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Short communications

Neuroprotective effect of rice bran enzymatic extract-supplemented diets in a murine model of Parkinsońs disease

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ABSTRACT

Neurodegenerative disorders such as Parkinson's disease, present a global health concern with limited therapeutic options. In this context, dietary interventions have emerged as a potential strategy to counteract the oxidative stress and inflammation underlying these conditions. Rice bran enzymatic extract (RBEE), rich in bioactive compounds, has shown ability in modulating neuroinflammatory responses and improving mitochondrial function. This study investigates the neuroprotective potential of RBEE in a murine model of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The results reveal that RBEE supplementation effectively preserves the dopaminergic population and reduces MPTP-induced gliosis in the Substantia Nigra (SN). Moreover, RBEE enhances mitochondrial Complex I activity in mouse brains.

These findings underscore the potential of RBEE as a dietary supplement to mitigate neuronal loss, neuroinflammation, and mitochondrial dysfunction associated with PD. RBEE is shown as a promising novel candidate in neuroprotective strategies, offering hope in the quest for effective preventive and therapeutic measures in PD.

1. Introduction

Parkinsońs disease (PD) is a progressive neurological disorder characterized by the degeneration of dopaminergic neuronal population causing motor and no-motor symptoms. While in the field of Alzheimeŕs disease (AD), recent clinical trials based on targeting the presence of Aβ plaques showed certain success (Huang et al., 2023), in the field of PD there has not been any therapeutic breakthrough, and current treatments aim to alleviate some of PD symptoms (Kalia & Lang, 2015). As the world population ages, the increase number of PD patients represents a great concern to public health (Tate et al., 2023), prompting a critical need for innovative strategies to combat these pathologies. Despite PD unknown etiology, there is mounting evidence indicating that oxidative stress, misfolded protein accumulation, mitochondrial dysfunction, and chronic inflammation are key interconnected players in both the initiation and progression of PD (Picca et al., 2020).

Currently, numerous studies have highlighted the potential of dietary nutraceuticals as a new therapeutic approach based on their capacity to mitigate oxidative stress, mitochondrial dysfunction, and inflammation associated with the etiopathogenesis of neurodegenerative disorders, including PD (Ascherio & Schwarzschild, 2016; Lee et al., 2020; Park & Ellis, 2020). Dietary nutraceuticals represent a therapeutic approach with low or absent risk for the patient (Gomez-Inhiesto et al., 2020), making dietary nutraceuticals perfect candidates as therapeutic treatments *per se* or in combination with other treatments.

Among the different dietary nutraceuticals, rice bran enzymatic extract (RBEE) has gather a lot of attention due to its antioxidant and anti-inflammatory properties (Behl et al., 2021; Candiracci et al., 2014). Derived from rice bran, a by-product of rice milling, RBEE presents in its composition a rich array of bioactive compounds, including antioxidants such as γ-oryzanol, tocopherols, tocotrienols, polyphenols, and proteins with exceptional nutritional value (Parrado et al., 2006). RBEE has

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demonstrated the capacity to modulate microglial activation and enhance mitochondrial function in the brain both, *in vitro* and *in vivo* experimental set ups (Bhatia et al., 2016; El-Din et al., 2021; Hagl et al., 2016; Hagl et al., 2015). In this study, we assess RBEE potential neuroprotective effect in PD using the *in vivo* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model (Meredith & Rademacher, 2011). MPTP (and its toxic metabolite 1-methyl-4-phenylpyridinium (MPP+)) is a neurotoxin that induces PD-like symptoms both in animals (Mustapha & Mat Taib, 2021) as well as in humans (Henrich et al., 2023) which directly affects dopaminergic survival. MPTP triggers an acute neuroinflammatory response (known as gliosis) which also contributes to dopaminergic neuronal death.

Here, we observe a positive effect over the dopaminergic population upon administration of RBEE diet in the MPTP-induced dopaminergic neuronal cell death, probably by enhancing mitochondrial function, reducing oxidative stress, and mitigating neuroinflammation. The results of this study suggests RBEE could serve as a promising dietary supplement for protection against the onset and progression of PD.

2. Materials and methods

2.1. RBEE preparation.

Rice bran (*Oryza sativa,* var. indica) raw material was provided by Herba Ricemills, S.L.U (Seville, Spain). Rice bran is obtained during the polishing/milling of raw rice grains once their husks have been stripped. Rice bran was processed followed a well-established protocol (Henrich et al., 2023) using the hydrolytic agent subtilisin (EC 3.4.21.62; Biocom, Spain), a protease from *Bacillus licheniformis,* in a bioreactor with controlled temperature (60 °C) and pH (pH = 8) (Parrado et al., 2006). The processing of this product follows different steps, including solid separation and concentration. The final product RBEE is a brown syrup that is completely water-soluble. To characterize the nutritional composition of the final product, RBEE, both macro and micronutrients were assessed using methods outlined in a previously (Parrado et al., 2006).

2.2. Standard and RBEE diets preparation.

The RBEE diet was generated by blending RBEE with the powdered standard diet (LASQCdiet® Rod14-H; Altromin) at a concentration of 5 % (w/w), as used in previous studies (Perez-Ternero, Claro, et al., 2017; Perez-Ternero, Herrera, et al., 2017; Perez-Ternero et al., 2016). The resulting mixture underwent pelleting once more. For the standard diet followed the same procedure but water was added instead of RBEE.

2.3. Characterization of chemical and bioactive compounds of RBEE

The chemical characterization of RBEE was analyzed by Laboratorios MICROAL (Seville, Spain). The corresponding methods were: PNT 09/MIC/00-a/17_GRAVIMETRY for fats; PI/FQ/63-CALCULATION for carbohydrates; PNT 09/MIC/00-a/36-DUMAS for proteins and PNT 09/MIC/00-a/44_GRAVIMETRY for ashes.

The bioactive compounds were analyzed by the Analysis Unit at Instituto de la Grasa (CSIC, Seville, Spain). Tocopherols and tocotrienols were analyzed through ISO 9936:2016 method and HPLC. Fatty acids were determined by ISO 12966-2:2011 (4.3) general method and ISO 12966–4:2015, and gas chromatography of fatty acid methyl esters, obtained by cold transmethylation of the oil with methanolic KOH. γ-oryzanol has been analyzed by prior extraction with ethyl acetate ethanol 80/20 (Calvo-Castro et al., 2019), followed by analysis using HPLC-UV–visible diode array detector (Bucci et al., 2003). Quantification was performed via external calibration.

2.4. Animal feeding and MPTP treatment

Cohorts of 3-month-old male C57BL/6 mice were organized into two different dietary groups, each group consisting of 4–6 individuals. One group received a standard control diet, while the other group was exposed to RBEE diet for one month. These mice had unrestricted access to both food and water. After one month, the mice underwent treatment involving four intraperitoneal injections of MPTP hydrochloride (Catalog No. S4732, Selleckchem) or Saline (Burguillos et al., 2011). Each injection was administered at a dosage of 16 mg/kg, with a 2-hour interval between injections.

After 96 h of MPTP treatment, mice were euthanized by overdose of anesthetics and brains were collected and processed for immunohistochemistry. The brains were immediately fixed in 4 % PFA in PBS, pH 7.4, for 5–7 days. The fixed brains were cryoprotected by incubating in 10 % sucrose in PBS the first 24 h and 30 % until sunk (3–5 days extra). The brains were finally fast frozen in isopentane surrounded by dry-ice for 30 min and kept at −80 °C until usage.

All experiments conducted with animals were previously approved by the Ethical Committee for Experimental Research from University of Seville (ethical code number: 30/05/2023/034) and fulfilled the requirements for experimental animal research in accordance with the U. K. Animals (Scientific Procedures) Act, 1986 and with the Guidelines of the European Union Council (86/609/EU) and the Spanish regulations (BOE 34/11370–421, 2013) for the use of laboratory animals.

2.5. Immunohistochemistry

Thirty μm thick brain coronal sections were cryostat-cut at −20 °C and mounted on glass slides. Antigen retrieval was performed by incubating sections in 10 mM citrate buffer (pH 6.0) using the 2100-Retriever pressure cooker (Aptum Biologics Ltd). Endogenous peroxidase activity was blocked with 0.3 % hydrogen peroxide in methanol. Sections were then incubated in a blocking solution of PBS-Triton X-100 0.25 % with 5 % normal donkey serum for 1 h. Primary antibodies targeting tyrosine hydroxylase (TH) (T8700-1VL, Sigma-Aldrich; 1:300) and Galectin-3 (GAL-3) (AF1179, R&D Systems; 1:500) were applied overnight at 4 °C. Following rinsing, sections were incubated with secondary antibodies and then processed using the VECTASTAIN® Elite ABC HRP kit and DAB Substrate Kit. After PBS washes, sections were dehydrated, mounted with DPX, and subjected to stereological analysis to quantify TH-positive neurons and optical microscopy for GAL-3-positive cells in the substantia nigra area.

2.6. Mitochondrial complex I activity assay

Mitochondria were isolated from fresh brains of healthy mice, feeding conventional diet, as described by Bougria et al. (Bougria et al., 1995). Briefly, brain tissues underwent mincing, washing, and homogenization in an ice-cold medium consisting of 10 mM Tris/HCl (pH 7.4), 0.32 M sucrose, 1 mM EDTA, and 0.1 % (w/v) BSA, with the aid of a 3 ml Tissue Grinder Potter-Elvehjem (Avantor). The homogenates were centrifuged at 1000 g for 10 min, and the collected supernatants underwent further centrifugation at 12,500 g for 15 min. The resulting pellet, rich in mitochondria, was resuspended in the same medium at a protein concentration of 5 mg/ml. All procedures were conducted at 4 °C.The activity of Complex I within isolated mitochondria was evaluated using the Mitochondrial Complex I Activity Assay Kit (MAK359, Sigma-Aldrich), following the manufacturer's instructions. Each reaction used 4 μg of mitochondrial protein, and RBEE was used at 0.5–1 mg/ml. The absorbance was measured at a wavelength of 600 nm. The mitochondrial complex I inhibitor Rotenone was used as negative control.

2.7. Statistical analysis.

Each experimental condition involved at least four animals. Data were presented as mean ± SD. Statistical analysis was performed using One- or Two-Way ANOVA followed by Tukey's post hoc test for multiple range comparisons, with a significance level (alpha) set at 0.05. GraphPad Prism 8.4.0 software was used for these analyses.

3. Results

3.1. RBEE chemical characterization.

For the production of RBEE, rice bran was processed by enzymatic hydrolysis using subtilisin (EC3.4.21.62) to reduce the size of original rice bran proteins into soluble peptides (Macias-Benitez et al., 2021) and to solubilize hydrophobic compounds as lipids and bioactive metabolites forming an emulsion (Revilla et al., 2009).

This protease hydrolysis yields protein fractions mainly comprising peptides <5 kDa, which interact with lipids, enhancing solubility of fatty acids and hydrophobic bioactives like polyphenols, phytosterols, tocopherols, and tocotrienols in water. This boosts bioavailability while preserving bioactive content (Revilla et al., 2009).

The chemical composition of RBEE utilized in this work was predominantly composed of lipids, constituting 44.6 % (w/w), with protein and carbohydrates presenting nearly equal proportions at 25.0 % and 25.4 % (w/w), respectively.

Our RBEE effectively preserves the bioactive compounds in rice bran, including γ-oryzanol (representing a 10 % of total sterols), tocopherols and tocotrienols shown by Santa María *et al.* [23]. Among these, γ-tocotrienols were the most abundant, followed by δ-tocotrienols and γ-tocopherols (Table 1).

Furthermore, RBEE also contains polyunsaturated fatty acids, with linoleic acid and linolenic acid constituting 38.48 % and 1.16 % of the total fatty acid content, respectively (Table 1).

Table 1
Bioactive molecules in RBEE.

COMPONENTS	CONCENTRATION (dry weight, component/ RBEE)
Tocopherols by HPLC (mg/Kg)	
α-Tocopherol (Vitamin E)	4
β-Tocopherol	9
γ-Tocopherol	14
δ-Tocopherol	<2
Total Tocopherols	26
Tocotrienols by HPLC (mg/Kg)	
α-Tocotrienol	<2
β-Tocotrienol	<2
γ-Tocotrienol	59
δ-Tocotrienol	36
Total Tocotrienols	95
Fatty Acid Composition (g/100 g fat)	
C-12:0 (Lauric)	0.02
C-14:0 (Myristic)	0.35
C-16:0 (Palmitic)	15.86
C-16:1 (Palmitoleic)	0.25
C-17:0 (Margric)	0.05
C-17:1 (Margaroleic)	0.03
C-18:0 (Stearic)	1.70
C-18:1 (Oleic)	39.71
C-18:2 (Linoleic)	38.48
C-20:0 (Arachic)	0.63
C-18:3 (Linolenic)	1.16
C-20:1 (Eicosenoic)	0.49
C-22:0 (Behenic)	0.39
C-22:1 (Erucic)	<0.01
C-24:0 (Lignoceric)	0.89
Trans Oleic (t-C18:1)	0.27
Trans Linoleic + Trans Linolenic	0.50
Sterols (ppm)	
γ-oryzanol (mixture of ferulic acid esters)*	720
Total Sterols	7009

(*) δ-7-Stigmasteryl ferulate, Stigmasteryl ferulate, Cycloartenyl ferulate, 24-Methylenecycloartanol ferulate, Campesteryl ferulate, β-Sitosteryl ferulate, Campestanol ferulate and Sitostanol ferulate.

3.2. RBEE exhibits neuroprotective effects against MPTP-Induced neuronal loss.

MPTP induces neurodegeneration of dopaminergic neurons in the SN due to a combination of mitochondrial dysfunction, oxidative stress, energy depletion and gliosis. In our model such neurodegenerative loss can be observed clearly 96 h after the intraperitoneal injection of MPTP. In mice fed with the control diet (Fig. 1 C, D) around 50 % of TH-positive neurons die. Conversely, mice fed with RBEE diet showed a robust neuroprotection of TH-positive neurons compared to control diet plus MPTP (Fig. 1 G, H). These findings highlight the neuroprotective properties of RBEE, suggesting its potential role in mitigating neurodegenerative processes triggered in PD.

3.3. RBEE decreases MPTP-induced gliosis.

The MPTP administration used for this study initially provokes a first wave of non-apoptotic dopaminergic cell death that as a consequence causes the activation of microglia cells within the area inducing a proinflammatory response (Boza-Serrano et al., 2014; Garcia-Revilla et al., 2023). This neuroinflammatory response exacerbate further neuronal damage and contribute to the progression of PD (Burguillos et al., 2011; Kavanagh et al., 2015). This neuroinflammatory response can be measured by the upregulation of markers for microglial/macrophages activation, including galectin-3 (GAL-3). GAL-3 is a lectin that is upregulated in microglia in different neuroinflammatory conditions such as ischemic stroke (Burguillos et al., 2015), traumatic brain injury (TBI) (Yip et al., 2017) and neurodegenerative diseases, including AD (Boza-Serrano et al., 2019) and more importantly for our study in PD (Boza-Serrano et al., 2014; Garcia-Revilla et al., 2022). The analysis of GAL-3-positive (GAL-3+) cells within the SN showed a significant upregulation of GAL-3 96h after the MPTP treatment in animals fed with the control diet (Fig. 2. I). This analysis also unveiled a marked and significant reduction in gliosis in mice that were exposed to RBEE diet upon MPTP treatment (Fig. 2. G and H) in comparison to those subjected to standard diet following MPTP treatment (Fig. 2. C and D). This observation suggests that RBEE possesses the capability to attenuate MPTP-induced neuroinflammatory responses, thereby further validating its neuroprotective attributes.

3.4. RBEE increases mitochondrial activity in mouse brains

Mitochondrial dysfunction is implicated in the degenerative process of PD, contributing to energy deficits, oxidative stress, and the selective vulnerability of dopaminergic neurons. Therefore, understanding if RBEE affects mitochondrial activity helps elucidate its potential mechanisms of action. Mitigating mitochondrial dysfunction could potentially slow down the progression of neurodegeneration. Hence, we next wanted to test if RBEE positively influences mitochondrial function in the brain, as it may have preventive implications for neurodegenerative diseases, including PD.

The evaluation of mitochondrial function *in vitro* revealed that RBEE, in isolated mitochondria, induced a significant augmentation in mitochondrial complex I activity (Fig. 3). Two different doses of RBEE were analyzed (0,5 mg/ml and 1 mg/ml), based on a previous study that tested the ability of RBEE on cell proliferation (Revilla et al., 2013).

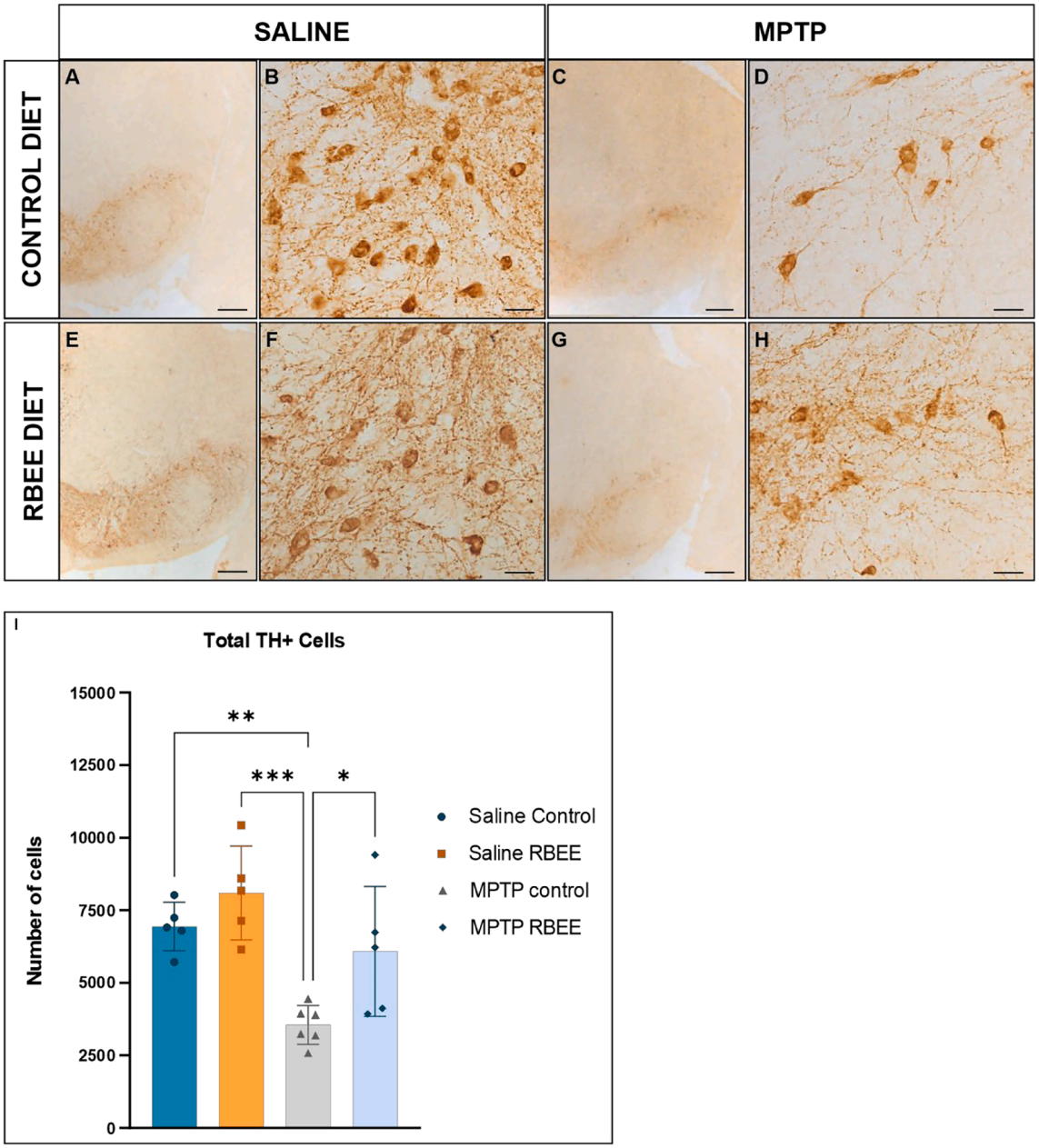

Fig. 1. Stereological analysis of nigral TH-positive neurons in the SN of mice fed with control or RBEE diet and treated with saline or MPTP for 96 h. **A, C, E** and **G.** Crops of micrographs at 1.25X magnification displaying one side of the SN for each experimental condition. Scale bars of 0.04 mm. **B, D, F** and **H.** Representative zoomed images of TH + cells at 20X magnification. Scale bars of 30 μm. **I.** Quantitative analysis of total TH + cells. 5–6 mice per group were used. Statistical significance was calculated by analysis of variance (One-way ANOVA) followed by Tukey test. Data are expressed as mean ± SD. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Intriguingly, no discernible differences in mitochondrial function was observed between those two concentrations. These findings hint at the possibility that RBEE may exert its neuroprotective effects, as well, through the increase of mitochondrial function.

4. Discussion

This study explores the neuroprotective potential of RBEE in a well-established murine model of PD induced by MPTP. We focused on the ability of RBEE to mitigate neurodegenerative processes, emphasizing its effects on neuroinflammation/gliosis, and mitochondrial dysfunction associated with PD.

In our study we observed several factors that may explain the beneficial effect of RBEE diet observed in mice treated with MPTP. First of all, the enzymatic hydrolysis process performed in our laboratory, significantly enhances the bioavailability of the resulting RBEE (Revilla et al., 2009), since subtilisin digestion was used to break down insoluble proteins, reducing their size to soluble peptides. This transformation induced by subtilisin also extends to other bioactive compounds in rice bran, including antioxidants, making its bioactive compounds more readily absorbable by the body. The composition analysis of RBEE shows a rich array of bioactive compounds, including polyphenols (such as γ-oryzanol), tocopherols, tocotrienols and polyunsaturated fatty acids. These bioactive compounds have been shown to successfully cross the blood–brain barrier and penetrate into the brain (Ferri et al., 2015; Kato et al., 2021; Kozuka et al., 2015; Vauzour, 2012). Remarkably, 1 h after single oral administration of γ-oryzanol, among different tissues, it was mainly accumulated in the brain of mice (Kozuka et al., 2013).

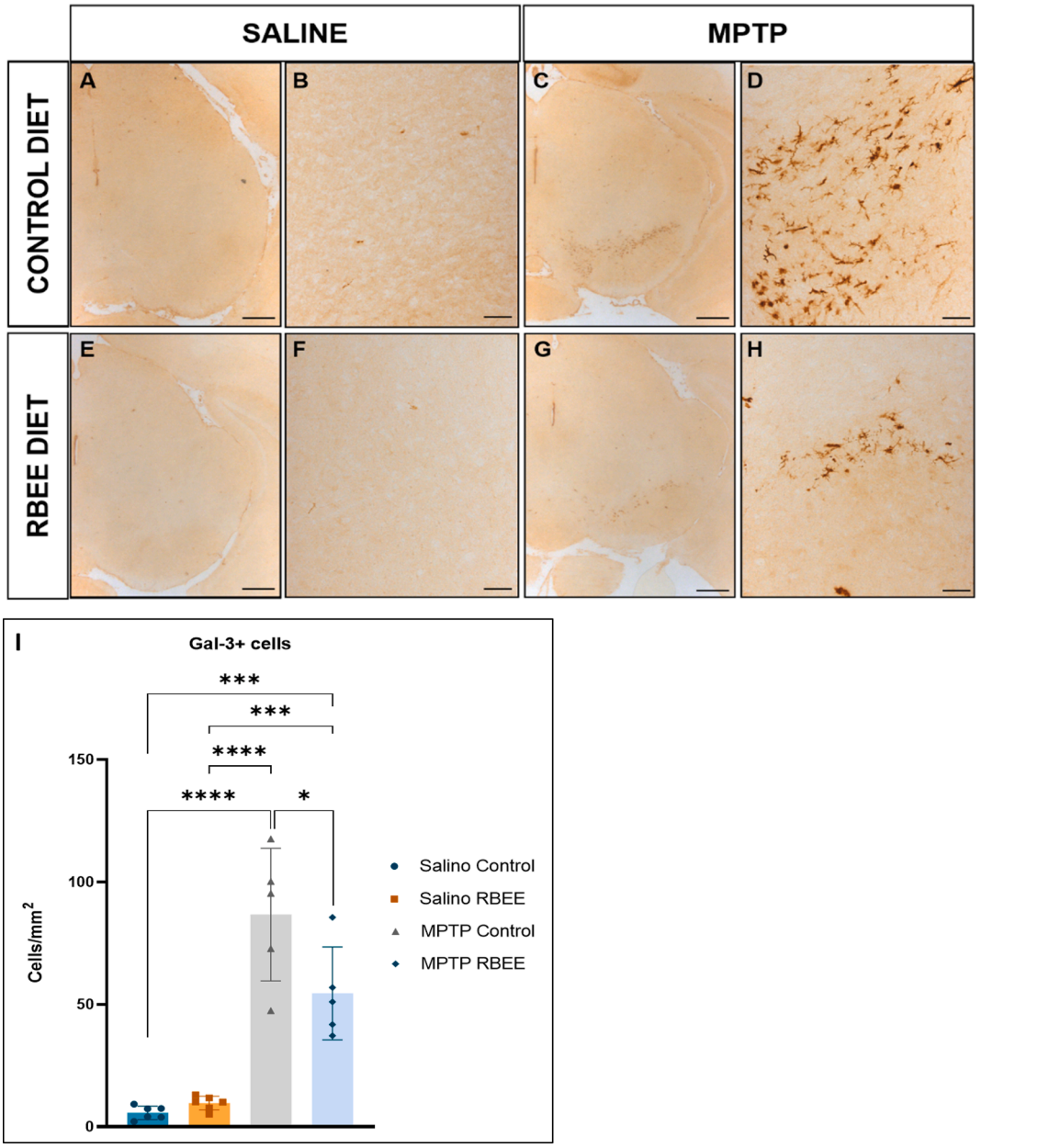

Fig. 2. Immunohistochemical analysis of nigral GAL-3 + microglial cells in the SN of mice subjected or not to dietary RBEE and treated with saline or MPTP for 96 h. **A, C, E** and **G.** Crops of micrographs at 1.25X magnification displaying one side of the SN for each experimental condition. Scale bars of 0.04 mm. **B, D, F** and **H.** Representative images of GAL-3 + cells at 20X magnification. **I.** Quantitative analysis of total GAL-3 + cells. 5–6 mice per group were used. Statistical significance was calculated by analysis of variance (One-way ANOVA) followed by Tukey test. Data are expressed as mean ± SD. *$p < 0.05$, ***$p < 0.001$, ****$p < 0.0001$.

In our extracts, γ- and δ-tocotrienols were the most abundant tocotrienols, and they have demonstrated the greater efficacy in ameliorating neurodegeneration and motor deficits in different *in vivo* models of AD and PD (Ibrahim et al., 2021; Kumari et al., 2021). In fact, in the context of neuroprotection, γ-oryzanol has been shown to be effective in reducing neuromotor deficits, dopamine depletion and oxidative stress in a model of PD induced by rotenone in *Drosophila melanogaster* (Araujo et al., 2015). Likewise, ferulic acid *per se* confers neuroprotection against cerebral ischemia/reperfusion injury in rats by inhibiting ICAM-1 mRNA expression and attenuating oxidative stress-induced apoptosis (Cheng et al., 2008). Similarly, in vitro and in vivo studies suggest that the members of the vitamin E family, (such as tocopherols and tocotrienols), protect cell membranes from oxidative damage, mitochondrial dysfunction, and abnormal cholesterol synthesis, confers neuroprotection affecting positively cognitive function (Chin & Tay, 2018; Grimm, Mett, et al., 2016; Grimm, Regner, et al., 2016; Naomi et al., 2021). Among the different vitamin E analogs, γ-tocotrienol demonstrates great efficacy in reducing Aβ oligomerization and aggregation, offering a potential therapeutic approach for AD (Ibrahim et al., 2021). In the PD context, rats treated with 6-hydroxydopamine (6-OHDA), tocotrienols showed a significant neuroprotective effect through a reduction in neuronal loss in the SN and amelioration of associated motor deficits (Kumari et al., 2021). Mechanistically, tocotrienols may exert their neuroprotective effects through modulation of 12-lipoxygenase activity (12-LOX), and reducing glutamate-induced neurodegeneration (Khanna et al., 2003).

These bioactive compounds possess antioxidant properties, crucial for counteracting oxidative stress implicated in PD (Bianchi et al., 2023; Chin & Tay, 2018). The observed effect over the dopaminergic population and hindered gliosis may be attributed, at least in part, to the

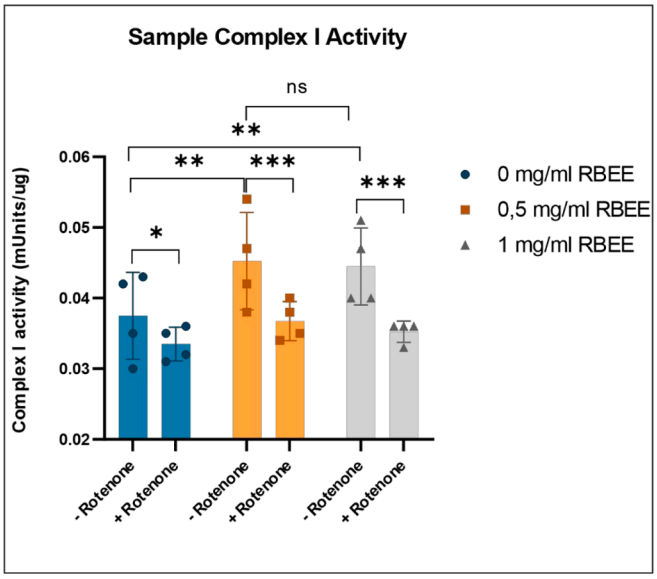

Fig. 3. Measurement of Mitochondrial Complex I activity in mouse brains following RBEE treatments (0.5 and 1 mg/ml). 4 mice were used for this analysis. Statistical significance was calculated by analysis of variance (Two-way ANOVA) followed by Tukey test. Data are expressed as mean ± SD. *p < 0.05, **p < 0.01, ***p < 0.001.

antioxidant capacity of these constituents (Araujo et al., 2015; Behl et al., 2021; Grabska-Kobylecka et al., 2023). Further research is crucial to elucidate the specific mechanisms through which these bioactive compounds exert their neuroprotective effects and to establish RBEE as a valuable strategy for maintaining optimal brain health. Moreover, the significant enhancement of mitochondrial Complex I activity that we observe in our study suggests the RBEE potential role in preserving mitochondrial function. The tocopherols and tocotrienols have been associated with protecting mitochondria against oxidative stress and maintaining cellular homeostasis (Ibrahim et al., 2021; Kumari et al., 2021). This improvement in mitochondrial function aligns with previous studies highlighting the impact of RBEE on enhancing mitochondrial function both *in vitro* and *in vivo* (Bhatia et al., 2016). The consistent positive effect of RBEE on mitochondrial activity suggests a potential mechanistic link between RBEE and neuroprotection, at least in part, through the preservation of mitochondrial integrity.

Finally, another positive feature of RBEE that could explain the neuroprotection in our MPTP model is its immunomodulatory properties over the microglia population (El-Din et al., 2021). One of the proteins that has shown to play an important role in neuroinflammation in different neurodegenerative conditions including PD, is GAL-3 (Boza-Serrano et al., 2014; Garcia-Revilla et al., 2022; Garcia-Revilla et al., 2023). We observe in our system that RBEE supplementation resulted in a marked reduction in GAL-3+ microglia. This anti-inflammatory effect is consistent with previous reports showing RBEE potential to modulate microglial activation and reduce proinflammatory cytokines (Bhatia et al., 2016; Grabska-Kobylecka et al., 2023), and could be also one of the possible mechanisms conferring neuroprotection our MPTP model.

The evidence presented in this study supports the idea that incorporating RBEE into the diet may hold potential in preventing neurodegeneration and mitigating the progression of PD pathology. Further research is warranted to elucidate the specific molecular mechanisms underlying its effects.

5. Conclusion

These data demonstrate that diet supplementation with the bioactive compounds found in RBEE (with antioxidant, anti-inflammatory, and mitochondrial protective properties) improve mitochondrial function *in vitro* and prevents MPTP-associated neuronal loss and GAL-3+ microglia in the SN *in vivo*, supporting the hypothesis that dietary RBEE may prevent neurodegeneration and alleviate the progression of PD pathology.

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Author contributions

E.G and A.F treated the animals, processed the tissues, performed the immunohistochemistry and the analysis of the results. E.G, prepared and quantified the mitochondrial complex I assay. L.M-P, prepared the RBEE and control diets and processed RBEE for the biochemical analysis. A.C., B.B-K, R.M-G, helped to process the tissue and in the immunohistochemistry. J.P and M.A.B designed the study and E.G and M.A.B wrote the manuscript. All authors reviewed and contributed to manuscript revisions.

CRediT authorship contribution statement

Elena Gavilán: . Alicia Flores: Visualization, Validation, Methodology, Formal analysis. **Angélica Castaño:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Luis Martin-Presas:** Visualization, Validation, Methodology, Investigation. **Bazhena Bahatyrevich-Kharitonik:** Visualization, Validation, Methodology. **Rafael Medina-Guzman:** Visualization, Validation, Methodology. **Juan Parrado:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Miguel Ángel Burguillos:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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