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Research Article
Neuroprotective Potential of *Swietenia macrophylla* Seed Extract in Lead-induced Neurodegeneration in Albino Rats

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Abstract

Background and Objective: Neurodegeneration is a critical conditions that rising social and economic issue with consequent decrease in the quality of life in developing countries. Due to increasing life expectancy, the incidence of neurodegeneration increased over the years and still has been under research. This study evaluated the neuroprotective activity of *Swietenia macrophylla* seed extract in lead-induced neurodegeneration in albino rats. **Materials and Methods:** *Swietenia macrophylla* seed extract (SMSE) was prepared in a solvent mixture of water and methanol (4:6) through the cold maceration method. Albino Wistar rats (180±20 g) of either sex were used in this study, all rats randomly divided into 5 groups (n = 6) such as Group 1 served as normal control (administered 0.9% saline); Group 2 rats treated with lead acetate (20 mg kg^{-1} i.p.); Group 3 and 4 rats were orally treated with a low dose of SMSE (50 mg kg^{-1}) and a high dose of SMSE (100 mg kg^{-1}), respectively after induction of neurodegeneration by lead and Group 5 rats served as a standard control (administered Donepezil 2.5 mg kg^{-1}) after lead-induced neurodegeneration. The parameters such as spatial learning and memory, serum nitrate and lead concentration, TNF-α level in brain homogenate and antioxidant enzymes were assessed. **Results:** The effect of SMSE 100 mg kg^{-1} shows excellent improvement in behavioural activity with significant (**$p<0.05$) improvement in the level of nitrate concentration and reduction in lead concentration as compared to disease control. The lead acetate markedly causes increase GSH, SOD level and reduces CAT, T-BARS. The administration of SMSE 100 mg kg^{-1} shows significant (**$p<0.05$) improvement in these elevated parameters, while the Donepezil group shows a little improvement. **Conclusion:** The protective effect of the SMSE at a dose of 100 mg kg^{-1} was more effective and significantly improves the elevated parameters induced by lead in rats.

Key words: *Swietenia macrophylla*, lead acetate, neurodegeneration, donepezil, T-BARS, TNF-α, nitrate

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The term "neurodegeneration" may probably valuable to several conditions that result in the loss of nerve structure and function which lead to progressively causes a loss of cognitive abilities like memory, learning and decision making[1]. Some critical consideration has been largely centred on just grouped as the majority and extremely named like Parkinson's disease, Huntington disease and Alzheimer's disorder. This worsening condition progressively causes brain injury and lead to neurodegeneration[2]. Although these three diseases manifest with different clinical features, the disease processes at the cellular level with a similar appearance[3].

It is reported that the Parkinson's disease affects the basal ganglia of the brain and depleting the dopamine, which leads to the typical features like stiffness, rigidity and tremors within the major muscles of the body[4,5]. Whereas in Alzheimer's disease, the deposition of tiny protein plaques injured different parts of the brain and causes progressive loss of memory[6]. Huntington's disease may know as a progressive inherited disorder that affects major muscles of the body leading to severe motor restriction. The other disorders like dementias presenting approximately 60-70% burden of neurodegenerative diseases[7]. The most common symptoms of neurodegenerative diseases are memory loss, forgetfulness, apathy, anxiety, agitation, loss of inhibition, mood changes disability[1].

Neurodegenerative could be serious and life-threatening that depends on the disease condition in which some has non-curable but treatments may help to cure symptoms, relieve pain and increase mobility. Neurodegenerative diseases affect various bodies' activities such as balance, movement, talking, breathing and heart function. Sometimes, it may be happens due to the genetic defect causing neurodegeneration[8].

Swietenia macrophylla King is a big plant belonging to the family Meliaceae commonly known as big-leaf mahogany, sky-fruit that highly used to treat diabetes and high blood pressure. The seed has been reported to have anti-inflammatory, anti-mutagenic, antitumor activities, effective against diabetes and other traditional benefits like anti-pyretic, anti-fungal and anti-hypertensive properties[9]. In Malaysia, these seeds are chewed or pounded and swallowed to treat high blood pressure; whereas in India, it is used to manage both diabetes and hypertension[10]. Patient with neurodegeneration continuously progresses mild to moderate memory impairment that leads to Alzheimer, Parkinson and dementia. To suppress this disorder, the study has been designed to investigate the neuroprotective potential of *Swietenia macrophylla* seed extract in lead-induced neurodegeneration in Albino rats and also explain the mechanism underlying these properties.

MATERIALS AND METHODS

The research work was conducted in the month of March-April, 2018 for the duration of 42 days of the study at Hygia Institute of Pharmaceutical Education and Research, Prabandh Nagar, Lucknow, India.

Animals: Adult albino Wistar rats having weight 180-200 g were obtained from the Institute's Animal House. The animals were separately housed in polypropylene cages and acclimatization for 7 days under the standard environmental condition with a 12 h light-dark cycle and had free access to the pellet diet and water *ad libitum*. The study was conducted after approval of experimental protocol from the IAEC committee (Reference No. HIPER/IAEC/15/18/04) of the Institute and the official guidelines framed by the CPCSEA was followed during performing the experiment.

Collection and extraction of plant material: The fresh shad dried sky fruit seed was brought from Prem Industries No. 13 LIG 1st Floor D1 Thiruvalluvar Salai, NH-1, Maraimalai Nagar, Kancheepuram (FSSAI approved; licensed under Tamil Nadu FDA). Seeds were dried in an incubator for 2 h at 40°C, crushed in an electric grinder and then pulverized. About 50 g powder was suspended in the mixture solvent comprising of 80 mL water and 120 mL methanol and the mixture was kept in an incubator at 37°C for 48 h. The mixture was stirred intermittently at every 2 h interval. The mixture was filtered and concentrated by the rotatory evaporator. Concentrated extract was freeze-dried to get the dried powder and subsequently stored in a closed container at room temperature[11,12].

Chemicals and preparation of stock solution: Chemicals (LR grade) were purchased from Corning Technologies India Pvt., Ltd., Gurgaon. The standard drug Donepezil tablet (Alzil 10 mg) was purchased from the local pharmacy.

The following stock solution was prepared for the study: Solution of NaCl (0.9% w/v); Lead acetate (0.05% w/v) and Donepezil (0.05% w/v) were prepared in distilled water. *Swietenia macrophylla* seed extract (SMSE) powder 10 g was dissolved in 100 mL distilled water with vigorous shaking and stored in an amber color bottle with an appropriate label.

Phytochemical analysis: The preliminary phytochemical analysis of Swietenia macrophylla seed extract was used for preliminary qualitative screening of phytochemical such as

alkaloids (Dragendorff test and Mayer's test), tannins (Ferric chloride test), flavonoids (HCL test and lead acetate test), glycosides (Fehling's test and Glacial acetic acid test), terpenoids and steroids (H_2SO_4 test), saponins (Foam test), fixed oil (Spot test), amino acids and proteins (Ninhydrin test and copper sulphate test) and terpenes (Liebermann-Burchard)[13].

Experimental design: All the rats were divided into 5 groups containing 6 animal each (n = 6) and treated as per the experimental designed mentioned:

Group 1 : Normal control only administered with 0.9% saline for 42 days

Group 2 : Disease control rats were administered with Lead acetate 20 mg kg^{-1}/day i.p. for 7 days prior to the commencement of study to develop neurodegeneration and fed with free access of standard diet

Group 3 : Diseased rats treated with a low dose of test drug (SMSE) 50 mg kg^{-1}/day oral

Group 4 : Diseased rats treated with a high dose of test drug (SMSE) 100 mg kg^{-1}/day oral

Group 5 : Diseased rats treated with the standard drug (Donepezil) 2.5 mg kg^{-1}/day oral for the rest of 35 days

Pharmacological analysis: All the groups of the animal were used to assess spatial learning and memory activity by using rota rod, elevated plus maze, photoactometer, williams maze and morris water for the measurement of neuroprotective activity.

Biochemical analysis: Serum nitrate and lead concentration were measured at the end of the study by the spectrophotometer determined by the method of Giustarini *et al.*[14] and another method by Sastry *et al.*[15]. The concentration of TNF-α in brain homogenate was also measured at the end of the study by ELISA Method for quantitative determination described by Rendevski *et al.*[16]. The anti-oxidant enzymes such as acetylcholinesterase (AChE), malondialdehyde (MDA), lipid peroxidation (LPO), thiobarbituric acid reactive substances (TBARS), superoxide dismutase (SOD), catalase (CAT) activity, nitric oxide (NO) and reduced glutathione (GSH) content in brain homogenate was measured by using the kits under auto analyzer determined by the method of Weydert and Cullen[17].

Brain histopathology: The assessment of histopathological was performed in rats' brain by randomly selected from each group. The brain was removed carefully and immediately fixed in 10% phosphate-buffer solution, embedded in paraffin and 5 µm longitudinal sections were prepared by the microtome. The sections of the brain were stained with haematoxylin and eosin (H and E) for a clear picture of the thin section and examined under the light microscope[18].

Acute oral toxicity study: The toxicity of the extract was studied as per organization for economic co-operation and development (OECD) guideline number 423. Rats were administered at a dose of 2000 mg kg^{-1} b.wt., of SMSE prepared with water as recommended in the guideline. After the administration of drugs, each animal was observed every alternate hour for signs of toxicity and abnormality in behaviour up to the 48th h. After this, daily observations for toxicity and mortality were concluded up to the 14 days. The body weight of the animals was recorded every 3rd day. At the end of the study, all the rats were sacrificed and processed for gross necropsy[19].

Statistical analysis: All the experimental data have been expressed as the Mean±SEM (n = 6). The statistical analysis was performed by One-way ANOVA followed by Bonferroni-compare selected pairs of the column by graph pad prism software. The value $^{\#}p<0.05$ statistically significant against normal control and $^{**}p<0.05$ statistically significant against disease control.

RESULTS

Phytochemical analysis: The hydro-alcoholic extract of *Swietenia macrophylla* seed contained the alkaloids, terpenoids, amino acids, proteins, tannins, flavonoids, saponins, carbohydrate, steroids and a smaller amount of volatile oils (Table 1).

Table 1: Phytoconstituents in the *S. macrophylla* seed extract

Phytoconstituents	Seed extract
Alkaloids	++
Tannins	++
Steroids	++
Terpenoids	++
Flavonoids	+
Saponins	+
Carbohydrate	++
Glycosides	–
Amino acid	+
Proteins	+
Volatile oils	+

-: Negative, +: Positive, ++: Strong positive result

Pharmacological analysis: The behavioural activities of the animal were examined as follows:

- **Rota-rod activity:** The time spend by the rat on rota-rod showed memory deficit in disease group seeing as significant ($^{\#}p<0.05$) decrease in time spend as compared to normal control. The low dose (SMSE 50 mg kg^{-1}) treatment group shows a little increased in time, while the high dose (SMSE 100 mg kg^{-1}) and standard drug (Donepezil 2.5 mg kg^{-1}) treated group showed better improvement in time spend by rat against disease control (Fig. 1)
- **Morris Water Maze (MWM):** The low dose of SMSE (50 mg kg^{-1}) treated group showed significant (**p<0.05) decrease in time to search platform that shows a little improvement in memory as compared to disease group, while the high dose of SMSE (100 mg kg^{-1}) and standard control (Donepezil 2.5 mg kg^{-1}) showed highly significant (**p<0.05) decrease in time, which was the sign of excellent improvement in the memory as compared to disease group (Fig. 1)
- **Photoactometer:** The animal treated with lead acetate shows statistically significant ($^{\#}p<0.05$) decreased in time spend on Photoactometer. The high dose of SMSE (100 mg kg^{-1}) treated rats showed highly significant (**p<0.05) improvement in locomotors activity as compared to disease control and other treatment groups (Fig. 2)
- **Williams maze:** Lead acetate caused memory deficit spend more time to reach near to the food, which was statistically significant ($^{\#}p<0.05$) as compared to normal control. The rat treated with the SMSE 50 and 100 mg kg^{-1} observed that they spend equal time to reach near the food, while the rat treated with Donepezil 2.5 mg kg^{-1} spend less time that shows highly significant (**p<0.05) improvement as compared to disease control (Fig. 2)
- **Elevated plus maze:** The disease control rat takes more time to spend in the close arm and less time spent in open arm as compare to normal control. The low dose of SMSE (50 mg kg^{-1}) shows lesser time spend in the closed arm as compared to disease group, while the high dose of SMSE (100 mg kg^{-1}) spend very less time in closed arm that shows highly significant (**p<0.05) improvement and more effective as compared to disease control. The standard drug treatment group shows non-significant improvement in time spend on elevated plus maze as compared to disease control (Fig. 3)

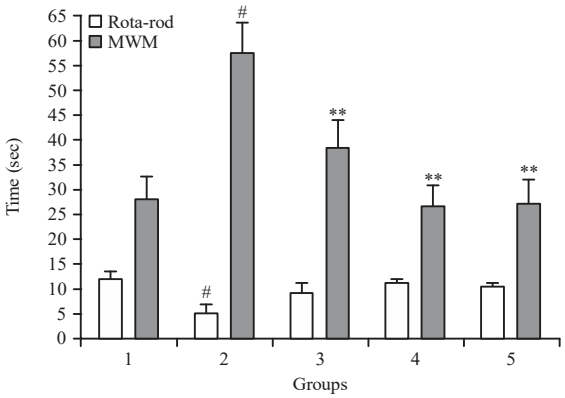

Fig. 1: Behavioural activity of rats by using Rota-rod and MWM apparatus

Data are expressed as Mean±SEM (n = 6), $^{\#}p<0.05$ statistically significant against normal control, **p<0.05 statistically significant against disease control

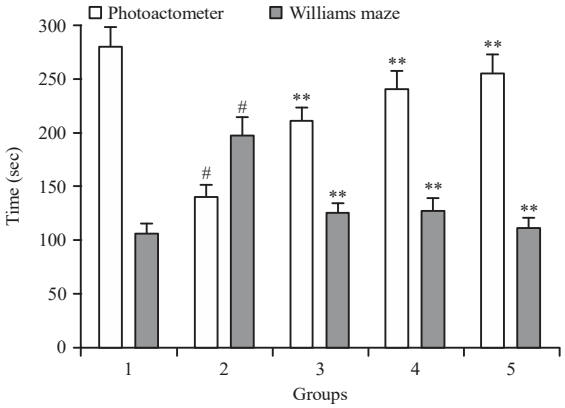

Fig. 2: Behavioural activity of SMSE and donepezil on photoactometer and WM apparatus

Data are expressed as Mean±SEM (n = 6), $^{\#}p<0.05$ statistically significant against normal control, *p<0.05 statistically significant against disease control

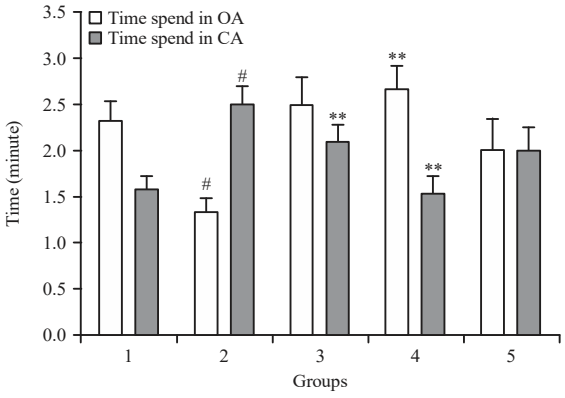

Fig. 3: Behavioural activity of SMSE and donepezil on elevated plus maze apparatus

Data are expressed as Mean±SEM (n = 6), $^{\#}p<0.05$ statistically significant against normal control, **p<0.05 statistically significant against disease control, OA: Open arm, CA: Close arm

Table 2: Effect of SMSE and donepezil as the biochemical test in the serum sample

Activity	Nitrate concentration (μM L^{-1})	Lead concentration (μg dL^{-1})	TNF-α (ng mL^{-1}) concentration
Group 1	12.72±0.20	13.50±0.18	1.33±0.26
Group 2	6.80±0.25#	86.22±0.51#	2.01±0.16
Group 3	8.54±0.53**	53.80±2.34**	1.63±0.18
Group 4	10.34±0.32**	20.43±0.72**	1.40±0.19
Group 5	11.01±0.12**	18.92±0.91**	1.35±0.24

Data are expressed as Mean±SEM (n = 6), #p<0.05 statistically significant against normal control, **p<0.05 statistically significant against disease control

Table 3: Effect of SMSE and donepezil as antioxidants in lead-induced neurotoxicity

Groups	MDA (nmol mg^{-1} of protein)	NO (μmol g^{-1} protein)	SOD (U g^{-1})	GSH (μM mg^{-1} of protein)
Group 1	20.90±2.26	80.18±6.59	610.39±7.94	18.11±1.77
Group 2	57.00±10.08#	108.33±8.84#	445.33±6.50#	6.57±1.06#
Group 3	39.50±6.53	90.83±6.36	515.42±9.62	10.17±1.07
Group 4	33.50±5.32**	87.04±3.02**	533.62±8.96**	13.12±1.90**
Group 5	29.62±2.64**	85.04±3.40**	574.76±10.80**	15.17±3.34**

Data are expressed as Mean±SEM (n = 6), #p<0.05 statistically significant against normal control, **p<0.05 statistically significant against disease control

Table 4: Effect of SMSE and donepezil on enzymes as AchE, CAT, T-BARS

Groups	AchE (μM mg^{-1} protein)	CAT (μg g^{-1} protein)	T-BARS (nM mg^{-1} protein)
Group 1	4.07±1.12	119.25±5.42	4.30±0.96
Group 2	17.67±2.98#	96.50±6.13#	12.67±3.35#
Group 3	9.13±0.45	106.14±6.41	9.91±0.98
Group 4	6.88±0.50**	112.05±6.26**	8.22±0.75**
Group 5	5.00±0.54**	115.75±10.42**	6.81±0.52**

Data are expressed as Mean±SEM (n = 6), #p<0.05 statistically significant against normal control, **p<0.05 statistically significant against disease control

Estimation of biochemical parameters: The oral administration of a high dose of SMSE (100 mg kg^{-1}) and donepezil (2.5 mg kg^{-1}) groups shows significant (**p<0.05) improvement in the level of nitrate concentration and significant (**p<0.05) reduction in the level of lead concentration, while the level of TNF-α was non-significant as compared to disease control and other treatment group (Table 2).

Estimation of antioxidant enzymes: The disease group showed statistically significant (#p<0.05) increase in MDA and NO concentration but decreased GSH and SOD level observed in brain homogenates as compared to normal control. The rats treated with a high dose of SMSE (100 mg kg^{-1}) and donepezil (2.5 mg kg^{-1}) showed statistically significant (**p<0.05) improvement as compared disease control (Table 3).

The other antioxidant enzymes such as AchE, CAT, T-BARS reveals that the rats treated with lead acetate showed significant (#p<0.05) increase in Ach and T-BARS concentration but decreased level of CAT as compared to normal group. The rats treated with a high dose of SMSE (100 mg kg^{-1}) and Donepezil (2.5 mg kg^{-1}) showed statistically significant (**p<0.05) improvement in these elevated parameters as compared disease control (Table 4).

Histological analysis: The histological changes were observed in the rat's brain of the control group exhibited the normal appearance of the pyramidal layer with normal pyramidal cells. The lead-exposed rats showed distinctive pathologic alterations such as a distortion of the pyramidal layer, abnormal vasculation, necrotic cells, abnormal nerve fibers in some areas and some degenerated pyramidal cell. Evidence shows that the changes with disease control were widespread and neurotoxin. The hydro-alcoholic extract of SMSE at a dose of 50 and 100 mg kg^{-1} dramatically reduced lead-induced neurotoxicity as evidenced by normal vasculation, nerve fibers, small number of established pyramidal cell and in hippocampus region normal appearance of the pyramidal layer observed as similar to those of the normal control group. The donepezil 2.5 mg kg^{-1} treated rat showing the normal vasculation and nerve fibers but a little degenerated pyramidal cells that could not achieved the normal structure as compare to SMSE (100 mg kg^{-1}) treated group (Fig. 4).

DISCUSSION

The study observed that the effect of SMSE 100 mg kg^{-1} shows excellent improvement in memory (escape latency behaviour), locomotors activity[20] and other elevated maze

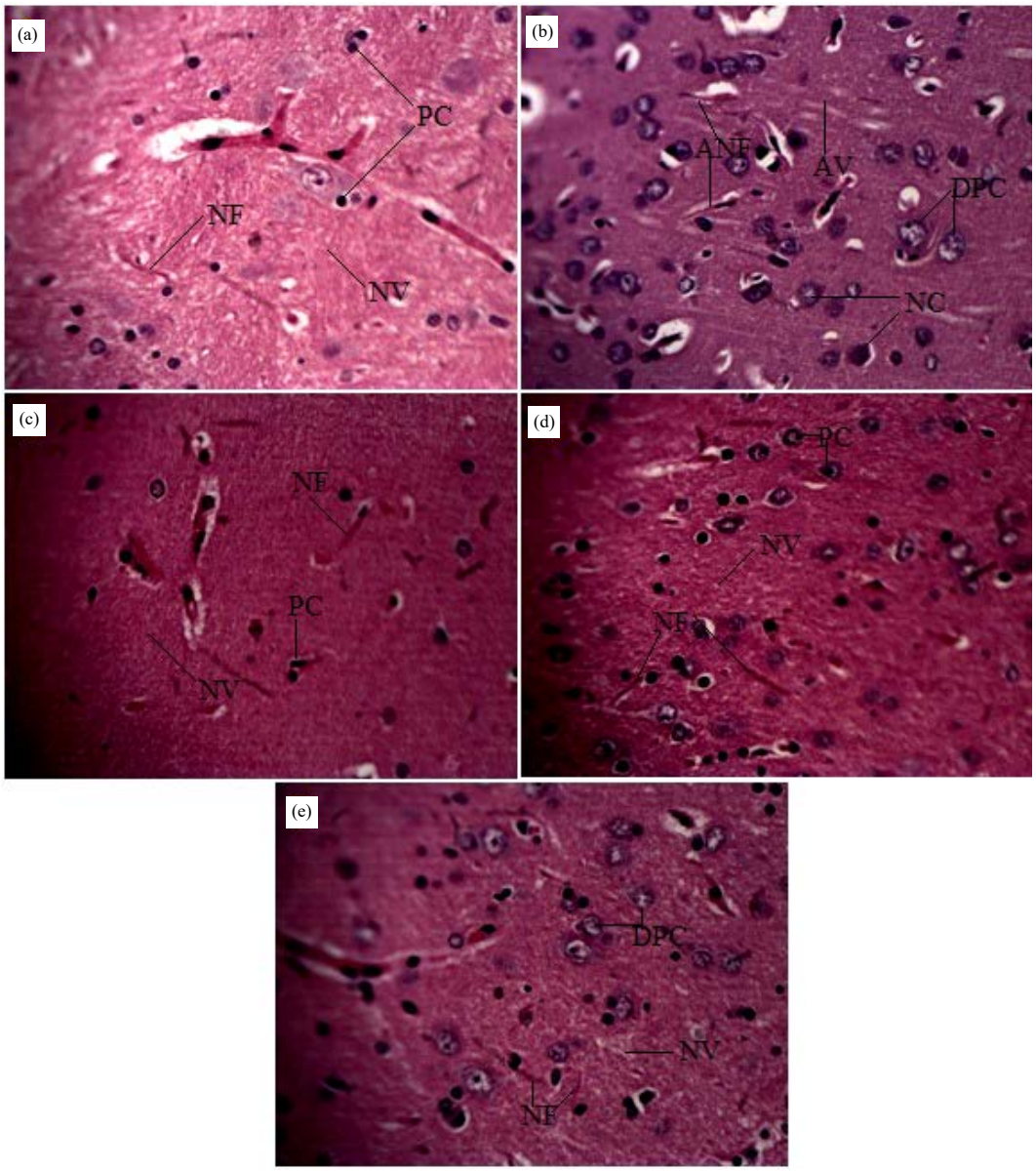

Fig. 4(a-e): Brain histopathology of all experimental groups at 40×, (a) Normal control group, (b) Disease group (lead acetate 20 mg kg^{-1}), (c) Treatment with low dose of SMSE (50 mg kg^{-1}), (d) Treatment with high dose of SMSE (100 mg kg^{-1}) and (e) Standard drug (Donepezil 2.5 mg kg^{-1}) treated rat

PC: Pyramidal cells, NV: Normal vasculation, NF: Nerve fibers, AV: Abnormal vasculation, ANF: Abnormal nerve fibers, DPC: Degenerated pyramidal cell, NC: Necrotic cells

activity with statistically significant (**$p<0.05$) improvement in the level of nitrate concentration and reduction in lead concentration as compared to disease control. The lead acetate markedly causes increase GSH, SOD level and reduces CAT, T-BARS. The administration of SMSE 100 mg kg^{-1} shows significant (**$p<0.05$) improvement in these elevated parameters. These changes suggested that the neuroprotective effect of SMSE on lead-induced memory and cognitive impairment may be related to the mediation of the cholinergic nervous system[21]. The phytoconstituents present in *S. macrophylla* seed extract i.e., tannins, saponins, flavonoids and alkaloid possess admirable neuroprotective activity. The lead-induced oxidative damage observed by reducing anti-defense at the cellular level mechanism response in the central nervous system such as nitrate concentration, lead concentration and TNF-α level[22].

The SMSE directly induces microglial activation, diminishing inflammatory cascades, directly decrease the pro-inflammatory effect of TNF-α in neurons, including the reduction in lead accumulation in β-amyloid cells, decreased the accumulation of microglia, activation of anti-oxidant enzymes, ROS suppression, improve the synthesis of hems that inhibited by the lead acetate[23]. These changes occurred due to the presence of phenolic acids, flavonoids and tannins that possess tremendous antioxidant activity[24]. Histological examination of brain tissue revealed that the rat treated with a dose of SMSE 100 mg kg^{-1} shows the reduction of pericellular and perivascular edema in the brain as normal control, the accumulation of the β-amyloid, the blood vessels, accumulation of microglia and gliosis has been disappeared[25]. The donepezil 2.5 mg kg^{-1} treated rat showed almost comparable changes as compared to the normal control. However, the neuroprotective potential of *S. macrophylla* is still uncertain and will required prospective study on large animal to explore the exact mechanism for its action.

CONCLUSION

Finally, it was concluded that the protective effects *Swietenia macrophylla* seed extract capable of reducing free radical damage by directly acting as a free radicals scavenger and by indirectly stimulating antioxidant enzyme activities. Evidence from the biochemical analysis ascertains supported by histological study confirms that the SMSE 100 mg kg^{-1} has the potent neuroprotective properties in rats. Although further studies needed to intensify the exact molecular mechanisms of *S. macrophylla* seed extract as neuroprotective potential.

SIGNIFICANCE STATEMENT

The protective activity of *Swietenia macrophylla* seed against lead-induced neurotoxicity endorsed by its ability to scavenging free radicals that generated by lead acetate, therefore, it was confirmed that the *Swietenia macrophylla* seed could be moderately useful in neurotoxicity. The present study may capable in the development of novel strategies for the prevention of the neurodegenerative disorder. Thus, a new herbal therapy may arrive for such types of patients that did not bear a conventional therapy and hospital burden.

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