Evaluation of effect of *Madhuca longifolia* against Lipopolysaccharide-Induced neuro-inflammation in Alzheimer's disease in Mice

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Abstract

The Sapotaceae family includes the evergreen plant Madhuca longifolia, commonly referred to as the butternut tree or Mahua. At almost 17 meters, it is remarkably tall. This tree, which is indigenous to India, Sri Lanka, and Nepal, is well known for containing a variety of chemical components that provide it many medicinal advantages. The purpose of the current study was to assess the impact of Madhuca longifolia fruit ethanolic (EEML) extract on rats with LPS-induced Alzheimer's disease. Tests for behavioural and memory deficits were conducted in addition to several biochemical analyses, such as the levels of SOD, GSH, and catalase in brain tissue. The results suggest that EEML extract may have neuroprotective properties to improve cholinergic cognitive dysfunctions in Alzheimer's disease.

Keywords: *Madhuca longifolia, Alzheimer's disease, Cognitive Skills, Learning and Memory.*

1. Introduction

The widespread neurodegenerative disease known as Alzheimer's disease (AD) is a protein misfolded disease brought on by an accumulation of abnormally folding tau and A-beta proteins in the brain. AD affects approximately 50 million people worldwide and has grown to be a significant medical and social burden; by 2050, it will affect nearly 152 million people. It is characterized by significant memory loss, cognitive impairment, and personality disorders along with diffuse structural abnormalities in the brain of the aged population (1). Alzheimer's disease is divided into four stages based on clinical classification. Preclinical, first, with a little memory loss. The second is the mild or early stage of AD, in which patients experience mood swings, depression, loss of memory and focus, and confusion about time and location (3). The third stage is moderate AD, which is characterized by greater memory loss, difficulties identifying friends and family, and challenges with speaking, writing, and reading. Fourth, severe AD, also known as late-stage, is characterized by the development of neurotic plaques and neurofibrillary tangles, which cause progressive cognitive and functional impairments that ultimately result in the patient's death (4).

Anatomically, there are four main changes to the anatomy of the brain: Degeneration of cholinergic and other neurons, formation of neuritic plaques (beta amyloid plaques), presence of neurofibrillary tangles (NFTs), and cortical atrophy. The development of extracellular senile plaques (SPs) and intraneuronal tau protein neurofibrillary tangles (NFTs) in particular brain regions, which result in the loss of neuronal cells, are the primary pathogenic features of AD. While A-beta peptides are produced when the beta-

and gamma-secretases sequentially cleave Amyloid Precursor Protein (APP), A-beta synthesis is reduced when APP is cleaved alternately by the beta- and gamma-secretases (5). The main process in the pathophysiology of AD is the oligomerization and aggregation of A-beta peptides (6). Memory and learning are mediated by the cholinergic system in the brain, which is known to be impacted in AD. This is particularly true of the basal forebrain projections to the cortex and hippocampus. Alzheimer's disease is commonly characterized by the expansion of brain ventricles and the shrinking of the cerebral cortex and medial temporal lobe (7). Since the symptoms of AD might be confused with those of several other neuropathological illnesses, the diagnosis is very challenging. Furthermore, only a morphological and histological analysis of the brain at autopsy can produce a definitive diagnosis of AD. Rivastigmine, Galantamine, Donepezil (AChE inhibitors), and Memantine (NMDA antagonist) are currently licensed anti-AD medications that only provide symptomatic relief; they do not stop the disease's progression (8) and have limited efficacy and adverse effects.

Herbal medicine has many effects, few or no negative effects, and is reasonably priced. According to scientific research, managing neurodegenerative diseases may involve a variety of lifestyle modifications and the use of suitable herbal remedies. The potential of herbs as a source of novel bioactive components has long been acknowledged by modern research. Many plant-derived medications with unknown chemical structures have been shown to be clinically beneficial in many alternative medical systems, such as homeopathy, Ayurveda, and Unani medicine. Recent advances in phyto pharmaceutical science have sparked renewed interest in herbal medication research as a means of finding novel treatments for a range of illnesses (9).

Madhuca longifolia, a member of the Sapotaceae family, is often known as the butternut tree or Mahua. Its height is roughly 17 meters. The tree *Madhuca longifolia* is evergreen. India, Sri Lanka, and Nepal are the main locations for it. It has a wealth of chemical components that provide it a variety of therapeutic benefits. Terpenoids, proteins, starch, phenolic compounds, anthraquinone glycosides, mucilage, cardiac glycosides, tannins, and saponins are among its constituents. Erthrodiol, palmitic acid, myricetin, 3-O-arabionoside, 3-O-L-rhamnoside, quercetin-carotene, β 3-galactoside, and xanthophylls are also found in leaves. The wood is used to build doors, cartwheels, and buildings. A useful source for fixing nitrogen is this one. Different components of the tree are utilized as intercrops, fertilizer, and cattle feed. Mahua leaves are used to treat rheumatism, headaches, eczema, wound healing, anti-burns, bone fractures, anthelminthic, and emollient skin conditions. The bark is used to treat rheumatism, chronic bronchitis, and diabetes mellitus; the leaves are used as an expectorant and to treat chronic bronchitis and Cushing's disease; and the flowers are used as a tonic, analgesic, and diuretic. The synonyms, botanical description, phytochemicals, pharmacological activity, and medicinal applications of Mahua (10), are the main topics of this review.

According to recent study, there is an urgent need to discover innovative, safe, and affordable therapeutic molecules derived from natural resources that can modify the neurotransmitter expression in Alzheimer's disease because of the disease's complicated nature. The current study attempted to evaluate the impact of *Madhuca longifolia* fruit extract on a few chosen parameters in an A.D.-induced rat model, which is a novel approach to developing anti-Alzheimer's bioactive compounds from herbs, based on the fruit's beneficial medicinal effects.

2. Materials and Methods

2.1 Preparation of Ethanolic extract of fruits of M. longifolia

Fresh *Madhuca longifolia* fruits were gathered from the Bilaspur local market in the Indian state of Chhattisgarh. The Department of Botany's plant taxonomist verified the fruits' authenticity. Fresh *Madhuca longifolia* fruits were gathered, cleaned with tap water, and then let to air dry. About two kilograms of fresh fruits were cleaned, their seeds removed, sliced into small pieces, and allowed to air dry entirely in the shade. Dried fruit bits were then ground into a fine powder. 500 g of crude powder was mixed with two liters of 80% ethanol to create an ethanolic extract, which was then left for a full day. Using a Soxhlet system, the filtrate was separated and taken for extraction preparation. Three iterations of the identical procedure were carried out using the leftover residue. To separate the filtrate from the residues, the mixture was filtered. Soxhlet was used to concentrate the entire filtrate, and the remaining residues were gathered and lyophilized to create powder.

2.2 Procurement and Maintenance of Experimental Animals

Male Albino (Wister Strain) rats weighing 150±25 grams at 3 months of age served as the experimental model for this study. The rats were purchased from a Chhattisgarh state-approved vendor. The rats were housed in polypropylene cages at the department's animal home, where they were kept at 28°±2°C, with a photoperiod of 12 hours of light and 12 hours of darkness, and with a relative humidity of 75%. Rats were provided with a standard pellet diet purchased from Hindustan Lever Ltd. in Mumbai, as well as unrestricted access to water. The CPCSEA-Institutional Ethical Committee Guidelines for the Protection and Care of Laboratory Animals were followed when caring for the rats. The ethanolic extract of *Madhuca longifolia* fruit will undergo pharmacological analysis at the faculty of pharmacy's pharmacology department in Bilaspur, India. CPCSEA has authorized this institute's animal facility. The animals were categorized as shown in table 1 below.

Table no. 2.2 Experimental Grouping of animals for present study

S. No.	Groups	Treatment	No. of Animals
1.	Normal	Distilled water (6ml/kg, p.o/day.)	6
2.	Control (toxin)	Lipopolysaccharide (10 mg/kg I.P.)	6
3.	Standard Drugs	Lipopolysaccharide+Galantamine10mg Oral	6
4.	Treatment-I	Lipopolysaccharide+100mg/kg b.w. *Madhuca longifolia* Oral	6
5.	Treatment-II	Lipopolysaccharide+200mg/kg b.w. *Madhuca longifolia* Oral	6

2.3 LPS induction of Alzheimer's disease

Although many researchers have created many techniques to cause Alzheimer's disease in rodents, lipopolysaccharide (LPS) treatment is thought to be a very effective approach. Intraperitoneal injections of LPS produce symptoms that mimic the aging process that naturally results in Alzheimer's disease, including abnormal changes in biochemical markers, retrograde alterations in brain neural cells, memory difficulties, and more (11).

2.4 Study of Behavioral Parameters

The behavioral evaluation was conducted prior to the experiment's commencement and then on a regular basis seven days thereafter, that is, on the seventh, fourteenth-, and twenty-first-days following dosing. After the animals were killed and their tissue homogenates were prepared, the biochemical parameters were examined on day 21. The tests comprised the Y maize test, the Actophotometer test, and the novel object recognition test.

16 infrared emitter/detector pairs were used in the Actophotometer to assess animal activity along a single axis of motion. The digital data was shown as ambulatory motions on the front panel meters. The rats were given two minutes to get used to the observation chamber. For five minutes, the activity was continuously observed. Total photo beam counts per five minutes for each animal were used to quantify locomotion (12).

Only three sessions are needed for the novel object recognition (NOR) test: one for habituation, one for training, and one for testing. In training, two similar objects are simply studied visually, however in testing, one of the previously explored objects is swapped out for a new one. A mouse that remembers the familiar object will spend more time investigating the new object since rodents are naturally drawn to novelty (13,14).

A maze structure with three arms forming a Y shape is used for the Y-maze test (figure 5.12). Animals are placed in a maze as part of the experimental process, and their movements and arm choices are closely observed and documented. This test's main objective is to assess animals' working memory by having them remember which arm they previously entered and select a different arm for subsequent trials. They measured 35 cm by 6 cm by 15 cm (width x height x length) for each arm. The Y-maze offers a more organic form and features seamless 120-degree arm transitions (15).

2.5 Biochemical and Histopathological study

Tissue homogenates were made for this phase. After weighing the tissues, 10% tissue homogenate was made using 0.025 M Tris-HCl buffer at pH 7.5. The following biochemical parameters were measured using the clear supernatant following centrifugation at 10,000X g for 10 minutes.

2.5.1 Superoxide dismutase (SOD) activity

0.5 ml of the tissue homogenate supernatant was transferred to a test tube. After adding 0.5 ml of 0.1 m EDTA and 0.4 ml of epinephrine to 1.5 ml of carbonate buffer pH10.2, the optical density (OD) was measured at 480 nm. Just prior to taking the OD, epinephrine was added. Units/min/mg protein was used to express SOD activity. The amount of enzyme that reduces the rate of adrenaline auto-oxidation by 50% is known as one unit of the enzyme.

2.5.2 Reduced glutathione (GSH) content estimation

Ellman reagent (3 ml) and 0.1 M phosphate buffer at pH 6.5 (250 ml) were added to 20 µL of tissue homogenate supernatant in order to measure the GSH level in the experimental animals. The absorbance at 412 nm was measured using spectrophotometry after standing for an hour at the room's sustained temperature.

2.5.3 Catalase activity

The approach outlined by Omar et al. (1999) was used to estimate catalase. As a substrate, hydrogen peroxide (H2O2) was employed (16).

3. Results and Discussion

30% w/w of crude ethanolic extract was produced from 500g of *M. longifolia* fruit powder. The residue had a brownish hue. In order to qualitatively assess whether any medically significant secondary metabolites were present, the plant extract was also examined. When compared to steroids and flavonoids, this study showed that the majority of the extracts had more tannins, phenols, saponins, terpenoids, alkaloids, reducing sugars, and carbohydrates.

3.1 Assessment of Behavioral Outcomes

Various behavioral tests related to particular motor functions were also conducted because AD is a motor condition characterized by rigidity, resting tremor, postural instabilities, and slowness of movement. Weekly behavioral tests, as detailed below, were administered to the animals in various groups.

3.2 Evaluation of Actophotometer test

The spontaneous locomotor activity of mice did not alter statistically significantly from day 1 to day 7, as the Table and Figure 1 further explain. On days 14 and 21, however, mice's spontaneous locomotor activity in the actophotometer dramatically ($p<0.001$) dropped for all three doses of ethanolic plant extract (100 mg/kg, 200 mg/kg) in comparison to the control. Additionally, for these doses, a dose response relationship was noted. In summary, the test drug's reduction in spontaneous locomotor activity was similar to that of the common Galantamine.

Table 3.2: Effect of oral administration of EEML on spontaneous locomotor activity of mice in seconds (mean ± SD) in Actophotometer

Days	Control	Standard Galantamine	EEML-100	EEML-200
Day 1 (Before)	265.50±15.63	264±30.35	263.83±30.20	264.50±31.48
Day 1 (After)	270.33±82.41	162.33±20.14	157±32.23	160±71.16
Day 7	263.50±7.55	178.66±40.91	169±23.06	175.66±17.55
Day 14	266.66±7.28	195.50±27.34	181±24.24	188.33±22.31
Day 21	268.66±6.43	215.50±26.28	194.66±27.63	207.83±15.51

Where: EEML = Ethanolic Extract of M. longifolia

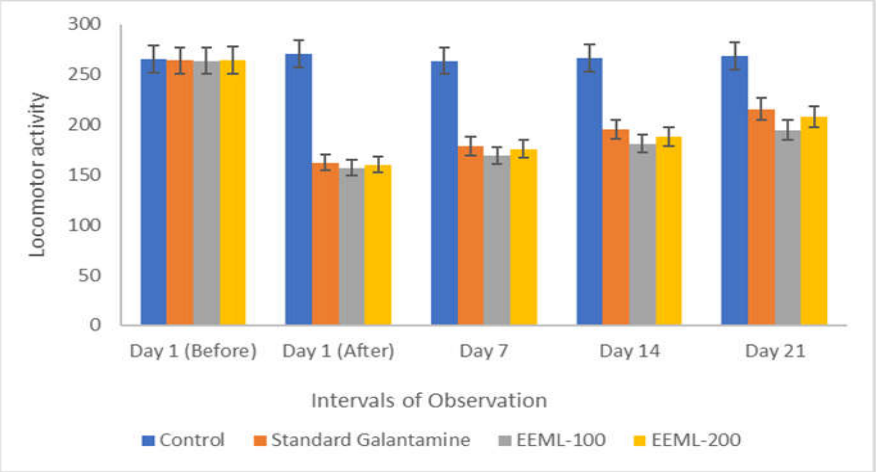

Figure 3.2: Graphical representation of effect of oral administration of EEML on spontaneous locomotor activity

According to the findings of the Actophotometer Experiment, at a 200 mg/kg body weight concentration, plant extract was found to be just as effective as galantamine at reversing the memory deficits caused by AD.

3.3 Novel Object Recognition Evaluation

Every group explored the three distinct objects for a comparable amount of time during the training session. Furthermore, the overall amount of time spent exploring did not vary significantly. Mice administered with the vehicle demonstrated a marked increase in the amount of time spent investigating item D throughout the testing period. In a dose-dependent manner, the administration of plant extract considerably increased the amount of time spent investigating object D. In the 200 mg/kg EEML-treated group, this increase was comparable to the standard and higher than that of the vehicle-treated/control group.

Table 3.3 (a): Effect of plant ethanolic extract on the Training Day

Treatments	**% Exploration**		
	Object A	**Object B**	**Object C**
Control	37±0.63	30±0.18	32±0.21
Standard	36±0.23	31±0.53	32.5±0.63
100 mg/kg EEML	34.5±0.21	33.5±0.71	30.5±0.42
200 mg/kg EEML	35.5±0.24	30.5±0.09	34±0.12

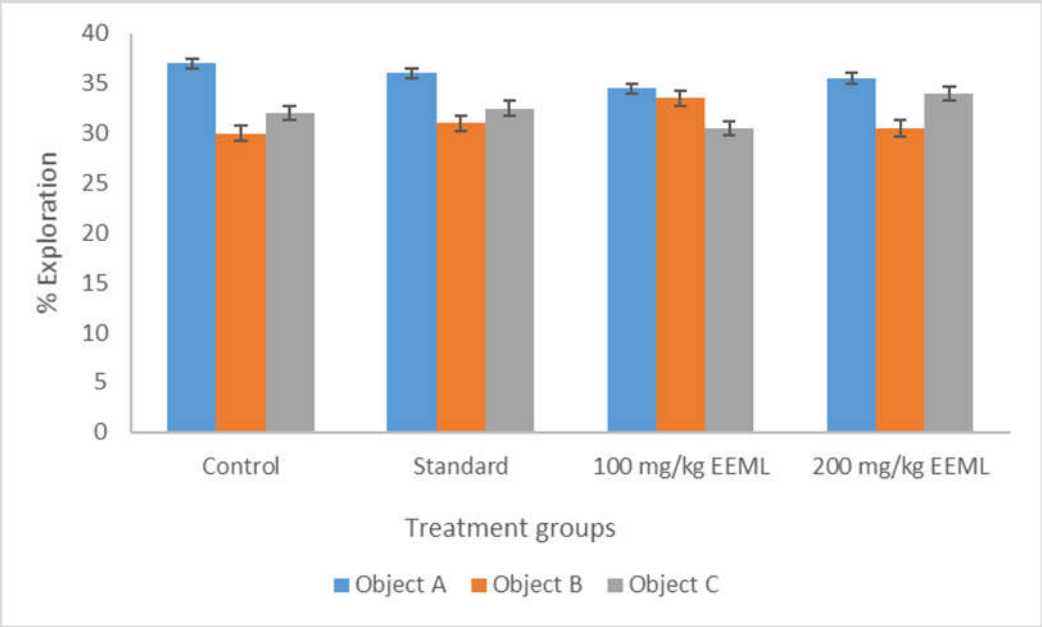

Figure 3.3 (a): Effect of plant ethanolic extract on the Training Day

Table 3.3 (b): Effect of plant ethanolic extract on the Testing Day

Treatments	% Exploration		
	Object A	Object B	Object D
Control	31±0.53	32.5±0.12	36.5±0.62
Standard	31.5±0.63	33±0.53	38±0.31
100 mg/kg EEML	29±0.34	27±0.07	40.2±0.41
200 mg/kg EEML	30.5±0.12	29±0.46	47.2±0.56

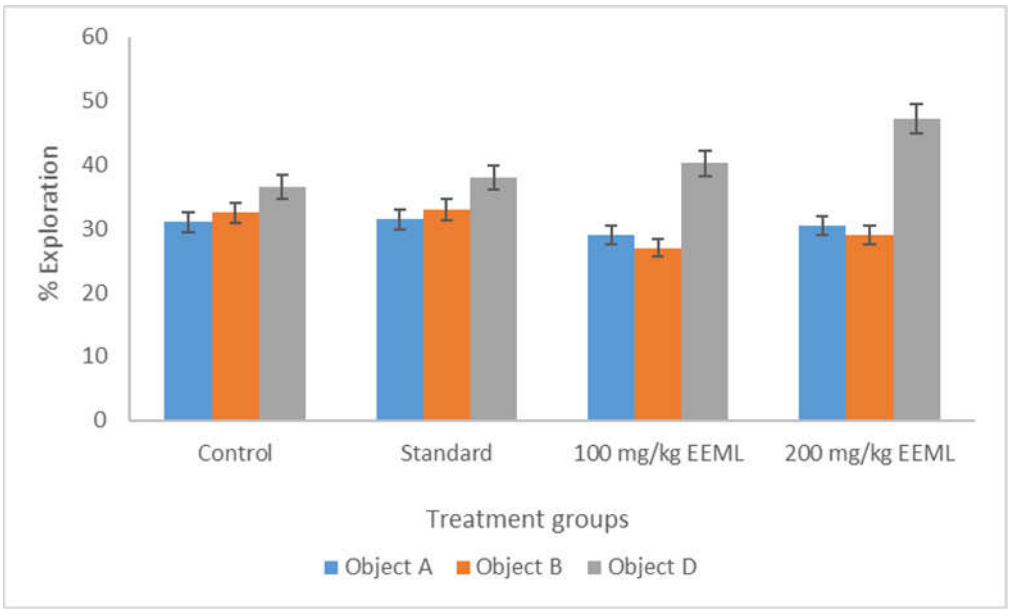

Figure 3.3 (b): Effect of plant ethanolic extract on the Training Day

The data are displayed as a percentage of the overall exploration time for each object (A, B, or C, where on the testing day, C is substituted with D). The animals do not

exhibit a preference for investigating any specific object on the day of training. Mice treated with EEML exhibit a preference for exploring the novel object D on the day of testing. Every data point is displayed as % exploration ± SEM. Yoo et al. used Cynomorium singaricum extract in 2014 and reported results similar to the current investigation (17).

3.4 Evaluation of Y maize test

Although there was no discernible difference at days 1 and 2 ($P<0.05$), our results showed that the correct rate in the Alzheimer-induced group was significantly lower than that of the control group over days 3 to 9 ($P<0.05$, $P<0.01$) (Figure 4 and table 5). Additionally, the correct rate in Alzheimer mice at behavioral training days 4–9 was considerably elevated by 100 or 200 mg/kg EEML ($P<0.05$, $P<0.01$). In the control group, the total number of trials and training days required to meet the arbitrary learning threshold of 90% accurate rate were 100±10.4 and 4.8±1.3, respectively. Nonetheless, it took 190±12.2 trials and 9.5±1.6 training days, respectively, to meet the learning requirement in Alzheimer mice ($P<0.01$).

These findings imply that the Y-maze learning performance of Alzheimer's disease animals is impaired. Next, we looked at how *M. longifolia* extract affected the Alzheimer mice's performance on the Y-maze learning challenge. The 100 mg/kg EEML-treated group required 139±11.8 trials and 7.1±2.1 training days to meet the learning criteria, while the 200 mg/kg EEML-treated group required 110±13.1 and 5.5±1.3 training days. According to these findings, taking *M. longifolia* extract orally significantly improves the learning and memory impairments brought on by LPS in Alzheimer's patients.

Table 3.4 (a): Effects of *M. longifolia* extract on Y-maze learning performance in Alzheimer's mice

Time in days	% Correct rates				
	Control	Alzheimer's group	Standard	100mg/kg EEML	200mg/kg EEML
1	52.3± 0.02	47.5± 0.03	54.3± 0.11	51.8± 0.02	58.3± 0.03
2	74.4± 0.01	58.2± 0.02	71.1± 0.12	63.5± 0.11	73.1± 0.02
3	85.2± 0.02	62.3± 0.01	74.5± 0.02	73.4± 0.02	76.5± 0.02
4	88.1± 0.11	65.2± 0.04	84.8± 0.02	77.6± 0.01	79.8± 0.04
5	91.2± 0.02	67.3± 0.02	89.7± 0.01	84.9± 0.01	88.7± 0.05
6	93.1± 0.01	70.8± 0.02	92.4± 0.03	88.7± 0.05	91.4± 0.11
7	94.2± 0.01	73.6± 0.05	94.1± 0.04	92.5± 0.04	93.2± 0.04
8	95.3± 0.12	75.4± 0.03	96.2± 0.02	93.4± 0.02	94.1± 0.12
9	96.1± 0.02	78.6± 0.04	96.9± 0.05	94.2± 0.03	96.8± 0.02

10	96.5± 0.01	85.2± 0.02	98.1± 0.11	95.6± 0.11	97.2± 0.05

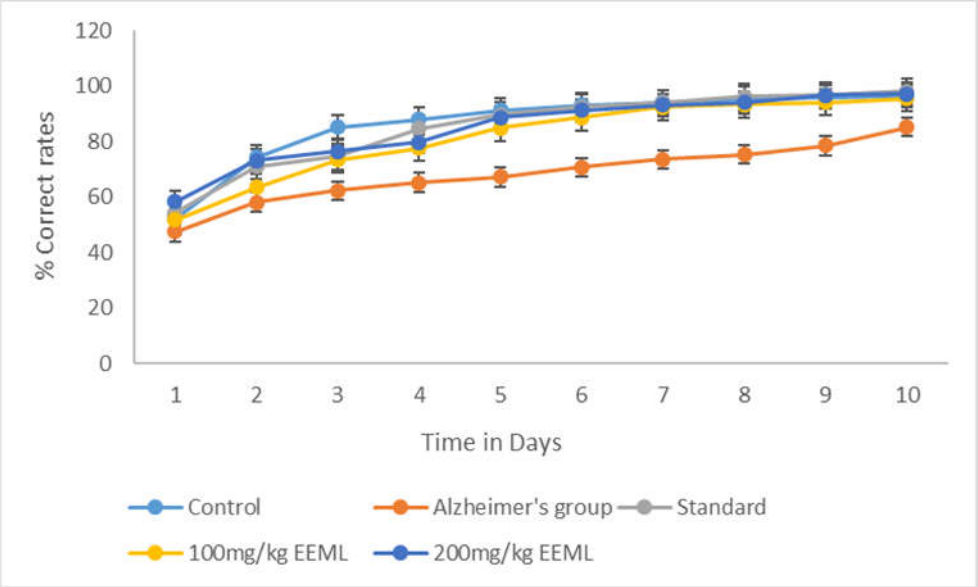

Figure 3.4 (a): Effects of *M. longifolia* extract on Y-maze learning performance in Alzheimer's mice

Table 3.4 (b): Effect of *M. longifolia* extract on number of total trials and training days in Alzheimer's mice

Treatment groups	Trials to reach criterion	Days to reach criterion
Control	100±10.4	4.8±1.3
Alzheimer's group	190±12.2	9.5±1.6
Standard	108±14.2	5.2±0.89
100mg/kg EEML	139±11.8	7.1±2.1
200mg/kg EEML	110±13.1	5.5±1.3

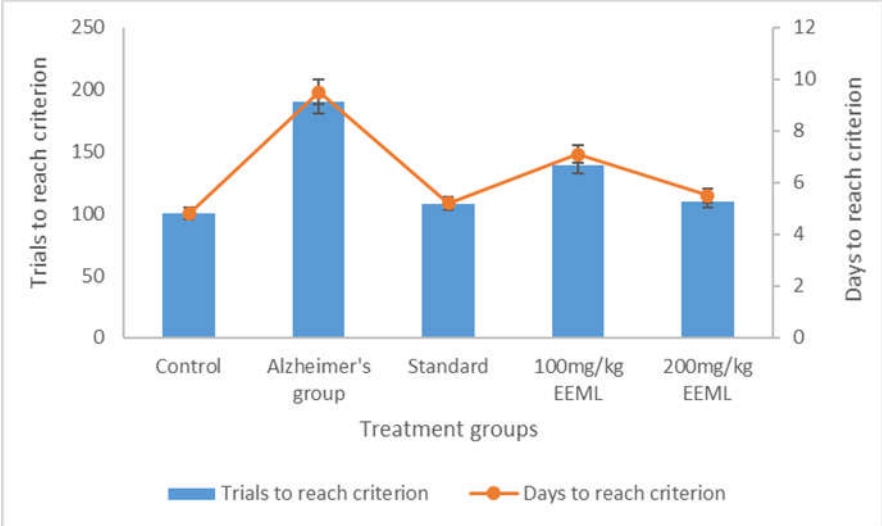

Figure 3.4 (b): Effect of *M. longifolia* extract on number of total trials and training days in Alzheimer's mice

The results show that in ischemia mice with a dose response relationship, the number of trials and training days required to meet the learning threshold was considerably decreased by treatment with *M. longifolia* extract at 100 and 200 mg/kg. $P<0.01$ when compared to both the control and Alzheimer's groups.

3.6 Evaluation of Biochemical Parameters

Rats given LPS exhibited a significant ($P<0.05$) drop in antioxidant activities such as SOD and catalase, as well as an increase in GSH levels, when compared to the normal control group. The decreased activities of these antioxidants brought on by LPS were restored in rats treated with EEML. Additionally, the extract was able to reverse the changes in antioxidant enzyme activity brought on by LPS. Rats given EEML alone have likewise displayed a normal range of antioxidant measures. In the brain tissue of the animals under study, EEML at a dose of 200 mg/kg showed greater promise in restoring the antioxidant levels than did 100 mg/kg.

Table 3.6: Effect of EEML on antioxidant parameters of LPS-induced rats

Parameters	Control (G-I)	Alzheimer group (LPS induced) (G-II)	Standard Galantamine group (G-III)	EEML 100mg/kg (G-IV)	EEML 200mg/kg (G-V)
SOD (Units/min/mg protein)	89.46±0.63	21.96±1.1a*	84.36±1.23b*	83.67±0.51a*b*c*	83.51±0.31b*d*
Catalase (Units/min/mg protein)	77.98±0.56	44.45±0.62a*	74.21±1.31a*b*	67.21±0.23a*b*c*	75.71±1.41b*c*d*
GSH (nmol/mg protein)	43.41±1.53	32.53±1.31a*	41.72±1.32b*	43.41±1.71b*	42.51±1.25b*

Each value represents the mean ± SD of six rats. Comparisons were made as follows: a-Group-I vs groups-II, III, IV, V; b- Group-II vs Group-III, IV, V; c-Group-III vs Group-IV, V; d-Group-IV vs Group-V. The symbols represent statistical significance at *$p < 0.05$. Statistical analysis was calculated by one-way ANOVA.

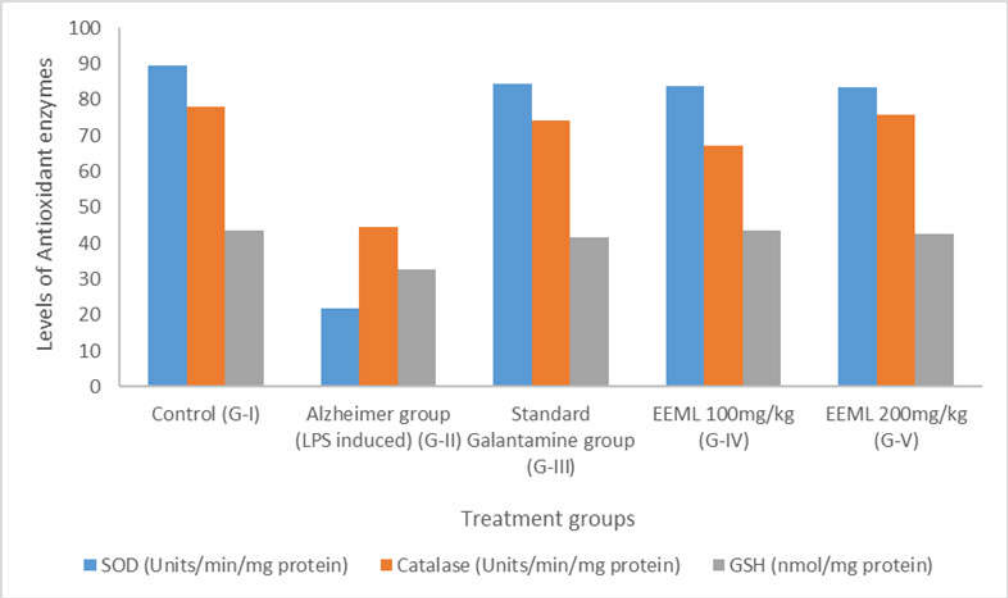

Figure 3.6: Effect of EEML on the levels of different antioxidant enzymes in rat brain tissue

ROS problems can be avoided by using antioxidant enzymes, both enzymatic and non-enzymatic. SOD, CAT, GST, Gpx, and GSH are factors in the enzymatic antioxidant process. Vitamins C, E, total and direct bilirubin, and uric acid are all involved in the non-enzymatic antioxidant system (18). In this study, it was found that the brain tissue of rats given LPS had reduced antioxidant levels. SOD plays a vital role in removing ROS by breaking down the dismutation of superoxide radicals into O2 and H2O2. Because SOD is less active in breaking down ROS, LPS has a lower SOD level. In contrast, the LPS-induced group that received EEML had a restored SOD level.

An essential enzyme in shielding cells from oxidative damage is catalase (CAT). Animals given LPS have lower levels of CAT, which has a decreased ability to protect tissues. Rats given EEML were shown to normalize their CAT range.

The reduced capacity of GSH conjugation to prevent cellular damage is the cause of the drop in GSH levels. In contrast, rats given EEML showed a restoration of the reduced GSH range, which may be because of its ability to improve GSH conjugation, which guards against tissue damage. In both plants and animals, GSH is an essential antioxidant that aids in preventing cellular damage caused by ROS (19).

4. Conclusion

In the current work, experimental rats given intraperitoneal LPS showed a marked decline in behavioral activity and many biochemical indicators in the brain areas that showed signs of oxidative damage. However, these AD-induced effects were significantly mitigated by EEML extract, demonstrating the anti-inflammatory and neuroprotective benefits of *M. longifolia* extract on the nervous system. Based on the aforementioned findings, it was determined that oral administration of *M. longifolia* fruit extract is crucial for preserving normal brain function in AD patients. Additional pre-clinical and clinical research can be conducted to validate the current findings.

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