

## Title: Pharmacological evaluation of the anti-Parkinson activity of leaf extract of *Senna auriculata*: In vivo animal models and In vitro experimental studies

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### Abstract

**Background:** Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra, resulting in motor dysfunction, oxidative stress, neuroinflammation, and impaired quality of life. Current pharmacological therapies primarily provide symptomatic relief and are associated with long-term adverse effects, highlighting the need for safer and more effective therapeutic alternatives. Medicinal plants rich in bioactive phytoconstituents have gained considerable attention because of their antioxidant and neuroprotective properties.

**Objective:** The present study aimed to evaluate the anti-Parkinson potential of the leaf extract of *Senna auriculata* using in vivo experimental animal models and in vitro antioxidant and neuroprotective assays.

**Materials and Methods:** Leaf extract of *Senna auriculata* was subjected to phytochemical evaluation followed by assessment of antioxidant activity using in vitro methods such as DPPH, nitric oxide, and hydrogen peroxide scavenging assays. Anti-Parkinson activity was investigated using established experimental animal models, including haloperidol-induced catalepsy and reserpine-induced Parkinsonism. Behavioral parameters including catalepsy, locomotor activity, muscle rigidity, and motor coordination were evaluated. Biochemical estimations such as superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), malondialdehyde (MDA), and dopamine levels were performed, along with histopathological examination of brain tissues to assess neuroprotection.

**Results:** The leaf extract demonstrated significant antioxidant activity in vitro and improved behavioral performance in Parkinsonian animal models. Treatment significantly reduced catalepsy and motor deficits, restored endogenous antioxidant enzyme levels, decreased lipid peroxidation, preserved dopamine content, and improved neuronal architecture compared with disease control animals, indicating marked neuroprotective activity.

**Conclusion:** The findings suggest that *Senna auriculata* leaf extract possesses promising anti-Parkinson potential through its antioxidant, anti-inflammatory, and neuroprotective mechanisms. The plant may serve as a potential natural therapeutic candidate for the management of Parkinson's disease. However, further molecular investigations and clinical studies are warranted to confirm its efficacy and safety.

**Keywords:** *Senna auriculata*; Parkinson's disease; Neuroprotection; Antioxidant activity; Haloperidol-induced catalepsy; Dopaminergic neurons; Oxidative stress.

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## CHAPTER 1: INTRODUCTION (Part 1)

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized primarily by loss of dopaminergic neurons in the substantia nigra pars compacta and consequent striatal dopamine depletion. Clinically, it produces bradykinesia, resting tremor, muscular rigidity and postural instability, together with non-motor manifestations such as cognitive, mood, sleep, autonomic and olfactory disturbances [1-5].

The burden of PD increases markedly with age and is rising worldwide. Its etiology is multifactorial, involving aging, genetic susceptibility and environmental exposures. Genes including SNCA, LRRK2, PARK2, PINK1 and DJ-1 have been implicated, while pesticides, metals and other neurotoxic exposures are recognized environmental contributors [10-22].

Major pathological mechanisms include oxidative stress, mitochondrial dysfunction, alpha-synuclein aggregation and chronic microglial activation. Reactive oxygen species, lipid peroxidation and pro-inflammatory cytokines promote progressive dopaminergic neuronal injury and provide important targets for neuroprotective intervention [23-31].

Levodopa with carbidopa remains the principal symptomatic treatment, while dopamine agonists, MAO-B inhibitors, COMT inhibitors and amantadine are used as adjuncts. Long-term therapy may be limited by motor fluctuations and dyskinesia, and no currently established treatment reliably halts neurodegeneration [27-31].

Medicinal plants are therefore being investigated as complementary sources of multitarget neuroprotective agents. Flavonoids, alkaloids and related phytoconstituents may reduce oxidative stress, neuroinflammation, mitochondrial dysfunction and apoptosis. *Senna auriculata* was selected for phytochemical, antioxidant and anti-Parkinson evaluation in the present study [32-48].

### Materials and Methods

#### Collection and Authentication of Plant Material

**Plant:** *Senna auriculata*

**Site of collection:**

The plant part of *Senna auriculata* was collected from .....India.

#### Authentication by:

The plant material was authenticated by .....

#### Soxhlet extraction:

*Senna auriculata* leaf powder (100.0 g) was weighed and extracted by ethanol using Soxhlet apparatus. Extraction was performed for 8 cycles and temperature was kept at 65 °C. Solvent was evaporated and extract was further dried at 40 °C for 24 h. Obtained ethanol extract was put in glass vials, sealed and stored at -18 °C prior analysis [116].

#### Extractive yield

After extraction, the filtrate was concentrated and dried to obtain a constant weight of the extract ( $W_2$ ). The weight of the initial dried plant material ( $W_1$ ) was noted. The percentage extractive yield was then calculated using the formula [117]:

$$\% \text{ Yield} = (W_2 / W_1) \times 100$$

#### Preliminary phytochemical screening

**Table 3: Preliminary phytochemical screening for *Senna auriculata* [118,119]**

| Sr . no | Test name                             | Procedure                                                                                                                                        | Observation           |
|---------|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 1.      | Carbohydrates Test A) Fehling's test: | Boiled together 2 ml of extract solution and 2 ml of Fehling's solution (a mixture of Fehling's solution A and B). brick red precipitate formed. | Brick red precipitate |
|         | B) Benedict's test                    | 2ml extract + 0.5 ml benedict's reagent + boiled for 2 min. The                                                                                  | Orange colour         |

|    |                                           |                                                                                                                                                                  |                                       |
|----|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
|    |                                           | solution may be green, yellow, or orange                                                                                                                         |                                       |
| 2. | Alkaloid Test<br>A) Dragendroff's test    | 2-3 ml of test solution and 0.1 ml of Dragendroff's reagent. production of an orange-brown precipitate shows that alkaloids are present                          | Orange-brown precipitate              |
|    | B) Wagner's test                          | 2ml extract + 1-2 drops of Wagner's reagent (along the sides of test tube). The presence of alkaloids is shown by the production of a reddish-brown precipitate. | Reddish brown precipitate             |
| 3. | Glycosides Test<br>A) Keller Killani test | 1 ml extract + 1.5 ml glacial acetic acid + 1 drop of 5 % ferric chloride + conc.H <sub>2</sub> SO <sub>4</sub> . Blue colour formed when test is present.       | Blue colored solution ( in the layer) |

|    |                                           |                                                                                                                                                                               |                             |
|----|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
|    | B) Borntrager's test                      | Add 3 ml of test extract to sulfuric acid, boil, and then filter it. Add the equal quantity of chloroform, shake. The ammoniacal layer turns pink or red when you add ammonia | Pink or red colour          |
| 4. | Flavonoid Test<br>A) Ferric chloride test | Extract solution + few drops 10 % ferric chloride solution. Green ppt may form if test is positive                                                                            | Green precipitate           |
|    | B) Lead acetate test                      | A few drops of 10% lead acetate are added to the test extract. Getting yellow colour                                                                                          | Yellow colour               |
| 5. | Steroids Test<br>A) Salkowski's test      | Extract + few drops of conc. H <sub>2</sub> SO <sub>4</sub> . The reddish-brown color may formed                                                                              | Red colour (in lower layer) |
| 6. | Tannins & Phenolic compounds              | 2 ml of extract mixed with 1 ml of a 5% ferric chloride solution. A deep blue-black colour shows that Tannins & Phenolic                                                      | Deep blue-black colour      |

|  |  |                  |  |
|--|--|------------------|--|
|  |  | compound present |  |
|--|--|------------------|--|

#### TLC for Phytoconstituents [120]

**Table 4: TLC for phytoconstituents**

| Phytoconstituents | Mobile phase               |
|-------------------|----------------------------|
| 1. Alkaloids      | Toluene:<br>Methanol (9:1) |
| 2. Flavonoids     | n Hexane:<br>Ethanol (6:4) |

#### Column Chromatography [121,122]

Column chromatography was performed on silica gel (60-120 mesh) using n-hexane, ethyl acetate and ethanol as eluents. Fractions of approximately 100 mL were collected at a controlled flow rate and screened for phytoconstituents; active fractions were further examined by TLC [121,122].

#### In vivo animal study

##### IAEC Approval

The study protocol was approved by the Institutional Animal Ethics Committee and experiments were performed according to CPCSEA guidelines, with measures to minimize animal suffering.

##### Experimental Animals

Healthy adult Wistar rats (150-250 g) and Swiss albino mice (20-30 g) were maintained under standard temperature, humidity and 12 h light/dark conditions with food and water ad libitum.

##### Acute Oral Toxicity Study

Acute oral toxicity was assessed according to OECD guideline 423. Animals were observed for 14 days after oral dosing for mortality, behavioral changes, body weight, food intake and other signs of toxicity; experimental doses were selected from the tolerated range [123-127].

| Group     | Treatment                            |
|-----------|--------------------------------------|
| Group I   | Normal Control                       |
| Group II  | Disease Control                      |
| Group III | Standard Drug (Levodopa + Carbidopa) |
| Group IV  | Test Drug – Low Dose                 |
| Group V   | Test Drug – High Dose                |

#### Haloperidol-Induced Catalepsy Model

Rats were allocated to normal, disease, standard (levodopa + carbidopa), low-dose and high-dose extract groups. Haloperidol (1 mg/kg, i.p.) induced catalepsy, which was quantified by the bar test; reduced cataleptic duration indicated protective activity [133-137].

#### Reserpine-Induced Parkinsonism Model

Reserpine (5 mg/kg, i.p.) was used to induce Parkinsonian motor deficits. Treated and control groups were assessed for rigidity, hypokinesia, locomotor activity and motor coordination using established behavioral tests [138-142].

#### MPTP-Induced Parkinsonism Model

MPTP was used as a dopaminergic neurotoxic model. Behavioral performance was assessed and brain tissue was subsequently analyzed for dopamine, oxidative stress markers and MAO-B activity to evaluate neuroprotection [143-147].

#### Evaluation of Catalepsy by Bar Test

Catalepsy was quantified as the time required to remove a forepaw from a horizontal bar; longer immobility represented greater Parkinsonian rigidity [148-152].

#### Rotarod Test

Motor coordination and balance were assessed by rotarod retention time; longer retention indicated improved motor performance [153-157].

#### Open Field Test

Spontaneous locomotor and exploratory activity was assessed in an open-field arena using square crossings, rearing and immobility as behavioral indices [158-162].

#### Pole Test

Bradykinesia was evaluated by recording turning and descent times on a vertical rough-surfaced pole; shorter times indicated improved motor function [163-167].

#### Actophotometer Test

Spontaneous locomotor activity was recorded for 5 min with an actophotometer; higher locomotor counts indicated improved dopaminergic motor function [168].

#### Estimation of Lipid Peroxidation (LPO)

Brain lipid peroxidation was estimated as malondialdehyde by the TBARS method at 532 nm; lower MDA reflected reduced oxidative stress [169].

#### Estimation of Reduced Glutathione (GSH)

Reduced glutathione in brain homogenate was estimated with Ellman's reagent at 412 nm; restoration of GSH indicated improved antioxidant defense [170].

#### Estimation of Superoxide Dismutase (SOD)

SOD activity was estimated spectrophotometrically using inhibition of nitro blue tetrazolium reduction; increased activity indicated antioxidant protection [171].

### Estimation of Dopamine Levels

Brain dopamine was estimated after tissue extraction using a spectrophotometric color-development procedure; restoration of dopamine was considered evidence of anti-Parkinson activity [172].

### Estimation of MAO-B Activity

Brain MAO-B activity was estimated spectrophotometrically with an appropriate substrate system; reduced activity was interpreted as a favorable dopaminergic and neuroprotective effect [173].

### Statistical Analysis

All experimental results were expressed as mean  $\pm$  standard error of mean (SEM). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by suitable post hoc test for multiple comparisons using GraphPad Prism software. Values of  $p < 0.05$  were considered statistically significant [174].

### Results and Discussion

#### Collection and Drying of plant

The plant material of *Senna auriculata* was collected from Pune, a region located in Maharashtra, India. The collection was conducted following proper botanical practices and guidelines. It was done in the shade dry at room temperature. After drying, the obtained coarse powder was crushed in a grinder and then passed through a 40-mesh screen to remove the fine particles. The remaining coarse powder was then utilized for the next step.

#### Percentage extractive yield

Table 6: % extractive yield

| Sr. No. | Color      | Nature    | Percentage Yield (% W/W) |
|---------|------------|-----------|--------------------------|
| 1.      | Dark Brown | Semisolid | 15.76 %                  |

The ethanolic leaf extract was a dark-brown semisolid with an extractive yield of 15.76% w/w.

#### Preliminary phytochemical screening

Table 7: Preliminary phytochemical screening for *Senna auriculata*

| Sr. no. | Test name                              | Observation              | Result                |
|---------|----------------------------------------|--------------------------|-----------------------|
| 1       | Carbohydrate s Test A) Fehling's test: | No brick red precipitate | Carbohydrate s absent |

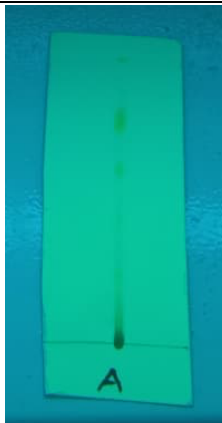
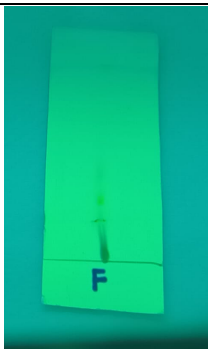
|    |                                        |                                          |                                     |
|----|----------------------------------------|------------------------------------------|-------------------------------------|
|    | B) Benedict's test                     | No orange colour                         | Carbohydrate s absent               |
| 2. | Alkaloid Test A) Dragendroff's test    | Orange-brown precipitate                 | Alkaloids present                   |
|    | B) Wagner's test                       | Reddish brown precipitate                | Alkaloids present                   |
|    | Glycosides Test A) Keller Killani test | No blue colored solution ( in the layer) | Cardiac glycosides absent           |
|    | B) Borntrager's test                   | No pink or red colour                    | Anthraquinone glycosides absent     |
|    | Flavonoid Test A) Ferric chloride test | No green precipitate                     | Flavonoid absent                    |
|    | B) Lead acetate test                   | Yellow colour                            | Flavonoid present                   |
|    | Steroids Test A) Salkowski's test      | No red colour (in lower layer)           | Steroids absent                     |
|    | Tannins & Phenolic compounds           | No deep blue-black colour                | Tannins & Phenolic compounds absent |

Qualitative screening showed prominent alkaloids and flavonoids, whereas carbohydrates, glycosides, steroids, tannins and phenolic compounds were not detected in the reported tests.

#### TLC for Phytoconstituents

Table 8: TLC for phytoconstituents

| Phytoconstituents | Rf value | TLC plate image |
|-------------------|----------|-----------------|
|-------------------|----------|-----------------|

|               |       |                                                                                   |
|---------------|-------|-----------------------------------------------------------------------------------|
| a) Alkaloids  | 0.875 |  |
| b) Flavonoids | 0.530 |  |

#### Phytochemical tests for fractions

Table 9: Phytochemical tests for fractions of column chromatography

| S r. n o | Test name                          | n-Hex ane | n-Hex ane: Eth yl acet ate | Eth yl acet ate | Etha nol: Ethy l acet ate | Eth anol |
|----------|------------------------------------|-----------|----------------------------|-----------------|---------------------------|----------|
| 1        | Carbohy drates Test Fehling's test | -         | -                          | -               | -                         | -        |
|          | Benedic t's test                   | -         | -                          | -               | -                         | -        |
| 2        | Alkaloid Test Dragend roff's test  | -         | +                          | +               | +                         | +        |
|          | Wagner's test                      | -         | +                          | +               | +                         | +        |

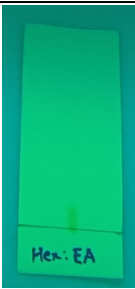
|   |                                      |   |   |   |   |   |
|---|--------------------------------------|---|---|---|---|---|
| 3 | Glycosi des Test Keller Killani test | - | - | - | - | - |
|   | Borntra ger's test                   | - | - | - | - | - |
| 4 | Flavono i d T e s t                  | - | - | - | - | - |
|   | Ferric chloride test                 | - | - | - | - | - |
| 5 | Lead a c e t a t e t e s t           | - | - | + | - | - |
|   | Steroids Test Salkows ki's test      | - | - | - | - | - |
| 6 | Tannins & Phenolic compou nds        | - | - | - | - | - |

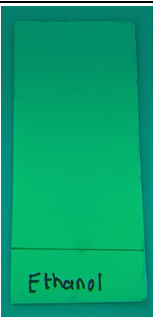
Fraction screening showed alkaloids in several medium-to-polar fractions and flavonoids mainly in the ethyl acetate fraction.

#### TLC for active fractions

Table 10: TLC for active fractions

| Phytoconstituents | Rf valu e | TLC plate image |
|-------------------|-----------|-----------------|
|-------------------|-----------|-----------------|

|                                                             |           |                                                                                     |
|-------------------------------------------------------------|-----------|-------------------------------------------------------------------------------------|
| <b>a) n-Hexane:</b><br><b>Ethyl acetate</b><br>1. Alkaloids | 0.17<br>0 |    |
| <b>b) Ethyl acetate</b><br>1. Alkaloids                     | -         |    |
| 2. Flavonoids                                               | 0.11      |   |
| <b>c) Ethanol:Ethyl acetate</b><br>1. Alkaloids             | -         |  |

|                                   |   |                                                                                     |
|-----------------------------------|---|-------------------------------------------------------------------------------------|
| <b>d) Ethanol</b><br>1. Alkaloids | - |  |
|-----------------------------------|---|-------------------------------------------------------------------------------------|

TLC supported fractionation of alkaloids and flavonoids, with reported Rf values dependent on the selected solvent systems.

#### In vivo animal study

##### Acute Oral Toxicity Study

The acute oral toxicity study of *Senna auriculata* leaf extract was performed according to OECD guideline 423. The extract was administered orally at different dose levels, and animals were observed for mortality and toxic manifestations for a period of 14 days.

At the dose level of 1000 mg/kg, one animal died on the 7th day of observation. At the dose level of 2000 mg/kg, two animals died on the 5th day after administration of the extract. Animals treated with higher doses also showed signs of reduced locomotor activity, mild lethargy, and decreased food intake. Based on the toxicity observations, the extract was considered relatively safe at lower dose levels. Therefore, 1/10th and 1/5th of the safe dose were selected as experimental doses for pharmacological studies. Hence, 200 mg/kg and 400 mg/kg body weight were selected as low and high doses respectively for evaluation of anti-Parkinson activity.

##### Effect of *Senna auriculata* Leaf Extract on Haloperidol-Induced Catalepsy

##### Figure 15: Effect of *Senna auriculata* Leaf Extract on Haloperidol-Induced Catalepsy

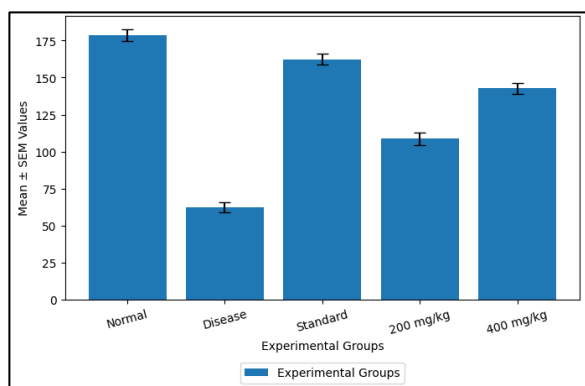


Figure 16: Effect of *Senna auriculata* Leaf Extract on Rotarod Performance

Figure 20: Effect of *Senna auriculata* Leaf Extract on Brain Lipid Peroxidation Levels

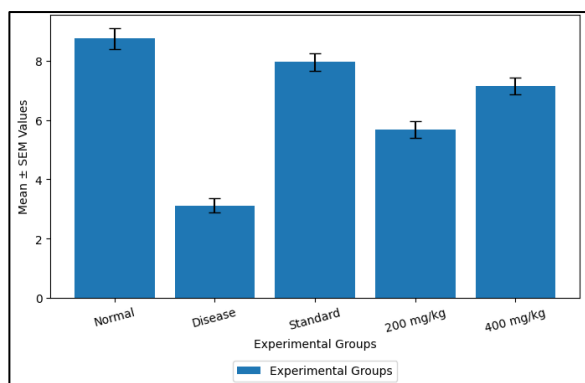


Figure 21: Effect of *Senna auriculata* Leaf Extract on Brain GSH Levels

Figure 23: Effect of *Senna auriculata* Leaf Extract on Brain Dopamine Levels

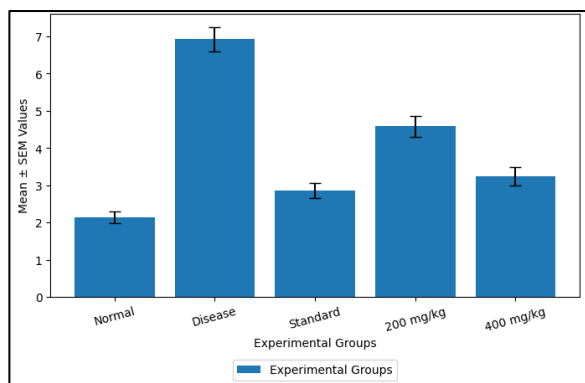


Figure 24: Effect of *Senna auriculata* Leaf Extract on Brain MAO-B Activity

## Reserpine-Induced Parkinsonism Model Effect of *Senna auriculata* Leaf Extract on Open Field Activity

Figure 25: Effect of *Senna auriculata* Leaf Extract on Open Field Activity in Reserpine-Induced Parkinsonism

## Effect of *Senna auriculata* Leaf Extract on Locomotor Activity Using Actophotometer

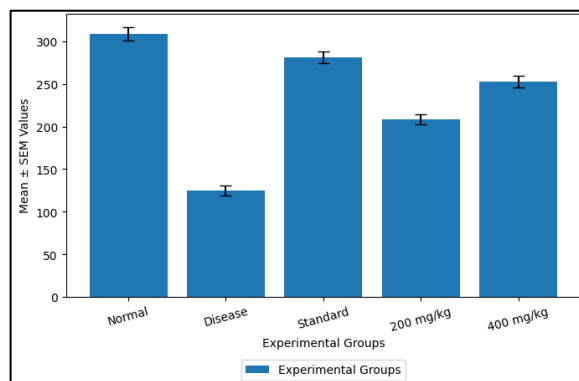


Figure 26: Effect of *Senna auriculata* Leaf Extract on Locomotor Activity in Reserpine-Induced Parkinsonism

## MPTP-Induced Parkinsonism Model Effect of *Senna auriculata* Leaf Extract on Pole Test Performance

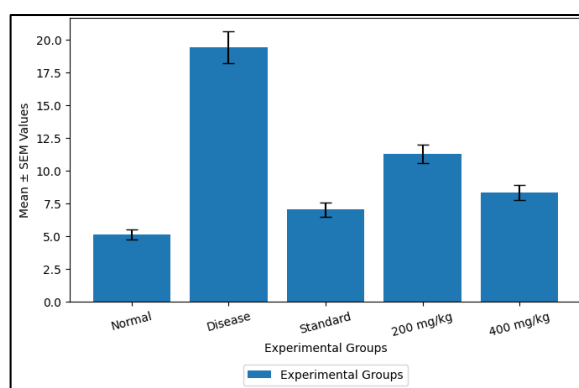


Figure 29: Effect of *Senna auriculata* Leaf Extract on Pole Test in MPTP-Induced Parkinsonism

### Effect of *Senna auriculata* Leaf Extract on Brain Dopamine Levels

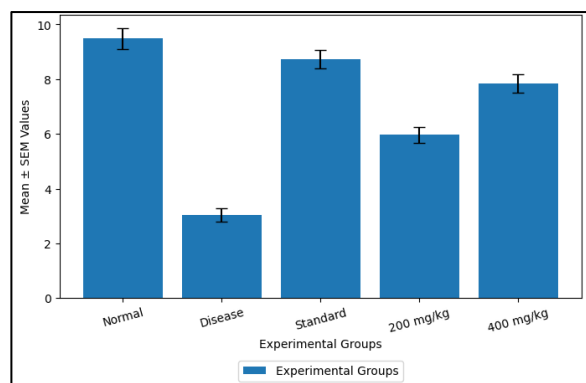


**Figure 30: Effect of *Senna auriculata* Leaf Extract on Brain Dopamine Levels in MPTP-Induced Parkinsonism**

### Effect of *Senna auriculata* Leaf Extract on Brain MAO-B Activity

#### 7.7.4.6 Effect of *Senna auriculata* Leaf Extract on Superoxide Dismutase (SOD) Activity

#### Discussion

The present study demonstrated that the leaf extract of *Senna auriculata* possesses significant anti-Parkinson and neuroprotective activity in experimental models of Parkinsonism. Preliminary phytochemical analysis confirmed the presence of alkaloids and flavonoids, while column chromatography indicated that the ethyl acetate fraction contained the highest concentration of these bioactive constituents. These phytochemicals are well recognized for their antioxidant, anti-inflammatory, and neuroprotective properties, which may collectively contribute to the observed pharmacological effects.

In the in vivo studies, treatment with *Senna auriculata* significantly improved motor function in haloperidol-, reserpine-, and MPTP-induced Parkinsonian models. The extract effectively reduced catalepsy, enhanced locomotor activity, and improved motor coordination in a dose-dependent manner. These findings indicate that the extract protects dopaminergic neuronal function and attenuates motor deficits associated with dopamine depletion. The higher dose (400 mg/kg) produced effects comparable to the standard treatment with Levodopa + Carbidopa, suggesting considerable therapeutic potential.

Biochemical investigations further supported these observations by demonstrating a significant reduction in lipid peroxidation and MAO-B activity, along with increased levels of endogenous antioxidant enzymes such as SOD and GSH. Restoration of brain dopamine levels indicates preservation of dopaminergic neurons

and improved neurotransmission. In addition, the in vitro antioxidant assays confirmed strong free radical scavenging activity, supporting the role of antioxidant mechanisms in the neuroprotective effects of the extract.

Overall, the findings suggest that *Senna auriculata* exerts anti-Parkinson activity through multiple mechanisms, including antioxidant defense, reduction of oxidative stress, inhibition of MAO-B activity, and preservation of dopaminergic neurons. These results scientifically support its traditional medicinal use and highlight its potential as a promising herbal therapeutic agent for the management of Parkinson's disease.

### Conclusion

The present investigation demonstrated that the leaf extract of *Senna auriculata* possesses significant anti-Parkinson and neuroprotective activity in both in vivo and in vitro experimental studies. Phytochemical screening confirmed the presence of important bioactive constituents, particularly alkaloids and flavonoids, which are likely responsible for its pharmacological activity. The extract significantly improved behavioral parameters, including catalepsy, locomotor activity, and motor coordination, in haloperidol-, reserpine-, and MPTP-induced Parkinsonian models. Furthermore, it restored brain dopamine levels, reduced lipid peroxidation and MAO-B activity, and enhanced endogenous antioxidant defenses by increasing SOD and GSH levels. The in vitro antioxidant assays also demonstrated marked free radical scavenging activity, supporting its neuroprotective potential.

Among the tested doses, 400 mg/kg produced greater therapeutic effects and showed activity comparable to the standard drug Levodopa + Carbidopa. These findings indicate that the anti-Parkinson effect of *Senna auriculata* is primarily mediated through antioxidant, anti-inflammatory, and dopaminergic neuroprotective mechanisms. Therefore, the study scientifically validates the traditional use of *Senna auriculata* and suggests that it may serve as a promising natural therapeutic candidate for the management of Parkinson's disease. Further preclinical and clinical investigations are warranted to establish its long-term efficacy and safety.

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