Neuro-Cell Molecular Research

Research Article

Neuro-Cell Mol Res 2025;2(3):95-101

Antioxidant and Neuroprotective Effects of Xanthohumol in an *in Vitro* Model of Parkinson's Disease

Sidika Genc[1*], Ali Taghizadehghalehjoughi[1], Esmanur Nigde[1], Kübra Karabulut[1], Yunus Emre Aydın[1], Özlem Utme[1], Rafig Gurbanov[2]

[1]Department of Medical Pharmacology, Faculty of Medicine, Bilecik Şeyh Edebali University, Bilecik, Türkiye

[2]Department of Bioengineering, Bilecik Şeyh Edebali University, Central Research Laboratory, Bilecik Seyh Edebali University, Bilecik, Türkiye

***Corresponding Author:**
Sidika Genc
Department of Medical Pharmacology, Faculty of Medicine, Bilecik Şeyh Edebali University, Bilecik, Türkiye
Email: sidika.genc@bilecik.edu.tr
ORCID ID: 0000-0003-0000-5103

DOI: 10.5281/zenodo.18084657

Received: 25 November 2025
Accepted: 10 December 2025
Published: 30 December 2025

The author(s) - Available online at **www.neurocellmolres.com.tr**

ABSTRACT

This study aimed to evaluate the neuroprotective effects of Xanthohumol (XAN), on Parkinson's disease and an in vitro model by focusing on PPAR-γ and oxidative stress.

To establish a Parkinson's Disease (PD) model, SH-SY5Y cells were exposed to 200 µM 6-OHDA for 15 minutes. The SH-SY5Y cells were treated with different concentrations of XAN (50, 100, and 200 µg/mL). At the end of the experiment, cytotoxicity and Oxidative stress were assessed using the MTT assay, the total antioxidant capacity (TAC) and total oxidant status (TOS) assays, and the PPAR-γ assay.

These results suggest that specific doses of XAN may have neuroprotective effects with potential relevance for the treatment of neurodegenerative diseases. The Parkinson's control group shows a decrease in cell viability of up to 50% in SH-SY5Y cells compared with the control group. XAN prevented 6-OHDA-induced apoptosis and increased cell viability in a dose-dependent manner. TAC and TOS analyses showed that 100 and 200 µg/mL XAN more effectively increased TAC capacity by 60% but caused a 30% decrease in TOS. In contrast, elevated PPAR-γ levels were measured in correlation with the MTT result.

XAN results indicate that it may be part of the treatment strategy for Parkinson's disease.

Keywords: 6-OHDA, Neuroblastoma, Parkinson's disease, SH-SY5Y cells, Xanthohumol.

Cite this article as: Genç S, Taghizadehghalehjoughi A, Nigde E, et al. Antioxidant and Neuroprotective Effects of Xanthohumol in an in Vitro Model of Parkinson's Disease. Neuro-Cell Mol Res. 2025;2(3):95-101. doi:10.5281/zenodo.18084657

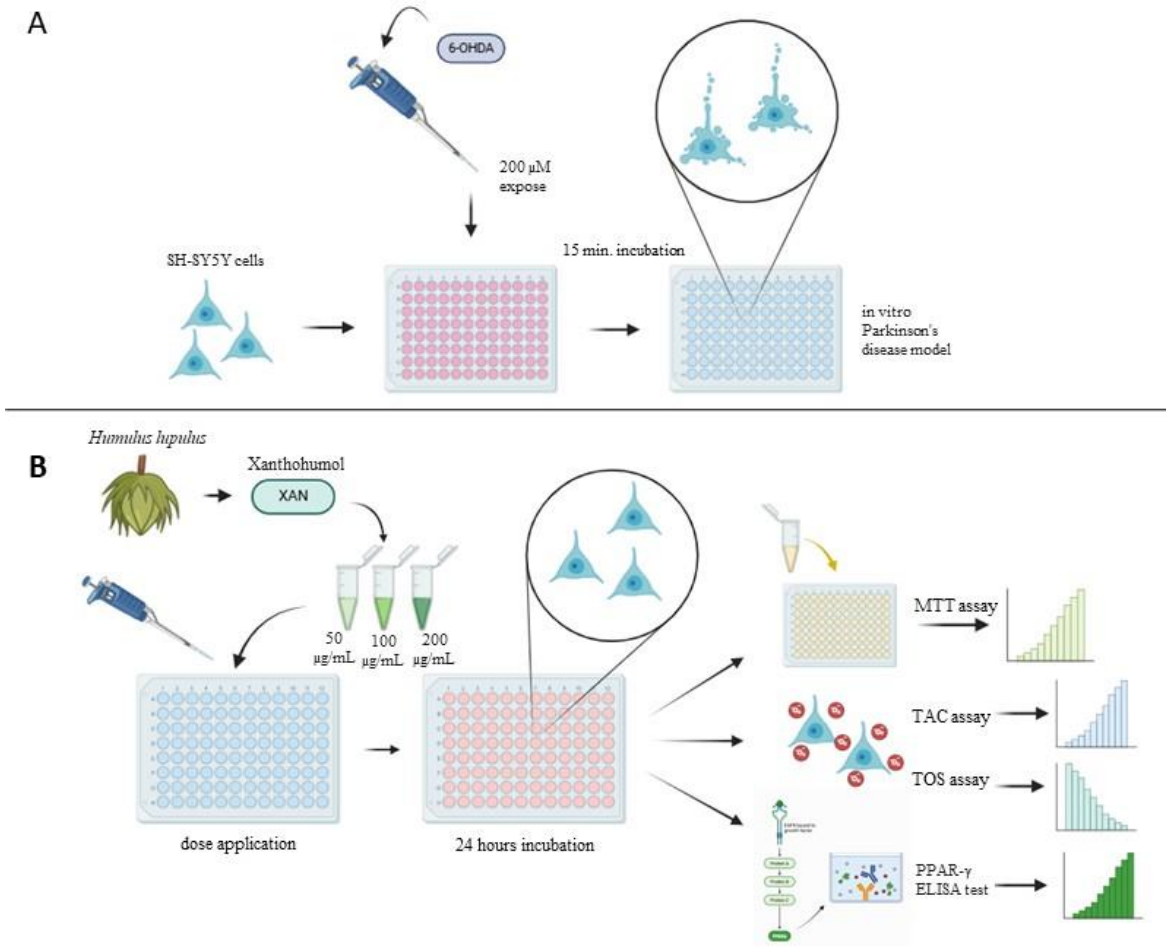

***Figure 1**. Graphical abstract. A: SH-SY5Y cells were seeded into 96-well plates and incubated until reaching 80% confluence. Then, 200 µM 6-OHDA was applied, followed by a 15-minute incubation. Using this method, an in vitro model of Parkinson's disease was established. B: Xanthohumol (XAN) obtained from Humulus lupulus was prepared at concentrations of 50, 100, and 200 µg/mL and applied to the in vitro Parkinson's model. The cells were incubated for 24 hours. Subsequently, MTT, TAC, TOS, and PPAR-γ ELISA assays were performed. Statistical analysis of the data was then carried out.*

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, with a global incidence of 516 per 100,000 individuals [1, 2]. The disease often manifests with symptoms such as autonomic nervous system dysfunction, cognitive decline, and various neuropsychiatric problems, typically appearing in individuals in their 60s. PD results from the progressive loss of dopaminergic neurons located in the substantia nigra pars compacta (SNpc) [3, 4]. The leading cause of neuronal loss is a deficiency of dopamine [5]. At the molecular level, the accumulation of misfolded α-synuclein within neurons, forming Lewy bodies, is recognized as a key pathological hallmark of the disease [6]. These protein aggregations are known to accelerate neuronal degeneration by triggering mitochondrial dysfunction, increased oxidative stress, and neuroinflammatory responses[7]. Consequently, progressive dopamine depletion becomes the primary determinant of the clinical manifestations of Parkinson's disease. Therefore, current treatment strategies focus on targeting the dopaminergic system to restore dopamine levels [8].

However, dopaminergic therapies currently in use only provide temporary symptomatic relief and fail to halt the underlying neurodegenerative mechanisms [9]. Particularly, levodopa (L-DOPA) and dopamine agonists may lose their efficacy over time, compete with dietary amino acids for gastrointestinal absorption, and cause undesirable side effects such as dyskinesia [10, 11]. Given these limitations, no curative treatment for Parkinson's disease currently exists. As a result, recent studies have focused on alternative pathways such as peroxisome proliferator-activated receptor gamma (PPAR-γ), which exerts neuroprotective effects by targeting

oxidative stress and neuroinflammation [12].

In recent years, PPAR-γ has gained attention as an essential therapeutic target due to its ability to modulate key mechanisms involved in neurodegeneration, including mitochondrial dysfunction, oxidative stress, and chronic neuroinflammation. Research has shown that PPAR-γ agonists can inhibit the NF-κB pathway, thereby suppressing the propagation of inflammatory signals and reducing the release of pro-inflammatory cytokines, ultimately delaying dopaminergic neuronal loss[13, 14]. PPAR-γ activation may also enhance cellular resilience by promoting mitochondrial biogenesis and supporting antioxidant defense mechanisms[15]. Based on these findings, PPAR-γ may function as an anti-inflammatory agent, minimizing oxidative damage [16, 17]. Consequently, natural compounds with the potential to exert neuroprotective effects via PPAR-γ activation have become a focal point in current research, particularly among phytochemical-rich medicinal plants. One such plant of interest is *Humulus lupulus* [18].

Humulus lupulus L. (commonly known as hops) is a perennial climbing plant belonging to the *Cannabaceae* family [19, 20]. *H. lupulus* has been widely used in traditional medicine due to its rich phytochemical content, including xanthohumol (XAN), isoxanthohumol (IX), 6-prenylnaringenin (6-PN), and 8-prenylnaringenin (8-PN) [21]. Xanthohumol exhibits a broad spectrum of pharmacological activities, including antioxidants, anti-inflammatory, chemopreventive, antimicrobial, anticarcinogenic, antidiabetic, metabolic, neuroprotective, prebiotic, and detoxifying properties. These effects are mediated by signaling pathways such as NF-κB (nuclear factor κB) and AMPK (AMP-activated protein kinase), as well as by receptor interactions involving the estrogen receptor (ER) and the aryl hydrocarbon receptor (AhR). This multifaceted bioactivity makes XAN a highly promising molecule for research **[22, 23]**. Moreover, XAN has been shown to increase dopamine levels while reducing oxidative stress and neuroinflammation, suggesting its potential therapeutic role in Parkinson's disease [24].

This study established an in vitro Parkinson's model by exposing SH-SY5Y cells to 200 µM 6-hydroxydopamine (6-OHDA). After this exposure, the cells were treated with different concentrations of XAN. The antioxidant and neuroprotective effects of XAN were assessed using the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, TAS (total antioxidant status), TOS (total oxidant status), and PPAR-γ ELISA tests.

METHODS

Cell Culture

SH-SY5Y cells (ATCC: CRL-2266) were acquired from the Department of Medical Pharmacology at Bilecik Şeyh Edebali University's Faculty of Medicine (Bilecik, Turkey). The cells were passaged and seeded into 96-well plates once they reached 85% confluence [25].

6-OHDA Induced in Vitro Parkinson's Model: Xanthohumol Dose Application and Experimental Groups

The cells were cultured in a 5% CO_2 incubator until achieving 80% confluence. To establish a PD model in cell culture, SH-SY5Y cells were subjected to 200 µM 6-OHDA (dissolved in saline solution containing 0.2% DMSO) (MedChemExpress, Cat. No.: HY-B1081A) and incubated for 15 minutes. After removal of the medium containing 6-OHDA, the SH-SY5Y cells were divided into groups receiving XAN at concentrations of 50 µg/mL, 100 µg/mL, or 200 µg/mL. The cell groups were defined as follows:

Table 1. Experimental groups.

1-	Control
2-	6-OHDA (200 µM)
3-	Xanthohumol 50 µg/mL
4-	Xanthohumol 100 µg/mL
5-	Xanthohumol 200 µg/mL

One day later, cell viability was determined by MTT analysis. Oxidative stress was evaluated using TAC and total oxidant status TOS analyses. Additionally, PPAR-γ levels were examined.

MTT Assay

The cells were resuspended in fresh DMEM media supplemented with 10% FBS and 1% antibiotic (penicillin, streptomycin, and amphotericin B). Xanthohumol was administered at concentrations of 50 µg/mL, 100 µg/mL, and 200 µg/mL for 24 hours. The optical density of the solutions was measured at 570 nm using a Multiskan™ GO microplate spectrophotometer (Thermo Fisher, Porto Salvo, Portugal) [26].

ELISA Tests

To investigate the effects of the substances on the ROS mechanism, PPAR-γ (BT Lab, LOT: 202408010) levels were

measured using an ELISA kit. Each experimental group was independently repeated three times. The experiment followed the kit protocol, and the optical densities of each sample were measured at 450 nm [26].

Total Antioxidant Capacity (TAC) Assay

The Total Antioxidant Capacity Kit (RL0017, Rel Assay Diagnostics) was used in the analysis. Following the manufacturer's protocol, the reagents were added to the supernatant. The color change was measured at 660 nm for TAC, and the resulting values were expressed as mmol Trolox Equiv./L [26].

Total Oxidant Level (TOS) Assay

The Total Oxidant Status Kit (RL0024, Rel Assay Diagnostics) was used in the analysis. Following the manufacturer's protocol, the reagents were added to the supernatant. The color change resulting from the reaction was measured at 530 nm for TOS, and the resulting values were expressed as mmol H_2O_2 Equiv./L [26].

Statistical Analysis

To compare the groups statistically, a one-way ANOVA was employed. For statistical analysis, GraphPad Prism 8 was used for all computations. A difference was deemed statistically significant in all tests if it was less than 0.05. The mean and standard deviation (mean ± SD) of the results were displayed.

RESULTS

After SH-SY5Y cells reached 80% confluence, an *in vitro* Parkinson's model was established by treating the cells with 200 µM 6-OHDA, followed by treatment with the respective experimental groups. Subsequently, MTT, TAC, TOS, and ELISA assays were performed.

MTT Assay Result

The control group was compared with the 6-OHDA group, and the 6-OHDA group was compared with the XAN (50, 100, and 200 µg/mL) treatment groups (Figure 2). The cells treated with XAN were subjected to the MTT assay after 24 hours of incubation to determine cell viability. The results showed that the 6-OHDA group exhibited a significant 50% decrease in viability compared to the control group ($p<0.01$). Treatment with 100 µg/mL XAN resulted in approximately a 25% increase in viability compared with the 6-OHDA group ($p<0.05$). At a concentration of 200 µg/mL, XAN increased cell viability by 40%, showing the highest level of viability among all doses and a statistically significant improvement ($p<0.01$).

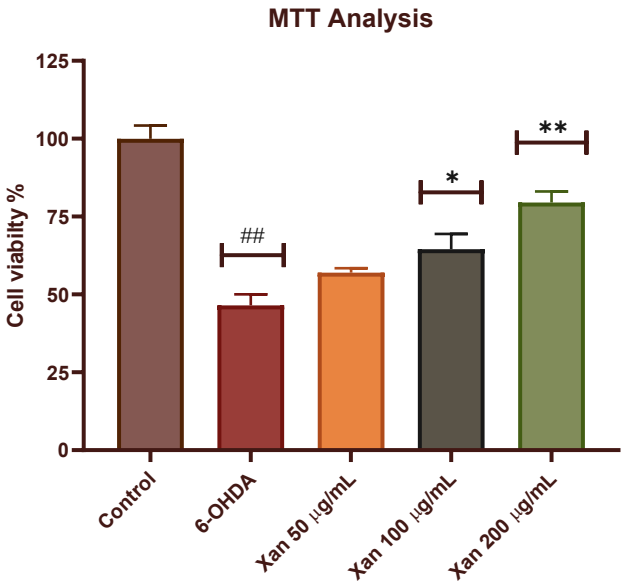

Figure 2. *MTT analysis results. 6-OHDA: 6-hydroxydopamine, XAN: Xanthohumol, µg/mL: microgram per milliliter. 6-OHDA reduced cell viability by approximately 50% compared to the control group ($p<0.01$). XAN treatment provided a dose-dependent improvement; at 100 µg/mL, viability increased by 25% ($p<0.05$), while at 200 µg/mL, the highest effect was observed with a 40% increase ($p<0.01$). (*$p<0.05$, **,## $p<0.01$).*

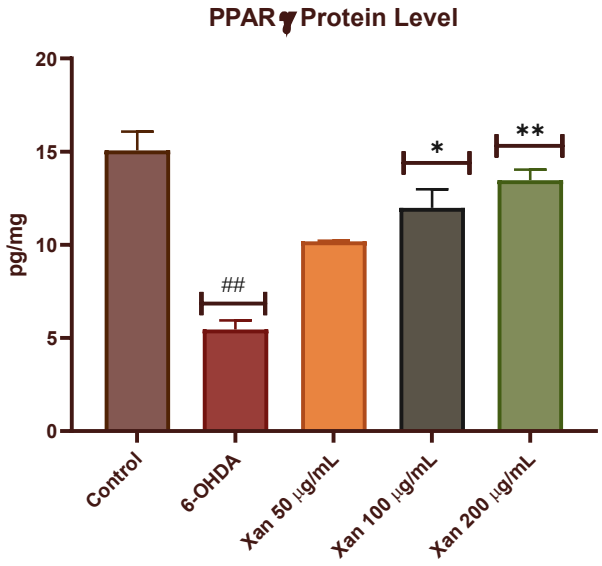

Figure 3. *PPAR-γ ELISA analysis results. 6-OHDA: 6-hydroxydopamine, XAN: Xanthohumol, µg/mL: microgram per milliliter. The study showed that PPAR-γ levels were approximately 65% lower in the 6-OHDA group compared to the control group ($p<0.01$). XAN treatment increased PPAR-γ levels in a dose-dependent manner; the highest increase was observed at 100 µg/mL with 55% ($p<0.05$) and at 200 µg/mL with 60% ($p<0.01$). (*$p<0.05$, **,## $p<0.01$).*

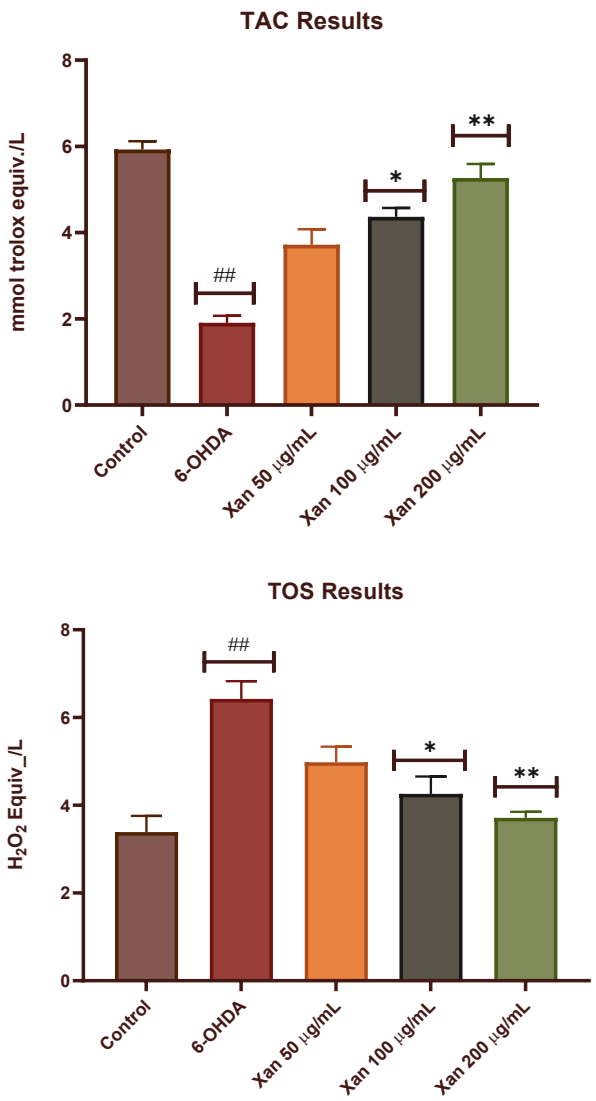

Figure 4. *TAC (Total Antioxidant Capacity) and TOS (Total Oxidant Status) analysis results. 6-OHDA; 6-hidroksidopamin, Xan; Xanthohumol, µg/ml; mikrogram/mililitre. TAC decreased by 70% in the 6-OHDA group compared to the control group ($p<0.01$), while TOS increased by 45% ($p<0.01$). XAN treatment increased TAC levels; particularly at the 200 µg/mL dose, an increase of approximately 60% was achieved, closest to control values ($p<0.01$). TOS levels decreased with XAN; a 30% decrease was observed at 100 µg/mL and a 35% decrease at 200 µg/mL (*$p<0.05$, **$p<0.01$). (*$p<0.05$, **,## $p<0.01$).*

ELISA Test Result

PPAR-γ ELISA Result

The control group was compared with the 6-OHDA group, and the 6-OHDA group was compared with the XAN (50, 100, and 200 µg/mL) treatment groups (Figure 3). PPAR-γ protein levels were analyzed using ELISA. Compared to the control group, the 6-OHDA group showed an approximately 65% decrease in PPAR-γ protein levels ($p<0.01$). In the treatment groups, XAN at 100 µg/mL increased PPAR-γ levels by approximately 55% compared with the 6-OHDA group ($p<0.05$), whereas the 200 µg/mL dose showed the most significant increase, with a 60% elevation ($p<0.01$).

TAC and TOS Assay Result

The control group was compared with the 6-OHDA group, and the 6-OHDA group was compared with the XAN (50, 100, and 200 µg/mL) treatment groups (Figure 4). TAC and TOS analyses were performed using a spectrophotometer at the wavelengths specified by the respective assay kits. In the TAC analysis, the 6-OHDA group showed a 70% decrease compared to the control group ($p<0.01$), while in the TOS analysis, a 45% increase was observed ($p<0.01$). In the TAS results, the XAN 200 µg/mL treatment group showed approximately a 60% increase relative to the 6-OHDA group, with values closest to those of the control group ($p<0.01$).

In contrast to its antioxidant activity, the TOS level showed a 30% reduction in the XAN 100 µg/mL group and a 35% reduction in the XAN 200 µg/mL group compared to the 6-OHDA group, indicating that oxidative damage was alleviated ($p<0.05$, $p<0.01$).

DISCUSSION

In recent years, the SH-SY5Y cell line has been widely utilised in in vitro models of Parkinson's disease [27]. This is due not only to its human origin but also to its ability to express genes and signaling pathways that are dysregulated in Parkinson's disease pathogenesis, as well as to its ease of maintenance and capacity for long-term culture under laboratory conditions [27, 28]. In this model, 6-OHDA is used as a neurotoxin. Jeerang et al. (2021) also employed this compound in differentiated SH-SY5Y cells and reported that it induced neurodegeneration [29].

Currently, Parkinson's disease is treated with L-DOPA (levodopa), which aims to compensate for dopamine deficiency [30]. However, L-DOPA therapy has several limitations, including reduced efficacy due to competition with dietary amino acids for gastrointestinal absorption and side effects that emerge with prolonged use [10, 31]. Therefore, the need for complementary or supportive therapeutic approaches in Parkinson's disease has been increasing [32]. In this context, research has focused on traditional medicinal plants and their bioactive compounds with known pharmacological properties, exploring their potential to protect dopaminergic neurons [33]. Among these, Xanthohumol, the main prenylated chalcone found in *Humulus lupulus*, has been shown to exhibit significant anti-inflammatory properties by inhibiting IκBα (inhibitor of NF-κB alpha) degradation and subsequent NFκB

activation in acute liver injury [34]. XAN has been shown to reduce intracellular oxidative stress, suppress reactive oxygen species (ROS) production, and enhance the activity of antioxidant defense enzymes [35]. A study conducted by Alam et al. (2024) demonstrated that XAN exerted neuroprotective effects in a mouse model of Parkinson's disease [24]. Additionally, Zhang et al. (2014) examined XAN using 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging and ferric reducing antioxidant power (FRAP) assays, reporting that XAN exhibited potent antioxidant activity [36]. In our study, we demonstrated dose-dependent reductions in oxidative damage induced by the neurotoxin 6-OHDA using the TAC and TOS assays. The oxidative stress data obtained in this study support previous reports on the antioxidant properties of XAN.

In the present study, XAN treatment reduced oxidative stress and increased cell viability in a dose-dependent manner following 6-OHDA-induced neurotoxicity. Among the concentrations tested, 200 µM was the most effective. This finding is consistent with the literature; however, the concentration of XAN is a critical factor to consider. Effects were observed at the lower dose of 50 µg/ml, whereas significant antioxidant enhancement and improvements in cell viability were observed at 100 µg/ml and 200 µg/ml. Upon evaluating total antioxidant capacity (TAC) and total oxidant status (TOS), the increase in TAC and the decrease in TOS indicated that XAN enhanced cellular antioxidant defense and exhibited neuroprotective potential by scavenging ROS [24].

Moreover, Parkinson's disease is characterized by a marked increase in inflammation as a result of elevated oxidative stress [37]. Numerous markers are involved in inflammatory signaling, including peroxisome proliferator-activated receptor gamma (PPAR-γ), which is known for its anti-inflammatory role [38]. Martin et al. demonstrated in a Parkinson's disease model that treatment with PPAR-γ agonists reduced cellular inflammation and provided neuroprotection for dopaminergic neurons [39]. Consistent with these findings, our study revealed that increasing doses of XAN led to elevated PPAR-γ levels and reduced inflammation [40]. As oxidative damage and associated inflammation decreased, cellular viability increased in a dose-dependent manner in the treatment groups.

CONCLUSION

In conclusion, our study demonstrated that XAN exhibits neuroprotective effects in 6-OHDA-induced SH-SY5Y cells by reducing oxidative stress and modulating PPAR-γ levels. Based on the current literature, these effects are likely mediated through antioxidant and anti-inflammatory mechanisms. Our findings suggest that XAN may be a promising therapeutic agent for the treatment of Parkinson's disease. However, further studies are needed to elucidate its precise molecular mechanisms and to confirm these effects in vivo models.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Disclosure

The authors have reported no conflicts of interest in preparing and publishing this article.

Ethics Committee Approval

Ethics committee approval is not required in this study. The study was conducted following the international declaration, guidelines, etc.

Funding

The authors have no funding to disclose.

Referee Evaluation Process

Externally peer-reviewed

REFERENCES

1. Pringsheim T, Jette N, Frolkis A and Steeves, TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2014;29(13):1583-1590. https://doi.org/10.1002/mds.25945
2. Pereira GM, Teixeira-dos-Santos D, Soares NM, Marconi GA, Friedrich DC, Saffie Awad P. et al. A systematic review and meta-analysis of the prevalence of Parkinson's disease in lower to upper-middle-income countries. npj Parkinsons Dis. 2024;10(1):181. https://doi.org/10.1038/s41531-024-00779-y
3. Jankovic J., Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry, 2008;79(4):368-376. https://doi.org/10.1136/jnnp.2007.131045
4. De Lau LM. and Breteler MM, Epidemiology of Parkinson's disease. Lancet Neurol. 2006;5(6):525-535. https://doi.org/10.1016/S1474-4422(06)70471-9
5. Lang AE, and Lozano AM, Medical Progress: Parkinson's Disease First of Two Parts. N Engl J Med. 1998;339(15):1044-1053. https://doi.org/10.1056/NEJM199810083391506
6. Dauer W, and Przedborski S. Parkinson's disease: mechanisms and models. Neuron. 2003;39(6):889-909. https://doi.org/10.1016/s0896-6273(03)00568-3
7. Rocha EM, De Miranda B, and Sanders LH. Alpha-synuclein: Pathology, mitochondrial dysfunction, and neuroinflammation in Parkinson's disease. Neurobiol. Dis. 2018;109:249-257. https://doi.org/10.1016/j.nbd.2017.04.004
8. Zhou ZD, Yi LX, Wang DQ, Lim TM, Tan EK. Role of dopamine in the pathophysiology of Parkinson's disease. Transl Neurodegener. 2023;12(1):44. https://doi.org/10.1186/s40035-023-00378-6
9. Dong-Chen X, Yong C, Yang X, Chen-Yu S, & Li-Hua P. Signaling pathways in Parkinson's disease: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther. 2023;8(1):73.

https://doi.org/10.1038/s41392-023-01353-3
10. Fahn S. Parkinson's disease, the effect of levodopa, and the ELLDOPA trial. Arch. Neurol. 1999;56(5):529-535. https://doi.org/10.1001/archneur.56.5.529
11. Ogawa N. Levodopa and dopamine agonists in the treatment of Parkinson's disease: advantages and disadvantages. Eur. Neurol. 1994;34(Suppl. 3):20-28. https://doi.org/10.1159/000119538
12. Pérez-Segura I, Santiago-Balmaseda A, Rodríguez-Hernández LD, Morales-Martínez A, Martínez-Becerril HA and Martínez-Gómez PA. PPARs and their neuroprotective effects in Parkinson's disease: a novel therapeutic approach in α-synucleinopathy? Int. J. Mol. Sci., 2023;24(4): 3264. https://doi.org/10.3390/ijms24043264
13. Bernardo A, and Minghetti L. PPAR-γ agonists as regulators of microglial activation and brain inflammation. Curr. Pharm. Des. 2006;12(1):93-109. https://doi.org/10.2174/138161206780574579
14. García-Bueno B, Madrigal JL, Lizasoain I, Moro MA, Lorenzo P, and Leza JC. Peroxisome proliferator-activated receptor gamma activation decreases neuroinflammation in brain after stress in rats. Biol. Psychiatry. 2005;57(8):885-894. https://doi.org/10.1016/j.biopsych.2005.01.007
15. Corona JC and Duchen MR. PPARγ and PGC-1α as therapeutic targets in Parkinson's. Neurochem. Res. 2015;40(2):308-316. https://doi.org/10.1007/s11064-014-1377-0
16. Behl T, Madaan P, Sehgal A, Singh S, Sharma N, and Bhatia S. Elucidating the neuroprotective role of PPARs in Parkinson's disease: a neoteric and prospective target. Int. J. Mol. Sci., 2021;22(18):10161. https://doi.org/10.3390/ijms221810161
17. Carta AR., Pisanu A, and Carboni E. Do PPAR-Gamma Agonists Have a Future in Parkinson′ s Disease Therapy? Parkinson's Dis. 2011;2011(1):689181. https://doi.org/10.4061/2011/689181
18. Kiyofuji A, Yui K, Takahashi K, and Osada K. (Effects of xanthohumol-rich hop extract on the differentiation of preadipocytes.J. Oleo Sci. 2014;63(6):593-597. https://doi.org/10.5650/jos.ess14009
19. Korpelainen H. Pietiläinen M. Hop (Humulus lupulus L.): Traditional and present use, and future potential. Econ. Bot. 2021;75(3):302-322. https://doi.org/10.1007/s12231-021-09528-1
20. Murakami A, Darby P, Javornik B, and Pais MSS. Seigner, E., Lutz, A., Molecular phylogeny of wild hops, Humulus lupulus L. Hered. 2006;97(1):66-74. https://doi.org/10.1038/sj.hdy.6800839
21. Zanoli P and Zavatti M. Pharmacognostic and pharmacological profile of Humulus lupulus L. J. Ethnopharmacol. 2008;116(3):383-396. https://doi.org/10.1016/j.jep.2008.01.011
22. Bolton JL, Dunlap TL, Hajirahimkhan A, Mbachu O, Chen SN, ChadwickmL. The multiple biological targets of hops and bioactive compounds. Chem. Res. Toxicol. 2019;32(2):222-233. https://doi.org/10.1021/acs.chemrestox.8b00345
23. Xiao-Lei S, Tian-Shuang X, Yi-Ping J, Na-Ni W, Ling-Chuan X and Ting H. Humulus lupulus L. extract and its active constituent xanthohumol attenuate oxidative stress and nerve injury induced by iron overload via activating AKT/GSK3 β and Nrf2/NQO1 pathways. J. Nat. Med. 2023;77(1):12-27. https://doi.org/10.1007/s11418-022-01642-1
24. Alam MS, Khandale N, Birla D, Bashir B, Vishwas S and Kulkarni, M. P. Formulation and optimization of xanthohumol loaded solid dispersion for effective treatment of Parkinson's disease in rats: In vitro and in vivo assessment. J Drug Deliv Sci Technol. 2024;102:106385. https://doi.org/10.1016/j.jddst.2024.106385
25. Genç S, Karabulut K, Niğde E, Aydin YE, Aydın B and Aydın AE. Amygdalin (Vitamin B17) Effect on Glioblastoma: Focus on Oxidant Capacity and Antioxidant Status. Recent Trends in Pharmacology, 2024;2(2):75-78. https://doi.org/10.62425/rtpharma.1523732
26. Genç S, Karabulut K, Niğde E, Büyükgöçmen Ş, and Taghizadehghalehjoughi A. Evaluation of Bee Venom Induced Toxicity: Toxicity and Management. Journal of Anatolian Environmental and Animal Sciences, 2025;10(4):514-520. https://doi.org/10.35229/jaes.1658697
27. Długosz A, Błaszak B, Czarnecki D, and Szulc J. Mechanism of Action and Therapeutic Potential of Xanthohumol in Prevention of Selected Neurodegenerative Diseases. Molecules, 2025;30(3):694. https://doi.org/10.3390/molecules30030694
28. Xicoy H, Wieringa B, and Martens GJ. The SH-SY5Y cell line in Parkinson's disease research: a systematic review. Mol. Neurodegener. 2017;12(1):10. https://doi.org/10.1186/s13024-017-0149-0
29. Wongtrakul J, Thongtan T, Kumrapich B, Saisawang C, and Ketterman, AJ. Neuroprotective effects of Withania somnifera in the SH-SY5Y Parkinson cell model. Heliyon. 202;7(10). https://doi.org/10.3233/JPD-130186
30. Salat D, Tolosa E. Levodopa in the treatment of Parkinson's disease: current status and new developments. J Parkinsons Dis, 2013;3(3):255-269. https://doi.org/10.3233/JPD-130186
31. Rusch C, Flanagan R, Suh H, and Subramanian I. To restrict or not to restrict? Practical considerations for optimizing dietary protein interactions on levodopa absorption in Parkinson's disease.npj Parkinsons Dis. 2023;9(1):98. https://doi.org/10.1038/s41531-023-00541-w
32. Hauser RA. Future treatments for Parkinson's disease: surfing the PD pipeline. Int. J. Neurosci. 2011;121(sup2):53-62. https://doi.org/10.3109/00207454.2011.620195
33. Carbone K, and Gervasi F. An updated review of the genus Humulus: a valuable source of bioactive compounds for health and disease prevention. Plants, 2022;11(24):3434. https://doi.org/10.3390/plants11243434
34. Piekara J, and Piasecka-Kwiatkowska D.Antioxidant Potential of Xanthohumol in Disease Prevention: Evidence from Human and Animal Studies. Antioxidants. 2024;13(12):1559. https://doi.org/10.3390/antiox13121559
35. Li F, Yao Y, Huang H, Hao H, and Ying M. Xanthohumol attenuates cisplatin-induced nephrotoxicity through inhibiting NF-κB and activating Nrf2 signaling pathways. Int. Immunopharmacol. 2018;61: 277-282. https://doi.org/10.1016/j.intimp.2018.05.017
36. Zhang XiuLi ZX, Zhang YongDong ZY, Wang Tao WT, Guo HongYun GH, and Liu QiMing L Q. Evaluation on antioxidant effect of xanthohumol by different antioxidant capacity analytical methods. J. Chem. 2014;2014(1):249485. https://doi.org/10.1155/2014/249485
37. Taylor JM, Main BS., Crack PJ. Neuroinflammation and oxidative stress: co-conspirators in the pathology of Parkinson's disease. Neurochem Int. 2013;62(5):803-819. https://doi.org/10.1016/j.neuint.2012.12.016
38. Villavicencio Tejo F, and Quintanilla RA. Contribution of the Nrf2 pathway on oxidative damage and mitochondrial failure in Parkinson and Alzheimer's disease. Antioxidants. 2021;10(7):1069. https://doi.org/10.3390/antiox10071069
39. Carta AR, and Pisanu A. Modulating microglia activity with PPAR-γ agonists: a promising therapy for Parkinson's disease? Neurotox. Res. 2013;23(2):112-123. https://doi.org/10.1007/s12640-012-9342-7
40. Martin HL, Mounsey RB, Mustafa S, Sathe K, and Teismann P. Pharmacological manipulation of peroxisome proliferator-activated receptor γ (PPARγ) reveals a role for anti-oxidant protection in a model of Parkinson's disease. Exp. Neurol. 2012;235(2):528-538. https://doi.org/10.1016/j.expneurol.2012.02.017