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Effect of Polyherbal Formulation on Learning and Memory in Scopolamine Induced Animal Model of Alzheimer's Disease Neuroprotective effect of Sumanas

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ABSTRACT

Context: - Since there is no any scientific data is available in the management of Alzheimer's disease by using Sumanas. Hence, the present study is designed to systematically demonstrate the memory enhancing property of Sumanas (SMS) in experimental animal models of Alzheimer's disease.

Objective: - The present study was intended to scientificallyvalidate the effect of Sumanas (SMS), a polyherbal formulation, against scopolamine induced animal model of Alzheimer's disease.

Methods: - The memory upgrading action of SMS was established by in vivo (Radial 8 arm maze) process. The Anti- Alzheimer action of Sumanas was evaluated by assessing serum levels of GSH, SOD, total protein, lipid profile and also byhistopathological examination of the brain.

Results and Discussion: -The outcome of Sumanas on biochemical parameters in Scopolamine induced model exhibits a significant alteration in GSH, SOD, total protein, lipid profile contents were noticed. In the current investigation it was observed that, Sumanas (25, 50, 100 mg/Kg) in a dose dependent manner significantly attenuated thesealtered biochemical parameters.The results of current research indicated that, the Sumanas got beneficial outcome in the management ofAlzheimer's disease. The statistical results and histopathological observations alsoconfirmed that the Sumanas is a best polyherbal formulation in the management of Alzheimer's disease due to the presencevarious phytoconstituents in it.

Conclusion: - The outcome of presentinvestigation indicates that, Sumanas can be suitable as appropriate herbal formulation to treat Alzheimer's disease models since it has improved the cognitive impairment through memory enhancing property. Which was established by the assessment of different biochemical parameters in scopolamine induced animal modelutilized wasestablished by statistical analysis and also confirmed by histopathological report.

Key words: - Alzheimer's disease, Sumanas, Scopolamine, Memory enhancer, cognitive defect.

Key message:- The neuroprotective property of sumanas in the management of Alzheimer's disease.

I. INTRODUCTION

Alzheimer's disease (AD) is a degenerative brain disease, most general form of dementia that typically begins in late middle age or in old age which brings about reformist cognitive decline, bewilderment, weakened reasoning, and changes in character, temperament and checked histological changes by the degeneration of cerebrum neurons particularly in the cerebral cortex and by the presence of neurofibrillary tangles and plaques containing beta-amyloid.

The disease was named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer observed changes in the brain tissue of a lady who had died of asurprising psychological sickness. Her indications included cognitive decline, language troubles, and flighty conduct. After she passed on, he analyzed her cerebrum and discovered numerous strange bunches (presently called amyloid plaques) and tangled heaps of filaments (presently called neurofibrillary, or tau, tangles).

These plaques and tangles in the brain are as yet thought to be a portion of the primary highlights of AD. Another component is the deficiency of associations between nerve cells (neurons) in the cerebrum. Neurons send messages

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between various pieces of the brain, and from the cerebrum to muscles and organs in the body. Numerous other complex brain changes are thought to assume a part in Alzheimer's as well. This harm at first seems to happen in the hippocampus, the piece of the cerebrum fundamental in shaping recollections. As neurons pass on, extra pieces of the mind are influenced. By the last phase of Alzheimer's, harm is boundless, and brain tissue has contracted effectively.

Presently, the management of Alzheimer's disease is non acceptable and allopathic drugs for management of Alzheimer's disease is not sufficient and not much benefited so in this concern, natural products probably signify an wonderful source to develop safe and effective agents for management of AD. The polyherbal formulation, Sumanas (SMS) used by Ayurvedic practitioner to treat cognitive decline cases. The component of this includes, Brahmi, Shankhapushpi, Jatamamsi, Sarpagandha, Parasika Yavani and Vacha. The Bramhi (Bacopa monnieri), Shankhapushpi (Clitoria ternatea), Jatamamsi Nardostachys (jatamansi), Sarpagandha (Rauwolfia serpentina), Parasika Yavani (Hyoscyamus niger), Vacha (Acorus calamus)reported to possess memory enhancing activity in AD.

However in any case, no scientific data is available for the management of Alzheimer's disease by using Sumanas. Hence, the presentstudy is designed to systematicallydemonstrate thememory enhancing property of Sumanas (SMS) in experimental animal models of AD.

II. METHODOLOGY

- **Materials and methods:**

Source of data: All the data collected from the animal experiments and standard parameters for the study.

- **Methods of collection of data**

Collection of SMS

SMS powder collected from pavaman Pharmaceuticals, Vijayapur, Karnataka, India

- **Method for the evaluation of SMS tablet for anti-Alzheimer activity**

Animals: Young male Swiss albino rats (150–200 g) were used for the study. Animals were acclimatized to laboratory conditions at room temperature prior to experimentation. Animals were kept under standard conditions of a 12-hour light/12-dark cycle with food and water ad libitum in groups of 2, in plastic cages with soft bedding. The protocol was approved by the Institutional Animal Ethics Committee (IAEC) of B.L.D.E.A's SSM College of Pharmacy and Research Centre Vijayapur. [IAEC file no. BLDE/BPC/2019-20/645] on 21-9-2019

Before initiation of the experiment and all the experiments carried out in accordance with the CPCSEA Guidelines for the use and care of laboratory animals, the present research work not funded by any agencies and the author declared that there is no conflict of interest in this study.

Model 2: Scopolamine induced Alzheimer's diseasemodel:-

The animals divided into different groups:-

Groups	Treatment
Sham	Untreated-received distilled water orally for 15 days
Control	Received scopolamine (2mg/kg i.p) for 15 days.
Standard	Received scopolamine (2mg/kg i.p) and Rivastigmine (2mg/kg orally) for 15 days.
Treated	Received scopolamine (2mg/kg i.p) and Low dose (25mg/kg) of SMS orally for 15days.
Treated	Received scopolamine (2mg/kg i.p) and Moderate dose (50mg/kg) of SMS orally for 15days.
Treated	Received scopolamine (2mg/kg i.p) and High dose (100mg/kg) of SMS orally for 15days.

Radial 8 Arm Maze Test

- In radial arm maze the study of spatial reference and working memory process in rats were assessed.
- It is a wooden elevated 8 arm radial maze with arms extending from a central platform having a diameter of 20 cm.
- Each arm is 56 cm long and 5 cm wide with height of 2 cm. Food pellets which serve as reward at the end of the arm.

Apparatus:

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- Animals are trained daily to collect food pellets.
- The session terminates after 8 choices and the rat has to obtain the maximum no. of rewards with least no of errors.
- The baited arms- 2, 4, 6, 8 (reference memory error) and non baited arms-1, 3, 5, 7 (working memory error) are arranged for further analysis of cognitive performance of the animal.

Biochemical Estimations:-

i) Preparation of brain homogenate for the estimation of,

A. SOD
B. Protein
C. GSH

1) Dissection: The rats are decapitated; brains are removed quickly and placed in ice-cold saline. Frontal cortex, hippocampus and septum (and any other regions of interest) are quickly dissected out on a petridish chilled on crushed ice.

2) A homogenate **(10 % w/v)** is prepared in **0.1Mphosphate buffer (pH 7.4).** The homogenate was centrifuged at 10,000 rpm for **15 minutes** and aliquots of supernatant was separated and used for biochemical estimation.

A. Superoxide dismutase (SOD): The SOD activity (U/mg of protein) was calculated by using the standard plot.

B. Protein: The protein concentration in samples was determined.

C. Glutathione (GSH): The GSH activity (U/mg of protein) was calculated by using the standard plot.

ii) Determination of serum Lipid profile

A. Total Cholesterol
B. Triglycerides
C. High density lipoprotein (HDL) cholesterol
D. LDL-cholesterol

Statistical analysis: All the data was expressed in mean ± SEM. The significance level of mean between control and treated animals for different parameters was determined by one way ANOVA followed by Dunnett's Multiple Comparison Test. P value < 0.05 was considered as statistically significant.

Histopathological studies:-

The brains of all the animals were fixed with 10% formalin and embedded in paraffin wax and cut into longitudinal section of 5 µm thickness. The sections were stained with haemotoxylin and eosin dye for histopathological observation.

III. RESULTS

Anti-Alzheimer's Activity:-

➢ **Scopolamine induced Alzheimer's disease model:-**

In the present model, control animals showed increased level of LDL, TC, TG and total protein content whereas SOD, GSH and HDL levels were decreased. Animals pretreated with SMS at different doses significantly restored these altered biochemical parameters in a dose dependent manner.

The data thus obtained of SMS was comparable with the standard drug (Rivastigmine 2mg/kg). The results were shown in Table-1, 2.Hence the memory enhancing property of SMS polyherbal formulation in graded doses (25, 50 and 100 mg/kg) was found to be almost equal potent to the reference slandered drug, Rivastigmine in this model.

Table-1
Effect of SMS in scopolamine induced AD Model

Groups mg/kg	SOD (U/mg of protein)	Total protein (U/mg of protein)	GSH (nmoles/mg of protein)
Sham	6.8±0.31	0.79±0.12	18.9±0.03
Control	2.8±0.21[a]	1.03±0.11[a]	14.3±0.06[a]
Standard	6.4±0.26***	0.71±0.23***	18.2±0.05***

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SMS(25mg)	3.9±0.62*	1.00±0.13[ns]	15.9±0.07*
SMS(50mg)	5.8±0.68**	0.66±0.21**	16.6±0.05**
SMS(100mg)	6.1±0.41***	0.63±0.15***	17.1±0.04**

All the values are expressed as mean±SEM, n=6, [a]p<0.001, as compared to sham group; and*p<0.05, **p<0.01, ***p<0.001, [ns]Nonsignificant (One way Analysis of Variance [ANOVA] followed by Dunnett's test for multiple comparisons) as compared to control group.
Note: SMS: Sumanas tablet; GSH: Reduced Glutathione; SOD: Superoxide dismutase.

Table-2
Effect of SMS on lipid profile in scopolamine induced AD model.

Groups mg/kg	**lipid profile**			
	TC	**TG**	**HDL**	**LDL**
Sham	113.39±0.25	61.78±0.42	58.66±0.32	70.94±1.31
Control	143.11±0.65[a]	82.69±1.11[a]	49.23±0.87[a]	103.86±1.31[a]
Standard	120.78±1.64**	60.04±1.87**	59.21±0.84**	72.44±0.68***
SMS(25mg)	132.21±2.12*	75.01±1.73*	50.43±1.12*	89.23±0.64*
SMS(50mg)	129.15±2.91**	69.18±1.65**	53.76±0.89*	81.01±1.31**
SMS(100mg)	123.18±2.14**	63.79±1.14**	59.32±0.88**	76.76±0.98***

All the values are expressed as mean±SEM, n=6, [a]p<0.001, as compared to sham group and *p<0.05, **p<0.01, ***p<0.001, (One way Analysis of Variance [ANOVA] followed by Dunnett's test for multiple comparisons) as compared to control group.
Note: SMS: Sumanas; TC: Total Cholesterol; TG: Triglyceride; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotei.

Effect of SMS on histopathological studies in scopolamine induced model:-

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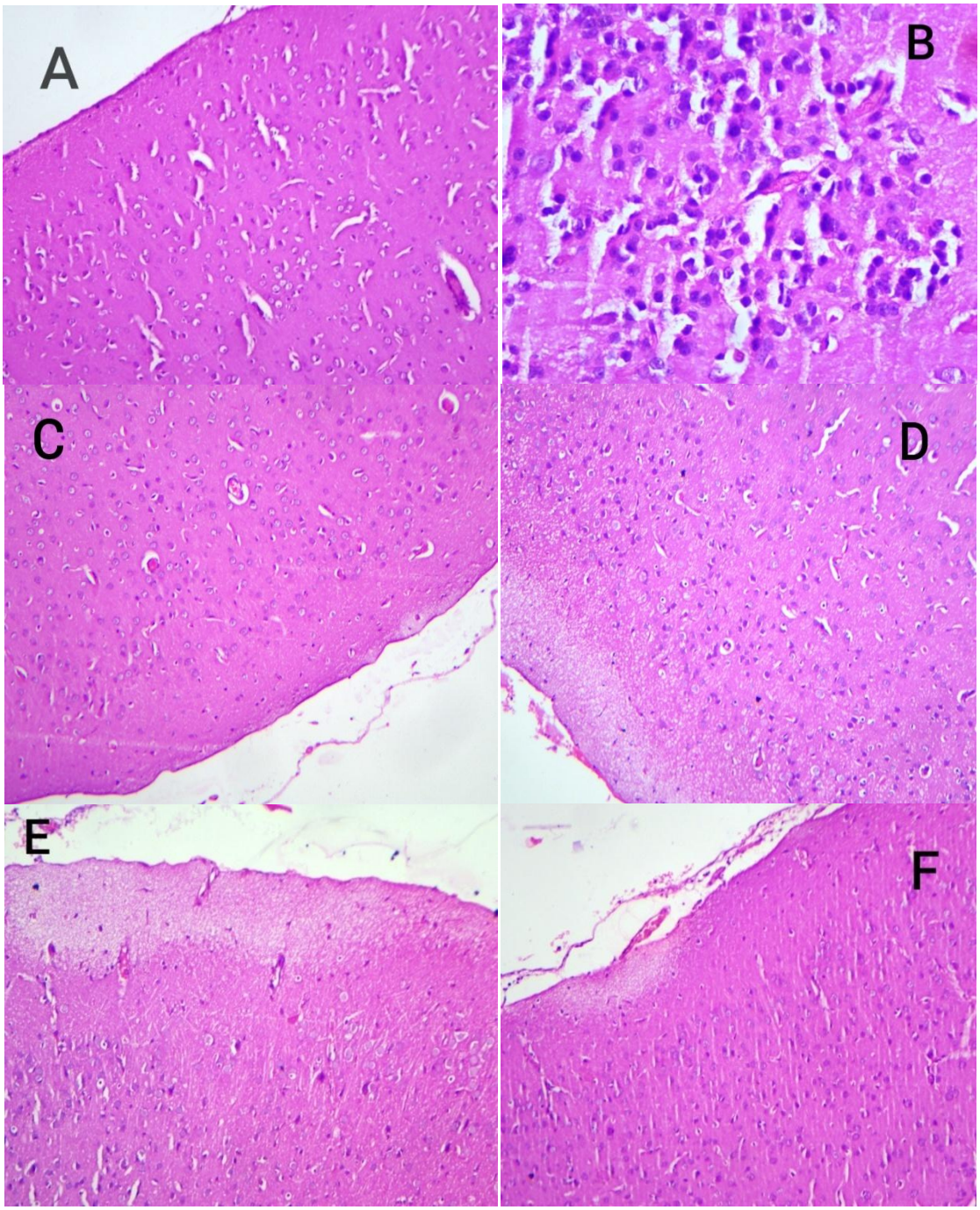

Fig.1. Effect of SMS in scopolamine induced AD in rat. Photograph of brain section of various treatment groups stained with Haemotoxylin and Eosin. Plates; A: Sham group, B: Control group, C: Standard D: SMS (25mg/kg) E: SMS (50mg/kg) F: SMS (100mg/kg).

Histopathological profile:-

In control group, the animals (Plate-B) showed severe changes in degeneration and pyknosis in hippocampal neurons and gliosis with increased infiltration of neutrophils. And moderate changes observed in congestion and hippocampal oedema with increased neuronal degeneration in cerebral cortex, when compared sham operated group (Plate-A).

In treated groups, the animals (Plate-D, E and F) showed decreased infiltration of neutrophils and infraction size, reduced

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intracellular space, increased density of cells and regained normal architecture and moderate necrosis was observed in striatum region of brain as compared to control group.

High dose of SMS (100 mg/kg - Plate F) showed significant improvement in striatum region of brain which can be comparable with standard (Rivastigmine) group (Plate-C).

IV. DISCUSSION

Alzheimer's disease is one type of brain disease which is also known as neurodegenerative disease withcognitive defectsand memory impairment. At the beginning stage the persons with AD wont experience any symptoms but later slowly brain start changing then the symptoms are visible such as loss of memory and problems in communication. These symptoms occur because of severe damage in neurons (nerve cells). Over the long term, manifestations will in general increment and begin meddling with person's capacity to perform regular exercises, now the individual is said to have dementia because of AD. The AD patient fails to perform routine activities which he did earlier in his life very easily that used to be core to the individual's identity, such as combing, cleaning, washing clothes, operating phone and planning family events or participating in sports. Finally, neurons in parts of the cerebrum that empower an individual to do fundamental real capacities, like strolling and gulping, are influenced. Individuals in the last phases of AD bed-bound and need nonstop consideration therefore over all it was confirmed that, the Alzheimer's disease is mortal and dangerous.

Scopolamine is famous anti cholinergic drug which blocks the functions of cholinergic system through muscarinic receptors hence known asanti muscarinic agent. And often it is used as a standard drug to produce cognitive impairment in experimental animals. Especially when scopolamine administrated intraperitoneally that leads to cholinergic dysfunction and impaired cognition in rats.

It was reported that, scopolamine cause memory impairment by causing oxidative stress. Previously, it was used in the conditions like child birth in obstetrics to induce twilight state and amnesia. Further specialists detailed that, scopolamine caused decline in choline acetyltransferase (the compound answerable for combination of acetylcholine) in cortex of AD patients, hence scopolamine used in cognitive research in AD patients. Scopolamine is also induced cerebral blood flow and glucose metabolism, which was studied with the help PET (Positron Emission Tomography).

Research reports also indicated that, cholinergic system plays vital role in balancing the memory function.The loss of memory and disorientation of AD was mainly due to decrease in central cholinergic system and Blockade of its functions hence loss of cholinergic neurons in brain areas like hippocampus, cortex, nucleus basal of meynert leads to loss of memory and learning. A cognitive deficit was mainly associated with reduction in cholinergic activity. Researchers reported that, scopolamine non- selectively occludes the adhesion site of Ach muscarinic receptors in cerebral cortex which alters the level of acetylcholine and induce learning and memory defects in dose dependent manner. Scopolamine can be either infused in amygdala (72 µg/ 219 0.5 µl at a rate of 1 µl/min) or given by intraperitoneal route (0.3 or 0.5 mg/kg) for cognitive dysfunction and memory impairment.This Scopolamine induced animal model successfully impairs the memory which causes the defects in cognition therefore it is one of the most widely used models because not having any difficult surgical procedures is not required.

Current study showed that, intraperitoneal administration of scopolamine caused significant loss in learning and memory associated with decreased level of GSH, SOD because of increased generation of free radicals and reduced activity of glutathione system in combating oxidative stress. Increased total protein level in the brain is due to an enhanced production in neurons associated with the progression of ADand decreased level of HDL while increase in LDL, TC, TG in lipid profile analysis because change in lipid metabolism and increased synthesis of amyloid –β protein leads to increase in cellular protein and cholesterol level in brain which responsible for AD. But these elevated levels in lipid profile were successfully restored by lower dose, moderate dose (50mg/kg) and high dose (100mg/kg) of SMS comparable with standard drug rivastigmine (2mg/kg).

Rivastigmaine is a carbamate-based, reversible, noncompetitive inhibitor of AChE hence it may acts by selectively inhibiting AChE enzyme which leads to enhance the cholinergic function this increases the availability of Ach therefore used as the standard drug for experimental animals in AD but exact mechanism is unknown.

SMS polyherbal formulation belongs to the group of Bramhi (Bacopa monnieri), Shankhapushpi (Clitoria ternatea), Jatamamsi

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Nardostachys (jatamansi), Sarpagandha (Rauwolfia serpentina), Parasika Yavani (Hyoscyamus niger), Vacha (Acorus calamus)Hence SMS acts as Medhya Rasayanas which strengthen the brain by enhancing the memory andintellectual functions and it is also involved in grasping and fast recall, improves learning by modulating dopamine, 5-Hydroxytryptamine receptor, and noradrenaline systems, which was also reported in a study on rats.

SMS reduces stress which is one among the factors leading to memory impairment by reduction in raised circulating corticosterone. SMS also shows immunomodulatory activity and strong antioxidant activity as revealed by increased level of Catalase, glutathione peroxidase, and glutathione in animals.

In SMS, Sankhapushpi is the most effective among all medicinal plants andis also effective in preventing the cognitive deficits as well as oxidative stress because it improve H_2O_2 in oxidative stress by creasing lipid peroxidation via alteration of the antioxidant defense system in rats and it also reduces anxiety and stress by controlling the production of body's stress hormones, adrenaline and cortisol. It is reported to possess anxiolytic and memory-enhancing and mood-elevating effects, and is claimed to retard brain aging. Neuroprotective role of C. pluricaulis has been proved in the study by Bihaqi et al. on aluminum-induced neurotoxicity in rat brain.

Hence it was confirmed that, the Anti-Alzheimer property of SMS was due to its memory enhancing property because it contains chief chemical constituents like alkaloids saponin flavonoidsetc,. These chemical constituents showed synergic effect, hence successfully act as memory enhancer in the management of animal models of AD.

Further histopathological study confirm that, SMS act as memory enhancer and cerebroprotective against AD models by decreasing the infiltration of neutrophils, and increased density of cells and reduce intracellular space with regained normal architecture by significant improvement in striatum region of brain.

Ayurvedic practitioner employing Sumanas for management of Alzheimer's disease like memory defects but lacks scientific validation therefore this research work was aimed to scientifically validate its use in the management of AD. Several researchers have been investigated the anti-Alzheimer's activity of the various plant extracts but no such reports available on Sumanas in the literature and this is the 1st research finding showing the enhancement of learning and memory by SMS.

V. CONCLUSION

The present investigation demonstratedthe neuroprotective property of Sumanas by improving the cognitive defects induced by scopolamine dueto its memory enhancing property. The outcomes of present study scientifically authenticate the traditional use of Sumanas as a appropriate polyherbal formulation for the management of Alzheimer's disease.

VI. ACKNOWLEDGEMENT

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Definition of intellectual content	✓	✓		
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Clinical studies				
Experimental studies	✓			✓
Data acquisition	✓			✓
Data analysis	✓	✓		✓
Statistical analysis	✓		✓	✓
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Manuscript editing	✓	✓	✓	✓
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