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EVALUATION OF NOOTROPIC ACTIVITY OF VANILLIC ACID ON SCOPOLAMINE INDUCED DEMENTIA IN RATS

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ABSTRACT

The Objective of study is "Dementia is also a symptom of a variety of specific structural brain diseases as well as several system degenerations. Dementia is 7th leading cause of death globally.50 million people lives with dementia. A new case of dementia diagnosed every 3 seconds. Dementia shows huge economic impact. Dementia targets person's life. Alzheimer's disease (AD) accounts for nearly 50% of all cases of dementia. It affects about 6% of the population aged over the 65 and increases the incidence with age .Alzheimer's disease (AD) is a neurodegenerative disorder that destroys cells in the brain associated with loss of neurons in distinct brain areas. Currently, various Nootropic drugs are available in the market for treating AD as well as dementia like physostigmine, rivastigmine, piracetam, donepezil, galantamine and tacrine. These drugs are effective but they are associated with side effects like excitement, convulsions, and tremors and are required to be used cautiously in peptic ulcer, asthmatic and hypotensive patients. Hence, there is need of a drug which is effective for neuroprotection, learning and memory enhancement; Hence in present investigation, an attempt will be made to evaluate beneficial effect of a phytoconstituent on Nootropic activity.

Keywords: Vanillic acid (VA), Dementia, Nootropic activity, Alzheimer's disease (AD)

INTRODUCTION

Brain is the organ that is responsible for what we call the mind. It is the basis for thinking, feeling, wanting, perceiving, learning and memory, curiosity, and behavior **[1, 2]**. Memory is an original mental process, and without memory we are capable of nothing but simple reflexes and stereo type behaviors .Cognition modulating drugs today command a large share in the pharmaceutical sales worldwide **[3, 4]** . Cognitive deficits have long been recognized as severe and consistent neurological disorders associated with numerous psychiatric and neuro-degenerative states. An increase in the human life span in developed countries is directly associated with an increased number of patients suffering from loss of memory due to aging **[5]**.

Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder that is slow in onset but leads to dementia, unusual behavior, personality changes, ultimately death. AD is characterized by the presence of excessive amounts of neurotic plaques containing amyloid protein loss of cholinergic markers in brain **[6]**. The loss of cholinergic neurons, predominantly in the basal forebrain, is accompanied by loss of the neurotransmitter acetylcholine. A decrease in brain acetylcholine (Ach) level appears to be a critical element in producing dementia in AD patients **[7]**. Dementia is also a symptom of a variety of specific structural brain diseases as well as several system degenerations. Dementia is 7th leading cause of death globally. 50 million people lives with dementia. A new case of dementia diagnosed every 3 seconds. Dementia shows huge economic impact. Dementia targets persons's life **[8]**.

Alzheimer's disease (AD) accounts for nearly 50% of all cases of dementia. It affects about 6% of the population aged over the 65 and increases the incidence with age. Alzheimer's disease (AD) is a neurodegenerative disorder that destroys cells in the brain associated with loss of neurons in distinct brain areas **[9]**.

Currently, various nootropic drugs are available in the market for treating AD as well as dementia like physostigmine, rivastigmine, piracetam, donepezil, galantamine and tacrine. These drugs are effective but they are associated with sideeffects like excitement, convulsions, and tremors and are required to be used cautiously in peptic ulcer, asthmatic and hypotensive patients **[10]**. Hence, there is

need of a drug which is effective for neuroprotection, learning and memory enhancement; Hence in present investigation, an attempt will be made to evaluate beneficial effect of a phytoconstituent on nootropic activity.

METHODOLOGY

Material

Animals

Wistar albino rats (150-200 m) either sex were used for study

Housing conditions

Animals were maintained under the standard laboratory conditions at 25 ± 2C, relative humidity 50 ± 15% and normal photoperiod (12 h dark \ 12 h light). The animal had free access to pellet diet and water were provided ad libitum **[11]**.

Institutional Animal Ethics Committee (IAEC) approval

The animals were maintained under standard condition in an animal house approved by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

The study protocol was approved by IAEC. YSPM/YTC/PHARMA-IAEC/44/2020

Apparatus **(Table 1)**.

Chemicals and drugs

All the chemicals used in the study of analytical grade and the list of various reagents used for study are given in following **Table 2**.

Table 1: List of apparatus used in study

Sr. No.	Apparatus/Instrument	Manufacturer
1	Digital weighing balance	Asiatechnweih-India
2	Ultra-sonicator	Bio-technics-India
3	Syringe	Dispovan
4	Oralfeedingneedles	Birdspark
5	Elevatedplusmaze	In house fabrication
6	Radialarmmaze	In house fabrication

Table 2: List of chemicals

Sr. No.	Drugs/Chemicals	Manufacturer/Suppliers
1	Vanilic acid	Dolphin pharmacy
2	Scopolamine	APP pharmaceutical
3	Piracetam	Dr. Reddy's Laboratories

Table 3: Grouping of animal

Sr. No	Group of animal	No. of animal	Treatment	Dose (mg/kg)	Route of administration
1	Control	06	Vehicle	1ml/kg	p.o.
2	Negative control	06	Scopolamine	0.4mg/kg	p.o.
3	Standard group	06	Scopolamine + Piracetam	0.4+200 mg/kg	p.o.
4	Test group with low dose	06	Scopolamine +Vanilic acid	0.4+ 25 mg/kg	p.o.
5	Test group with intermediate Dose	06	Scopolamine +Vanilic acid	0.4+ 50 mg/kg	p.o.
6	Test group with high dose	06	Scopolamine +Vanilic acid	0.4+100 mg/kg	p.o.

Elevated plus maze model

Principle

Elevated plus maze test is a novel test for the selective identification of anxiogenic and anxiolytic drug effects in rodents **[12]**. The test is principally based on the observations of Montgomery showing that exposure of animals to an elevated (open) maze alley evokes anapproach- avoidance conflict that is considerably stronger than that evoked by exposure to an open maze alley **[13]**. Exposure of rats to novel stimuli can evoke both exploratory drive and fear drive and generate approach-avoidance conflict response. Elevation of the maze causes greater fear and more avoidance conflict and study the effect on learning and retention memory **[14]**.

Requirements

Animal

36 Wistaral binomice (either sex) Body weight- 22-25gm

Chemicals & others

Saline solution, Vanillic acid, Piracetam, Digital weighing balance, Scopolamine, Elevated plus maze apparatus.

Figure 1: Elevated plus maze

Procedure

Select the albino mice of either sex having weight between 22-25gm and grouped as 6 animals each in 6 groups, as follows:

Group 1: Control group received saline solution (10ml/kg. p.o.),

Group 2: Negative group received Scopolamine (0.4mg/kgi.p

Group 3: Standard group received Piracetam (200mg/kg, p.o.)

Group 4: Test group received VA (25mg/kg,p.o.)

Group 5: Test group received VA (50mg/kg, p.o.)

Group6: Test group received VA (100mg/kg,p.o.)

The specific marking will be made on paw region of each rat with the picric acid for identification. Before the experiment animals will be kept in elevated plus maze for acclimatization for 7days and will be housed in group of six mice in one cage under the standard condition like room temperature is 22 + 3°C, relative humidity 45-55% and light and dark cycle of 12 hours **[14]**. All animals will be fed with standard diet and water will be supplied ad libitum under hygienic conditions. On the first day, each mouse will be placed at the end of open arm, facing away from the central platform **[15]**. Transfer latency (TL) will be taken as the time taken

by the mouse to move into any of the covered arms with all its four legs. TL will be recorded on the first day. If mouse does not enter into one of the covered arms within 90 sec, it will be gently pushed into one of two covered arms and TL will be assigned as 90sec **[16]**. The mouse will be allowed to explore the maze for 10 sec and the nitre turns to it's home cage. The TL on the first day serves as acquisition learning) and the retention consolidation (memory) will be examined 24hrs after the first day trial! **[17]**.

Evaluation

Reduction in transfer latency score was observed.

Percent of time taken to enter open arm to closed arm.

Radial arm maze model

Principle

Working memory is analogous to recent memory in humans, which refers to a brain system that provides temporary storage and manipulation of the information necessary for such complex cognitive tasks as comprehension, learning and reasoning **[18]**. This type of memory is more severely impaired than remote memory inhuman dementia, a radial arm maze is used to evaluate the working memory in animals **[19]**.

Requirements:

Animal

36 Wistar albino rats (either sex) Body weight-150-200gm

Chemicals & others

Citrate buffer, alloxanmonohydrate, saline solution, Vanillic acid, Piracetam, Digital weighing balance, Radial arm maze apparatus **[20]**.

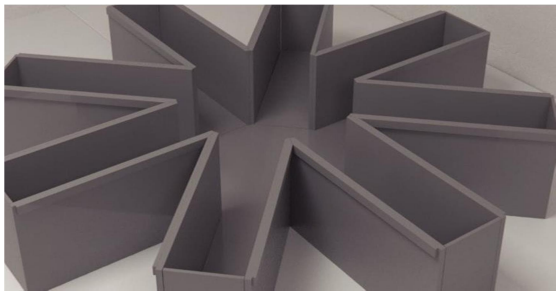


Figure 2: Radial arm maze

Procedure

Select the albino rats of either sex having weight between 150-200gm and grouped as 6 animals each in 6 groups, as follows:

Group1: Control group received saline solution (10ml/kg.p.o.), Group 2; Negative group received Scopolamine (0.4mg/kg i.p.) Group 3: Standard group received Piracetam (200mg/kg, p.o.) Group 4: Test group received VA (25mg/kg,p.o.)

Group 5: Test group received VA (50mg/kg, p.o.); Group 6: Test group received VA (100mg/kg,p.o.)

The specific marking has been made on paw region of each rat with the picric acid for identification Before the experiment animals will be kept in radial arm maze for

acclimatization for 7 days and they will be housed in group of two rats in one cage under the standard condition like room temperature is 26 + 2°C, relative humidity 45-55% and light and dark cycle of 12 hours **[21]**. All animals were fed with standard diet and water is supplied ad libitum under hygiene conditions. The beginning of trial, a food pellet will be placed in end of arms, the trial animals will be fasted over night prior to test but water will be supplied ad libitum **[22]**. Overnight fasted rat will be placed at central hub and allow to choose the arm freely to get the food pellet. The trial will be considered to be complete when rat visits all eight arms **[23]**. Observe the entry of rat in the arms is not previously visited will be recorded as a correct response and re-entry will be recorded as error. In trial the animal made no error and one error at the 8 choice are recorded as successful trial **[24]**. The percentage of successful trial will be calculated as the index of radial arm maze task performance. On11th day, 60 minutes after the last dose, each rat will be placed on central hub and tested again for successful trial **[25]**.

Evaluation

The index of radial arm maze task performance of mice before and after drug treatment.

Estimation of acetyl cholinesterase activity

Animal

36 Wistar albino rat (Either sex) Body weight:150-200gm.

Chemicals & other

Digital weighing balance, saline solution, Vanillic acid, Piracetam, 0.05 Mphosphate buffer (pH 7.2), 5, 5-dithiobisnitrobenzoic acid (DTNB), acetylcholine Chloride (10mm), formalin Solution.

Principle:

Acetylcholine is considered to be the most important transmitter involved in the regulation of cognitive functions such as learning and memory **[26]**. ACHE inhibitors which enhance the availability of acetylcholine in the synaptic cleft. There are extensive evidences are present in the decrease of ACHE enhancement of memory. In this study, we used a photometric method to determine the ACHE quantity in the brain tissue **[27]**. The enzyme activity is measured by following the increase of yellow produced from thiocholine when it reacts with dithiobis nitrobenzoate ion. There action is acetylthiocholine-thiocholine + acetate Thiocholine + dithiobisnitro benzoic Yellow **[28]**.

Procedure Selected Wistar rats of either sex having weight between 150-200gm and

grouped as 6 animals each in 6 groups, as follows,

Group1: Control group received saline solution (10ml/kg p.o.)

Group 2: Negative group received Scopolamine (0.4mg/kg i.p.)

Group 3: Standard group received Piracetam (200mg/kg, p.o.)

Group 4: Test group received VA (25mg/kg, p.o.)

Group 5: Test group received VA (50mg/kg, p.o.)

Group 6: Test group received VA (100mg/kg, p.o.)

The specific marking was made on paw region of each rat with picric acid for identification. Before the experiment animal was kept in acclimatization for 7days and housed in group of two rats in one cage under the standard condition like room temperature is 26°C. Relative humidity 45-55% and light and dark cycle of 12 hours. All animals were fed with standard diet and water was supplied ad libitum under hygienic conditions **[29]**. Wistar rats (150-200gm body weight) are used for the experiment.

The rats was sacrificed after 60 min of treatment with vehicle, Scopolamine, Piracetam, test drug: 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 **[30]**. The tissues was weighed and homogenized in 0.05M phosphate buffer (pH 7.2). 0.4ml aliquot of the homogenate is added to a cuvette containing 2.6ml phosphate buffer and 100ul of DTNB. The contents of the cuvette were mixed thoroughly by bubbling air and absorbance is measured at 412 nm in a spectrophotometer. When the absorbance reaches a stable value, it is recorded as the basal reading. Acetylthiocholine iodide was added and change in absorbance is recorded for a period of 10 minutes at intervals of 2 minutes. Change in the absorbance per minute is determined **[31]**. The mean change in absorbance was considered for calculation and acetyl cholinesterase activity is measured as M/U/min/gm of tissue evaluation of Level of actylcholine easterase **[32]**.

RESULTS

Effect of Vanillic acid on Transfer latency and memory retention by using elevated plus maze (Table 4).

Effect on transfer latency and memory retention in scopolamine induced dementia in rats (paired test) (Graph 1).

Effect on transfer latency in scopolamine induced dementia in rats

Elevated plus maze Treatment (Graph 2).

Interpretation

Negative group compared with control group only showed significant increase ($p<0.001$) in transfer latencies.

Animal treated with standard (piracetam 200mg/kg) showed significant decrease ($p<0.001$) in transfer latencies as compared to negative group.

Animal treated with VA (25mg/kg) showed significant decrease ($p<0.001$) in transfer latencies as compared to negative group.

Animal treated with VA (50mg/kg) showed significant decrease ($p<0.001$) in transfer latencies as compared to negative group.

Animal treated with VA (100mg/kg) showed significant decrease ($p<0.001$) in transfer latencies as compared to negative group.

Animal treated with VA (25mg/kg) showed significant decrease ($p<0.001$) in transfer latencies as compared to positive group (piracetam200mg/kg).

Animal treated with VA (50mg/kg) showed significant decrease ($p<0.001$) in transfer latencies as compared to positive group (piracetam200mg/kg).

Effect on Memory retention in scopolamine induced dementia in rats (Graph 3)

Interpretation

Negative group compared with control group only showed significant increase ($p<0.001$) in memory retention.

Animal treated with standard (piracetam 200mg/kg) showed significant decrease ($p<0.001$) in memory retention as compared to negative group.

Animal treated with VA (25mg/kg) showed significant decrease ($p<0.001$) in memory retention as compared to negative group.

Animal treated with VA (50mg/kg) showed significant decrease ($p<0.001$) in memory retention as compared to negative group.

Animal treated with VA (100mg/kg) showed significant decrease ($p<0.001$) in memory retention as compared to negative group.

Animal treated with VA (25mg/kg) showed significant decrease ($p<0.001$) in memory retention as compared to positive group (piracetam 200mg/kg).

Animal treated with VA (50mg/kg) showed significant decrease ($p<0.001$) in memory retention as compared to positive group (piracetam 200mg/kg).

Effect of Vanilic acid on time taken to reach reward arm (sec) by using radial arm maze (Table 5).

Effect of Vanilic acid on time taken to reach reward arm (sec) by using radial arm maze (Graph 4).

Graph 5: Effect of Vanilic acid on time taken to reach reward arm (sec) by using radial arm maze (Graph 5).

Effect of Vanilic acid on time taken to reach reward arm (sec) by using radial arm maze (Graph 6).

Interpretation

Negative group compared with control group only showed significant increase ($p<0.001$) in time taken to reach reward arm.

Animal treated with standard (piracetam 200mg/kg) showed significant decrease ($p<0.001$) in time taken to reach reward arm as compared to negative group.

Animal treated with VA (25mg/kg) showed significant decrease ($p<0.001$) in time taken to reach reward arm as compared to negative group.

Animal treated with VA (50mg/kg) showed significant decrease ($p<0.001$) in time taken to reach reward arm as compared to negative group.

Animal treated with VA (100mg/kg) showed significant decrease ($p<0.001$) in time taken to reach reward arm as compared to negative group.

Animal treated with VA (25mg/kg) showed significant decrease ($p<0.001$) in time taken to reach reward arm as compared to positive group (piracetam 200mg/kg).

Animal treated with VA (50mg/kg) showed significant decrease ($p<0.001$) in time taken to reach reward arm as compared to positive group (piracetam 200mg/kg).

Animal treated with VA (100mg/kg) showed significant decrease ($p<0.001$) in time taken to reach reward arm as compared to positive group (piracetam 200mg/kg).

Effect of Vanilic acid on Acetylcholinesterase activity (Table 6), **(Graph 7)**

Effect of Vanilic acid on acetylcholinesterase activity

AChE activity

Interpretation

Negative group compared with control group only showed significant increase ($p<0.01$) in AChE level.

Animal treated with standard (piracetam200mg/kg) showed significant decrease ($p<0.01$) in AChE level as compared to negative group.

Animal treated with VA (25mg/kg) showed significant decrease ($p<0.01$) in AChE level as compared to negative group.

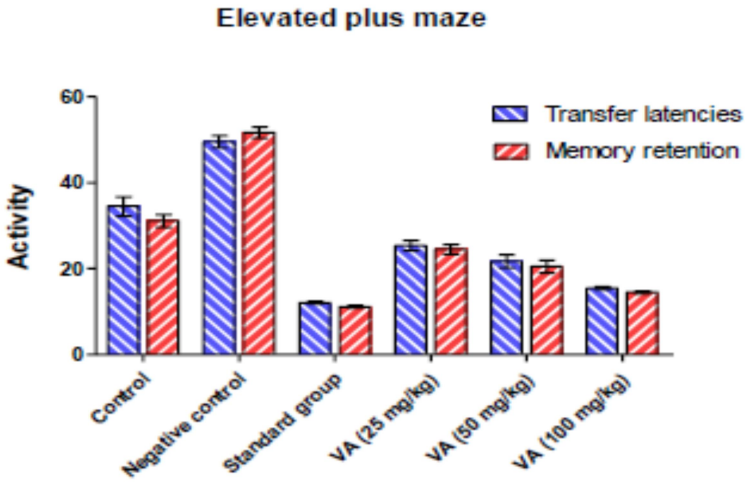
Animal treated with VA (50mg/kg) showed significant decrease ($p<0.01$) in AChE level as compared to negative group.

Animal treated with VA (100mg/kg) showed significant decrease ($p<0.01$) in AChE level as compared to negative group.

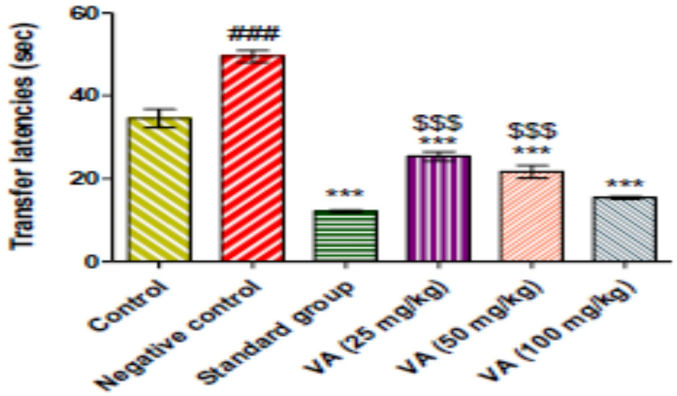
Table 4: Effect of Vanillic acid onTransfer latency and memory retention by using elevated plus maze

Group No.	Group	Elevated plus maze	
		Transfer latencies	Memory retention
1	Control	34.50± 2.2320	31.12± 1.4550
2	Negative control	49.50± 1.4120###	51.67± 1.3540###
3	Standard group	12.08± 0.3220***	11.17± 0.3220***
4	VA(25mg/kg)	25.36± 1.1250***$$$	24.50± 1.1250***$$$
5	VA(50mg/kg)	21.67± 1.4890***$$$	20.50± 1.4690***$$$
6	VA(100mg/kg)	15.43± 0.3136***	14.50± 0.3066***

Note- All values are presented as mean ± sem. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparison posttest. # indicate comparison with control group. * indicate comparison of negative group. $ indicate comparison with positive control. #/*/$ indicate p<0.05, ##//$$ indicate p<0.01and ###/***/$$$indicate p<0.001**

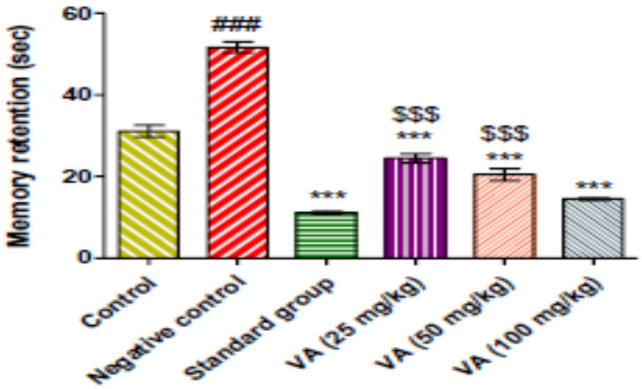


Graph 1: Effect on transfer latency and memory retention in scopolamine induced dementia in rats (paired test)
Note: All values are presented as mean±sem. Analysis was performed using paired t-test



Graph 2: Effect on transfer latency in scopolamine induced dementia in rats

Note- All values are presented as mean ± sem. Analysis was performed using one way ANOVA followed byBonferroni multiple comparison posttest. # indicate comparison with control group. * indicate comparisonof negative group. $ indicate comparison with positive control. #/*/$ indicate p<0.05, ##//$$ indicate p<0.01and ###/***/$$$indicatep<0.001**



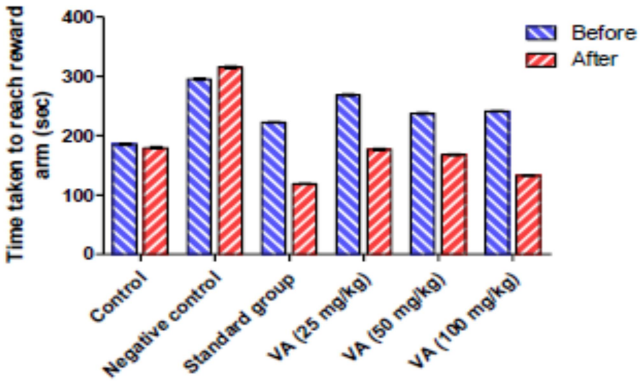
Graph 3: Effect on Memory retention in scopolamine induced dementia in rats

Note- All values are presented as mean ± sem. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparison posttest. # indicate comparison with control group. * indicate comparison of negative group. $ indicate comparison with positive control. #/*/$ indicate p<0.05, ##//$$ indicate p<0.01and ###/***/$$$ indicate p<0.001**

Table 5: Effect of Vanilic acid on time taken to reach reward arm (sec) by using radial arm maze

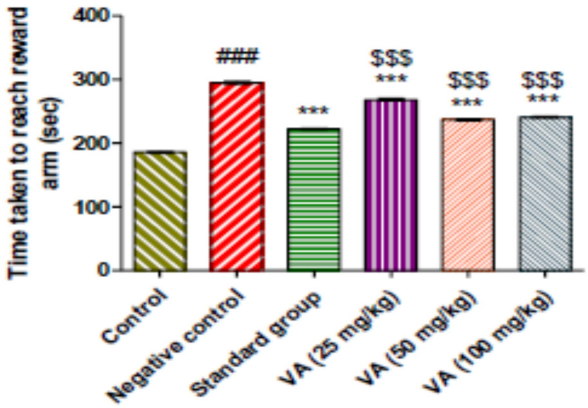
Group no	Group	Time taken to reach reward arm (sec)	
		Before	After
1	Control	185.7± 1.4990	179.6± 1.4990
2	Negative control	295.3± 1.7880###	315.4± 1.7880###
3	Standard group	222.4± 0.6878***	118.5± 0.6819***
4	VA(25mg/kg)	268.6± 1.4510***$$$	177.0± 1.4510***$$$
5	VA(50mg/kg)	237.4± 1.1980***$$$	167.9± 1.1980***$$$
6	VA(100mg/kg)	241.0± 0.7816***$$$	132.7± 0.7816***$$$

Note- All values are presented as mean ± sem. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparison post test. # indicate comparison with control group. * indicate comparison of negative group. $ indicate comparison with positive control. #/*/$ indicate p<0.05, ##//$$ indicate p<0.01and ###/***/$$$indicatep<0.001**



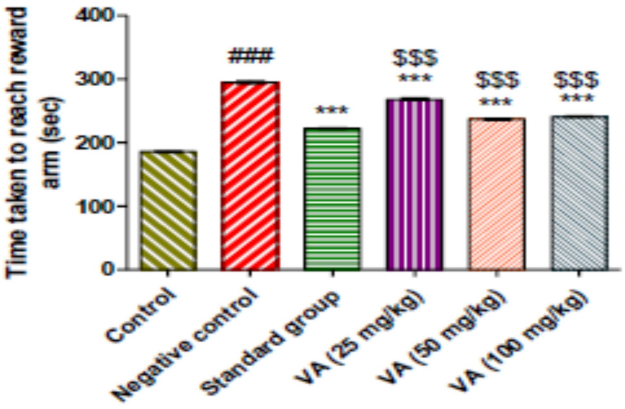
Graph 4: Effect of Vanilic acid on time taken to reach reward arm (sec) by using radial arm maze

Note- All values are presented as mean±sem. Analysis was performed using paired t-test



Graph 5: Effect of Vanilic acid on time taken to reach reward arm (sec) by using radial arm maze

Note- All values are presented as mean ± sem. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparison posttest. # indicate comparison with control group. * indicate comparison of negative group. $ indicate comparison with positive control. #/*/$ indicate p<0.05, ##//$$ indicate p<0.01and ###/***/$$$indicatep<0.001**



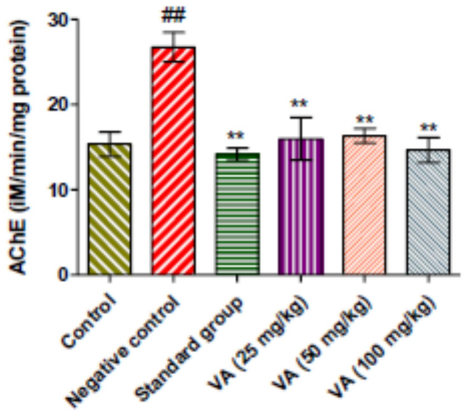
Graph 6: Effect of Vanilic acid on time taken to reach reward arm (sec) by using radial arm maze

Note- All values are presented as mean ± sem. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparison posttest. # indicate comparison with control group. * indicate comparison of negative group. $ indicate comparison with positive control. #/*/$ indicate p<0.05, ##//$$ indicate p<0.01and ###/***/$$$indicate p<0.001**

Table 6: Effect of Vanilic acid on acetylcholinesterase activity

Group no	Group	Acetylcholinesterase level (iM/min/mg protein)
1	Control	15.36± 1.460
2	Negative control	26.72± 1.737##
3	Standardgroup	14.17± 0.7326**
4	VA(25mg/kg)	15.99± 2.507**
5	VA(50mg/kg)	16.33± 0.8819**
6	VA(100mg/kg)	14.68± 1.466**

Note- All values are presented as mean ± sem. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparison posttest. # indicate comparison with control group. * indicate comparison of negative group.#/*indicate p<0.05,##/indicate p<0.01**



Graph 7: Effect of Vanilic acid on acetylcholinesterase activity

Note- All values are presented as mean ± sem. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparison posttest. # indicate comparison with control group. * indicate comparison of negative group.#/*indicate p<0.05,##/indicate p<0.01**

DISCUSSION

The concept and definition of a "nootropic drug" was first proposed in 1972 by C E Guirgea and coined the term "nootropic" from the italic words "noos" (mind) and "tropein" (toturn toward), to mean enhancement of memory. Typically nootropics are thought to work by increasing the brain's supply of neurochemicals (neurotransmitters, enzymes and hormones) improving brain oxygen supply or by stimulating nerve growth **[34]**.

ACh as a neurotransmitter primarily involved in learning and memory. ACh is a neurotransmitter that has long received much attention in memory research. Although the effects of ACh on memory have to be regarded separately for the acquisition, consolidation, and recall phase and for different memory systems, it remains a fact that ACh acts on cholinergic receptors that are widely distributed throughout in the brain. Cholinergic antagonism is reported to produce cognition deficit which imitates Alzheimer's disease similar to hippo camp a llesion-induced cognitive deficits **[35]**.

Several studies have now established the association of neuronal oxidative stress with Alzheimer disease (AD). This stress is manifested by damage to proteins, lipids, and nucleic acids, i.e. nuclear and mitochondrial DNA as well as RNA. Apolipoprotein E (Apo E) 4 allele (corresponding protein, ApoE4), a major risk factor for AD, is associated with oxidative damage in brain tissue of cases of AD. Studies support an important role for Aß in oxidative balance, some of the margue AB is the cause while others argue AB is the result of oxidative stress **[36]**.

Scopolamine, an anti-muscarinic agent, competitively antagonizes the effect of

acetylcholine on the muscarinic receptors by occupying postsynaptic receptor sites with at elicity and increases ACE activity in the cortex and hippocampus. Scopolamine also interferes with memory and cognition function in humans and experimental animals by blocking muscarinic receptors and produce transient memory deficit. Scopolamine diminish cerebral blood flow due to cholinergic hypofunction. Scopolamine additionally triggers ROS, inducing free radical injury and an increase in a scopolamine-treated group brain MDA levels and deterioration in antioxidant status. Scopolamine induces neuro-inflammation by promoting high level of oxidative stress and pro inflammatory cytokines the hippocampus. Scopolamine is proven to increase levels of APP and Tau. Administration of scopolamine led to marked histopathological alterations in the cerebral cortex, including neuronal degeneration **[37]**.

The standard drug piracetam plays an important role in neurotransmission by acting on various neurotransmitter system like glutaminergic, cholinergic, serotoninergic and noradrenergic system. Piracetam acts by enhancing postsynaptic receptors or restart the receptor functions. The functions of neurotransmitters are altered by membrane fluidity according to the membrane hypothesis in AD. Neurotransmitters bind to these proteins embedded within the membrane and alter the ions and other substances flow in and out of the cell. Due to the alteration in membrane fluidity, the action of neurotransmitter and cell signaling is also altered. The improper functioning of cholinergic and glutaminergic systems may be responsible for memory impairment. So, if piracetam is used as a therapy for cognitive disorders, it may alter acetylcholine levels in hippocampus and enhance the number of muscarinic cholinergic receptorsin the frontal cortex of the brain. At the other hand piracetam act as antioxidant/neurotonic it also enhances number of acetylcholine receptor thus it might cause for enhancement of learning and memory **[38]**.

In elevated plus maze model of VA possess nootropic activity by scopolamine induced dementia. The VA treated group showed significantly ($p<0.001$) decrease in transfer latency and memory retention. When compared with negative group at (acquisition 7^{th}) and (retention 8^{th}) day of the study, which is an indicative of cognition improvement **[39]**.

In radial arm maze model of VA possess nootropic activity by scopolamine induced dementia. The VA treated group showed significantly ($p<0.001$) decreasing the time

taken to reach reward arm (sec), when compared with negative group.

In this estimation acetylcholine is considered as the most important neurotransmitter involved the regulation of cognitive functions. Cholinergic neurons plays important role in cognitive deficit associated with AD and neurodegenerative disease. It has been demonstrated that impairment in learning, memory and behaviour observed in the patients with dementia are caused at least by change within cholinergic system. In present study of VA inhibited acetylcholinesterase enzyme, thereby elevating acetylcholine concentration in the brain **[40]**.

The finding suggest the possible Neuroprotective role for VA, therefore it seem that VA may prove to be useful anti Alzheimer agent. In the present study, scopolamine (0.4 mg/kg) significantly elevated brain AChE activity. Piracetam (200 mg/kg) and VA (25, 50 and 100mg/kg), on the other hand, significantly ($p<0.001$) lowered this activity. However further investigations is warranted to explore the possible involvement of other neurotransmitters responsible for nootropic property of Vanilic acid **[41]**.

CONCLUSION

In the conclusion, presence study suggested that Vanilic acid selected for evaluation of nootropic activity. Vanilic acid at dose 25, 50 and 100 mg/kg was administered orally for 7 days, which have improved learning and memory of rat significantly in the elevated plus maze model. In radial arm maze model Vanilic acid possess nootropic activity by decreasing the time taken to reach reward arm (sec).In present study of Vanilic acid inhibited acetylcholinesterase enzyme, there by elevating acetylcholine concentration in the brain. Thus, present data indicates that Vanilic acid is to be a safe Neuroprotective, memory enhancer effect and could be used as a part of therapy to treat dementia.

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CONFLICT OF INTEREST

No conflict of interest.

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