Protective Effect of *Dalbergia sissoo* Extract Against Amyloid-β (1-42)-induced Memory Impairment, Oxidative Stress, and Neuroinflammation in Rats

*Dalbergia sissoo* Ekstresinin Sıçanlarda Amiloid-β (1-42) ile İndüklenen Hafıza Bozukluğuna, Oksidatif Strese ve Nöroinflamasyona Karşı Koruyucu Etkisi

**Objective:** The ayurvedic literature reports that *Dalbergia sissoo*, a common medicinal plant for gastric and skin problems, has brain-revitalizing effects. However, the neuroprotective effect of this herb on an amyloid-β (Aβ) 1-42 model of Alzheimer’s disease (AD) is yet unknown. The current study describes the protective effect of ethanolic extracts of *D. sissoo* leaves (EEDS) against Aβ (1-42)-induced cognitive deficit, oxidative stress, and neuroinflammation in rats.

**Materials and Methods:** EEDS (300 and 500 mg/kg) was orally administered to rats for 2 weeks prior to intracerebroventricular Aβ (1-42) treatment. The neuroprotective effect of EEDS was assessed by evaluating behavioral, biochemical, and neuroinflammatory parameters in the rat hippocampus. Memory function was assessed via the Morris water maze (MWM) task 2 weeks after Aβ (1-42) administration. After 3 weeks, surgery was performed, all biochemical parameters were evaluated, and histopathological examination of the tissues was carried out.

**Results:** EEDS improved the cognitive ability of Aβ (1-42)-administered rats in the MWM task. It reduced oxidative stress by significantly decreasing nitrite and malondialdehyde levels and increasing catalase activity and glutathione levels in the rat brain. Moreover, EEDS mitigated neuroinflammation in rats by decreasing the concentration of neuroinflammatory markers in a dose-dependent manner.

**Conclusion:** *D. sissoo* leaf extract has a beneficial role in alleviating cognitive deficits in AD by modulating cholinergic function, oxidative stress, and neuroinflammation.

**Key words:** Alzheimer’s disease, *Dalbergia sissoo*, cognitive deficit, oxidative stress, amyloid-β (1-42)
INTRODUCTION

*Dalbergia sissoo* Roxb. ex DC., commonly known by the names Indian rosewood, Sheesham, and Shinshapa (Fabaceae), is a perennial tree belonging to the Indian subcontinent and Southern Iran. The leaves and bark of *D. sissoo* are extensively used in traditional medicine for various gastric and skin problems, including dysentery, dyspepsia, and leucoderma. The juice of *D. sissoo* leaves is used to treat senility and revitalize brain functions. *D. sissoo* is known to possess diverse phytoconstituents, including biochanin A, tectorigenin, mesoinositol, isocaviumin, tectorigenin, dalbergin, dalbergionone, tannins, fixed oils, and essential oils. A number of studies have reported the antiinflammatory, antioxidant, antispermaticogenic, memory-enhancing, cardioprotective, and antiinfectious properties of this plant. Extracts of *D. sissoo* leaves were recently shown to have neuroprotective effects against 3-nitropropionic acid-induced neurodegeneration in rats. Biochanin A, the major isoflavone glycoside present in *D. sissoo* leaves, has also been demonstrated to exhibit antioxidant and neuroprotective effects in different studies.

To date, however, no study has yet evaluated the beneficial effect of *D. sissoo* against amyloid-β (Aβ) 1-42-induced memory impairment, oxidative stress, and neuroinflammation in rats. Alzheimer’s disease (AD), a major neurodegenerative disorder, is a form of dementia that affects approximately 50 million people worldwide; indeed, the disease is recognized as a global public health challenge. AD is characterized by gradual declines in memory function and impaired ability to learn, think, communicate, and make judgments. During the course of the disease, cholinergic neuronal degeneration and dysfunction occur primarily in the cerebral cortex, hippocampus, and amygdala, ultimately resulting in memory impairment. Neuropathological changes in the AD brain are manifested by the deposition of Aβ senile plaques and neurofibrillary tangles. Accumulation of pathogenic Aβ peptides in the aggregated form (i.e., as dimers or oligomers) in specific regions of the brain cause synaptic loss and the breakage of neuronal circuits, which results in neuronal dysfunction. Intracerebroventricular (ICV) administration of aggregated Aβ in rodents mimics the pathological features of AD and induces amnesic effects resulting in memory impairment.

Increased oxidative stress is widely regarded as a crucial factor in the progression of AD. Recent evidence indicates that Aβ-induced neurotoxicity may be associated with increased oxidative stress. Studies have confirmed that antioxidant treatment improves learning ability in Aβ-treated rats and delays the clinical progression of the disease. Increased oxidative stress has also been linked with neuronal inflammation and apoptosis. The implication of oxidative stress and neuroinflammation in the pathogenesis of various neurodegenerative diseases, including AD, has rendered treatment with agents possessing antioxidant and antiinflammatory properties a promising approach for managing these diseases.

Various approaches to treat AD, including cholinesterase inhibitors, gene therapy, immunotherapy, modulation of Aβ and tau deposition, and modulation of inflammation and oxidative damage, have been investigated in recent years. Symptomatic treatment with galantamine, donepezil and rivastigmine (cholinesterase inhibitors), and memantine (NMDA receptor antagonist) is currently approved for AD. However, because none of these drugs target the underlying disease mechanism, the search for new drugs that can prevent or delay disease progression remains a crucial undertaking. Plant-based medicines are attractive targets for the treatment of diseases in which the major underlying cause is oxidative stress. Therefore, the current study explores the protective role of *D. sissoo* against Aβ-(1-42)-induced oxidative stress and cognitive dysfunction in rats.

MATERIALS AND METHODS

Drugs and chemicals

Aβ (1-42), donepezil, and commercial kits were obtained from Sigma-Aldrich, USA. Biochanin A was purchased from Clearsynth Labs Ltd., Mumbai, India. All of the reagents used in the experimental work were of analytical grade.

Plant extraction

The green leaves of Indian rosewood were obtained from the medicinal garden of JCDM College of Pharmacy, Sirsa, India. A specimen voucher was submitted to the Raw Materials Herbarium and Museum at the National Institute of Science Communication and Information Resources (NISCAIR), New Delhi, India, and authenticated (ref. no. NISCAIR/RHMD/Consult/2017/3104-53-2). The leaves were properly washed, dried under a shade for 1 week, ground, and defatted with hexane. The powdered leaves were then macerated with ethanol in a beaker and kept at 25°C±2°C for 5–6 days. The extract was filtered and evaporated under reduced pressure to remove the solvent completely. The final dried ethanolic extracts of *D. sissoo* leaves (EEEDS, 8 g) was obtained and stored at 2°C-4°C in the dark for subsequent experiments.
**Extract standardization**

EEDS standardization was carried out using high-performance liquid chromatography (HPLC) with biochanin A as the standard compound; this substance is the major constituent of *D. sissoo* leaves. The HPLC instrument (Shimadzu) was supplied with an SPD-10AVP ultraviolet-visible detector, reciprocating LC-10 ATVP pumps, a Phenomenex C-18 column (250 mm x 4.6 mm, 5 μm), and a Rheodyne injector. The data were acquired and processed using LC-solution software, version 6.42.

**Animals**

Male Wistar rats (350-400 g) were acquired from Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, Haryana, India, housed in an animal house maintained under standard laboratory conditions (temperature: 24°C±2°C, relative humidity: 60%-70%, light cycle: 12 h natural light, 12 h dark), and provided water and food as required. The research protocol was approved by the Institutional Animal Ethics Committee (approval date:13.6.2016; approval no: JCDMCOP/IAEC/06/16/36) of JCDM College of Pharmacy. Ethical guidelines were followed during all animal experiments.

**Animal groups and drug treatment**

The rats were randomly assigned to five groups with eight animals in each group as follows: Group 1; sham control group; Rats were administered the vehicle (4 μL) ICV group 2; Aβ group; Rats were injected with Aβ (1-42) (4 μL) ICV; group 3; Aβ + EEDS (300 mg/kg) group; Aβ model rats were pre-treated with EEDS (300 mg/kg) for 2 weeks; group 4; Aβ + EEDS (500 mg/kg) group: Aβ model rats were pre-treated with EEDS (500 mg/kg) for 2 weeks; group 5; standard group; Aβ model rats were treated with the standard anti AD drug donepezil (5 mg/kg). The doses of *D. sissoo* extract used for treatment were selected on the basis of previous reports. The drug treatment schedule is presented in Figure 1.

**Intracerebroventricular administration of Aβ (1-42)**

Stereotaxic surgery was performed in rats for ICV administration of Aβ (1-42) to induce AD. Anesthesia was induced in rats by intraperitoneal injection of ketamine (100 mg/kg). The scalp was shaved, positioned in a stereotaxic frame, and dissected from the midline to expose the skull. Burr holes were drilled 2 mm posterior to the bregma, 1.5 mm lateral to the midline on either side of the skull, and 1.0 mm below the cortical surface to allow for cannula entry into the hippocampus. Exactly 4 μL of Aβ (1-42) dissolved in saline (1 μg/μL) was slowly infused into the hippocampal region through the installed holes using a Hamilton syringe. The sham group animals were treated with the same surgical procedure and received the same volume (4 μL) of vehicle after surgery. For post-surgical care, the animals were administered gentamycin (5 mg/kg, i.p.) to prevent infection.

**Assessment of behavioral parameters**

**Morris water maze task**

Two weeks after induction of AD in rats, memory acquisition and retention were evaluated by the MWM task. The MWM apparatus was equipped with a water tank measuring 130 cm in diameter and 60 cm in height. The tank was filled with water (23°C±1°C) to a height of 35 cm. The water was mixed with tempera paint to achieve opacity. The tank was partitioned into four quadrants of the same size, and a platform was installed 2 cm below the water surface in one of the quadrants to allow the animals to escape. The animals were trained for 4 days in succession from day 16 to day 19 (sessions 1-4) with four trials per day. During the training sessions, the animals were left in the pool for 60 s and allowed to locate the platform. Once the platform was correctly located, the rats were guided to and allowed to sit on it for 30 s before the next trial. Escape latency was documented after each trial. On day 20, a probe trial was conducted; here, the platform was removed from the pool, and the animals were randomly released into the tank. The time spent by the animal in the target quadrant was recorded.

**Assessment of locomotor activity**

On day 21, the motor activity of the rats was measured using a digital actophotometer equipped with infrared light-sensitive photo cells (IMCORP, India). Each animal was placed in the actophotometer for 10 min, and the number of motor counts displayed on the accompanying digital counter was recorded as a measure of motor performance.

**Assessment of biochemical parameters**

**Sample preparation and measurement of total protein**

The rats were sacrificed by decapitation for biochemical estimations on day 22 following surgery. The brains were cleaned with ice-cold saline and dissected to isolate the hippocampus. The dissected hippocampal tissue was homogenized with ice-cold phosphate buffer (0.1 mM/L, pH=7.4) and ultracentrifuged (Remi cold centrifuge) at 3000 rpm for 15 min. The clear supernatant obtained was stored at -80°C and used for further biochemical assays. The amount of protein in each sample was determined using Lowry’s method with bovine serum albumin as the standard. Total protein contents are presented in milligrams (mg).

**Figure 1.** Schematic of the drug treatment schedule.

EEDS: Ethanolic extracts of *Dalbergia sissoo* leaves, ICV: Intracerebroventricular, MWM: Morris water maze, Aβ: Amyloid-β
Measurement of oxidative stress markers
Glutathione (GSH) assay was performed by following the method reported by Ellman. The GSH concentrations are presented as micromoles per milligram of protein (μmoL/mg protein). Malondialdehyde (MDA) in tissue samples was assessed using the procedure reported by Ohkawa et al. A standard curve was prepared, and the concentration of MDA was estimated and expressed in nanomoles per milligram of protein (nmoL/mg protein). Nitrite in the supernatant was measured via colorimetric assay using Griess reagent. A standard curve of sodium nitrite was plotted, and the amount of nitrite was determined and presented as micromoles per milligram of protein (μmoL/mg protein). Catalase activity was measured using the method reported by Aebi, and absorbance was recorded at 240 nm. Enzymatic activity was presented as nanomoles of H₂O₂ consumed per minute per milligram of protein (nmol/min/mg protein).

Measurement of acetylcholinesterase
Acetylcholinesterase (AChE) activity was estimated via the procedure previously demonstrated by Ellman et al. and presented as nanomoles per milligram of protein (nmol/mg protein).

Measurement of neuroinflammatory markers
The concentrations of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in the samples were measured using commercial Quantikine rat assay kits (Becton Dickinson Biosciences, India Pvt. Ltd.)

Histology of brain tissue
The brains of the animals were removed, stored in 10% formalin solution, sliced into thick sections, and then subjected to histopathological examination. The sections were dehydrated, embedded in paraffin blocks, cut into 5-6 μm-thick slices using a microtome, and then stained with hematoxylin-eosin.

Statistical analysis
All of the data were analyzed using Graph Pad Prism software (San Diego, CA, USA). One-Way ANOVA was applied to analyze the biochemical measurements. Tukey’s post hoc test was applied for multiple comparisons among groups. Two-Way ANOVA was applied to evaluate the data of escape latency. The results are presented as mean ± standard deviation, and p<0.05 was considered significant.

RESULTS

Quantity of biochanin A in EEDS
HPLC analysis revealed that the content of biochanin A, the major constituent of EEDS, was 63.262 μg/mg. The peaks of EEDS (sample) and biochanin A are presented in Figure 2a, b.

Effect of EEDS on reversing Aβ (1-42)-induced memory dysfunction in the MWM task
Two-Way ANOVA showed no significant decrease in escape latencies over four consecutive sessions compared with those at session 1 (day 1) in Aβ (1-42)-lesioned animals. However, in the EEDS pre-treated (300 and 500 mg/kg) groups, escape latencies significantly (p<0.001) decreased compared with those at session 1, indicating improvements in cognitive performance. No significant difference in the memory-retaining effects of EEDS (500 mg/kg) and the standard drug donepezil (Figure 3a) was observed. In the probe trial, Aβ (1-42)-injected animals were unable to locate the platform and spent significantly less time in the target quadrant (p<0.001, F=593.7, df=39) than the sham-operated animals (Figure 3b).

Effect of EEDS on oxidative stress markers
Compared with sham-operated rats, Aβ (1-42)-injected rats revealed significant increases in MDA and nitrite concentrations, as well as decreases in catalase activity and GSH concentration (p<0.001). Compared with the lesioned group, EEDS (300 and 500 mg/kg) significantly decreased MDA and nitrite concentrations and increased catalase activity and GSH concentration (p<0.001) compared with the lesioned group.
500 mg/kg) administration significantly attenuated oxidative stress by reducing elevated MDA (p<0.001, F=231.9, df=29) and nitrite (p<0.001, F=123.0, df=29) levels and restoring GSH (p<0.001, F=555.5, df=29) and catalase (p<0.001, F=1191, df=29) levels. Compared with that of donepezil, the effect EEDS (500 mg/kg) on oxidative stress parameters was not significant (Table 1).

**Effect of EEDS on AChE activity**

AChE activity was significantly augmented in the hippocampus of Aβ (1-42)-injected rats compared with that in sham-operated animals (p<0.001). EEDS administration (300 and 500 mg/kg) significantly attenuated the observed increases in AChE activity (p<0.001, F=366.2, df=29) (Table 1).

**Effect of EEDS on locomotor activity**

EEDS administration (300 and 500 mg/kg) had no significant effect on locomotor activity in all groups (p>0.05) (Figure 4).

**Effect of EEDS on neuroinflammatory markers**

Aβ (1-42) infusion significantly increased TNF-α and IL-6 levels in the hippocampus compared with those in sham-operated rats (p<0.001). Pre-treatment with EEDS (300 and 500 mg/kg) significantly attenuated TNF-α (p<0.001, F=990.0, df=29) and IL-6 (p<0.001, F=480.8, df=29) levels in a dose-dependent manner compared with the Aβ (1-42) model group. No significant difference between the effects of EEDS (500 mg/kg) and donepezil (5 mg/kg) was noted (Figure 5a, b).

**Histopathological studies**

The findings of histopathological studies suggested severe neuronal degeneration in the Aβ (1-42)-treated group. The neurons of Aβ (1-42)-administered brains were reduced in size and had irregular shapes; white patches were also observed (Figure 6). By comparison, the EEDS (300 mg/kg)-treated group showed reduced neurodegeneration and clear nuclei. Moreover, in the EEDS (500 mg/kg)-treated group, neurons retained their original shape and structure, and neuronal degeneration was not visible.

**DISCUSSION**

AD is accompanied by a progressive decline in memory function, which has been associated with the deposition of hyperphosphorylated tau proteins and senile plaques in neuronal cells. Because Aβ has a pathological role in the progression of AD, the Aβ-injected rat model is regarded as the most reliable model for understanding the pathophysiology and pathogenesis of AD. Previous studies revealed that ICV Aβ (1-42) infusion in rodents causes marked reductions in acetylcholine in the hippocampus and cerebral cortex and dopamine release in the striatum. Administration of Aβ (1-42) in rats also causes impaired learning and memory function. The protein aggravates the production of free radicals, causing oxidative stress and neuronal cell apoptosis. These findings suggest the involvement of multiple neuronal pathways in Aβ (1-42)-induced neurotoxicity. In the current study, we observed declines in memory function after ICV infusion of Aβ (1-42) in rat brain, which is in accordance with previous findings. Plant-derived natural products are of great interest to researchers owing to their versatile applications. Medicinal plants and their phytoconstituents have tremendous potential for development into effective anti-AD drugs. Various plant extracts and bioactive molecules with antioxidant property show protective effects against Aβ (1-42)-induced neurotoxicity. The protective effect of Tetraclinis articulata essential oil against

| Group                  | GSH (μM/mg protein) | MDA (nmol/mg protein) | Nitrite (μM/mg protein) | Catalase (nmol H2O2 consumed/mg protein) | AChE (nmol/min/mg protein) |
|------------------------|---------------------|-----------------------|--------------------------|----------------------------------------|---------------------------|
| Sham                   | 11.15±0.4148        | 4.04±0.6871           | 21.33±2.805              | 35.89±3.262                            | 20.77±1.465               |
| Aβ (1-42)              | 1.528±0.5620*       | 17.28±0.7268*         | 47.83±2.927*             | 11.80±1.795*                           | 62.20±1.819*              |
| Aβ (1-42) + EEDS 300   | 3.917±0.4286c       | 11.97±0.7575c         | 42.83±2.927c             | 17.24±2.81l                            | 57.08±4.524               |
| Aβ (1-42) + EEDS 500   | 10.25±0.6797c       | 7.892±0.4769c         | 25.67±2.582c             | 32.52±1.951c                           | 30.69±1.534               |
| Aβ (1-42) + donepezil  | 10.89±0.3765c       | 6.733±1.281f          | 22.67±2.338c             | 33.42±2.067c                           | 22.42±1.813               |

*p<0.001 compared with the sham control, *p<0.05 compared with the Aβ (1-42) control, *p<0.01 compared with the Aβ (1-42) control, *p<0.001 compared with the Aβ (1-42) control. Data are expressed as mean ± SD.

EEDS: Ethanolic extracts of Dalbergia sissoo leaves, GSH: Glutathione, MDA: Malondialdehyde, AChE: Acetylcholinesterase, SD: Standard deviation.
Aβ (1-42) administration in rats also resulted in increased AChE activity, which indicates cholinergic deficits. Moreover, Aβ (1-42)-injected animals showed significant augmentation of nitrite and MDA levels and diminution of GSH levels and catalase activity, resulting in increased lipid peroxidation. These findings support the role of oxidative stress in Aβ-induced neurotoxicity. Finally, Aβ (1-42) infusion in the hippocampus elevated TNF-α and IL-6 levels, thus suggesting that Aβ (1-42)-induced neurotoxicity is associated with neuroinflammation.

EEDS pre-treatment decreased the latency and improved the performance of rats exposed to Aβ in the MWM task in a dose-dependent manner. It also decreased AChE activity and improved cholinergic functions in Aβ (1-42)-treated rat brains. EEDS administration significantly depleted MDA and nitrite levels but increased GSH levels and catalase activity in Aβ (1-42)-lesioned rats. In addition, levels of the neuroinflammatory mediators IL-6 and TNF-α significantly decreased following EEDS pre-treatment, thereby indicating that the extract has ameliorative effects on neuroinflammation.

The outcomes of the present study demonstrated that D. sissoo attenuates the oxidative stress and memory dysfunction induced by Aβ (1-42) in rats. In addition, D. sissoo reduced AChE activity and neuroinflammation. Therefore, D. sissoo may have neuroprotective effects against Aβ(1-42)-induced neurotoxicity. These properties may be attributed to the abundant presence of the phytoconstituent biochanin A in the herb.

CONCLUSION

EEDS ameliorated the effect of Aβ (1-42) on cognitive functions and attenuated oxidative stress and neuroinflammation in rats. The present findings demonstrate that D. sissoo may potentially be useful in the prevention or treatment of AD.

ACKNOWLEDGMENTS

The authors sincerely thank JCDM College of Pharmacy, Sirsa, India, and IKG Punjab Technical University, Jalandhar, India, for providing the support and technical assistance necessary to complete this research.

Conflicts of interest: No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.

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