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RESEARCH ARTICLE

Musk melon in the role of a memory melon

MILIND PARLE AND KULWANT SINGH

ABSTRACT

The seed kernels (commonly known as Magaj) of *Cucumis melo* (Musk melon) are edible and nutritive in nature. The present study was undertaken to explore the anti-Alzheimer effect of CMS (*Cucumis melo* seed) kernels powder, when admixed in diet of mice. A total of 318 mice divided in 53 groups were employed in this study. The brain acetylcholinesterase activity, blood cholesterol and blood glucose levels were also estimated in the present study. The administration of CMS for 14 consecutive days significantly protected the animals from developing memory deficits due to diazepam and scopolamine. In the present study, the seed kernels exhibited memory improving effect as indicated by decreased transfer latency, increased TSTQ, decreased escape latency time, increased discrimination index and increased step down latency. The CMS administration also significantly decreased the acetyl cholinesterase activity indicating its pro-cholinergic effect. The CMS administration significantly decreased the total blood cholesterol level and blood glucose levels in the present study. Thus, CMS may prove to be a useful remedy for the management of Alzheimer's disease owing to its seven-fold mechanism (i) the flavonoids present in muskmelon possess powerful antioxidant property (ii) linoleic acid and arachidonic acid present in muskmelon seeds are responsible for growth and regeneration of cholinergic neurons (iii) phosphatidylethanolamine and phosphatidylcholine present in musk melon seeds serve as the precursors for the synthesis of acetylcholine (iv) α-linoleic acid abundantly present in the seed kernel stimulates the release of neuroprotectin D_1, which performs a neuro-protective role (v) the inhibition of acetyl cholinesterase enzyme by musk melon seeds (vi) lowering of blood cholesterol and (vii) finally, anti-hyperglycemic effect of muskmelon seeds help in the prevention of brain damage due to excessive glucose.

Key words : *Cucumis melo*, Dementia, Magaj

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INTRODUCTION

Alzheimer's disease (AD), a neurodegenerative disorder characterized by progressive memory loss and cognitive deterioration, has become a major health problem (Xu *et al.*, 2011). Despite the fact that more than 35 million people are suffering from AD worldwide, there are only few treatment options available (Xu *et al.*, 2011). Nootropic agents such as piracetam and acetyl choline-esterase inhibitors like donepezil are being primarily used to improve memory, mood and behaviour. Considering the adverse effects of allopathic drugs, continuous search for safe natural remedies is need of the hour. Therefore, natural products may provide a new source of beneficial neuropsychotropic drugs. According to Ayurveda, Alzheimer's disease is an imbalance of vata, pitta and kapha (Joshi and Parle, 2006). *Cucumis melo* (Kharbooja) has been shown to possess useful medicinal properties (Parle and Singh, 2011) such as analgesic, anti-inflammatory, anti-oxidant, anti-ulcer, anti-cancer, anti-microbial, and immunomodulatory activity. The seed kernels of *Cucumis melo* (Musk melon) are edible and nutritive in nature. Furthermore, no scientific reports are available on the usefulness of musk melon in the management of dementia till date. Therefore, the present study was undertaken to explore the memory enhancing potential of musk melon seed kernels.

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MATERIALS AND METHODS

Plant material:

The seed kernels (magaj) of *Cucumis melo* (Kharbooja)

were purchased from local market of Hisar (Haryana), in February 2011. The healthy looking seed kernels were selected for authentication from Raw Materials Herbarium and Museum, National Institute of Science Communication and Information Resources, New Delhi (Ref. NISCAIR /RHMD /Consult/-2011-12/1721/21). Different concentrations of seed kernel powder (250 and 500 mg/kg) were fed to separate groups of mice through a specially prepared diet. This special diet comprised of a mixture of *Cucumis melo* seed kernel powder (CMS) wheat flour kneaded with water, and a pinch of salt (sodium chloride), to impart taste.

Fig. A : Musk melon seeds

Animals:

Swiss mice of either sex were procured from the disease-free small animal house of CCS Haryana Agricultural University, Hisar (Haryana), India. The animals had free access to food and water and they were housed in a natural (12h each) light-dark cycle. The Institutional Animal Ethics Committee (IAEC) approved the experimental protocol and the care of laboratory animals was taken as per the guidelines of CPCSEA, Ministry of Forests and Environment, Government of India (Registration number 0436).

Following laboratory models were employed for testing memory in the present study.

Exteroceptive behavioural models:

- Elevated plus maze
- Morris water maze
- Object recognition task
- Passive avoidance task

Interoceptive behavioural models:

- Diazepam induced amnesia
- Scopolamine induced amnesia

Experimental design:

A total of 318 young mice (3-4 months old) divided in 53 different groups were employed in the present investigation. Each group comprised of a minimum of 6 animals. *Cucumis melo* Seed kernel Powder (CMS) was administered for 14 days.

Biochemical estimations:

Estimation of brain acetylcholinesterase:

Brain acetylcholinesterase activity (AChE) was measured by Ellman method with a slight modification (Ellman *et al.,* 1961; Voss and Sachsse, 1970, Vasudevan and Parle, 2006).

Estimation of serum total cholesterol:

CHOD-PAP method was used for the estimation of serum total cholesterol (Allain *et al.,* 1974).

Estimation of blood glucose level:

GOD-POD method was used for the estimation of blood glucose using semi autoanalyzer (Miksch and Wiedemann, 1973).

Statistical analysis:

All the results were expressed as Mean ± Standard Error (SEM). Data were analyzed using one-way ANOVA followed by Tukey's test.

RESULTS AND DISCUSSION

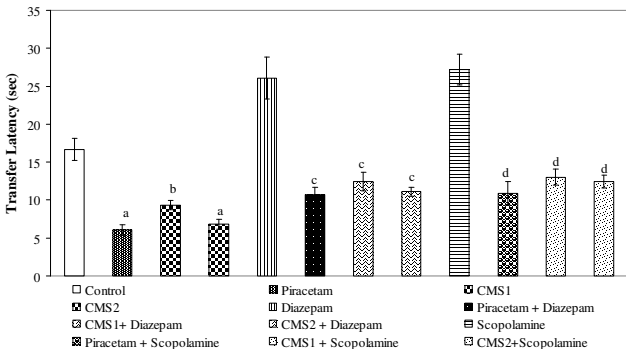
The results obtained from the present investigation have been discussed in the following sub heads:

Effect of CMS on TL using EPM:

The animals treated with CMS (*Cucumis melo* seed kernel powder), at the dose of 500 mg/kg, showed remarkable reduction ($P<0.001$) in TL of the 15th day, indicating significant improvement in memory whereas administration of CMS at the dose of 250 mg/kg, for 14 consecutive days showed less significant ($P<0.05$) effect (Fig.1). Scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) injected before training significantly increased ($P<0.001$) TL on the fifteenth day indicating impairment in memory. The CMS administration for 14 days successfully reversed memory deficits induced by scopolamine and diazepam. Piracetam (used as a positive control) at the dose of 400 mg/kg; i.p., also improved memory and reversed the amnesia induced by scopolamine and diazepam as expected.

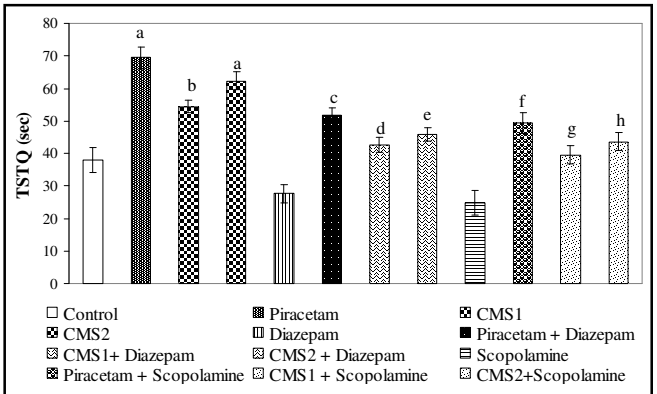
Effect of CMS on ELT and TSTQ using MWM:

Escape latency time (ELT) is the time taken by the mouse to locate the hidden platform in water maze. A marked decrease in ELT during subsequent trials, as compared to the first exposure, indicates normal acquisition. The mice of control group and test group showed reduction in ELT on day 4 as compared to ELT of respective control groups on day 1($P<0.001$) indicating normal acquisition and retention in mice. The administration of scopolamine (0.4mg/kg; i.p.) and diazepam (1



CMS = *Cucumis melo* seed kernel powder.
Values are in Mean ± SEM (n = 6). (One-way ANOVA followed by Tukey's test)

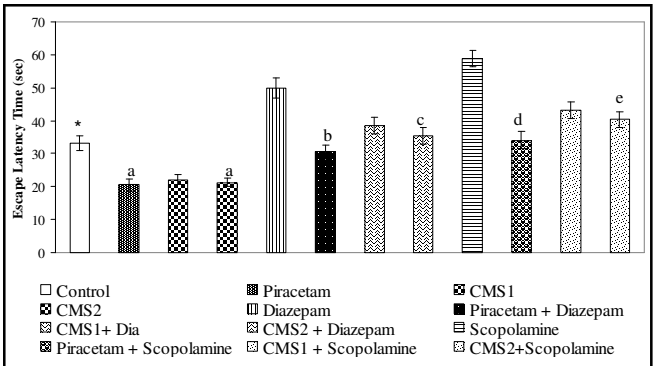
Fig. 1 : Effect of CMS on transfer latency of mice



CMS = *Cucumis melo* seed kernel powder. Values are in mean ± SEM (n = 6)

Fig. 3 : Effect of CMS on TSTQ of mice using Morris water maze

mg/kg; i.p.) impaired the process of acquisition as indicated by increased ELT on day 4. CMS administration reversed the scopolamine and diazepam-induced memory loss, as indicated by decreased ELT as compared to the 4th day's ELT of respective control groups (P<0.01) (Fig. 2). Significant increase in the time spent in target quadrant (TSTQ) indicates enhanced memory. Target quadrant represented that region of Morris water maze, where hidden platform was initially provided to mice for escape. The mice, treated with diazepam (1 mg/kg) and scopolamine (0.4 mg/kg) spent less time in target quadrant



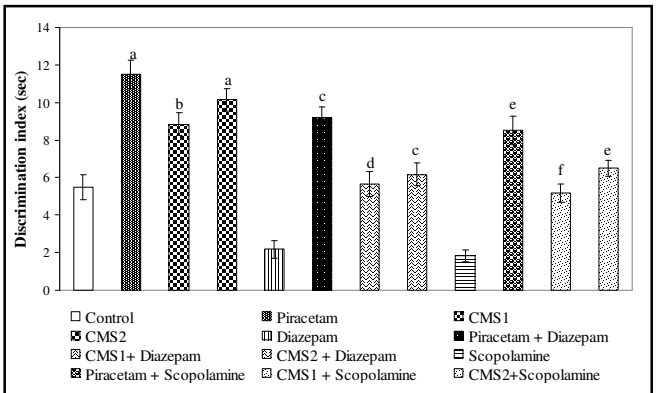
CMS = *Cucumis melo* seed kernel powder. Values are in mean ± SEM (n = 6)

Fig. 2 : Effect of CMS on escape latency time of mice in Morris water maze model

(Q4) on day 5 as compared to the respective control group mice indicating impairment of memory. The administration CMS at the dose of 250 mg/kg (P<0.01) and 500 mg/kg (P<0.001), for consecutive 18 days significantly increased the time spent in target quadrant on day 5 as compared with scopolamine and diazepam-treated mice suggesting that CMS attenuated diazepam and scopolamine-induced amnesia (Fig. 3).

Effect of CMS on dI using ORT:

Discrimination index (dI) is the difference between the exploration time of novel object and familiar object. Increase in dI indicates enhanced recognition memory. CMS (500 mg/kg, mixed in diet) administered orally for 14 days produced significant (P<0.001) increase in discrimination index indicating improvement in memory. Scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) produced significant (P<0.01) impairment in memory as indicated by decreased dI. CMS administered orally for 14 consecutive days successfully reversed (P<0.001) the memory deficits induced by scopolamine and diazepam (Fig. 4).



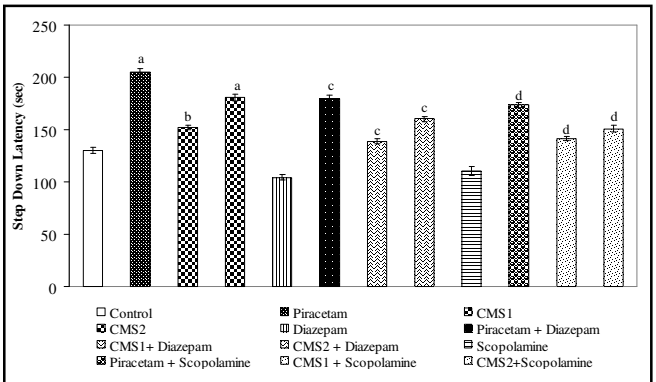
CMS = *Cucumis melo* seed kernel powder. Values are in mean ± SEM (n = 6)

Fig. 4 : Effect of CMS on discrimination index using object recognition task

Effect of CMS on SDL using passive avoidance task:

Step down latency (SDL) is defined as the time taken by the mouse to step down from wooden platform to grid floor

with its entire paw on the grid floor. Significant increase in SDL values reflected memory enhancement, whereas low SDL values reflected memory impairment. SDL of fifteenth day (24 h after last dose) reflected the long-term memory of animals. The administration of CMS (250 and 500 mg/kg, mixed in diet) for 14 days markedly increased SDL ($P<0.001$) as compared to the respective control groups (Fig. 5). Scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) significantly ($P<0.001$) decreased SDL as compared to control group of mice, indicating impairment of memory (amnesia). CMS administered for 14 days reversed the amnesia induced by both scopolamine and diazepam. The groups of mice, which were treated with piracetam (400 mg/kg, i.p.) for fourteen successive days showed significant improvement ($P<0.001$) in memory of mice. Piracetam also reversed amnesia induced by scopolamine and diazepam.



CMS = *Cucumis melo* seed kernel powder. Values are in mean ± SEM (n = 6)

Fig. 5 : Effect of CMS on step down latency of mice using passive avoidance task

Effect of CMS on brain acetylcholinesterase level:

CMS showed a remarkable dose-related reduction in brain cholinesterase activity of mice. The percentage reduction in cholinesterase activity was 29.01 per cent ($P<0.05$). Donepezil (0.1 mg/kg i.p.), used as the standard drug, showed remarkable reduction of brain cholinesterase activity to the extent of 40 per cent ($P<0.01$) in mice as expected.

Effect of CMS on total cholesterol level:

The animals receiving CMS for 14 days consecutively showed significant reduction in total serum cholesterol levels at both the doses *i.e.* 250 mg/kg ($P<0.05$) and 500 mg/kg ($P<0.001$) in mice, when tested using auto analyzer. The extent of reduction in total cholesterol levels of mice were 9.43 per cent and 16.56 per cent at the doses of 250 and 500 mg/kg of CMS, respectively. The extent of reduction in total cholesterol levels with simvastatin (a standard cholesterol lowering agent) were 33.75 per cent.

Effect of CMS on blood glucose level:

CMS administered orally for 14 consecutive days significantly decreased blood glucose level at both the doses (250 and 500 mg/kg) to the extent of 9.55 per cent ($P<0.05$) and 15.11 per cent ($P<0.01$), respectively.

Alzheimer 's disease (AD) is the most common cause of dementia in the elderly, accounting for 60–70 per cent of all demented cases. Neurofibrillary tangles, amyloid plaques and degeneration of cholinergic neurons are the pathological hallmarks of AD. Diazepam and other benzodiazepines produce amnesia in laboratory animals by activation of benzodiazepine receptors, whereas Scopolamine produces memory loss due to its anti-cholinergic property (Parle and Bansal, 2011). In the present study, we studied the effect of seed kernels of *Cucumis melo* (CMS) on cognitive function of mice using various exteroceptive and interoceptive models of memory. Recognition is the process by which a subject is aware that a stimulus has been previously experienced. It requires that the characteristics of events are perceived, discriminated, identified and then compared (matched) against a memory of the characteristics of previously experienced events (Steckler *et al.,* 1998). Discrimination index (dI) is the difference between the exploration time of novel object and familiar object. In object recognition task, increase in discrimination index after the CMS administration indicated significant improvement of memory of mice. In this study, the CMS administration also significantly decreased the acetyl cholinesterase activity indicating pro-cholinergic effect. Excessive accumulation of cholesterol is associated with increased risk of neurodegenerative disorders like Alzheimer disease. The CMS administration significantly decreased the total blood cholesterol level and blood glucose level indicating beneficial effects in AD.

Acetylcholine (ACh) is the main neurotransmitter involved in the regulation of cognitive functions (Parle and Singh, 2007). Different strategies, including increase of ACh synthesis, the augmentation of presynaptic ACh release, and the stimulation of cholinergic post synaptic muscarinic and nicotinic receptors and the inhibition of ACh synaptic degradation by employing cholinesterase inhibitors; are adopted for the management of AD (Parle and Bansal, 2011). The seed kernels of *Cucumis melo* contain phosphatidylethanolamine and phosphatidylcholine . These phospholipids act as a precursor for the synthesis of Ach in neuronal cell line (Blusztajn *et al.,* 1987). Thus, this mechanism may be involved in the anti-amnesic effect of musk melon seed kernels. The seed kernels of *Cucumis melo* are very good source of essential polyunsaturated fatty acids (Ismail *et al.,* 2010). Essential fatty acids also play an important structural role in brain tissue, especially in cell membranes, and the functional implications. The variation in the supply of essential and non-essential lipids may affect the structural composition of the brain and of myelin sheaths. The dietary deficiency of n-3 fatty

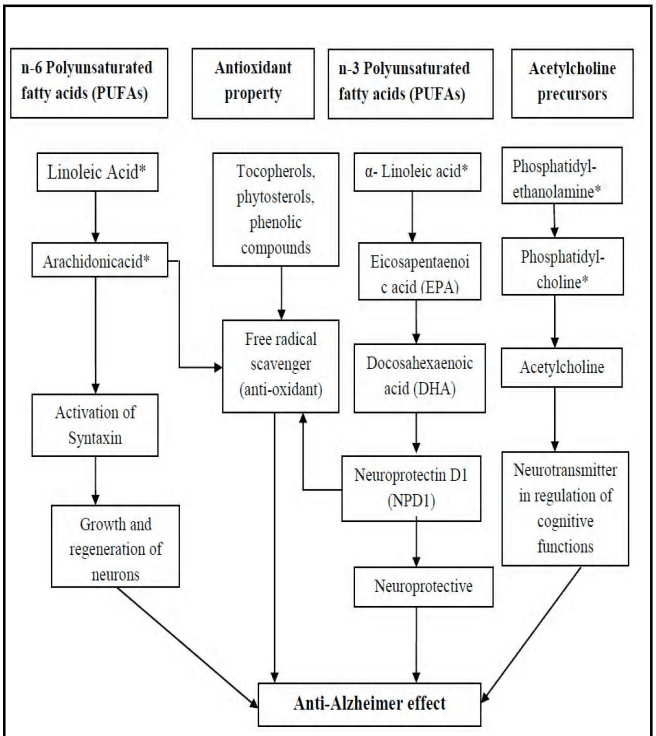


Fig. 6 : Mechanism of anti-alzheimer effect of Musk melon

acids, or of linoleic acid in combination with linolenic acid results in reduction of brain (Uauy *et al.,* 2006) phospholipid arachidonic acid (AA) and Docosahexaenomic acid (DHA). DHA may be protecting hippocampal neurons from apoptosis via the ability of neuroprotectin D1 to counteract oxidative stress-triggered DNA damage. It is possible that presence of the essential fatty acids in seed kernels contributes to its anti-amnesic effect. Several findings point out that oxidative stress plays the role of a villain in the pathogenesis of Alzheimer disease. Musk melon seeds have been found to possess good antioxidant potential due to the presence of tocopherols, phytosterols and phenolic compounds (Ismail *et al.,* 2010). Therefore, this antioxidant property may further be adding to the neuro-protective role of musk melon seed kernels.

Conclusion:

In present study, musk melon seed kernel powder produced significant improvement in the memory of mice, when tested employing various experimental models. Furthermore, the musk melon seed kernel powder also reversed memory deficits induced by diazepam and scopolamine, while concomitantly reducing blood cholesterol and glucose levels. The underlying mechanism of action for the beneficial effects of musk melon seed appears to be to seven-fold (i) the flavonoids present in muskmelon possess powerful antioxidant property (ii) linoleic acid and arachidonic acid present in musk melon seeds are responsible for growth and regeneration of cholinergic neurons (iii) phosphatidylethanolamine and phosphatidylcholine present in musk melon seeds serve as the precursor for the synthesis of acetylcholine (iv) á-linoleic acid abundantly present in the seed kernel stimulates the release of neuroprotectin D1, which has been shown to evoke anti-Alzheimer effect (v) the inhibition of acetyl cholinesterase enzyme by musk melon seeds leads to increased availability of acetylcholine at the receptor site (vi) lowering of blood cholesterol facilitates cognitive function (vii) finally anti-hyperglycaemic effect of musk melon seeds help in the prevention of brain damage due to excessive glucose.

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