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Original article

Rosinidin inhibits NF-κB/ Nrf2/caspase-3 expression and restores neurotransmitter levels in rotenone-activated Parkinson's disease

Amira M. Alghamdi [a], Fahad A. Al-Abbasi [a], Shareefa A. AlGhamdi [a,b], Farhat Fatima [c], Sami I. Alzarea [d], Imran Kazmi [a,*]

[a] Department of Biochemistry, Faculty of Sciences, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[b] Experimental Biochemistry Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[c] Department of Pharmaceutics, College of Pharmacy, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia
[d] Department of Pharmacology, College of Pharmacy, Jouf University, Sakaka 72341, Aljouf, Saudi Arabia

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ABSTRACT

Objectives: The examination was sighted to study the preventive effects of rosinidin against rotenone-activated Parkinson's disease in rats.
Methods: Animals were randamoized into five groups: I-saline, II-rotenone (0.5 mg/kg/b.wt.), III- IV-10 and 20 mg/kg rosinidin after rotenone and V-20 mg/kg rosinidin per se for 28 days and were assigned for behavioral analysis., Biochemical parameters i.e. lipid peroxidation, endogenous antioxidants, nitrite level, neurotransmitter levels, proinflammatory biomarkers such as interleukin- 6 (IL-6), tumor necrosis factor-α, IL-1β, nuclear factor kappa B, nuclear factor erythroid 2–related factor 2, and caspase-3 were assessed on the 29th day of the research.
Results: Rosinidin augmented the effectiveness of rotenone on akinesia, catalepsy, forced-swim test, rotarod, and open-field test. Biochemical findings indicated that treatment of rosinidin showed restoring neuroinflammatory cytokines, antioxidants, and neurotransmitter levels in rotenone-injected rats.
Conclusion: As a result of rosinidin treatment, the brain was protected from oxidative stress-induced neuronal damage and inhibited neuroinflammatory cytokines.

1. Introduction

Parkinson's disease (PD) is a hypokinetic neuro- cumulative disorder that primarily influences the nigrostriatal pathway and causes a disparity in the neurotransmitters acetylcholine and dopamine levels (Poewe et al., 2017, Balestrino and Schapira 2020). Over 6 million (2–2.5 %) elderly age population are been affected by the loss of dopaminergic signaling (Anandhan et al., 2017). The predominating symptoms occurring due to loss of neuronal circuits are tremors, bradykinesia, the rigidity of muscle, postural infirmity, and lack of gait (Jellinger 2015, Sveinbjornsdottir 2016). Abnormal protein accumulation in the brain is called 'Lewy bodies', usually alpha-synuclein deposits which are generally observed in people affected by PD (Wakabayashi et al., 2013, Friedman 2018). The factors that drive dopaminergic nigrostriatal degeneration are oxidative stress, disturbance in the homeostasis of cellular calcium, environmental, mitochondrial dysfunction, overproduction of glutamate through NMDA receptors causing excitotoxicity of neurons (Henchcliffe and Beal 2008, Hwang 2013).

Rotenone, a hydrophobic pesticide is used as an inducing agent for PD. Investigations presented that pesticide usage leads to mitochondrial dysfunction and causes destruction of dopaminergic neurons (Xiong et al., 2012, von Wrangel et al., 2015). Rotenone is a blood–brain barrier (BBB) penetrator, generate oxidative stress, neuroinflammation, insufficiency of neurotransmitters, and neuronal degeneration. Previous findings suggest that the management of PD with drugs possessing antioxidant and anti-inflammatory properties can be beneficial (Zhang et al., 2016, Pan et al., 2020, Siracusa et al., 2020).

* Corresponding author.
E-mail addresses: Amaalghamdi1@kau.edu.sa (A.M. Alghamdi), fabbasi@kau.edu.sa (F.A. Al-Abbasi), saaalghamdi1@kau.edu.sa (S.A. AlGhamdi), f.soherwardi@psau.edu.sa (F. Fatima), samisz@ju.edu.sa (S.I. Alzarea), ikazmi@kau.edu.sa (I. Kazmi).
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L-dopa is a classic therapy treating Parkinson but long-term exposure to L-dopa is linked with motor-related dysfunctions like dyskinesia which affects the normal motor functioning of PD patients (Jaunarajs et al., 2011). Dopamine agonists, catecholamine-O-methyl transferase (COMT), monoamine oxidase inhibitors (MAO) and surgical treatment are second-line management options for PD (Malar et al., 2020). The current treatment only aims to correct the symptoms of Parkinson's, none of them reverse the pathology of the disorder and are related with Various undesirable effects (Thanvi and Lo 2004).

Natural sources include a variety of plant-derived phytoconstituents which have a promising role in chronic disorders and are considered as safe alternatives to current synthetic drugs (Hussain et al., 2018). Rosinidin, an anthocyanin is found in the flowers of *Catharanthus roseus* Linn belonging to the Apocynaceae family (Vikaskurhekar 2020). Rosinidin is known to have a strong antioxidant activity that protects against free radicals generated from cell damage (Alshehri and Imam 2021). The anthocyanin pigment has wide medicinal applications like wound healing, anti-inflammatory, anti-cancer, tuberculosis, flatulence, memory enhancer, and hypoglycemic property (Ksouri et al., 2012). Anthocyanidins activate the proinflammatory cytokine pathway by modulating the mitochondrial dysfunction thus targeting to reduction the growth of PD (Ksouri et al., 2012, Winter and Bickford 2019). Previously rosinidin reported as an anti-nephrotoxic, reduced diabetic complexity, minimize lipopolysaccharide and streptozotocin-activated neurotoxicity via its antioxidant, flavonoids property and anti-Inflammatory (Monteiro et al., 2018, Alshehri and Imam 2021, Alharbi et al., 2022, Gilani et al., 2022). In our study, we chose the benefit of rosinidin, which has not been demonstrated to support neurotoxicity caused by rotenone in experimental rats in PD paradigms. In this study, efficacy of rosinidin was tested in animals for the ability to inhibit rotenone-induced PD.

2. Methods

2.1. Chemicals

A source of Rotenone was Sigma Aldrich (USA). Rosinidin was given away as a sample by SRL, India. Interleukins- (IL-1β), IL-6, tumor necrosis factor alpha (TNF-α), nuclear factor-κB (NF-κB), nuclear factor erythroid 2–related factor 2 (Nrf2) and caspase-3 (Casp3) were analysed by rat enzyme-linked immunosorbent assay (ELISA) kit (MyBio Source, USA).

2.2. Animals

Male Wistar rats (10–12-week-old; 180 cm/220 g) were kept in propylene cages with a 12hr light/dark cycle at ambient temperature (23 °C), humidity (50–65%), and free allowance to tap water and pellet diet. The behavioural tests were assessed during the active phase between 19.00 and 24.00 hr. The proposal was permitted by institutional ethics committee for animals and work directed as per the ARRIVE guidelines.

2.3. Experimental

After being adapted for at least 7 days 30 rats into five groups were randomly divided (n = 6):

Group I (Control): received 5 ml/kg i.p. (saline) throughout the study.

Group II (Disease control): received rotenone -injected for 28 days 0.5 mg/kg/b.wt. s.c. (Teerapattarakan et al., 2018, Sharma et al., 2020).

Group III-IV: For 28 days, received rotenone 0.5 mg/kg/b.wt. s.c with subsequent given of rosinidin (10 and 20 mg/kg).

Group V: Rosinidin (20 mg/kg/day) per se for 28 days.

The behavioural quantification was executed on 29th day. After that biochemical parameters were performed. (Fig. 1).

2.4. Motor functional parameters

2.4.1. Akinesia

The time in which the rats move all the paws from their position was noted and should not exceed more than 180 s. The animals were positioned on a raised wooden platform (40 cm D × 40cmH × 30 cm W) and acclimatized for at least 5–10 mins. The time when all the paws were displaced from its place was observed. Six times a day, the test was conducted and the mean was calculated (Anandhan et al., 2013).

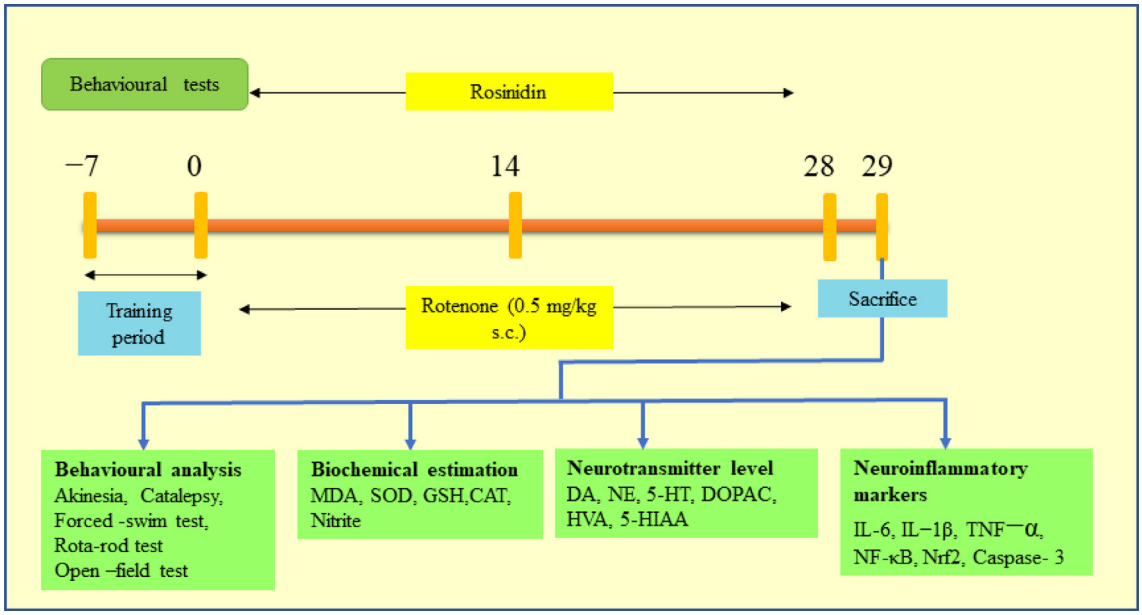

Fig. 1. Schematic presentation of experimental plan. MDA (Malonaldehyde), SOD (Superoxide), GSH (Glutathione-S transferase), CAT (Catalase), NE (Norepinephrine), 5-HT (Hydroxy tryptamine), DOPAC(3,4-dihydroxyphenylacetic acid), HVA (homovanillic acid), and 5-HIAA (5-hydroxyindoleacetic acid), IL-6 (Interleukin-6), IL-1β (Interleukin-1β), TNF-α (Tumor necrosis factor), NF- ĸB (Nuclear factor kappa factor), Nrf2 (Nuclear factor erythroid 2–related factor 2), Casp3 (caspase-3).

2.4.2. Catalepsy

The catalepsy is constructed on the lack of posture correction by rats. In this test, rats were aligned in such a way that their hind limbs were placed on the 10 cm wooden bar above the base level. Rats were positioned such that their front paws were on the wooden floor The period of time that the rats used their two hindlimbs to support the situation on the wooden bar was recorded. The test was taken repeatedly 6 times to calculate the mean value (Costall and Naylor 1974, Balakrishnan et al., 2018).

2.4.3. Forced swim

This test is depends on the despair or immobility of the animal after placing in water. According to the conventional method, an acrylic transparent cylinder (10cmD × 25 cm H × 9 cm W) was filled with water (22 ± 2℃). The rats were placed for 2–6 mins and the immobility time was noted. The treatment groups received drug 1 hr (p.o) and 30mins (i.p. /s.c)prior starting the test (Yamada et al., 2013, Unal and Canbeyli 2019).

2.4.4. Rotarod

The rotarod activity was conducted to measure the motor and grip control in rodents. The rats were acclimatized to a training duration before starting the main exercise. The rats were kept one by one on the rotating rod (7 cm D) having set the speed at 25 rpm. The time taken for the animal to fall was noted with an average cut-off time of 180 sec. The drug was administered 1 hr (p.o.) and 30mins (i.p./s.c) prior starting the test and evaluated for motor functionality (Sheibani et al., 2017, Zhang et al., 2017, Singh et al., 2021).

2.4.5. Open field

Spontaneous motor activity was estimated using plexiglass wooden base equipment (100 cm W, 100 cm D, 40 cm H) was divided into 25 (595) squares. Rats were sited on the immovable situation every time and their behavior change were recorded for 5–10 mins by a video camera. The crossing of the animal was considered only when all the paws were positioned on another square. Succeeding monitoring were recorded (a) Number of square-box travelled; The number of centers (9 squares) and squares (16 squares) moved by the rat was noted. (b) Grooming; i.e., licking the paw and fur, (c) Rearing; i.e., sniffing, standing upright on hind limbs, bending on the wall with forelimbs (Kuniishi et al., 2017, Sun et al., 2019).

2.5. Biochemical estimation

The brains were collected and homogenized using phosphate buffer (0.1 M) at last day. The homogenate is then centrifuged at 15,000–20,000 rpm for at least 20mins. The supernatant was accumulated for biochemical examination.

2.6. Malondialdehyde estimation (MDA)

Lipid peroxidation is the oxidative degeneration of lipid molecules causing cell death. Equal quantity (2 ml) of the brain homogenate and trichloroacetic acid (10% w/v) were cooled and subjected to centrifugation. To the 0.5 ml of supernatant, thiobarbituric acid was added, and kept in hot water for 15 mins. The absorbance was recorded at 535 nm on ultraviolet (UV) spectrophotometer. The amount of MDA was presented as nmol of MDA/mg of wet tissue (Chonpathompikunlert et al., 2018, Zahedi-Amiri et al., 2019).

2.7. Reduced glutathione estimation (GSH)

GSH measurement was done using the DTNB method. The homogenate was reacted with trichloroacetic acid centrifugated for 10 mins. To 1 ml of supernatant, 0.2 M 3 ml phosphate buffer (pH 8) and 0.5 ml DTNB reagent (5-5′-Dithio-Bis (2 Nitro-benzoic acid)) was added. The reaction mixture was spectrophotometrically estimated at 412 nm. The values were indicated as nmol GSH/mg of wet weight tissue (Pan et al., 2020).

2.8. Superoxide dismutase (SOD)

SOD was estimated by the following technique using brain homogenate and NADH incubated for 90 sec. To the mixture, acetic acid and butanol was mixed and the extracted butanol layer were measured spectrophotometrically at 520 nm. The activity of SOD was presented in units/mg protein (Weydert and Cullen 2010, Deveci and Karapehlivan 2018).

2.9. Catalase (CAT) estimation

The assay procedure includes brain homogenate which is mixed with H_2O_2 (30 mM) and phosphate buffer(0.05 M) which is then analyzed spectrophotometrically at 212 nm and the expressed activity was calculated in units of catalase/ mg of wet tissue weight (Ghaffari et al., 2018).

2.10. Nitrite level

Nitric oxide level is measured by using Griess reagent by colorimetry assay. The supernatant was reacted with Griess reagent (mixture of naphthyl ethylene diamine and sulphanilamide in H_3PO_4). The reaction mixture was measured at 540 nm spectrometrically (Parkhe et al., 2020, Koppula et al., 2021).

2.11. Neurotransmitter levels

HPLC was used to determine the concentrations of dopamine (DA), serotonin (5-HT), norepinephrine (NE), and their metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA). The brain tissue samples were homogenized in 0.17 M perchloric acid. Using a reversed-phase liquid chromatography system with electrochemical detection, supernatants from tissue homogenates were injected directly into the chromatography system in a 20 µl volume (Kim et al., 1987, Garabadu et al., 2011, Ghaffari et al., 2018, Garabadu and Agrawal 2020).

2.12. Neuroinflammatory markers

The commercial ELISA kits were employed for the determination of inflammatory biomarkers such as IL-1β, IL-6, TNF-α, and NF-κB (Singh and Kumar 2016).

2.13. Nrf2 and Casp3 estimation

Using an ELISA kit and performing the assay in conformance with the protocol, determine the concentrations of Nrf2 and Casp3. Casp3 concentration was expressed in pg/g, and Nrf2 concentrations were displayed in ng/mL.

2.14. Statistical investigation

The outcomes generated were presented as mean ± SEM. Employing the Prism software (Version 8.0.1), the analysis of variance one way (ANOVA) was used to compare between group in

order to define the level of significance. In statistical analysis, the level of significance with<0.05 was indicated as a significant value.

3. Results

3.1. Behavioural parameters

3.1.1. Rosinidin ameliorates rotenone-induced movement disabilities

Fig. 2(A-B) displayed the motor coordination in disease control and treatment groups. The rotenone-induced group revealed a sharp rise in the akinesia time and catalepsy time when correlated to the rotenone injected rats. The treatment group when correlated with the rotenone group revealed a noticeable decrease with 10 and 20 mg/ kg respectively akinesia time [F (4, 25) = 52.12, (P < 0.0001)] and catalepsy time [F (4, 25) = 53.68, (P < 0.0001)].

The daily administration of rotenone substantially improved the immovability time in the rotenone injected rats in contrast to the controls. On administration of 10 and 20 mg/kg rosinidin were reduced in immovability time [F (4, 25) = 30.70, (P < 0.0001)] when compared with rotenone-injected rats (Fig. 2C).

On evaluation of rotarod test, the rotenone group presented a marked decline in the motor control activity (rotarod test) when correlated to the controls. During treatment, at both doses of rosinidin revealed a pronounced rise in the performance time in comparison with the rotenone-injected group [F (4, 25) = 56.16, (P < 0.0001)] (Fig. 2D).

Number of squares travelled decreased markedly in rotenone induced groups when correlated with controls. While treatment with rosinidin at both doses revealed a significant rise in the distance travelled than the rotenone-injected rats [F (4, 25) = 68.74, (P < 0.0001)] (Fig. 2E).

A noticeable decline in the rearing frequency was examined in the rotenone- prompted animals while a substantial rise in the rearing frequency when treated with rosinidin at both doses when correlated to the rotenone-injected group [F (4, 25) = 29.92, (P < 0.0001)] (Fig. 2F).

The above behavioral test did not reveal any significant effects related to rosinidin per se.

3.2. Effect of rosinidin on biochemical parameters

3.2.1. MDA determination

MDA level was raised (p < 0.001) in rotenone-injected cluster as correlated to control. Dose of rosinidin showed significant reduction in MDA when correlated to rotenone-injected rats [F (4, 25) = 24.43, (P < 0.0001)]. (Fig. 3A).

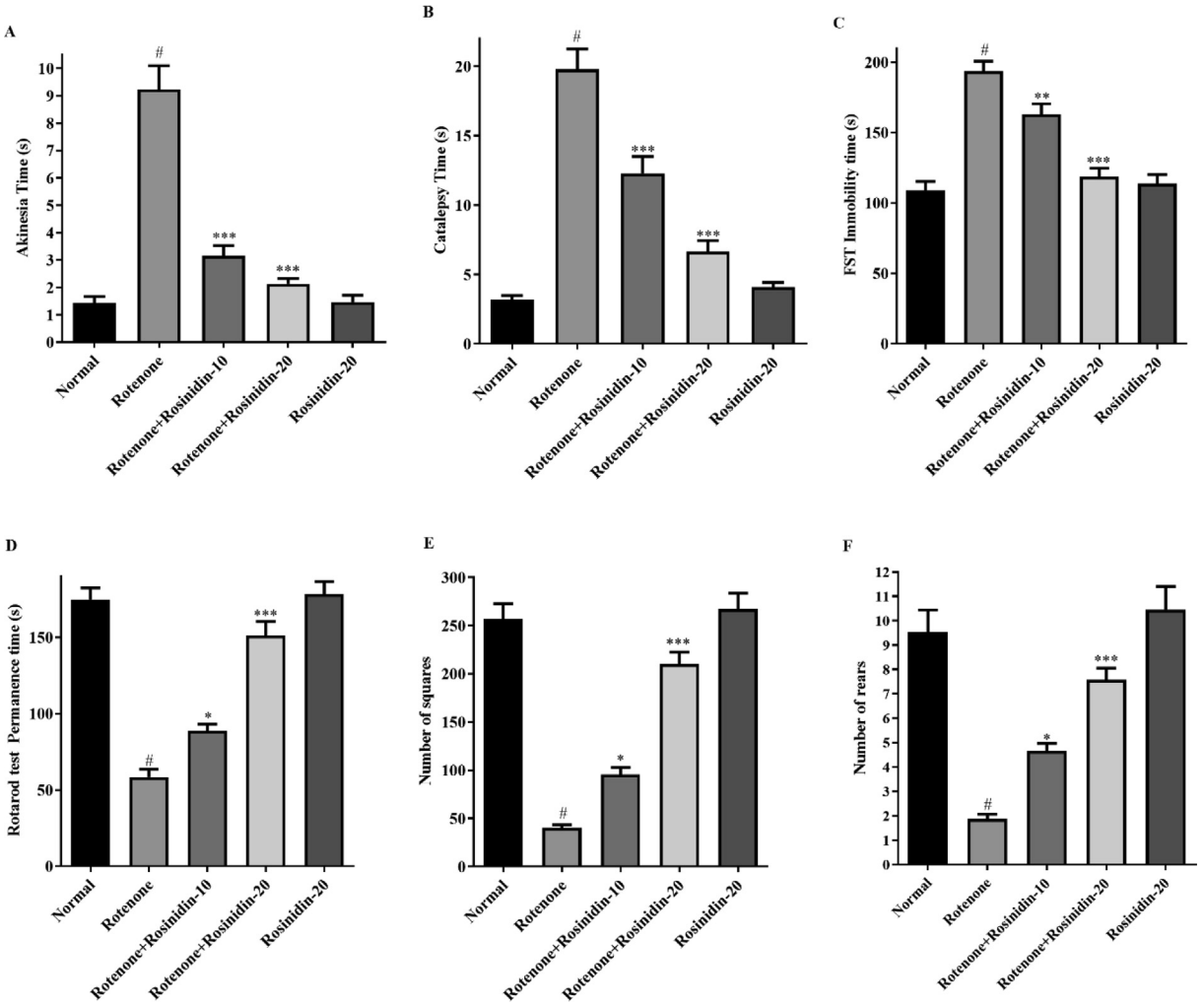

Fig. 2. A-F. Alteration in Behavioural parameters by A. akinesia, B. catalepsy, C. forced swim test, D. rotarod test, E. Number of squares and F. Number of rears. P value < 0.05, 0.01,0.001 were presented as *, **, *** respectively when compared with disease control group. P value < 0.001 was presented as # which signifies disease control group when correlated with control group.

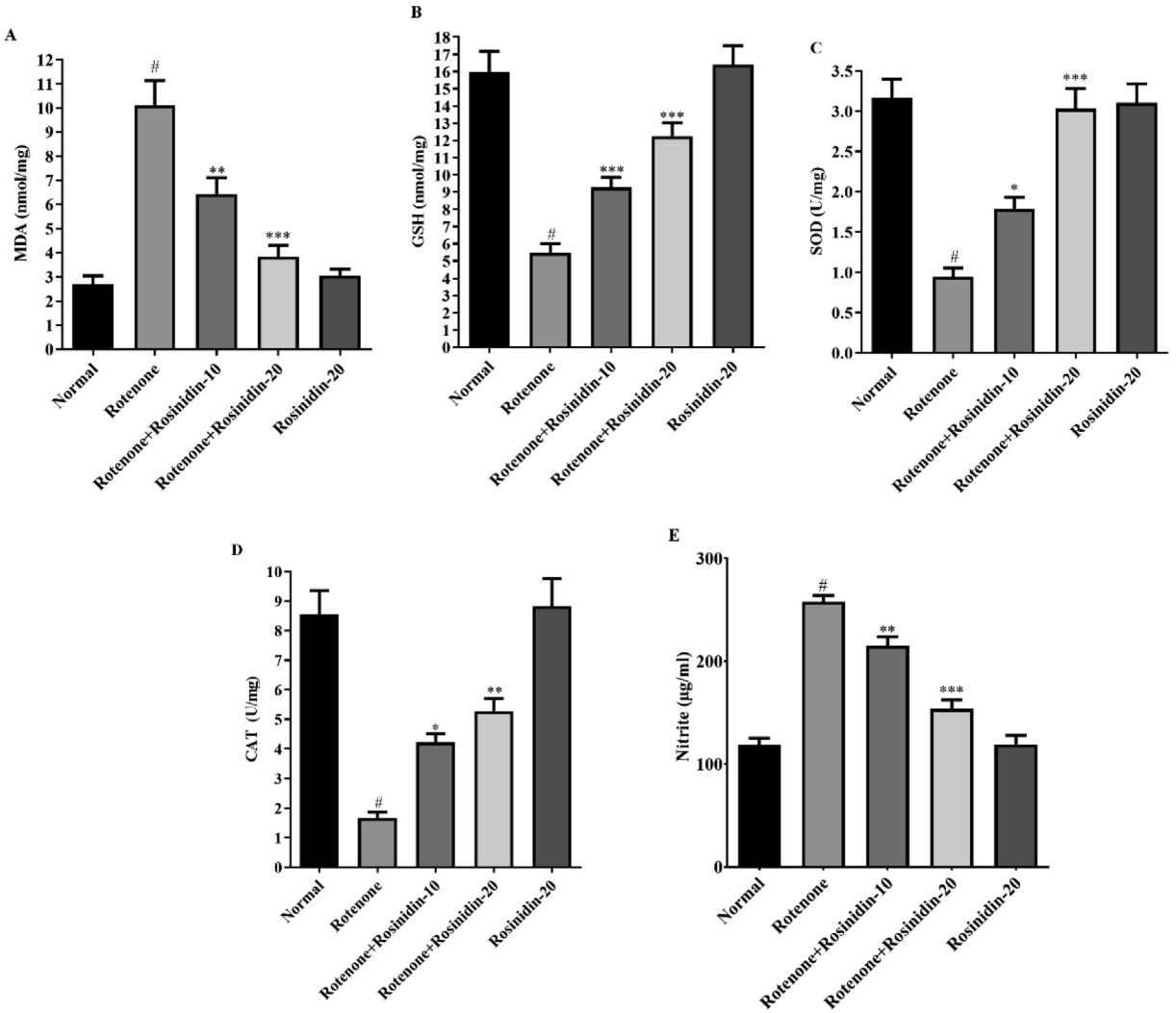

Fig. 3. A-E. The neuroprotective effect of rosinidin on antioxidant parameters. A. MDA, B. GSH, C. SOD, D. CAT, E. P value < 0.05, 0.01,0.001 were presented as *, **, *** respectively when compared with disease control group P value < 0.001 was presented as # which signifies disease control group when correlated with control group.

3.2.2. Gsh determination

An increase in the GSH activity in rotenone-injected rats ($p < 0.001$) when correlated to the control. A pronounced reduction in GSH [F (4, 25) = 26.97, (P < 0.0001)] and noticeable rise in both lower, higher dose (10 mg/kg & 20 mg/kg) of rosinidin as correlated to disease control (Fig. 3B).

3.2.3. Sod determination

In the rotenone-induced rats, the SOD level was remarkably decreased ($p < 0.001$) when correlated to the controls. The SOD level in the treatment with 10 and 20 mg/kg rosinidin was elevated considerably [F (4, 25) = 24.45 (P < 0.0001)] when correlated to rotenone-injected rats. (Fig. 3C).

3.2.4. Cat determination

The rotenone injected rats revealed a marked drop in the catalase activity when corelated to the controls. When compared to the rats who had received rotenone injections, rosinidin administration at both doses resulted in an impressive rise [F (4, 25) = 25.35, (P < 0.0001)] (Fig. 3D).

3.2.5. Nitrite content

The rotenone group revealed a noticeable uprise in the nitrite level when correlated with the controls. A noticeable decline in the nitrite content was noted with both dose of rosinidin when allied with the rotenone-injected rats [F (4, 25) = 61.12, (P < 0.0001)] (Fig. 3E).

3.2.6. Effect of rosinidin on neurotransmitter level

A marked downfall in the dopamine, NE, 5-HT, and 5-HIAA intensities were noted in the rotenone injected rats when correlated with the normal group. An increase in dopamine [F (4, 25) = 271.2, (P < 0.0001)] and 5-HIAA levels [F (4, 25) = 32.16, (P < 0.0001)] was marked when 10 mg/kg ($p < 0.05$), 20 mg/kg was administered. Also, a marked elevation in NE [F (4, 25) = 58.14, (P < 0.0001)] and 5-HT [F (4, 25) = 98.13, (P < 0.0001)] when rosinidin at both doses was administered. While a remarkable upsurge in the DOPAC and HVA intensities in the rotenone group was observed. When both dosages of rosinidin were given, a considerable decline was remarked in the DOPAC [F (4, 25) = 22.19, (P < 0.0001)] and HVA levels [F (4, 25) = 68.35, (P < 0.0001)] (Fig. 4A-F). When both dosages of rosinidin were given, there was a significant drop in the DOPAC (p0.001).

3.2.7. Effect of rosinidin on neuroinflammatory cytokine level

It showed that the disease control rotenone group exhibited elevated levels in proinflammatory markers like IL-6, IL-1ß, TNF-α. Treatment with rosinidin at both doses exhibited a downregula-

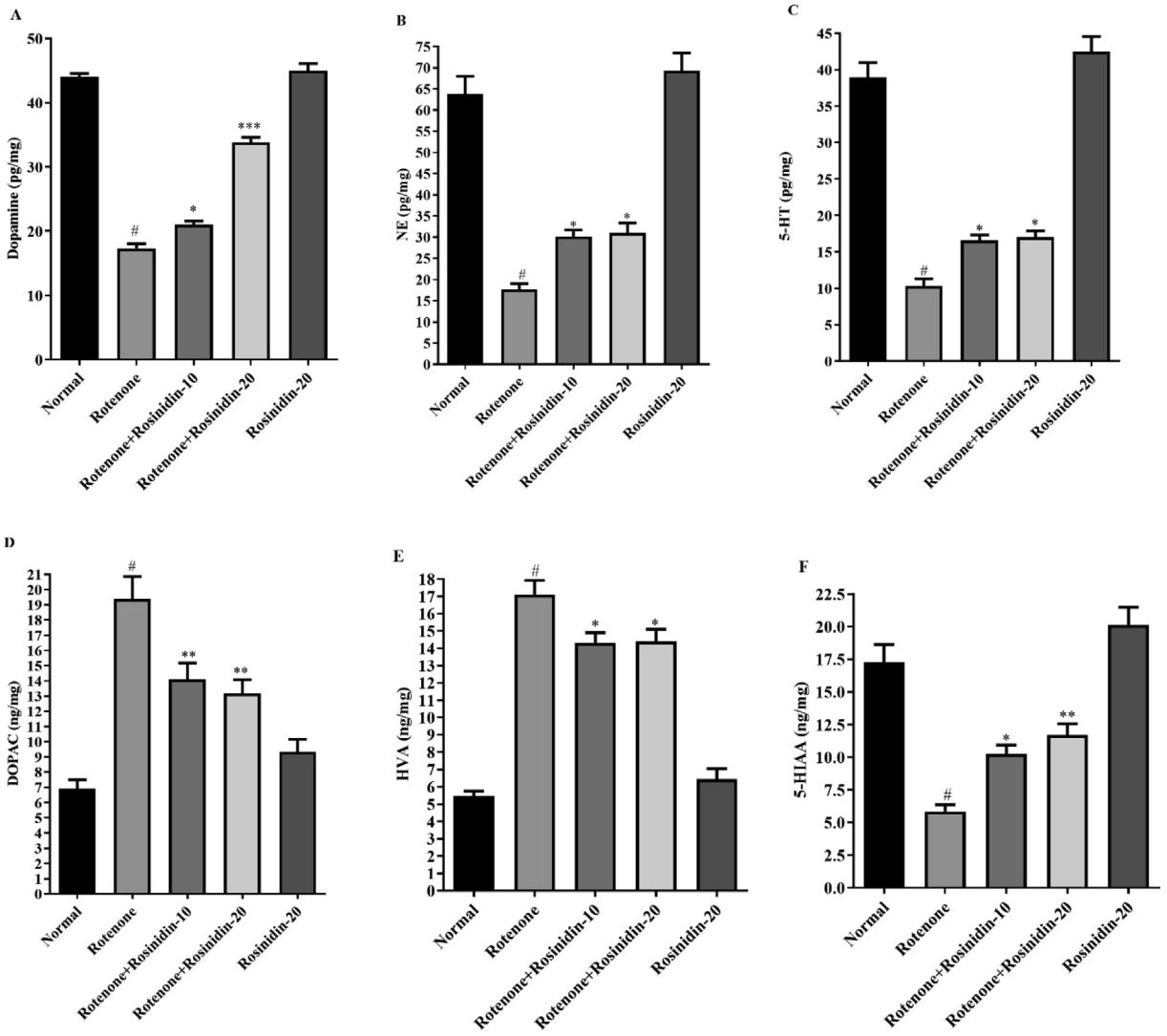

Fig. 4. A-F. The neuroprotective effect of rosinidin on neurotransmitter level. A. Dopamine, B. NE, C. 5-NT, D. DOPAC, E. HVA, F. 5-HIAA. P value < 0.05, 0.01,0.001 were presented as *, **, *** respectively when compared with disease control group. P value < 0.001 was presented as # which signifies disease control group when correlated to control group.

tion in cytokines IL-1ß [F (4, 25) = 51.59, (P < 0.0001)], TNF-α [F (4, 25) = 23.92, (P < 0.0001)], IL-6 [F (4, 25) = 75.93, (P < 0.0001)], NFκB [F (4, 25) = 24.41, (P < 0.0001)] when associated to rotenone injected rats (Fig. 5A-D).

3.2.8. Effect of rosinidin on Nrf2 and Casp3

It revealed that neuroinflammatory indicators shown downregulation of Nrf2 and upregulation of Casp3 in the rotenone-injected rats as associated with normal cluster. Tukey's post-hoc test exhibited that rosinidin at both doses a pronounced upregulation in Nrf2 [F (4, 25) = 27.96, (P < 0.0001)] and downregulation in Casp3 expression [F (4, 25) = 67.88, (P < 0.0001)] when correlated to rotenone group (Fig. 6A-B).

4. Discussion

PD is a slow neuro-depressive disorder marked with neuronal degeneration causing postural imbalance, stiffness, tremor(Russo and Tyler 2015, Ball et al., 2019).The disease progression starts from the autonomic nervous system to the olfactory lobe and then spread through the nervous system (Katzenschlager et al., 2008, Del Tredici and Braak 2016). The dopamine insufficiency interrupts the normal motor functions like tremor, stiffness, and posture imbalance and also non-motor signs with mood, thinking, behavior (Truong et al., 2008, Asakawa et al., 2016, Jagadeesan et al., 2017). The use of standard pharmacotherapy for PD focuses on symptomatic relief for PD symptoms and is cause for developing adverse events which lead to other conditions (Savitt et al., 2006, Oertel and Schulz 2016, Baxi et al., 2018, Jankovic and Tan 2020).The present study showed that rosinidin possesses potent antioxidant activity which alleviates motor impairments and improved behavioural attributes.

Rotenone, a potent lipophilic pesticide targeting the mitochondrial complex thus damaging neuronal growth causing behavioural, neurochemical pathological changes (Betarbet et al., 2000, Ramkumar et al., 2018, Lawana and Cannon 2020, Ibarra-Gutiérrez et al., 2023). In the recent study, rotenone impaired the behavioural parameters with a gradual increase in the akinesia and catalepsy and decline in the locomotor functions as mentioned in previous researches (Ramkumar et al., 2019, El-Shamarka et al., 2023, Ibarra-Gutiérrez et al., 2023). Rosinidin decreased the akinesia and catalepsy time while an increase in the locomotor functional test like rotarod and forced swim test. Dopaminergic loss

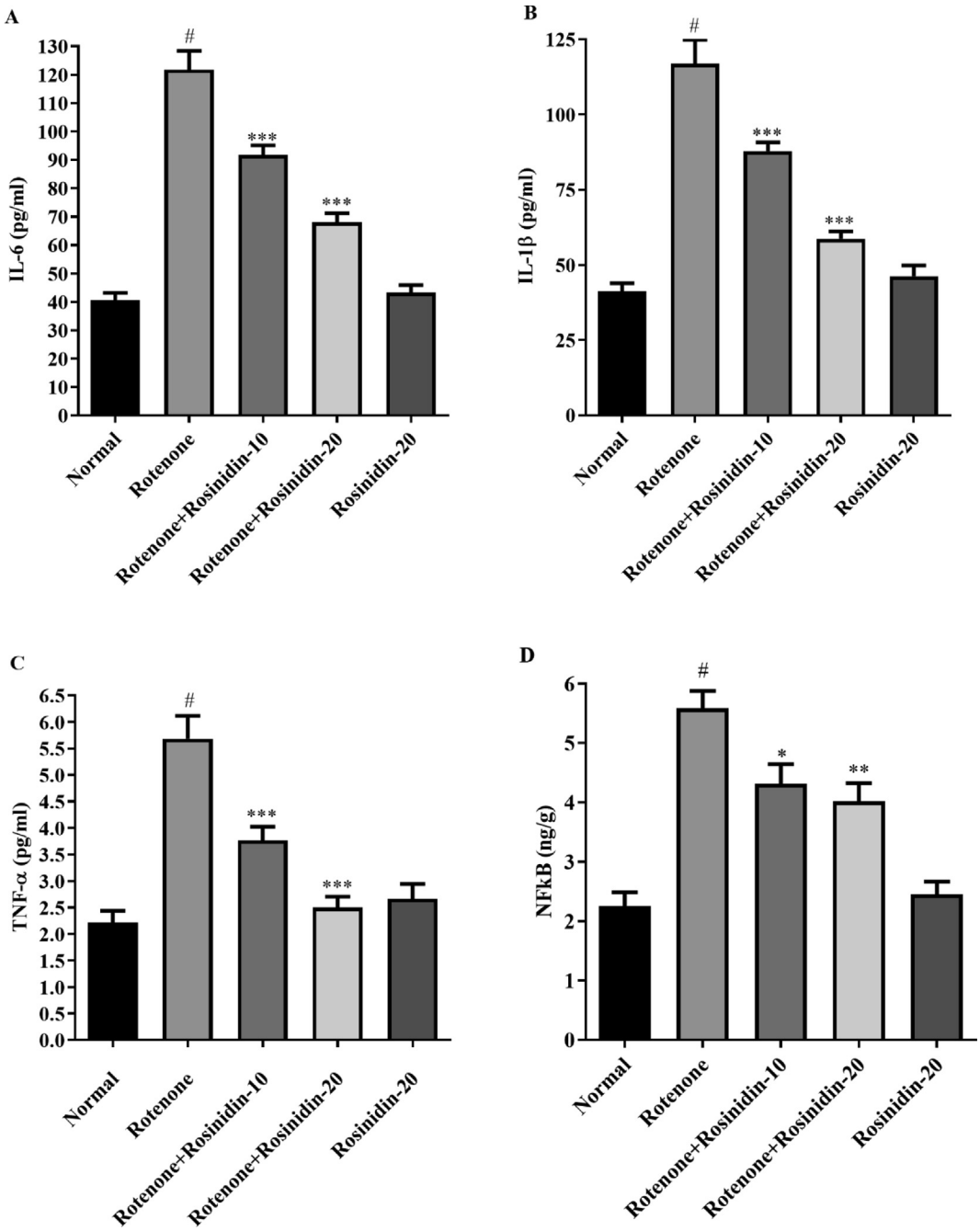

Fig. 5. A-D. The neuroprotective effect of rosinidin on neuroinflammatory parameters. A. IL-6, B. IL-1ß, C. TNF-α, D. NFκB. P value < 0.05, 0.01,0.001 were presented as *, **, *** respectively when compared with disease control group. P value < 0.001 was presented as # which signifies disease control group when correlated with control group.

may be associated with behavioural parameters (Samantaray et al., 2007, Sharma et al., 2020, Alharthy et al., 2023). The results exhibited that rosinidin improved that motor performance which is correlated with the increased dopamine level.

Reactive oxygen species formed by oxidative damage is the main contributor to the pathogenesis of PD (Grootveld 2022). Mitochondrial dysfunction cause generation of ROS which negatively affects the cellular structure like lipids, DNA and protein (Elfawy and Das 2019, Trist et al., 2019, Juan et al., 2021). Increased MDA and nitrite content and decline in GSH, SOD, CAT levels were detected in rotenone- prompted rats as correlated in previous investigations (Javed et al., 2020, Alikatte et al., 2021, Afzal et al., 2022, Alharthy et al., 2023). Rosinidin significantly reduces the MDA and nitrite content and marked elevation in GSH, SOD, CAT levels. Results suggested that both dose of rosinidin showed favorable effects may have been caused by its anti-oxidant properties.

Neurotransmitter level in the PD patients depends upon the neuronal damage or degeneration especially downfall in the dopamine level (Alharthy et al., 2023). The present study displayed significant loss in dopaminergic activity and decreased dopamine level in rotenone-lesioned rats similar to previous observation (Monti et al., 2010, Barbiero et al., 2022). Rosinidin ameliorated rotenone-induced PD by increasing dopamine, NE, 5-HT, 5-HIAA and decrease DOPAC and HVA levels.. Thus, rosinidin showed improvement in the dopaminergic damage by moderating the enzymatic pathway of dopamine. In addition to other neurotransmitters, studies have shown that rosinidin may alter the levels of dopamine, a neurotransmitter that is reduced in PD. Additionally,

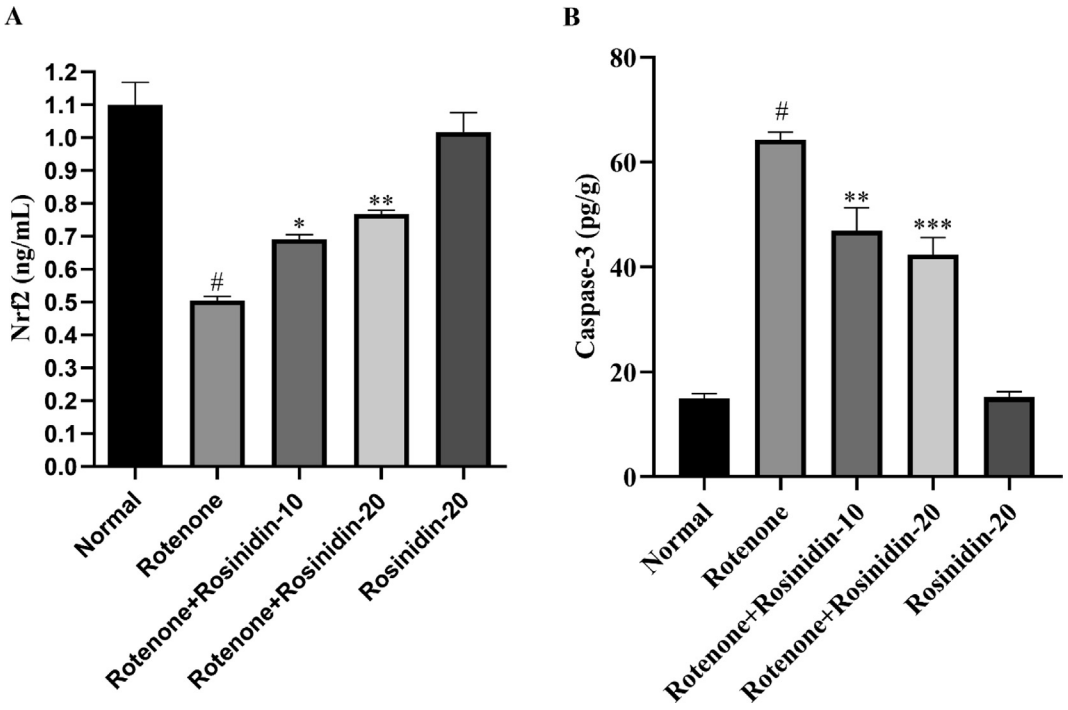

Fig. 6. (A-B). The neuroprotective effect of rosinidin on neuroinflammatory biomarkers. A. Nrf2 B. Casp3. P value < 0.05, 0.01,0.001 were presented as *, **, *** respectively when compared with disease control group. P value < 0.001 was presented as # which signifies disease control group when correlated with control group.

according to some studies, rosinidin may have neuroprotective properties by lowering oxidative stress and neuroinflammation, which are related to the onset of PD (Ebrahimi and Schluesener 2012, Calis et al., 2020, López-Pedrouso et al., 2020, Gilani et al., 2022).

Neuroinflammatory pathway is a pivotal factor causing rise in the disease progression as cytokines activate the degeneration pathway (Hirsch and Hunot 2009, Maes et al., 2011, Shabab et al., 2017, Yang et al., 2020, Saha et al., 2022, Tiwari and Pal 2022). The administration of rotenone showed a profound rise in the inflammatory markers like IL-6, IL-1ß, TNF-α, NFκB same as other investigations (Ojha et al., 2016, Zhang et al., 2017). Whereas cure with rosinidin (10 and 20 mg/kg) prevented any alterations in the cytokine level resulting in neuronal protection against the produced damage. Several preclinical research have looked into how rosinidin affects levels of neuroinflammatory cytokines in PD. Results from these studies suggest that rosinidin may have a potential anti-inflammatory effect and can modulate the intensities of various cytokines involved in neuroinflammation, such as TNF-α and IL-1β (Alshehri and Imam 2021, Alharbi et al., 2022). These outcomes recommended that rosinidin may have a therapeutic potential in the management of neuro inflammation in PD.

The Nrf2 pathway has been demonstrated to be activated by the small molecule rosinidin. This route controls the fight against free radicals and the cellular reaction to stress. Neuroinflammation and oxidative stress both substantially support to the growth of neurodegeneration in PD (Mosley et al., 2006, Yan et al., 2022). Rosinidin may therefore have neuroprotective benefits in PD by lowering oxidative stress and neuroinflammation done by upregulation of the Nrf2 expression.

By lowering oxidative stress and neuroinflammation, rosinidin is a substance that has been demonstrated to have neuroprotective benefits in PD. However, it is unclear how it affects casp 3, an enzyme involved in the procedure of apoptosis or cell death. Rosinidin may prevent cell death in PD by inhibiting casp 3 activity, according to some research, although others find no appreciable difference (Calis et al., 2020, López-Pedrouso et al., 2020). To fully comprehend how rosinidin affects casp 3 in Parkinson's, more study is required. The precise mechanism of rosinidin by which it affects the levels of endogenous antioxidant, neurotransmitters, neuroinflammatory cytokine, Nrf2 and Casp3 in PD is unclear. To confirm the effects of rosinidin on neurotransmitter levels in PD and identify whether it has therapeutic potential, more study is required including other genetic models, estimation of immunohistochemical analysis, histopathology and western blotting. Limitation of study, used small number of animals with short duration.

5. Conclusion

Our finding suggests that rosinidin possesses antioxidant and anti-inflammatory activity, decreased neuroinflammation by inhibiting inflammatory cytokines, regulated neurotransmitter level, and ameliorated locomotor function. Rosadinidin has been shown to protect against neuro-inflammatory markers, neurotransmitters and behavioral tests in animals, suggesting that it may be useful for treating Parkinson's disease. However, further research are needed to establish its reliability and efficacy in treating the condition.

Statement of ethics

This study protocol was reviewed and approved by Transgenica Research Institution's Animal Ethics Committee, India, approval number IAEC/918/CPCSEA/01.

CRediT authorship contribution statement

Amira M. Alghamdi: Conceptualization, Methodology.

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.

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