

ORIGINAL RESEARCH ARTICLE

Lactiplantibacillus plantarum mitigates aluminum chloride-induced neurotoxicity in Wistar rats

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Abstract

Aluminum chloride (AlCl₃) has been associated with neurological disorders. This study assesses the potential neuroprotective effects of *Lactiplantibacillus plantarum* PQ104969 in alleviating AlCl₃-induced neurotoxicity in Wistar rats, with emphasis on the hippocampus. Thirty male Wistar rats were divided into six groups ($n = 5/\text{group}$): Group A received normal saline (control group), Groups B and C received 0.5 and 1.0 mL, respectively, of lactic acid bacteria (LAB; *L. plantarum* PQ104969; 1×10^8 CFU/mL), Group D received 200 mg/kg AlCl₃ (neurotoxicity group), and Groups E and F received 200 mg/kg AlCl₃ and treated with 0.5 and 1.0 mL LAB, respectively. The brain tissues of all groups were harvested after 21 days of treatment and analyzed for their malondialdehyde (MDA), myeloperoxidase (MPO), protein, nitrite, nitrate, and total protein concentration using standard biochemical methods. Tissue histology of the hippocampus was performed using hematoxylin and eosin staining techniques. AlCl₃ caused extensive neurodegeneration, which improved with LAB administration. Groups E and F showed significantly lower levels of MDA, MPO, nitrite, and nitrate concentrations compared to Group D, except for the nitrate level in Group F. The total protein concentrations were consistent across all groups. Histological examination showed that AlCl₃ induced neurodegenerative changes in the hippocampus, while LAB introduction following AlCl₃ administration attenuated the observed pathological damages and preserved the neuronal architecture. These findings suggest that *L. plantarum* PQ104969 possesses negative dose-dependent neuroprotective effects against AlCl₃-induced neurotoxicity, offering a promising therapeutic approach for inflammation-induced neurotoxicity.

Keywords: Neurotoxicity; Hippocampus; Aluminum chloride; Neurodegeneration; Inflammation; *Lactiplantibacillus plantarum*

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1. Background

Exposure to certain substances has its way of impacting the human system either positively or negatively. Aluminum, a metal, is of great biological concern. It has been linked to neurological conditions. Some recent studies aim to clarify these connections.^{1,2} Studies have demonstrated that aluminum exposure is associated with activating microglia and astrocytes in the brain.^{2,3} This causes the release of pro-inflammatory molecules and oxidative stress.⁴ Owing to the extensive usage of aluminum in most products, including utensils, food additives, water purifiers, and pharmaceuticals, there are high chances of aluminum compound exposure to humans,⁵ pointing toward a risk of health consequences such as neuroinflammation. For example, Maksoud *et al.*⁶ demonstrated that the mere exploitation of bauxite mines and the effects of acid rain can cause significantly high volumes of aluminum salts to release unstable minerals, further exposing humans to aluminum.

Aluminum chloride (AlCl_3) is an inorganic compound consisting of aluminum and chloride ions in its structure. It can cause neuroinflammation in animals; hence, it has become an excellent model to understand how a neuroinflammatory condition develops.⁷ When AlCl_3 enters the systemic circulation, it has the potential to disrupt tight junctions in the brain and increase blood–brain barrier (BBB) permeability, allowing AlCl_3 to enter the brain.⁸ Accumulation of aluminum predominantly occurs in the hippocampus and frontal cortex.⁹ Epidemiological and animal model studies have indicated that aluminum buildup in the hippocampus is associated with maladaptive amyloid beta ($\text{A}\beta$) aggregation, neuroinflammation, and neuronal necrosis.⁶ This study primarily focuses on the preliminary oxidative and inflammatory markers that precede these events.

According to Antonelli and Kushner,¹⁰ inflammation may be defined as the innate immune response to harmful stimuli, such as pathogens, injury, and metabolic stress. It is marked by heat, redness, swelling, pain, and loss of function.¹¹ Inflammation is typically categorized into two groups: Acute and chronic. Neuroinflammation refers to an inflammatory reaction occurring within the central nervous system (CNS), facilitated by the generation of various substances such as cytokines, chemokines, reactive oxygen species (ROS), and other secondary molecules.¹² It is widely considered a chronic form of inflammation in the CNS, as opposed to acute inflammation, and is typically associated with neurodegenerative diseases.¹³ The neuroinflammatory process involves changes in the interaction between glial cells and neurons due to the activation of microglia and astrocytes.¹⁴ Initially,

neuroinflammation is primarily beneficial and protective; however, evidence from both clinical and experimental studies indicates that prolonged or excessive inflammation is a crucial pathological driver of several neurological disorders, such as multiple sclerosis, chronic pain, traumatic brain and spinal cord injuries, neurodegenerative diseases, epilepsy, and cerebrovascular diseases.¹⁵

Probiotics exhibit several beneficial functions in the host, including promoting intestinal development, maintaining barrier integrity, and regulating the immune system and functioning of the CNS.^{16,17} Lactic acid bacteria (LAB) possessing antimicrobial properties are commonly found in food products. LAB strains that can survive the acidic environment of the stomach, resist exposure to bile salts, adhere to the intestinal mucosa, and exhibit an inhibitory effect toward pathogenic bacteria may have the characteristics of potential probiotics with significant health benefits.¹⁸ They have been the focus of investigations regarding their potential in addressing neuroinflammation. A comprehensive review has underscored the neuroprotective attributes of LAB, demonstrating that treatment with specific LAB strains such as *Lactocaseibacillus rhamnosus*, *Lactobacillus reuteri*, and *Lactobacillus plantarum* significantly inhibited lipopolysaccharide (LPS)-induced elevation of tumor necrosis factor- α , a marker of neuroinflammation.¹⁹ Furthermore, a study on mice has illustrated that LAB supplementation mitigated LPS-induced gut inflammation and dysbiosis, which are associated with neuroinflammation and cognitive impairment.²⁰

L. plantarum, a beneficial LAB found in the gut, has been demonstrated to exert diverse effects on the immune system and inflammation. Notably, recent research has revealed significant findings related to *L. plantarum*. For example, Shukla *et al.*²¹ reported that *L. plantarum* administration following chronic ethanol-induced injury mitigated systemic inflammation and neuroinflammation. In addition, Wu *et al.*²² found that *L. plantarum*-derived postbiotics, particularly metabolites, effectively prevented *Salmonella enterica* serovar Typhimurium infection in mice, as evidenced by reduced weight loss, bacterial translocation, and tissue damage. The findings indicate potential therapeutic uses of *L. plantarum* and its postbiotics on the prevention and treatment of neuroinflammation-related diseases. However, additional research is needed to ensure that the mechanisms underlying these influences are properly understood and that the most effective strategies to employ *L. plantarum* in the treatment of neuroinflammation are identified.

Neuroinflammation is associated with many neurological disorders and presents a complex challenge

due to its inhomogeneous nature and the limitations of current treatment approaches. Issues such as cognitive fluctuations and neurodegeneration that are the consequences of neuroinflammation underline the necessity to develop new therapeutic strategies. Future treatment is usually hampered by side effects that are not intended, penetration of the BBB, and lack of a target biomarker in response to the treatment. Therefore, the current study aims to address these drawbacks through research on the neuroprotective effects of *L. plantarum* as a strain with anti-inflammatory properties. By authenticating the strain and determining its effects on AlCl_3 -induced neuroinflammation in Wistar albino rats, this study provides information toward developing a new intervention targeting neuroinflammation—a key factor underlying the shortcomings of existing treatment methodologies. This paper aims to assess the potential of *Lactiplantibacillus plantarum* PQ104969 in managing neurotoxicity caused by AlCl_3 in Wistar rats, necessitating a conventional mode of therapy.

2. Materials and methods

2.1. Preparation of *L. plantarum* PQ104969

The *L. plantarum* PQ104969 strain used in this study was originally isolated from “Pap” (a Nigerian fermented maize gruel), as previously described by Bamigbade *et al.*²³ The strain was identified through morphological and biochemical characterization and confirmed by molecular analysis using 16S *rDNA* gene sequencing. The sequence has been deposited in the GenBank database under the accession number PQ104969. The organism was cultured in de Man, Rogosa, and Sharpe broth at 37°C for 24 h to achieve the required concentration of 1×10^8 CFU/mL before administration.

2.2. Animals, chemicals, and treatments

Thirty male Wistar albino rats, average weight of 150 g, were purchased from Breeder's Lodge in Akure, Ondo, Nigeria. They were housed in cages made of stainless steel at the Microbiology Department at the Federal University of Technology Akure (FUTA), where they were provided with rat pellets and water. A week was allowed for acclimatization. The AlCl_3 used to induce neurotoxicity was sourced from Sigma-Aldrich (United States of America [USA]). All other biochemical reagents used for the assessment of oxidative stress and inflammatory markers were of analytical grade. The details of the primary chemicals are summarized in Table 1.

The experimental procedures were carried out in accordance with the guidelines of the National Institute of Health for laboratory animal care and use.²⁴ The ethical

Table 1. List of chemicals and reagents

Chemical/reagent	Manufacturer	Catalog number	Country of origin
Aluminum chloride hexahydrate ($\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$)	Sigma-Aldrich	206911	USA
2-Thiobarbituric acid	Sigma-Aldrich	T5500	USA
Trichloroacetic acid	Sigma-Aldrich	T6399	USA
Griess reagent (modified)	Sigma-Aldrich	G4410	USA
<i>o</i> -Dianisidine dihydrochloride	Sigma-Aldrich	D9154	USA
Hydrogen peroxide (H_2O_2)	Sigma-Aldrich	H1009	USA
Bovine serum albumin	Sigma-Aldrich	A2153	USA

Abbreviation: USA: United States of America.

guidelines set by the Centre for Research and Development at FUTA were followed. Approval was obtained from the Research Ethical Committee at FUTA in accordance with ethical guidelines (FUTA/ETH/24/138).

The rats were divided into six groups, with each containing five rats ($n = 5$). The sample size per group was selected based on the 3Rs principle (Reduction), aimed at minimizing animal use while ensuring scientific validity. This number is consistent with previous neurotoxicity studies that demonstrated sufficient statistical power to detect significant biochemical and histological changes in AlCl_3 -induced models.^{25,26} For the dosage of AlCl_3 , 200 mg/kg of AlCl_3 was administered per body weight of rats at a volume of 1.0 mL,²⁷ while LAB was administered at volumes of 0.5 mL or 1.0 mL (1×10^8 CFU/mL *L. plantarum* PQ104969) depending on the dosage groups. The control group (Group A) received normal saline; Groups B and C received 0.5 mL and 1.0 mL of the LAB dose, respectively; Group D received AlCl_3 (200 mg/kg); and Groups E and F received AlCl_3 (200 mg/kg) followed by 0.5 mL and 1.0 mL of the LAB dose, respectively. This regimen was administered orally once daily for 21 days, with a 30-min interval between the administration of AlCl_3 and the probiotic, after which the rats were euthanized. This interval was strictly observed to prevent direct chemical interaction between the metal salts and the live bacteria within the stomach, ensuring the viability of the probiotic on reaching the intestine.

2.3. Brain sample collection

The animals were sacrificed, and their brains were extracted following the guidelines of the Institutional Animal Ethics Committee and the Centre for Research and Development of FUTA. Ethical approval was obtained from the FUTA Research Ethical Committee (FUTA/ETH/24/138). Subsequently, the brains were individually weighed and documented using an electronic weighing

balance (DT 1000 model, G&G Scales Electronic Balance Store, USA) with a weighing capacity ranging from 0.01 to 100 g. Following the weighing process, the brains were divided into two equal parts and securely preserved. The brains were fixed by immersing in 10% formalin rather than transcardial perfusion to allow for the simultaneous collection of fresh tissue from the same subjects for histological analysis and biochemical assays.

2.4. Histology

The brain tissues were fixed in 10% neutral buffered formalin, and tissue processing was performed before the histological staining process. Pre-treatment with increasing grades of alcohol was performed. Afterward, paraffin embedding was carried out. The hematoxylin and eosin staining method was utilized according to Avwioro.²⁸ The stained slices were observed using a DSX1000 digital microscope (DSX1000, Olympus, Japan) at a magnification of $\times 40$ using a snapshot tool of Topview software (Version 7.3.1 SP1, ToupTek Photonics, China).

2.5. Biochemical assays

A mechanical homogenizer (Bead Ruptor Elite, OMNI International, USA) was employed at a velocity of 45 m/s to disrupt the tissues and produce a homogenate. The homogenates were then centrifuged at $1,000\times g$ for 10 min at 4°C to remove debris, followed by $10,000\times g$ for 20 min to obtain the cytosolic fraction. The processed samples were used for the subsequent biochemical assays.

2.5.1. Determination of malondialdehyde (MDA) level

The level of MDA, a biomarker of lipid peroxidation, was measured using the thiobarbituric acid reactive substances (TBARS) assay, as originally described by Varshney and Kale.²⁹ Briefly, a part of the specimen was added to Tris-KCl buffer and mixed thoroughly, followed by the addition of equal volumes of trichloroacetic acid and thiobarbituric acid. The mixture was vortexed and then incubated in a water bath at 80°C for 45 min. The solution was then cooled in an ice bath and centrifuged at $3,000\times g$ for 15 min. The clear supernatant was collected, and its absorbance was measured spectrophotometrically (DS-Cuvette Spectrophotometer, DeNovix, USA) at 532 nm against a distilled water blank. MDA concentration was calculated according to the technique described by Adam-Vizi and Seregi,³⁰ using a molar extinction coefficient of $1.56 \times 10^5 \text{ M}^{-1}\cdot\text{cm}^{-1}$, and expressed as lipid peroxidation per mg of protein or per g of tissue.

2.5.2. Determination of total nitrite

Nitrite levels were determined using the method described by Ignarro *et al.*,³¹ based on the diazotization

reaction originally reported by Peter Griess in 1879.³² This assay involves a chemical reaction between naphthylethylenediamine dihydrochlorate (NED) and sulfanilamide under acidic conditions. Sulfanilamide and NED in the Griess reaction compete with nitrite. The Griess reagent was prepared by mixing equal volumes of 0.1% NED and 1% sulfanilic acid in 5% phosphoric acid. A 50 μL aliquot of each sample was added in duplicate to a 96-well plate, followed by the addition of 100 μL of Griess reagent. The mixture was incubated at room temperature, protected from light, for 10 min to allow color development. Absorbance was then measured within 30 min using a microplate reader (BK-EL10C, Biobase, China) at 550 nm.

2.5.3. Determination of myeloperoxidase (MPO) activity

The *o*-dianisidine dihydrochloride (*o*-dianisidine) solution was prepared fresh for each assay by dissolving 16.7 mg of *o*-dianisidine in 90 mL of distilled water and 10 mL of potassium phosphate buffer. Then, 50 μL of diluted H_2O_2 (4 μL of 30% H_2O_2 diluted in 96 μL of distilled water) was added to the *o*-dianisidine mixture. For the assay, 70 μL of tissue homogenate was added to 200 μL of the *o*-dianisidine mixture containing H_2O_2 in each well. Absorbance was measured at 450 nm using a spectrophotometer, with readings taken 3 times at 30-s intervals.³³

2.5.4. Determination of nitrate level

The spectrophotometer was allowed to warm up for 30 min before use. An aliquot of the extract was then pipetted into a 50 mL Erlenmeyer flask and mixed thoroughly with 0.8 mL of 5% (w/v) salicylic acid. After incubating at room temperature for 12 min, 19 mL of 2N NaOH was added to the mixture to adjust the pH to above 12, creating an alkaline environment. The sample was allowed to cool, and its absorbance was measured at 410 nm.³⁴

2.5.5. Determination of total protein concentration

The total protein concentration was estimated using the Biuret method as described by Gornal *et al.*,³⁵ with slight modifications to serve as a crucial internal normalization factor. In biochemical assays of tissue homogenates, expressing results solely as absolute terms (e.g., total concentration in the tube) can be misleading due to variations in tissue weight, water content, or homogenization efficiency. Data of MDA, MPO, nitrite, and nitrate levels were normalized to total protein content to ensure that observed changes reflect true physiological alterations in brain tissue rather than technical variations in sample preparation.

2.6. Statistical analysis

Data are presented as mean $\pm$ standard error of the mean (SEM). Statistical comparison was performed across the

groups using GraphPad Prism 9 (GraphPad Software, Inc., USA) and Microsoft Excel 2019. Differences across groups were assessed through analysis of variance, followed by Turkey's multiple comparisons test for *post hoc* analysis. The Brown-Forsythe test was used to assess the homogeneity of variances for parametric variables. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Effects of *L. plantarum* administration on MDA level in the brain

From the results of MDA concentrations (Figure 1), Group D (AlCl_3 -treated) exhibited a significant increase ($p < 0.05$) in MDA levels compared to the control group, indicating marked lipid peroxidation. Interestingly, treatment with *L. plantarum* PQ104969 (0.5 mL [Group E] and 1.0 mL [Group F]) following AlCl_3 application resulted in a significant reduction in MDA levels compared to Group D (AlCl_3 -treated). These findings demonstrate the potent antioxidant capacity of the probiotic in mitigating AlCl_3 -induced oxidative stress.

3.2. Effects of *L. plantarum* administration on nitrite level in the brain

Figure 2 shows that there was a significant increase ($p < 0.05$) in the nitrite level of Group D (AlCl_3 -treated) compared

to Group A (control). Furthermore, a significant decrease ($p < 0.05$) was observed in the nitrite levels of Groups E (AlCl_3 + 0.5 mL LAB-treated) and F (AlCl_3 + 1.0 mL LAB-treated) compared to Group D (AlCl_3 -treated). In contrast, no significant difference was observed in the nitrite levels of Groups B (0.5 mL LAB-treated) and C (1.0 mL LAB-treated) in comparison to Groups A (control), E (AlCl_3 + 0.5 mL LAB-treated), and F (AlCl_3 + 1.0 mL LAB-treated).

3.3. Effects of *L. plantarum* administration on MPO activity in the brain

The MPO activity significantly increased ($p < 0.05$) in Group D (AlCl_3 -treated) compared to Groups A (control), B (0.5 mL LAB-treated), and C (1.0 mL LAB-treated) (Figure 3). Both Groups E (AlCl_3 + 0.5 mL LAB-treated) and F (AlCl_3 + 1.0 mL LAB-treated) demonstrated significantly reduced ($p < 0.05$) MPO activities compared to Group D (AlCl_3 -treated). Significant decrease ($p < 0.05$) in MPO activities was also observed in Groups B (0.5 mL LAB-treated) and C (1.0 mL LAB-treated) compared to Groups A (control) and D (AlCl_3 -treated).

3.4. Effects of *L. plantarum* administration on nitrate level in the brain

Group D (AlCl_3 -treated) demonstrated a significantly increased ($p < 0.05$) nitrate level compared to Group A

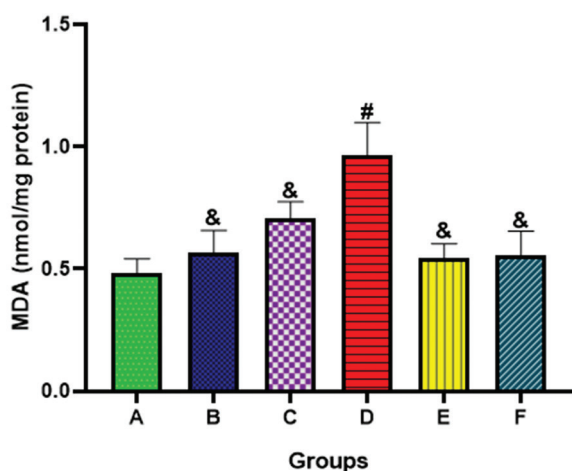


Figure 1. Effects of *Lactiplantibacillus plantarum* on malondialdehyde (MDA) levels in an AlCl_3 -induced neuroinflammation model in Wistar rats. Notes: Statistical analyses are performed using one-way analysis of variance followed by Tukey's multiple comparisons test. Results are expressed as mean $\pm$ standard error of the mean. $n = 5$. & indicates statistically significant ($p < 0.05$) compared to Group D; # indicates statistically significant compared to Groups A, E, and F. Group A: Control; Group B: 0.5 mL LAB-treated; Group C: 1.0 mL LAB-treated; Group D: AlCl_3 -treated; Group E: AlCl_3 + 0.5 mL LAB-treated; Group F: AlCl_3 + 1.0 mL LAB-treated.

Abbreviations: LAB: Lactic acid bacteria; AlCl_3 : Aluminum chloride.

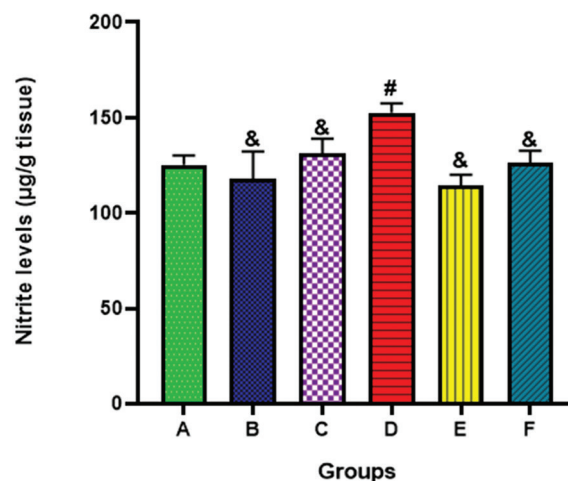


Figure 2. Effects of *Lactiplantibacillus plantarum* on nitrite levels in an AlCl_3 -induced neuroinflammation model in Wistar rats.

Notes: Statistical analyses are performed using one-way analysis of variance followed by Tukey's multiple comparisons test. Results are expressed as mean $\pm$ standard error of the mean. $n = 5$. & indicates statistically significant ($p < 0.05$) compared to Group D; # indicates statistically significant compared to Groups A, E, and F. Group A: Control; Group B: 0.5 mL LAB-treated; Group C: 1.0 mL LAB-treated; Group D: AlCl_3 -treated; Group E: AlCl_3 + 0.5 mL LAB-treated; Group F: AlCl_3 + 1.0 mL LAB-treated.

Abbreviations: LAB: Lactic acid bacteria; AlCl_3 : Aluminum chloride.

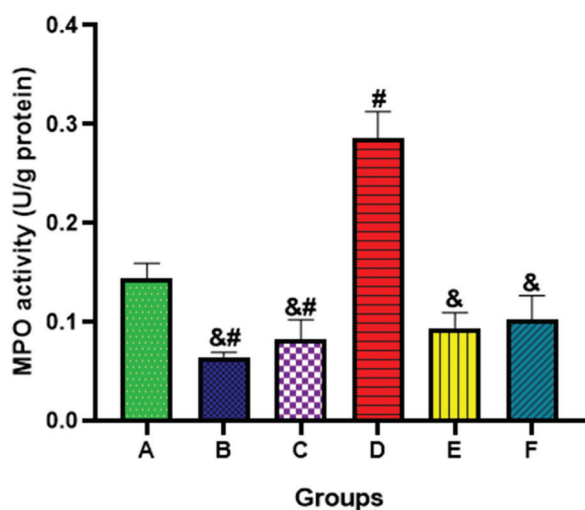


Figure 3. Effects of *Lactiplantibacillus plantarum* on myeloperoxidase (MPO) in an AlCl_3 -induced neuroinflammation model in Wistar rats
Notes: Statistical analyses are performed using one-way analysis of variance followed by Tukey's multiple comparisons test. Results are expressed as mean $\pm$ standard error of the mean. $n = 5$. & indicates statistically significant ($p < 0.05$) compared to Group D; # indicates statistically significant compared to Groups A, E, and F. Group A: Control; Group B: 0.5 mL LAB-treated; Group C: 1.0 mL LAB-treated; Group D: AlCl_3 -treated; Group E: AlCl_3 + 0.5 mL LAB-treated; Group F: AlCl_3 + 1.0 mL LAB-treated.

Abbreviations: LAB: Lactic acid bacteria; AlCl_3 : Aluminum chloride.

(control) (Figure 4). Group E (AlCl_3 + 0.5 mL LAB-treated) showed a significant decrease ($p < 0.05$) in nitrate level compared to Group D (AlCl_3 -treated). In contrast, there was no significant difference between Group F (AlCl_3 + 1.0 mL LAB-treated) and Group D (AlCl_3 -treated). Furthermore, both Groups B (0.5 mL LAB-treated) and C (1.0 mL LAB-treated) showed no significant difference in nitrate levels compared with each other.

3.5. Effects of *L. plantarum* administration on total protein concentration in the brain

As shown in Figure 5, all groups showed no significant difference in the total protein concentrations compared to Groups A (control) and Group D (AlCl_3 -treated).

3.6. Effects of *L. plantarum* treatment on the histology of the hippocampus

The photomicrographs depicted in Figure 6 provided detailed insights into the characteristic areas of the hippocampus: *Cornu Ammonis* (CA) regions, dentate gyrus, and subiculum. Figure 6A shows normal pyramidal neurons in CA1–CA4 in Group A (control). The dentate gyrus showed well-defined granule cells, and the subiculum appeared structurally organized. Groups B (0.5 mL LAB-treated; Figure 6B) and C (1.0 mL LAB-treated; Figure 6C)

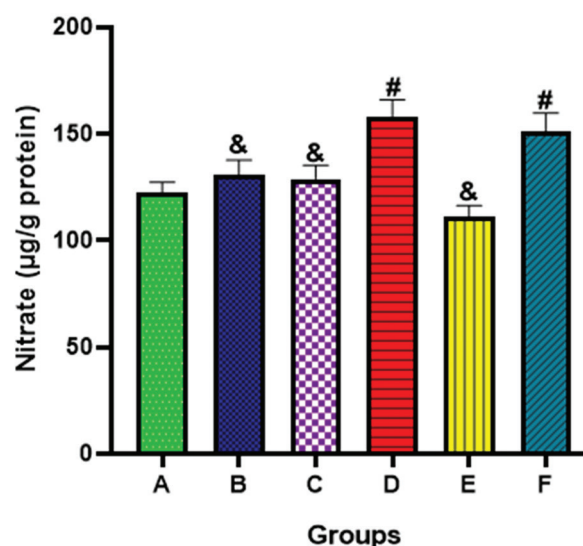


Figure 4. Effects of *Lactiplantibacillus plantarum* on Nitrate concentration (NO_3^-) in an AlCl_3 -induced neuroinflammation model in Wistar rats

Notes: Statistical analyses are performed using one-way analysis of variance followed by Tukey's multiple comparisons test. Results are expressed as mean $\pm$ standard error of the mean. $n = 5$. & indicates statistically significant ($p < 0.05$) compared to Group D; # indicates statistically significant compared to Groups A and E. Group A: Control; Group B: 0.5 mL LAB-treated; Group C: 1.0 mL LAB-treated; Group D: AlCl_3 -treated; Group E: AlCl_3 + 0.5 mL LAB-treated; Group F: AlCl_3 + 1.0 mL LAB-treated.

Abbreviations: LAB: Lactic acid bacteria; AlCl_3 : Aluminum chloride.

were comparable to Group A (control), with normal histoarchitecture, no obvious signs of neurodegeneration, and a visually observed trend of increasing neuronal density, suggesting a neurogenic potential. Group D (AlCl_3 -treated; Figure 6D) showed marked histological alterations observable under the microscope, characterized by lower neuronal density in the CA regions; disorganized granule cells and reduced neuronal density in the dentate gyrus; and focal areas suggestive of gliosis in the subiculum. Groups E (AlCl_3 + 0.5 mL LAB-treated; Figure 6E) and F (AlCl_3 + 1.0 mL LAB-treated; Figure 6F) showed near-complete neuroprotection and preservation of pyramidal neurons and granule cells with seemingly reduced gliosis and improved cellular arrangement, as observed through the microscope.

4. Discussion

Neuroinflammation refers to the inflammatory response that occurs within the CNS, which encompasses the brain and spinal cord. Unlike peripheral inflammation, the CNS is an immune-privileged site guarded by the selective BBB.³⁶ The primary immune cells involved in neuroinflammation are microglia, the resident innate immune cells that make

up 10–15% of the total glial cell population in the brain and spinal cord.³⁷ Microglia have a fundamental role in active immune response in the CNS and serve as the initial means against threats or stimuli, including brain injury, infections, and immunogenic factors. In their resting state, microglia are ramified and constantly explore the

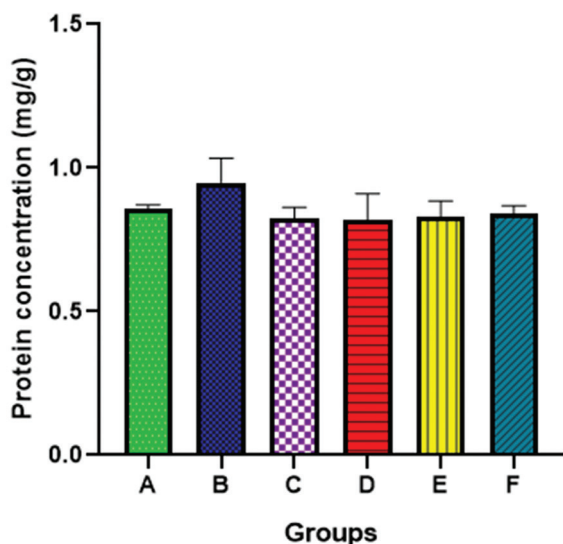


Figure 5. Effects of *Lactiplantibacillus plantarum* on protein concentration in an AlCl_3 -induced neuroinflammation model in Wistar rats

Notes: Statistical analyses are performed using one-way analysis of variance followed by Tukey's multiple comparisons test. Results are expressed as mean $\pm$ standard error of the mean. $n = 5$. Group A: Control; Group B: 0.5 mL LAB-treated; Group C: 1.0 mL LAB-treated; Group D: AlCl_3 -treated; Group E: AlCl_3 + 0.5 mL LAB-treated; Group F: AlCl_3 + 1.0 mL LAB-treated.

Abbreviations: LAB: Lactic acid bacteria; AlCl_3 : Aluminum chloride.

brain to detect abnormalities. When harmful stimuli are detected, microglia are activated, where they experience morphological changes, migrate to damaged sites, and increase their expression of immunoactive molecules.³⁸ However, it has been observed that AlCl_3 can induce neuroinflammation and oxidative stress in rat brain models through the engagement of glia, supporting its capacity to model some aspects of neurological diseases experimentally.²

This study examined the possibility of using *L. plantarum*, which is a LAB, to treat AlCl_3 -induced neuroinflammation in male Wistar rats. Neuroprotective effects of supplements that contain neuroprotective probiotics, including *L. plantarum*, have been suggested in recent studies due to their anti-inflammatory, antioxidant, and neuromodulatory properties.³⁹ Nevertheless, the precise dose and action of probiotic neuroprotection are unknown. This work aimed at investigating the neuroprotective properties of two doses of *L. plantarum* against AlCl_3 -induced neuroinflammation and oxidative stress in a rat model using histological and biochemical approaches. The findings ultimately indicate that *L. plantarum* treatment enhances brain histopathology of the rats, thus showing its neuroprotective potential. Surprisingly, 0.5 mL LAB showed a tendency for better protection compared to 1.0 mL LAB, indicating a potential negative dose-dependent effect.

Biochemical analysis revealed that AlCl_3 administration significantly elevated MDA levels, a hallmark of lipid peroxidation and oxidative membrane damage in the brain. This is consistent with the findings of Walton,⁴⁰ who reported that aluminum disrupts the

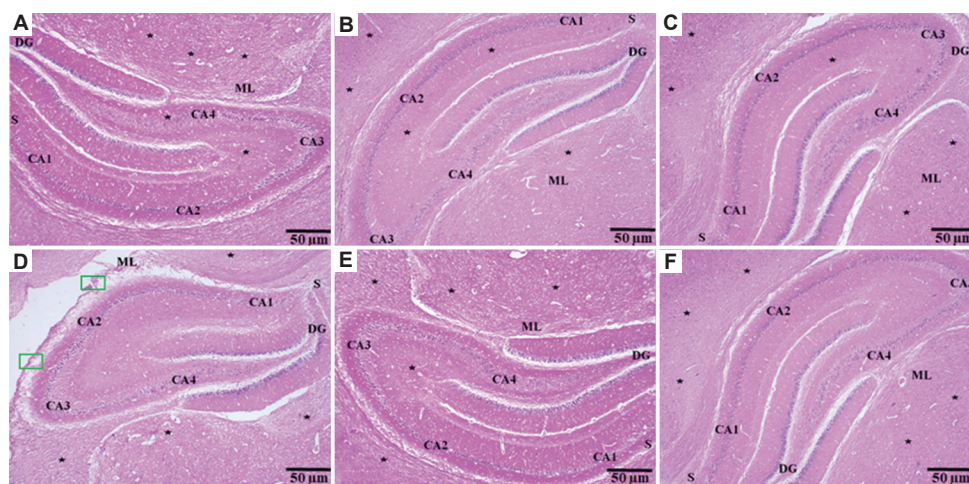


Figure 6. Hematoxylin and eosin staining micrographs of different areas of the hippocampal formation across groups. (A) Control. (B) 0.5 mL LAB-treated group. (C) 1.0 mL LAB-treated group. (D) AlCl_3 -treated group. (E) AlCl_3 + 0.5 mL LAB-treated group. (F) AlCl_3 + 1.0 mL LAB-treated group. CA1–CA4, subiculum (S), dentate gyrus (DG), and marginal layer (ML) are indicated. Green boxes indicate histological alterations. Scale bars: 50 μm ; magnifications: $\times 40$. Abbreviations: LAB: Lactic acid bacteria; AlCl_3 : Aluminum chloride.

pro-oxidant/antioxidant balance. Interestingly, our data confirm that *L. plantarum* PQ104969 effectively mitigated this damage. Probiotics have been shown to modulate the nuclear factor erythroid 2-related factor 2 (NRF2) signaling pathway, enhancing the production of endogenous antioxidants that neutralize ROS, thereby preventing the degradation of polyunsaturated fatty acids in the neuronal membranes. An interesting observation in this study was the non-significant but slight elevation of cerebral MDA levels in rats treated with *L. plantarum* alone compared to the saline control. While probiotics are generally regarded as antioxidants, the introduction of exogenous live bacteria into the gastrointestinal tract can initially trigger a mild, transient oxidative response. This phenomenon, often referred to as hormesis, suggests that a low-level oxidative challenge is necessary to activate the host's endogenous antioxidant defense pathways, such as the NRF2–Kelch-like ECH-associated protein 1 (Keap1) signaling pathway. Therefore, the basal increase in MDA level observed in the LAB-only groups potentially represents a physiological adaptation or “priming” of the immune–metabolic axis rather than neurotoxicity, distinguishing it from the pathological oxidative damage induced by AlCl_3 .

Nitrite (NO_2^-) is a marker of oxidative stress. The result obtained in the biochemical assay of the inflamed brain tissues demonstrated the onset of inflammation, which was indicated by the increase in the nitrite level of AlCl_3 -treated rats. AlCl_3 induced the chronic inflammation of the glial cells in the brain, resulting in lysis, and some of the neural contents induced oxidative stress, which the biochemical assay of the nitrite was trying to fight against compared to the control. The AlCl_3 + LAB-treated rats had significantly lowered nitrite levels compared to the AlCl_3 -treated group, indicating that, as much as AlCl_3 could have induced chronic inflammation in the brain tissue, the probiotics *L. plantarum* were able to effectively mitigate neuroinflammation, attenuating brain inflammatory changes and nitrosative damage triggered by chronic AlCl_3 ingestion. This indicates that LAB possesses a potential preventative quality and may be an effective treatment option with regard to adjacent neuroinflammation. This finding agrees with the other literature that demonstrates reduced nitric oxide generation and protein nitration mediated by activated microglia under neuroinflammatory conditions through probiotic strains.⁴¹

MPO is one of such enzymes and is mainly secreted by neutrophils.⁴² High levels of serum MPO have been linked with inflammation and oxidative damage.⁴³ The findings indicate that AlCl_3 induced a significantly higher MPO activity than the control group. These MPO elevations were reversed in a potentially dose-dependent manner with *L. plantarum*

during treatment, indicating the antioxidant and anti-inflammatory activity of LAB. LAB potentially maintains the viability of neurons by modifying the phenotype of the microglia, glutamate dysregulation, and cytokine signaling, all of which should be further considered at the level of the mechanism of action.⁴⁴ The high levels of MPO observed in the AlCl_3 group denote high-level neuroinflammation, potentially through the microglia pro-inflammatory cascades that have been identified to disrupt the health of neurons following exposure to AlCl_3 .⁴⁰ A positive feedback in such neurotoxicity is mediated by cascading ROS and glutamate excitotoxicity.⁴⁵ The neuroinflammatory response is well reflected using MPO activity, and thus, it has become a useful investigational biomarker. The treatment with *L. plantarum* (LAB) was able to reduce the effects of AlCl_3 , probably through the microglia shift toward anti-cytotoxic phenotypes and the influence on the signaling environment that helps avoid oxidative harm. Nonetheless, the specific mechanisms still need full elucidation, but align with the growing recognition of LAB's neuroprotective capacities. The MPO differences between 0.5 mL and 1.0 mL LAB-only groups suggest an optimal effect within this dosage range. Further histological, behavioral, and dosage testing could provide clarification on potential therapeutic optimization toward clinical translation. Notably, very high LAB levels risk potential microglia over-activation.⁴⁶

The nitrate (NO_3^-) assay suggests the occurrence of neuroinflammation in rats treated with AlCl_3 , evidenced by a significant increase in nitrate level compared to the control group. However, a significant decrease in nitrate level was observed in the group treated with AlCl_3 + 0.5 mL LAB, indicating the ability of AlCl_3 to induce inflammation and the antioxidant potential of *L. plantarum* to reduce oxidative stress. This is consistent with the findings by Fatima and Tabassum,⁴⁷ who reported increased nitric oxide levels and oxidative stress in the brains of rats exposed to AlCl_3 , and that *Salvia officinalis* supplementation attenuated AlCl_3 -induced neuroinflammation and oxidative stress in male albino Wistar rats, potentially by modulating inflammatory mediators and enhancing antioxidant defense mechanisms. The group treated with AlCl_3 + 1.0 mL LAB showed no significant difference compared to the AlCl_3 -treated group, suggesting the dose-dependent bidirectional probiotic effects on oxidative stress.⁴⁸

While A β aggregation and BBB integrity were not directly measured in this study, the observed reduction in oxidative stress (MDA) and inflammatory markers (MPO and nitrites) suggests a preserved microenvironment that is typically conducive to BBB stability and reduced amyloidogenic pathways.

The results of total protein concentration indicated that there was no significant difference in protein expression level in the AlCl_3 -treated group compared to the control group. This is contrary to previous research by Omayone and Ogaji⁴⁹ and Attia *et al.*⁵⁰ This indicated an increase in protein concentration as a result of inflammation. According to Dey and Singh,⁵¹ prolonged exposure to aluminum leads to its buildup in the brain; therefore, they conducted a long-term (24 weeks) study. The relative stability of total protein concentrations across all experimental groups in the current study indicates that neither AlCl_3 administration nor *L. plantarum* treatment caused massive, non-specific protein degradation or total tissue atrophy within 21 days. This stability is significant as it validates the use of total protein as a reliable and consistent reference for the normalization of oxidative and inflammatory markers. It further ensures that the significant shifts observed in MPO and nitrite levels are specifically due to the biochemical impact of the treatments on those pathways rather than a general loss of cellular protein mass.

From the present study, the extensive neurodegeneration induced by AlCl_3 aligns with evidence that aluminum disrupts calcium signaling, triggers inflammation, affects amyloid processing, hyperphosphorylates tau, disrupts neurotrophic pathways, and generates free radicals, leading to neuronal damage.^{52,53} Several recent reports suggest that probiotics such as *L. plantarum* counteract aluminum-mediated neurotoxicity.⁵⁴ Proposed mechanisms include antioxidative activity, regulation of neurotransmitters, immunomodulation, maintenance of gut-brain interactions, and suppression of cell death pathways.⁵⁵ However, variations across studies highlight the need to optimize probiotic selection, dosage, duration, and delivery method to maximize neuroprotection.^{56,57}

The histological results of this study indicate that AlCl_3 causes profound neurodegenerative effects in the hippocampus, especially the CA areas, dentate gyrus, and subiculum. This aligns with the earlier evidence suggesting that AlCl_3 can induce oxidative stress, neuroinflammation, and mitochondrial dysfunction that contribute to the damage of the hippocampus and memory impairment.^{58,59} The AlCl_3 -treated group showed classic signs of neuronal damage, such as disorganization of neurons, demonstrating the neurotoxic potential of aluminum. These findings are similar to the reports by Zhao *et al.*⁶⁰ that found aluminum-induced cytoskeletal damage and glia in hippocampal subfields. By contrast, in AlCl_3 + LAB-treated groups (0.5 mL and 1.0 mL), these histological abnormalities were ameliorated. LAB resulted in restored

neuronal morphology and seemingly decreased gliosis in the hippocampus, even with a high dose given. Such neuroprotection is attributable to the antioxidant, anti-inflammatory, and gut-brain modulating effects of LAB. These observations are aligned with recent studies, such as that by Huang *et al.*,⁶¹ showing that LAB alleviates cognitive impairment and hippocampal damage in mouse models of Alzheimer's disease by inhibiting neuroinflammation and reducing levels of oxidative stress. Likewise, Choi *et al.*⁶² demonstrated LAB-regulated microglial activation and induced neurotrophic factors, such as brain-derived neurotrophic factor, which is critical to neuronal survival and the formation of synapses.

A limitation of the current study is the absence of behavioral assessments to correlate histological damage with functional cognitive deficit. However, the significant neurodegeneration observed in the AlCl_3 -treated group's hippocampus is a well-established anatomical substrate for memory impairments reported in similar models.³ Furthermore, while our biochemical findings regarding MPO and nitrite levels indicate a clear anti-inflammatory effect of *L. plantarum*, the study did not include immunohistochemical staining for ionized calcium-binding adapter molecule 1 or cluster of differentiation 68. The absence of these markers is a limitation, as direct visualization and quantification of microglial activation would have provided a more granular understanding of the neuroinflammatory milieu and the specific glial responses modulated by the probiotic intervention.⁶⁰ Future studies incorporating both behavioral and immunohistochemical analyses are warranted to fully elucidate the phenotypic and cellular shifts induced by LAB treatment.

5. Conclusion

This study demonstrates that *L. plantarum* PQ104969 exerts significant neuroprotective effects against AlCl_3 -induced toxicity in Wistar rats. Following AlCl_3 application, LAB treatment resulted in a marked reduction in the levels of MDA, MPO, nitrites, and nitrates (except for the nitrate level in Group F), which were significantly elevated in the AlCl_3 -treated group. These biochemical improvements were directly supported by histological observations, which showed that LAB treatment preserved the neuronal architecture of the hippocampus, preventing the extensive neurodegeneration seen in the AlCl_3 -treated group. Overall, the findings indicate that *L. plantarum* PQ104969 effectively mitigates the oxidative and inflammatory damage associated with aluminum exposure, suggesting its potential as a protective agent against neurotoxic insults. Further studies are required to evaluate its long-term efficacy and behavioral impact.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Ethical approval was obtained from the Centre for Research and Development (CERAD) of The Federal University of Technology, Akure (FUTA/ETH/24/138).

Consent for publication

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Further disclosure

Not applicable.

References

- Shaw CA, Tomljenovic L. Aluminum in the central nervous system (CNS): Toxicity in humans and animals, vaccine adjuvants, and autoimmunity. *Immunol Res*. 2013;56(2-3):304-316.
doi: 10.1007/s12026-013-8403-1
- Lukiw WJ, Kruck TP, Percy ME, *et al*. Aluminum in neurological disease - a 36 year multicenter study. *J Alzheimers Dis Parkinsonism*. 2019;8(6):457.
doi: 10.4172/2161-0460.1000457
- Kumar V, Gill KD. Aluminium neurotoxicity: Neurobehavioural and oxidative aspects. *Arch Toxicol*. 2009;83(11):965-978.
doi: 10.1007/s00204-009-0455-6
- Simpson DS, Oliver PL. ROS generation in microglia: Understanding oxidative stress and inflammation in neurodegenerative disease. *Antioxidants (Basel)*. 2020;9(8):743.
doi: 10.3390/antiox9080743
- Bondy SC. Prolonged exposure to low levels of aluminium leads to changes associated with brain aging and neurodegeneration. *Toxicology*. 2014;315:1-7.
doi: 10.1016/j.tox.2013.10.008
- Maksoud HA, Said AM, Abdeldaiem MA, Hassan MA. Aluminium chloride induced inflammatory process in rat's brain. *Scholars Int J Biochem*. 2020;3(10):1-4.
doi: 10.36348/sijb.2020.v03i10.00X
- Zhu X, Hao W, Liu Z, *et al*. Aluminium induces neuroinflammation via P2X7 receptor activating NLRP3 inflammasome pathway. *Ecotoxicol Environ Saf*. 2023;249:114373.
doi: 10.1016/j.ecoenv.2022.114373
- Huat TJ, Camats-Perna J, Newcombe EA, Valmas N, Kitazawa M, Medeiros R. Metal toxicity links to Alzheimer's disease and neuroinflammation. *J Mol Biol*. 2019;431:1843-1868.
doi: 10.1016/j.jmb.2019.01.018
- Cheng XJ, Gu JX, Pang YP, *et al*. Tacrine-hydrogen sulfide donor hybrid ameliorates cognitive impairment in the aluminium chloride mouse model of Alzheimer's disease. *ACS Chem Neurosci*. 2019;10(8):3500-3509.
doi: 10.1021/acscchemneuro.9b00120
- Antonelli M, Kushner I. It's time to redefine inflammation. *FASEB J*. 2017;31(5):1787-1791.
doi: 10.1096/fj.201601326R
- Mariotti A. A primer on inflammation. *Compend Contin Educ Dent*. 2004;25(7):7-15.
- Cavaliere G, Traina G. Neuroinflammation in the brain and role of intestinal microbiota: An overview of the players. *J Integr Neurosci*. 2023;22(6):148.
doi: 10.31083/j.jin2206148
- Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. *Nat Rev Immunol*. 2014;14(7):463-477.
doi: 10.1038/nri3705
- Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: The roles of microglia and astrocytes. *Transl*

- Neurodegener.* 2020;9:42.
doi: 10.1186/s40035-020-00221-2
15. Gorji A. Neuroinflammation: The pathogenic mechanism of neurological disorders. *Int J Mol Sci.* 2022;23(10):5744.
doi: 10.3390/ijms23105744
 16. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science.* 2012;336(6086):1268-1273.
doi: 10.1126/science.122349
 17. Braniste V, Al-Asmakh M, Kowal C, *et al.* The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med.* 2014;6(263):158-158.
doi: 10.1126/scitranslmed.3009759
 18. Kamsan N, Mohammad NR. *The Prevalence of Lactic Acid Bacteria as Probiotic in Malaysian Fermented Food Products: A Review.* Virtual. Paper Presented at Inaugural Symposium of Research and Innovation for Food; 2021. p. 54-57. Available from: <https://ir.uitm.edu.my/id/eprint/57210>
 19. Abd Mutalib N, Syed Mohamad SA, Jusril NA, Hasbullah NI, Mohd Amin MC, Ismail NH. Lactic acid bacteria (LAB) and neuroprotection, what is new? An up-to-date systematic review. *Pharmaceuticals (Basel).* 2023;16(5):712.
doi: 10.3390/ph16050712
 20. Bhatia R, Sharma S, Bhadada SK, Bishnoi M, Kondepudi KK. Lactic acid bacterial supplementation ameliorated the lipopolysaccharide-induced gut inflammation and dysbiosis in mice. *Front Microbiol.* 2022;13:930928.
doi: 10.3389/fmicb.2022.930928
 21. Shukla PK, Meena AS, Rao R. Prevention and mitigation of alcohol-induced neuroinflammation by *Lactobacillus plantarum* by an EGF receptor-dependent mechanism. *Nutr Neurosci.* 2022;25(4):871-883.
doi: 10.1080/1028415X.2020.1819105
 22. Wu Y, Wang Y, Hu A, *et al.* *Lactobacillus plantarum*-derived postbiotics prevent *Salmonella*-induced neurological dysfunctions by modulating gut-brain axis in mice. *Front Nutr.* 2022;9:946096.
doi: 10.3389/fnut.2022.94609
 23. Bamigbade BO, Oladejo BO, Omayone TP. Assessment of lactic acid bacteria treatments on some biochemical indices associated with ulcerative colitis induced in wistar rats. *Niger J Microbiol.* 2024;38(2):7243-7249.
 24. National Research Council. *Guide to the Care and Use of Laboratory Animals.* 8th ed.: Washington, DC: The National Academies Press; 2011. p. 246.
 25. Akinrinade ID, Memudu AE, Ogundele OM. Fluoride and aluminium disturb neuronal morphology, transport functions, cholinesterase, lysosomal and cell cycle activities. *Pathophysiology.* 2015;22(2):105-115.
doi: 10.1016/j.pathophys.2015.03.001
 26. Ahmed GA, Khalil SK, Abbas L, *et al.* ATR-IR and EPR spectroscopy for detecting the alterations in cortical synaptosomes induced by aluminium stress. *Spectrochim Acta Part A Mol Biomol Spectrosc.* 2020;228:117535.
doi: 10.1016/j.saa.2019.117535
 27. Chiroma SM, Moklas, MA, Taib CN, Baharuldin MT, Amon Z. D-galactose and aluminium chloride induced rat model with cognitive impairments. *Biomed Pharmacother.* 2018;103:1602-1608.
doi: 10.1016/j.biopha.2018.04.152
 28. Avwioro G. Histochemical uses of haematoxylin-a review. *JPCS.* 2011;1(5):24-34.
 29. Varshney R, Kale RK. Effects of calmodulin antagonists on radiation-induced lipid peroxidation in microsomes. *Int J Radiat Biol.* 1990;58(5):733-743.
doi: 10.1080/09553009014552121
 30. Adam-Vizi V, Seregi M. Receptor independent stimulatory effect of noradrenaline on Na,K-ATPase in rat brain homogenate. Role of Lipid Peroxidation. *Biochem Pharmacol.* 1982;31:2231-2236.
doi: 10.1016/0006-2952(82)90106-x
 31. Ignarro LJ, Byrns RE, Buga GM, Wood KS. Endothelium-derived relaxing factor from pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical. *Circ Res.* 1987;61(6):866-879.
doi: 10.1161/01.res.61.6.866
 32. Granger DL, Taintor RR, Boockvar KS, Hibbs JB Jr. Measurement of nitrate and nitrite in biological samples using nitrate reductase and Griess reaction. *Methods Enzymol.* 1996;268:142-151.
doi: 10.1016/s0076-6879(96)68016-1
 33. Kim Y, Yoon S, Kim SJ, Kim JS, Cheong JW, Min YH. Myeloperoxidase expression in acute myeloid leukemia helps identifying patients to benefit from transplant. *Yonsei Med J.* 2012;53(3):530-536.
doi: 10.3349/ymj.2012.53.3.530
 34. Cataldo DA, Maroon M, Schrader LE, Youngs VL. Rapid colorimetric determination of nitrate in plant tissue by nitration of salicylic acid. *Commun Soil Sci Plant Anal.* 1975;6(1):71-80.
doi: 10.1080/00103627509366547
 35. Gornal AC, Bardawill CJ, David MM. Determination of serum proteins by means of the biuret reaction. *J Biol Chem.* 1949;177(2):751-766.
 36. Ransohoff RM, Brown MA. Innate immunity in the central nervous system. *J Clin Invest.* 2012;122(4):1164-1171.

- doi: 10.1172/JCI58644
37. Subhramanyam CS, Wang C, Hu Q, Dheen ST. Microglia-mediated neuroinflammation in neurodegenerative diseases. *Semin Cell Dev Biol.* 2019;94:112-120.
doi: 10.1016/j.semcdb.2019.05.004
 38. Ransohoff RM, Cardona AE. The myeloid cells of the central nervous system parenchyma. *Nature.* 2010;468(7321):253-262.
doi: 10.1038/nature09615
 39. Winiarska-Mieczan A, Kwiecień M, Jachimowicz-Rogowska K, Donaldson J, Tomaszewska E, Baranowska-Wójcik E. Anti-inflammatory, antioxidant, and neuroprotective effects of polyphenols-polyphenols as an element of diet therapy in depressive disorders. *Int J Mol Sci.* 2023;24(3):2258.
doi: 10.3390/ijms24032258
 40. Walton JR. Functional impairment in aged rats chronically exposed to human range dietary aluminum equivalents. *Neurotoxicology.* 2009;30(2):182-193.
doi: 10.1016/j.neuro.2008.11.012
 41. Soheili M, Alinaghipour A, Salami M. Good bacteria, oxidative stress and neurological disorders: Possible therapeutical considerations. *Life Sci.* 2022;301:120605.
doi: 10.1016/j.lfs.2022.120605
 42. Hoffmann A, Pfeil J, Mueller AK, et al. MRI of iron oxide nanoparticles and myeloperoxidase activity links inflammation to brain edema in experimental cerebral malaria. *Radiology.* 2019;290(2):359-367.
doi: 10.1148/radiol.2018181051
 43. Davies MJ, Hawkins CL. The role of myeloperoxidase in biomolecule modification, chronic inflammation, and disease. *Antioxid Redox Signal.* 2020;32(13):957-981.
doi: 10.1089/ars.2020.8030
 44. Li B, He Y, Ma J, et al. Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. *Alzheimers Dementia.* 2019;15(10):1357-1366.
doi: 10.1016/j.jalz.2019.07.002
 45. Exley C, Mamutse G, Korchazhkina O, et al. Elevated urinary excretion of aluminium and iron in multiple sclerosis. *Mult Scler.* 2006;12(5):533-540.
doi: 10.1177/1352458506071323
 46. Lavasani S, Dzhambazov B, Nouri M, et al. A novel probiotic mixture exerts a therapeutic effect on experimental autoimmune encephalomyelitis mediated by IL-10-producing regulatory T cells. *PLoS One.* 2010;5(2):e9009.
doi: 10.1371/journal.pone.0009009
 47. Fatima N, Tabassum A. Effect of *Salvia officinalis* on neuromodulating and oxidative stress status in brain of male albino Wistar rats intoxicated with aluminium. *ACTA Pharma Sci.* 2020;58(3):277.
doi: 10.23893/1307-2080.APS.05816
 48. Sun W, Zhu J, Qin G, et al. *Lonicera japonica* polysaccharides alleviate D-galactose-induced oxidative stress and restore gut microbiota in icr mice. *Int J Biol Macromol.* 2023;245:125517.
doi: 10.1016/j.ijbiomac.2023.125517
 49. Omayone TP, Ogaji IP. Methyl jasmonate ameliorates liver oxidative stress associated with acetic acid-induced ulcerative colitis in wistar rats. *J Biomed Biosens.* 2023;3(2):19-28.
doi: 10.58613/jbb322
 50. Attia H, Albuhayri S, Alaraidh S, et al. Biotin, coenzyme Q10, and their combination ameliorate aluminium chloride-induced Alzheimer's disease via attenuating neuroinflammation and improving brain insulin signaling. *J Biochem Mol Toxicol.* 2020;34(9):22519.
doi: 10.1002/jbt.22519
 51. Dey M, Singh RK. Chronic oral exposure of aluminum chloride in rat modulates molecular and functional neurotoxic markers relevant to Alzheimer's disease. *Toxicol Mech Methods.* 2022;32(8):616-627.
doi: 10.1080/15376516.2022.2058898
 52. Bondy SC. The neurotoxicity of environmental aluminium is still an issue. *Neurotoxicology.* 2010;31(5):575-581.
doi: 10.1016/j.neuro.2010.05.009
 53. Exley C. Why industry propaganda and political interference cannot disguise the inevitable role played by human exposure to aluminum in neurodegenerative diseases, including Alzheimer's disease. *Front Neurol.* 2014;5:212.
doi: 10.3389/fneur.2014.00212
 54. Abd-Elghaffar SK, El-Sokkary GH, Sharkawy AA. Aluminum-induced neurotoxicity and oxidative damage in rabbits: Protective effect of melatonin. *Neuroendocrinol Lett.* 2005;26(5):609-616.
 55. Hu J, Li Y, Pakpour S, et al. Dose effects of orally administered Spirulina suspension on colonic microbiota in healthy mice. *Front Cell Infect Microbiol.* 2019;9:243.
doi: 10.3389/fcimb.2019.00243
 56. Bonfili L, Cecarini V, Berardi S, et al. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. *Sci Rep.* 2017;7(1):2426.
doi: 10.1038/s41598-017-02587-2
 57. Athari Nik Azm S, Djazayeri A, Safa M, et al. Lactobacilli and bifidobacteria ameliorate memory and learning deficits and oxidative stress in β -amyloid (1-42) injected rats. *Appl Physiol Nutr Metab.* 2018;43(7):718-726.
doi: 10.1139/apnm-2017-0648

58. Ahmed MA, El Morsy EM, Ahmed AA. Neuroprotective effects of antioxidants against aluminum-induced neurotoxicity in rats. *NeuroToxicology*. 2021;83:61-71.
doi: 10.3390/ph15081008
59. Shahani L, Rathore N, Patel T. Aluminium-induced neurotoxicity: A review. *Bull Env Pharmacol Life Sci*. 2020;9(3):63-71.
60. Zhao Y, Dang M, Zhang W, *et al*. Neuroprotective effects of Syringic acid against aluminium chloride induced oxidative stress mediated neuroinflammation in rat model of Alzheimer's disease. *J Funct Foods*. 2020;71:104009.
doi: 10.1016/j.jff.2020.104009
61. Huang HJ, Chen JL, Liao JF, *et al*. *Lactobacillus plantarum* PS128 prevents cognitive dysfunction in Alzheimer's disease mice by modulating propionic acid levels, glycogen synthase kinase 3 beta activity, and gliosis. *BMC Complement Med Ther*. 2021;21(1):259.
doi: 10.1186/s12906-021-03426-8
62. Choi J, Hur TY, Lee KW. Neuroprotective properties of *Lactobacillus plantarum* in Alzheimer's disease mouse model: Attenuation of neuroinflammation and amyloid-beta. *Nutrients*. 2020;12(11):3252.