative stress · Histopathology

Introduction

The incorporation of nanoparticles into everyday life constitutes an important toxic hazard to humans and animals. Alumina (aluminum oxide) nanoparticles (AlNPs) account for about 20% of the global nanoparticle market (Sengul and Asmatulu 2020). They have multiple uses in cosmetics, medicines, electronics, aerospace, chemical engineering, food contact materials, catalysts, ceramics, and rubber (Li et al. 2020).

The widespread use of AlNPs is associated with possible exposure of humans and animals (Dawood et al. 2019a; El-Seedi et al. 2019; Zahin et al. 2020; Bhattacharya et al. 2021). They may enter the body through food, water, inhalation, or

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dermal contact, where they can readily penetrate biological barriers due to their small size and high surface reactivity and accumulate in different organs and tissues (El-Sayed and Kamel 2020; Krause et al. 2020). Moreover, because the cell surface is negatively charged and AlNPs are positively charged, these particles are drawn to the interior of cells through electrostatic interactions (Liu et al. 2020a). This in turn produces many toxic effects including hematological changes (De et al. 2020), genotoxicity (Zhang et al. 2017), testicular toxicity (De et al. 2020), carcinogenicity (Dey et al. 2008), immunotoxicity (Li et al. 2020), hepatotoxicity, nephrotoxicity (Morsy et al. 2016), and pulmonary toxicity (Yun et al. 2020).

The CNS was mentioned as a potential target for AlNPs. They penetrate the blood-brain barrier (BBB) easily owing to their small size (De et al. 2020) and their effect on BBB permeability through downregulation of the tight junction protein expression such as occludin and claudin-5 (Chen et al. 2008). The penetrating AlNPs were reported to accumulate in the hippocampus, olfactory bulb, cerebral cortex, and striatum causing learning and memory dysfunction and depression-like behavior (Shah et al. 2015; Zhang et al. 2021a). Furthermore, AlNPs were recognized as a major contributor to many neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (Zhang et al. 2018).

Acetylcholinesterase (AChE) has an essential role in cholinergic neurotransmission and non-cholinergic functions such as its effect on cell survival, neurite outgrowth, and voltage-dependent calcium currents (Whyte and Greenfield 2003). Thus, assessment of the AChE activity is a useful marker of neurotoxicity. Oxidative damage to nerve cell is the first event in a sequence leading to deleterious effects after nanoparticles intoxication (Shah et al. 2015; Abdel-Daim et al. 2019; Kandeil et al. 2020). However, cellular enzymatic and non-enzymatic antioxidants can alleviate this oxidative injury. Thus, the determination of MDA and 8-OHdG can be used as valuable markers of oxidative damage to membrane lipids and DNA. In addition, assessment of GSH, SOD, CAT, and GST indicates the antioxidant status (Mohammed and Safwat 2013; Dawood et al. 2019b).

Apoptosis has been reported as a major pathway of cellular death consequent to nanoparticle evoked oxidative stress (Nogueira et al. 2019; Liu et al. 2020a; Mohammed et al. 2020). As the mitochondria are potential targets for oxidative stress (Manke et al. 2013), cascade reactions occur in the intrinsic (mitochondrial) apoptotic pathway including mitochondrial outer membrane permeabilization (MOMP) and cytochrome c release to the cytoplasm activating caspase-9 and subsequent caspase-3 (Xiong et al. 2014). Thus, assessment of caspase-3 is a valuable marker for ROS-mediated cell death via mitochondrial pathway.

Nanoparticle-mediated oxidative injury has been shown to orchestrate a series of inflammatory responses (Manke et al.

2013; Samak et al. 2018) with the release of pro-inflammatory mediators via NF-κB/MAPK activation (Mohammed and Safwat 2020; Zhang et al. 2021a). The produced neuroinflammation has been linked to Alzheimer's disease and other neurodegenerative disorders (Win-Shwe and Fujimaki 2011). Thus, assessment of the inflammatory cytokines IL-1β, IL-6, and TNF-α evaluates the inflammatory response in intoxicated animals.

Research in the field of toxicology has always focused on offering natural plant products to alleviate various toxic insults (Abou-Zeid et al. 2018). They contain phytochemicals with little harm and strong antioxidant activity making them valuable drugs (Farag et al. 2021; Kabir et al. 2021). Among them is sesame (*Sesamum indicum*) oil which contains sesamol (SML), a natural phenolic lignan with the chemical structure 3,4-(methylenedioxy) phenol (Majdalawieh and Mansour 2019). Sesamol was reported to be a potent antioxidant with strong scavenging activity against free radicals (Kanimozhi and Prasad 2009). After oral administration, it was readily absorbed and detected in multiple organs due to its unique solubility in both aqueous and oily phases (Jan et al. 2008). In addition, it has a great ability to penetrate the BBB due to its high lipophilicity (Ren et al. 2018).

Evidences have been accumulated regarding the therapeutic uses of sesamol specially as antimutagenic and anticancer drug (Majdalawieh and Mansour 2019). Recently, sesamol has been receiving considerable attention as a neuroprotective agent. It alleviated the cognitive deficits and detrimental effects produced in rat models of induced diabetic neuropathy (VanGilder et al. 2009; Chopra et al. 2010), Huntington's disease (Kumar et al. 2010), epilepsy (Hassanzadeh et al. 2014), chronic intermittent hypoxia (Zhang et al. 2021b), and natural aging model in mouse (Ren et al. 2018, 2020).

We hypothesized that sesamol may exhibit a neuroprotective effect towards AlNP-induced brain injury. Thus, the present study aimed at investigating the antioxidant, anti-inflammatory, and anti-apoptotic potentials of sesamol in AlNP-intoxicated rats via assessment of AChE activity, oxidative stress markers, antioxidants, proinflammatory cytokines, and caspase-3 gene expression. In addition, the histopathological alterations in the brain were investigated.

Materials and methods

Chemicals

Aluminum oxide (Al_2O_3) or alumina nanoparticles (ALNPs) (particle size < 50 nm) and sesamol (SML) were obtained from Sigma-Aldrich (Germany). All other chemicals used were of analytical grade.

Characterization of AlNPs

AlNPs were characterized as previously mentioned by Li et al. (2020) using transmission electron microscopy (TEM). The diameters of AlNPs were analyzed by the Image-Pro Plus software. Suspensions of freshly prepared AlNPs in bi-distilled water were used after ultrasonic vibration (100 W, 30 kHz, 30 min). In the TEM, a suspension droplet was placed on a 200-mesh Cu-lacy lace carbon TEM grid. The film on the TEM grid was dried overnight in a vacuum oven at room temperature (25 °C). After water evaporation, the AlNPs were dispersed over the TEM grid. TEM measurements were conducted on a JEOL model 2100 F instrument (Japan) operated at an accelerating voltage of 200 kV.

Animals

All experimental procedures in this study were approved in advance (approval number: VUSC-007-1-20) by the Institutional Animal Care and Use Committee of University of Sadat City, Egypt, and conducted out following National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

Eighty young adult male Sprague–Dawley rats (140–160 g) were obtained from the Laboratory Animal Farm, Faculty of Veterinary Medicine, University of Sadat City, Egypt, and were acclimated in our facility for 1 week, prior to the experiment. Animals were caged at standardized conditions (12 h light/ dark period; temperature 23 ± 2 °C; humidity 50%) and allowed free access to food and distilled water during the acclimatization period and throughout the experiment. Animals were randomly allocated into four groups, 20 rats each.

Experimental design

All experimental groups received the treatments daily by stomach tube for 28 days. Group I (Control): received distilled water. Group II (SML group): received SML at a dose level of 100 mg/kg/day. Group III (AlNP group): received AlNPs at 100 mg/kg bw/day. Group IV (AlNPs + SML): received SML followed (after 2 h) by AlNPs, at the dose levels indicated for groups II and III. The exposure levels of SML and AlNPs were selected based on previous studies of Hemalatha et al. (2013) and Jo et al. (2016), respectively.

AlNPs were daily dispersed in bi-distilled water (at 4 °C) using ultrasonic vibration (100 W, 30 kHz) for 30 min before administration to ensure homogeneous distribution. The solution was subjected to sonication and vigorous vortexing as per requirement, to ensure uniform suspension. Sesamol was freshly prepared daily by dissolving the required amount of sesamol powder in a suitable amount of distilled water (Hemalatha et al. 2013).

Sampling

At the end of experiment, blood samples were collected from the retro-orbital plexus, and were allowed to sit for 30 min, then centrifuged at 3000 rpm at 4 °C for 15 min. Sera were collected and stored at $-$ 80 °C to be used for interleukin analysis.

Rats from all experimental groups were euthanized by cervical dislocation under sodium pentobarbital anesthesia (60 mg/kg). Brains were dissected and assigned into three sets. The first set was homogenized, using Teflon homogenizer in cold PBS (pH 7.4), and the obtained homogenates were centrifuged at 4 °C for 20 min ($14,000 \times g$). Supernatants were obtained and stored at $-$ 80 °C to be used for investigation of MDA, 8-OHdG, and antioxidants. The second brain set was immediately frozen in liquid nitrogen and stored at $-$ 80 °C until being processed for RT-qPCR expression and assessment of AChE activity. The third set of brains was fixed in neutral buffered formalin 10% solution to be used in the histopathological investigation.

Acetylcholinesterase (AChE)

The brain acetylcholinesterase (AChE) activity was measured using enzyme -linked immunosorbent assay (ELISA) Kit obtained from MyBioSource Biotechnology company, Egypt (Catalog No. MBS2501434), according to manufacturer instructions. Standards are added to the wells of a micro-ELISA plate precoated with RatAChE specific antibodies. A biotinylated detection antibody specific for RatAChE and Avidin-Horseradish Peroxidase (HRP) conjugate are added to each well. This was followed by washing free components and addition of the substrates. A sulfuric acid solution was added to terminate the reaction. The optical density (OD) was measured spectrophotometrically at 450 nm.

Oxidative stress/antioxidant biomarkers

The concentrations of the lipid peroxidation product malondialdehyde (MDA) and reduced glutathione (GSH), and the activities of catalase (CAT) and super-oxide dismutase (SOD) were assessed in brain tissue using assay kits from the Biodiagnostic Company, Egypt, (Catalog No: MD2529, GR2511, CA2517, SD2521, respectively) according to Ohkawa et al. (1979), Beutler et al. (1963), Aebi (1984), and Nishikimi et al. (1972), respectively.

8-hydroxy-2'-deoxyguanosine (8-OHdG)

Brain 8-OHdG was quantified using 8-OHdG ELISA kit (Catalog No: MBS008851) obtained from MyBioSource Biotechnology company, Egypt.

Inflammatory response markers

Serum IL-1β and IL-6 levels were assessed using the commercial rat ELISA kits obtained from MyBioSource, San Diego, CA, USA (Catalog No: MBS825017 and MBS175908, respectively). The assessment protocols were followed as provided by the manufacturer.

Quantitative real-time polymerase chain reaction (qRT-PCR) of Glutathione-S-transferase (GST), tumor necrosis factor-alpha (TNF-α), and caspase-3 genes

Total RNA in brain samples was extracted using QIAmp RNA mini kit (Qiagen, Hilden, Germany) as indicated by the manufacturer. Total RNA purity and concentration were determined using a nanodrop ND-2000 spectrophotometer. The isolated RNA was used for cDNA synthesis using reverse transcriptase (Fermentas, EU). Real-time PCR (qPCR) was performed in a total volume of 20-μl using a mixture of 1 μl cDNA, 0.5 mM of each primer (Table 1), iQ SYBR Green Premix (Bio-Rad 170-880, USA). PCR amplification and analysis were achieved using Bio-Rad iCycler thermal cycler and the MyiQ real-time PCR detection system. Each assay includes triplicate samples for each tested cDNAs and no-template negative control; the expression relative to the control is calculated using the equation $2-\Delta\Delta CT$ (Livak and Schmittgen 2001).

Histopathological examination

The brain of each rat was removed completely and fixed in 10% neutral buffered formalin solution for 72 h. For histopathological investigation, samples were trimmed, washed, dehydrated, embedded in paraffin wax, serially sectioned with a microtome at 3-μm thickness and stained with hematoxylin and eosin (H&E) stain. Additionally, histological photos were taken using Lieca DMLB microscopes and Leica EC3 digital camera. The comparative histopathological lesion scoring in different brain regions was conducted according to Gibson-Corley et al. (2013).

Statistical analysis

The obtained data are presented as means ± S.E of the mean. All experimental data were subjected to one-way analysis of variance (ANOVA) followed by Duncan's multiple range test for post hoc analysis using SPSS software, version 17 (IBM, USA). The level of significance was set at $p \leq 0.05$.

Results

Characterization of AlNPs

As displayed in Fig. 1, the ultrasonicated aluminum oxide nanoparticles appeared as crystals, in the form of rods, with an average length of 20–35 nm and an average thickness of 3–6 nm.

Brain acetylcholinesterase (AChE) activity

We have observed that subacute daily oral administration of AlNPs (100 mg/kg) for 28 days significantly ($p \leq 0.05$) elevated the activity of brain AChE (Table 2). However, concomitant administration of SML (100 mg/kg) with AlNPs reduced the elevated enzyme activity, compared to AlNP group, but a significant difference from control value was still present.

Oxidant/antioxidant biomarkers findings

When compared to respective control values, the level of brain MDA level was significantly ($p \leq 0.05$) elevated, while that of GSH was significantly reduced in AlNP-treated rats. Additionally, the activities of CAT and SOD were significantly inhibited. The group of rats that received both AlNPs and

Table 1 Primer sequences reference of GST, TNF-α and caspase-3 genes of Rattus norvegicus

Target genes	Accession no.	Sequence (5' to 3')	Product size
GAPDH (reference gene)	NM_017008.4	F: 5'-GAGACAGCCGCATCTTCTTG-3'	224bp
		R: 5'-TGACTGTGCCGTTGAACTTG-3'	
GST	NM_031509.2	F:5'GACCAGAGCCATTCTCAACTACA3'	261bp
		R:5'CTCAGCCTATTGCCAACGAGATA3'	
TNF-α	NM_012675.3	F: 5'ACACACGAGACGCTGAAGTA3'	235bp
		R: 5'GGAACAGTCTGGGAAGCTCT3'	
Casp-3	NM_012922.2	F: 5'-CATGCACATCCTCACTCGTG-3'	158bp
		R: 5'-CCCACTCCCAGTCATTCCTT-3'	
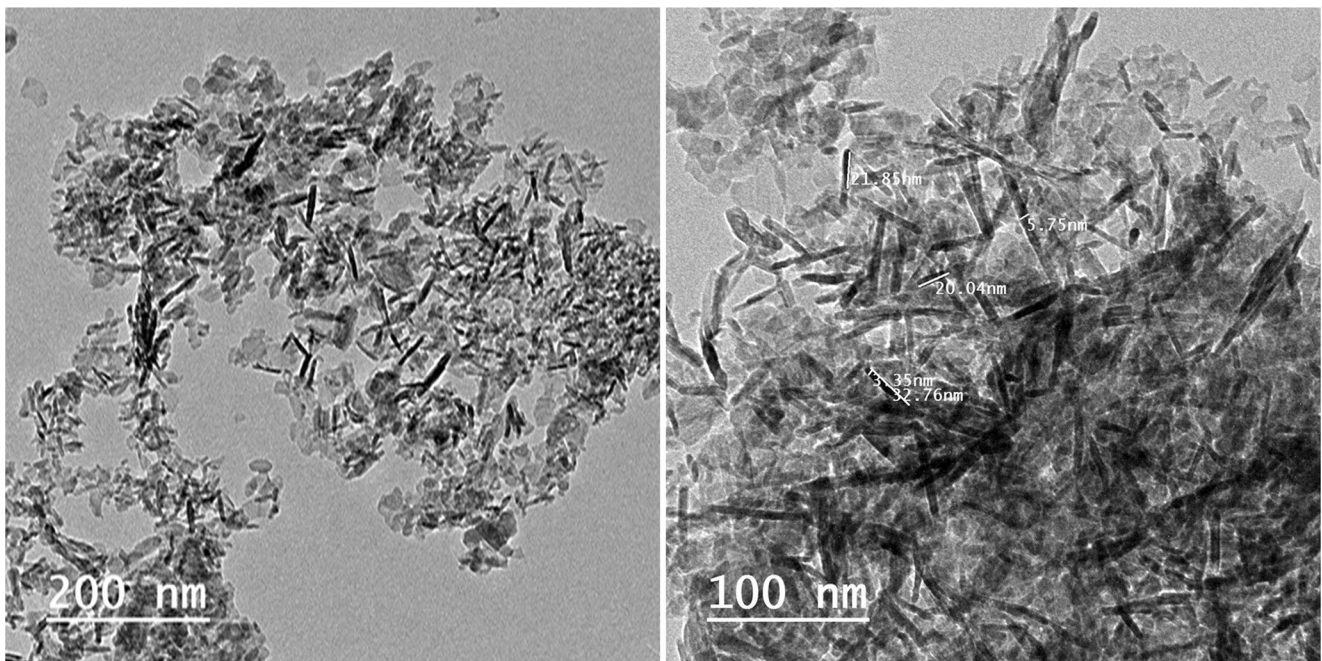
Fig. 1 Transmission electron microscope image of Al$_2$O$_3$ nanoparticles in stock solutions

SML showed significant improvement in all indices, in comparison to AlNP-treated group. However, values were still significantly different from control group, except for CAT which showed complete recovery (Table 2).

Concerning brain GST gene expression, we observed a significant 4.8-fold increase in the AlNP-treated group, compared to control. In the combined treatment group (AlNPs + SML), the expression significantly decreased to 56.3% of the AlNP group, but the value was significantly different from control (Fig. 2A and D).

8-OHdG findings

As shown in Table 2, AlNP-treated group presented significant elevation (p ≤ 0.05) of brain 8-OHdG concentration, relative to control. However, concurrent administration of SML

with AlNPs completely recovered the level of 8-OHdG to control value.

Inflammatory response findings

As summarized in Table 3, IL-1β and IL-6 levels in serum of AlNP-intoxicated rats were significantly (p ≤ 0.05) elevated, with respect to the corresponding controls. When SML was co-supplemented with AlNPs, it alleviated the effect on both interleukins, compared to AlNP-treated group. However, the values were still higher than corresponding controls.

In addition, we recorded 3.9-fold increase in the expression of TNF-α gene in the brain of AlNP-treated animals, in comparison to control. However, the concomitant administration of SML with AlNPs attenuated

Table 2 Effect of AlNPs and/or SML on biochemical indices in the brain of rats from all experimental groups

	Control	SML	AlNPs	AlNPs + SML
AChE (ng/ml)	9.81 ± 0.60[c]	11.66 ± 0.90[bc]	18.01 ± 0.94[a]	13.17 ± 0.82[b]
MDA (nmol/g)	28.75 ±1.12[c]	26.15 ± 1.23[c]	68.15 ± 2.03[a]	44.15 ± 1.86[b]
GSH (mg/g)	87.75 ± 2.73[a]	84.74 ± 2.57[a]	45.59 ± 1.65[c]	76.22 ± 2.03[b]
CAT (U/g)	2.04 ± 0.086[a]	2.06 ± 0.053[a]	1.53 ± 0.070[b]	1.89 ± 0.048[a]
SOD (U/g)	21.56 ± 0.99[a]	20.94 ± 1.01[a]	10.48 ± 0.75[c]	13.18 ± 0.82[b]
8OHdG (ng/ml)	8.33 ± 0.39[b]	8.25 ± 0.41[b]	14.33 ± 0.62[a]	8.93 ± 0.27[b]

Values are means ± SE, n = 5. Means in the same row with different superscripts (a, b, and c) are statistically significant (*p* ≤ 0.05). *ALNPs* alumina nanoparticles, *SML* sesamol, *AChE* acetylcholinesterase, *MDA* malondialdehyde, *GSH* glutathione, *CAT* catalase, *SOD* superoxide dismutase, *8-OHdG*: 8-hydroxy-2'-deoxyguanosine
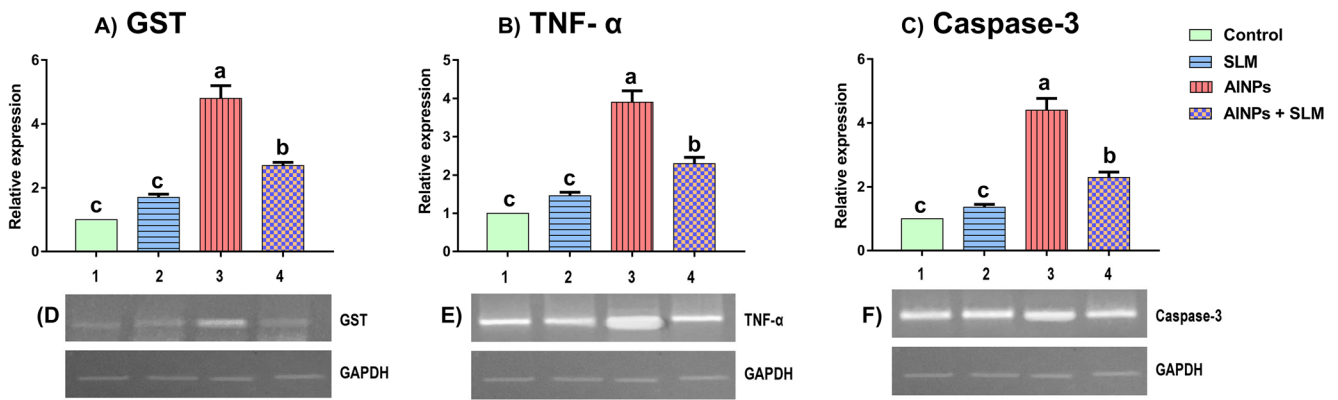
Fig. 2 Effect of AlNPs and/or SML on brain gene expression. Fold-change of mRNA gene expression of: **A** GST, **B** TNF-α, and **C** caspase-3 using quantitative RT-PCR. Values are expressed as mean ± SE, n = 5. Bars carrying different letters (a, b, and c) are significantly different at p ≤ 0.05. Cropped gel of electrophoretic mobility of quantitative RT-PCR products of **D** GST, **E** TNF-α, and **F** caspase-3 genes, with GAPDH as internal control, on 2% agarose gel. Lane 1: control, lane 2: sesamol, lane 3: AlNPs, and lane 4: AlNPs + sesamol

the expression to be 58.97% of the AlNP value, although still significantly higher than control value (Fig. 2B and E).

Brain caspase-3 finding

As indicated in (Fig. 2C and F), caspase-3 gene expression presented 4.4-fold increase in the brain of AlNP-treated animals, relative to control. However, the concurrent administration of SML with AlNPs ameliorated this overexpression to be 52.27% of the AlNP group, although still significantly higher than control.

Histopathological findings

Histopathologically, all examined brain regions in the negative control group and in the SML-treated group (Fig. 3) showed a normal histological architecture. On the other hand, AlNP administration induced necrosis and complete loss of several Purkinje cells: congestion and edema in molecular layer of the cerebellum (Fig. 4a). Medulla oblongata showed multiple hemorrhage, edema, neuronal necrosis, microglia activation (Fig. 4c), and apoptosis on neurons (Fig. 4e). In cerebrum, AlNP toxicity induced a widespread perivascular edema, hyalinization of vascular walls, a widespread apoptosis of neurons, neuronal necrosis, and edema in neuropil (Fig. 5a and c). Additionally, midbrain red nucleus showed a neuronal degeneration of multiple neurons (Fig. 5e).

As summarized in Table 4, co-supplementation of SML with AlNPs alleviated the histopathological alterations induced by the nanometal. The brain tissues showed necrosis of a few Purkinje cells in cerebellum (Fig. 4b). In medulla oblongata, mild neuronal necrosis and edema were observed (Fig. 4d and f). In cerebrum, a slight perivascular edema and a few apoptotic neurons were detected (Fig. 5b). In midbrain red nucleus, neuronal degeneration of a few neurons was recorded (Fig. 5f).

Discussion

Excessive or long-term exposure to aluminum nanoparticles (AlNPs) constitutes a major hazard to human and animal nervous system. Thus, search is continuous for phytochemicals with neuroprotective effects. In the present study, we have studied the impact of sesamol (SML) co-supplementation on the AlNP-induced toxic effects in the brain of rats. The small size of AlNPs and their large surface area enable them to penetrate biological membranes easily through all routes (De et al. 2020). In the current investigation, we adopted the oral route of administration, as it is the most common route of exposure. Our results regarding TEM photomicrographs revealed that the AlNPs were rods with an average length of 20–35 nm and an average thickness of 3–6 nm, which were approximately within the range of < 50 nm, as provided by the manufacturer.

Table 3 Effect of AlNPs and/or SML on serum proinflammatory cytokines in rats

	Control	SML	AlNPs	AlNPs + SML
IL-1β (pg/ml)	200.40 ± 3.70^{c}	194.60 ± 3.23^{c}	235.00 ± 4.01^{a}	211.60 ± 3.78^{b}
IL-6 (pg/ml)	314.00 ± 3.63^{c}	318.00 ± 3.33^{c}	436.20 ± 5.14^{a}	368.80 ± 4.19^{b}

Values are means ± SE, n = 5. Means in the same row with different superscripts (a, b, and c) are statistically significant ($p \leq 0.05$). *ALNPs* alumina nanoparticles, *SML* sesamol
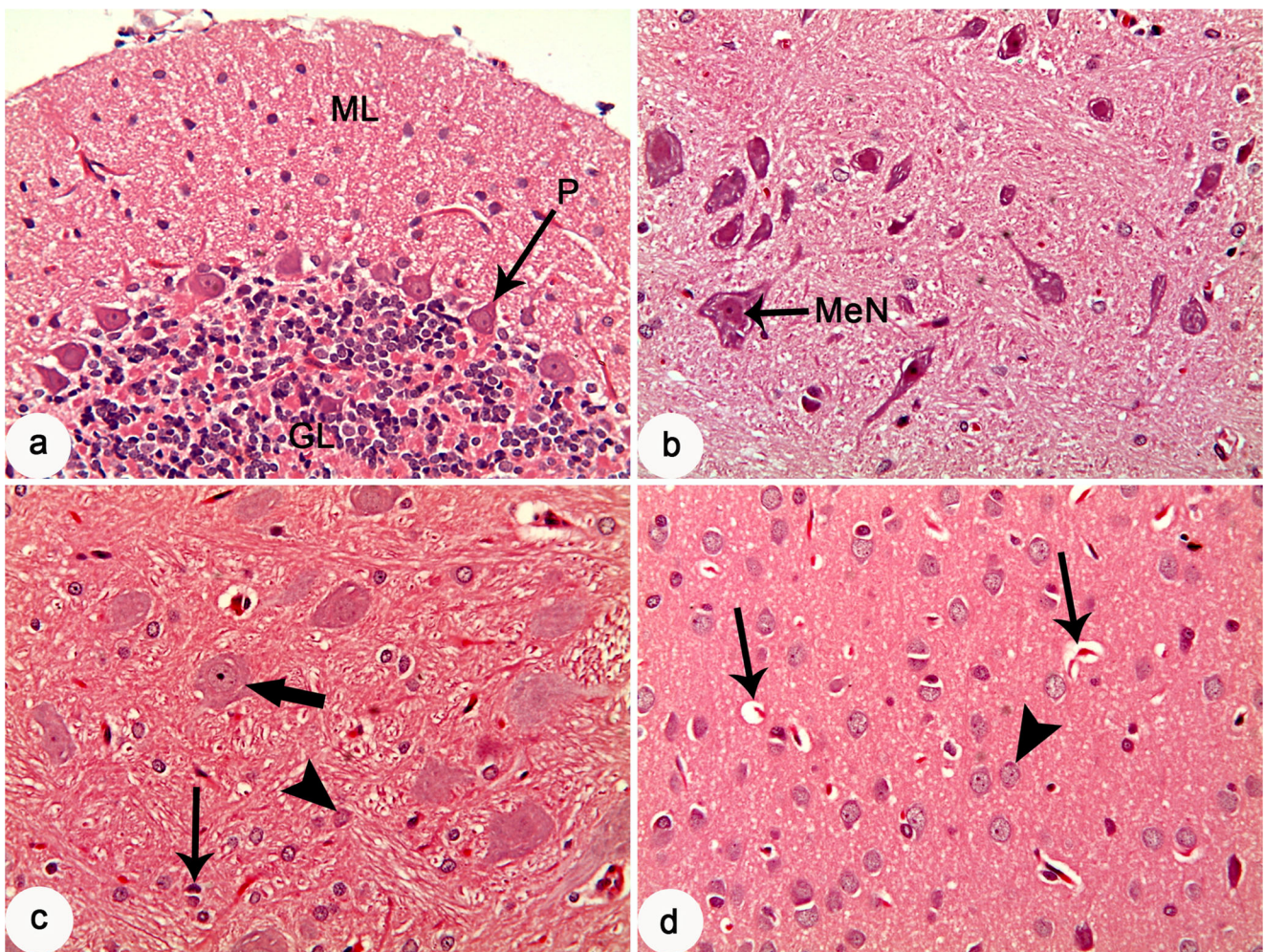
Fig. 3 Brain, rat, sesamol (SML)-treated group. **a** Cerebellum: showing normal histological architectures. GL, granular layer; P, Purkinje cell layer; ML, molecular layer. **b** Medulla oblongata: showing normal histological architectures. MeN, medulla o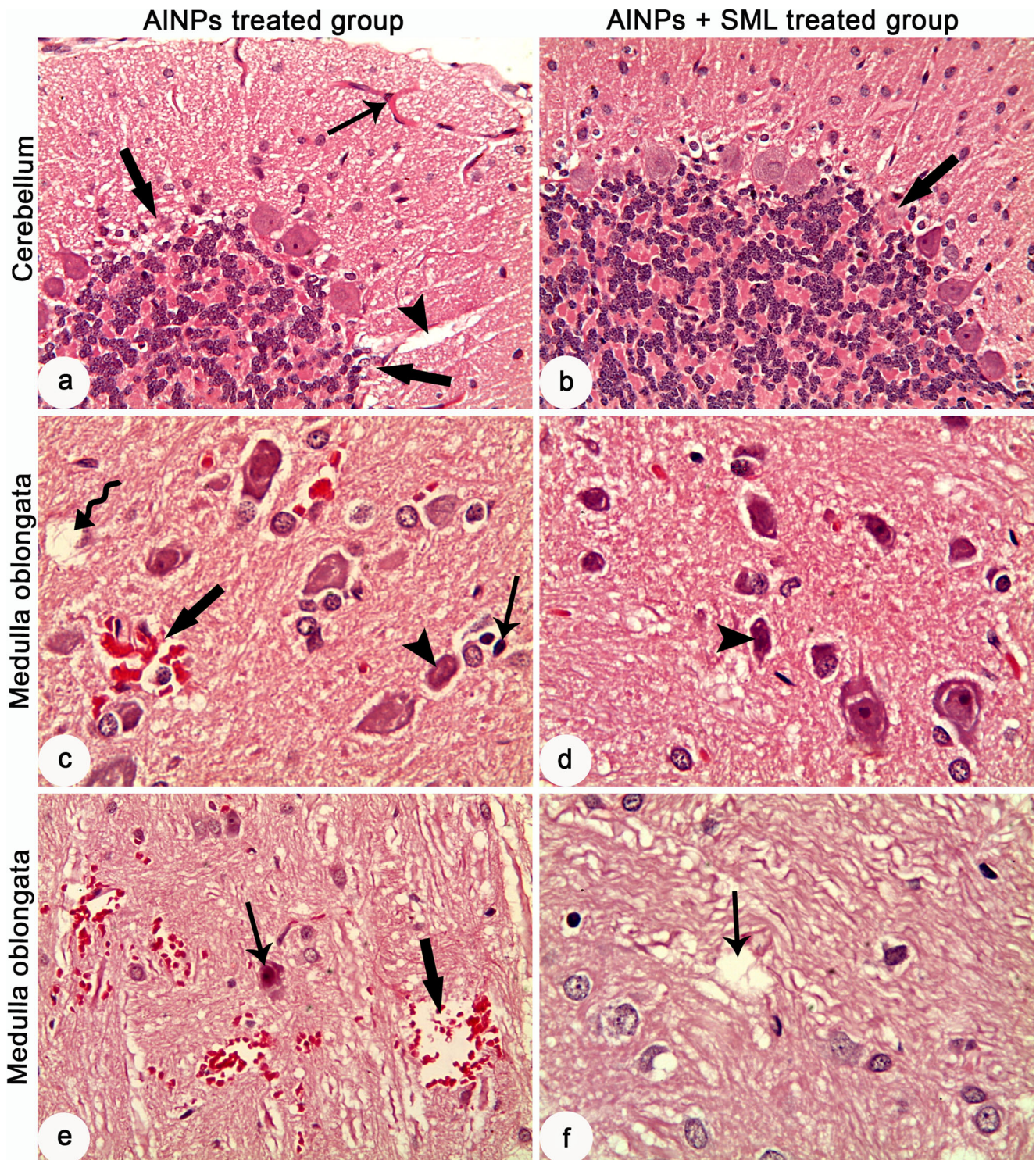blongata neurons. **c** Midbrain red nucleus: showing normal histological architectures motor neurons (thick arrow), oligodendrocyte (thin arrow), astrocyte (arrowhead). **d** Cerebrum: showing normal histological architectures. Cerebral neurons (arrowhead), blood vessels (arrows). HE stain, × 20

Acetylcholinesterase (AChE) is a key enzyme involved in catalyzing acetylcholine into choline and acetic acids at nerve synapses and neuromuscular junctions. Our findings demonstrated that oral administration of AlNPs to rats for 28 days increased the activity of brain AChE, which is expected to reduce the level of brain acetylcholine. This may contribute to AlNP-induced neurodegeneration, as the onset of degenerative diseases such as Alzheimer's disease was linked to reduced acetylcholine level (Emmett and Greenfield 2004; Arya et al. 2021). The elevated AChE activity may result from allosteric interaction of Al^{3+} cation with the enzyme peripheral sites causing modifications in the enzyme secondary structure and thus enhances its activity (Zatta et al. 1994). Our findings are in accordance with previous studies demonstrating elevated brain AChE activity in response to aluminum treatment (Auti and Kulkarni 2019; Aboelwafa et al. 2020; Liu et al. 2020b).

Of note, when SML was co-administered with AlNPs, it lowered the elevated AChE activity, reflecting the neuroprotective effect of SML. Likewise, SML was previously reported to produce a similar effect in experimental paradigm of diabetes associated cognitive decline (Kuhad and Chopra 2008) and Alzheimer's disease induced by intracerebroventricular injection of streptozotocin (ICV-STZ) in rats (Sachdeva et al. 2015).

The brain is more susceptible to oxidative stress due to poor antioxidant content, high oxidizable polyunsaturated fatty acids and iron content, and great metabolic rate (Casetta et al. 2005). Herein, we recorded elevation of brain MDA, depletion of GSH, and inhibition of activities of SOD and CAT in AlNP-treated rats. Consistent with our results, Manke et al. (2013) showed that ROS generation with consequent oxidative stress is the major mechanism of nanoparticle-induced toxicity, due to large surface area, compared to their larger counterparts. Similar to our results, AlNPs administered
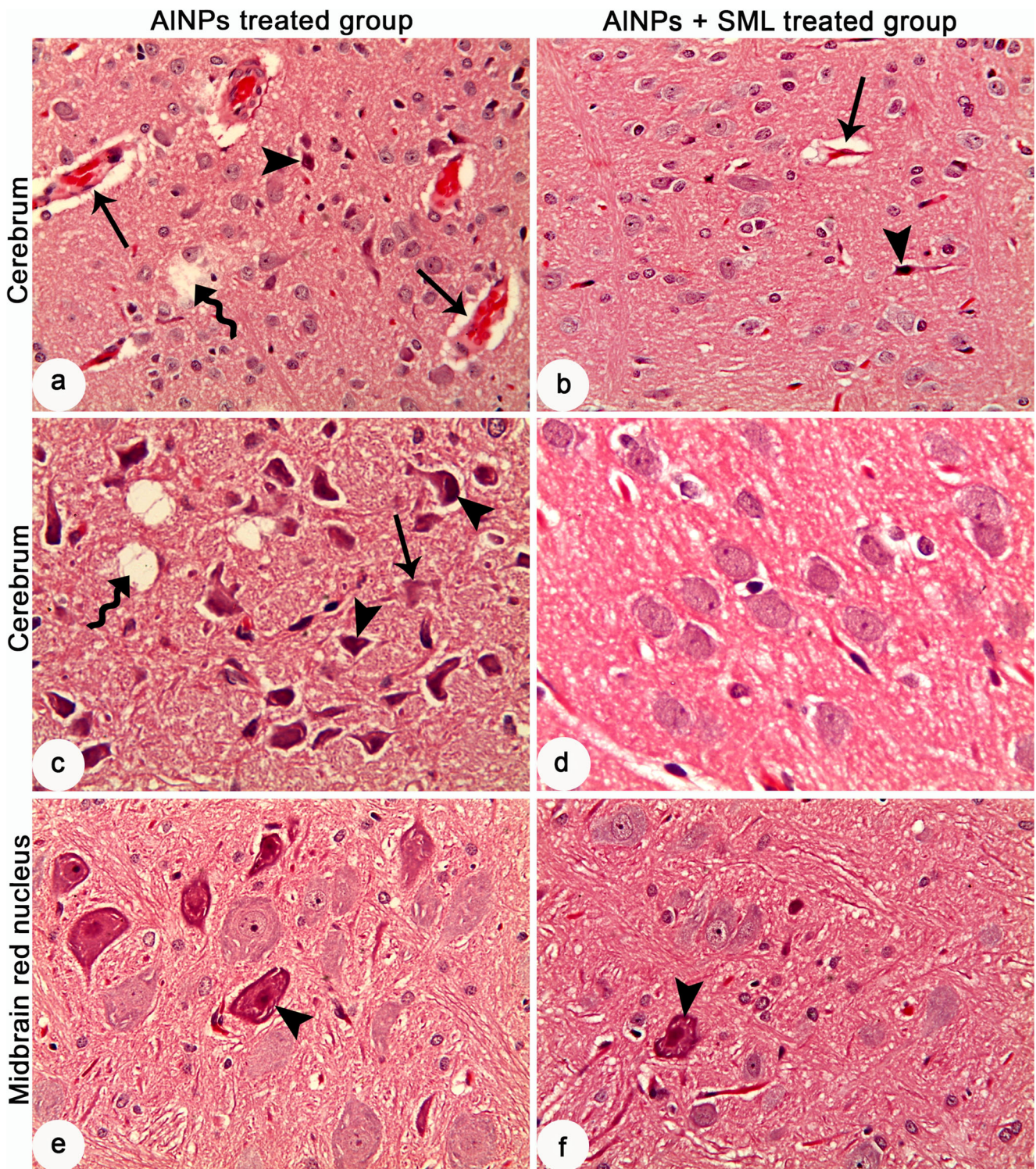
AlNPs treated group

AlNPs + SML treated group

Cerebellum

Medulla oblongata

Medulla oblongata

Fig. 4 Brain, rat. **a**, **c**, and **e** Aluminum nanoparticle (AlNP)-treated group. **b**, **d**, and **f** AlNPs plus sesamol (SML)-treated group. **a** Cerebellum: showing necrosis and complete loss of several Purkinje cells (thick arrows), congestion (thin arrow) and edema (arrowhead) in molecular layer. **b** Cerebellum: showing necrosis of a few Purkinje cells (arrow). **c** Medulla oblongata: showing hemorrhage (thick arrow), edema (bended arrow), neuronal necrosis (arrowhead). and microglia activation (thin arrow). **d** Medulla oblongata: showing mild neuronal necrosis (arrowhead). **e** Medulla oblongata: showing multiple hemorrhage (thick arrow) and apoptosis on neurons (thin arrow). **f** Medulla oblongata: showing edema (arrow). HE stain, × 20

Fig. 5 Brain, rat. **a**, **c**, and **e** Aluminum nanoparticle (AlNP)-treated group. **b**, **d**, and **f** AlNPs plus sesamol (SML)-treated group. **a** Cerebrum: showing a widespread perivascular edema and hyalinization of vascular walls (arrows), apoptosis of neurons (arrowhead) and edema (bended arrow). **b** Cerebrum: showing a slight perivascular edema (arrow) and apoptosis of neurons (arrowhead). **c** Cerebrum: showing a widespread apoptosis of neurons (arrowhead), neuronal necrosis (arrow) and edema in neuropil (bended arrow). **d** Cerebrum: showing normal histological architectures. **e** Midbrain red nucleus: showing neuronal degeneration of multiple neurons (arrowhead). **f** Midbrain red nucleus: showing neuronal degeneration of a few neurons (arrowhead). HE stain, × 20

Table 4 A comparative lesion scoring in examined brain regions between different groups

Brain regions	Cerebellum				Medulla oblongata				Cerebrum				Midbrain red nucleus			
Lesions	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
Hemorrhage	-	-	-	-	-	-	+++	-	-	-	-	-	-	-	-	-
Degeneration	-	-	+++	+	-	-	+++	++	-	-	++	+	-	-	+++	+
Necrosis	-	-	+++	+	-	-	++	+	-	-	++	-	-	-	-	-
Apoptosis	-	-	-	-	-	-	+	-	-	-	++++	+	-	-	-	-
Edema	-	-	+	-	-	-	++	+	-	-	++	+	-	-	-	-

G1, G2, G3, and G4 represent negative control group, SML-treated group, AlNP-treated group, and SML + AlNP-treated groups, respectively. -, +, ++, +++, ++++ means normal, mild, moderate, and severe, respectively

orally to rats were shown to increase lipid peroxidation and deplete GSH with suppression of GPx and SOD activities in the brain (Arslanbaş and Coşar 2019; De et al. 2020; Zhang et al. 2021a). In addition, brain oxidative stress was reported in rats received AlNPs intraperitoneal (Li et al. 2009; Morsy et al. 2016), intravenous (Mrad et al. 2017), or via intranasal instillation (Ji et al. 2011).

The elevated level of MDA with depletion of GSH indicated redox imbalance. MDA, a lipid peroxidation marker, is a toxic adduct which contributes to neuronal cell death (Serteser et al. 2002). Low GSH level could be attributed to excessive utilization in scavenging ROS (De et al. 2020). The reduced activity of CAT and SOD may result from being utilized in detoxication of H_2O_2 and superoxide radical (Abou-Zeid et al. 2021). We also observed upregulation of brain GST gene expression in AlNP-intoxicated rats. This may occur in response to increased ROS generation. The increased utilization of GSH by GST enzyme may contribute to the recorded GSH depletion. In agreement with our findings, Prabhakar et al. (2012) reported increased GST activity in the brain of AlNP-treated rats, while GSH concentration was decreased.

Interestingly, when AlNP-treated rats were co-supplemented with SML, amelioration of all biochemical indices of oxidative stress was observed, reflecting the antioxidant potential of SML. This could be attributed to the capacity of SML to scavenge hydroxyl, superoxide, NO, ABTS, and DPPH radicals (Kanimozhi and Prasad 2009; Mishra et al. 2011) through its phenolic hydroxyl group (Majdalawieh and Mansour 2019). SML exhibited 1.8-fold greater radical scavenging activity than ascorbic acid (Majdalawieh and Mansour 2019) and 20 times stronger antioxidant ability compared to melatonin (Mishra et al. 2011).

In agreement with our findings, SML reduced lipid peroxidation and improved GSH and enzymatic antioxidants in the brain of rat experimental paradigm of diabetes (VanGilder et al. 2009), Alzheimer's disease (Sachdeva et al. 2015), Huntington's disease (Kumar et al. 2010), chronic intermittent hypoxia (Zhang et al. 2021b), and focal cerebral ischemia/

reperfusion injury (Gao et al. 2017). The induction of antioxidant enzymes by SML was thought to be mediated through activation of Nrf2 transcriptional pathway and its nuclear translocation (Ren et al. 2018) and activation of SIRT1-SIRT3-FOXO3a expression (Ruankham et al. 2021).

Moreover, we demonstrated elevation of brain 8-OHdG concentration in AlNP-intoxicated animals, reflecting oxidative DNA damage. In accordance with our results, previous studies documented the ability of AlNPs to induce DNA damage in mouse brain (De et al. 2020), bone marrow, and sperm (Zhang et al. 2017) secondary to oxidative stress. Notably, when SML was co-administered with AlNPs, it reduced the brain 8-OHdG level. Similar to our findings, SML was reported to inhibit the radiation-induced DNA damage both in vivo and in vitro (Prasad et al. 2005; Kumar et al. 2018).

Accumulation of ROS may initiate apoptosis (Hsin et al. 2008). Our findings showed upregulation of caspase-3 in the brain of rats intoxicated with AlNPs. Similar to our results, Nano-Al_2O_3 produced apoptosis manifested by downregulation of bcl-2 and upregulation of p53 and Bax gene expression in the brain of rats (Liu et al. 2020a), and by caspase-3 gene overexpression in mouse brain (Zhang et al. 2011). Similar effect was demonstrated in vitro in astrocytes of neonatal rat cerebral cortex (Dong et al. 2019) and mouse neuroblastoma cells (Nogueira et al. 2019). The AlNP-induced apoptosis seems to be mediated via mitochondrial (intrinsic) pathway via activation of p53 pathway consequent to increased oxidative DNA damage (Liu et al. 2020b). Our histopathological findings revealed a widespread neuronal apoptosis in the cerebral neurons in the AlNP-treated group, which is in line with the upregulation of caspase-3 gene.

Of note, coadministration of SML with AlNPs downregulated the expression of caspase-3 in the brain. Similar effect of SML was reported in the brain of rats with rotenone-induced Parkinson's disease (Sonia Angeline et al. 2013), focal cerebral ischemia/reperfusion injury (Gao et al. 2017), and experimental diabetes (Chopra et al. 2010). The molecular mechanisms underlying the anti-apoptotic activity of SML in nerve cells may

include activating SIRT1-SIRT3-FOXO3a expression, upregulation of the anti-apoptotic protein Bcl-2, and inhibition of the proapoptotic protein Bax (Ruankham et al. 2021).

It has been documented that oxidative damage is a major initiator of inflammatory cascade via several mechanisms (Manke et al. 2013). We recorded overexpression of brain TNF-α gene and increased levels of IL1-β and IL-6 in serum of AlNP-intoxicated rats, reflecting inflammatory response which may contribute to development of neurodegenerative deficits (Win-Shwe and Fujimaki 2011; Guo et al. 2018). Similar to our results, AlNP increased the levels of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α in the brain of rats (Arslanbaş and Coşar 2019; Liu et al. 2020a; Zhang et al. 2021a) and in vitro in astrocytes of neonatal rats (Dong et al. 2019). Compelling evidence has suggested activation of NF-κB as a major pathway of aluminum-induced neuroinflammation (Zhang et al. 2018). Yun et al. (2020) have shown that the activation of notch pathway is the main mechanism of lung inflammation induced by AlNPs.

Importantly, concomitant SML treatment with AlNPs alleviated the inflammatory response as evidenced by downregulation of brain TNF-α expression and reduction of IL-1β and IL-6 levels. This is in line with the previous studies reporting the anti-inflammatory activity of SML in the brain of rats with diabetic neuropathy (Chopra et al. 2010; Misra et al. 2011; Sachdeva et al. 2015), focal cerebral ischemia/reperfusion injury (Gao et al. 2017), and chronic intermittent hypoxia (Zhang et al. 2021b) and in the lungs of rats with endotoxemia (Chu et al. 2010). The anti-inflammatory effect of SML was suggested to be mediated via suppressing NF-κB/MAPK activation and upregulating AMP kinase signaling (Wu et al. 2015; Liu et al. 2017).

Histopathologically, a notable neuronal degeneration and/or necrosis were observed in different areas in the brain of AlNP-treated group. Interestingly, the most affected neurons were motor neurons (motor neurons of medulla oblongata and midbrain red nucleus) or neurons with an inhibitory action on certain motor neurons (Purkinje cells of cerebellum). Hemorrhages and inflammatory edema were recorded especially in medulla oblongata. Additionally, perivascular edema and hyalinization of vascular walls were observed in the cerebellum. The nanosized aluminum can easily penetrate the blood-brain barrier and accumulate in brain tissues (De et al. 2020) resulting generation of ROS. The latter may produce oxidative damage on lipids in the cell and mitochondrial membranes and on the cellular macromolecules like DNA and protein and thus induce histopathological changes with degradation of neurons. Our findings are in agreement with previous reports demonstrating histopathological changes in the brain of rats and mice (Morsy et al. 2016; Mrad et al. 2017; De et al. 2020; Liu et al. 2020a, b; Zhang et al. 2021a). Finally, all the observed histopathological alterations in brain tissue of AlNP-treated rats have been ameliorated upon concomitant administration of SML with AlNPs. This protective effect of

SML is in line with our findings concerning the oxidative stress markers and inflammatory cytokines.

Conclusion

In conclusion, administration of AlNPs to rats at 100 mg/kg was associated with neurotoxicity and brain damage. We hypothesized oxidative injury, apoptosis, and inflammatory response as underlying mechanisms. Concomitant administration of SML with AlNPs exerted neuroprotective effect probably through the antioxidant, anti-apoptotic, and anti-inflammatory activities of SML. The present study presents SML as a protective agent from AlNP-induced neurodegenerative disorders.

Availability of data and materials Not applicable

Declarations

Ethics approval and consent to participate Ethics approval and consent to participate this study was approved by the Institutional Animal Care and Use Committee (IACUC) (Approval number: VUSC-007-1-20), Faculty of Veterinary Medicine, University of Sadat City, Egypt.

Consent for publication All the authors have given the consent to publish the paper.

Competing interests The authors declare no competing interests.

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