Anti-parkinsonian Activity of Borago Officinalis Ethanolic Extract in Rotenone-Induced Rat Model of Parkinson's Disease

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Abstract—**Background: Parkinson disease (PD) was one of the most prevalent slow-moving, age-related neurodegenerative diseases, which is characterized by the death of dopaminergic neurons in the substantia nigra (SN). Bradykinesia, stiffness, postural instability, akinesia, and tremor are some clinical motor signs of PD.This study aims to investigate the antioxidant and anti-inflammatory effects of B.Officinalis extract.**

Materials and Methods:The 70 healthy male Albino rats used in this experiment study,the first group was designated as the healthy control group and other rats were orally administered sinemet (10mg/kg) and B. Officinalis extracts concentrations of (62.5,125,250 and 500mg/kg) respectively followed by intraperitonially (IP) 2.5 mg/kg of rotenone every other day for 21 days.At day 22, 24 hours following the last dose, behavioral tests were carried out to compare the progression of Parkinsonism and the efficacy of the treatment. Each rat was put on a rotarod for three trials and then left in the open field test for ten minutes.The mid-brain samples from each animal were then taken to analyze the tissue levels of interleukin-1β(IL-1β),malondialedyhde (MDA) and total antioxidant capacity (TAOC).

Results:Rats treated with B. Officinalis concentrations (125,250 and500 mg/kg) significantly increased the rotation distance, time of rotation,number of visits to the center area andnumber of crossing lines of the rats with Parkinsonism. Rats treated withB. Officinalis concentrations of(125,250 and500 mg/kg) exhibits a significant decrease in MDA, IL-1□ levels and increase in TAOC.

Conclusion:Investigations indicate the anti-Parkinsonlike activity of B. Officinalis,which alleviates the Parkinsonism induced by rotenone (ROT) in male rats through exerting anti-inflammatory and antioxidant properties.

***Index Terms*— Borago officinalis, parkinson′s disease,Rotenone.**

I. INTRODUCTION

Parkinson disease(PD) isone of the most prevalent slow-moving, age-related neurodegenerative diseases.Which is characterized by the death of dopaminergic neurons in the substantia nigra (SN)(1). Bradykinesia, stiffness, postural instability, akinesia, and tremor are some clinical motor signs of PD(2). It is also identified by several non-motor symptoms encompassing autonomic dysfunction, cognitive disorders, sleep disorders and sensory abnormalities (3). Numerous environmental and genetic factors have a role in the pathogenesis of PD. Oxidative stress, microglial activation, mitochondrial dysfunction, neuroinflammation, and the production of Lewy bodies which are associated with dopaminergic neuronal death(4).Oxidative stress causes the dopamine-secreting neurons in the substantia nigra pars compacta (SNpc) to deteriorate. Mitochondrial dysfunction, reactive oxygen species(ROS), and dopamine metabolism are thought to be the initial stages in development of oxidative stress in dopamine-producing neuronal cells(5). Proinflammatory cytokines like interleukin-1β(IL-1□), interleukin-6(IL-6), and tumor necrosis factor-α(TNF-□), as well as free radicals like ROS and inducible nitric oxide synthase (iNOS), when activated and released, negatively impact the survival of dopaminergic neurons in the SN(6).

Levodopa (L-dopa) cause a highly successful improvement of early-stage PD's motor symptoms. Tremor mighty be slightly decreased, although bradykinesia and stiffness respond better. Patients eventually need higher dosages of L-dopa, which are linked to increased side effects such as dyskinesia(7).Rotenone, a well-known natural insecticide(8). It can penetrate the blood brain barrier(BBB) due to its lipophilic structure(9). Furethermore, rotenonecaused inhibition of mitochondrial complex-1(MC-I) and generation of oxidative stress(8). As a result, ROT was a novel inducer of animal models because it resembles the early signs of Parkinsonism(9).

Borago officinalis (Boraginaceae), the herb known as borage, was chosen in this investigation due to it is ability to scavenge reactive oxygen species (10).The flowers of the B. Officinalis plant have been used as an anxiolytic, sedative, analgesic,anti-inflammatory and antioxidant in medicine(11).Phenolics, flavonoids, and fatty acids included in the B. officinalis flower are thought to be responsible for the flower's antioxidant, anti-inflammatory and antibacterial properties (12).This study aims to investigate the antioxidant and anti-inflammatory effects of B.Officinalis extract in rotenone induce Parkinson disease.

II. MATERIALS AND METHODS

A. Animals

In this study, we used 70 adult male Albino rats whose weights range between 200-300 grams. The rats were housed in the

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Animal House of the College of Medicine/ University of Babylon. They were kept in 14cages, 5 rats in each cage at25° C temperatures with 14 hours in daylight and 10 hours in darkness cycle with water and food ad libitum. The animals were randomly divided after two weeks of adaptation into the healthy control group, sinemet treated group (10mg/kg) and B.Officinalis extract treated group (62.5,125,250 and 500mg/kg) respectively , followed by intra-peritonially (IP) 2.5 mg/kg of rotenone from day to day for 21 days.

B. Plant Preparation

Flowers of B. officinalis were collected from local markets (Babylon, Iraq). About 30g of air-dried flower grained and dissolved in 300 ml of ethanol (95%) and theextract was done using soxhletfor 4 hours and temperature ranged between 80°C and 85°C. A rotary flash evaporator was used to remove the solvent from the extract, and the resultant extract was stored at 20° C until use. Then,5 grams of B.officinalisextract were dissolved in 10 ml of distilled water,to produced final concentration 500mg per each ml(13)(14).

C. Rotenone Preparation

To cause Parkinsonism, rats were intraperitoneally (IP) administered ROT (2.5 mg/kg Body Weight). Initial dilution of 125 mg of ROT was carried out in 1 mL of a stock solution of 50X dimethyl sulfoxide (DMSO) (15). A fresh solution was made twice a week, and 40 µl of the stock solution was added to 1960 µl of olive oil to dilute it.Before giving the rat the solution,it was mixed uniformly using a vortex.The animals in the control group, which only receivedthe vehicle (DMSO/Olive oil), each rat received 1ml/kg of the produced solution(16).

D. Behavioural Tests

1.Rotarod Apparatus

The motor capacity and coordination of rodents are assessed using this behavioural test. Rats must balance on a rotating cylinder with a variable speed to complete the task. The rotating cylinder was used to inspect each rat for three minutes at a speed of 20 rpm. Rat performance was graded for motor coordination based on the number of spins. After each test, the apparatus was sterilized using 70% ethanol (17).

2.Open Field Box

The activity of each rat was measured for about 10 minutes by placing the rat in the centre of the apparatus. The total number of squares crossing throughout the test time is referred to as crossings, and it is used to determine the animals' locomotor activity, the total numbers of erect postures exhibited by the rat with the intent of exploring is referred to as rearing, and the total number of visits to the centre of the open field is used to assess risk-taking behavior. The term grooming refers to the overall amount of period spent grooming(18).

E. Brain Dissection

Each rat was sacrificed on the 22nd day,the skull was dissected posteriorly from the foramen magnum, and the brains were removed. The brain, cerebellum, and olfactory pulps were carefully removed from the skull, along with the midbrain and forebrain being removed, dissected, rinsed with phosphate buffer solution, and weighting.

Procedures for Preparing Brain Samples

- Brain homogenization: Remaining blood was washed away using a pH 7.4 pre-chilled phosphate buffer saline (PBS).
- After being weighed, the brain was homogenized using a homogenizer on ice in PBS (pH = 7.4).
- freezing them at -20□C.

F. Statistical Analysis

Statistical analysis was carried out by using the 26th edition of Statistical Package of Social Sciences (SPSS v26)for Windows 10 was utilized. One-way ANOVA is the statistical formula used to determine the significant differences.p-value<0.05was considered significant.

III. RESULTS

A. Rotation Distance

In comparison to control(healthy/untreated) group, the rotations distance significantly decreased (p value<0.05) in rats treated with allplantextract concentrations, sinemet (SIN) treated group and inrotenone(ROT) group. Whereas,there was a significant increased (p value<0.05) in rats treated with plant extractconcentrations of(125,250 and 500 mg/kg)and SIN treated group as compared with ROT group.Furthermore, rotation distancesignificantly increased (p value<0.05)in rats treated with plant extractconcentrationof (125mg/kg) as compared to SIN treated group(Figure 1).

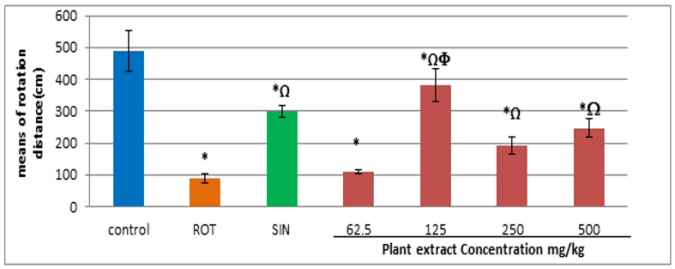

Figure 1: Means of rotation distance ± SEM of all groups. Control: healthy untreated group, ROT: rotenone treated group (2.5 mg/kg), SIN: Sinemet treated group (10mg/kg).
*=significantly decreased (p value<0.05) compared to the control group.
Ω=significantly increased (p value<0.05)compared to theROT group.
□=significantly increased (p value<0.05) compared to the SIN group.

B. Time of Rotation

The time of rotations significantly decreased (p-value <0.05) in the rotenone (ROT) treated group, Sinemet treated group, and in rats treated withB.officinalisconcentrations of (62.5,125,250 and 500 mg/kg) as compared to control (healthy) group. Whereas, there was a significant increased (p-value <0.05) in rats treated with Sinemet and B.officinalisconcentrations of (125, 250 and 500 mg/kg) as compared to ROT group. Furthermore, there was a significant decreased (p-value <0.05)in rats treated with B.officinalisconcentrations of (62.5,250 and 500 mg/kg), but there was no significant difference in rats treated withB.officinalisconcentration of 125 mg/kg in comparison with Sinemet group (Figure 2).

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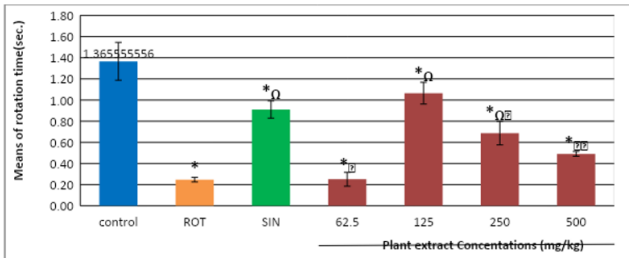

Figure 2: Means of rotation time (sec.) ± SEM of all groups. control: healthy untreated group, ROT: (2.5 mg/kg), SIN: (10mg/kg).
*=significant decrease (p-value <0.05) as compared to the control group.
Ω=significant increase (p-value <0.05) as compared to the ROT group.
♦=significant decrease (p-value <0.05) as compared to the SIN group.

C. *Number of Visits to the Center Area*

The number of visits to the center area significantly decreased (p-value <0.05) in rotenone (ROT) group, sinemet (SIN) treated group and in rats treated withB.officinalis concentrations of (62.5,125,250 and 500 mg/kg) as compared to control (healthy) group.Whereas, number of visits to the center areasignificantly increased (P-value <0.05) in SIN treated group and in rats treated with B.officinalis concentrations of (62.5,125,250 and 500 mg/kg) as compared to ROT group. Furthermore, there was significantly decreased (P-value <0.05) in rats treated with B.officinalis concentrations of (62.5 and 250 mg/kg) ,but there was no significant difference in rats treated with B.officinalis concentrations of (125 and 500 mg/kg) as compared to SIN treated group (Figure 3).

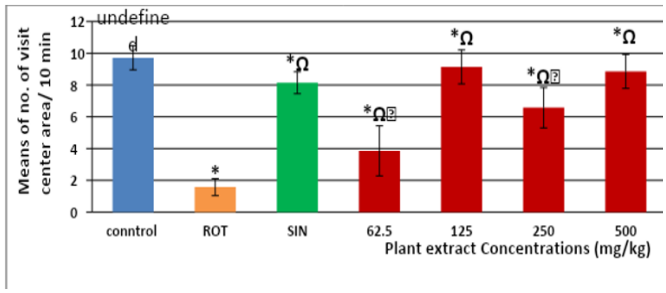

Figure 3: Means of number ofvisitsto center area ± SEM of all groups.control: healthy untreated group, ROT: (2.5 mg/kg), SIN: (10mg/kg).
*=significant decrease (p-value <0.05) as compared to the control group.
Ω=significant increase (p-value <0.05) as compared to the ROT group.
♦=significant decrease (p-value <0.05) as compared to the SIN group.

D. *Line Crossing (no. Of squares)*

In comparison to control(healthy) group, line Crossing significantly decreased (p value<0.05) in rats treated with all plant extractconcentrations, sinemet(SIN) treated group and rotenone(ROT) group. Whereas, line crossing significantly increased (P value<0.05) in rats treated with plant extract concentrations of (125,250 and 500 mg/kg) and SIN treated group as compared to ROT group. Additionally, there was significantly increased (p value<0.05)in rats treated with plant extractconcentration of (125mg/kg)ascompared to SIN treated group, (Figure 4).

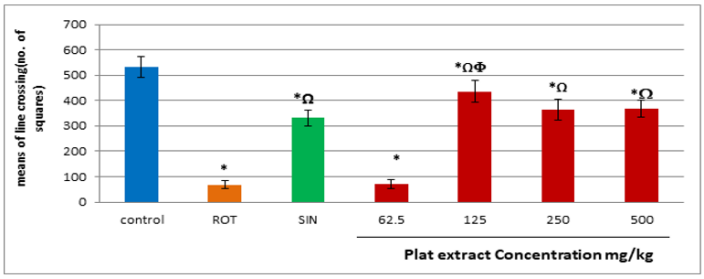

Figure 4: Means of (line crossing) no. of squares ± SEM of all groups. control: healthy untreated group, ROT: rotenone treated group (2.5 mg/kg), SIN: Sinemet treated group (10mg/kg).
*=significantly decreased (p value <0.05) compared to the control group.
Ω=significantly increased (p value <0.05) compared to the ROT group.
□=significantly increased (p value <0.05) compared to the SIN group.

E. *Malondialdehyde(MDA) levels*

In Figure 5, MDA level significantly increased (p value<0.05) in rats treated with all plant extract concentrations,SIN treated group and ROT groupas compared to control group.While,MDA significantly decreased (p value<0.05)in rats treated with allplant extract concentrations and SIN treated group as compared with ROT group.Furthermore, there was significantlyincreased (p value<0.05) in rats treated withplant extract concentrations of(62.5,250 and 500mg/kg),except (125mg/kg) has no significant difference as compared with SIN treated group.

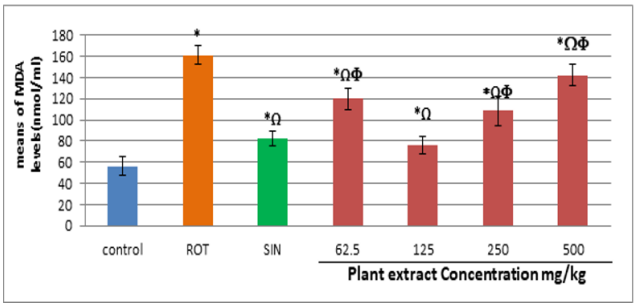

Figure 5:Means of MDA levels ± SEM of all groups. control: healthy untreated group, ROT: (2.5 mg/kg), SIN: (10mg/kg).
*=significantly increased (p value <0.05)compared to thecontrol group.
Ω=significantly decreased (p value <0.05) compared to the ROT group.
□=significantly increased (p value <0.05) compared to the SIN group.

F. *Interleukin-1beta (IL-1β) levels*

In comparison to control group,IL -1β level significantly increased (p value<0.05)in rats treated with plant extract concentrations of (62.5,250 and 500mg/kg) and ROT group. There was no significant difference in SIN treated group and in rats treated withplantconcentrationof(125mg/kg). Whereas,IL-1βsignificantly decreased(p value<0.05)in rats treated with all plant extract concentrations and SIN treated group as compared with ROT group. Additionally, there wasa significant increased(p value<0.05)in rats treated withplant extract concentrations of (62.5,250 and 500mg/kg), but no significant difference at plant concentration of 125mg/kg as compared to SIN treated group,(Figure 6) .

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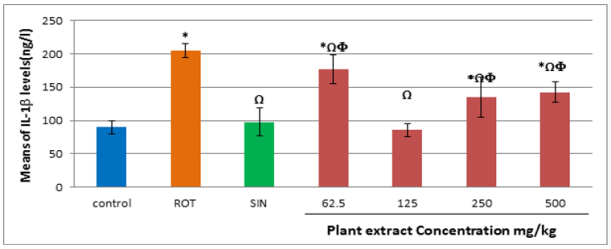

Figure 6:Means of IL-1□ level ± SEM of all groups. control: healthy untreated group, ROT:(2.5 mg/kg), SIN: (10mg/kg).
*=significantly increased (p value <0.05) compared to the control group.
Ω=significantly decreased (p value <0.05) compared to the ROT group.
□=significantly increased (p value <0.05) compared to the SIN group.

G. *Total Antioxidant Capacity (TAOC) Levels*

Total antioxidant capacity levels significantly decreased (p-value <0.05) in rotenone (ROT) group, SIN treated group and in rats treated withB.officinalisconcentrations of (62.5,250 and 500mg/kg) and there was no significant difference in rats treated with B.officinalis concentration of 125 mg/kg as compared to control (healthy) group. Whereas, TAOC significantly increased (p-value <0.05) in SIN group and in rats treated with all B.officinalis concentrations as compared to ROT group . Furthermore, TAOC significantly increased (p-value <0.05) in rats treated with B.officinalis concentration of 125 mg/kg and no significant difference in B.officinalis at concentrations (62.5,250 and500 mg/kg) as compared to SIN group (Figure 7).

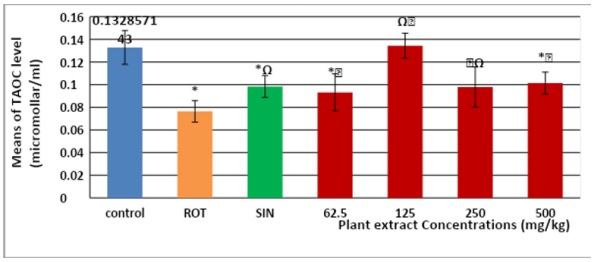

Figure 7: Means of TAOC levels ± SEM of all groups.control: healthy untreated group, ROT: (2.5 mg/kg), SIN: (10mg/kg).
*=significant decrease (p-value <0.05) as compared to the control group.
Ω=significant increase (p-value <0.05) as compared to the ROT group.
Φ=significant increase (p-value <0.05) as compared to the SIN group.

IV. DISCUSSION

PD has several pathologic features, including altered protein homeostasis, mitochondrial dysfunction, nitric oxide production,and neuroinflammation. However, it is unknown how these factors interact to create the disease.The continuing loss of dopaminergic neurons in the substantial nigra (SN) in PD exacerbates the fundamental motor symptoms of resting tremor, bradykinesia, muscle rigidity, and postural instability, which results in dopamine depletion in the striatum. Environmental pollutants, medications, pesticides, age, brain microtrauma,hereditary abnormalities, and localized cerebrovascular injury are among the risk factors for PD(19).
Rotarod apparatus has been used to compare between groups.It has been shown that repeated exposure to rotenone(ROT) substantially decreased muscular coordination (number of rotations, the distance between rotations, and duration between rotations) .Our work results were the same as the results revealed by the study ofAslam et al., 2021(20). In which, administration of ROT-induced muscular rigidity, loss of muscle control, and reduced body movement(5)(20) .
B. Officinalis administration enhanced rotation number, rotation distance, and rotation time while maintaining muscular coordination in the rotarod apparatus as compared to ROT group. This demonstrates that B. Officinalis positively alleviated Parkinson disease(PD) symptoms in rats, particularly in the rats which received 125 mg/kg of plant. Moreover, Both vitro and vivo tests showed B.officinalis to has neuroprotective and antioxidant properties. The antioxidant enzyme activity has been increased, and the extracts decreased the reactive oxygen speies(ROS) production. These properties have been found also in the study of Moliner et al., 2022(13). Furthermore, Phenolic compounds, especially (rosmarinic acid, synergic acid, synaptic acid, rutin, and chlorogenic acid) were found in borage contribute to the antioxidant properties (21).
Compared to animals treated with ROT, the Sinemet group was significantly improved the rotarod performance on day 21 due to the standard levodopa (l-dopa) and carbidopa administration. This might be because of the increased dopamine level , which agrees with the study of Peshattiwar et al., 2020(3). Levodopa has been demonstrated to be the most efficient pharmaceutical treatment for symptoms of PD, increasing lifespan and quality of life. L-dopa might be the best way to PD (22).
Exposure to ROT significantly decreased in the number of line crossings and reduced locomotors activity as compared with rats treated withB. Officinalis at concentrations (62.5,125,250 and 500mg/kg) and Sinemet treated group. Rats exposed to ROT have motor impairments because it destroys dopaminergic neurons in the substantial nigra (SN) region and lowers striatal dopamine levels(8).
In rats treated with B. Officinalis extract concentrations (62.5,125,250 and 500 mg/kg) improved the motor coordination of Parkinsonian rats as compared with the ROT group. As demonstrated instudy ofRabiei and Lorigooini 2016 that medicinal plants' flavonoid and phenolic components could reduced symptoms by blocking the activity of the cholinesterase in the cholinergic system(23).
In sinemet treated group, there was a significant increased in line crossing compared to the ROT group, these findings agree with Maniyath and Solaiappan 2017(24).Treatment with L-dopa enhanced the levels of dopamine and norepinephrine, as well as their metabolites and their production and release. As a result, L-dopa is the main therapy for compensating for decreased dopamine levels in PD (18).
The current study revealed that the MDA level in the rotenone(ROT) group significantly increased compared to the control(healthy) group, these finding were consistent with the findings of Wang et al., 2020(2). Preclinical studies clearly showed that environmental variables such as neurotoxins, insecticides, pesticides, and dopamine induce oxidative stress in Parkinson disease(PD). Oxidative stress has been associated with the development of PD in both preclinical and clinical investigations particularly elevation in the concentration of oxidative markers such MDA. Pesticides like ROT have been proven to increase reactive oxygen species(ROS) by inhibiting mitochondrial complex-1(MC-I) function. This leads to oxidative stress, which might be the cause of α-synuclein

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accumulation (25).

On the other hand, there was a significant decreased in MDA levels in PD-affected the rat groups which were treated with B. Officinalisconcentrations (125,250,500 mg/kg) respectively. The flowers of B. Officinalis are an excellent source of polyunsaturated fatty acids (PUFA), flavonoid (kaempferol) and several polyphenols (caffeic, rosmarinic, and chlorogenic acid) which play a significant role in reducing a wide range of free radicals , reactive oxygen species(ROS) , and preventing lipid peroxidation(21). The mechanism by which PUFA reduces lipid peroxidation appears to include detoxifying peroxy radicals (16). Furthermore, Kaempferol increased catalase, superoxide dismutase(SOD) and glutathione(GSH) levels and decreased the level of lipid peroxidation, indicating its anti-oxidative potential, and might explain its neuroprotective effect (26).Therefore, an oxidative stress inhibitor could be one of the mechanisms of the antiparkinson effects of B. officinalis.

MDA levels significantly increased in the Sinemet treated group as compared to the control group, but less than the ROT group, which agrees with the studyMotawi et al., 2020(27). Treatment with L-dopa caused oxidative stress by significantly lowering glutathione levels and raising MDA levels and oxidized glutathione. Repeated L-dopa administration increases the production of dopamine, which could then result in an excessive free radical generation that overwhelms the body's natural defences and causes an excess of oxidative stress (18).

According to this study, the IL-1β level increased significantly in the rotenone(ROT) group compared to the control (healthy)group. This increased suggested that ROT activates microglia and astrocytes. Nitric oxide and superoxide are free radicals released by activated microglia, and pro-inflammatory marker expression in rats like TNF-α, IL-6, and IL-1β might be increased and triggering various inflammatory cascades. These inflammatory cascades reduce neuronal function, demonstrating the significance of neuroinflammation in neurological conditions like Parkinson's disease, which agrees with the previous study bySharma and Raj 2020(28).

After B. Officinalis treatment, IL-1β levels in the Parkinson's-affected rats significantly decreased at all B. Officinalis treated concentrations as compared with the ROT group. Gamma Linolenic Acid (GLA) has shown to reduce the effects of pro-inflammatory cytokines and pathways like tumor necrosis factor-α(TNF-α), nuclear factor kappa light chain(NF-κB), nitric oxide(NO) production from inducible nitric oxide synthase(iNOS), and production of prostaglandin PG. NF-κB may be responsible for the activation of many inflammatory cytokines and enzymes like iNOS and cyclooxygenase (COX) and activation of many pathways linked with oxidative stress, the decrease in the activity of NF-κB can decrease the production of NO, TNF-α and ROS, thus decreasing the levels of inflammation and oxidative stress in the body(21).

In the Sinemet treated group, IL-1β significantly decreased as compared with the rotenone(ROT) group ,which agrees with a previous study Chen et al., 2021(29).

TAOC levels significantly decreased in ROT group as compared with the control (healthy) group, which is consistent with the earlier study's findings (16).

Dopaminergic neuronal death in the brains of PD patients might be caused by excessive ROS generation in the brain causes more oxidative stress,metabolism of dopamine increased oxidative stress leaded to mitochondrial dysfunction, elevated iron and calcium levels in substantial nigra, and neuroinflammation (30). AfterB.officinalis treatment, a significant increase in TAOC levels was noticed in rats affected by Parkinson'sat concentrations (62.5,125,250 and 500 mg/kg) when compared with the ROT group, especially at plant treated concentration 125mg/kg, which shows a significant increase in TAOC when compared with other treated concentrations of plant. B.officinalisflower exhibited the highest total phenolic and flavonoid contents, especially chlorogenic, caffeic acids and quercetin. Caffeic acid is believed to remove excess reactive oxygen species /reactive nitrogen species generation, and is known to stimulate antioxidative enzyme activities including SOD, GPx and CAT (7).Quercetin, was capable of decreasing the oxidative load on neuronal cells in the striatum as evidenced by increase in total GSH and SOD levels (31).

CONCLUSION

The primary finding of this study is that B. Officinalis is a reliable plant that safely diminishes Parkinsons disease symptoms.According to the study's findings,this plant is beneficial in lowering MDA, IL-1 levelsandincreasing TAOC amounts in brain tissues. As a result, it is strongly advised that people with Parkinson's utilize B. Officinalis as a dietary supplement. Additionally, its extract may be used in conjunction with anti-Parkinson medications.

Declaration

There is no conflict of interest.

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