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Short Communication

EGCG Mediates Neuroprotection in a Parkinson's Disease Model via a Caspase-3-Independent Pathway

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Abstract | Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuron loss in the substantia nigra, mainly due to apoptosis triggered by reactive oxygen species (ROS) and α-synuclein aggregation. Investigating natural compounds with anti-apoptotic potential is essential for developing neuroprotective strategies. This study aimed to evaluate the effect of epigallocatechin gallate (EGCG) from *Camellia sinensis* on neuronal apoptosis markers, caspase-3 and Bcl-2, in a rat model of Parkinson's disease. Thirty male Wistar rats were divided into five groups, including normal and PD models induced by intraperitoneal 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). EGCG was administered to the treatment groups, while control groups received placebo. On the seventh day, rats were sacrificed and substantia nigra samples were examined immunohistochemically for caspase-3 and Bcl-2 expression. EGCG administration did not significantly alter caspase-3 or Bcl-2 expression ($p > 0.05$) compared to placebo; however, neuronal degeneration was significantly reduced in EGCG-treated normal rats ($F = 4.491$, $p < 0.05$). EGCG exhibits neuroprotective effects independent of caspase-3 and Bcl-2 modulation, suggesting a potential caspase-3-independent pathway in neuroprotection.

Keywords | Parkinson's disease, *Camellia sinensis*, apoptosis, Epigallocathecin gallate, Caspase-3, bcl-2

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INTRODUCTION

Parkinson's disease is a neurodegenerative disease of neurons of the substantia nigra pars compacta. Histologically it is accompanied by the presence of protein α-synuclein containing eosinophil cytoplasmic inclusions (Lewy bodies) thus reducing neurotransmitters in the form of dopamine which is useful for regulating movement and is characterized by motor symptoms such as tremors at rest, muscle and joint stiffness (rigidity), slowness of movement (bradykinesia) and speech and postural instability (Kouli *et al*., 2018). In Parkinson's disease, α-synuclein radicals misfolding and aggregation disrupt other normal system functions. Aggregates of the oligomeric form of α-synuclein cause loss of dopaminergic neurons in the substantia nigra *pars compacta*, thereby causing dopamine deficiency in the striatum region (Kumari *et al*., 2023). This dopaminergic neuronal loss is attributed to increased rate of apoptosis and pyroptosis. Among all enzymes regulating apoptosis, caspase-3 is the most important apoptosis-regulating enzyme in neurodegenerative diseases, such as Parkinson's and Alzheimer's disease (Wójcik *et al*., 2024). Caspase-3 has important final executor role and is activated by caspase-9 and caspase-8 (Li *et al*., 2022). In addition to being activated by caspase-9 and caspase-8, caspase-3 itself also activates both enzymes. The involvement of caspase-9 and caspase-8 also indicates that caspase-3 responds to both extrinsic and intrinsic inducers, in which the latter is associated with oxidative mitochondrial stress (Sun, 2024).

Oxidative stress is an important mechanism of α-synuclein aggregation in Parkinson disease. In Parkinson's disease, α-synuclein become radicalized through reactive oxygen species (ROS) (Kumar *et al*., 2016). These ROS attacks methionine residues of α-synuclein, converting them into methionine sulfoxides (Uceda *et al*., 2023; Glaser *et al*., 2005). Failed intracellular repair attempt of oxidation-damaged α-synuclein leads to the accumulation of chemically and functionally altered α-synuclein in cells, triggering apoptosis, and slowly resulting as neuronal impairment in the Parkinson's disease (Binolfi *et al*., 2016). Epigallocatechin gallate (EGCG) is one of the most abundant and important active polyphenols of tea (*Camellia sinensis*) (Shaukat et al., 2023). Various polyphenols from *C. sinensis* are often studied as an apoptosis modulator in cancer cells (Seo *et al*., 2016; Rajabi *et al*., 2021; Karatuğ *et al*., 2019). However, not many studies have linked the potential of EGCG as an therapeutic adjuvants in neurodegenerative diseases. The finding that EGCG is able to regulate the cell death response suggests that there is potential for EGCG to work in neurodegenerative diseases, especially those induced by ROS (Utami *et al*., 2023). The ROS itself is known to affect biomarkers of inflammation and apoptosis such as TNF-α (Dong-Chen *et al*., 2023), NF-κB (Dolatshahi *et al*., 2021), caspase-3 (Qian *et al*., 2022; Vringer and Tait, 2023) and PKCδ (Dong-Chen *et al*., 2023).

It is not yet known how EGCG can affect biomolecular processes in Parkinson's disease. This study will explore on how the mechanism of EGCG may affect Parkinson's disease, especially in the regulation of neuronal apoptosis. We focused on how the EGCG will affect apoptosis pathways, whether it is extrinsic or intrinsic by examining the activity of neuronal caspase-3 in Parkinson's disease animal model.

MATERIALS AND METHODS

Study design

This study is a laboratory experimental study using randomized post-test only control group design. The use of animal models was chosen due to homogeneity criteria and the same characteristics between population units, as well as difficulty to obtain sample of human midbrain.

In this study, the independent variable is the type of therapy administered, specifically epigallocatechin gallate (EGCG). The dependent variable is the extent of neuronal cell death presented as caspase-3 and Bcl-2 level. Controlled variables encompassed various factors to ensure consistency across experimental conditions, including the diet and water intake of the test animals, their overall health status, the characteristics and conditions of the animal housing, the care and handling of the test animals, the procedures used to establish the Parkinson's disease model, the method and timing of treatment administration, and the techniques used for evaluating the test subjects. This study ethical clearance is issued by Animal Care and Use Committee of Faculty of Veterinary Medicine, Airlangga University, with clearance No. 2.KEH.061.04.2024

Methods

The experimental subjects used in this study were male Wistar strain rats (*Rattus norvegicus*) with white fur, aged four months, and weighing between 180 and 200 grams. The rats were in a healthy condition as confirmed by a veterinary consultant and met both the inclusion and exclusion criteria. The inclusion criteria required that the rats be male to eliminate the potential influence of hormonal fluctuations observed in females, be at an adult stage with an age of four months, and have a pre-treatment body weight within the range of 180–200 grams. Additionally, all selected rats were confirmed to be free from disease and had no potential for transmitting infections.

Exclusion criteria were applied to eliminate any rats that exhibited signs of illness before the study began or

those that died prior to the experiment. Furthermore, dropout criteria were established to account for accidental losses due to factors beyond the researchers control, including stress, starvation, illness during the study, or contamination. Additionally, any rats that had been exposed to the experimental treatment before data collection was completed were also considered dropouts.

Materials for injection preparation included cotton, 70% alcohol, and povidone iodine. For anesthesia prior to MPTP injection, ketamine was used at a dose of 7 mg per 100 grams of body weight, administered intraperitoneally. To achieve Parkinson's disease, intraperitoneal neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was used in group K2 and K4. The neurotoxin MPTP was prepared as an injectable solution and administered at a total dose of 16 mg/kg body weight. The placebo used in this study consisted of a 10% dextrose solution (glucose 10%) dissolved in distilled water, administered via oral gavage. The experimental treatment involved EGCG extract at a dose of 30 mg/kg body weight, which was administered orally using a gavage pipette.

The experimental rats underwent an acclimatization period of seven days before being assigned to their respective groups according to the study design. Following this adaptation phase, the rats were divided into five groups: A normal group without any manipulation (K0), a normal control group receiving a placebo (K1), a Parkinson's disease model control group receiving a placebo (K2), a normal group receiving EGCG treatment (K3), and a Parkinson's disease model group receiving EGCG treatment (K4). Each group was subjected to its respective treatment conditions as outlined in the research protocol.

The MPTP injections were administered intraperitoneally at a total dose of 16 mg/kg body weight, divided into four separate injections over a 24-hour period with a two-hour interval between each injection. Following the final injection, a 24-hour observation period was implemented to monitor the animals for any signs of dropout, such as severe illness or mortality, before proceeding with further experimental procedures. Both EGCG and placebo were given in 7 days to the respective groups prior to histological sampling. On the seventh day, animals were sacrificed. Blood sample was taken from caudal veins. Histological sample was taken from substantia nigra.

Extrinsic and intrinsic pathway was examined by comparing caspase-3 and Bcl-2 level. Expression of caspase-3 is defined as cells underwent apoptosis through extrinsic pathway. Bcl-2 expression was examined to determine whether substantia nigra underwent apoptosis through intrinsic pathway. Sample examination was conducted using light microscopy on 100x, 4000x, and 1000x magnification on the substantia nigra of the experimental animals, utilizing immunohistochemical staining to assess the expression of caspase-3.

RESULTS

A total of fifty rats were subject to placebo and intervention. During acclimatization, four rats died in the group, causing the study to take maximum six rat per groups with total of thirty rats. The rats were divided into five groups with corresponding allocations and interventions. The negative control group were sacrificed at zeroth day as pre-test. The remaining rats are assigned as post-test group, all survived the seventh day of intervention and sacrificed for sampling. Sample from substantia nigra were harvested and underwent light microscopy under ten different field location.

Bcl-2 level

One-way ANOVA were performed for Bcl-2 with F = 1.099 under $p = 0.379$, suggesting non-significance between groups. There is no difference of Bcl-2 level between any of placebo-treated groups and EGCG-treated groups ($p > 0.05$). Post-hoc LSD were performed between pre-test and post-test group. The full post-hoc test result is presented in Table 1.

Table 1: Data analysis of Bcl-2 levels.

Group	N	Mean ± SD	95% CI		p-value (Post Hoc LSD)				
			Lower	Upper	K0	K1	K2	K3	K4
K0	6	5.93 ± 3.20	3.47	8.15	-	0.052	0.259	0.286	0.487
K1	6	3.28 ± 0.94	2.63	3.90	0.052	-	0.385	0.352	0.192
K2	6	4.43 ± 2.04	2.78	5.88	0.259	0.385	-	0.949	0.657
K3	6	4.52 ± 2.45	2.98	6.47	0.286	0.352	0.949	-	0.704
K4	6	5.02 ± 2.01	3.53	6.52	0.487	0.194	0.657	0.704	-
Levene Sig.		0.131							

Table 2: Data analysis of Caspase-3 levels.

Group	N	Mean ± SD	95% CI		p-value (Post Hoc LSD)				
			Lower	Upper	K0	K1	K2	K3	K4
K0	6	4.38 ± 1.86	2.97	5.70	-	0.885	0.536	0.503	0.702
K1	6	4.57 ± 1.87	3.13	5.87	0.885	-	0.635	0.416	0.812
K2	6	5.17 ± 3.21	2.72	7.35	0.536	0.635	-	0.203	0.812
K3	6	3.53 ± 1.90	2.23	4.92	0.503	0.416	0.203	-	0.296
K4	6	4.87 ± 1.59	3.77	6.05	0.702	0.812	0.812	0.296	-
Levene Sig.		0.181							

Table 3: Data analysis of neuronal degeneration.

Group	N	Mean ± SD	95% CI		p-value (Post Hoc LSD)				
			Lower	Upper	K0	K1	K2	K3	K4
K0	6	0.23 ± 0.23	0.07	0.40	-	0.000	0.008	0.066	0.024
K1	6	0.80 ± 0.22	0.67	1.00	0.000	-	0.240	0.040	0.105
K2	6	0.63 ± 0.15	0.53	0.73	0.008	0.240	-	0.345	0.635
K3	6	0.50 ± 0.37	0.23	0.77	0.066	0.040	0.345	-	0.635
K4	6	0.57 ± 0.15	0.47	0.67	0.024	0.105	0.635	0.635	-
Levene Sig.		0.181							

Caspase-3 level

One-way ANOVA were performed for Caspase-3 with F = 0.490 under p = 0.743, suggesting non-significance between groups. There is no difference of caspase-3 level between any of placebo-treated groups and EGCG-treated groups (p > 0.05). Post-hoc LSD were performed between pre-test and post-test group. The full post-hoc test result is presented in Table 2.

Neuronal degeneration

One-way ANOVA were performed for neuronal degeneration count with F= 4.491 under p= 0.007, suggesting significant difference of neuronal degeneration between groups. There is higher neuronal degeneration in all treatment groups compared to neutral control, except in K3 group (p < 0.05). In all groups, Parkinson's disease model receiving placebo showed highest neuronal degeneration compared to neutral control (p < 0.001) but not placebo (p = 0.240). The Parkinson's disease model group receiving EGCG (K4) showed no neuronal degeneration difference compared to Parkinson's disease model receiving placebo (K2) (p = 0.105). Post-hoc LSD were performed between pre-test and post-test group. The full post-hoc test result is presented in Table 3.

DISCUSSION

This study showed no reduction of caspase-3 between EGCG-treated and non-treated group. The caspase cascade is an apoptotic pathway mediated by caspase enzyme. In Parkinson's disease, the presence of caspase-3 activity indicates the activation of extrinsic and intrinsic pathways due to the formation of α-synuclein radicals (Kumar *et al*., 2016). The α-synuclein protein in healthy brain cells has small levels and is neuroprotective through MAPK regulation (Musgrove *et al*., 2013). However, on activation of the extrinsic pathway that ends in caspase-3, there is an increase in cytochrome-c activity that leads to an increase in free oxide radicals. This increase in free oxide radicals leads to the formation of α-synuclein radicals (Wójcik *et al*., 2024). Aggregates of α-synuclein radicals can activate the NLRP3 inflammasome which triggers the inflammatory process through the activation of pro-IL-1β into IL-1β (Huang *et al*., 2023; Akbal *et al*., 2022). The inflammatory activity of IL-1β itself is known to activate caspase-3 through the IL-1β/Fas/caspase-8 pathway which ultimately triggers extrinsic apoptosis, especially in Parkinson's disease (Hui *et al*., 2017). The results of this study, along with evidence from the literature, show that neuronal apoptosis in Parkinson disease model is not solely controlled through caspase-3-dependent pathways, suggesting the role of alternative pathways.

Caspase-3 is a well-known apoptosis pathway in Parkinson's disease. In Parkinson's disease, the activation process of the intrinsic pathway is initiated by an increase in α-synuclein which causes activation of MMP-3 in the endoplasmic reticulum (Bluhm *et al*., 2022). Increased MMP-3 activity can cause endoplasmic reticulum stress that activates Apaf-1 protein of apoptosome. Apaf-1 ultimately activates caspase-3 through caspase-9 (Kim *et al*., 2014; Wright *et al*., 2007). MPTP is converted into its toxic metabolite, 1-methyl-4-phenylpyridinium (MPP^+), through metabolism by monoamine oxidase-B

(MAO-B) present in astrocytes. The resulting MPP^+ is subsequently transported into dopaminergic (DA) neurons via the dopamine transporter (DAT). Inside these neurons, MPP^+ disrupts mitochondrial oxidative phosphorylation, ultimately inducing neuronal necrosis. This neurotoxic process replicates the pathology of Parkinson's disease (PD) by selectively destroying DA neurons, particularly within the substantia nigra and diencephalon. The degeneration of these neurons leads to hallmark PD symptoms, including tremors and muscle rigidity, as well as a marked reduction in dopamine levels and neuronal density in affected brain regions. Because of its ability to closely reproduce the biochemical and cellular features of PD, MPTP serves as a valuable experimental model for studying PD and related neurodegenerative disorders (Anichtchik *et al*., 2003). In Parkinson's disease induced by MPTP, caspase-9 also has an important role in activating the Bid protein-mediated apoptotic pathway through caspase-8 (Viswanath *et al*., 2001) via caspase-3 activation (Kim *et al*., 2014; Wright *et al*., 2007). Although caspase-3 pathway activity has been shown to cause apoptosis in Parkinson's disease, studies show that direct and complete inhibition of caspase-3 is not a solution. Complete inhibition of the caspase-3 pathway through Casp3 gene deletion leads to activation of a more destructive necrosis pathway due to activation of more inflammatory pathways (García-Revilla *et al*., 2024). This suggests that regulation of apoptosis is much more important at the pre-cascade level of caspases as well as at the ligand level. At the pre-cascade level, modulation of apoptosis may involve the caspase-3 pathway may be assisted by ubiquitylation through the XIAP pathway of caspase-9 (Unnisa *et al*., 2023). Modulation of the extrinsic caspase-3 pathway may involve free radical control through regulation of the Bax/cytochrome-c pathway (Eid and El-Shitany, 2021). The intrinsic apoptosis pathway that led to caspase-3 activation is characterized by expression of Bcl-2. Bcl-2-induced apoptosis is mainly related to MOMP (mitochondrial outer membrane permeabilization) which is widely associated with ROS (Qian *et al*., 2022). Permeabilized mitochondria trigger inflammation, in part, through the release of mitochondrial-derived damage-associated molecular patterns (DAMPs). Caspase, although it can cause cell death during mitochondrial apoptosis, inhibits the activation of pro-inflammatory pathways following MOMP (Vringer and Tait, 2023). If MOMP occurs, the pro-apoptotic protein Bcl-2 located in the mitochondrial membrane gap is released into the cytoplasm, triggering a caspase cascade that promotes cell apoptosis (Qian *et al*., 2022).

While there are overwhelming evidences on how caspase-3 controls apoptosis in Parkinson's disease, alternative apoptosis pathway to caspase-3 also has been suggested. The PKCδ apoptosis pathway is one of the apoptosis pathways that does not involve caspase. This pathway can be activated through various mediators. Studies in mice have shown that activation of PKCδ by IL-1β is known to promote apoptosis through activation of the JNK and p38-MAPK signaling pathways (Lu *et al*., 2023). Studies show that PKCδ can be activated cytosolically due to ROS. This pathway involves dysfunction of the p65 protein due to a response to oxidative stress. The PKCδ modulates inflammation at least in part through NF-κB-mediated chemokines (Ren *et al*., 2014).

The conclusion on whether *C. sinensis* extract is able to regulate apoptotic pathway is heavily affected by compounds isolate of the *C. sinensis* extract. For example, the flower saponin of *C. sinensis* has been studied to significantly upregulate Bax and Bad proteins while downregulate Bcl-xL and Bcl-2 proteins, thus modulating the apoptosis rate in ovarian cancer cells through intrinsic pathways (Ren *et al*., 2020). Meanwhile another *C. sinensis* compound, quercetin, has been studied to affect caspase-3 but not decrease the mitochondrial membrane potential and did not affect the levels of B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X protein (BAX), suggesting extrinsic pathway role (Seo *et al*., 2016). Based on the aforementioned evidences, the *C. sinensis* EGCG extract in should show regulatory role in the extrinsic apoptotic pathway, which is not proven in our study.

It should be emphasized that evidences on the modulation of apoptosis by *C. sinensis* compounds are heavily dependent on the cellular state. There are at least two evidence categories that classify such cellular state. The first category of evidence includes a group of studies in animal models using apoptosis-aberrant cells such as cancer cells without additional cellular stressors (Seo *et al*., 2016; Xin *et al*., 2018; Rajabi *et al*., 2021; Karatuğ *et al*., 2019) which leads to increased apoptosis rather than reduction (Chaudhry *et al*., 2022). The second evidence category includes a group of studies on models using apopotosis-normal cells, in which various compounds of *C. sinensis* have been instead reported to reduce inflammation and oxidative-stress-related apoptosis (Seo *et al*., 2021; Priyandoko *et al*., 2023; Ahmed *et al*., 2019; Dey *et al*., 2021). The neuronal pyroptosis in Parkinson's disease is associated with NLRP3 inflammasome activation by α-synuclein radicals, as well as IL-1β activities (Huang *et al*., 2023; Akbal *et al*., 2022). This showed that the neuronal pyroptosis in Parkinson's disease falls into the latter category, suggesting the anti-inflammatory and apoptosis-reducing role of *C. sinensis* extract in Parkinson's disease if given before neuronal insult happen.

This study has several limitations. The first limitation is we did not isolate a specific compound from *C. sinensis,* but instead using premade *C. sinensis* EGCG extract. This

may affect the result interpretation which target overall *C. sinensis* capability rather than its specific compound. The second limitation is while neuronal apoptosis is detected in the models, the use of MPTP in rat is known to non-specifically target dopaminergic neuron compared to MPTP in mice. This suggest that clinical signs of Parkinson's disease in our model are also affected by other neuronal deaths outside substantia nigra *pars compacta*. The third limitation includes the study scope beyond non-caspase-3 apoptosis pathway, in which there is no examination on PKCδ as alternative apoptosis pathway.

CONCLUSION

This study suggests the neuroprotective and preventive role of *C. sinensis* compounds, especially EGCG in Parkinson's disease models. This study is unable to provide evidence on neuroprotection against Bcl-2 and caspase-3-dependent apoptotic activities such as Parkinson's disease, but suggest such neuroprotective effect in normal neuron might be achieved through modulation of caspase-3-independent pathway. This study emphasis the neuroprotective role of EGCG in normal brain, while confirming its inability to protect against direct damage that causes neuronal apoptosis, such as MPTP. Considering the well-known safety of various *C. sinensis* preparates, we suggest future clinical investigation of *C. sinensis* EGCG efficacy in reducing Parkinson's disease progressivity in human subject.

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NOVELTY STATEMENT

This study is unique in that it suggests that EGCG exerts a neuroprotective effect on dopaminergic neurons via a caspase-3-independent pathway.

AUTHOR'S CONTRIBUTION

PN and WW performed the expression assays and evaluated the results. PN, WW, MH, BP, S, PS, AM, and A. participated in the study design, sampling, and statistical analysis. PN. VFH drafted the manuscript. All authors read and approved the final manuscript.

Generative AI and AI-assisted technology statement

The author declares that no Genrative AI was used in the creation of this manuscript.

Conflict of interest

The authors have declared no conflict of interest.

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