ORIGINAL ARTICLE

Effect of methanolic extract of *Triticum aestivum* (Wheat grass) on learning and memory in mice

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Abstract

Objectives: To study the effects of methanolic extract of *Triticum aestivum* (META) supplementation on normal memory function and scopolamine-induced impaired memory in mice. **Methods:** The gum acacia suspension of META was administered by gavage at the dose of 200 and 400 mg/kg orally once daily in mice for 30 days to evaluate memory-enhancing potential on normal and scopolamine-induced impaired memory in albino mice. Escape latency (EL) in the Morris water maze (MWM) and transfer latency (TL) in the elevated plus maze (EPM) were recorded respectively. Mice were given four trial sessions per day to locate the platform for 6 days in the MWM model. Scopolamine 1 mg/kg was injected i.p. on the 30th day to produce memory impairment in mice. **Results:** META suspension at the dose of 200 mg/kg and 400 mg/kg showed a significant ($P < 0.05$) dose-dependent reduction of mean EL and TL as compared to the control group in normal mice. META suspension at the dose of 200 mg/kg and 400 mg/kg with scopolamine 1 mg/kg showed significant ($P < 0.05$) dose dependent reduction of EL and TL as compared to negative control group in impaired memory mice. Mean EL and TL reduction at the dose of 400 mg/kg was comparable ($P > 0.05$) to that of the standard nootropic agent Piracetam at the dose of 200 mg/kg in normal and scopolamine-treated mice. META at the dose of 200 and 400 mg/kg showed a better memory-enhancing effect in normal mice than in impaired memory mice using MWM and EPM models. **Conclusion:** The study revealed that the chronic administration of META exhibited significant learning and memory-enhancing activity in the normal as well as the scopolamine-treated impaired memory mice.

Key words: Elevated plus maze, Morris water maze, piracetam, scopolamine, *Triticum aestivum*

INTRODUCTION

Learning is generally defined as the act of acquiring information or skill such that knowledge and/or behavior change. It takes place in a variety of different ways. Memory is the power of the brain to recall past experiences or information. Memory is essential to all learning because it lets you store and retrieve the information that you learn. Memory is principally nothing more than the record left by a learning process.[1] Learning and memory are largely interrelated and cannot be completely understood independently of each other. Processes of learning and memory are typically conceptualized as involving three stages: encoding, storage, and retrieval. Encoding is the original enrollment and acquisition of information, storage is the maintenance of information over time in the nervous system (represented as a memory trace), and retrieval is the process whereby stored information is brought back into conscious awareness or otherwise affects ongoing behavior.[2]

To acquire, store, and use intellectual knowledge is referred to as cognition. Drugs like piracetam (PCT), oxiracetam, and aniracetam recognized as cognitive enhancer act by increasing the brain's supply of acetylcholine, improves blood and oxygen supply to the brain, and rejuvenates the cells to normal functioning but their therapeutic effects are low and most of them have undesirable side effects like nervousness, weight gain, sleeplessness, dizziness, and nausea, further, they may not be suitable for all people.[3] Acetylcholinesterase

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Received: 03-04-2023
Revised: 04-06-2023
Accepted: 15-06-2023

inhibitors (AChEIs) are the most common drugs used for Alzheimer's disease. However, these drugs may cause peripheral cholinergic side effects that may restrict their use.[4]

There is a need for new medicines that can prevent memory decline with fewer adverse effects. Herbal medicine could be a good source of drugs for the treatment of Alzheimer's disease and memory deficit with fewer or no side effects. Several medicinal plants have been used for decades in different cultures to improve memory such as *Valeriana officinalis, Punica granatum Linn, Salvia officinalis, Myristica fragrans, Bacopa monnieri Linn, Centella asiatica Linn, Evolvulus alsinoides,* and *Cynodon dactylon,* etc.[5,6]

Triticum aestivum known as "Wheat grass" in English and "Jwara" in Hindi is perennial, creeping grass growing throughout the country. *T. aestivum* possesss a variety of biological activities such as antiviral, antibacterial, antidiabetic, immunomodulatory, anti-inflammatory, antidepressant, antioxidant, hypolipidemic, and wound healing properties.[7,8] It is traditionally used to treat epilepsy, dropsy, piles, and wound infections.[9] Little information is available regarding the effect of *T. aestivum* on memory.[10] No information is available regarding the study of the effect of methanol extract of *T. aestivum* on normal and impaired memory. Therefore, the present study was carried out to study the effect of methanolic extract of *T. aestivum* (META) on normal and impaired memory in mice.

MATERIALS AND METHODS

Plant Material

The grass of *T. aestivum* used in this study was grown indoors at home. The earthen pot was filled with 2.5 inches of growing medium composed of three parts of soil and one part of compost. Overnight soaked *T. aestivum* seeds were then evenly spread over it and further covered with 0.5 inch of soil. Small quantities of water were sprinkled evenly over the soil and 3–7 h indirect sunlight was allowed daily for the growth of grass on the 10th day, when grass is about 6 inches tall, it is cut 0.5 inch above the surface of soil.[11]

T. aestivum (Wheat) grass is identified and authenticated by Dr. Arti Garg scientist E and head of office, Government of India, Ministry of Environment, Forest and Climate Change, Botanical Survey of India, Central Regional Centre, 10 Chatham Lines, Allahabad–211002. (Authentication certificate dated 05 August 2022).

Preparation of Extract

The collected grass was washed thoroughly with tap water and dried at room temperature in the absence of sun light. One kg of dry grass was obtained from 6.25 kg of wet wheat grass. The dried grass was powdered using the grinder and extracted with 2.5 L of 99.9% pure methyl alcohol (V/V) using soxhlet apparatus for 16 h giving 8.5% (W/W) of extract of *T. aestivum.* Quality control measures were taken in the drug testing laboratory to ensure the purity and consistency of the extract. META was then stored in the amber color bottle for further use.

Phytochemical Screening

META was subjected to phytochemical tests for the presence of bioactive compounds by standard methods as described by Harbourne.[12]

Drugs and Chemicals

1. Distilled water
2. Gum acacia (GA)-2% suspension
3. Methanol 99.9% (V/V)
4. Glass wool
5. Scopolamine Butylbromide (Inj. Buscogast- Sovereign Pharma Pvt. Ltd.)
6. PCT (Tab. Cerecetam 800- Intas Pharmaceuticals Ltd.)
7. Fluoxetine (Capsule Flunil 10 mg- Intas Pharmaceuticals Ltd.)
8. Diazepam (Tablet Valium 2 mg- Abbott Healthcare Pvt. Ltd.).

Drugs used in the study were purchased from local medical stores. All drugs were administered as 2% GA suspension by gavage.

Animals

Albino male mice weighing 25–30 g raised in the animal house of the Department of Pharmacology, Gajra Raja Medical College, Gwalior, were used for the study. These were maintained at 24 ± 2°C, humidity 50 ± 5% with 12 h light and dark cycle and kept on standard pellet diet (Pranav Agro Industries, Delhi, India) and water *ad libitum*. The care and maintenance of animals were as per the approved guidelines of the Committee for Control and Supervision of Experiments on Animals in India. The Institutional Animal Ethics Committee approved the protocol (Registration number 846/GO/Ere/S/04/CPCSEA).

Morris Water Maze (MWM)

The MWM is a white, circular pool with an inner diameter of 110 cm and walls 20 cm high. It was filled with normal tap water to a depth of 13 cm. The water was at room temperature (22°C) and made opaque by adding a small amount of milk powder with no noticeable side effects to the animals. The entire pool was divided into four quadrants of equal size by

two (imaginary) diagonal lines running through the center of the pool. A circular escape platform, which is removable (diameter: 10 cm) could be positioned in the middle of a quadrant. The pool was placed at the far end of a rectangular room dimly lit by white light. The walls of the room were equipped with a variety of spatial cues which remained unchanged during the whole experiment.

Behavioral Procedure

Drugs were administered orally once daily by gavage for 30 days in normal and impaired memory groups. Mice were trained for 6 days starting on day 24. The mice were transferred from their housing facility to the behavior room and were kept in an area where they cannot see the pool or spatial cues to adjust to the new environment for at least ½-h before testing. During the six subsequent days, the mice were given four trial sessions per day with the platform in place. If mice located the platform, it was permitted to remain on it for 10 s. If the mice did not locate the platform within 1 min, it was placed on the platform for 10 s. The time interval between trial sessions was half-hour. Escape latency (EL) was noted after 45 min of administration of the last dose on the 30th day and again after 24 h, that is, on the 31st day in normal mice. In scopolamine-treated groups (II-V) of impaired memory, scopolamine (1 mg/kg) was injected i.p. after 45 min of administration of respective treatments and EL was recorded after 45 min of injection of scopolamine on the 30th day and after 24 h, that is, on 31st day.[13]

Elevated Plus Maze (EPM)

The plus maze is in the shape of a cross or plus with two closed arms each with a roof open measuring 30 cm × 5 cm × 20 cm, extending from the central region (5 cm × 5 cm) running along aNorth–South axis and two open arms each measuring 30 cm × 5 cm running East–West. The wooden apparatus is elevated to a height of 50 cm from the floor in a dimly illuminated room.

Behavioural Procedure

The test drug was administered orally once daily by gavage between 10 AM to 1 PM for 30 days. On the 30th day, animals were placed individually at the end of either of the open arms facing away from the central platform. The time taken by each animal to move from the open arm to either of the closed arms was recorded. This duration of time was called transfer latency (TL). If the animal does not enter into any of the enclosed arms within 60 s it was gently pushed into any of the enclosed arms and TL was considered as120s. Later, TL measured on the 30th day serves as a parameter for acquisition (learning), while TL on the 31st day indicates retention of learning (memory).[14] TL was recorded after 45 min of administration of the last dose of META on the 30th day and again after 24 h, that is, on the 31st day in normal mice. To study the effect on impaired memory scopolamine (1 mg/kg) was injected i.p. after 45 min of administration of META or standard drugs or vehicle on the 30th day and TL was recorded after 45 min of injection of scopolamine on the 30th day and after 24 h that is, on 31st day.

Study Design

To ensure consistency of experience before the test session, animals were brought to the testing room 1 h before the start of behavior testing. Test room lighting, temperature, and noise level were kept constant for all mice used in the study. META or standard drugs were given for 30 days. The dose of META was chosen based on the earlier study on the extract of *T. aestivum* in an experimental animal model.[15]

To study the effects on normal memory using MWM and EPM mice were divided into four groups of six animals each.

- Group I: 2% GA aqueous suspension 10 mL/kg
- Group II: META200 mg/kg
- Group III: META400 mg/kg
- Group IV: PCT200 mg/kg

To study the effects on impaired memory mice using MWM and EPM were divided into five groups of six animals each:

- Group I: 2% GA aqueous suspension 10 mL/kg (positive control)
- Group II: 2% GA aqueous suspension 10 mL/kg + scopolamine 1 mg/kg on the 30th day (negative control)
- Group III: META200 mg/kg + scopolamine 1 mg/kg on 30th day
- Group IV: META400 mg/kg + scopolamine 1 mg/kg on 30th day
- Group V: PCT200 mg/kg + scopolamine 1 mg/kg on 30th day.

Statistical Analysis

Statistical evaluation was done using one-way ANOVA followed by Tukey's multiple comparison tests. $P < 0.05$ were considered statistically significant. Data were presented as mean ± standard error of the mean. All statistical analysis was performed by Sigma Stat software version 2.0, Jandel Scientific Inc. USA.

RESULTS

Effect of META on Normal Memory

In normal mice mean EL decreased by 13% and mean TL decreased by 14% using MWM and EPM respectively with META at the dose of 200 mg/kg as compared to control and was significant ($P < 0.05$). Mean EL and TL decreased by 20% and 38% at the dose of 400 mg/kg, respectively,

and was significant ($P < 0.05$) as compared to control and META200 mg/kg dose. Thus memory-enhancing effect of META is dose dependent. Mean EL decreased by 39% and mean TL by 48% with standard drug PCT and was significant as compared to control and META at the dose of 200 mg/kg ($P < 0.05$). The effect of META400 mg/kg was comparable ($P > 0.05$) to PCT200 mg/kg [Tables 1 and 2].

Effect of META on Impaired Memory

In the second part of the study administration of scopolamine, 1 mg/kg alone increased mean EL by 51% and mean TL by 43% as compared to GA treated control group and was statistically significant ($P < 0.05$) demonstrating memory impairment. Mean EL and TL decreased by 10% and 8% respectively by the META200 mg/kg and scopolamine-treated group and was significant ($P < 0.05$) as compared to negative control. Mean EL decreased by 18% and mean TL by 24% by the META400 mg/kg and scopolamine-treated group and was statistically significant ($P < 0.05$) as compared to negative control and META at the dose of 200 mg/kg and scopolamine. Thus memory-enhancing effect of META is dose dependent. Administration of PCT in scopolamine-treated animals decreased mean EL by 21% and mean TL by 27% and was significant ($P < 0.05$) as compared to negative control and META200 mg/kg and scopolamine-treated group. Effect of META400 mg/kg was comparable ($P>0.05$) to PCT200 mg/kg in scopolamine-treated mice [Figures 1 and 2].

The effect of META is more marked in normal memory mice than in impaired memory mice using both models.

Table 1: Effect of META grass on mean escape latency using MWM in normal mice

Treatment	Mean EL (s)	
	On 30th day	On 31st day
GA10	42.00±0.856	39.33±0.494
META200	35.83±1.16[a]	34.16±1.35[a]
META400	34.50±0.428[a,b]	31.50±0.428[a,b]
PCT200	32.16±0.54[a,b]	29.83±0.30[a,b]

Values are expressed as mean±SEM, each group consists of 6 animals (n=6). GA10=Gum acacia 10 mL/kg, META200 and META400=Methanolic extract of *Triticum aestivum* 200 mg/kg and 400 mg/kg respectively, PCT200=Piracetam 200 mg/kg (standard drug). [a]P<0.05 as compared to GA10, [b]P<0.05 as compared to META200 using ANOVA and Tukey's multiple comparisons test. MWM: Morris water maze, EL: Escape latency

Table 2: Effect of META on mean transfer latency using EPM in normal mice

Treatment	Mean TL (s)	
	On 30th day	On 31st day
GA10	32.00±0.86	28.67±0.42
META200	26.50±0.43[a]	24.67±0.67[a]
META400	20.83±0.60[a,b]	17.83±0.48[a,b]
PCT200	17.66±0.49[a,b]	14.83±0.48[a,b]

Values are expressed as mean±SEM, each group consists of 6 animals (n=6). GA10=Gum acacia 10 mL/kg, META200 and META400=Methanolic extract of *Triticum aestivum* 200 mg/kg and 400 mg/kg, respectively, PCT200=Piracetam 200 mg/kg (standard drug). [a]P<0.05 as compared to GA10, [b]P<0.05 as compared to META200 using ANOVA and Tukey's multiple comparisons test. TL: Transfer latency, EPM: Elevated plus maze

DISCUSSION

When a stimulus in the form of learning is transmitted to brain it is encoded in to memory by formation of new synaptic connections involving higher brain areas. Learning and memory functions are pivotal in the interaction of an individual with the environment and involve the interplay of large, distributed brain networks. Recent technical advances to explore neurobiological correlates of neuropsychological paradigms have increased our knowledge about learning and memory. As per the opinions of psychologists different types of memory, can be distinguished in relation to the types of information they process (e.g. words versus pictorial information), their capacity or persistence (e.g. short-term versus long-term), and their operating characteristics (e.g. the mental codes in which information is held).[16]

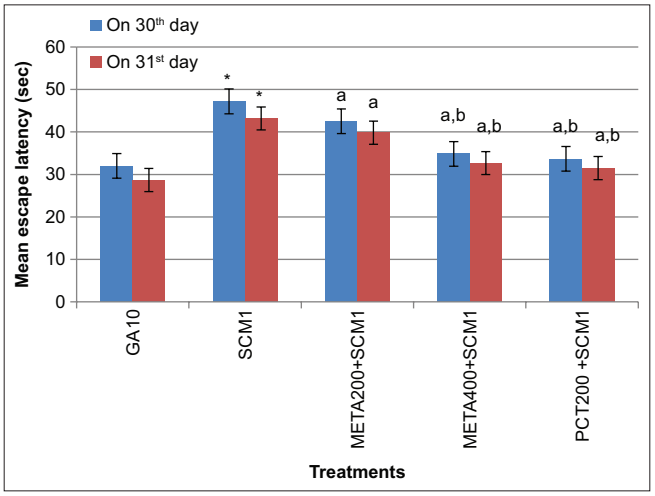

Figure 1: Effect of methanolic extract of *Triticum aestivum* (META) on mean escape latency using Morris water maze in scopolamine treated mice. Values are expressed as mean ± SEM, Each group consists of 6 animals (n = 6). GA10 = Gum acacia 10 mL/kg, SCM1=Scopolamine 1 mg/kg, META200 + SCM1 = Methanolic extract of *T. aestivum* 200 mg/kg and scopolamine 1 mg/kg treated group, META400 + SCM1 = Methanolic extract of *T. aestivum* 400 mg/kg and scopolamine 1 mg/kg treated group, PCT200 + SCM1 = Piracetam 200 mg/kg (standard drug) and scopolamine mg/kg treated group. *P < 0.05 as compared to positive control GA10, [a]P < 0.05 as compared to SCM 1, [b]P < 0.05 as compared to META200 + SCM1 using ANOVA and Tukey's multiple comparisons test

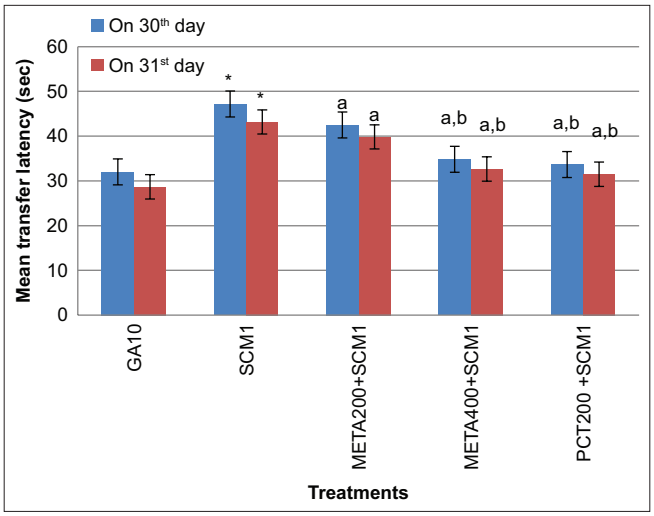

Figure 2: Effect of methanolic extract of *Triticum aestivum* (META) on mean transfer latency using elevated plus maze in Scopolamine treated mice. Values are expressed as mean ± SEM, each group consists of 6 animals ($n = 6$). GA10 = Gum acacia 10 mL/kg; SCM1 = Scopolamine 1 mg/kg treated group META200 + SCM1 = Methanolic extract of *T. aestivum* 200 mg/kg and scopolamine 1 mg/kg treated group, META400 + SCM1 = Methanolic extract of *T. aestivum* 400 mg/kg and scopolamine 1 mg/kg treated group PCT200 + SCM1 = Piracetam 200 mg/kg (standard drug) and scopolamine 1 mg/kg treated group. $^{*}P < 0.05$ as compared to positive control GA10, $^{a}P < 0.05$ as compared to SCM 1, $^{b}P < 0.05$ as compared to META200 + SCM1 using ANOVA and Tukey's multiple comparisons test

Animal models have been instrumental in the field of learning and memory, in shaping our understanding of how the normal and damaged brain processes information. Animal research has taught us that there are multiple memory systems in the brain that may interact competitively, cooperatively, or in parallel- that depends on the cognitive demands and psychological nature of the task.[17]

The MWM was described 30 years ago as a device to probe spatial learning and memory in laboratory rats. Spatial learning in general and MWM performance, in particular, appear to depend on the coordinated actions of different brain regions and systems constituting a functionally integrated neural network. MWM task has often been used in the validation of rodent models for neurocognitive disorders and the evaluation of possible neurocognitive treatments.[18]

EPM served as the exteroceptive behavioral model to evaluate memory in rats. The spontaneous alteration in behavior in the EPM is considered to reflect working memory. Based on the natural aversion of mice of high and open space reported that TL (the time in which mouse moves from the open arms to the enclosed arm) on the 2nd day onward was shortened than on the 1st day and suggested that this shortened TL can be employed as a parameter for learning and memory.[19]

In the present study, chronic administration of META in normal mice significantly decreased EL in MWM and TL in EPM suggesting enhancement in normal memory. This improved spatial learning performance, in mice, could be due to the presence of flavonoids in *T. aestivum*. This is in agreement with earliar study suggesting plant flavonoids contribute in neurogenesis.[20] Another mechanism for enhancement in normal memory with *T. aestivum* may be due to decreased functioning of hippocampal protein kinase C (PKC). This agrees with the earliar study demonstrating increased PKC is involved in the impairment of working memory and plant product acts by modulation of PKC.[21,22] Normal memory protection in the present study may also be attributed to increased Bcl-2 gene expression in response to several antioxidants present in *T. aestivum*.[8] This is analogous with the earlier plants studies showing increased Bcl-2 gene expression prevents apoptosis and provides protection against neuronal degeneration.[23,24]

In mice with impaired memory in the present study, chronic administration of META significantly reversed scopolamine-induced increased EL to reach the platform in MWM and TL in EPM, respectively, suggesting a spatial memory-enhancing effect. Memory impairment in the Scopolamine-induced animal model is associated with increased oxidative stress.[25,26] Reactive oxidative species can damage cellular components leading to cognitive dysfunction.[27] Cognitive-enhancing effect of META in Scopolamine-induced memory impairment in the present study could be due to the free-radical scavenging property of META and increased Bcl-2 expression.[28,29] However, the exact mechanism of memory-enhancing effect of *T. aestivum* on normal and impaired memory is not investigated in this study. There are several mechanisms for improvement in memory and it seems that *T. aestivum* acts by different mechanisms involved in neurogenesis and neuroprotection.

CONCLUSION

Thus, the data of the present study support the cognitive-enhancing effect of chronic META intake in normal and impaired memory mice. The memory-enhancing effect of META is more marked in normal mice than mice with impaired memory. Long-term interventional studies are required to know the exact mechanism of memory enhancing effect of *T. aestivum*

ACKOWLEDGEMENTS

We are thankful to Dr. Akshay Nigam, for his moral support to complete the study and Dr. Rahul Gupta, for his help to prepare META.

REFERENCES

1. Gupta A, Singh MP, Sisodia SS. A review on learning and memory. J Drug Deliv Ther 2018;8:153-7.
2. Avneet G, Pal SM, Siddhraj SS. A review on herbal Ayurvedic medicinal plants and its association with memory functions. J Phytopharmacol 2018;7:162-6.
3. Cohen PA, Zakharevich I, Gerona R. Presence of piracetam in cognitive enhancement dietary supplements. JAMA Intern Med 2020;180:458-9.
4. Palacios-Filardo J, Udakis M, Brown GA, Tehan BG, Congreve MS, Nathan PJ, *et al*. Acetylcholine prioritises direct synaptic inputs from entorhinal cortex to CA1 by differential modulation of feedforward inhibitory circuits. Nat Commun 2021;12:5475.
5. Akram M, Nawaz A. Effects of medicinal plants on Alzheimer's disease and memory deficits. Neural Regen Res 2017;12:660-70.
6. Roy A. Role of medicinal plants against Alzheimer's disease. Int J Complement Alt Med 2018;11:205-8.
7. Nalini GK, Patil VM, Ramabhimaiah S, Patil P, Vijayanath V. Anti-inflammatory activity of wheatgrass juice in albino rats. Biomed Pharmacol J 2011;4:301.
8. Aydos OS, Avci A, Ozkan T, Karadag A, Gurleyik E, Altinok B, *et al*. Antiproliferative, apoptotic and antioxidant activities of wheatgrass (*Triticum aestivum*L.) extract on CML (K562) cellline. Turk J Med Sci 2011;41:657-63.
9. Tirgar PR, Thumber BL, Desai TR. Isolation, characterization and biological evaluation of iron chelator from *Triticum aestivum* (wheat grass). Int J Pharm Biosci 2011;2:288-96.
10. Abu-Elfotuh K, Ragab GM, Salahuddin A, Jamil L, Al Haleem EN. Attenuative effects of fluoxetine and *Triticum aestivum* against aluminum-induced Alzheimer's disease in rats: The possible consequences on hepatotoxicity and nephrotoxicity. Molecules 2021;26:6752.
11. Kothari S, Jain AK, Mehta SC, Tonpay SD. Hypolipidemic effect of fresh *Triticum aestivum* (wheat) grass juice in hypercholesterolemic rats. Acta Pol Pharm 2011;68:291-4.
12. Harborne JB. Phytochemical Methods of Extraction: A Guide to Modern Techniques of Plant Analysis. 2nd ed. London: Chapmann and Hall; 1993. p. 135-203.
13. Vorhees CV, Williams MT. Morris water maze: Procedures for assessing spatial and related forms of learning and memory. Nat Protoc 2006;1:848-58.
14. Latha K, Rammohan B, Sunanda BP, Maheswari MU, Mohan SK. Evaluation of anxiolytic activity of aqueous extract of *Coriandrum sativum* Linn. in mice: A preliminary experimental study. Pharmacognosy Res 2015;7 Suppl 1:S47-51.
15. Borah M, Sarma P, Das S. A study of the protective effect of *Triticum aestivum* L. in an experimental animal model of chronic fatigue syndrome. Pharmacognosy Res 2014;6:285-91.
16. Mujawar S, Patil J, Chaudhari B, Saldanha D. Memory: Neurobiological mechanisms and assessment. Ind Psychiatry J 2021;30 Suppl 1:S311-4.
17. Morales L, Tomàs DP, Dalmau J, De la Rocha J, Jercog PE. High-throughput task to study memory recall during spatial navigation in rodents. Front Behav Neurosci 2020;14:64.
18. Venkataramaiah C, Swathi G, Rajendra W. Morris water maze-a benchmark test for learning and memory disorders in animal models: A review. Asian J Pharm Clin Res 2018;11:25-9.
19. Chauhan B, Chaudhary AK. Memory enhancing activity of methanolic extract of *Pterocarpus marsupium* Roxb. Phytopharmacology 2012;2:72-80.
20. Sasikumar P, Aswathy M, Prem PT, Radhakrishnan KV, Chakrapani PS. Plant derived bioactive compounds and their potential to enhance adult neurogenesis. Phytomed Plus 2022;2:100191.
21. Busquets-Garcia A, Gomis-Gonzalez M, Salgado-Mendialdua V, Galera-Lopez L, Puighermanal E, Martin-Garcia E, *et al*. Hippocampal protein kinase C signaling mediates the short-term memory impairment induced by delta9-tetrahydrocannabinol. Neuropsychopharmacology 2018;43:1021-31.
22. Singh RK, Kumar S, Tomar MS, Verma PK, Kumar A, Kumar S, *et al*. Putative role of natural products as protein kinase C modulator in different disease conditions. Daru 2021;3:397-414.
23. Bitra VR, Rapaka D, Mathala N, Akula A. Effect of wheat grass powder on aluminum induced Alzheimer's disease in Wistar rats. Asian Pac J Trop Med 2014;7:S278-81.
24. Callens M, Kraskovskaya N, Derevtsova K, Annaert W, Bultynck G, Bezprozvanny I, *et al*. The role of Bcl-2 proteins in modulating neuronal Ca^{2+} signaling in health and in Alzheimer's disease. Biochim Biophys Acta Mol Cell Res 2021;1868:118997.
25. Haider S, Tabassum S, Perveen T. Scopolamine-induced greater alterations in neurochemical profile and increased oxidative stress demonstrated a better model of dementia: A comparative study. Brain Res Bull 2016;127:234-47.
26. Budzynska B, Boguszewska-Czubara A, Kruk-Slomka M, Skalicka-Wozniak K, Michalak A, Musik I, *et al*. Effects of imperatorin on scopolamine-induced cognitive impairment and oxidative stress in mice. J Psychopharmacology (Berl) 2015;232:931-42.
27. Kandlur A, Satyamoorthy K, Gangadharan G. Oxidative stress in cognitive and epigenetic aging: A retrospective glance. Front Mol Neurosci 2020;13:41.
28. Khan GM, Ansari SH, Ahmad F. Pharmacognostic standardization, antioxidant and free radical scavenging activity of the seeds of *Triticum aestivum* L-a dietary staple. J Young Pharm 2013;5:54-9.
29. Akhtar RS, Ness JM, Roth KA. Bcl-2 family regulation of neuronal development and neurodegeneration. Biochim Biophy Acta 2004;1644:189-203.

Source of Support: Nil. **Conflicts of Interest:** None declared.