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EVALUATION OF COGNITION ENHANCING ACTIVITY OF *SESBANIA GRANDIFLORA* (L.) FRUITS EXTRACT ON HIGH FAT DIET INDUCED DEMENTIA

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ABSTRACT: The study was aimed to justify the traditional claim of fruits of *Sesbania grandiflora* (Leguminosae) as a medhya rasayana. Dementia was induced with chronic administration of a high fat diet for 90 days. Petroleum ether, benzene, chloroform, acetone, ethanol extracts of fruits of *Sesbania grandiflora* were evaluated for cognition-enhancing activity in high-fat diet-induced dementia in rats using an elevated plus maze and biochemical estimation of brain AchE and cholesterol level. Piracetam (200 mg/kg p.o.) as standard drug. Transfer latency (TL) was observed in HFD induced rats using EPM which showed significant increase ($p<0.01$) in TL as compared to the normal control group. The high-fat diet-induced rats showed a significant increase ($p<0.01$) in AchE and cholesterol levels as compared to normal control. Whereas petroleum ether extract treated rats showed a significant increase ($p<0.01$) in AchE and cholesterol level. Treatment with benzene, chloroform, acetone ethanol extract of *Sesbania grandiflora* fruits inhibited the rise in brain acetylcholinesterase and cholesterol level. These observations established traditional claim, and thus *Sesbania grandiflora* could be memory enhancer might be due to the presence of flavonoids.

INTRODUCTION: Dementia is characterized by a gradually decline in memory and loss of cognitive function [1]. Dementia associated with Alzheimer's disease is most common cause of memory impairment and cognitive dysfunction in the elderly population [2]. Alzheimer's disease (AD) is the gradual degeneration of neurons in specific brain areas such as frontal and temporal region [3]. Acetylcholine is considered as the most important neurotransmitter present in the CNS and peripheral autonomic and somatic nervous systems [4].

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Alzheimer's disease (AD) is represented by neuro-pathological markers such as 1) neuronal loss, 2) synaptic degeneration, 3) accumulation of Aβ (amyloid- β), 4) hyperphosphorylated tau protein [5, 6]. Currently available treatment for AD is symptomatic use of acetylcholine esterase inhibitors (AchEI) and N-methyl-D aspartate receptor antagonist memantine such treatment is short term not effective [7].

Due to the resulting side effect of these agents, they have limited their use [8]. Currently, there is no satisfactory therapeutic regimen available for the management of cognitive dysfunction. Ayurveda is the ancient science of medicine with the prime objective is to maintain good health and to cure disease [9]. The eight specialized branches of Ayurveda is Rasayana (rejuvenator). Rasayana is defined as the means of achieving the finest quality

of Rasadidhatu (body tissues) where it increases life span, improves Medha (intelligence), cures disease, stabilizes youthfulness, improves lustre, complexion, voice and makes body and senses strong and healthy *etc.* [10] Medhya rasayana is special class of Rasayana which acts on medha (intellect) to promote the cognitive function of the brain [11]. Medhya Rasayana (memory promoting rejuvenation therapy) herbs such as Mandukaparni (*Centella asiatica*), Yashtimadhu (*Glycyrrhiza glabra* Linn), Guduchi (*Tinospora cardifolia* Wild) Sankhapushpi (*Convolvulus pleuricaulis*). *Sesbania grandiflora* (Leguminosae) is a soft wooded tall, slender tree that reaches 6.9 m in height, 20-25 cm width. Leaves 5-30 cm long; leaflets 16-30 pairs, linear-oblong. Pods 50 cm long or 15-20 pale colored seeds. 10 cm long with showy, fleshy, white, crimson, red or pink petals. It is commonly known as Hadaga. It is usually cultivated in India, Australia, Indonesia, Malaysia, and Myanmar [12, 13].

The *Sesbania grandiflora* revealed the acetone and ethanol extract of *Sesbania grandiflora* was evaluated for antioxidant activity by using DPPH assay, total Phenolic content, reducing power assay, and inhibition of lipid oxidation in linoleic acid emulsion. Semwal *et al.* reported significant neuroprotective effects in celecoxib treated mice through the modification in the cholinergic system or the blockage of oxidative stress and inhibition of AchE enzyme [14]. Manmath K *et al.*, reported methanolic extract of *Sesbania grandiflora* fruits exhibited a significant anti-hyperglycemic activity in T2DM induced hyperglycemia [15]. The present study was aimed to justify pharmacological basis of the traditional use of *Sesbania grandiflora* fruits as Medhya rasayana which enhance cognition [16].

MATERIALS AND METHODS:

Plant Material: The fruits of *Sesbania grandiflora* were collected from the local market of karad, Maharashtra. The botanical identification and authentification were done by Priyanka A. Ingle, scientist B, Botanical survey of India, western regional center, Pune. Herbarium of *Sesbania grandiflora* was deposited at the Botanical Survey of India, western regional center, Pune with identification certificate no. 196.

Extraction Process: The fruits of *Sesbania grandiflora* were dried in the shade for 15 days. The shed dried powder of fruits of *Sesbania grandiflora* was reduced to a coarse powder and sieved. The powder was subjected to successive hot continuous extraction (soxhlet apparatus) with pet ether (60-80), benzene, chloroform, acetone, ethanol to about 40cycles per batch for 10 batches. The extraction was continued until the solvent in the thimble become clear then a few drops were collected in a test tube during the completion of the cycle (during siphoning) chemical test of that solvent was performed. Each time before extracting with the next solvent, the powdered material was dried at room temperature.

Phytochemical Screening: Preliminary phyto-chemical extract was carried out the presence of phytoconstituents like carbohydrate, alkaloids, flavonoids, steroids, saponin, proteins, glycosides, tannins, and polyphenol.

Laboratory Animals: The experiments were carried out using Sprague dawle rats weighing (125-150 gm) were used in the present study. The animal had free access to food and water, and they were housed in a natural 12 h light-dark cycle. The animals were acclimatized for at least 5 days to the laboratory conditions before behavioral experi-ment. The experimental protocol was presented in the IAEC meeting held on 22 January 2018. The approval for the use of lab animals (Reference no. IAEC/ABCO/09/2017-18) was taken from the Institutional Animal Ethics Committee (IAEC), Appasaheb Birnale College of Pharmacy, Sangali. All the experiments were conducted according to ethical principles and guidelines provided by the Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Acute Oral Toxicity Study: The acute oral toxicity study of the extract was carried out as per the guidelines set by Organization for Economic Cooperation and Development (OECD), received draft guidelines, received from Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India.

Elevated Plus Maze: The elevated plus maze served as the exteroceptive behavioral model (wherein the stimulus existed outside the body) to

evaluate learning and memory in mice. The apparatus consisted of two open arms (16 cm × 5 cm) and two covered arms (16 cm × 5 cm × 12 cm). The arms extended from a central platform (5 cm × 5 cm), and maze was elevated to a height of 25 cm from the floor. On the first day, each mouse was placed at the end of an open arm, facing away from the central platform. Transfer latency (TL) was taken as the time taken by the mouse to move into any one of the covered arms with all its four legs. TL was recorded on the first day. If the animal did not enter into one of the covered arms within 90 sec it was gently pushed into one of the two covered arms, and the TL was assigned as 90 sec.

The mouse was allowed to explore the maze for 10 sec and then returned to its home cage. Retention of this learned task (memory) was examined 24 h after the first-day trial (*i.e.* 9th day, 24 h after last dose). A significant reduction in TL value of retention indicated improvement in memory [17]. The TL was expressed as inflection ratio using formula given [18].

$$IR = (L_1 / L_O) / L_0$$

Where L_1 is the TL on day 8th and L_O is the TL on the 9th day.

HFD-induced Dementia: Animals were subjected to High fat diet (HFD) for 90 days to induce memory impairment [19].

Group I: Control group received distilled water.

Group II: Positive control group received a high fat diet for 90 days.

Group III: Standard group received a high-fat diet for 90 days + Piracetam (200 mg/kg p.o.)

Group IV: Test group received a high fat diet for 90 days + Pet ether (200 mg/kg p.o.)

Group V: Test group received a high fat diet for 90 days + Benzene (200 mg / kg p.o.)

Group VI: Test group received a high-fat diet for 90 days + Chloroform (200 mg/kg p.o.)

Group VII: Test group received a high fat diet for 90 days + Acetone (200 mg/kg p.o.)

Group VIII: Test group received a high fat diet for 90 days + Ethanol (200 mg/kg p.o.)

Biochemical Estimation:

Preparation of Enzyme Homogenate: Animals from each group were decapitated, and the brain was rapidly removed over ice and weighed.

The brain was homogenized (10 mg/ml) in 0.1 M phosphate buffer, pH 7.2, in a Teflon-glass Homogenizer (Remi, India). The reaction mixture consisted of 0.4 ml aliquot of homogenate, 2.6 ml of phosphate buffer (0.1 M, pH 8.0) and 0.1 ml of dithiobisnitrobenzoic acid (DTNB, 0.01 M).

After the addition of the substrate acetylthiocholine iodide (0.075 M), the absorbance was measured every 1 min for 3 min at 412 nm using spectro-photometer [20]. The rate of moles of substrate hydrolyzed per gram of tissue was later calculated as per the following equation:

$$R = \Delta A / C_0 \times 5.74 \ (10^{-4})$$

Where, $\triangle A$ = Change in absorbance per minute, C_0 = Original concentration of the tissue, R = Rate in moles substrate hydrolyzed per minute per gram of tissue.

Statistical Analysis: The result of the study were expressed as ± S.E.M. Data was analyzed by using one way analysis of variance test (ANOVA) followed by Dunnett's test for multiply comparisons. Statistical significance was set at $p<0.05$.

RESULTS:

Phytochemical Screening: Preliminary phyto-chemical screening of all the extracts of *Sesbania grandiflora* has shown the presence of flavonoids, steroids, saponin, proteins, glycosides, tannins, and polyphenol [21].

Elevated Plus Maze: Transfer latency (TL) was defined as the time (in seconds) taken by animals to move from the open arm into one of the closed arm with all its four legs.

Piracetam (200 mg / kg) used as standard drug improved memory ($P<0.01$) as compared to HFD induced group & reverse dementia induced by HFD. Ethanolic & Acetone extract (200 mg/kg) showed a reduction in TL on 8th day when compared to the HFD control group, indicating significant improvement in memory.

TABLE 1: PHYTOCHEMICAL CONSTITUENTS OF *SESBANIA GRANDIFLORA* FRUITS EXTRACTS

Plant Constituents	Petether Extract	Benzene Extract	Chloroform Extract	Acetone Extract	Ethanol Extract
Carbohydrate	+	-	-	+	+
Alkaloids	-	+	+	+	+
Flaonoids	-	+	+	+	+
Steroids	+	-	-	+	+
Saponin	+	+	+	+	+
Protein	-	-	-	+	+
Glycosides		-	-	+	+
Tannins	-	+	+	+	+
Polyphenol	-	-	-	+	+

+ = Present, - = Absent

TABLE 2: EFFECT OF *SESBANIA GRANDIFLORA* FRUITS EXTRACT ON TRANSFER LATENCY USING EPM

Group	Treatment	TL1	TL2
I	Control	73.66 ± 4.64	55.66 ± 2.83
II	HFD (Control)	88.16 ± 1.27	81.66 ± 1.33
III	Piracetam	69.66** ± 1.05	33** ± 1.43
IV	Pet ether	87.66^{ns} ± 1.05	85 ^{ns} ± 0.96
V	Benzene	89 ^{ns} ± 0.63	85.83 ^{ns} ± 0.60
VI	Chloroform	89.33 ^{ns} ± 0.42	83.83 ^{ns} ± 1.07
VII	Acetone	69.83** ± 1.83	51.83** ± 0.60
VIII	Ethanol	71.66** ± 2.09	55.5** ± 1.76

Values are mean ± SEM, ANOVA followed Dunnett's test (n = 6) *P < 0.05 Compared to HFD Control, **p < 0.01 Compared to HFD Control

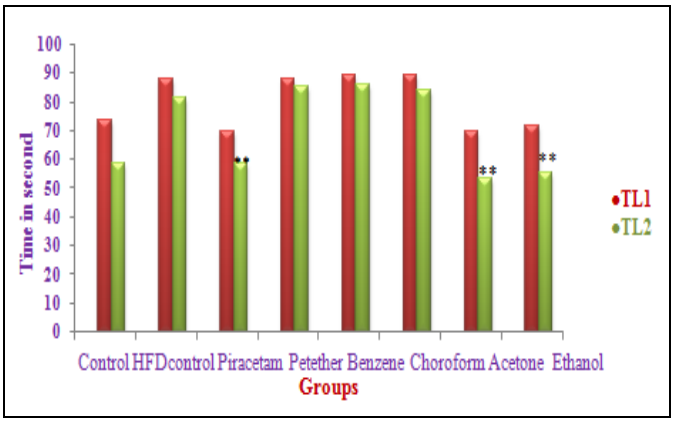

FIG. 1: EFFECT OF *SESBANIA GRANDIFLORA* FRUITS EXTRACT ON TRANSFER LATENCY USING ELEVATED PLUS MAZE. Values are mean ± SEM, ANOVA followed Dunnett's test (n=6). *P < 0.05 Compared to HFD Control, **p < 0.01 Compared to HFD Control

Brain Acetyl Cholinesterase: High fat diet treated animals showed elevated level of acetyl cholinesterase indicating its memory reducing potential.

The positive control group treated with standard drug piracetam produced significant (p<0.01) reduction of acetyl cholinesterase enzyme activity in comparision with normal control group. In the treatment group, the animals treated HFD and treated with ethanolic extract significantly decreased the acetylcholinesterase enzyme activity in comparison with negative control group. The animals treated HFD and treated with acetone extract (200 mg/kg) significantly decreased the acetylcholinesterase enzyme activity in comparison with the negative control group.

Rats subjected to HFD for 90 days showed a significant increase in the total serum cholesterol level of animals when compared with the control group. Treatment with ethanolic and acetone extract decreased HFD induced rise in total serum cholesterol level.

TABLE 3: EFFECT OF *SESBANIA GRANDIFLORA* FRUITS EXTRACTS ON BRAIN ACHE

Groups	Mean values of Acetylcholinesterase activity (In mole × 10^{-6})
Control	37.66 ± 1.382
HFD (Control)	127.5$^{\#}$ ±1.1784
Piracetam	94.16 ± 1.329
Pet ether	129.6 ± 0.95
Benzene	92.33** ± 1.033
Chloroform	81.66** ± 1.033
Acetone	83.83** ± 1.229
Ethanol	92.58** ± 1.357

Values are mean ± SEM, ANOVA followed Dunnett's test (n = 6). #p < 0.01 Compared to Control *P < 0.05 Compared to HFD control, **p < 0.01 Compared to HFD Control

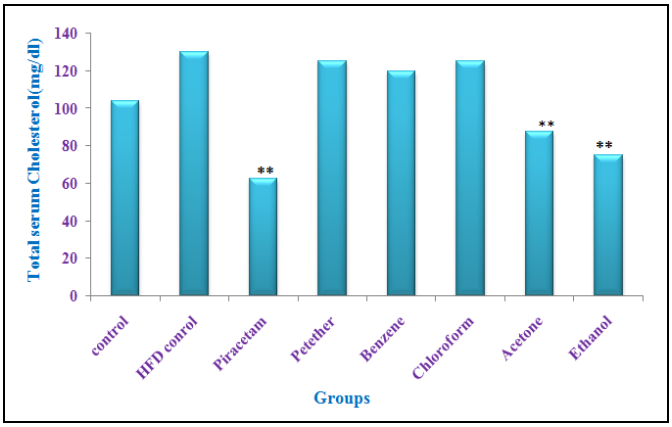

FIG 2: EFFECT OF *SESBANIA GRANDIFLORA* FRUITS EXTRACTS ON LEVELS OF CHOLESTEROL

DISCUSSION: Alzheimer's disease (AD) is progressive neurodegenerative disease characterized by cognitive and non-cognitive dysfunction such as difficulty in thinking, memory loss, disturbance in behavior and speech, and makes every task of day to day life complex [22]. First day Transfer latency indicated the learning ability of animals whereas Transfer latency of the second day indicated memory. Piracetam was first representative class of nootropic agents have been shown to improve impaired memory in children and geriatric.

High-fat diet (90 days) increase TL significantly on the first day and second day as compared to control group (distilled water), indicating impairment in learning and memory. Piracetam (200 mg/kg p.o.) for 8 days improves learning and memory. Ethanolic, Acetone, benzene, and choloroform extract of *Sesbania grandiflora* showed reversed impairment in learning and memory by a significant decrease in TL on second day whereas petether, extracts of *sesbania grandiflora* did not showed improvement in learning and memory.

Piracetam (200 mg/kg p.o.) was administered for 8 days to improve learning and memory significantly and reversed memory impairment effect due to chronic administration of a high-fat diet. The neuronal cell membrane of the brain composed of cholesterol, which performs several biological functions. Cholesterol plays a crucial role in the deposition and clearance of amyloidal peptide. Apolipoprotein-E is cholesterol transporting protein in the brain responsible for the deposition of amyloid plaque. Nowadays, an ample number of scientific reports showing a strong link between high cholesterol levels and high incidence of Alzheimer's disease. Therefore, a new therapeutic strategy aimed at reducing blood cholesterol levels is gathering momentum for the management of Alzheimer's disease. The main histological features of AD include extracellular protein deposits termed as β-amyloid (Aβ) plaques, Aβ deposits in blood vessels, and intraneuronal neurofibrillary tangles. A marked increase in cholesterol levels increases Aβ in cellular and most animal models of AD and drugs that inhibit cholesterol synthesis lower Aβ in these models. Clinical studies suggested that the net brain cholesterol concentration is regulated by serum cholesterol levels and that there is a crosstalk between the CNS and peripheral cholesterol pools. Therefore, it is plausible that peripheral cholesterol levels modulate CNS cholesterol levels and vice versa [23]. In the present study, treatment with benzene, chloroform, acetone, and ethanol extract of *Sesbania grandiflora* fruits inhibited the rise in brain acetylcholinesterase and cholesterol level. Acetylcholine is neurotransmitter synthesized from cholinergic neurons of the brain, which regulate the transmission of signals and delivery of messages in the brain [24]. AchE is the presynaptic (cholinergic) and postsynaptic (cholinoceptive) component of cholinergic pathway and responsible for termination of neurotransmission and plays important role in the regulation of cognitive function [25]. Selective loss of cholinergic neurons and decline in cholinacetyltransferase activity was hallmark of senile dementia of Alzheimer's type.

A high-fat diet (90 days) showed an elevated level of acetylcholinesterase, indicating its memory reducing potential. Treatment with benzene, chloroform, acetone, and ethanol extract of *Sesbania grandiflora* fruits inhibited the rise in brain acetylcholinesterase and cholesterol level.

CONCLUSION: The observations in the present study establish the traditional claim, and thus, plant *Sesbania grandiflora* should be a cognition enhancer in the future. In the present study, benzene, chloroform, acetone ethanol extract of *Sesbania grandiflora* fruits have significant cognition-enhancing activity.

Benzene, chloroform, ethanol, and acetone extracts of *Sesbania grandiflora* fruit have Presence of higher level of flavonoids may be responsible for the cognition-enhancing activity. Further investigations using more experimental paradigms are required for confirmation of *Sesbania grandiflora* fruit for cognition-enhancing potential in the treatment of various cognitive disorders.

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