Article | Received 2 July 2026; Revised 13 September 2026; Accepted 9 November 2026; Published XX November 2026
https://doi.org/10.55092/bm202600XX

Poly(ginger oil) organoparticles as a promising neuroprotective agent: *in vivo* evidence from an aluminum chloride-induced neurodegenerative model in rat

Duygu Alpaslan[1,*], Abdullah Turan[2], Seyma Arvas[3], Tuba Ersen Dudu[1] and Nahit Aktas[1]

[1] Van Yüzüncü Yıl University, Department of Chemical Engineering, Institute of Natural and Applied Science, Van, Turkey
[2] Van Yüzüncü Yıl University, Science Faculty, Department of Molecular Biologyand Genetic, Van, Turkey
[3] Van Yüzüncü Yıl University, Vocational School of Health Care, Van, Turkey

* Correspondence author; E-mail: alpaslanduygu@yyu.edu.tr.

Highlights:

- Synthesized poly(ginger oil) anti-Alzheimers potential was evaluated.
- Organ oxidative enzymes and brain ADA, MPO, TAS, TOS, and OSI were analyzed.
- Poly(gingerol)-organoparticles may advance biomedical and pharmaceutical applications.

Abstract: Neurodegenerative diseases are among the most common neurological disorders observed in society. Although it is well known that metals can exert neurotoxic effects, aluminum has been reported to be one of the significant contributors and major risk factors in the development of neurodegeneration. Since the molecular mechanisms, pathophysiology, and genetic background of neurodegenerative diseases have not been fully elucidated, there is still no effective treatment available. Therefore, the aim of this study was to investigate the protective effect of poly(ginger oil) (p(GgO)) particles against neurodegeneration. An *in vivo* neurodegenerative model was established using aluminum chloride ($AlCl_3$). Biochemical and histopathological evaluations were performed on rats induced as an experimental neurodegeneration model. The application of p(GgO) particles demonstrated preventive and curative effects at different levels in terms of oxidative stress and various parameters. p(GgO) particle administration provided both protection and recovery from oxidative damage caused by $AlCl_3$ toxicity *in vivo*. The findings of this study are thought to contribute to the development of potential therapeutic agents that exert protective and restorative effects of p(GgO) particles against $AlCl_3$-induced oxidative stress, neurodegeneration, and cognitive impairment. The present study aimed to test the hypothesis that p(GgO) particles attenuate $AlCl_3$-associated oxidative imbalance by modulating endogenous antioxidant defenses and reducing oxidative damage, with concomitant improvement in behavioral performance. To address this hypothesis, an $AlCl_3$-induced neurodegenerative model was evaluated in rat using behavioral assessments together with biochemical measurements of oxidative damage, antioxidant defense, and tissue-specific redox status.

Copyright©2026 by the authors. Published by ELSP. This work is licensed under Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

Keywords: neurodegeneration; Alzheimer; organoparticle; poly(ginger Oil)

1. Introduction

Neurodegenerative diseases are a group of progressive disorders that impair neuronal structure and function over time, leading to varying degrees of cognitive, behavioral, and motor dysfunction. Dementia is a major clinical consequence of these disorders and is characterized by a progressive decline in memory and other cognitive abilities, including language, reasoning, and executive function [1–3]. Among the different causes of dementia, Alzheimer's disease (AD) is the most prevalent, accounting for approximately 60%–80% of diagnosed cases. The pathological changes associated with AD can develop years before clinical symptoms become apparent. These changes include the accumulation of β-amyloid plaques and neurofibrillary tangles, which are widely recognized as characteristic neuropathological features of the disease [1,4]. However, AD is not driven by a single pathological mechanism. Oxidative stress, neuroinflammation, mitochondrial dysfunction, impaired neurotransmission, neuronal apoptosis, and other molecular disturbances contribute to disease progression alongside amyloid and tau pathology [1,4]. Nevertheless, AD development and progression involve multiple interacting pathological mechanisms rather than a single underlying process.

Several pharmacological agents, such as tacrine, donepezil, rivastigmine, and memantine, have been used in the treatment of AD [3,5–7]. Acrine, donepezil, and rivastigmine act primarily by inhibiting acetylcholinesterase and thereby enhancing cholinergic neurotransmission, whereas memantine exerts its effects through modulation of glutamatergic signaling. These medications may improve certain symptoms, but their ability to halt or reverse the underlying neurodegenerative changes remains limited. The search for effective disease-modifying approaches therefore continues to be an important area of research [3,5–7]. In this context, medicinal plants, essential oils, and other natural products have attracted interest as potential sources of bioactive compounds for neurodegenerative disease research [8–10].

Plants have been used in traditional medicine for centuries to address neurological and cognitive complaints. This interest has also extended to developed countries, where the use of complementary and alternative medicine has become increasingly common [7]. Herbals and essential oils have attracted particular scientific interest because they contain complex mixtures of volatile compounds, including terpenes and other secondary metabolites, with reported antioxidant, anti-inflammatory, neuromodulatory, and behavioral effects [11–13]. Nevertheless, the biological activity of herbs and essential oils depends strongly on their chemical composition, concentration, route of administration, [14] and experimental model. Therefore, evidence obtained from different plant species or different preparations cannot necessarily be considered equivalent.

Ethnopharmacological and experimental studies have identified numerous medicinal plants with potential effects on memory impairment, dementia, AD, and cholinergic dysfunction [12,15]. Supplementary Table S1 presents the plants reported to have anticholinesterase and memory-related effects. Reported memory-related or neuroprotective activities include those of *Valeriana officinalis L.*, *Abrus precatorius L.*, *Musa sapientum L.*, *Spondias mombin L.*, *Bryophyllum pinnatum L.*, *Dioscorea mangenotiana J. Miege*, *Centella asiatica (L.) Urb.*, *Convolvulus pluricaulis*, *Evolvulus alsinoides L.*, *Ficus exasperata Vahl.*, *Ficus racemosa*, *Jatropha curcas L.*, *Myristica fragrans Houtt.*, *Tinospora cordifolia*, *and Salvia officinalis L.* [16–34]. Other medicinal plants, *including Ocimum basilicum L.*, *Cissampelos pareira*, *Juglans regia L.*, *Cuminum cyminum L.*, *Crocus sativus*, *Melissa officinalis L.*,

Rosmarinus officinalis L., *Piper nigrum L.*, *Ginkgo biloba L.*, *Panax ginseng*, *and Emblica officinalis Gaertn.*, have also been investigated in relation to Alzheimer's disease, dementia1 [35–40], and cognitive function [41–47].

In addition to their reported effects on memory and cognition, numerous plant-derived preparations have been investigated for acetylcholinesterase inhibitory activity. These include *Brassica alba* (L.) *Rabenh., Brassica nigra* (L.) W. D. J. Koch., *Bacopa monnieri*, *Camellia sinensis* (L.) Kuntze., *Celastrus paniculatus*, *Cinchona officinalis L.*, *Citrus aurantifolia L.*, *Commiphora whighitti*, *Coriandrum sativum L.*, *Curcuma longa*, *Evolvulus alsinoides*, *Ferula assafoetida L.*, *Glycyrrhiza glabra*, *Humulus lupulus L.*, *Juglans regia L.*, *Juniperus sabina L.*, *Ilex paraguariensis*, *Lepidium meyenii*, *Moringa oleifera*, *Myristica fragrans*, *Magnolia officinalis*, *Nardostachys jatamansi*, *Panax ginseng*, *Punica granatum L.*, *Rheum officinale L.*, *Salix alba L.*, *Zizyphus vulgaris L.*, *Zingiber officinale*, *and Withania* [48–105]. Collectively, these studies demonstrated the broad pharmacological potential of medicinal plants in relation to oxidative stress, cholinergic dysfunction, inflammation, and cognitive impairment given Supplementary Table S1.

Although this broad literature supports the potential of medicinal plants, the reported effects should not be interpreted as evidence of equivalent efficacy among botanical agents. For example, Ginkgo biloba has been extensively investigated in relation to cognitive impairment and dementia; Panax ginseng has been associated with antioxidant, anti-inflammatory, and cognition-related effects, and Rosmarinus officinalis has been investigated for its antioxidant [44–47] and neuroprotective properties [91–94]. These plants therefore provide important comparative examples of the neuroprotective potential of medicinal botanicals. However, differences in plant composition, extraction method, dose, route of administration, experimental model, and study design make direct comparisons of efficacy difficult. The rationale for investigating ginger in the present study is consequently not that ginger is superior to these established medicinal plants, but that its complex chemical composition and reported biological activities provide a suitable basis for investigating a polymeric ginger-oil formulation under experimentally induced neurotoxic conditions.

Zingiber officinale (ginger) is particularly relevant because its bioactive constituents and preparations have been investigated for antioxidant, anti-inflammatory, anticholinesterase, and neuroprotective activities [97–99,106]. The biological effects of complex essential oils cannot always be attributed to a single major constituent. Instead, the combined contribution of multiple constituents may contribute to the overall biological response, and interactions among these compounds may produce additive or synergistic effects [102–105]. From a formulation perspective, preserving such a complex chemical composition may therefore be desirable when developing delivery systems for natural oils. However, the direct use of hydrophobic and volatile oils is limited by properties such as low aqueous dispersibility, volatility, and susceptibility to environmental degradation.

Several nanocarrier platforms have consequently been investigated to improve the delivery of hydrophobic natural products, including liposomes, nanoemulsions, lipid-based nanoparticles, and polymeric nanoparticles. Liposomes are versatile phospholipid-based systems capable of incorporating both hydrophilic and hydrophobic compounds and have been widely investigated because of their biocompatibility and formulation flexibility. Nevertheless, conventional liposomes may be affected by premature leakage, membrane instability, and storage-related changes that can influence formulation performance [14,106–108]. Nanoemulsions can improve the aqueous dispersion of hydrophobic

compounds through their small droplet size and large interfacial area and are therefore attractive for essential-oil delivery. However, they remain kinetically stabilized colloidal systems whose physical stability depends on factors such as oil composition, surfactant concentration, interfacial characteristics, temperature, and storage conditions.

Polymeric nanoparticles offer another way of incorporating bioactive compounds into drug delivery systems. In these formulations, the active compounds may be entrapped within a polymeric matrix or associated with its surface. This approach can be useful for volatile or oxidation-sensitive compounds, as the polymeric structure may help protect them from degradation and influence their retention and release. The properties of the resulting particles depend on several factors, including particle size, surface characteristics, polymer composition, and the conditions used during preparation. These factors may also affect how the particles interact with biological systems. For essential oils, polymeric encapsulation has been explored to improve their protection against degradation, dispersibility, formulation stability, and the availability of their bioactive constituents [106–108]. However, the use of polymeric organoparticles should not be interpreted as evidence that they are universally superior to liposomes or nanoemulsions. Rather, they represent a different formulation approach, which may offer particular advantages when working with complex, hydrophobic, and volatile natural oils [107,108].

The physicochemical properties of ginger oil provide a rationale for investigating polymer-associated particulate formulations. Its hydrophobic nature, volatility, limited aqueous dispersibility, and susceptibility to oxidation may present challenges for direct biological administration. Incorporating ginger oil into a polymer-associated particulate structure may alter the formulation environment and influence the interactions between oil-derived constituents and the surrounding biological milieu. Emulsion polymerization offers a practical approach for preparing polymeric particles in the presence of an oil phase, while the synthesis conditions can affect the properties of the resulting particles. From this perspective, p(GgO) organoparticles provides a formulation platform for investigating the biological effects of ginger oil while addressing some of the physicochemical challenges associated with hydrophobic natural oils.

However, the potential formulation-related benefits of p(GgO) should be distinguished from properties that have been experimentally demonstrated. The present study was not designed to determine encapsulation efficiency, release kinetics, bioavailability, blood–brain barrier (BBB) penetration, or brain biodistribution. Accordingly, enhanced bioavailability, sustained release, and targeted delivery cannot be inferred from the use of a polymer-associated particulate system alone. These parameters require dedicated formulation, pharmacokinetic, biodistribution, and *in vitro* or *in vivo* release studies. Such investigations would be necessary to establish whether p(GgO) offers advantages in these areas. The current study instead focuses on the biological effects of p(GgO) administration in an experimental model of $AlCl_3$-induced neurotoxicity.

Aluminum chloride ($AlCl_3$) is commonly used as an experimental neurotoxicant in studies examining oxidative stress, neuronal dysfunction, and cognitive impairment. Exposure to $AlCl_3$ has been associated with alterations in oxidative balance and antioxidant defense, making this model useful for investigating the potential protective effects of bioactive compounds. Nevertheless, an $AlCl_3$-induced model represents an experimental model of neurotoxicity and neurodegenerative-like changes rather than a complete reproduction of the multifactorial pathology of human Alzheimer's disease. This

distinction is important when interpreting behavioral and biochemical findings obtained from such experimental systems.

Based on this framework, the primary mechanistic question addressed in the present study was whether p(GgO) can attenuate the oxidative imbalance associated with $AlCl_3$-induced experimental neurotoxicity. This focus is supported by the biochemical endpoints evaluated in the study, which included enzymatic and non-enzymatic antioxidant parameters, lipid peroxidation, myeloperoxidase, adenosine deaminase, total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index. These parameters provide complementary information regarding oxidative damage and antioxidant defense across different tissues. Neuroinflammatory and cholinergic mechanisms are also biologically relevant to neurodegenerative disorders; however, inflammatory cytokine profiles, microglial activation, and acetylcholinesterase activity were not comprehensively quantified in the present study. Therefore, these pathways are considered literature-supported possibilities rather than mechanisms directly established by the present experiments.

Importantly, previous experimental studies have directly investigated ginger oil or ginger essential oil in $AlCl_3$-induced rat models of Alzheimer's disease. These studies reported improvements in cognitive performance and cholinergic function, together with changes in oxidative, inflammatory, apoptotic, and histopathological parameters [14,106,109]. These findings provide a direct preclinical rationale for investigating ginger oil as a neuroprotective bioactive agent. However, the use of ginger oil in the previously characterized synthesis of polymeric organoparticles represents a distinct approach that warrants further investigation.

Accordingly, we hypothesized that administration of p(GgO) would attenuate $AlCl_3$-associated oxidative stress by reducing oxidative damage and supporting endogenous antioxidant defense, and that these biochemical changes would be accompanied by improved behavioral performance. The primary objective of the study was therefore to determine the effects of p(GgO) on oxidative and antioxidant parameters in $AlCl_3$-exposed rats. Secondary objectives were to examine tissue-specific responses in the brain, liver, kidney, lung, spleen, heart, and erythrocytes and to determine whether these responses differed between the 5 and 10 mg/kg p(GgO) doses. Behavioral assessments, including the Morris water maze and modified maze tests, were included as functional outcomes to determine whether changes in oxidative status were accompanied by alterations in learning, memory, and related behavioral performance.

Thus, the novelty of the present study lies not in proposing ginger as superior to other medicinal plants, but in investigating a polymeric ginger-oil formulation in an $AlCl_3$-induced rat model using complementary behavioral and multi-tissue biochemical endpoints. The study provides preclinical evidence concerning the oxidative-stress-related neuroprotective potential of p(GgO) and establishes a basis for further mechanistic and formulation studies. Because BBB transport, sustained release, brain distribution, and specific inflammatory or cholinergic signaling pathways were not directly investigated, the present findings should not be extrapolated to clinical efficacy or the treatment of Alzheimer's disease.

2. Material and method

1. Synthesis of p(GgO) particles

Importantly, the p(GgO) organoparticles used in this study were not prepared by loading ginger oil into preformed polymeric particles. Ginger oil was directly used as the oil phase during the emulsion-polymerization process, while EGDMA served as the crosslinking agent and APS and TEMED were used as the initiator and accelerator, respectively. Thus, the particulate structure was generated during polymerization in the presence of ginger oil rather than through a subsequent loading or encapsulation step. Because no defined amount of ginger oil was subsequently loaded into preformed particles and quantified as free *versus* incorporated material, a conventional encapsulation-efficiency calculation was not applicable to this formulation architecture. The p(GgO) organoparticles used in the present study had previously been characterized in terms of particle size, zeta potential, SEM, FTIR, and TGA [108].

p(GgO) organoparticles used in the present study were prepared according to the previously reported emulsion-polymerization procedure developed by our group [108]. The physicochemical characterization of this p(GgO) organoparticles, including particle-size analysis, zeta-potential measurements, scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy (FTIR), and thermogravimetric analysis (TGA), has been reported in detail in our previous publication [108]. Therefore, the present study did not aim to develop or optimize the p(GgO) organoparticles or repeat its physicochemical characterization; rather, the previously established p(GgO) organoparticles was used for the subsequent *in vivo* investigation.

For preparation of the p(GgO) organoparticles, water (2 mL), ethanol (1 mL), and Tween 80 (8 mL) were initially mixed and stirred at 900 rpm for 10 min at room temperature. Ginger oil (0.5 mL) was then added to the mixture at 25 °C. Subsequently, 10 wt% ethylene glycol dimethacrylate (EGDMA) as the crosslinking agent, N, N, N′, N′-tetramethylethylenediamine (TEMED; 10 µL) as the accelerator, and ammonium persulfate (APS; 100 µL) as the initiator were added, and the mixture was stirred at 1000 rpm. Polymerization was continued for 3 h. The resulting p(GgO) particles were washed with acetone, dried at 40 °C, and stored at 4 °C until further use.

The previously reported characterization study demonstrated the successful formation of the p(GgO) organoparticles and provided their detailed physicochemical properties [108]. Accordingly, characterization data are not repeated in the present manuscript, and reference [108] is provided as the primary source for the physicochemical characterization of the material used in this study.

2. Animal groups

The study aimed to investigate the effects of aluminum chloride ($AlCl_3$) and p(GgO) on experimental subjects over a 52-day period. A total of 54 male Wistar rats (weighing 150–250 g, 3–6 monthly) were selected and divided into groups. The control and $AlCl_3$ groups consisted of 7 rats each, while the remaining groups contained 8 rats per group.

To induce experimental conditions, aluminum chloride was administered intraperitoneally at a dose of 40 mg/kg on the first day. Subsequently, the same dose (40 mg/kg) was given once a week for 30 days to maintain exposure. After the initial 30-day period, treatment with p(GgO) began. The p(GgO)

organoparticles were administered intraperitoneally at doses of either 5 mg/kg or 10 mg/kg per day. This treatment continued for 21 days, except on days when aluminum chloride was administered to prevent potential interactions.

Throughout the entire 52-day study, all subjects were provided with pellet feed and drinking water ad libitum to ensure adequate nutrition and hydration. Environmental conditions, including temperature and humidity, were maintained within standard laboratory parameters to minimize external variability.

Toxicity assessments were conducted following a modified version of the Organization for Economic Cooperation and Development (OECD) guideline 425, ensuring a structured and ethical approach to dose determination. The study groups were carefully designed to align with the research objectives, allowing for a comprehensive evaluation of the effects of aluminum chloride exposure and the potential role of p(GgO).

By the end of the experimental period, biological samples were collected for further biochemical analyses to assess any physiological changes induced by the treatments. The findings from this study are expected to provide into the protective effects of p(GgO) against aluminum chloride toxicity and contribute to the broader understanding of nanomaterials in biomedical applications.

0. Doze group (n = 7) (ad libitum).

I. Control group (n = 7) (ad libitum).

II. Alzheimer's Control group (n = 8) (ad libitum).

III. p(GgO) 5 mg (n = 8) (ad libitum).

IV. Alzheimer-p(GgO) 5 mg (n = 8) (ad libitum).

V. p(GgO) 10 mg (n = 8) (ad libitum).

VI. Alzheimer-p(GgO) 10 mg (n = 8) (ad libitum).

Supernatants from lung, brain, kidney, spleen, erythrocyte, heart, and liver tissues were collected and prepared for biochemical analysis. These samples were used to determine the enzymatic activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione S-transferase (GST), glutathione reductase (GR), and adenosine deaminase (ADA). Additionally, total oxidative status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), myeloperoxidase (MPO), malondialdehyde (MDA), and glutathione (GSH) levels were measured to evaluate oxidative stress and antioxidant defense mechanisms.

3. Morris water tank test

The Morris water tank used was made with a diameter of 155 cm and a depth of 60 cm. The tank was filled with room temperature water up to 30 cm was shown in Figure 1. The water in the tank was colored dark blue with paint to prevent the rat from seeing the platform. The escape platform, with a diameter of 10 cm, was placed in the tank so that it remained 1–2 cm below the water. Nothing was moved in the room during the experiment. It was taken after allowing the animal to spend 60 seconds on the platform. All of the animals were released into the water opposite the quadrant where the platform was previously located and allowed to swim for one minute. The animal's time to find the platform was recorded throughout all trials. Experiments were performed twice a week, on Tuesdays and Thursdays.

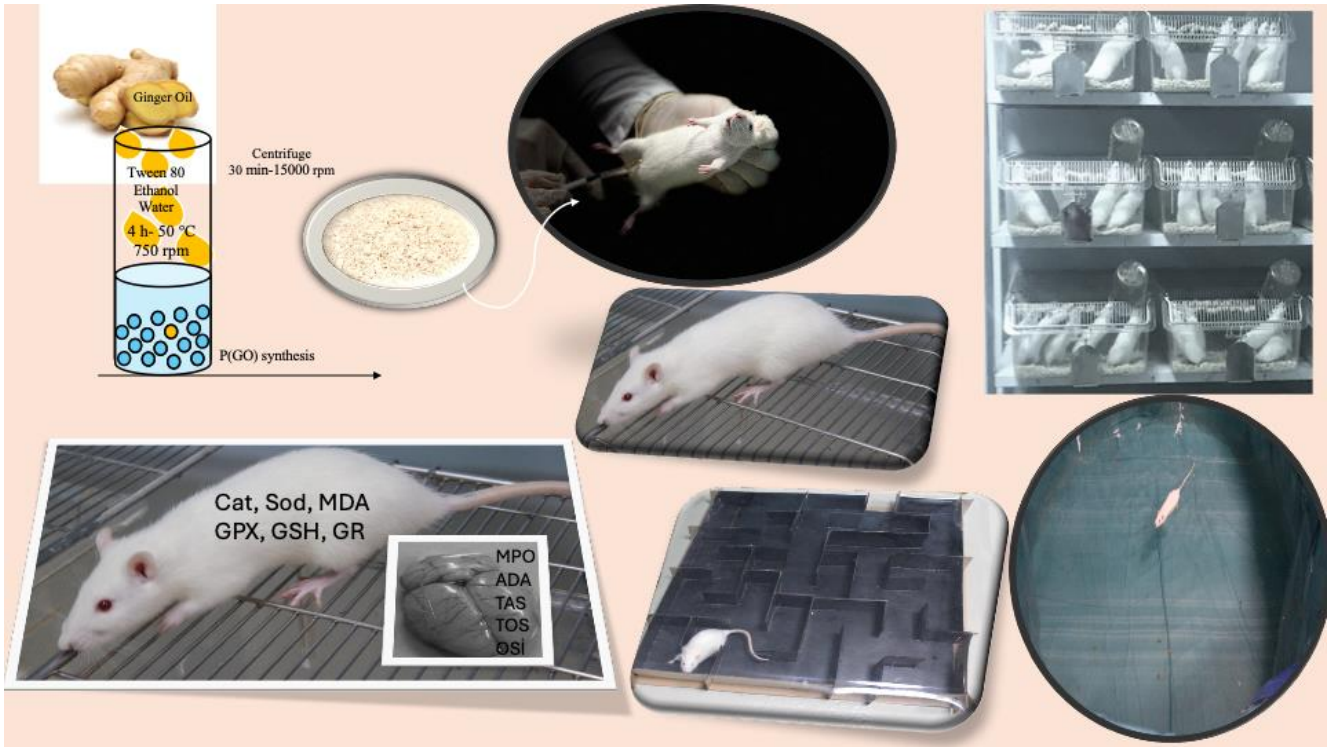


Figure 1. Synthesis of p(GgO) organoparticles, Morris water tank test, and modified Hampton Court Maze test were schematized.

4. Modified Hampton Court Maze test

Modified Hampton Court Maze test: It was built using a maze high above the ground, consisting of a mixed path, surrounded. Rats find the exit by traveling through normal routes was shown in Figure 1. Alzheimer's rats tend to sit in corners and spend a lot of time in the maze, unable to find the exit. The anxiety level of the subject who shows the behavior of knowing the environment and taking the exit in a shorter time on open roads is considered to be low. It allowed the animal to spend 5 minutes in the maze. All of the animals were released where the maze was previously and allowed to be known for 5 minutes. Modified Hampton Court Maze cleaned with %70 ethanol and tap water [110,111].

5. Enzyme analysis

Cat enzyme analysis: In determining catalase activity in seven different tissue homogenates, Turan *et al.* [112] method was used. SOD enzyme analysis:In determining superoxide dismutase activity in seven different tissue homogenates, Turan *et al*. [112] method was used. GST enzyme analysis: In determining Glutathione-S-Transferase activity in seven different tissue homogenates, Turan *et al*. [112] method was used. Reduced GSH analysis: In determining lipid peroxidation in seven different tissue homogenates, Turan *et al*. [112] method was used. GR Enzyme Analysis:In determining Glutathion ereductase in seven different tissue homogenates, Turan *et al*. [112] method was used. Glutathione peroxidase enzyme analysis: In determining Glutathione peroxidase (GSH-Px/GPx) in seven different tissue homogenates, Turan *et al*. [112] method was used. Lipid peroxidation analysis: In determining lipid peroxidation in brain tissue thomogenates, Turan *et al*. [112] method was used. MPO analysis: In determining Myeloperoxidase in brain tissue homogenates, Turan *et al*. [112] method was used. ADA

enzyme analysis: Using the Turan *et al*. [112] approach, the amount of adenosine deaminase in brain tissue homogenates was determined. TOS, TAS oxidative stress index analysis: In determining Total Oxidant Stress in brain tissue homogenates, Erel [113,114], method was used.

6. Statistical analysis

Statistical analysis of data obtained by SPSS® version 21.0 Results are given as mean ± standard deviation. For statistical evaluation, one-way analysis of variance (ANOVA) and post-hoc Duncan's test were used, and the statistical significance level was accepted as $p < 0.05$.

3. Results and discussion

The p(GgO) organoparticles used in the present study were prepared according to the previously established emulsion-polymerization procedure and had been comprehensively characterized in our previous study [108] The reported characterization included particle-size and zeta-potential measurements, scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy (FTIR), and thermogravimetric analysis (TGA). The previously reported p(GgO) particles had a hydrodynamic diameter of approximately 220 nm and a zeta potential of −162.48 mV. TGA analysis further demonstrated their thermal behavior over the investigated temperature range [108]. These previously established physicochemical characteristics provide the basis for identifying the material used in the present biological study as the previously characterized p(GgO) organoparticles. Accordingly, the characterization data are not reproduced here, as they have been reported in detail in our previous publication [108]. The present study focuses on the biological effects of this established p(GgO) organoparticle in an $AlCl_3$-induced experimental model, with particular emphasis on behavioral performance and oxidative/antioxidant responses.

Six experimental groups were included in the study: the control group, Alzheimer group, p(GgO) 5 mg group, p(GgO) 5 mg–Alzheimer group, p(GgO) 10 mg group, and p(GgO) 10 mg–Alzheimer group. The Alzheimer group and the p(GgO) 5 mg–Alzheimer and p(GgO) 10 mg–Alzheimer groups received 40 mg $AlCl_3$ per week during the first five weeks to establish the experimental neurotoxicity model. From the sixth week onward, p(GgO) was administered at doses of 5 or 10 mg to the corresponding treatment groups in addition to the $AlCl_3$ administration. The analyses were concluded in the 10th week. The weekly mean body weights of the animals over the 9-week observation period were presented in Table 1. The control, p(GgO) 5 mg, and p(GgO) 10 mg groups generally showed an increase in body weight over the experimental period, with the final measurements being higher than the initial values. This generally increase indicates that the animals in these groups maintained weight gain during the study period. In the Alzheimer group, body weight increased during the first five weeks but subsequently showed a decline. A similar fluctuation was observed in the p(GgO) 5 mg–Alzheimer and p(GgO) 10 mg–Alzheimer groups. In these groups, body weight increased during the first five weeks, decreased during the sixth week, and subsequently increased again during the later observation period. These temporal changes indicate that $AlCl_3$ exposure and the subsequent treatment period were associated with changes in the pattern of body-weight progression. The relatively greater recovery of body weight observed during the later weeks in the p(GgO)-treated Alzheimer groups may indicate a possible association between p(GgO) administration and maintenance of body weight under $AlCl_3$

exposure. However, body weight is a general physiological parameter and cannot, by itself, be interpreted as direct evidence of an improvement in Alzheimer-like pathology. Therefore, these findings should be considered together with the behavioral and biochemical results presented in the subsequent sections.

Table 1. Weight, water, and pellet feed consumption per rat per week.

Wezk	Control (n: 7)	Alzheimer (n: 7)	p(GgO) 5 mg (n: 8)	p(GgO) 10 mg (n: 8)	AL-p(GgO) 5 mg (n: 8)	AL-p(GgO) 10 mg (n: 8)	Mean
			Weight (gram)				
I	198 ± 12 C a	175 ± 15CD b	188 ± 1 E ab	183 ± 8 DE ab	156 ± 3 E c	176 ± 1.8 B–d b	179 ± 3
II	203 ± 14 C a	185 ± 15 B-D ab	197 ± 11 CDE ab	196 ± 1.2 DE ab	161 ± 6 E c	183 ± 2 B–d b	187 ± 1.2
III	205 ± 12 BC a	181 ± 12 B-D bc	192 ± 6 DE ab	198 ± 1 DE ab	164 ± 4 DE c	185 ± 1.9 B–d b	188 ± 1
IV	215 ± 11 A-C a	192 ± 13 BC bc	207 ± 4.6 B–D ab	208 ± 1.3 CD ab	180 ± 8CD c	198 ± 1.8 A–C ac	200 ± 1.9
V	224 ± 3 AB b	299 ± 14 A a	213 ± 4.7 A–C bc	212 ± 1.7 B–D bc	222 ± 6 A b	200 ± 2 A–C c	228 ± 1.8
VI	223 ± 11 AB b	292 ± 11 A a	0.215 ± 8 A–C b	222 ± 1.7 A–C b	188 ± 9 BC c	197 ± 1.6 A–C c	223 ± 9
VII	226 ± 12 A a	198 ± 25 B b	220 ± 13.1 AB a	224 ± 1.9 A–C a	193 ± 4 BC b	202 ± 1.6 AB b	211 ± 4
VIII	224 ± 8 AB ab	174 ± 19 CD d	224 ± 3.1 AB ab	231 ± 1.7 AB a	197 ± 9 BC c	208 ± 1.6 A bc	210 ± 7
IX	230 ± 9 A ab	171 ± 31 D d	231 ± 1.4 A c	236 ± 2.2 A a	203 ± 11 B ab	215 ± 2.2 A bc	214 ± 3
Mean	219 ± 1	211 ± 4	213 ± 1	188 ± 0.01	215 ± 0.01	0.198 ± 0.01	
	$p^{week} = 0.001$		$p^{Treatment} = 0.001$		$p^{Treatment\ x\ Week} = 0.001$		
			Water (mL)				
I	29.08 ± 3.3 F e	26.44 ± 3.7 E f	48.21 ± 1.05 D b	53.89 ± 1.51 E a	30.39 ± 1.8 E d	45.14 ± 1.11 E c	41.27 ± 1.3
II	27.21 ± 3.3 H e	27.04 ± 3.7 D f	68.33 ± 1.88 B c	66.57 ± 3.51 C d	70.00 ± 4.29 A b	63.57 ± 3.69 A a	53.79 ± 1.8
III	34.94 ± 0.4 C e	32.33 ± 1.7 A f	72.38 ± 1.77 A a	64.76 ± 0.84 D c	69.05 ± 2.94 B b	60.95 ± 1.33 C d	55.74 ± 3.3
IV	36.00 ± 8.3 B e	31.36 ± 6.6 B f	72.38 ± 1.79A b	75.71 ± 1.87 B a	60.48 ± 2.94 C d	62.38 ± 2.17 B c	56.39 ± 4.3
V	36.45 ± 1.0 A e	25.86 ± 2.0 F f	67.86 ± 0.86 C b	80.71 ± 8.4 A a	57.14 ± 1.08 D c	48.57 ± 1.48 D d	52.77 ± 5.2
VI	30.46 ± 1.05 E c	30.65 ± 7.09 C b	30.37 ± 0.96 F d	33.57 ± 2.47 F a	57.14 ± 3.6 G f	25.00 ± 5.20 H e	28.61 ± 2.8
VII	30.65 ± 3.95 D c	24.44 ± 1.73 G e	31.83 ± 7.08 E b	32.94 ± 5.50 G a	21.39 ± 3.76 H f	28.33 ± 7.64 F d	28.26 ± 3.7
VIII	28.24 ± 1. 53 G b	21.67 ± 1.44 H f	28.174 ± 0.9 G c	29.37 ± 1.98 H a	22.98 ± 1.44 F e	27.74 ± 2.93 G d	26.36 ± 1.98
IX	28.24 ± 1.53 G b	21.67 ± 1.44 H f	28.17 ± 0.9 G c	29.37 ± 1.98 H a	22.98 ± 1.44 F e	27.74 ± 2.93 G d	26.36 ± 1.98
Mean	31.53 ± 3.45	26.88 ± 2.24	49.94 ± 2.19	43.24 ± 1.66	51.63 ± 1.62	43.04 ± 1.90	
	$p^{week} = 0.001$		$p^{Treatment} = 0.001$		$p^{Treatment\ x\ Week} = 0.001$		
			Pellet Feed (gram)				
I	13.21 ± 1.2 G e	12.99 ± 2.0 E f	23.61 ± 0.63 D b	21.18 ± 0.67 D d	22.46 ± 0.59 C a	21.68 ± 0.57 E c	19.19 ± 1.63
II	14.59 ± 1.4 C e	13.92 ± 1.9 C f	29.19 ± 1.59 B d	29.86 ± 1.48 B c	30.24 ± 1.63 C b	35.33 ± 0.2 A a	25.52 ± 1.59
III	14.19 ± 0.03 E e	13.75 ± 1.9 D f	31.30 ± 0.76 A a	30.24 ± 0.63 A b	32.86 ± 0.68 A c	32.81 ± 0.83 B d	25.86 ± 1.78
IV	14.21 ± 0.9 D e	11.95 ± 0.7 F f	26.04 ± 0.37 C d	27.90 ± 0.35 C c	32.24 ± 0.74 B b	32.71 ± 0.72 C a	24.17 ± 2.3
V	15.16 ± 1.5 A e	9.66 ± 0.3 H f	18.33 ± 6.14 E c	17.43 ± 0.17 E d	30.00 ± 0.6 D b	31.71 ± 0.37 D a	20.38 ± 1.64
VI	13.52 ± 0.56 F c	17.32 ± 3.22 A a	10.28 ± 6.14 H f	16.25 ± 1.64 F b	13.33 ± 1.68 G d	11.00 ± 1.68 H e	13.61 ± 2.13
VII	14.65 ± 1.28 B d	14.45 ± 1.94 B f	14.63 ± 2.3 F e	15.94 ± 2.13 G b	16.88 ± 2.47 E a	14.89 ± 2.47 F c	15.24 ± 0.59
VIII	12.70 ± 1.44 H e	10.82 ± 1.80 G f	14.29 ± 5.58 G b	14.02 ± 0.66 H c	14.02 ± 0.66 H c	13.75 ± 2.29 G d	13.70 ± 1.1
IX	12.70 ± 1.44 H e	10.82 ± 1.80 G f	14.29 ± 5.58 G b	14.01 ± 0.66 H c	14.01 ± 0.66 H c	13.75 ± 2.29 G d	13.70 ± 1.1
Mean	13.97 ± 1.45	12.85 ± 1.24	19.79 ± 1.19	23.61 ± 1.66	20.70 ± 1.62	23.24 ± 1.90	
	$p^{weea} = 0.001$		$p^{Treatment} = 0.001$		$p^{Treatment\ x\ Week} = 0.001$		

A, B, C, D, E, F, G, H: The difference between aynı groups in the same week is significant ($p < 0.05$). a, b, c, d, e, f, g, h: The difference between different groups in the same week is significant ($p < 0.05$).

A statistically significant effect of treatment and observation week was observed for body-weight changes, indicating differences in the pattern of weight gain or loss among the experimental groups over the study period. The weekly mean water and pellet feed consumption of the six experimental groups over the 9-week observation period was presented in Table 1. Water and pellet feed consumption in the control group remained relatively stable throughout the experimental period. In contrast, the Alzheimer group showed a gradual decrease in both water and pellet feed consumption over the observation period. The p(GgO)-treated groups generally exhibited changes in consumption patterns over time, with the magnitude and direction of these changes varying according to treatment group and observation week.

In the p(GgO) 5 mg and p(GgO) 10 mg groups, the values recorded at the end of the observation period were higher than those recorded at the beginning of the experiment. In the $AlCl_3$-exposed groups treated with p(GgO), changes in water and pellet feed consumption were observed after p(GgO) administration began in the sixth week. These parameters varied during the experimental period, suggesting differences in the physiological responses of the treatment groups. However, changes in water and feed intake alone cannot be interpreted as direct evidence of cognitive improvement or neuroprotection. Statistical analysis revealed significant differences in both water and pellet feed consumption between the treatment groups and across the observation weeks ($p < 0.05$). These findings indicate that treatment condition and experimental time were associated with changes in these physiological parameters. The corresponding mean ± SD values and statistical comparisons were provided in Table 1.

The Morris water maze (MWM) is commonly used to evaluate spatial learning and memory. The test typically includes an acquisition phase, during which the animals are trained to find a submerged escape platform using visual cues around the pool, followed by a probe trial in which the platform is removed and the animals swim freely for 60 s. In the present study, escape latency during the acquisition phase, as well as time spent in the target quadrant and swimming speed during the probe trial, were evaluated as behavioral measures [115]. The MWM findings were summarized in Table2. Compared with the untreated control group, the $AlCl_3$-exposed group generally showed longer escape latencies at the later measurement points. This pattern indicates poorer performance in locating the hidden platform and may be consistent with impairment in spatial learning and/or memory retention. However, interpretation of MWM performance should take into account changes over time and the overall pattern of performance across the acquisition and probe phases rather than relying on individual time points alone.

In contrast, the p(GgO)-treated $AlCl_3$-exposed groups showed changes in escape latency over the experimental period, with progressive reductions observed at several measurement points. The changes observed in the 5 and 10 mg/kg p(GgO) groups were not identical, either in magnitude or in their timing during the experimental period. Neither treatment group showed consistently shorter escape latencies than the control group at every measurement point. For this reason, the behavioral effects of p(GgO) should be considered in terms of the overall pattern of performance across the experimental period rather than based on individual weekly comparisons alone. The observed changes suggest that p(GgO) administration may have modified spatial-task performance in $AlCl_3$-exposed animals; however, the behavioral findings alone do not establish a direct therapeutic effect on Alzheimer's disease. Swimming speed was also considered when interpreting the MWM results because differences in motor performance could influence escape latency independently of spatial learning. The inclusion of this parameter therefore provides an additional basis for distinguishing changes in task performance from potential alterations in general locomotor ability. The modified maze test was used as an additional behavioral assessment of memory-related performance and anxiety-like behavior. The test consisted of practice and test sessions, and the time required to complete the maze was recorded. As shown in Table 2, the control group completed the maze in a shorter time than the $AlCl_3$-exposed group. The p(GgO)-treated groups generally showed shorter completion times than the untreated $AlCl_3$-exposed group, although the magnitude of the response differed between treatment doses and experimental measurements. Generally, the MWM and modified maze findings indicate that $AlCl_3$ exposure was associated with alterations in behavioral performance, whereas p(GgO) administration was associated with changes in the temporal

pattern of task performance. These behavioral findings should be considered together with the biochemical results, particularly the oxidative stress and antioxidant parameters, rather than being interpreted independently as evidence of clinical Alzheimer's disease improvement. Statistical analysis revealed significant differences associated with treatment and observation period in the behavioral measurements ($p < 0.05$). Because behavioral performance was repeatedly assessed over time in the same animals, the statistical interpretation focused on the longitudinal pattern of the data and the corresponding treatment-related changes rather than treating measurements obtained from different weeks as independent observations.

Table 2. Weekly rat groups Morris water tank and Modified Maze test values.

Morris	**Control (n:7)**	**Alzheimer (n:7)**	**p(GgO) 5 mg (n: 8)**	**p(GgO) 10 mg (n: 8)**	**AL-p(GgO) 5 mg (n: 8)**	**AL-p(GgO) 10 mg (n: 8)**	**Mean**
I	1.35 ± 0.96 A f	2.03 ± 0.12 A b	1.57 ± 0.60 A d	1.62 ± 0.8 A c	2.40 ± 0.73 A a	1.45 ± 0.1 A e	1.73 ± 0.37
II	0.40 ± 0.36 B e	0.80 ± 0.05 B a	0.61 ± 0.04 B b	0.59 ± 0.05 B c	0.50 ± 0.04 B d	0.61 ± 0.03 B b	0.58 ± 0.12
III	0.21 ± 0.11 C e	0 .32 ± 0.02 E c	0.19 ± 0.01 C f	0.29 ± 0.02 C d	0.47 ± 0.04 C b	0.52 ± 0.03 C a	0.33 ± 0.12
IV	0.22 ± 0.13 C e	0.30 ± 0.04 F c	0.13 ± 0.01 E f	0.28 ± 0.02 C d	0.38 ± 0.05 DE b	0.50 ± 0.02 D a	0.30 ± 0.12
V	0.19 ± 0.01 D d	0.30 ± 0.03 F c	0.17 ± 0.02 D f	0.15 ± 0.02 D f	0.38 ± 0.03 E b	0.40 ± 0.04 E a	0.26 ± 0.10
VI	0.13 ± 0.08 E d	0.59 ± 0.04 C a	0.10 ± 0.06 F e	0.11 ± 0.08 E e	0.40 ± 0.02 D b	0.35 ± 0.04 F c	0.27 ± 0.18
VII	0.12 ± 0.09 DE d	0.49 ± 0.04 D a	0.13 ± 0.07 E d	0.09 ± 0.05 F e	0.18 ± 0.2 F c	0.24 ± 0.02 G b	0.20 ± 0.14
VIII	0.11 ± 0.08 E c	0.48 ± 0.04 D a	0.08 ± 0.06 F e	0.08 ± 0.05 F f	0.09 ± 0.03 G d	0.24 ± 0.04 G b	0.18 ± 0.14
Mean	0.34 ± 0.05	0.65 ± 0.04	0.37 ± 0.09	0.60 ± 0.06	0.40 ± 0.02	0.54 ± 0.01	
	$p^{week} = 0.001$		$p^{Treatment} = 0.001$		$p^{Treatment\ x\ Week} = 0.001$		
Labirent	Control (n:7)	Alzheimer (n:7)	p(GgO) 5 mg (n:8)	p(GgO) 10 mg (n:8)	AL-p(GgO) 5 mg (n:8)	AL-p(GgO) 10 mg (n:8)	Mean
I	2.93 ± 0.25 A f	3.39 ± 0.2 B d	3.34 ± 0.22 A b	2.56 ± 0.14 A e	3.28 ± 0.17 B c	3.96 ± 0.25 A a	3.12 ± 0.54
II	1.81 ± 0.12 B e	2.86 ± 0.22 E b	1.24 ± 0.09 C f	2.23 ± 0.16 B d	2.38 ± 0.27 C c	3.69 ± 0.32 B a	2.37 ± 0.80
III	1.61 ± 0.1 C d	3.24 ± 0.24 A a	1.96 ± 0.21 B c	1.23 ± 0.14 C e	3.32 ± 0.3 A b	3.31 ± 0.24 D b	2.46 ± 0.94
IV	1.00 ± 0.05 D f	2.75 ± 0.16 H c	0.87 ± 0.05 D e	1.22 ± 0.13 C d	2.40 ± 0.2 C b	3.27 ± 0.19 E a	1.76 ± 0.96
V	0.87 ± 0.05 D f	3.10 ± 0.2 C b	0.74 ± 0.07 F e	1.09 ± 0.07 D d	2.19 ± 0.22 D c	3.60 ± 0.2 C a	1.85 ± 0.16
VI	0.77 ± 0.06 E f	2.93 ± 0.24 F b	0.71 ± 0.07 G e	0.74 ± 0.05 E d	1.89 ± 0.18 E c	2.89 ± 0.21 F a	1.54 ± 0.94
VII	0.66 ± 0.02 F f	2.52 ± 0.18 G b	0.76 ± 0.07 E c	0.57 ± 0.03 F d	0.75 ± 0.06 F c	2.72 ± 0.18 G a	1.26 ± 0.94
VIII	0.67 ± 0.01 G f	2.45 ± 0.17 D a	0.53 ± 0.01 H d	0.47 ± 0.04 G e	0.76 ± 0.05 F c	1.73 ± 0.1 H b	1.06 ± 0.10
Mean	1.29 ± 0.05	2.91 ± 0.24	1.24 ± 0.19	2.12 ± 0.66	1.26 ± 0.62	3.14 ± 0.90	
	$p^{week} = 0.001$		$p^{Treatment} = 0.001$		$p^{Treatment\ x\ Week} = 0.001$		

A, B, C, D, E, F, G, H: The difference between aynı groups in the same week is significant ($p < 0.05$). a, b, c, d, e, f, g, h: The difference between different groups in the same week is significant ($p < 0.05$).

Aluminum chloride ($AlCl_3$) exposure has been associated with disturbances in cellular redox homeostasis and increased oxidative stress through several mechanisms [116–118]. Aluminum may interact with negatively charged cellular components, including membrane phospholipids, and may contribute to oxidative damage involving reactive oxygen species (ROS). Because membrane phospholipids contain polyunsaturated fatty acids that are particularly susceptible to ROS-mediated oxidation, an imbalance between ROS production and antioxidant defense may promote lipid peroxidation [116–118]. Malondialdehyde (MDA), a secondary product of lipid peroxidation, is

therefore commonly used as an indicator of oxidative membrane damage. Lipid peroxidation involves the oxidation of unsaturated fatty acids in membrane phospholipids and the subsequent formation of lipid hydroperoxides and secondary products, including MDA [119,120].

In the present study, as shown in Table 3, MDA levels varied among the experimental groups, with the highest levels of lipid peroxidation generally observed in the $AlCl_3$-exposed group. In the p(GgO)-treated groups, MDA levels were generally closer to those of the control group in the tissues examined. This finding may indicate a reduction in lipid peroxidation following p(GgO) administration under $AlCl_3$ exposure. However, changes in MDA cannot be explained solely by alterations in antioxidant enzyme activity. Lipid peroxidation is affected by several interrelated factors, including ROS production, antioxidant capacity, membrane composition, and the overall cellular redox state. Therefore, the lower MDA levels observed in the p(GgO)-treated groups may reflect a broader change in oxidative balance rather than a single antioxidant mechanism.

The antioxidant defense system consists of several enzymatic and non-enzymatic components that work together to control ROS and limit oxidative damage. As shown in Table 3, among the major antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathioneS-transferase (GST) have important roles in maintaining cellular redox homeostasis [121]. CAT is particularly abundant in liver peroxisomes and catalyzes the conversion of hydrogen peroxide (H_2O_2) into water and molecular oxygen, thereby contributing to the removal of this potentially harmful ROS.

In the present study, CAT activity was lower in the liver and erythrocytes of some p(GgO)-treated groups than in the control group, whereas higher CAT activity was observed in some of the other tissues examined. These findings indicate that the response to p(GgO) was not uniform across tissues. The significant increases observed in some tissues, particularly at the higher p(GgO) dose, may indicate an increased capacity to metabolize H_2O_2 under oxidative challenge. At the same time, CAT activity should not be considered independently when assessing oxidative stress. Its interpretation is more meaningful when considered together with MDA and the other antioxidant parameters measured in the study.

SOD provides an important first line of enzymatic defense against oxidative stress by catalyzing the conversion of superoxide anions ($O_2\bullet^-$) into H_2O_2 and molecular oxygen [122]. n this study, SOD activity increased significantly in erythrocytes and heart tissue following p(GgO) administration. An increase was also observed in the other tissues examined, although the statistical significance of the changes differed between tissues and treatment groups. The increase in SOD activity may represent an adaptive response to changes in ROS levels. Since the reaction catalyzed by SOD generates H_2O_2, however, changes in SOD activity need to be considered together with CAT and GSH-Px, which participate in the subsequent removal of H_2O_2.

In generally, the MDA, CAT, and SOD findings point to tissue-dependent changes in oxidative status and antioxidant defense following p(GgO) administration in $AlCl_3$-exposed rats. The lower MDA levels observed in conjunction with changes in antioxidant enzyme activities are consistent with a possible modulatory effect of p(GgO) on redox homeostasis. These findings, however, do not establish a specific molecular mechanism. Further investigation of ROS production, antioxidant-related gene expression, inflammatory pathways, mitochondrial function, and other molecular markers would be needed to clarify the mechanisms responsible for the observed effects.

Gamma-glutamyl-cysteinyl-glycine (GSH) is an important non-enzymatic antioxidant involved in maintaining cellular redox homeostasis, detoxification, regulation of cellular functions, and scavenging

reactive species [123]. In the present study, GSH levels were generally higher in the p(GgO)-treated groups than in the $AlCl_3$-exposed group across the tissues examined. In brain tissue, GSH levels in the p(GgO)-treated groups were also higher than those observed in the untreated control group. These findings indicate that p(GgO) administration was associated with changes in the tissue GSH status under $AlCl_3$ exposure. However, changes in GSH concentration alone cannot establish an increase in antioxidant capacity, as GSH homeostasis depends on its synthesis, utilization, oxidation, and regeneration. Glutathione S-transferase (GST) is an important component of the cellular detoxification system and catalyzes the conjugation of reduced glutathione with a broad range of endogenous and exogenous electrophilic compounds. In the present study, GST activity was significantly increased in liver tissue compared with the other tissues examined. An increase in GST activity was also observed following p(GgO) administration in several tissues relative to the control group. The relatively pronounced response in the liver may be related to the central role of this organ in xenobiotic metabolism and detoxification. Nevertheless, the tissue-specific variation in GST activity indicates that the response to p(GgO) was not uniform across organs.

Table 3. GSH-px, GR, GSH, GST, CAT, SOD and MDA levels in tissues.

	Antioxidant Enzyme Values						
	GSH-Px X ± SD	**GR X ± SD**	**GSH X ± SD**	**GST X ± SD**	**CAT X ± SD**	**SOD X ± SD**	**MDA X ± SD**
Spleen							
Control (n:7)	1.99 ± 0.273 B	0.15 ± 0.27 BC	8.08 ± 0.67 A	0.44 ± 0.16 BC	42.06 ± 2.47 A	563.59 ± 45 D	2.25 ± 1.22 C
Alzheimer (n:7)	0.85 ± 0.774 A	0.09 ± 0.77 D	6.39 ± 1.33 C	0.34 ± 0.04 B	27.72 ± 8.01 C	535.00 ± 67 A	3.95 ± 0.58 B
p(GgO) 5 mg (n:8)	1.17 ± 0.336 B	0.16 ± 0.34 A	9.26 ± 0.78 D	0.41 ± 0.10 C	46.42 ± 7.00 B	660.56 ± 33 BC	2.23 ± 0.87 C
AL-p(GgO) 5 mg (n:8)	1.02 ± 0.402 B	0.12 ± 0.40 AB	8.05 ± 1.70 B	0.41 ± 0.05 C	41.41 ± 5.37 A	627.53 ± 24 AB	2.17 ± 0.89 A
p(GgO) 10 mg (n:8)	1.43 ± 0.277 B	0.18 ± 0.28 A	8.73 ± 1.07 C	0.51 ± 0.08 A	45.70 ± 7.32 AB	531.78 ± 52 A-C	2.30 ± 0.90 B
AL-p(GgO) 10 mg (n:8)	0.92 ± 0.527 B	0.13 ± 0.53 AB	7.69 ± 0.95 C	0.46 ± 0.06 A	37.95 ± 6.86 BC	368.08 ± 46 C	1.77 ± 0.54 AB
Erythrocyte							
Control (n:7)	6.76 ± 0.12 C	0.31 ± 0.12 A	0.66 ± 0.0014 A	0.25 ± 0.02 A	215.46 ± 5.7 A	961.04 ± 83 B	1.94 ± 0.21 C
Alzheimer (n:7)	1.5 ± 0.48 D	0.02 ± 0.01 E	0.67 ± 0.0016 A	0.13 ± 0.12 B	112.11 ± 4.3 D	2030.30 ± 77 A	3.32 ± 0.25 AB
p(GgO) 5 mg (n:8)	4.86 ± 0.83 B	0.05 ± 0.04 B	0.67 ± 0.002 A	0.26 ± 0.05 A	170.01 ± 3.2 B	1655.30 ± 38 B	1.62 ± 0.69 C
AL-p(GgO) 5 mg (n:8)	4.72 ± 0.96 B	0.03 ± 0.03 D	0.66 ± 0.0014 A	0.22 ± 0.05 A	164.32 ± 2.3 BC	1545.45 ± 42 B	2.32 ± 0.53 BC
p(GgO) 10 mg (n:8)	4.89 ± 0.08 A	0.03 ± 0.02 BC	0.66 ± 0.0012 A	0.21 ± 0.06 A	181.49 ± 3.5 BC	1331.44 ± 59 AB	1.59 ± 0.7 AB
AL-p(GgO) 10 mg (n:8)	5.88 ± 0.15 A	0.05 ± 0.02 B	0.67 ± 0.0034 A	0.29 ± 0.02 A	151.59 ± 3.7 C	1980.52 ± 61 A	4.00 ± 1.14 A
Heart							
Control (n:7)	0.90 ± 0.41 B	0.10 ± 0.03 A	9.14 ± 1.34 BC	0.58 ± 0.07 A	108.48 ± 1.3 B	661.70 ± 7.5 B	0.89 ± 0.64 C
Alzheimer (n:7)	0.57 ± 0.57 C	0.06 ± 0.04 A	9.78 ± 1.2 AB	0.37 ± 0.23 C	78.53 ± 5.4 C	830.16 ± 3.0 B	1.18 ± 0.5 B
p(GgO) 5 mg (n:8)	0.95 ± 0.21 B	0.10 ± 0.05 A	10.42 ± 0.93 A	0.55 ± 0.08 AB	110.85 ± 7.5 B	1094.23 ± 5.9 A	0.84 ± 0.23 C
AL-p(GgO) 5 mg (n:8)	0.67 ± 0.13 C	0.09 ± 0.03 A	9.61 ± 0.4 B	0.39 ± 0.20 C	111.37 ± 6.0 B	1054.55 ± 11.1 B	1.53 ± 0.78 C
p(GgO) 10 mg (n:8)	0.90 ± 0.54 A	0.10 ± 0.02 A	9.88 ± 0.4 C	0.45 ± 0.07 BC	116.37 ± 1.9 A	796.01 ± 11.7 A	1.04 ± 0.51 A
AL-p(GgO) 10 mg (n:8)	1.40 ± 0.48 B	0.05 ± 0.01 A	8.26 ± 0.3 BC	0.45 ± 0.05 A	143.99 ± 1.4 B	1239.28 ± 6.41 A	1.67 ± 0.36 A

Table 3. *Cont.*

	Antioxidant Enzyme Values						
	GSH-Px X ± SD	**GR X ± SD**	**GSH X ± SD**	**GST X ± SD**	**CAT X ± SD**	**SOD X ± SD**	**MDA X ± SD**
Liver							
Control (n:7)	0.14 ± 0.03 B	0.026 ± 0.011 A	5.37 ± 1.07 A	5.39 ± 0.93 BC	167.13 ± 3.8 A	428.61 ± 34 C	3.28 ± 1.21 D
Alzheimer (n:7)	0.10 ± 0.07 B	0.015 ± 0.005 A	3.20 ± 0.82 C	4.89 ± 0.88 CD	137.63 ± 2.9 B	635.70 ± 65 B	4.22 ± 1.2 A
p(GgO) 5 mg (n:8)	0.07 ± 0.08 B	0.021 ± 0.009 A	4.67 ± 1.39 B	6.05 ± 0.89 A	135.92 ± 3.2 B	615.81 ± 11 A	3.53 ± 1.27 C
AL-p(GgO) 5 mg (n:8)	0.06 ± 0.03 B	0.016 ± 0.004 A	3.42 ± 0.71 C	5.73 ± 1.48 AB	127.91 ± 4.6 D	628.95 ± 75 D	3.85 ± 2.00 B
p(GgO) 10 mg (n:8)	0.28 ± 0.2 A	0.045 ± 0.031 A	4.24 ± 0.73 C	5.56 ± 0.6 DE	129.36 ± 4.6 C	645.64 ± 10 D	2.71 ± 0.45 E
AL-p(GgO) 10 mg (n:8)	0.30 ± 0.22 A	0.015 ± 0.008 A	2.92 ± 0.39 C	4.28 ± 0.6 E	133.82 ± 1.1 C	601.95 ± 18 D	2.77 ± 0.6 E
Lung							
Control (n:7)	0.92 ± 0.15 B	0.08 ± 0.004 BC	4.98 ± 0.57 A	0.48 ± 0.06 BC	176.25 ± 5.8 A	428.61 ± 26 A	2.54 ± 0.3 C
Alzheimer (n:7)	0.48 ± 0.3 A	0.05 ± 0.006 D	4.13 ± 0.89 C	0.51 ± 0.01 B	119.52 ± 8.3 C	635.70 ± 52 D	3.21 ± 0.94 B
p(GgO) 5 mg (n:8)	1.13 ± 0.11 B	0.11 ± 0.004 A	4.78 ± 0.61 B	0.41 ± 0.08 C	182.12 ± 2.3 A	615.81 ± 21 BC	2.78 ± 0.95 C
AL-p(GgO) 5 mg (n:8)	1.16 ± 0.48 B	0.07 ± 0.003 BC	3.86 ± 0.4 D	0.42 ± 0.05 C	173.18 ± 9.6 A	628.95 ± 46 AB	3.65 ± 0.64 A
p(GgO) 10 mg (n:8)	1.78 ± 0.53 B	0.12 ± 0.003 A	4.34 ± 0.61 C	0.51 ± 0.09 A	198.05 ± 3.0 AB	645.64 ± 48 A-C	2.84 ± 0.76 B
AL-p(GgO) 10 mg (n:8)	0.96 ± 00.5 B	0.09 ± 0.004 AB	4.12 ± 0.63 C	0.6 ± 0.01 A	136.60 ± 1.6 BC	601.95 ± 35 C	3.47 ± 0.13AB
Kidney							
Control (n:7)	0.33 ± 0.4 A	0.014 ± 0.0064 A	9.91 ± 1.19 A	0.82 ± 0.14 A	50.28 ± 0.16 D	948.46 ± 0.35 A	1.86 ± 0.12 D
Alzheimer (n:7)	0.14 ± 0.16 B	0.006 ± 0.0026 A	8.51 ± 1.24 D	0.52 ± 0.37 B	39.83 ± 0.3 C	767.68 ± 0.36 BC	2.12 ± 0.4 CD
p(GgO) 5 mg (n:8)	0.32 ± 0.22 A	0.011 ± 0.0026 A	9.27 ± 1.64 B	0.82 ± 0.11 A	98.36 ± 0.21 B	963.34 ± 31 A	1.67 ± 0.24 D
AL-p(GgO) 5 mg (n:8)	0.33 ± 0.23 A	0.011 ± 0.0037 A	8.47 ± 1.09 D	0.56 ± 0.27 B	109.53 ± 0.12 A	817.17 ± 41 B	2.65 ± 0.13 BC
p(GgO) 10 mg (n:8)	0.38 ± 0.8 A	0.052 ± 0.0011 A	9.59 ± 0.85 BC	0.97 ± 0.08 A	97.29 ± 0.12 A	877.18 ± 23 BC	1.93 ± 0.35 AB
AL-p(GgO) 10 mg (n:8)	0.29 ± 0.15 A	0.014 ± 0.0074 A	8.87 ± 1.04 C	0.76 ± 0.13 A	116.16 ± 0.12 A	710.49 ± 13 C	3.39 ± 0.66 A
Brain							
Control (n:7)	0.11 ± 0.02 A	0.022 ± 0.0027 A	1.67 ± 0.14 A–C	0.56 ± 0.01 C	2.70 ± 0.03 C	791.34 ± 3.7 BC	2.47 ± 0.14 B
Alzheimer (n:7)	0.09 ± 0.08 A	0.008 ± 0.003 A	1.56 ± 0.09 D	0.47 ± 0.02 D	2.30 ± 0.01 D	634.07 ± 2.8 C	3.01 ± 0.51 A
p(GgO) 5 mg (n:8)	0.15 ± 0.02 A	0.019 ± 0.008 A	1.76 ± 0.19 A	0.58 ± 0.05 B	3.03 ± 0.05 B	728.97 ± 5.5 BC	2.06 ± 0.26 C
AL-p(GgO) 5 mg (n:8)	0.12 ± 0.09 A	0.016 ± 0.004 A	1.72 ± 0.01 AB	0.54 ± 0.02 A	2.99 ± 0.05 B	841.952.1 AB	1.89 ± 0.317 D
p(GgO) 10 mg (n:8)	0.19 ± 0.01 A	0.022 ± 0.009 A	1.61 ± 0.21 CD	0.60 ± 0.05 A	2.96 ± 0.01 A	572.92 ± 1.1 AB	2.18 ± 0.25 C
AL-p(GgO) 10 mg (n:8)	0.017 ± 0.04 A	0.018 ± 0.009 A	1.64 ± 0.15 B-D	0.60 ± 0.01 A	3.53 ± 0.08 A	1012.02 ± 5.9 A	2.01 ± 0.34 CD

A, B, C, D, E, F, G, H: The difference between different groups in the organs for oxidative enzymes is significant ($p < 0.05$).

Glutathione reductase (GR), which contributes to the maintenance of intracellular GSH by regenerating reduced glutathione from oxidized glutathione, also showed tissue-dependent responses following p(GgO) administration. No statistically significant differences were detected in GR activity in the heart, liver, or brain tissues, whereas significant changes were observed in the lung, kidney, and erythrocyte tissues. These findings further demonstrate that the response of the glutathione-dependent antioxidant system differed among tissues. Such tissue specificity should be considered when interpreting the overall effect of p(GgO) on redox homeostasis.

GSH-Px and CAT constitute complementary enzymatic systems involved in the removal of H_2O_2, although their relative contribution can vary according to substrate concentration, cellular localization, and tissue type [124]. Therefore, differences in GSH-Px and CAT activities may reflect differences in

the oxidative environment and the relative contribution of these enzymatic pathways in individual tissues. In the present study, the observed changes in GSH-Px activity were not uniform among tissues. Rather than attributing these differences solely to an assumed increase in H_2O_2 production following $AlCl_3$ exposure, the results are more appropriately interpreted as tissue-dependent alterations in peroxide-metabolizing capacity.

The distribution and activity of antioxidant and cytoprotective systems, including α-tocopherol, GSH, SOD, CAT, GSH-Px, and GR, differ among tissues [125]. The liver generally possesses a particularly well-developed antioxidant and detoxification capacity, whereas antioxidant enzyme activities may differ substantially in the heart, spleen, brain, kidney, lung, and erythrocyte [125]. Therefore, the tissue-specific differences observed in the present study are biologically plausible and emphasize the importance of evaluating multiple tissues when assessing the systemic effects of p(GgO) administration.

Taken together, the changes observed in GSH, GST, GR, GSH-Px, and CAT suggest that p(GgO) administration was associated with modulation of the glutathione-dependent and enzymatic antioxidant systems in a tissue-dependent manner. When considered together with the MDA, SOD, and CAT findings, these results support the possibility that p(GgO) influences redox homeostasis under $AlCl_3$-induced oxidative challenge. However, the present data do not establish a specific molecular mechanism or demonstrate that p(GgO) directly stimulates antioxidant enzyme synthesis. Further studies involving glutathione-related gene expression, ROS measurements, redox-sensitive signaling pathways, and enzyme kinetics would be required to clarify the molecular basis of these observations.

The brain is particularly vulnerable to oxidative damage because of its high oxygen consumption, abundance of polyunsaturated fatty acids, and the relatively limited capacity of certain antioxidant defense systems compared with other tissues [126]. Polyunsaturated fatty acids in neuronal membranes are highly susceptible to ROS-mediated oxidation, and excessive lipid peroxidation can consequently contribute to alterations in membrane integrity and cellular function. MDA, a secondary product of lipid peroxidation, is therefore commonly used as a biochemical indicator of oxidative damage. Such oxidative imbalance has been implicated in the pathophysiology of several neurodegenerative disorders, including Alzheimer's disease.

Myeloperoxidase (MPO) is a heme-containing enzyme predominantly associated with neutrophils and other inflammatory cells and contributes to the generation of reactive oxidants through the utilization of H_2O_2 and chloride, resulting in the formation of hypochlorous acid [126]. Consequently, increased MPO activity may be associated with inflammatory and oxidative processes. In the present study, MPO activity in brain tissue was relatively low in the p(GgO)-treated group, whereas higher values were observed in the $AlCl_3$-exposed group and in the $AlCl_3$-exposed groups receiving p(GgO). These findings indicate that the response of MPO to p(GgO) administration was not uniform across the experimental groups. Therefore, although MPO may provide information regarding oxidative and inflammatory status, the present MPO findings alone cannot be interpreted as direct evidence of a specific neuroinflammatory pathway. Confirmation of neuroinflammatory mechanisms would require additional measurements, such as inflammatory cytokines, microglial activation markers, or related signaling pathways.

Adenosine deaminase (ADA) catalyzes the irreversible deamination of adenosine and 2′-deoxyadenosine to inosine and 2′-deoxyinosine, respectively, and consequently contributes to the regulation of intracellular purine metabolism [127]. Because alterations in adenosine metabolism can influence cellular and immune responses, ADA activity has also been investigated as a biochemical indicator of

cellular and immunological status. In the present study, ADA activity in brain tissue was closer to the control values in the p(GgO)-treated group, whereas higher values were observed in the $AlCl_3$-exposed group and the $AlCl_3$-exposed groups receiving p(GgO). The tissue-specific response of ADA suggests that p(GgO) administration may influence purine-metabolism-related processes under $AlCl_3$ exposure. However, ADA activity alone is insufficient to establish a specific neuroprotective or immunomodulatory mechanism. An increase in GSH levels was observed in the brain tissue of p(GgO)-treated rats compared with the $AlCl_3$-exposed group, and the observed differences were statistically significant. Because GSH is an important component of the cellular antioxidant defense system, the increase in brain GSH levels may indicate an enhanced capacity to maintain redox homeostasis under oxidative challenge. This finding is consistent with the changes observed in other antioxidant parameters in the present study. Nevertheless, the increase in GSH should be interpreted as an association with altered antioxidant status rather than as direct evidence that p(GgO) stimulated GSH synthesis or directly neutralized ROS.

The antioxidant properties of ginger-derived preparations have been attributed to their complex composition, including phenolic and terpenoid constituents such as gingerols, shogaols, and zingiberene. These compounds have been reported to possess antioxidant and other biological activities. However, the present study did not separately quantify the contribution of individual ginger-oil constituents to the observed biological responses. Therefore, the effects observed following p(GgO) administration should be attributed to the p(GgO) formulation rather than to a specific constituent. The observed increase in GSH and changes in other oxidative stress-related parameters may reflect the combined biological activity of the incorporated ginger-oil constituents and the physicochemical characteristics of the polymeric formulation. Under physiological conditions, ROS generation is counterbalanced by enzymatic and non-enzymatic antioxidant systems. Oxidative stress occurs when ROS production exceeds the capacity of these defense mechanisms to maintain redox equilibrium. The brain is particularly sensitive to such disturbances because of its high metabolic activity and oxygen demand [128] Oxidative stress has consequently been implicated as an important component of the pathological processes associated with several neurodegenerative disorders, including Alzheimer's and Parkinson's diseases and other cognitive disorders.

The TOS, TAS, and OSI findings presented in Table 4 provide additional information regarding the overall oxidative balance in brain tissue. Statistically significant differences were observed among the experimental groups for these parameters. TOS levels were significantly lower in the p(GgO)-treated groups, whereas TAS levels showed a significant increase. In particular, p(GgO) administration was associated with increased TAS levels in the $AlCl_3$-exposed groups. The concurrent reduction in TOS and increase in TAS resulted in changes in the OSI, indicating a shift in the overall oxidative–antioxidative balance toward a less oxidative state in the p(GgO)-treated groups. Taken together, the brain-tissue findings, including MDA, GSH, MPO, ADA, TOS, TAS, and OSI, indicate that p(GgO) administration was associated with alterations in several biochemical parameters related to oxidative and cellular homeostasis following $AlCl_3$ exposure. The reduction in TOS and MDA, together with the increase in GSH and TAS, is broadly consistent with attenuation of oxidative imbalance. However, these findings should be interpreted as evidence of an association between p(GgO) administration and improved oxidative status rather than as proof of a specific molecular pathway. Further mechanistic studies incorporating ROS measurements, inflammatory mediators, microglial markers, mitochondrial parameters, and redox-regulatory signaling pathways would be necessary to determine the precise mechanisms underlying the observed neuroprotective effects.

Table 4. MPO, ADA, TAS, TOS and OSI values in brain tissue.

Parameters	MPO X ± SD	ADA X ± SD	TOS X ± SD	TAS X ± SD	OSİ X ± SD
Control (n:7)	1.02 ± 0.42 A	19.85 ± 1.4 A	0.27 ± 0.4 A	1.59 ± 0.4 B	17.17 ± 0.3 A
Alzheimer (n:7)	1.059 ± 0.33 B	30.69 ± 3.0 F	1.33 ± 0.2 E	1.28 ± 0.2 A	103.53 ± 0.1 E
p(GgO) 5 mg (n:8)	1.20 ± 0.30 B	20.39 ± 8.6 B	1.21 ± 0.15 D	2.45 ± 0.1 E	49.49 ± 0.6 C
AL-p(GgO) 5 mg (n:8)	1.40 ± 0.53 C	28.48 ± 1.3 E	0.69 ± 0.32 B	1.66 ± 0.2 C	41.21 ± 0.2 B
p(GgO) 10 mg (n:8)	1.31 ± 0.1 D	25.78 ± 0.5 D	0.80 ± 0.01 C	1.90 ± 0.2 D	42.03 ± 0.6 B
AL-p(GgO) 10 mg (n:8)	1.61 ± 0.1 E	22.60 ± 0.5 C	1.78 ± 0.03 E	2.45 ± 0.7 E	72.68 ± 0.3 D

A, B, C, D, E, F, G, H: The difference between different groups in the brains for MPO, ADA, TAS, TOS and OSI is significant ($p < 0.05$). ($p < 0.05$).

An increase in GSH levels was observed in the brain tissues of p(GgO)-treated rats compared with the $AlCl_3$-exposed group, and this increase was statistically significant. Since GSH is an important component of the endogenous antioxidant system, the observed increase may indicate improved maintenance of redox homeostasis following p(GgO) administration. Consistent with this finding, TOS levels decreased significantly, whereas TAS levels increased in the p(GgO)-treated groups (Table 4), resulting in an overall shift in the oxidative–antioxidative balance. These findings provide biochemical support for the potential of p(GgO) to attenuate oxidative imbalance associated with $AlCl_3$ exposure.

Natural antioxidants and ginger-derived compounds have previously been investigated for their potential neuroprotective effects. Ginger (Zingiber officinale) extracts have been reported to reduce lipid peroxidation and exert antioxidant, free-radical-scavenging, and metal-chelating activities [129]. 6-Gingerol and other ginger constituents have also been associated with reduced oxidative stress, modulation of inflammatory pathways, and improvement of cognitive deficits in experimental models [130]. In addition, the reported anticholinesterase and antioxidant activities of ginger and ginger oil may contribute to their potential effects on learning and memory [131–133]. In addition, the reported anticholinesterase and antioxidant activities of ginger and ginger oil may contribute to their potential effects on learning and memory [132–137]. Experimental studies have further reported improvements in brain morphology following ginger extract administration, which have been associated with antioxidant and anti-inflammatory effects [137–139]. The present findings are broadly consistent with these previous observations, as p(GgO) administration was associated with reduced oxidative stress and increased antioxidant status in brain tissue. However, the present study did not directly determine the contribution of individual ginger constituents or specific molecular pathways. Therefore, the observed effects should be attributed to the p(GgO) rather than to a single compound. Similarly, the present findings do not establish direct inhibition of amyloid aggregation, acetylcholinesterase activity, or neuroinflammatory signaling.

The primary hypothesis of this study was that p(GgO) would attenuate $AlCl_3$-associated oxidative imbalance by enhancing endogenous antioxidant defenses and reducing oxidative damage. The changes observed in GSH, TOS, TAS, OSI, and other oxidative stress-related parameters provide partial support for this hypothesis. The responses varied among tissues, indicating that the biological effects of p(GgO) were tissue dependent.

From a p(GgO) perspective, incorporation of ginger oil into a polymeric organoparticle may provide advantages beyond the intrinsic biological activity of the oil by potentially improving its stability, dispersion, and interaction with biological interfaces. The p(GgO) system used in this study was previously characterized, providing a physicochemical basis for its use as a particulate ginger oil. However, the present study did not directly evaluate BBB penetration, brain biodistribution, pharmacokinetics, or release kinetics. Therefore, sustained release and BBB penetration should be considered potential p(GgO)-related advantages rather than demonstrated properties. The absence of an *in vitro* release profile is another limitation of the present study. Because ginger oil was used directly as the oil phase during polymerization rather than being subsequently loaded into preformed particles, the formulation was not designed as a conventional drug-loaded carrier system for which a standard release profile was determined. The present experiments focused on the biological responses produced by the previously characterized p(GgO) organoparticles *in vivo*. Nevertheless, direct investigation of the release or partitioning behavior of ginger-oil-derived constituents from the polymeric structure would provide useful information about the formulation and should be addressed in future studies. Therefore, controlled or sustained release should not be considered a demonstrated property of the p(GgO) system in the current study. An important limitation of the study is the absence of a free ginger oil comparison group and an established pharmacological positive control. The experimental design was primarily intended to investigate the biological response to the previously characterized p(GgO) organoparticles under $AlCl_3$-induced oxidative challenge rather than to directly compare the particulate formulation with free ginger oil or a standard anti-Alzheimer drug. Consequently, the present results cannot determine whether the observed effects are specifically attributable to the particulate organization of ginger oil or whether p(GgO) provides an advantage over the free oil. Similarly, the study does not allow direct comparison with an established pharmacological treatment. Therefore, no claim of superiority of p(GgO) over free ginger oil or conventional treatment is made. Direct comparisons with free ginger oil and an appropriate positive control should be included in future studies to better define the specific contribution of the polymeric formulation). An additional limitation is that the present study was conducted exclusively *in vivo* and did not include a neuronal cell-based injury model. Thus, although the biochemical and behavioral findings support an association between p(GgO) treatment and attenuation of $AlCl_3$-associated alterations, they do not establish a direct neuronal cytoprotective mechanism. Future studies using neuronal models such as PC12 or HT22 cells and examining intracellular ROS, mitochondrial function, apoptosis, and redox-related signaling would help clarify the underlying cellular mechanisms.

4. Conclusion

$AlCl_3$-induced oxidative imbalance was associated with alterations in behavioral performance and antioxidant status in the experimental rat model used in this study. Administration of p(GgO) at 5 and 10 mg was associated with changes in Morris water maze and modified maze performance, as well as with tissue-dependent alterations in oxidative stress and antioxidant-related parameters.

The Morris water maze findings should be interpreted in the context of the longitudinal learning process. Although $AlCl_3$-exposed animals generally exhibited higher escape latencies during the later testing periods, p(GgO)-treated groups showed progressive changes in performance over time. However, p(GgO)-treated animals did not consistently outperform the untreated control group at every measurement

point. Therefore, the behavioral findings are best interpreted as evidence of a modification of the longitudinal performance pattern rather than complete normalization of spatial learning.

Biochemical analyses further indicated that p(GgO) administration was associated with changes in MDA, GSH-Px, GR, GST, GSH, SOD, and CAT activities across the tissues examined, together with alterations in brain MPO, ADA, TOS, TAS, and OSI levels. In particular, the changes in GSH, TOS, TAS, and OSI in brain tissue, together with the tissue-dependent antioxidant responses, provide partial support for the hypothesis that p(GgO) may modulate $AlCl_3$-associated oxidative imbalance. These findings should be interpreted as an overall alteration in redox homeostasis rather than as evidence of a single molecular mechanism.

The potential significance of p(GgO) may arise from the incorporation of ginger oil into a previously characterized polymeric organoparticle system. However, the present study did not directly compare p(GgO) with free ginger oil or determine BBB penetration, brain biodistribution, pharmacokinetics, or release kinetics. Therefore, the specific contribution of the polymeric formulation to the observed biological effects remains to be established.

Generally, the present findings provide preclinical evidence supporting further investigation of p(GgO) as a potential modulator of oxidative and behavioral alterations in an $AlCl_3$-induced experimental model. Nevertheless, the study does not establish p(GgO) as a treatment for Alzheimer's disease. Future studies incorporating free-ginger-oil controls, established positive controls, neuronal cell-based models, longer treatment periods, and pharmacokinetic, biodistribution, BBB-transport, and mechanistic analyses will be necessary to determine its therapeutic relevance and the mechanisms underlying the observed effects.

Data availability statement

The data generated and analyzed during this study are not publicly available due to ethical and institutional restrictions. A supplementary file containing detailed materials, experimental procedures, and analytical methods is provided with this article.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used ChatGPT and NotebookLM to assist with the literature review and to improve the language, grammar, and readability of the manuscript. These tools were not used to generate or develop the scientific content of the manuscript. All scientific ideas, analyses, interpretations, and conclusions were developed by the authors. The authors carefully reviewed the manuscript and take full responsibility for its content, including its originality, accuracy, and integrity. The manuscript was prepared in accordance with accepted principles of academic integrity and publication ethics.

Acknowledgments

Authors' contribution

Formal analysis, investigation, methodology, experimental animals, original draft, writing—review and editing, D.A; experimental animals; formal analysis, A.T., S.A.; formal analysis, T.E.D.; methodology, N.A. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical statement

Van Yüzüncü Yıl University Animal Experimentation Ethics Committee's decision dated 30/03/2023 and numbered 2023/05-19. All animal procedures complied with the principles of 3Rs and relevant Turkish national regulations for laboratory animal experimentation

References

[1] Barrera-Ocampo A, Lopera F. Amyloid-beta immunotherapy: the hope for Alzheimer disease? *Colomb. Med.* 2016, 47(4):203–212.

[2] Frisoni GB, Altomare D, Thal DR, Ribaldi F, van der Kant R, *et al.* The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. *Nat. Rev. Neurosci.* 2022, 23(1):53–66.

[3] Cummings JL, Cole G. Alzheimer disease. *JAMA* 2002, 287(18):2335–2338.

[4] Frautschy SA, Hu W, Kim P, Miller SA, Chu T, *et al.* Phenolic anti-inflammatory antioxidant reversal of Aβ-induced cognitive deficits and neuropathology. *Neurobiol. Aging* 2001, 22(6):993–1005.

[5] Ismail Z, Creese B, Aarsland D, Kales HC, Lyketsos CG, *et al.* Psychosis in Alzheimer disease—mechanisms, genetics and therapeutic opportunities. *Nat. Rev. Neurol.* 2022, 18(3):131–144.

[6] Karran E, De Strooper B. The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. *Nat. Rev. Drug Discovery* 2022, 21(4):306–318.

[7] Chakraborty B, Mukerjee N, Maitra S, Zehravi M, Mukherjee D, *et al.* Therapeutic potential of different natural products for the treatment of Alzheimer's disease. *Oxid. Med. Cell. Longev.* 2022, 2022:6873874.

[8] Wojsiat J, Zoltowska KM, Laskowska-Kaszub K, Wojda U. Oxidant/antioxidant ımbalance in Alzheimer's disease: therapeutic and diagnostic prospects. *Oxid. Med. Cell. Longev.* 2018, 2018(1):6435861.

[9] Thenmozhi AJ, Raja TRW, Janakiraman U, Manivasagam T. Neuroprotective effect of hesperidin on aluminium chloride induced Alzheimer's disease in Wistar rats. *Neurochem. Res.* 2015, 40(4):767–776.

[10] Syarifah-Noratiqah SB, Naina-Mohamed I, Zulfarina MS, Qodriyah HMS. Natural polyphenols in the treatment of Alzheimer's disease. *Current Drug Targets* 2018, 19(8):927–937.

[11] Natarajan S, Shunmugiah KP, Kasi PD. Plants traditionally used in age-related brain disorders (dementia): an ethanopharmacological survey. *Pharm. Biol.* 2013, 51(4):492–523.

[12] Akram M, Nawaz A. Effects of medicinal plants on Alzheimer's disease and memory deficits. *Neural Regen. Res.* 2017, 12(4):660–670.

[13] Gregory J, Vengalasetti YV, Bredesen DE, Rao RV. Neuroprotective herbs for the management of Alzheimer's disease. *Biomolecules* 2021, 11(4):543.

[14] Ahmed HH, Zaazaa AM, Abd El-Motelp BA. Zingiber officinale and Alzheimer's disease: Evidences and mechanisms. *Int. J. Pharm. Sci. Rev. Res.* 2014, 27(2):142–152.

[15] Xu H, Liu Z, Liu Y, Zhang W, Xu B, *et al.* Administration of midazolam in infancy does not affect learning and memory of adult mice. *Clin. Exp. Pharmacol. Physiol.* 2009, 36(12):1144–1148.

[16] Elufioye TO, Oladele AT, Cyril-Olutayo CM, Agbedahunsi JM, Adesanya SA. Ethnomedicinal study and screening of plants used for memory enhancement and antiaging in Sagamu, Nigeria. *Eur. J. Med. Plants* 2012, 2(3):262–275.

[17] Soumyanath A, Zhong YP, Henson E, Wadsworth T, Bishop J, *et al.* Centella asiatica extract ımproves behavioral deficits in a mouse model of Alzheimer's disease: ınvestigation of a possible mechanism of action. *Int. J. Alzheimers Dis.* 2012, 2012:381974.

[18] Gohil KJ, Patel JA, Gajjar AK. Pharmacological review on centella asiatica: a potential herbal cure-all. *Indian J. Pharm. Sci.* 2010, 72(5):546–556.

[19] Rao MK, Rao MS, Rao GS. Treatment with Centalla asiatica (Linn) fresh leaf extract enhances learning ability and memory retention power in rats. *Neurosciences* 2007, 12(3):236–241.

[20] Veerendra Kumar MH, Gupta YK. Effect of Centella asiatica on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. *Clin. Exp. Pharmacol. Physiol.* 2003, 30(5–6):336–342.

[21] Bihaqi SW, Singh AP, Tiwari M. *In vivo* investigation of the neuroprotective property of Convolvulus pluricaulis in scopolamine-induced cognitive impairments in Wistar rats. *Indian J. Pharmacol.* 2011, 43(5):520–525.

[22] Dubey RS. Protein synthesis by plants under stressful conditions. In *Handbook of Plant and Crop Stress*. New York: Marcel Dekker, 1994. pp. 277–299.

[23] Malik J, Karan M, Vasisht K. Nootropic, anxiolytic and CNS-depressant studies on different plant sources of shankhpushpi. *Pharm. Biol.* 2011, 49(12):1234–1242.

[24] Nahata A, Patil UK, Dixit VK. Effect of Evolvulus alsinoides Linn. on learning behavior and memory enhancement activity in rodents. *Phytother. Res.* 2010, 24(4):486–493.

[25] Sharma K, Bhatnagar M, Kulkarni SK. Effect of Convolvulus pluricaulis choisy and Asparagus racemosus willd on learning and memory in young and old mice: a comparative evaluation. *Indian J. Exp. Biol.* 2010, 48:479–485.

[26] Nahata A, Patil UK, Dixit VK. Effect of Convulvulus pluricaulis Choisy. On learning behaviour and memory enhancement activity in rodents. *Nat. Prod. Res.* 2008, 22(16):1472–1482.

[27] Vasundhara S, Hafsa A, Rajiv G. Memory enhancing effects of Ficus carica leaves in hexane extract on interoceptive behavioral models. *Asian J. Pharm. Clin. Res.* 2013, 6(3):109–113.

[28] Ahmed F, Chandra JN, Manjunath S. Acetylcholine and memory-enhancing activity of Ficus racemosa bark. *Pharmacogn. Res.* 2011, 3(4):246–249.

[29] Asgary S, Naderi GH, Askari N. Protective effect of flavonoids against red blood cell hemolysis by free radicals. *Exp. Clin. Cardiol.* 2005, 10(2):88–90.

[30] Lannert H, Hoyer S. Intracerebroventricular administration of streptozotocin causes long-term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. *Behav. Neurosci.* 1998, 112(5):1199–1208.

[31] Malve HO, Raut SB, Marathe PA, Rege NN. Effect of combination of Phyllanthus emblica, Tinospora cordifolia, and Ocimum sanctum on spatial learning and memory in rats. *J. Ayurveda Integr. Med.* 2014, 5(4):209–215.

[32] Reddy NM, Reddy R. Tinospora cordifolia chemical constituents and medicinal properties: a review. *Sch. Acad. J. Pharm.* 2015, 4(8):364–369.

[33] Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, *et al.* Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. *J. Clin. Pharm. Ther.* 2003, 28(1):53–59.

[34] Eidi M, Eidi A, Bahar M. Effects of Salvia officinalis L. (sage) leaves on memory retention and its interaction with the cholinergic system in rats. *Nutrition* 2006, 22(3):321–326.

[35] Haider S, Batool Z, Tabassum S, Perveen T, Saleem S, *et al.* Effects of walnuts (Juglans regia) on learning and memory functions. *Plant Foods Hum. Nutr.* 2011, 66(4):335–340.

[36] Koppula S, Choi DK. Cuminum cyminum extract attenuates scopolamine-induced memory loss and stress-induced urinary biochemical changes in rats: a noninvasive biochemical approach. *Pharm. Biol.* 2011, 49(7):702–708.

[37] Farokhnia M, Shafiee Sabet M, Iranpour N, Gougol A, Yekehtaz H, *et al.* Comparing the efficacy and safety of Crocus sativus L. with memantine in patients with moderate to severe Alzheimer's disease: a double-blind randomized clinical trial. *Hum. Psychopharmacol.* 2014, 29(4):351–359.

[38] Akhondzadeh S, Shafiee Sabet M, Harirchian MH, Togha M, Cheraghmakani H, *et al.* A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease. *Psychopharmacology* 2010, 207(4):637–643.

[39] Taiwo AE, Leite FB, Lucena GM, Barros M, Silveira D, *et al.* Anxiolytic and antidepressant-like effects of Melissa officinalis (lemon balm) extract in rats: influence of administration and gender. *Indian J. Pharmacol.* 2012, 44(2):189–192.

[40] Kennedy DO, Scholey AB, Tildesley NTJ, Perry EK, Wesnes KA. Modulation of mood and cognitive performance following acute administration of Melissa officinalis (lemon balm). *Pharmacol. Biochem. Behav.* 2002, 72(4):953–964.

[41] Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, *et al.* Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. *J. Neurol. Neurosurg. Psychiatry* 2003, 74(7):863–866.

[42] Ozarowski M, Mikolajczak PL, Bogacz A, Gryszczynska A, Kujawska M, *et al.* Rosmarinus officinalis L. leaf extract improves memory impairment and affects acetylcholinesterase and butyrylcholinesterase activities in rat brain. *Fitoterapia* 2013, 91:261–271.

[43] Hritcu L, Noumedem JA, Cioanca O, Hancianu M, Kuete V, *et al.* Methanolic extract of Piper nigrum fruits improves memory impairment by decreasing brain oxidative stress in amyloid beta(1–42) rat model of Alzheimer's disease. *Cell. Mol. Neurobiol* 2014, 34(3):437–449.

[44] Shi C, Liu J, Wu F, Yew DT. Ginkgo biloba extract in Alzheimer's disease: from action mechanisms to medical practice. *Int. J. Mol. Sci.* 2010, 11(1):107–123.

[45] Walesiuk A, Braszko JJ. Preventive action of Ginkgo biloba in stress- and corticosterone-induced impairment of spatial memory in rats. *Phytomedicine* 2009, 16(1):40–46.

[46] Chandrasekaran K, Mehrabian Z, Spinnewyn B, Drieu K, Fiskum G. Neuroprotective effects of bilobalide, a component of the Ginkgo biloba extract (EGb 761), in gerbil global brain ischemia. *Brain Res.* 2001, 922(2):282–292.

[47] Wesnes KA, Ward T, McGinty A, Petrini O. The memory enhancing effects of a Ginkgo biloba/Panax ginseng combination in healthy middle-aged volunteers. *Psychopharmacology* 2000, 152(4):353–361.

[48] Vasudevan M, Parle M. Memory enhancing activity of Anwala churna (Emblica officinalis Gaertn.): an Ayurvedic preparation. *Physiol. Behav.* 2007, 91(1):46–54.

[49] Ramachandran PS, Baird RW, Markey P, Singleton S, Lowe M, *et al.* Neurosyphilis: still prevalent and overlooked in an at risk population. *PLoS One* 2020, 15(10):e0238617.

[50] Aguiar S, Borowski T. Neuropharmacological review of the nootropic herb Bacopa monnieri. *Rejuvenation Res.* 2013, 16(4):313–326.

[51] Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, *et al.* Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial. *J. Altern. Complement. Med.* 2008, 14(6):707–713.

[52] Russo A, Borrelli F. Bacopa monniera, a reputed nootropic plant: an overview. *Phytomedicine* 2005, 12(4):305–317.

[53] Singh SK. Phytochemical analysis of leaf callus of Bacopa monnieri L. *Int. J. Sci. Res. Publ.* 2012, 2(9):1–3.

[54] Uabundit N, Wattanathorn J, Mucimapura S, Ingkaninan K. Cognitive enhancement and neuroprotective effects of Bacopa monnieri in Alzheimer's disease model. *J. Ethnopharmacol.* 2010, 127(1):26–31.

[55] Godkar PB, Gordon RK, Ravindran A, Doctor BP. Celastrus paniculatus seed oil and organic extracts attenuate hydrogen peroxide- and glutamate-induced injury in embryonic rat forebrain neuronal cells. *Phytomedicine* 2006, 13(1–2):29–36.

[56] Kumar MHV, Gupta YK. Antioxidant property of Celastrus paniculatus Willd.: a possible mechanism in enhancing cognition. *Phytomedicine* 2002, 9(4):302–311.

[57] Bhanumathy M, Harish MS, Shivaprasad HN, Sushma G. Nootropic activity of Celastrus paniculatus seed. *Pharm. Biol.* 2010, 48(3):324–327.

[58] Katekhaye S, Duggal S, Singh AP. An inside preview of nutritional and pharmacological profile of Celastrus paniculatus. *Int. J. Recent Adv. Pharm. Res.* 2011, 1:19–24.

[59] Saxena G, Singh SP, Pal R, Singh S, Pratap R, *et al.* Gugulipid, an extract of Commiphora whighitii with lipid-lowering properties, has protective effects against streptozotocin-induced memory deficits in mice. *Pharmacol. Biochem. Behav.* 2007, 86(4):797–805.

[60] Raja SG, Dreyfus GD. Statins: much more than just a lipid-lowering therapy. *Indian Heart J.* 2004, 56(3):204–209.

[61] Jazayeri SB, Amanlou A, Ghanadian N, Pasalar P, Amanlou M. A preliminary investigation of anticholinesterase activity of some Iranian medicinal plants commonly used in traditional medicine. *DARU J. Pharm. Sci.* 2014, 22(1):17.

[62] Ambawade S, Kasture VS, Kasture SB. Anxiolytic activity of Glycyrrhiza glabra linn. *J. Nat. Remed.* 2001, 2(2):130–134.

[63] Dhingra D, Parle M, Kulkarni SK. Memory enhancing activity of Glycyrrhiza glabra in mice. *J. Ethnopharmacol.* 2004, 91(2–3):361–365.

[64] Heck CI, de Mejia EG. Yerba mate tea (Ilex paraguariensis): a comprehensive review on chemistry, health implications, and technological considerations. *J. Food Sci.* 2007, 72(9):RR138–151.

[65] Colpo G, Trevisol F, Fachinetto ALMTR, Athayde RPPML, Rocha JBT, *et al.* Ilex paraguariens has antioxidant potential and attenuates haloperidol-induced orofacial and memory dysfunction in rats. *Neurotox. Res.* 2007, 12(3):171–180.

[66] Bastos DHM, Oliveira DMd, Matsumoto RLT, Carvalho PdO, Ribeiro ML. Yerba maté: pharmacological properties, research and biotechnology. *Med. Aromat. Plant Sci. Biotechnol.* 2007, 1(1):37–46.

[67] Prediger RD, Fernandes MS, Rial D, Wopereis S, Pereira VS, *et al.* Effects of acute administration of the hydroalcoholic extract of mate tea leaves (Ilex paraguariensis) in animal models of learning and memory. *J. Ethnopharmacol.* 2008, 120(3):465–473.

[68] Wang R, Yan H, Tang X. Progress in studies of huperzine A, a natural cholinesterase inhibitor from Chinese herbal medicine. *Acta Pharmacol. Sin.* 2006, 27(1):1–26.

[69] Rubio J, Qiong W, Liu X, Jiang Z, Dang H, *et al.* Aqueous extract of Black Maca (Lepidium meyenii) on memory impairment induced by ovariectomy in mice. *Evid. Based Complement. Alternat. Med.* 2011, 2011:253958.

[70] Rubio J, Dang H, Gong M, Liu X, Chen S, *et al.* Aqueous and hydroalcoholic extracts of Black Maca (Lepidium meyenii) improve scopolamine-induced memory impairment in mice. *Food Chem. Toxicol.* 2007, 45(10):1882–1890.

[71] Obulesu M, Rao DM. Effect of plant extracts on Alzheimer's disease: an insight into therapeutic avenues. *J. Neurosci. Rural Pract.* 2011, 2(1):56–61.

[72] Pakade V, Cukrowska E, Chimuka L. Comparison of antioxidant activity of Moringa oleifera and selected vegetables in South Africa. *S. Afr. J. Sci.* 2013, 109(3):1–5.

[73] Ganguly R, Guha D. Alteration of brain monoamines & EEG wave pattern in rat model of Alzheimer's disease & protection by Moringa oleifera. *Indian J. Med. Res.* 2008, 128(6):744–751.

[74] Maeda A, Tanimoto S, Abe T, Kazama S, Tanızawa H, *et al.* Chemical constituents of Myristica fragrans houttuyn seed and their physiological activities. *Yakugaku Zasshi* 2008, 128(1):129–133.

[75] Asgarpanah J, Kazemivash N. Phytochemistry and pharmacologic properties of Myristica fragrans hoyutt.: a review. *Afr. J. Biotechnol.* 2012, 11(65):12787–12793.

[76] Parle M, Dhingra D, Kulkarni SK. Improvement of mouse memory by Myristica fragrans seeds. *J. Med. Food* 2004, 7(2):157–161.

[77] Narasimhan B, Dhake AS. Antibacterial principles from Myristica fragrans seeds. *J. Med. Food* 2006, 9(3):395–399.

[78] Lee YK, Yuk DY, Kim TI, Kim YH, Kim KT, *et al.* Protective effect of the ethanol extract of Magnolia officinalis and 4-O-methylhonokiol on scopolamine-induced memory impairment and the inhibition of acetylcholinesterase activity. *J. Nat. Med.* 2009, 63(3):274–282.

[79] Lo YC, Teng C, Chen C, Chen C, Hong C. Magnolol and honokiol isolated from magnolia officinalis protect rat heart mitochondria against lipid peroxidation. *Biochem. Pharmacol.* 1994, 47(3):549–553.

[80] Lee JW, Lee YK, Lee BJ, Nam SY, Lee SI, *et al.* Inhibitory effect of ethanol extract of Magnolia officinalis and 4-O-methylhonokiol on memory impairment and neuronal toxicity induced by beta-amyloid. *Pharmacol. Biochem. Behav.* 2010, 95(1):31–40.

[81] Li Q, Weng X. Antioxidant activity of Magnolia officinalis. *Chin. Oils Fats* 2005, 30:37–40.

[82] Chiu JH, Ho CT, Wei Y, Lui W, Hong C. *In vitro* and *in vivo* protective effect of honokiol on rat liver from peroxidative injury. *Life Sci.* 1997, 61(19):1961–1971.

[83] Kong C, Tsai K, Chin J, Chan W, Hong C. Magnolol attenuates peroxidative damage and improves survival of rats with sepsis. *Shock* 2000, 13(1):24–28.

[84] Dikalov S, Losik T, Arbiser JL. Honokiol is a potent scavenger of superoxide and peroxyl radicals. *Biochem. Pharmacol.* 2008, 76(5):589–596.

[85] Hou YC, Chao PDL, Chen SY. Honokiol and magnolol ıncreased hippocampal acetylcholine release in freely-moving rats. *Am. J. Chin. Med.* 2000, 28(3–4):379–384.

[86] Lee MK, Kim SR, Sung SH, Lim D, Kim H, *et al.* Asiatic acid derivatives protect cultured cortical neurons from glutamate-induced excitotoxicity. *Res. Commun. Mol. Pathol. Pharmacol.* 2000, 108(1–2):75–86.

[87] Wang J, Ho TF, Chang L, Chen C, Anti-inflammatory effect of magnolol, isolated from Magnolia oficinalis, on A23187-induced pleurisy in Mice. *J. Pharm. Pharmacol.* 1995, 47(10):857–860.

[88] Lyte M. Probiotics function mechanistically as delivery vehicles for neuroactive compounds: microbial endocrinology in the design and use of probiotics. *Bioessays* 2011, 33(8):574–581.

[89] Joshi H, Parle M. Nardostachys jatamansi improves learning and memory in mice. *J. Med. Food* 2006, 9(1):113–118.

[90] Karkada G, Shenoy KB, Halahalli H, Karanth KS. Nardostachys jatamansi extract prevents chronic restraint stress-induced learning and memory deficits in a radial arm maze task. *J. Nat. Sci. Biol. Med.* 2012, 3(2):125–132.

[91] Heo JH, Lee ST, Chu K, Oh MJ, Shim JY, *et al.* An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease. *Eur. J. Neurol.* 2008, 15(8):865–868.

[92] Lee ST, Chu K, Sim JY, Heo JH, Kim M. Panax ginseng enhances cognitive performance in Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 2008, 22(3):222–226.

[93] Cho IH. Effects of Panax ginseng in neurodegenerative diseases. *J. Ginseng Res.* 2012, 36(4):342–353.

[94] Kim HJ, Kim P, Shin CY. A comprehensive review of the therapeutic and pharmacological effects of ginseng and ginsenosides in central nervous system. *J. Ginseng Res.* 2013, 37(1):8–29.

[95] Cambay Z, Baydas G, Tuzcu M, Bal R. Pomegranate (Punica granatum L.) flower improves learning and memory performances impaired by diabetes mellitus in rats. *Acta Physiol. Hung.* 2011, 98(4):409–420.

[96] Das AK, Mandal SC, Banerjee SK, Sinha S, Das J, *et al.* Studies on antidiarrhoeal activity of Punica granatum seed extract in rats. *J. Ethnopharmacol.* 1999, 68(1–3):205–208.

[97] Malhotra S, Singh AP. Medicinal properties of ginger (Zingiber officinale Rosc.). *Nat. Prod. Rad.* 2003, 2(6):296–301.

[98] Joshi H, Parle M. Zingiber officinale: evaluation of its nootropic effect in mice. *Afr. J. Tradit. Complement. Altern. Med.* 2006, 3(1):64–74.

[99] Ghribi O. Potential mechanisms linking cholesterol to Alzheimer's disease-like pathology in rabbit brain, hippocampal organotypic slices, and skeletal muscle. *J. Alzheimers Dis.* 2008, 15(4):673–684.

[100] Auddy B, Hazra J, Mitra A, Abedon B, Ghosal S. A standardized Withania somnifera extract significantly reduces stress-related parameters in chronically stressed humans: a double-blind, randomized, placebo-controlled study. *JANA* 2008, 11(1):50–56.

[101] Kuboyama T, Tohda C, Komatsu K. Neuritic regeneration and synaptic reconstruction induced by withanolide A. *Br. J. Pharmacol.* 2005, 144(7):961–971.

[102] Isman MB, Wilson JA, Bradbury R. Insecticidal activities of commercial rosemary oils (Rosmarinus officinalis.) against larvae of Pseudaletia unipuncta. and Trichoplusia ni. in relation to their chemical compositions. *Pharm. Biol.* 2008, 46(1–2):82–87.

[103] Properzi A, Angelini P, Bertuzzi G, Venanzoni R. Some biological activities of essential oils. *Med. Aromat. Plants* 2012, 2(5):1000116.

[104] Langeveld WT, Veldhuizen EJ, Burt SA. Synergy between essential oil components and antibiotics: a review. *Crit. Rev. Microbiol.* 2014, 40(1):76–94.

[105] Bassole IH, Juliani HR. Essential oils in combination and their antimicrobial properties. *Molecules* 2012, 17(4):3989–4006.

[106] El-Banna AH, Abo El-Ela FI, Abdel-Wahab A, Gamal A, Abdel-Razik ARH, *et al.* Therapeutic efficacy of amygdaline and amygdaline-loaded niosomes in a rat model of Alzheimer's disease via oxidative stress, brain neurotransmitters, and apoptotic pathway. *Beni-Suef Univ. J. Basic Appl. Sci.* 2024, 13(1):117.

[107] Dudu TE, Alpaslan D, Aktas N. Hydrogen production from methanolysis of sodium borohydride by non-metal p(CO) organo-particles synthesized from castor oil. *J. Polym. Environ.* 2022, 30(11):4562–4570.

[108] Alpaslan D, Ersen Dudu T, Aktas N. Synthesis of poly(ginger oil) organo particles as a metal free catalysis and their use in hydrogen production from sodium borohydride methanolysis. *J. Polym. Environ.* 2023, 31(3):1191–1201.

[109] Talebi M, İlgün S, Ebrahimi V, Talebi M, Farkhondeh T, *et al.* Zingiber officinale ameliorates Alzheimer's disease and Cognitive Impairments: lessons from preclinical studies. *Biomed. Pharmacother.* 2021, 133:111088.

[110] Scott TC. The hampton court maze. *Pedagog. Semin. J. Genet. Psychol.* 1931, 39(2):287–289.

[111] Mohseni F, Behnam SG, Rafaiee R. A review of the historical evolutionary process of dry and water maze tests in rodents. *Basic Clin. Neurosci.* 2020, 11(4):389–402.

[112] Turan A, Çelik İ. Antioxidant and hepatoprotective properties of dried fig against oxidative stress and hepatotoxicity in rats. *Int. J. Biol. Macromol.* 2016, 91:554–559.

[113] Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. *Clin. Biochem.* 2004, 37(2):112–119.

[114] Erel O. A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. *Clin. Biochem.* 2004, 37(4):277–285.

[115] Aksoy A, Öztürk ZN. Concept of animal experimentation model and experiment design with specific experimental models. In *Laboratuvar Hayvanlarında İlaç Kullanımı*, Ankara: Türkiye Klinikleri, 2024. pp. 62–74.

[116] Verstraeten SV, Nogueira LV, Schreier S, Oteiza PI. Effect of trivalent metal ions on phase separation and membrane lipid packing: role in lipid peroxidation. *Arch. Biochem. Biophys.* 1997, 338(1):121–127.
[117] Exley C. What is the risk of aluminium as a neurotoxin? *Expert Rev. Neurother.* 2014, 14(6):589–591.
[118] Exley C. The pro-oxidant activity of aluminum. *Free Radic. Biol. Med.* 2004, 36(3):380–387.
[119] Yahia R, Masoud MA, Sheded MS, Mansour HA. The possible neurobehavioral protective effects of natural antioxidant against phototoxicity attenuation of antimicrobial quinolone group in rats. *J. Biochem. Mol. Toxicol.* 2020, 34(7):e22495.
[121] Zhang R, Liu R, Zong W. Bisphenol S interacts with catalase and induces oxidative stress in mouse liver and renal cells. *J. Agric. Food Chem.* 2016, 64(34):6630–6640.
[122] Younus H. Therapeutic potentials of superoxide dismutase. *Int. J. Health Sci.* 2018, 12(3):88–93.
[123] Lucio CF, Silva LCG, Regazzi FM, Angrimani DSR, Nichi M, *et al.* Effect of reduced glutathione (GSH) in canine sperm cryopreservation: *in vitro* and *in vivo* evaluation. *Cryobiology* 2016, 72(2):135–140.
[124] Sharma N, Butterworth J, Cooper BT, Tselepis C, Iqbal TH. The emerging role of the liver in iron metabolism. *Am. J. Gastroenterol.* 2005, 100(1):201–206.
[125] Crichton R. Inorganic biochemistry of ıron metabolism: from molecular mechanisms to clinical consequences, 2nd ed. Chichester: John Wiley & Sons, 2001.
[126] Żebrowska E, Maciejczyk M, Żendzian-Piotrowska M, Zalewska A, Chabowski A. High protein diet induces oxidative stress in rat cerebral cortex and hypothalamus. *Int. J. Mol. Sci.* 2019, 20(7):1547.
[127] Aratani Y. Myeloperoxidase: its role for host defense, inflammation, and neutrophil func tion. *Arch. Biochem. Biophys.* 2018, 640:47–52.
[128] Mahajan M, Tiwari N, Sharma R, Kaur S, Singh N. Oxidative stress and its relationship with adenosine deaminase activity in various stages of breast cancer. *Indian J. Clin. Biochem.* 2013, 28(1):51–54.
[129] Howes MJR, Perry NS, Houghton PJ. Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders. *Phytother. Res.* 2003, 17(1):1–18.
[130] Adetuyi BO, Farombi EO. 6-Gingerol, an active constituent of ginger, attenuates lipopolysaccharide-induced oxidation, inflammation, cognitive deficits, neuroplasticity, and amyloidogenesis in rat. *J. Food Biochem.* 2021, 45(4):e13660.
[131] Wattanathorn J, Jittiwat J, Tongun T, Muchimapura S, Ingkaninan K. Zingiber officinale mitigates brain damage and improves memory impairment in focal cerebral ischemic rat. *Evid. Based Complement. Alternat. Med.* 2011, 2011:429505.
[132] Sahardi NFNM, Makpol S. Ginger (Zingiber officinale Roscoe) in the prevention of ageing and degenerative diseases: review of current evidence. *Evid. Based Complement. Alternat. Med.* 2019, 2019:5054395.
[133] Fuhrman B, Rosenblat M, Hayek T, Coleman R, Aviram M. Ginger extract consumption reduces plasma cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E-deficient mice. *J. Nutr.* 2000, 130(5):1124–1131.

[134] Grzanna R, Phan P, Polotsky A, Lindmark L, Frondoza CG. Ginger extract inhibits beta-amyloid peptide-induced cytokine and chemokine expression in cultured THP-1 monocytes. *J. Altern. Complement. Med.* 2004, 10(6):1009–1013.

[135] Parihar MS, Hemnani T. Alzheimer's disease pathogenesis and therapeutic interventions. *J. Clin. Neurosci.* 2004, 11(5):456–467.

[136] Masuda Y, Kikuzaki H, Hisamoto M, Nakatani N. Antioxidant properties of gingerol related compounds from ginger. *BioFactors* 2004, 21(1–4):293–296.

[137] Topic B, Tani E, Tsiakitzis K, Kourounakis PN, Dere E, *et al.* Enhanced maze performance and reduced oxidative stress by combined extracts of zingiber officinale and ginkgo biloba in the aged rat. *Neurobiol. Aging* 2002, 23(1):135–143.

[138] Akinyemi AJ, Ademiluyi AO, Oboh G. Aqueous extracts of two varieties of ginger (Zingiber officinale) inhibit angiotensin I-converting enzyme, iron(II), and sodium nitroprusside-induced lipid peroxidation in the rat heart *in vitro*. *J. Med. Food* 2013, 16(7):641–646.

[139] Kitphati W, Wattanakamolkul K, Lomarat P, Phanthong P, Anantachoke N, *et al.* Anticholinesterase activity of essential oils and their constituents from Thai medicinal plants in human neuroblastoma SK-N-SH cells. *JAASP* 2012, 1(1):51–61.