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*Research Article*

# Effect of Grape Seed Extract (Vitis vinifera) on Alternations of ACh and AChE Activities in Memory Defected Male Albino Rats

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**Abstract**

A great source of different polyphenols with powerful antioxidant and disease-prevention qualities is grape seed extract (VGSE), which comes from the vine species Vitis vinifera. There is a lack of research about the health advantages of VGSE on DNA damage, protein damage, labile iron activity, and enzyme inhibitory effects, despite the fact that VGSE has a wide range of biological activities that have the potential to improve human health. By exerting anti-oxidative, anti-inflammatory, anti-acetylcholinesterase, and anti-amyloidogenic effects, grape-derived extracts are natural sources of polyphenols that may promote healthy brain ageing. The acetyl cholinesterase enzyme, which is discussed in this article, is involved in the cessation of cholinergic transmission, and it has been demonstrated that Alzheimer disease increases this enzyme's activity. We focus on the processes behind the neuromodulating properties of polyphenolic extracts and chemicals obtained from grapes, particularly resveratrol, grape seed extract, and extracts from grape leaves. However, additional study is needed to determine the most potent medicinal extracts and chemicals, as well as their brain bioavailability.

**Keywords:** Polyphenols, VGSE, Memory impairment, Neuromodulating properties

## INTRODUCTION

The central and peripheral nervous systems both use the choline and acetic acid ester acetylcholine as a nerve impulse transmitter. Acetylcholine serves as the main neurotransmitter of the parasympathetic nervous system, a part of the autonomic nervous system that lowers heart rate, contracts smooth muscles, widens blood vessels and

stimulates bodily secretions. Acetylcholine can either promote or inhibit a process, therefore it can have both excitatory and inhibitory effects. Acetylcholine-containing vesicles are found at the terminals of cholinergic neurons. When a motor neuron's terminal receives a nerve impulse from the peripheral nervous system, acetylcholine is released into the neuromuscular junction.

Acetylcholinesterase is a crucial enzyme in the cholinergic nervous system (AChE). Many different types of neurons degenerate as AD develops, quite apart from the massive loss of forebrain cholinergic neurons, which is followed by a gradual decline in acetylcholine (Mara-Salud et al., 2011). AChE, which hydrolyzes acetylcholine, and choline acetyltransferase (ChAT), which synthesises it, are both affected. One of the main tenets of therapy designed to cure the cholinergic shortage is the importance of cholinergic function in cognition. AChE inhibitors (AChE-I), which improve cholinergic transmission but have negligible and transient therapeutic benefits, are the mainstay of current AD treatment (Mara-Salud et al., 2011). Even while AChE activity has largely decreased in the AD brain, this is still the case.

Cholinergic insufficiency is the most severe and pervasive metabolic disturbance in diseases that cause memory loss. It is now possible to observe acetylcholinesterase activity in the brain in real time. Acetylcholine, choline acetyltransferase, and acetylcholine levels are all reduced as a result. Piperidyl derivatives have been employed in positron emission tomography (PET) to evaluate cortical acetylcholinesterase activity, such as N-[11C] methylpiperidyl-4-acetate ([11C]MP4A or [11C]PMP)3 and [11C] methylpiperidyl-4-propionate ([11C]MP4P or [11C] PMP)3 ([11C]MP4A). Mild cognitive impairment is a result of early Memory Defect Disease and ageing naturally. Only a tiny fraction of people with moderate cognitive impairment have memory issues by definition, but their general cognitive function and capacity to do daily tasks are unchanged. But nothing is known about the role of the cholinergic system in mild cognitive impairment. We were interested in learning whether early memory impairment could be identified by changes to the cholinergic system in the temporal regions. (Rinne et al., 2003).

# MATERIALS AND METHODS

The present study was focused on the evaluation of the Cholinergic protective effect of Grape Seed extract on Memory defected rats Brain tissue.

Procurement and Maintenance of Experimental Animals

Healthy Wistar strain Albino rats, *Rattusnorvegicus* of the same age group of 3 months, weighing 160 ± 20 grams, obtained from Sri Venkateswara enterprises, Bangalore were used as the experimental model in the present investigation. Prior to experimentation, the rats were acclimatized according to the instructions given by (Behringer et al., 1973). They were housed in polypropylene cages under the controlled conditions of 28 ± 2°C temperature with photoperiod of 12 hours light and 12 hours dark and 75% relative humidity maintained in the animal house of the Department Zoology, according to the ethical guidelines for animal protection and welfare bearing the Resolution No. 04/(i)/a/CPCSEA/ IAEC/ SVU/ KY- KPR / Dt. 28-03-2011. The rats were fed with standard pellet diet supplied by Sri Venkateswara Enterprises, Bangalore and water *ad libitum* throughout the period of experimentation.

### Preparation of Grape Seed Extract:

Grape, as large clusters with red berries, was bought from a local fruit market in Tirupati, Pulivendula and Bangalore (Devanahalli) as *vitisvinifera*(Linn). Grape seeds were removed from the grapes, air dried (in shade) for one week and milled to fine powder (a particle size of < 0.4 mm). The grape seed powder was macerated in 75% ethanol for 72h at room temperature. The ethanol extract evaporated to remove ethanol, and grape seed extract was obtained as a lyophilized powder (Alireza Sarkaki et al., 2007). The resulting ethanolic crude extract was air dried and used in the present study.

# ADMINISTRATION OF TESTED SUBSTANCE:

Grape Seed extract (GSE) 100 mg/kg body weight was dissolved in distilled water and given to the rat. A gavage tube was used to deliver the substance by oral route, which is clinically expected route for administration of GSE. The volume of administration was kept at 0.2 ml to the animal.

### Grouping of Animals:

After the rats were acclimated to the laboratory conditions for 10 days before the experimentation, they were randomly divided into four groups. Each main group was again divided in to 2 sub-groups of six each and were housed in separate cages. These different groups of rats except control were treated with selected doses of Red grape seed ethanol extract and D-Gal as given below. Keeping in view the altered activity of rats during the nights compared to day time, all doses were given once in the morning hours in between 8 A.M. to 9 A.M. **Table 1**.

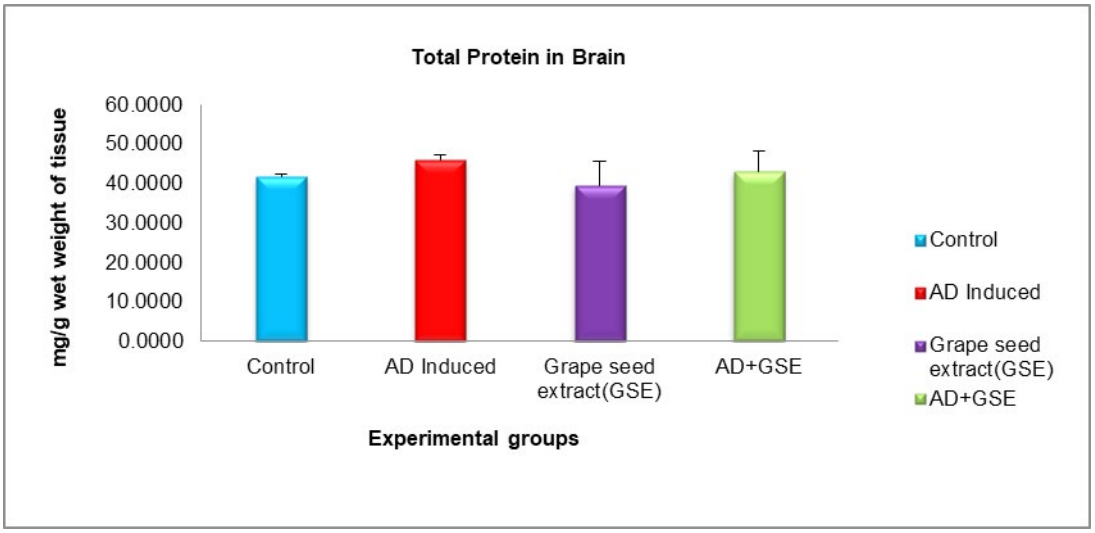
In the present study the experimental duration selected was 60days. D-Gal was given for first 30 days period to observe AD symptoms with the assessment of cognitive skills in rats (AD group). Further AD induced rats were again treated with D-Gal as well as Red grape seed ethanol extract simultaneously.

# RESULTS

From the results of the present research study, it was noticed that the Grape Seed Extract has significantly affected the total proteins and Cholinergic Neurotransmitters viz.,

**Table 1**. Grouping of Animals.

| | |
|---|---|
| **Group-I** (Control) | Control Rat |
| **Group-II** (AD) | Rat, Intraperitonealy(IP) administered with D-Gal (120 mg/kg body weight) up to end of the experiment (1st day to 90th day) (**Zhang *et al.*, 2006; Hua*et al.*, 2007**). |
| **Group-III** (GSE) | Rat, orally administered with Red grape seed ethanol extract (100mg/kg body weight) for 30 days. |
| **Group-IV** (AD+GSE) | Rat, Intraperitonealy injected with D-Gal (120 mg/kg body weight) once daily for first 30 days. From 31stday onwards rats were administered with Red grape seed ethanol extract (100mg/kg body weight) for 30 days. |




**Graph 1.** Graphical representation of Total Protein changes in rat brain tissue in control and experimental groups of rats.

ACh content and the AChE activity in brain tissue of D-Gal treated rats.

### Total proteins

Comparing experimental groups to control groups revealed significant differences in the amounts of total proteins; the AD-induced rats treated with D-Gal had the highest levels of protein. When compared to the AD-induced group, the AD-induced group treated with grape seed extract shown a notable increase in the level of total protein **Graph 1**.

### Cholinergic Neurotransmitters

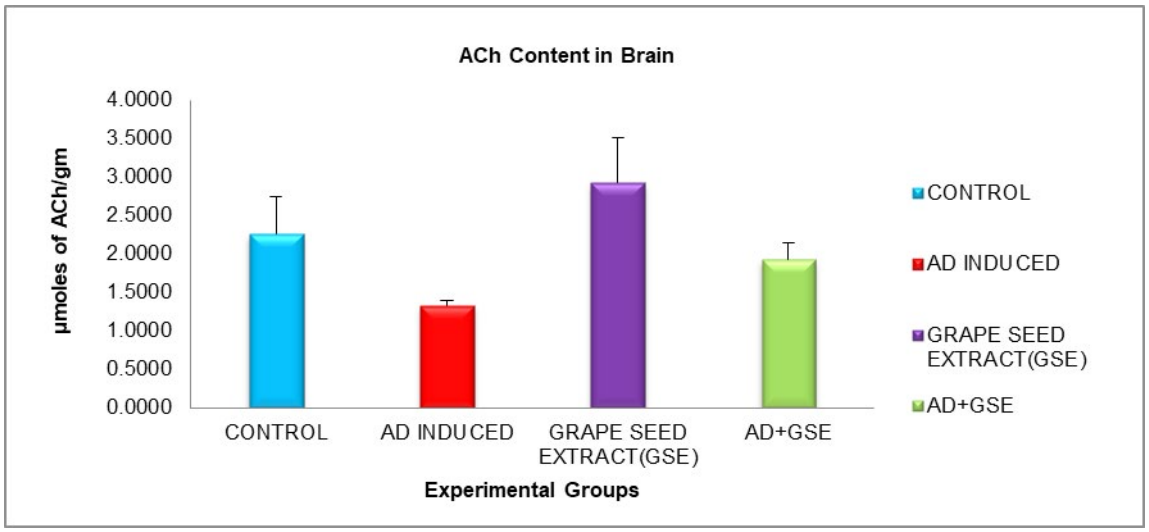
Acetylcholine (ACh) Content: The ACh content levels in all of the experimental groups significantly differed from control rats and the AD-induced rats treated with grape seed extract had the highest ACh content. In rats treated with grape seed extract alone, a substantial rise was seen. The amount of ACh significantly decreased in AD-induced rats. When compared to the AD-induced group, the AD-induced group treated with Grape Seed Extract (GSE) concurrently shown a notable rise in ACh content in the experimental group **Graph 2**.

Acetylcholinesterase (AChE): In contrast to ACh content, AD-induced rats showed higher AChE maximum activity levels than any other experimental groups. Rats administered with AChE Grape Seed Extract had considerably less activity overall when compared to the control group. The AD rats given with grape seed extract, however, showed the greatest inhibition. On the other hand, AD-induced rats had significantly higher AChE activity with the highest percent of elevation. The AChE activity was, however, recovered to nearly normal levels during the course of the trial in AD-induced rats treated with grape seed extract **Graph 3**.

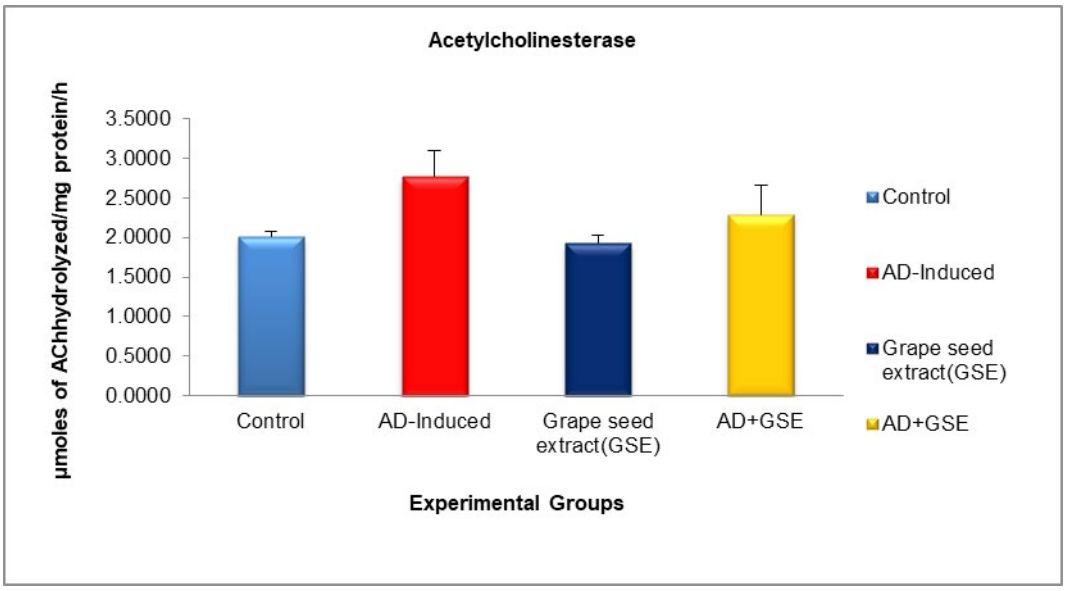
## DISCUSSION

The cholinergic system in rat brain tissue treated with Red Grape Seed Extract and D-Gal underwent considerable modifications in the current investigation. According to the findings, oral treatment of grape seed extract effectively preserved total protein levels and the activity of the cholinergic neurotransmitters ACh and AChE in experimental rats. It is thought that AChE's biological function is to stop impulse transmission by hydrolyzing the neurotransmitter ACh into acetic acid and choline (Nachmansohan and Neumann, 1975). By hydrolyzing the excitatory transmitter, Ach, AChE is a crucial regulatory enzyme that regulates the propagation of nerve impulses across cholinergic synapses (Milatovic et al., 2006).

Acetylcholine was the first neurotransmitter malfunction in Alzheimer's disease to be identified (ACh). It was thought that cholinergic dysfunction, which is necessary for short-term memory function, also contributed significantly to the




**Graph 2.** Graphical representation of changes in Acetylcholine content (µmoles of ACh/gm) in control and experimental groups of rat's brain tissue.




**Graph 3.** Graphical representation of changes in Acetylcholinesterase activity levels (µmoles of Ach hydrolyzed/mg protein/h) in brain tissue of control and experimental groups of rats.

short-term memory loss in AD (Francis et al., 1999). In the cortex and hippocampus, regions of the brain important in cognition and memory, markers for cholinergic neurons such as choline acetyltransferase and Acetylcholinesterase, enzymes responsible for synthesis and breakdown of ACh, respectively, are diminished (Francis et al., 1999). Cholinergic neurons are preferentially damaged in the nucleus basalis and the entorhinal cortex, where the early loss of neurons in AD patients occurs. Up to 90% of the cholinergic neurons in the nucleus basalis of Mynert may die as the disease worsens. (Wright et al., 1993).

Changes in the basal forebrain cholinergic system, notably in the hippocampus and cerebral cortex, have been linked to Alzheimer's disease (AD) pathology. Normal ageing populations also experience cholinergic and memory deficiencies, however these dysfunctions are different from those seen with AD (Greig et al., 2005) (Niewiadomska et al., 2009). When compared to the rats in the control group, the protein content in the AD-induced animals was considerably higher. This is a result of beta amyloid and tau protein production in the AD-affected brain. On treatment with GSE, levels of protein content were seen to be decreased, while in the AD+GSE experimental group of rats, levels of protein content were seen to be moderately elevated. Red Grape Seed Extract treatment, given concurrently, might return levels of protein content to normal. In Alzheimer's patients, choline acetyltransferase activity was found to be noticeably reduced. Given that -amyloid has been demonstrated to inhibit choline absorption and ACh release in vitro (Zhong et al., 2009), cholinergic neurotransmission may be a particular target for -amyloid.

The cholinergic system is crucial to memory and learning. Alzheimer's disease is linked with the loss of cholinergic neurons and decreased choline-acetyltransferase activity. Given that â-amyloid has been found to decrease choline absorption and ACh release in vitro, cholinergic neurotransmission may be a particular target for this substance. A number of negative behavioural symptoms associated with AD may potentially be influenced by changes in the central cholinergic system (i.e., depression, aggressive behavior, psychosis, and over activity). Cholinergic abnormalities have been observed in association with neurodegenerative conditions other than AD such as Parkinson's disease (Perry et al., 1999) (Furey et al., 2000).

# CONCLUSION

From the above results on brain cholinergic neurotransmitter system, it was finally concluded that, even though intake of grape Seed Extract for short term period improves all cholinergic neurotransmitters in ageing and delays the onset of Memory disfunctions.

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