



Original Article

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Grifola frondosa polysaccharides alleviate Alzheimer's disease in ratsSamira Behrad¹, Sina Pourranjbar², Mohammad Pourranjbar³, Saeid Abbasi–Maleki⁴, Samira Rostami Mehr⁴, Reza Hossein Gholizadeh Salmani⁵, Nasrollah Moradikor^{6✉}¹Department of Oral and Maxillofacial Pathology, Dental School, Semnan University of Medical Sciences, Semnan, Iran²Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran³Department and Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran⁴Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran⁵Department of Basic Sciences, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran⁶International Center for Neuroscience Research, Institute for Intelligent Research, Tbilisi, Georgia

ABSTRACT

Objective: To evaluate the effect of *Grifola frondosa* polysaccharides (GFP) in a rat model of Alzheimer's disease (AD).**Methods:** Seventy-five rats were divided into five groups: the normal control group and the AD group treated with or without GFP (100, 200, and 400 mg/kg). Behavioral responses in the open field test and elevated plus maze test were assessed. Additionally, the levels of malondialdehyde and ferric-reducing ability of plasma, and the mRNA expressions of *TNF- α* , *IL-6*, and *IL-1 β* in the hippocampus were measured.**Results:** Treatment with GFP significantly improved AD-induced behavioral changes in the open field test and elevated plus maze test ($P < 0.05$). In addition, the level of malondialdehyde and the mRNA expressions of *TNF- α* , *IL-6*, and *IL-1 β* were decreased by GFP treatment in a dose-dependent manner in AD rats ($P < 0.05$), while the level of ferric-reducing ability of plasma was significantly increased ($P < 0.05$).**Conclusions:** Oral administration of GFP can reduce inflammation and oxidative stress, as well as improve behavioral responses associated with AD, suggesting its potential use in AD treatment. However, additional studies are needed to elucidate its underlying mechanisms and efficacy.**KEYWORDS:** *Grifola frondosa*; Polysaccharides; Dementia; Behavioral responses; Inflammation; Alzheimer's disease

1. Introduction

It is estimated that approximately 150 million individuals

worldwide suffer from dementia[1]. While the exact cause remains elusive, the accumulation of amyloid- β (A β) in the brain is known to occur before symptom onset[2]. A β plaques induce morphological and functional changes in the surrounding astrocytes, leading to astrogliosis. These astrocytes play a crucial role in brain signaling, synaptic regulation, nutrient transport, homeostasis, and structural support[3]. Neuroinflammation is a key factor in the etiology of Alzheimer's disease (AD). Although acute inflammation serves a protective role against brain damage, including the presence of A β plaques[4], oxidative stress, mitochondrial dysfunction, and glucose

Significance

Grifola frondosa polysaccharides show neuroprotective and anti-inflammatory properties in earlier research; however, it is unclear how these properties work in models of Alzheimer's dementia. This study shows that *Grifola frondosa* polysaccharides can ameliorate behavioral response, and reduce oxidative stress and the levels of pro-inflammatory cytokines, indicating its potential use in the treatment of Alzheimer's dementia, but further study is required to confirm its efficacy and molecular mechanisms of neuroprotective action.

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hypometabolism are also characteristics of AD[5]. Various treatments for AD aim to restore neurotransmitter balance[6]. The use of natural antioxidants and anti-inflammatory agents has shown promise in improving symptoms of AD[7–9].

Medicinal mushrooms offer significant benefits due to their wide range of pharmacological activities, including anti-inflammatory, antioxidative, antiviral, cytotoxic, and immunomodulating properties[10,11]. *Grifola frondosa* (*G. frondosa*), a Basidiomycetes fungus from the Grifolaceae family and Polyporales order[12], has garnered recent attention for the therapeutic potential of its polysaccharides in various diseases. Polysaccharides, especially polysaccharide-protein complexes, are recognized as major bioactive constituents in mushrooms[13]. These polysaccharides are known for their pharmacological properties, such as immune modulation, and antioxidant and anti-inflammatory effects[14]. *G. frondosa* polysaccharides (GFP) have been noted for their positive impact on cognitive impairments[15] and memory deficits[16]. Polysaccharides, including homopolysaccharides (α/β -glucans), heteropolysaccharides, and glycoconjugates from fruiting bodies and fermented mycelia/broth, are considered the primary contributors to the various health-promoting properties of *G. frondosa*[17]. It has been reported that the structure of GFP consists of β -glucans, α -D-glucans, heteroglycans, D-grade, and MZ-grade components, each contributing to a range of functional properties[18].

However, their effects on AD remain to be fully understood. This study evaluates the effect of GFP in a rat model of AD, focusing on antioxidant, anti-inflammatory, and behavioral responses.

2. Materials and methods

2.1. Preparation of GFP

G. frondosa mushrooms were obtained from a local market, and their polysaccharides were extracted as described in previous studies[19]. Briefly, the mushrooms were dried at 40 °C, ground into a powder using an electric mill, and defatted with ethanol and hot water. Centrifugation at 14980 rpm was performed to separate the liquid extract from the solid residues, and vacuum evaporation at approximately 50 °C was employed to concentrate the extract. When the concentrated extract was combined with ethanol, the polysaccharides precipitated. Crude polysaccharide was obtained by lyophilizing the dialysate following centrifugation, allowing for further fractionation and nutritional analysis. Crude polysaccharide contained glucose (46.21% *w/w*), galactose (8.41% *w/w*), mannose (5.71% *w/w*), glucose-NH₃ (3.21% *w/w*), ribose (1.79% *w/w*), arabinose (1.20% *w/w*), protein (19.41% *w/w*), and phenolics (7.12% *w/w*).

2.2. Animals

A total of 75 adult male rats weighing (180 ± 8) g were acquired from the animal house facility located at the Department of Medical Research, Institute for Intelligent Research. The rats were given water and feed *ad libitum* and the temperature and humidity were maintained at (24 ± 2) °C and 65.00%, respectively. The animals were divided into five groups: normal control rats and AD rats untreated or treated with 100 mg/kg of GFP (100-GFP), 200 mg/kg of GFP (200-GFP), and 400 mg/kg of GFP (400-GFP). GFP was administered orally and given daily for eight weeks. The doses were determined from a pilot study that tested doses of 50, 100, 200, 300, 400, 500, 600, and 800 mg/kg over two weeks, with four rats per group monitored for 28 d after the last administration. No mortality was observed; however, diarrhea and vomiting occurred at the higher doses (600 and 800 mg/kg). Therefore, medium doses were chosen for further study.

2.3. Surgery and drug administration

AD was induced as reported by others[20]. In summary, xylazine and ketamine hydrochloride were used to anesthetize the rats. Subsequently, they were positioned in a stereotaxic apparatus (Narishige, Tokyo, Japan). Following established protocols, A β 1-42 (1 μ g/ μ L at each site) was bilaterally infused into the hippocampal CA1 area at a rate of 1 μ L every 5 min, using a 10- μ L Hamilton syringe connected to an infusion pump. Each rat was then given a recovery period.

2.4. Behavioral tests

The behavioral responses were assessed using the open-field test (OFT) and the elevated plus maze (EPM) test, as described in previous studies[21]. For the OFT, a dark area of 72 cm $\times$ 72 cm $\times$ 45 cm was utilized, and the test was conducted for 20 min. The EPM assessment involved an apparatus comprising two open arms (each 50 cm $\times$ 10 cm) and two enclosed arms (each 50 cm $\times$ 10 cm and surrounded by 40 cm-high wooden walls), which were elevated 50 cm above the floor.

2.5. Assessment of antioxidant-associated factors

The animals were euthanized, and brain slices were immediately frozen to assess antioxidant activity. After homogenizing these sections, the ferric-reducing ability of plasma (FRAP) and malondialdehyde (MDA) levels were measured using ELISA kits (Hangzhou Eastbiopharm Co., Ltd.), following the manufacturer's instructions.

2.6. Measurement of inflammatory factors

Real-time PCR assays were conducted following the methodology described by Zheng *et al.*[22] to evaluate the expression of pro-inflammatory cytokines in the hippocampus. Total ribonucleic acid was extracted using the Qiagen RNeasy Mini Kit (Qiagen, Valencia, CA, USA). A reverse transcriptase (TaKaRa Biotechnology, Otsu, Japan) was used to synthesize complementary deoxyribonucleic acid (cDNA). The temperature settings included an initial denaturation at 95 °C for 30 s, followed by 40 cycles of denaturation at 95 °C for 5 s and annealing at 60 °C for 34 s. The expression levels were normalized against β -actin. The primer sequences are as follows: β -actin forward 5'-TGGCAGCCAGCACAATGAA-3' and reverse 5'-CTAAGTCATAGTCCGCCTAG-3'; *TNF- α* forward 5'-CCCATGTTGTAGCAAACCTC-3' and reverse 5'-TATCTCTCAGCTCCACGCCA-3'; *IL-1 β* forward 5'-CCACCTCCAGGGACAGGATA-3' and reverse 5'-TGGGATCTACACTCTCCAGC-3'; *IL-6* forward 5'-CAATGAGGAGACTTGCCTGG-3' and reverse 5'-TGGGTCAGGGGTG-3'.

2.7. Statistical analysis

The data are expressed as mean $\pm$ SEM ($n=15$) and analyzed by one-way ANOVA. The Duncan test was employed to compare

differences between groups. Data analysis was conducted using GraphPad Prism (Version 6.07).

2.8. Ethical statement

This study adhered to the recommendations presented by the Ethics Committee of the International Center for Neuroscience Research (Ethics Code: ICNR-2023-14573, 20 March, 2023).

3. Results

3.1. Behavioral test

Figure 1 presents the effects of GFP on OFT responses in AD rats. The findings revealed that AD rats exhibited reduced center time, fewer visits, and shorter total distance traveled compared to normal rats ($P < 0.001$). Treatment with GFP enhanced center time, the number of visits, and total distance in a dose-dependent manner. However, no statistically significant differences were observed between the AD groups treated with 200 and 400 mg/kg GFP ($P > 0.05$).

Figure 2 shows the effects of GFP on EPM responses in rats with AD. The findings indicated that AD rats had lower responses compared to normal rats ($P < 0.001$). However, treatment with GFP

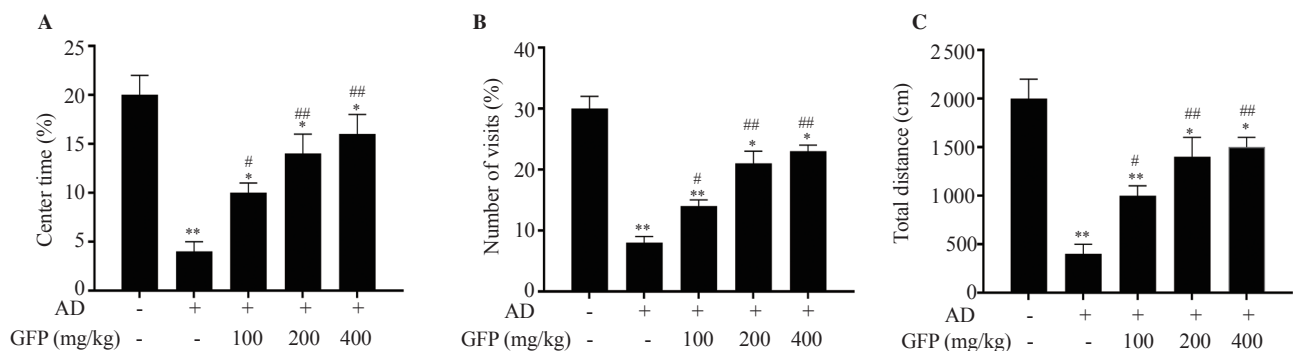


Figure 1. Effect of *Grifola frondosa* polysaccharides (GFP) on open field test (A: center time, B: number of visits, C: total distance) in rats with Alzheimer's disease (AD). The results are expressed as mean $\pm$ SEM ($n=15$) and analyzed by one-way ANOVA. * $P < 0.05$, ** $P < 0.001$ compared with the control group. # $P < 0.05$, ## $P < 0.001$ compared with the AD group.

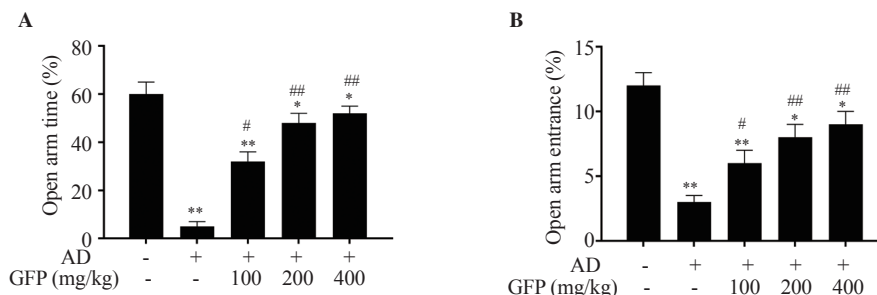


Figure 2. Effect of GFP on elevated plus-maze test in rats with AD. The results are expressed as mean $\pm$ SEM ($n=15$) and analyzed by one-way ANOVA. * $P < 0.05$, ** $P < 0.001$ compared with the control group. # $P < 0.05$, ## $P < 0.001$ compared with the AD group.

increased open-arm responses in a dose-dependent manner. There were no significant differences between the AD groups treated with 200 and 400 mg/kg GFP ($P > 0.05$).

3.2. Effect of GFP on antioxidant-related parameters

Figure 3 depicts the effects of GFP on FRAP and MDA in rats with AD. MDA level was markedly increased while FRAP was decreased in AD rats compared to control rats ($P < 0.001$). Treatment with GFP, especially at higher doses, decreased MDA level and increased FRAP level ($P < 0.05$).

3.3. Effect of GFP on the mRNA expression of pro-inflammatory cytokines

Figure 4 illustrates the impact of GFP on the mRNA expression of pro-inflammatory cytokines in rats with AD. Significantly upregulated mRNA expressions of *IL-1 β* , *TNF- α* , and *IL-6* were observed in the AD group compared to the control group ($P < 0.001$). Treatment with GFP notably reduced the mRNA expressions of *IL-1 β* , *TNF- α* , and *IL-6* compared to the AD group ($P < 0.05$).

4. Discussion

AD which is responsible for 60%-70% of dementia cases[23] typically starts slowly and worsens over time. Common early symptoms include short-term memory impairment and difficulty in recalling recent events, which can progress to language problems, challenges with situational awareness, mood swings, loss of motivation, neglect, and behavioral issues[24]. Current treatments primarily focus on symptomatic relief, managing behavioral disorders, and slowing disease progression. In this study, we explored the use of GFP, a polysaccharide derived from medicinal mushrooms, as a potential treatment for AD.

Historically, medicinal herbs have been effectively used to treat immune system-related diseases. However, knowledge about medicinal mushrooms is relatively limited compared to that of plants. Mushroom polysaccharides can bind to various immune receptors, triggering extensive immune responses and enhancing the activity of key immune cells. This process helps restore immune function and enables effective responses to pathogenic fungi, other microorganisms, and abnormal body cells[25,26].

Our findings indicate that AD impairs behavioral responses,

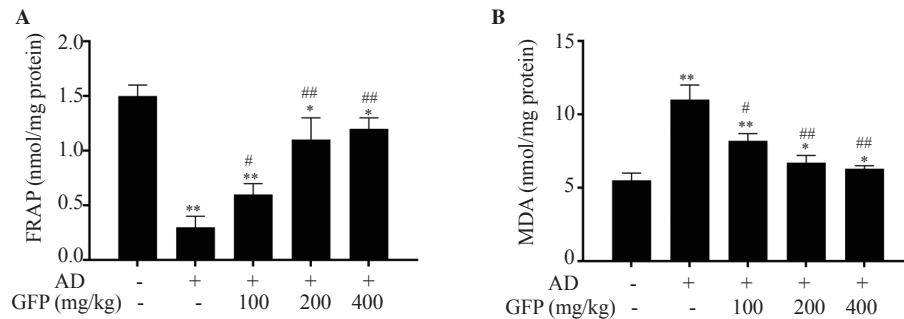


Figure 3. Effects of GFP on FRAP and MDA levels in rats with AD. The results are expressed as mean $\pm$ SEM ($n=15$) and analyzed by one-way ANOVA. * $P < 0.05$, ** $P < 0.001$ compared with the control group. # $P < 0.05$, ## $P < 0.001$ compared with the AD group. FRAP: ferric reducing ability of plasma; MDA: malondialdehyde.

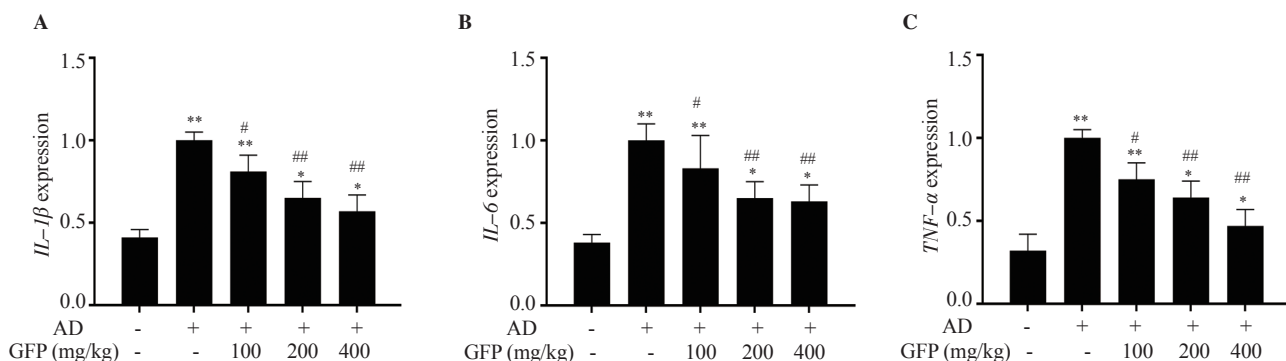


Figure 4. Effect of GFP on the mRNA expression of pro-inflammatory cytokines in rat brain. β -actin was used as an internal control. The results are expressed as mean $\pm$ SEM ($n=15$) and analyzed by one-way ANOVA. * $P < 0.05$, ** $P < 0.001$ compared with the control group. # $P < 0.05$, ## $P < 0.001$ compared with the AD group.

consistent with previous studies[27,28]. It has been reported that AD increases anxiety by elevating amyloid- β levels[29] and that oxidative stress exacerbates disease progression and anxiety[30,31]. Thus, AD affects behavioral responses through oxidative mechanisms. Our results demonstrated increased inflammation and oxidative stress in AD, confirming its impact on behavioral responses. GFP treatment improved these responses in a dose-dependent manner, aligning with findings from other studies[16]. The enhanced behavioral responses in the GFP group can be attributed to its neuroprotective, anti-inflammatory, and antioxidant properties[16].

Research suggests that alterations in amyloid beta and tau proteins lead to oxidative stress and chronic inflammation, which are linked to AD's pathology. Neuroinflammation, a hallmark of several neurodegenerative diseases, including dementia[32,33], negatively impacts the brain, particularly in AD patients. Activation of the hypothalamic-pituitary-adrenal axis can induce oxidative stress, leading to neuronal death and impaired neural communication. Age-related memory decline is associated with weakened brain defense mechanisms and reduced plasma antioxidant capacity[34,35]. Chronic brain inflammation, a primary cause of AD, reduces neuronal count in specific brain areas. Increased number of cells (including activated microglia and astrocytes), inflammatory mediators, and reactive oxygen species contribute to the inflammatory response, leading to the loss of neurons and synapses[36]. Furthermore, systemic inflammation also plays a significant role in AD's progression, as evidenced by elevated inflammatory mediators in the blood of patients[37–39].

Our study found that GFP treatment reduced inflammation and oxidative stress, which is consistent with other research[40,41]. The phenolic and protein components in GFP likely contribute to its antioxidant and anti-inflammatory effects[19]. Additionally, GFP appears to positively impact behavioral responses by modulating inflammation and oxidative stress.

However, this study has some limitations. Key obstacles include the short research period, which may not capture long-term impacts or illness progression, and the variations in physiology and metabolism between people and rats. The results are further complicated by the variations in polysaccharide content, the incomplete knowledge of its mechanism of action, and the constraints of cognitive tests in rats. Furthermore, the artificial production of AD in rats could not accurately represent the course of the illness in humans. The safety, effectiveness, and applicability of these discoveries are yet unknown in the absence of human trials.

In conclusion, GFP can alleviate AD by improving antioxidant responses and reducing inflammation, implying that GFP may be a potential treatment for AD, but more research is required to confirm its efficacy. Additionally, our understanding of GFP's effects on AD is constrained by the limited number of existing studies,

underscoring the need for future mechanistic research.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

SB, SP and MP performed data collection and drafted the article. SAM contributed to the final version of the manuscript. Both RGS and SRM performed data analysis and critical revision of the article. NM supervised the project.

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