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Effectiveness of sesamol in alleviating neuroinflammation associated with Parkinson's disease

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ABSTRACT

Objectives: A chronic progressive neurodegenerative disorder, Parkinson's disease (PD) is associated with motor impairment with elderly people. The cytokines and chemokines network are very complex and participate to balance the proinflammatory processes, apoptosis and cell existence. So, it is necessary to unravel the inflammatory process in PD. Increased nuclear factor kappa B, expression of cytokines, increased activation of microglia participate in the inflammatory process of PD. The activation of glial fibrillary acidic protein (GFAP) gene and protein results in the activation of astroglial cells which ends up with neurodegeneration and central nervous damage. Natural compounds carry a huge amount of antioxidant properties with health benefits and phenolic compounds is a natural dietary source.
Methods: Quantitative determination of serum CRP, immunohistochemical study was carried out along with the molecular studies such as (RT-PCR) and western blotting.
Results: Sesamol treatment decreased the C- Reactive protein level in serum of experimental animals. Sesamol also increased the tyrosine hydroxylase cells in rotenone-induced animals. The gene and protein expressions of NF-κB (p65), Tumor necrosis factor-α, cyclo oxygeanse-2, inducible nitric oxide synthase, interleukin-1β and GFAP were also reduced in SES treated animals.
Conclusion: Sesamol served as an anti-inflammatory compound in ROT-induced animal model of PD. This work mainly concentrates on the molecular mechanism of phenolic compound sesamol on rotenone induced PD.

1. Background

Parkinson's disease (PD) or Parkinsonism is a neurodegenerative condition developed due to genetic mutations and environmental exposures. It is established that 2 % of population above 65 years are commonly affected by PD and also found to increase two folds by the year 2030 (Dorsey et al., 2007). Numerous clinical and experimental observations proved that brain, blood and cerebrospinal fluid carry inflammatory mediators during brain injuries associated with reactive gliosis and neuronal loss (Li et al., 2023).

Microglial cells are the serious performers in neuro-inflammation. Two mechanisms are involved in the activation of microglia. The first one is by the environmental toxins and endogenous proteins whereas the second one is through the reactive microgliosis mechanism. Oxidative

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injuries are the noticeable cause in neurodegenerative diseases where microglia is the root source of oxidative injuries. Oxidative stress stimulates microglial NADPH (nicotinamide adenine dinucleotide phosphate reduced) oxidase and results in the up regulation of pro-inflammatory factors which is neurotoxic (Xu et al., 2023). NADPH oxidase is the chief enzyme in microglial cells for the generation of superoxide (extracellular) (Mali et al., 2023).

The mediators of neurodegeneration and neuro-inflammation has investigated and reported that cytokines along with chemokines are important in the pathogenesis of neuronal death (Lindsay et al., 2023). The cytokines and chemokines network are very complex and participate to balance the pro-inflammatory processes, apoptosis and cell existence.

Rotenone (ROT), MPTP, 6-hydroxydopamine (6-OHDA), and paraquat are commonly employed in experimental models to imitate PD pathology because they specifically produce dopaminergic neurodegeneration and activate microglial cells. Among them, ROT is regarded as one of the most dependable agents, as it closely mimics the clinical and behavioral aspects of human PD. ROT is a strong mitochondrial complex I inhibitor, impairing mitochondrial activity, reducing ATP generation, and increasing oxidative stress. These events eventually lead to the progressive destruction of dopaminergic neurons, which is similar to the gradual neurodegenerative process seen in Parkinson's disease (Ibarra-Gutiérrez et al., 2023; Tsalenchuk et al., 2025).

Natural phenolic compounds with high antioxidant and anti-inflammatory properties are increasingly being recognized for their medicinal potential in neurodegenerative illnesses. Sesamol (5-hydroxy-1,3-benzodioxole) (SES), a bioactive ingredient of *Sesamum indicum*, has been shown to have strong free radical scavenging action, protect against radiation-induced oxidative injury, and maintain blood-brain barrier integrity (Prasad et al., 2005; Khan et al., 2015; Koru and Atasever-Arslan, 2025). SES, unlike many phytochemicals, has great absorption, safety, and multifunctional pharmacological activities, making it an especially promising option for PD study (Javed et al., 2024).

Compared to many other phytochemicals, SES has several advantages, including high absorption, safety, and multifunctional pharmacological effects. SES has a high capacity to scavenge reactive oxygen and nitrogen species, thereby mitigating the oxidative stress linked to dopaminergic neuronal degeneration (Khan et al., 2015). SES has been shown to suppress pro-inflammatory signaling cascades, including as NF-κB activation and cytokine release, which contribute to microglial-mediated neuroinflammation. Furthermore, preclinical evidence supports the cognitive-enhancing benefits and ability of SES to modify mitochondrial dysfunction, both of which are extremely relevant to PD pathogenesis (Singh et al., 2023). These features make SES a prospective treatment candidate for reducing ROT-induced dopaminergic degeneration.

The current work was therefore undertaken to examine the neuroprotective potential of SES in a ROT-induced rat model of PD. We specifically looked at its effects on systemic and neuroinflammatory indicators, tyrosine hydroxylase expression, and astroglial activation to better understand its therapeutic potential in PD.

2. Methods

2.1. Experimental animals

The study employed male Wistar albino rats weighing 150–180 g. Food and water *ad libitum* were provided and the animals were maintained at a temperature of 24 ± 2 °C, in a 12 h dark/12 h light cycle. The investigations were conducted in accordance with the guidelines established by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi (India). The protocol of the study was approved by the Institutional Animal Ethical Committee of Sathyabama University, Chennai. (SU/CLATR/IAEC/VI/034/2016).

2.2. Experimental protocol

The animals were categorised into 5 groups, each containing 6 animals. Drugs were administered for 60 days. Group I: Vehicle (DMSO in corn oil intraperitoneal + Saline intraperitoneal). Group II: Rotenone (3 mg/kg.B.wt intraperitoneal). Group III: Co-treatment Rotenone (3 mg/kg.B.wt intraperitoneal) + Sesamol (50 mg/kg.B.wt intraperitoneal). Group IV: Co-treatment Rotenone (3 mg/kg.B.wt intraperitoneal) + Sesamol (50 mg/kg.B.wt intraperitoneal) + L-DOPA (10 mg/kg.B.wt oral). Group V: Co-treatment Rotenone (3 mg/kg.B.wt intraperitoneal) + L-DOPA (10 mg/kg.B.wt oral).

2.3. Determination of C- reactive protein (CRP)

A commercially available kit (Beacon Diagnostic kit) was purchased and the manufacturer's instructions were followed to perform the quantitative CRP test in serum of experimental animals.

2.4. Brain sample collection

After sacrifice, the brain samples of animals were collected and homogenized individually in ice-cold phosphate buffer at pH 7.5 and 15 % (*W/V*) concentration. At this condition, the soluble proteins were released and the non-vascular substances were found in the sediment state. Centrifugation of the homogenized samples was carried out for 10 min at 5000 rpm (rpm). For the expression analysis, these aliquots were used. The brain tissue homogenate was kept at -20 °C and used for further studies.

2.5. Immunohistochemistry

Mid-brain tissues were fixed with 4 % paraformaldehyde and permeabilized for 1 h at room temperature in Phosphate buffer saline (PBS) containing 0.2 % Triton X-100 and 10 % BSA. The primary antibodies were subsequently incubated with the tissue sections at 4 °C overnight. Next, the samples were washed with 1× PBS, followed by treatment with 3 % hydrogen peroxide to block the endogenous peroxidase activity. After three washes in 1× PBS, the sections were incubated with horseradish peroxidase (HRP)-conjugated polyclonal rabbit IgG at 37 °C for an hour. The sections were then developed using diaminobenzidine. Later, the sections were dehydrated and cleared before being examined under a light microscope.

2.6. Preparation of brain homogenate

100 mg of the brain tissue samples were homogenized in 1 ml of total RNA isolation reagent (Trizol). The diluted RNA samples were quantified spectrophotometrically at 260 nm.

2.7. Reverse transcription- polymerase chain reaction (RT-PCR)

The 2 μg of total RNA isolated from experimental samples were subjected to reverse transcription by Qiagen kit, Germany. RT-PCR was performed for NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β, GFAP and β-actin by using Qiagen two step RT-PCR kit. The primers used for NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β, GFAP and β-actin are listed in the Table 1.

The amplified products were eventually resolved by using 1 % agarose gel electrophoresis and stained with ethidium bromide. Then visualized and documented by Quantity one software (Bio-Rad, USA).

2.8. Western blotting

The separation of protein was performed using 12 % Sodium dodecyl

Table 1
List of both forward and reverse primers.

Genes	Forward primers	Reverse primers
NF-κB (p65)	5′TCACCAAAGACCCACCTCA CCG3′	5′GGACCGCATTCAAGTCATAGTC3′
TNF-α	5′CTCCCAGAAAAGCAAGCAAC3′	5′CGAGCAGGAATGAGAAGAGG3′
COX-2	5′GTGGGATGACGAGCGACTG3′	5′CCGTGTTCAAGGAGGATGG3′
iNOS	TCTGTGCCTTTGCTCATGAC3′	5′CATGGTGAACACGTTCTTGG3′
IL-1β	5′TGACCCATGTGAGCTGAAAG3′	5′CAGGGATTTTGTCGTTGCTT3′
GFAP	5′CTTTGCTAGCTACATCGA GAAGGTCCGCTT3′	5′CGATTCAACCTTTCT CTCCAAATCCACACG3′
β-Actin	5′GTAGACAAAATGGTGAAGG TCGGTG3′	5′CTCGCTCCTGGAAGATGGT GATGGG3′

sulphate polyacrylamide gel electrophoresis (SDS-PAGE). After the completion of electrophoresis, the proteins were transferred into the nitrocellulose membrane and blocked with 5 % non-fat dried milk in phosphate buffered saline- Tween 20 (PBS-T) at 2-8 °C, reacted with mouse monoclonal 1° antibodies (anti NF-κB (p65), anti TNF-α, anti COX-2, anti iNOS, anti IL-1β and anti GFAP) and allowed for incubation at 4 °C. The immune complex horseradish peroxidase-conjugated goat anti-mouse antibody was viewed by chemiluminescence ECL PLUS detection reagents (Amersham Bioscience).

2.9. Statistical analysis

The statistical analysis was performed by SPSS version 20 from IBM. The results were expressed as mean ± SD. For intergroup comparisons, Tukey's *post hoc* test is performed after an ANOVA (one-way). At least three independent repetitions of the experiments were conducted ($n = 6$ animals/group); significance threshold: $p < 0.05$. Blinding during analysis and biological replicates were used to verify reproducibility. The graphs were plotted using Graph Pad Prism version 5.03.

3. Results

The C-reactive protein in serum of experimental animals were performed [Fig. 1]. CRP level was found to be significantly increased ($p < 0.001$) in ROT induced animals (Group II) when compared to vehicle-treated animals (Group I). There was a significant reduction in the CRP level of animals treated with SES (Group III) ($p < 0.001$), SES + L-DOPA (Group IV) ($p < 0.01$) and L-DOPA (Group V) ($p < 0.05$).

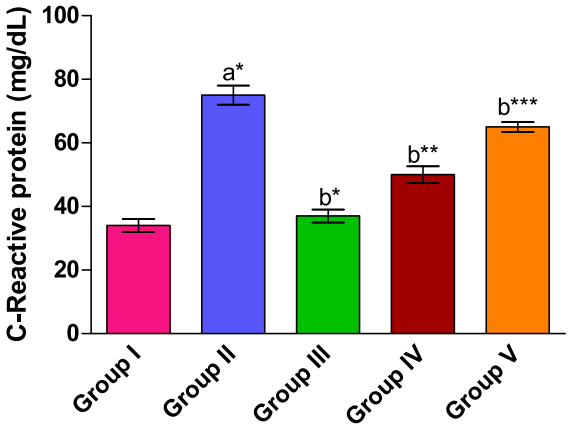

Fig. 1. C-reactive protein in serum of experimental animals.
Group I: Vehicle-treated animals, Group II: Rotenone-induced animals, Group III: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt), Group IV: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt), Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt). Statistical significance: *p < 0.001,**p < 0.01, ***p < 0.05, NS- Non-Significant. Comparison: a – as compared with Group I; b – as compared with Group II. Values are represented as mean ± standard deviation.

Fig. 2 (A-E) shows the immunohistochemical analysis of tyrosine hydroxylase in mid brain of experimental animals. Vehicle-treated animals (Group I) shows the normal pattern of increased expression of TH^{+ve} cells (tyrosine hydroxylase positive cells) whereas ROT-induced animals (Group II) show decreased expression of TH^{+ve} cells. SES treated animals (Group III) shows the increase in TH^{+ve} cells. SES and L-DOPA treated animals (Group IV) shows the marked increase in TH^{+ve} cells. L-DOPA treated animals (Group V) shows the increase in TH^{+ve} cells.

The gene expression of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP in brain of experimental animals detected by RT-PCR analysis [Fig. 3(A) and 3(B)]. The genes of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP was found to be up regulated ($p < 0.001$) in ROT-induced animals (Group II) when compared to vehicle-treated animals (Group I). Interestingly, SES (Group III) treated animals shows significant decrease ($p < 0.001$) in gene expression of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP when compared to ROT-induced animals (Group II).

The protein expression of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP in brain of experimental animals by Western blotting studies which is represented in the Fig. 4 (A) and 4 (B). The protein expression of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP were up regulated ($p < 0.001$) in ROT-induced animals (Group II) when compared to vehicle-treated animals (Group I). There was significant decrease ($p < 0.001$) in the protein expression of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP in SES treated animals (Group III) when compared to ROT-induced animals (Group II).

4. Discussion

The neuroprotective potential of SES in SHSY5Y cell line was observed in our previous study (Rohini and Vijayalakshmi, 2016). Additionally, SES also ameliorated the motor behavior in PD induced rat model (Rohini and Vijayalakshmi, 2017). Building on these findings, we expanded our research for further investigation. Researchers have found that CRP level was found to be elevated in response to an inflammation (Di Rosa et al., 2024). CRP has been used as a biomarker to track inflammation, which guides to address the several limitations of PD (Zhou et al., 2024; Mehta et al., 2023). The CRP levels in PD patients and the finding that elevated CRP levels were associated with a higher risk of developing PD were proven (Qiu et al., 2019). PD patients showed a significant rise in the levels of CRP and cytokines (Garmendia et al., 2024). Additionally, elevated chemokines were also observed which is directly connected to the infiltration of inflammatory cells (Wijeyekoon et al., 2020).

In another research, administering SES, sesamin, or a combination of the two (10 mg/kg) to male Wistar rats stimulated by LPS for 15 days was shown to dramatically lower the rise in blood levels of IL-1β, TNFα, and c-reactive protein (CRP), indicates decreased inflammation (Sakunthala et al., 2024). When compared to other phytoconstituents, SES was also discovered to have more beneficial effects in lowering the levels of other inflammatory mediators. Administration of ROT resulted in 45 % loss of TH^{+ve} cells in the dopaminergic neurons of substantia nigra (Ibarra-Gutiérrez et al., 2023). The decreased expression of TH^{+ve} cells reflects the recovery of protein transport along the fibers during MPTP administration (Gu et al., 2024).

Internal housekeeping controls for RT-PCR and western blot normalization, such as β-actin and GAPDH. By preventing the nuclear translocation of the NF-κB p65 subunit, SES suppresses the activation of NF-κB. In the ROT model, pro-inflammatory genes like TNF-α, COX-2, and iNOS have higher transcription levels when NF-κB is activated. SES suppresses NF-κB pathway signaling by dramatically lowering the mRNA and protein levels of these indicators.

Once activated, NF-κB regulates the expression of 400 genes which includes COX-2, iNOS, TNF-α, IL-1β, chemokines, adhesion molecules, cell cycle regulatory molecules and angiogenic factors. NF-κB is called as the smoke-sensor of whole body because of its association with different

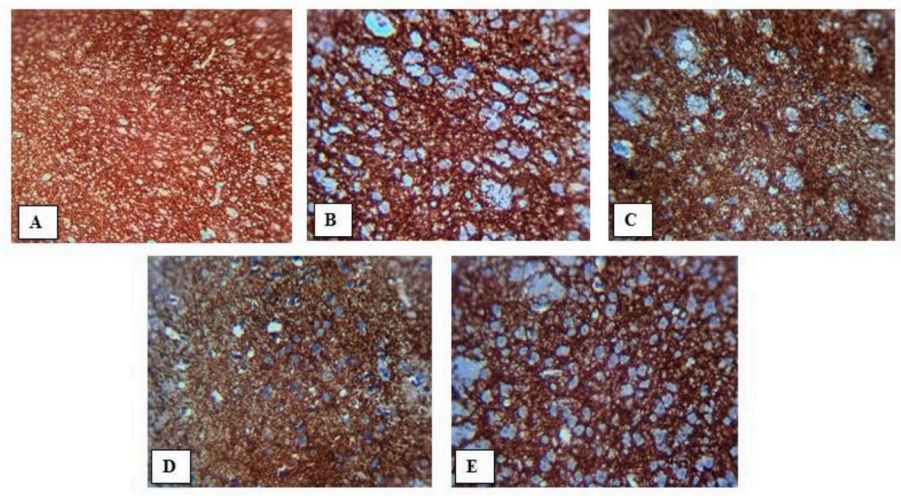

Fig. 2. (A-E): Tyrosine hydroxylase activity in mid brain of experimental animals.
A- Group I: Vehicle-treated animals shows increased expression of TH^{+ve} cells, B- Group II: Rotenone-induced rats (3 mg/kg.B.wt) reveals the decrease in TH^{+ve} cells, C- Group III: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt) shows the increase in TH^{+ve} cells, D- Group IV: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt) shows the marked increase in TH^{+ve} cells, *E*- Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt) shows increased TH^{+ve} cells. Magnification- 40×.

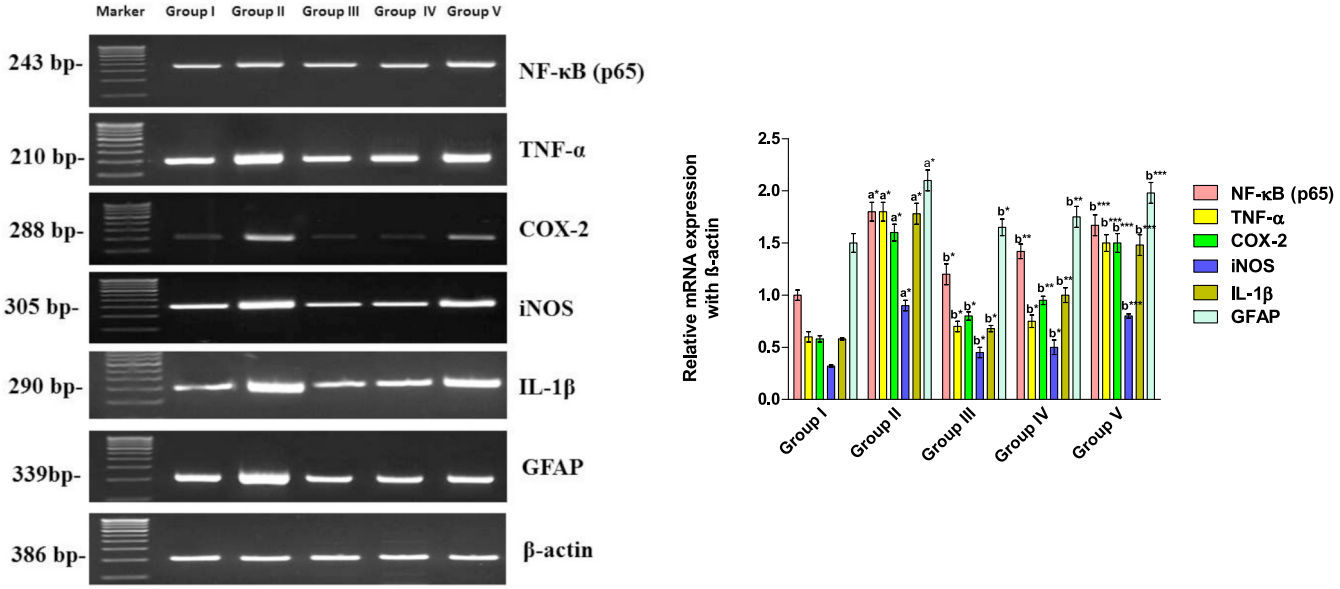

Fig. 3. (A): Gene expression of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP. (B): Gene expression of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP. Group I: Vehicle-treated animals, Group II: Rotenone-induced animals, Group III: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt), Group IV: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt), Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt). Statistical significance: $*p < 0.001$, $**p < 0.01$, $***p < 0.05$, NS- Non Significant. Comparison: a – as compared with Group I; b – as compared with Group II. Values are represented as mean ± Standard Deviation.

stress signal pathways (DeMaio et al., 2022; Dolatshahi et al., 2021; Singh et al., 2024). Thus, NF-κB is activated during ageing, oxidative damage, genotoxic conditions and inflammatory processes. Up regulation of NF-κB subunits (p65) also leads to age- related pathologies. The misfolded alpha synuclein that originated from injured neuronal cells, triggers the signaling pathways in both the neuronal and glial cells. The stimulation of these signaling pathways leads to the stimulation and expression of proinflammatory cytokines by the initiation of NF-κB. Several cells including neurons, astrocytes, microglia express the NF-κB signaling pathway and it also regulates the release of inflammatory mediators by neuroinflammation (Anilkumar and Wright-Jin, 2024).

The role of COX-2 in MPTP model of PD has witnessed. The study found that COX-2, the rate-limiting enzyme in the synthesis of prostaglandin E(2) is over expressed in the brain of MPTP induced mice (Teismann et al., 2003). ROT induced neuronal toxicity and astroglial activation which in turn elevated GFAP expression in mid brain and striatum. The over expression of GFAP in the caspase 3 expression increased and resulted in apoptosis. They also detected that astroglial cells are very much vulnerable to ROT when compared with microglial cells and neuronal cells (Thomas Broome and Castorina, 2022).

Researchers reported that GFAP has been hypophosphorylated and over-expressed in glial cells of PD patients and people with a typical parkinsonism. They also proved that glial cells play a significant role in PD progression. GFAP could also be a convenient biomarker to monitor

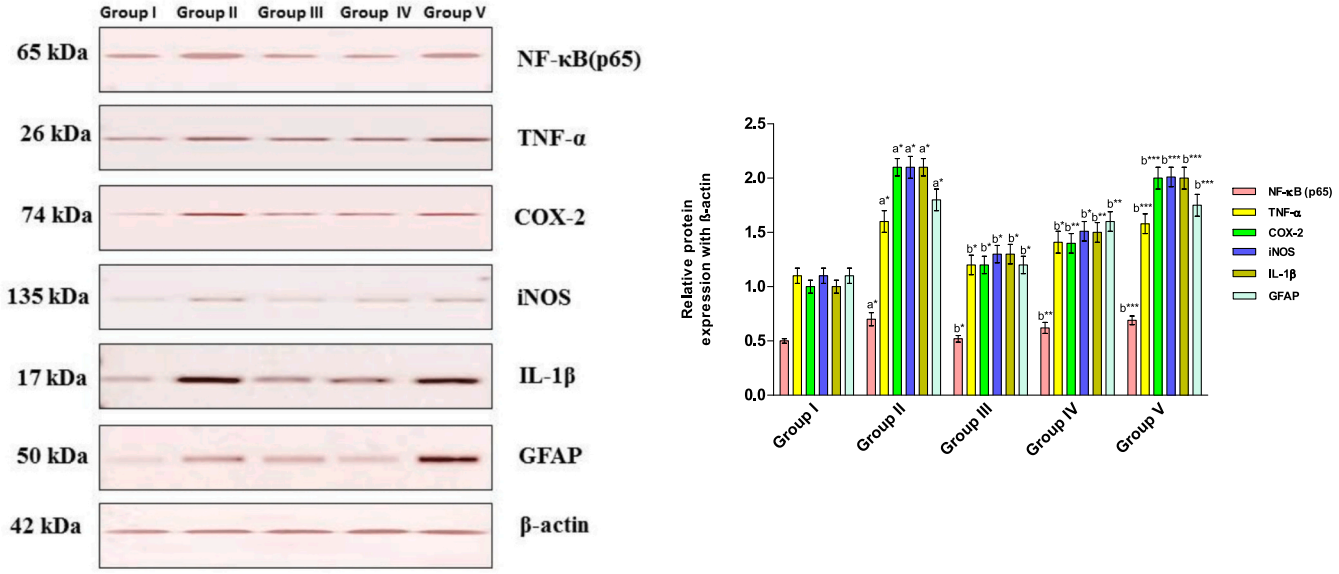

Fig. 4. (A): Protein expression of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP. (B): Protein expression of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP. Values are expressed as mean ± SD. Group I: Vehicle-treated animals, Group II: Rotenone-induced animals, Group III: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt), Group IV: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt), Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt). Statistical significance: *p < 0.001, **p < 0.01, ***p < 0.05, NS- Non Significant. Comparison: a – as compared with Group I; b – as compared with Group II.

non-motor, motor and cognitive abilities. Using RT-PCR and western blotting, specificity was deduced from decreases in the expression of GFAP, which are markers for astrocytes.

Behavioral studies were evaluated by experiments that were cited in earlier study and validated in subsequent investigations (pole test, ladder climbing test and open-field test) (Rohini et al., 2018). Phenolic compound SES suppresses neuroinflammation and results in neuroprotection. It provides neuroprotective effect through attenuation of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β and GFAP expression in brain. In neurodegenerative models, SES is more effective than sesamin and other phenolic antioxidants at lowering levels of TNF-α, IL-1β, and CRP. Compared to other lignans, its hydrophilic profile and smaller molecular size may improve bioavailability and CNS penetration. Neuroinflammation is the chief pathogenesis for PD and thus a natural compound like SES with rich antioxidant properties is much needed to control the inflammatory process and to monitor the secretion of inflammatory substances and activation of glial cells. It has been demonstrated that SES has reduced the oxidative stress and improved motor behavior in PD model (Shahidani et al., 2022). Because of their neuroprotective properties, phenolic compounds may be able to stop or reduce the progression of PD (Perdigão et al., 2023). SES, has been the focus of much research because of its strong antioxidant qualities, particularly its capacity to provide neuroprotection and successfully combat oxidative stress in the central nervous system. Although SES shows promise in the prevention and treatment of neurological disorders, its intricate and poorly understood mechanism of oxidative stress control remains a mystery (Guo et al., 2025). Javed et al., 2024 also emphasized that SES suppresses the expression of inflammatory markers such as cytokines, protein kinases, redox state, and many of the enzymes that cause inflammation. For a very long time, medicinal plants and natural items have been utilized to treat a variety of illnesses. Nowadays, a lot of people still primarily use herbal nutraceuticals for their medical needs. Natural ingredients now make up more than half of the drugs being tested in clinical settings. In recent years, a large number of researchers have investigated the use of various herbs and natural compounds in the treatment of PD (Roni et al., 2024; Butler, 2008). To assess the therapeutic and protective advantages of phytochemicals as potentially effective medications in the treatment of Parkinson's disease, more carefully planned clinical research is necessary (Balakrishnan et al., 2021). Subacute outcomes were the main focus of this investigation. Although long-term effects (beyond 15 days of treatment) were not evaluated, prior research may indicate that continued administration of the medication can have long-lasting anti-inflammatory benefits (Majdalawieh et al., 2023).

This work sought to determine if SES, a phenolic antioxidant with anti-inflammatory and BBB-protective properties, can reduce ROT-induced PD. Our findings indicate that SES- reduced systemic inflammation with lower CRP; reduced neuroinflammatory signaling with lower NF-κB-dependent mediators (TNF-α, IL-1β), iNOS, and COX-2; preserved dopaminergic phenotype with higher TH; and supported BBB/astroglial homeostasis with reduced GFAP upregulation and improved BBB indices. Together, these findings support our mechanistic hypothesis that addressing oxidative-inflammatory cascades might decrease ROT-induced dopaminergic degeneration.

Despite the promising results of the present study, few limitations were acknowledged to provide a balanced perspective. This study mainly focused on subacute treatment of SES whereas long term neuroprotective and anti-inflammatory effects were not investigated. This limits the extrapolation of findings to chronic PD progression, which occurs over time. The study also evaluated inflammatory mediators (NF-κB, COX-2, iNOS, TNF-α, IL-1β) and astroglial activation markers (GFAP), but did not directly assess mitochondrial function, α-synuclein disease, or comprehensive signaling cascades. Because mitochondrial dysfunction and protein aggregation are fundamental to PD pathogenesis, their absence limits the mechanistic interpretation.

Motor performance was evaluated using behavioral assays (pole test, ladder climbing, and open-field). However, non-motor symptoms of Parkinson's disease (such as cognitive impairments, anxiety, and olfactory dysfunction) were not addressed, limiting our understanding of SES benefits beyond motor recovery. Only male Wistar albino rats were used. This sex-specific constraint ignores potential sex-dependent changes in neuroinflammation and PD progression, limiting the generalizability of findings. Future research will address these limitations to determine the optimal dose and duration of SES treatment, clarify mechanisms beyond inflammation (including mitochondrial health and α-synuclein aggregation), evaluate long-term safety, and validate efficacy across both sexes and multiple PD models. Furthermore, comparison research with current medicines and, eventually, clinical trials will

be required to establish SES as a potential therapeutic candidate for PD.

5. Conclusion

Present study demonstrates that SES, a natural phenolic compound, exerts significant anti-inflammatory and neuroprotective effects in a rotenone-induced animal model of Parkinson's disease. SES treatment effectively reduced serum C-reactive protein levels and attenuated neuroinflammation by downregulating the gene and protein expressions of NF-κB (p65), TNF-α, COX-2, iNOS, IL-1β, and GFAP. Additionally, it enhanced the expression of tyrosine hydroxylase, suggesting a protective role in dopaminergic neuron survival. These findings highlights that SES can be a potential therapeutic candidate for modulating neuroinflammation and mitigating neurodegeneration in PD. Further studies are warranted to explore its clinical applicability in Parkinson's disease management. This study contributes to the increasing body of research showing that phenolic antioxidants protect neuronal integrity, lower oxidative stress, and modify inflammatory signaling pathways. For illnesses like PD that have a complicated pathophysiology, it supports the idea of multi-targeted natural agents. The oral bioavailability of SES, its capacity to cross the blood-brain barrier, and minimal toxicity make it a promising supplementary therapy for PD. It may be particularly useful for early-stage patients or in combination with L-DOPA to minimize neuroinflammation. The combination of SES with L-DOPA demonstrated additional neuroprotective effects, suggesting a possible synergistic interaction.

CRediT authorship contribution statement

Rohini Durairaj: Writing – original draft, Conceptualization. **Manjunathan Jagadeesan:** Funding acquisition, Formal analysis. **S. Shireen Farhana:** Software, Resources. **Shobana Chandrasekar:** Methodology, Investigation. **Usharani Boopathy:** Software, Resources. **Parthiban Brindha Devi:** Visualization, Validation. **Pasiyappazham Ramasamy:** Writing – review & editing, Validation.

Declaration of competing interest

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

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