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Potential Anti-Parkinsonian Activity of Gastrodia Elata: The Principle of Antioxidant Qualities in a Rat Model

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SHORT COMMUNICATION

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Potential Anti-Parkinsonian Activity of *Gastrodia Elata*: The Principle of Antioxidant Qualities in a Rat Model

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Abstract

Background: Parkinson's disease is a progressive, incurable, and the second most common neurological disorder resulting in the localized destruction of dopaminergic neurons in the pars compacta (PC) of the midbrain.

Objectives: Our study aimed to examine the antioxidant effect of *Gastrodia elata* on brain tissues of PD animal models depending on results obtained from previous investigations.

Materials and Methods: 40 Wistar adult male rats weighing 200–300 mg were placed into 5 separate groups at random, with 8 rats in each group. The course of the study was a 21-day behavioral test carried out on day 21 using an open-field device. Decapitation of rats' brains was performed on day 22, 24 hours after the last exposure to ROT, and brain tissues were gathered for examination of biochemistry by measuring levels of malondialdehyde (MDA).

Results: A significant reduction in motor action was observed (p-value < 0.05) in group 2 in comparison with group 1 on the open field apparatus, while groups 3, 4, and 5 showed a significant improvement in motor action (P-value < 0.05) in comparison with group 2. Results from biochemistry show a significant elevation in MDA levels (p-value < 0.05) in groups 2 and 3 in comparison with group 1, whereas groups 4 and 5 exhibited a significant decrease in MDA levels (p-value < 0.05).

Conclusion: GE alleviates oxidative damage associated with PD by lowering MDA levels in brain tissues of the PD rat model, so it possesses an antioxidant activity. *GE* enhances the collaboration of motion in PD rats in the open field apparatus. When used with L-dopa *GE* has a cumulative effect.

Keywords: Open-field, Malondialdehyde, Lewy bodies, *Gastrodia Elata*, Rearing, Grooming

1. Introduction

Parkinson's disease (PD) is a recognizable, fast-growing neurodegenerative disease with a wide range of motor symptoms, including muscular rigidity, bradykinesia, postural instability, and resting tremors, which influence a patient's life and daily work. Sleep disturbances, gastrointestinal dysfunction, impaired cognition, dizziness, and psychiatric problems are among the non-motor symptoms associated with PD [1].

Parkinson's disease is caused by the destruction of up to 80% of dopaminergic neuronal cells in the SNpc of the midbrain, resulting in diminished levels of the neurotransmitter dopamine (DA) which is responsible for the coordination of voluntary and motor activities of the body [2]. Another cause of PD is brain damage provoked by the formation of Lewy bodies in the nigrostriatal system [3].

"Oxidative stress" is a state in which there is an imbalance between the generation of reactive oxygen species (ROS) and the ability of a biological system

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to eliminate the reactive intermediates. This imbalance can be harmful to cells. ROS can be generated by many ways including direct interactions between redox-active metals and oxygen species and indirectly through the activation of enzymes like NADPH oxidases or nitric oxide synthase (NOS) [4]. Research indicates that increased oxidative stress and degeneration of DA-ergic neurons in PD patients' brains are brought on by neuroinflammation, mitochondrial failure, elevated calcium and iron levels in SN, and DA metabolism [5].

Dopamine auto-oxidation, which generates dopamine quinones and free radicals, may be a factor in the neurodegeneration seen in Parkinson's disease [6]. The cyclization of dopamine quinones results in aminochrome, which then inhibits the synthesis of the antioxidant nicotinamide adenine dinucleotide phosphate (NADPH) and creates superoxide. Monoamine oxidase-B (MAO-B) produces 3,4-dihydroxyphenyl-acetaldehyde, ammonia, and H_2O_2 as a consequence of the oxidative breakdown of DA. Hydroxyl radicals were formed from the interaction between H_2O_2 and Fe^{2+} resulting in the destruction of dopaminergic neurons [7].

Levodopa was the first and most effective medication for treating PD, which is a naturally occurring compound that has been readily absorbed and crosses the BBB then transformed into DA in the brain to replace DA deficit [8]. Carbidopa a peripheral decarboxylase inhibitor, prevents the conversion of levodopa to DA in the periphery, thus increasing the availability of levodopa and DA in the brain and enhancing PD therapy. DA agonists have also been used to stimulate brain DA in PD but are less efficacious than levodopa [9].

Enzyme inhibitors, including monoamine oxidase-B and catechol-o-methyl transferase inhibitors, have also been used in treating PD. These drugs act by inhibiting the metabolism of DA by the enzymes monoamine oxidase-B and catechol-o-methyl transferase in the brain and the periphery, respectively [10]. Another class of drugs used for treating PD is the anticholinergic agents, such as benztropine and trihexyphenidyl. Deep brain stimulation (DBS) is a surgical technique that has been licensed for the treatment of severe cases of PD that are unresponsive to drug therapy by stimulating the patient's brain using electrical impulses to ameliorate the irregular impulses caused by neuronal degeneration [11].

Gastrodia elata Blume (*GE*) is a commonly used traditional Chinese herbal medicine from the family Orchidaceae and the genus Gastrodia. *GE* has been used for the treatment of several conditions such as epilepsy, stroke, dizziness, amnesia, and headache. The dried rhizome of *GE* is the major medicinal portion of the plant. Researchers found that *GE* Blume (Tianma) can be added to PD therapy [12]. Recent studies show that *GE* and its bioactive components exhibit neuroprotective potential in numerous in vivo and in vitro models of PD. The principal active ingredients of *GE* include vanillic acid, gastrodin, anisalcohol, vanillin, and vanillyl alcohol possess a neuroprotective effect which gives it a powerful importance in treating PD [13].

Several epidemiological studies indicate a connection between pesticide use and the prevalence of Parkinson's disease. Rotenone (ROT) has been used as a lipid-soluble pesticide. Most neurotoxicity findings indicate that rotenone inhibits electron transport from complex I (NADH-quinone oxidoreductase) to complex II of the ETC on the inner surface of the mitochondria, hence preventing mitochondrial respiration and causing targeted dopaminergic degeneration [14].

2. Materials and methods

2.1. Animals

Forty adult, healthy male albino rats weighing between 200 and 300 grams were employed in this investigation. The University of Babylon/College of Medicine/Animal House is home to these animals, which are housed in ten cages with four rats each. The cages are kept at a temperature of twenty-five degrees Celsius, with a 24-hour light and dark cycle, as well as an unlimited supply of food and water. Rats were given fourteen days to acclimate before being divided into five groups of four rats each, which were assigned at random. From November 2023 to March 2024, the study was conducted at the University of Babylon/College of Medicine/Department of Pharmacology and Toxicology.

2.2. Preparation of the plant and chemicals

2.2.1. Preparation of Gastrodia Elata

Based on the Chinese Pharmacopoeia, powdered extract of *Gastrodia Elata* was diluted in distilled water at a concentration of 883.56 mg/kg for intragastric (oral) supply [15].

In March 2015, a Chinese producer introduced Tian Ma, a botanical extract of *GE*, as a dry powder dosage form. To get a final concentration of 150 mg per milliliter, three grams of the dried extract were dissolved in 20 milliliters of purified water.

2.2.2. Preparation of Levodopa/carbidopa (L/C)

Before being given orally, each rat in groups 3 and 5 received a newly prepared daily dose of 10 mg/kg of

L/C that was made by milling and dispersing a single tablet of L/C (250/25 mg) in 25 milliliters of D.W. to achieve a final solution having a concentration of 10 mg/ [16].

2.2.3. Preparation of rotenone

Rats were given an intraperitoneal (IP) injection of 2.5 mg/kg body weight to produce Parkinsonism. A sensitive balance was used to weigh 50 mg of rotenone, which was subsequently diluted in 1 milliliter of 50% dimethyl sulfoxide (DMSO) to create a stock solution [17].

By adding about 9.9 milliliters of olive oil to 0.1 milliliters of DMSO mixture, a solution with 0.5 mg/ml of rotenone was produced. Each rat was given 1 milliliter of the homogenized solution, which was created to provide a consistent mixture. Before every novel trial, rotenone was made as a new stock solution.

2.2.4. Study design

The 40 albino male rats were split into 5 groups arbitrarily with eight rats in each group, as follows:

Group 1: Are healthy untreated rats (control group).

To develop Parkinsonism the other 32 rats received intraperitoneal (IP) injections of rotenone at a rate of 2.5 mg/kg every 48 hours [18] and grouped as follows:

Group 2: PD rats without treatment (ROT group)

Group 3: Rats were given a single daily dose of 10 mg/kg L/C tablet orally for 21 days (L/C group).

Group 4: Rats were given a daily dose of 883.56 mg/kg of *GE* extract orally for 21 days (GE group).

Group 5: Rats were given a single daily dose of a combination of 10 mg/kg of L/C and 883.56 mg/kg of *GE* extract orally for 21 days (L/C + *GE* group).

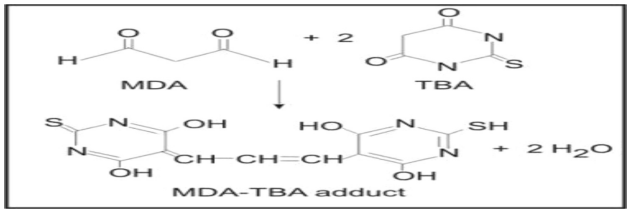
Behavioral assessments were performed on day 21 in order to compare the progression of Parkinsonism and the efficacy of therapy. Every action that each animal did during its three rotarod trials was recorded by a video camera. Each rat was sacrificed 24 hours after the final injection of rotenone on day 22 in order to obtain the complete brain samples needed to evaluate tissue levels of malondialdehyde (MDA).

2.2.5. Behavioral test, open-field test

The open-field is a conventional testing method used to examine both anxiety-driven actions and total locomotor activity [19]. This 100 × 100 cm wooden box was designed by researchers, according to [20]. It is made of a square floor that is divided into 100 identical squares by fine white lines. Each rat's activity may be measured for around ten minutes by placing it in the center of the box. Crossings and rearing behaviors are used in the open-field apparatus to quantify hyperactivity. The term "crossings" refers to the overall number of squares that traveled all over the test period and is used to evaluate the animals' locomotor activity. The total number of visits to the open field center is calculated to assess risk-taking behavior. Grooming time is defined as the entire amount of time spent grooming. 70% ethanol was used to sanitize the equipment after each test. A video camera recorded every action.

2.2.6. Malondialdehyde calorimetric assay kit

Using a spectrophotometer, malondialdehyde (MDA) was measured using the Thiobarbituric acid (TBA) assay method created by Buege & Aust in 1978. This method analyzes lipid peroxides by evaluating the aldehyde breakdown products of lipid peroxidation. The basic principle of the process is that a TBA-MDA red complex, which can be detected at 535 nm, is created when two molecules of TBA and one molecule of MDA join, as shown in the chemical reaction below.



A chemical reaction between one molecule of MDA and two molecules of TBA produces the MDA-TBA complex.

2.2.7. HCL-TBA-TCA stock reagent

A solution of 15% W/V TCA, 0.375% W/V TBA, and 0.25 N HCl was prepared to yield 100 milliliters (2.1 milliliters of concentrated HCl in 100 milliliters). 15 grams of TCA and 0.375 milligrams of TBA were dissolved in 0.25 N HCl, and the solution was then added to make 100 milliliters.

2.2.8. Procedure

0.6 ml of HCl-TBA-TCA reagent was added to 0.4 milliliters of the sample. After thorough mixing, it was placed in a boiling water bath for about ten minutes. Following cooling, 1.0 milliliter of a recently made 1N NaOH solution was added. At 535 nm, the absorbance of the pink color was measured in comparison to a blank that contained distilled water rather than a sample. In the blank, 0.6 milliliters of TCA-TBA-HCl reagent and 0.4 milliliters of distilled water were combined and heated.

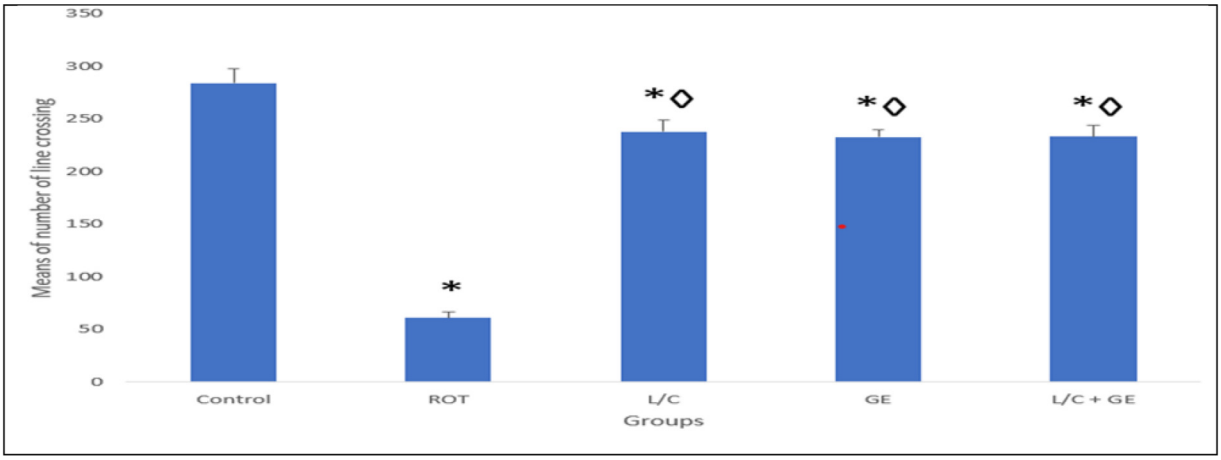


*Fig. 1. Means of the number of line crossings ± SD for all study groups. * = significant decrease (P-value < 0.05) compared to the control group; ◊ = significant increase (P-value < 0.05) compared to the ROT group.*

Malondialdehyde (mmol/l) = absorbance of the sample/E0 x L X D

Where:
E0 = extinction coefficient = 1.56×10^5 M^{-1} cm^{-1}
L = length path cm
D = dilution factor = 6.7×10^6

2.2.9. Statistical analysis

In this investigation, we utilized the Statistical Package for the Social Sciences (SPSS) version 26. The post hoc test and one-way ANOVA are statistical techniques employed to determine whether the differences were statistically significant. P-values less than or equal to 0.05 were considered significant since a significance level of 5% was set.

3. Results

3.1. Behavioral test: Open-field test

3.1.1. Number of line crossings

As depicted in Fig. 1 the number of lines traveled in the open field box was significantly decreased (P-value < 0.05) in ROT, L/C, *GE*, and L/C + *GE* groups compared to the control group. Conversely, there was a significant increase (P-value < 0.05) in the number of lines traveled by L/C, *GE*, and L/C + *GE* groups relative to the ROT group. Additionally, there was no significant difference (P-value > 0.05) in the number of lines traveled among L/C, *GE*, and L/C + *GE* groups.

3.1.2. Number of visits to the central area

As shown in Fig. 2 there was a significant decrease (P-value < 0.05) in the number of visits to the central area of the open field box in the ROT group compared to the control group and the other three groups. Furthermore, there was a significant increase (P-value < 0.05) in the number of visits to the central area in L/C, *GE*, and L/C + *GE* groups relative to the ROT group. Moreover, no significant difference (P-value > 0.05) in the number of visits to the central area was observed among L/C, *GE*, and L/C + *GE* groups when comparing these groups with the control group.

3.1.3. Rearing number

As presented in Fig. 3 there is a significant decrease (P-value < 0.05) in the rearing number in the ROT group relative to the control group and the remaining three groups. On the other hand, there is a significant increase (P-value < 0.05) in the number of rearings in L/C, *GE*, and L/C + *GE* groups relative to the ROT group. Also, there is no significant difference (P-value > 0.05) among L/C, *GE*, and L/C + *GE* groups when comparing these groups with the control group.

3.1.4. Grooming time

As shown in Fig. 4, there is a significant decrease (P-value < 0.05) in grooming time in the open-field box for the ROT group compared to the control group and the other three groups. Furthermore, there is a significant increase (P-value < 0.05) in grooming time in L/C, *GE*, and L/C + *GE* groups compared to the ROT group. There is no significant difference in grooming time among L/C, *GE*, and L/C + *GE* groups when comparing these groups with the control group.

3.1.5. Malondialdehyde (MDA)

As shown in Fig. 5 there is a significant increase (P-value < 0.05) in MDA levels in the ROT group and L/C group relative to the control group. Additionally, there is a significant decrease (P-value < 0.05) in MDA

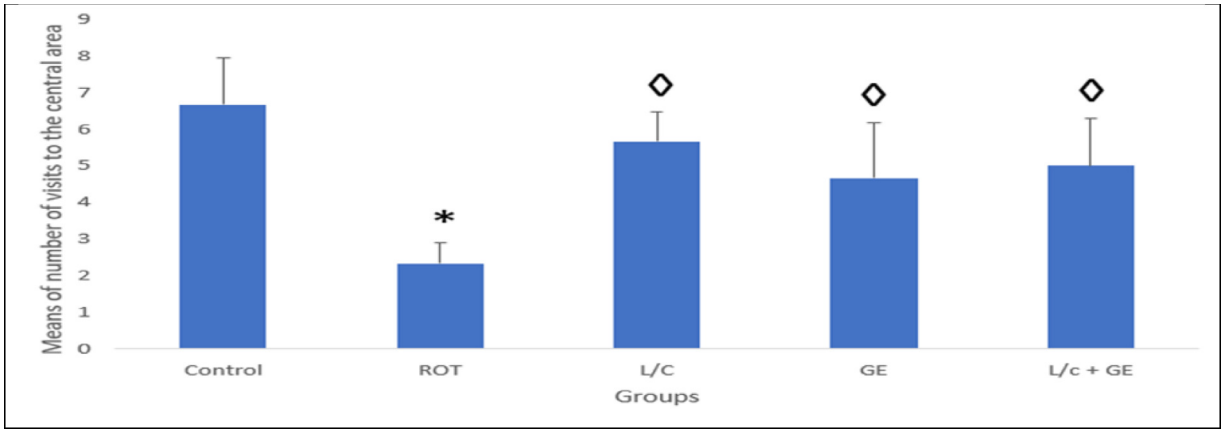


*Fig. 2. Means of the number of visits to the central area of the open-field box ± SD for all study groups. * = significant decrease (P-value < 0.05) compared to the control group; ◊ = significant increase (P-value < 0.05) relative to the ROT group.*

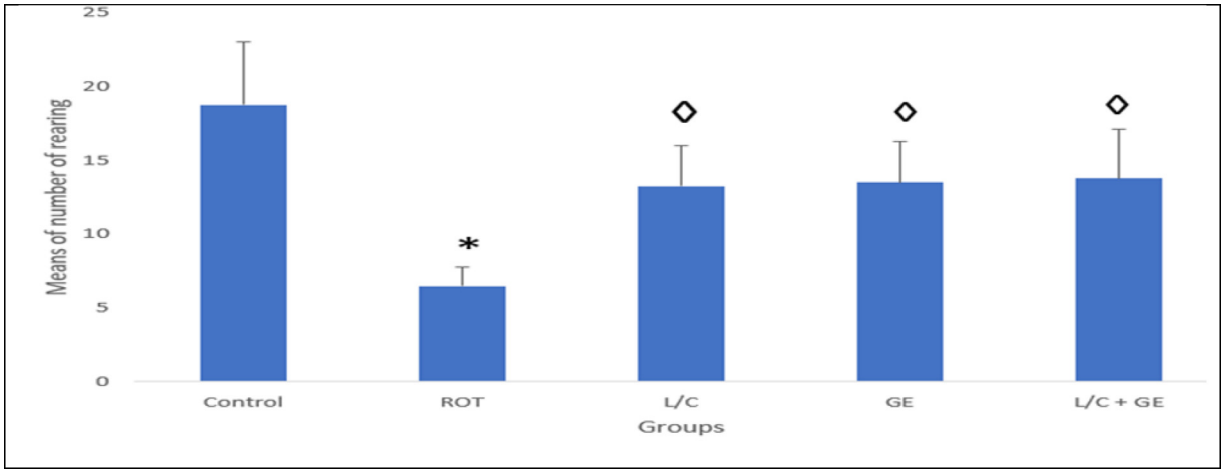


*Fig. 3. Means of number of rearing ± SD for all study groups. * = significant decrease (P-value < 0.05) compared to the control group; ◊ = significant increase (P-value < 0.05) compared to the ROT group.*

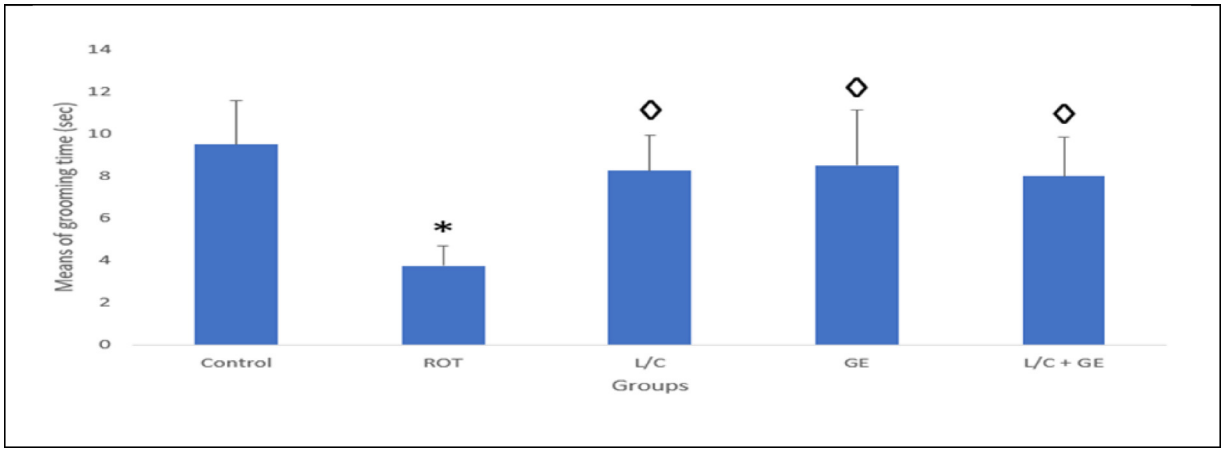


*Fig. 4. Means of grooming time ± SD for all of the study groups. * = significant decrease (P-value < 0.05) relative to the control group; ◊ = significant increase (P-value < 0.05) relative to the ROT group.*

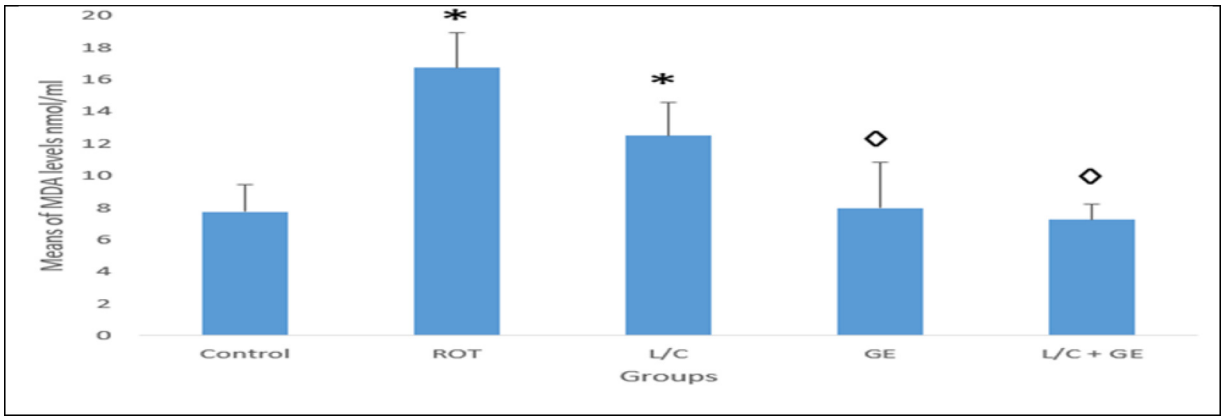


*Fig. 5. Means of MDA levels ± SD for all of the study groups. * = significant increase (P-value < 0.05) relative to the control group; ◊ = significant decrease (P-value < 0.05) relative to the ROT group.*

levels in the GE group and L/C + *GE* group relative to the ROT group. No significant difference (P-value > 0.05) exists in the *GE* group and L/C + *GE* group relative to the control group.

4. Discussion

The number of line crossings, visits to the center area, rearings, and grooming sessions were all significantly fewer in ROT-treated rats than in the other four groups. These findings were in accordance with other research that documented deficiencies in oxidative defenses, chemical messengers, and behavioral traits associated with dopaminergic neurodegeneration [21].

The main process responsible for rotenone's neurodegenerative effects is the development of oxidative stress, which leads to PD-like pathology. Dopaminergic neurons in the SNpc are essential for proper motor function; their loss causes the striatum's dopamine levels to drop, which impairs postural stability and significantly reduces mobility [22]. Comparing L-dopa-treated rats to ROT-treated rats, the former shows a substantial increase in the number of line crossings, visits to the center region, rearings, and grooming sessions. Since dopamine and norepinephrine levels, as well as the synthesis and release of their metabolites, all rose during L-dopa therapy, it is thought to be the cornerstone treatment for Parkinson's disease since it compensates for decreased dopamine levels [23].

Rats given *GE* extract either alone or in conjunction with L-dopa exhibit markedly higher numbers of line crossings, trips to the center area, rearings, and grooming sessions when compared to rats given ROT. Among the many active ingredients found in *GE* extract, gastrodin was thought to be the primary one. Analgesic, sedative, anti-inflammatory, antioxidant, anticonvulsant, and anxiolytic properties have all been proposed for gastrodin. Learning and memory may also be improved by it [24]. Gastrodin may help preserve DA neurons in PD animal models by lowering α-synuclein buildup and neuronal damage, based on recent studies. These outcomes support the idea that gastrodin can lessen brain inflammation, enhance intracellular antioxidant capacity, and help avoid DA neuronal death and the ensuing symptoms of Parkinson's disease [25].

Malondialdehyde levels were significantly higher in ROT-treated rats than in healthy control rats, which is consistent with the findings of de Faris. According to recent research, dopamine (DA) metabolism, protein misfolding, heavy metal pollutants, insecticides, pesticides, and neurotoxins can all cause PD by interfering with mitochondrial function, the action of the DA transporter, and DA metabolism [26]. A surplus of reactive oxygen species (ROS) is produced as a result of all of these processes [27].

ROS, which are byproducts of cellular metabolism, are essential for the maintenance of several physiological functions. However, if there is an imbalance between the production and elimination of ROS, negative consequences, including neurodegeneration, would result [28]. Malondialdehyde is a byproduct of the peroxidation of polyunsaturated fatty acids; an increase in free radicals leads to the overproduction of MDA, which is frequently employed as a marker of oxidative stress in neurological illnesses like Parkinson's disease and Alzheimer's disease [29]. MDA levels increased considerably after receiving L/C treatment compared to the control group, however, they were still lower than those of the rats that received ROT treatme. Oxidative stress was induced by L-dopa treatment, as evidenced by a significant increase in MDA levels and a significant decrease in reduced GSH levels.

This phenomenon could be attributed to the hypothesis that prolonged L-dopa therapy elevates dopamine production, This might lead to an excess of free radicals generation, which would overwhelm the body's defenses, and increase oxidative stress [23]. Rats administered with *GE* alone or in combination with L/C demonstrated a remarkable decrease in MDA levels compared to ROT-treated rats. Gastrodia elata has the potential to provide oxidative stress resistance through the suppression of glutamate, hindering glutamate-induced (Ca^{2+}) entry, and inhibiting calmodulin-dependent Kinase II production. Thus, these findings imply that *GE* may function as free radicals and possess certain neuroprotective properties [30]. In contrast to rats treated with ROT, Lu C. *et al*., discovered that co-administration of GE extract and L-dopa together dramatically reduced MDA levels [31].

5. Conclusion

Gastrodia elata improves muscular coordination, in terms of open-field test, in PD male rat model induced by ROT. It efficiently reduces oxidative stress by lowering levels of MDA in brain tissues, which indicates its potential antioxidant effects in the ROT-induced PD male rat model. Furthermore, it can enhance the antiparkinsonian effects of L/C in ROT-induced PD male rats induced by ROT.

To better understand the toxicological profiles, pharmacokinetics, and underlying molecular mechanisms associated with these natural compounds and their efficacy in treating and preventing Parkinson's disease, further research on *Gastrodia elata* and its primary constituents is imperative.

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