Evidence of Anti-Dementia Potential of Abana®: an Indian Ayurvedic Poly-Herbal Formulation in Rats

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Summary

The present study was aimed at investigating the effects of Abana, an Ayurvedic herbomineral preparation on memory in rats. Drug Abana was administered orally in three doses (50, 100 and 200 mg/kg) for fifteen days to different groups of young and aged rats. Elevated plus-maze and Hebb-Williams maze served as the exteroceptive behavioral models for testing memory. Diazepam-, scopolamine- and ageing-induced amnesia served as the interoceptive behavioral models. Abana (50, 100 and 200 mg/kg, p.o.) produced a dose-dependent improvement in memory scores of young and aged rats. Furthermore, it reversed the amnesia induced by scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.). It may prove to be a useful remedy for the management of Alzheimer's disease.

Key words: Abana, *Ayurveda*, amnesia, memory.

Running Head: Abana and Memory

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Introduction

Memory is the ability of an individual to record sensory stimuli, events, information, etc., retain them over short or long periods of time and recall the same at a later date when needed. Poor memory, lower retention and slow recall are common problems in today's stressful and competitive world. Age, stress, emotions are conditions that may led to memory loss, amnesia, anxiety, high blood pressure, dementia, to more ominous threat like schizophrenia and Alzheimer's diseases (AD) (1). AD is a neurodegenerative disorder characterized by a progressive loss of memory and cognation (2). Reducing oxidative stress by anti-oxidants, protecting brain inflammatory lesions using anti-inflammatory drugs and facilitation of brain cholinergic neurotransmission with anti-cholinesterase are some positive approaches to management for AD (3). The nature provides a new opportunity to regain one's full mental capacity. A number of herbs traditionally employed in the Indian System of Medicine "Ayurveda", have yielded positive results.

The current study was aimed to investigate the effects of Abana, an Indian Ayurvedic poly-herbal formulation on memory in rats. It has been clinically used as a cardioprotective drug (4, 5). Also, it was found as useful remedy for hypercholesterolemia, platelet aggregation, anxiety and depression (6-8). Each tablet consists of *Terminalia arjuna* 30 mg, *Withania somnifera* (Ashwagandha) 20 mg, *Tinospora cordifolia* (Giloe) 10 mg, *Nepeta hindostana* (Billilotan) 20 mg, *Phyllanthus emblica* (Amla) 10 mg, *Terminalia chebula* (Hirda) 10 mg, Dashamoola 20 mg (a mixture of ten herbs containing equal proportions of *Aegle marmelos, Premna integrifolia, Oroxylum indicum, Stereospermum suaveolens, Gmelina arborea, Desmodium gangeticum, Uraria picta, Solanum indicum, Solanum xanthocarpum* and *Tribulus terrestris*) *Eclipta alba* (Bhrangraj) 10 mg, *Glycyrrhiza glabra* (Yashtimadhu) 10 mg, *Centella asiatica* (Brahmi) 10 mg, *Asparagus racemosus* (Shatavari) 10 mg, *Boerhaavia diffusa* (Punarnava) 10 mg, *Convolvulus pluricaulis* (Shankhpushpi) 10 mg, *Ocimum sanctum* (Tulsi) 10 mg, *Nardostachys jatamansi* (Jatamansi) 10 mg, *Cyperus rotundus* (Motha) 5 mg, *Acorus calamus* (Vach) 5 mg, *Embelia ribes* (Vidanga) 5 mg, *Piper longum* (Pippali) 10 mg, *Carcum copticum* (Ajwain) 10 mg, *Zingiber officianale* (Sonth) 10 mg, *Syzygium aromaticum* (Lavanga) 5 mg, *Celastrus paniculatus* (Malkangni) 5 mg, *Santalum album* (Chandana) 5 mg, *Elettaria cardamomum* (Choti elaichi) 5 mg, *Foeniculum*

vulgare (Sonf) 5 mg, *Rosa damascena* (Gulat ka pool) 5 mg, *Cinnamomum cassia* (Taja) 5 mg, *Crocus sativus* (Keshar) 2 mg, Asphaltum (Shilajeet) 20 mg, Serpent stone, the silicate of magnesium and iron (Jaharmohra) 10 mg, conch (Shankh bhasma) 10 mg, sulphide of mercury (Makardhwaj) 10 mg, mica (Abhrak bhasma) 5 mg, *Mytilus magaritiferus* (Praval pishti) 5 mg, Agate (Akik pishti) 5 mg, Jade (Yeshab pishti) 5 mg, Ruby (Yakut pishti) 5mg and *Corallium rubrum* (Coral pishti). Bhasma and Pishti are the typical Ayurvedic preparations from the said raw materials.

Materials and Methods

Test Substance and Drugs

Commercially available Ayurvedic formulation Abana® tablets (Himalaya Drug Company, India) was obtained from local stockiest, Hisar, India. Scopolamine hydrobromide (Sigma-Aldrich, USA), diazepam injection (Calmpose®, Ranbaxy, India) and piracetam (UCB India Ltd., India).

Vehicle

Abana tablet was suspended with 0.5% w/v carboxymethylcellulose sodium (CMC) and given orally. Scopolamine hydrobromide, diazepam and piracetam were dissolved separately in normal saline and injected intraperitoneal. Volume of oral administrations and i.p. injections were 1 ml/kg of rats.

Animals

All the experiments were carried out using male, Wistar rats procured from the disease-free small animal house of CCS Haryana Agricultural University, Hisar (Haryana), India. Young (3-4 months old) rats weighing around 150 g and aged (12-15 months old) rats weighing around 250 g were used in the present study. The animals had free access to food and water, and they were housed in a natural (12h each) light-dark cycle. Food given to animals consisted of wheat flour kneaded with water and mixed with a small amount of refined vegetable oil. The animals were acclimatized for at least 5 days to the laboratory conditions before behavioral experiments. Experiments were carried out between 0900 h and 1800 h.

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and the care of laboratory animals was taken as per the guidance of CPCSEA, Ministry of Forests and Environment, Government of India (registration number 0436).

Drug Treatment

In the present investigation, the rats were divided in to different groups for employing various interoceptive and exteroceptive memory models. Each group comprised of a minimum of six animals. Abana (50, 100 and 200 mg/kg) was administered orally for 15 successive days to young and aged rats. After 90 minutes of the administration of the last dose (on 15th day), rats were exposed to the training session using elevated plus maze and Hebb-Williams maze. Retention (memory) was recorded after 24h (on 16th day). Amnesia was induced in separate groups (interoceptive models) of young rats by scopolamine (0.4 mg/kg, i.p.) or diazepam (1 mg/kg, i.p.) after 90 minutes of the last dose of drug (50, 100 and 200 mg/kg, p.o.) administration on 15th day. The animals were exposed to the training session (on 15th day) after 45 minutes of scopolamine or diazepam injection. The retention (memory) was measured after 24h (on 16th day). Piracetam (400 mg/kg, i.p.) was used as an established nootropic agent and was injected for seven days to positive control groups. All control group animals received vehicle (0.5% w/v CMC) for fifteen consecutive days.

Elevated Plus-Maze

Elevated plus-maze served as the exteroceptive behavioral model to evaluate memory in rats. The procedure, technique and end point for testing memory was followed as per the parameters described by the investigators working in the area of psychopharmacology (9-11). The elevated plus maze apparatus for rats consisted of a central platform (10 cm × 10 cm) connected to two open arms (50 cm × 10 cm) and two covered (enclosed) arms (50 cm × 40 cm × 10 cm) and the maze was elevated to a height of 50 cm from the floor (12). On the first day (i.e. 15th day of drug treatment), each rat was placed at the end of an open arm, facing away from the central platform. Transfer latency (TL) was recorded on the first day (training session) for each animal. TL was defined as the time (in seconds) taken by the animal to move from the open arm into any one of the covered arms with all its four legs.

The rat was allowed to explore the maze for another 2 min and then returned to its home cage. Retention of this learned-task (memory) was examined 24h after the first day trial (i.e. 16th day, 24h after last dose). Significant reduction in TL value of retention indicated improvement in memory.

Hebb-Williams Maze

Hebb-Williams maze is an incentive based exteroceptive behavioural model useful for measuring spatial working memory of rats (12). It consists of mainly three components. Animal chamber (or start box), which is attached to the middle chamber (or exploratory area) and a reward chamber at the other end of the maze in which the reward (food) is kept. All the three components are provided with guillotine removable doors. On the first day (i.e. 15th day of drug treatment), the rat was placed in the animal chamber or start box and the door was opened to facilitate the entry of the animal into the next chamber. The door of start box was closed immediately after the animal moved into the next chamber so as to prevent back-entry. Time taken by the animal to reach reward chamber (TRC) from start box was recorded on first day (training session) for each animal. Each animal was allowed to explore the maze for 3 minutes with all the doors opened before returning to its home cage. Retention of this learned task (memory) was examined 24 h after the first day trial (i.e. 16th day, 24h after last dose) (11).

Statistical Analysis

All the results were expressed as mean ± standard error (SEM). Data was analyzed using one-way ANOVA followed by Dunnett's t-test and Student's unpaired t-test. *P*-values <0.05 were considered as statistically significant.

Results

Effect on Transfer Latency Using Elevated Plus-Maze

The young ($p<0.01$) and aged ($p<0.001$) rats treated orally with Abana (50, 100 and 200 mg/kg) showed remarkable dose-dependent reduction in TL of 16th day, indicating significant improvement in memory (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 8th day indicating impairment in memory (Fig.2). All doses of Abana (50, 100 and 200 mg/kg, *p.o.*) successfully reversed memory deficits induced by scopolamine and diazepam. Piracetam (used as the positive control) at a dose of 400 mg/kg, *i.p.* also improved memory ($p<0.001$) in both young and aged rats and reversed the amnesia induced by scopolamine and diazepam.

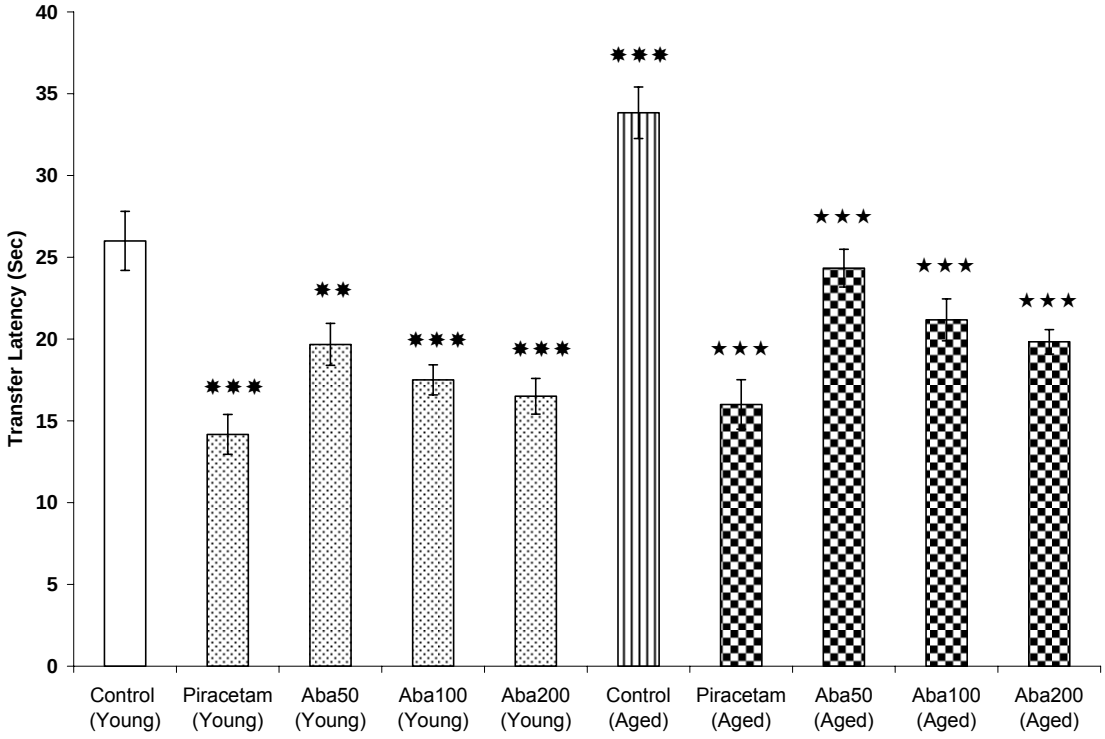

Fig. 1: Effect of Abana (Aba 50, 100 and 200mg/kg) administered orally for fifteen successive days on transfer latency of young (3-4 months) and aged (12-15 months) rats using elevated plus maze. Piracetam (400 mg/kg, *i.p.*) was used as a standard drug.
Values are in mean ± SEM. (n=6)
✸✸ denotes $p<0.01$ as compared to control group of young rats.
✸✸✸ denotes $p<0.001$ as compared to control group of young rats.
★★★ denotes $p<0.001$ as compared to control group of aged rats.
(One-way ANOVA followed by Dunnett's t-test and Student's unpaired t-test)

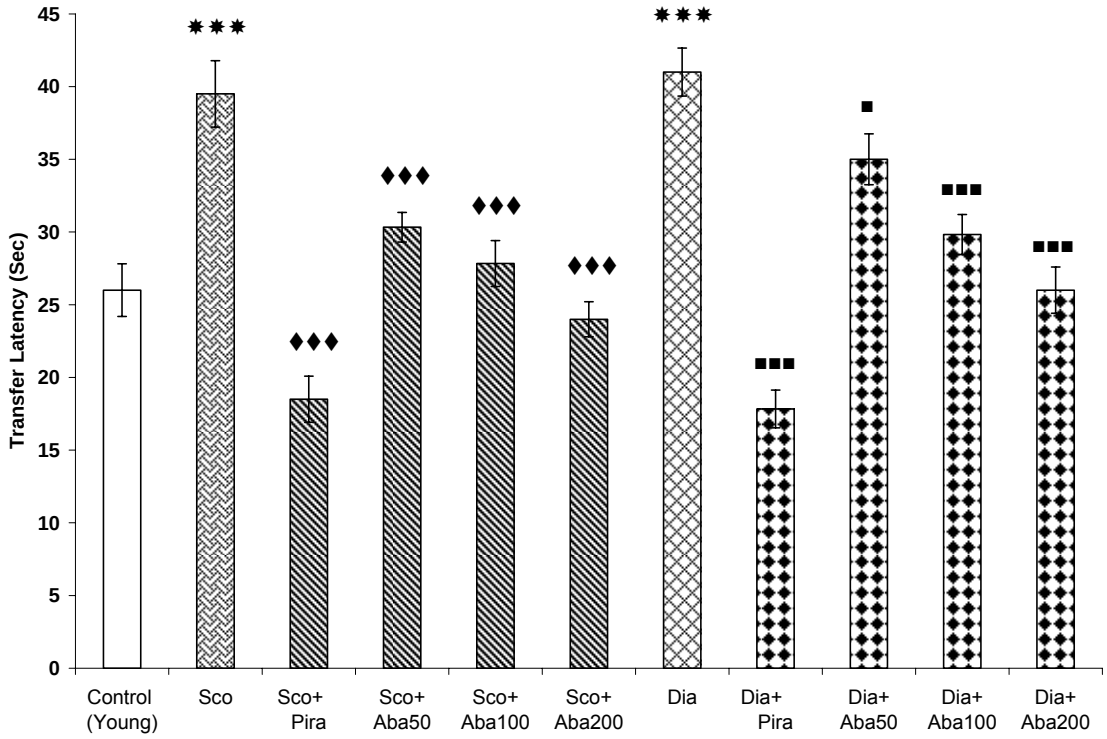

Fig. 2: Reversal of scopolamine (0.4 mg/kg, *i.p.*) or diazepam (1 mg/kg, *i.p.*) induced amnesia by Abana (Aba 50, 100 and 200mg/kg) in young rats using elevated plus maze. Piracetam (Pira) 400 mg/kg, *i.p.* was used as a standard drug.

Values are in mean ± SEM. (n=6)

✸✸✸ denotes $p<0.001$ as compared to control group of young rats.

♦♦♦ denotes $p<0.001$ as compared to scopolamine (Sco) alone.

■ denotes $p<0.05$ as compared to diazepam (Dia) alone.

■■■ denotes $p<0.001$ as compared to diazepam (Dia) alone.

(One-way ANOVA followed by Dunnett's t-test and Student's unpaired t-test)

Effect on Time Taken to Reach Reward Chamber Using Hebb -Williams Maze

Abana (50, 100 and 200 mg/kg) administered orally in young ($p<0.01$) and aged ($p<0.001$) rats for fifteen days markedly reduced TRC as compared to the respective control groups (Fig.3). Scopolamine (0.4 mg/kg, *i.p.*) and diazepam (1 mg/kg, *i.p.*) significantly increased ($p<0.001$) TRC as compared to control group of young rats, indicating impairment of memory (amnesia). Abana administered for fifteen days reversed the amnesia induced by both scopolamine and diazepam (Fig.4). The groups of rats, which were treated with piracetam (400 mg/kg, *i.p.*) for seven successive days showed improvement ($p<0.001$) in memory of young as well as aged rats. Piracetam also reversed amnesia induced by scopolamine and diazepam.

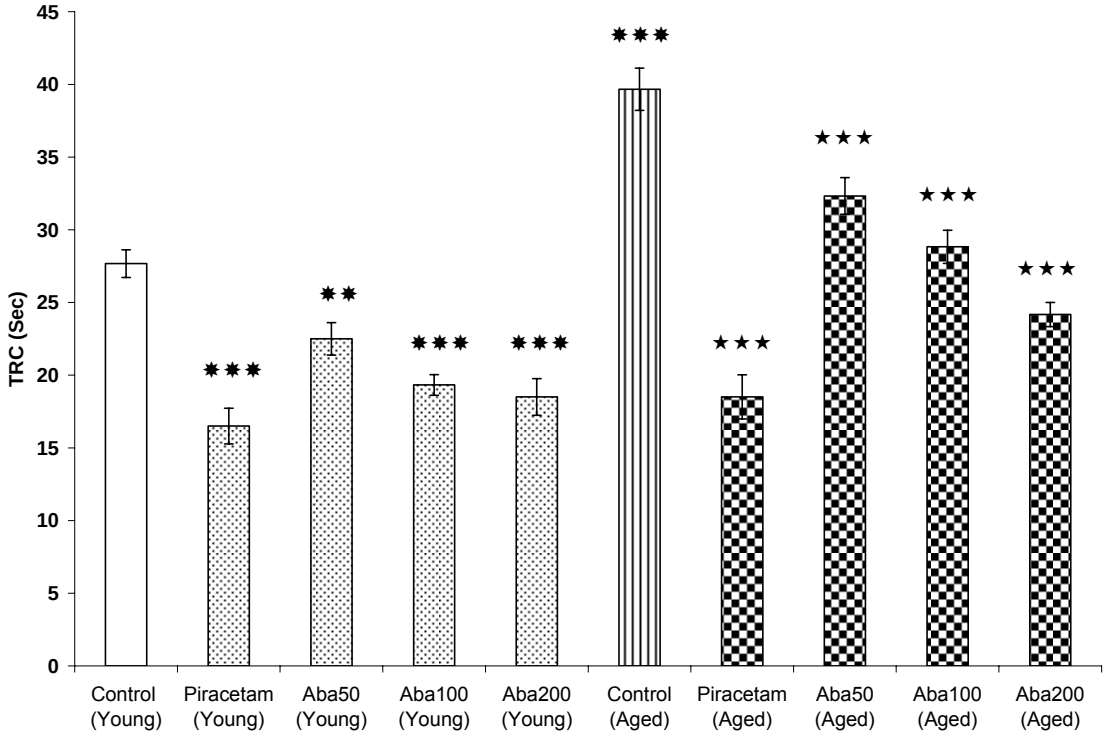

Fig. 3: Effect of Abana (Aba 50, 100 and 200mg/kg) administered orally for fifteen successive days on TRC of young (3-4 months) and aged (12-15 months) rats using Hebb-Williams maze. Piracetam (400 mg/kg, *i.p.*) was used as a standard drug.
Values are in mean ± SEM. (n=6)
✸✸ denotes p<0.01 as compared to control group of young rats.
✸✸✸ denotes p<0.001 as compared to control group of young rats.
★★★ denotes p<0.001 as compared to control group of aged rats.
(One-way ANOVA followed by Dunnett's t-test and Student's unpaired t-test)

Discussion

Alzheimer's disease (AD) is a progressive and fatal neurodegenerative disorder manifesting by cognitive and memory deterioration, progressive impairment of activities of living, and a variety of neuropsychiatric symptoms and behavioral disturbances (13). The clinical features of AD are an amnesic type of memory impairment, deterioration of language and visuospatial deficits. Motor and sensory abnormalities, gait disturbance and seizures are uncommon until the late phases of the disease (3). Despite the severity and high prevalence of this disease, Allopathic system of medicine is yet to provide a satisfactory antidote.

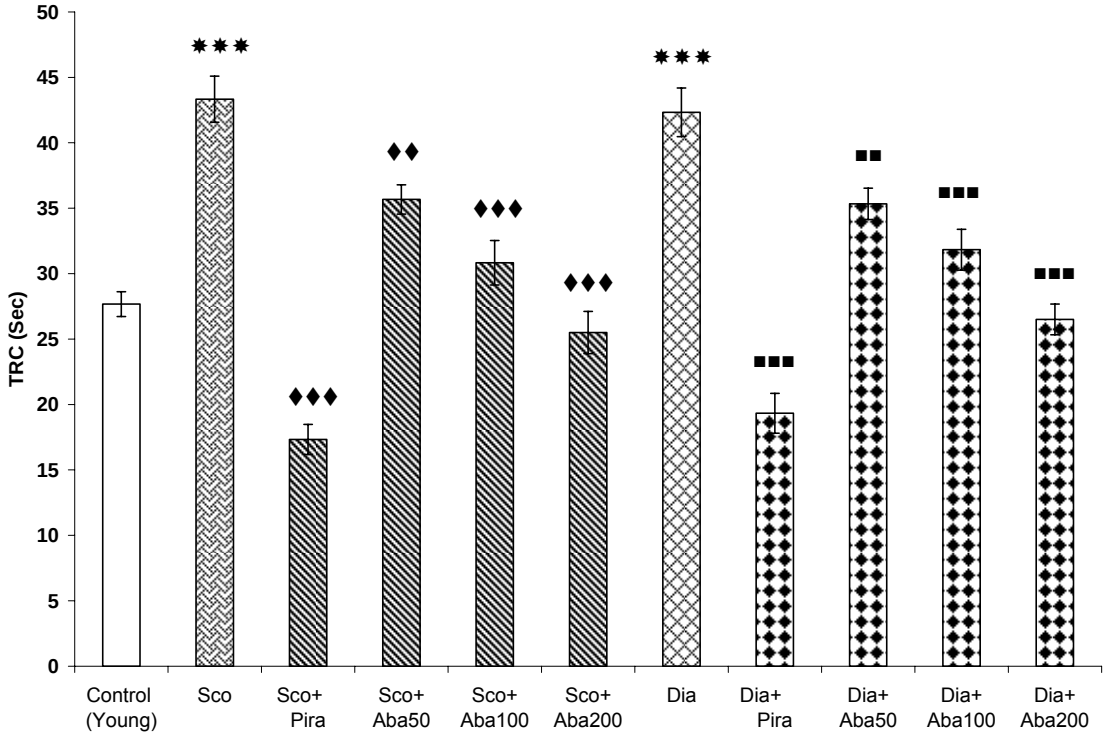

Fig. 4: Reversal of scopolamine (0.4 mg/kg, *i.p.*) or diazepam (1 mg/kg, *i.p.*) induced amnesia by Abana (Aba 50, 100 and 200mg/kg) in young rats using Hebb-Williams maze. Piracetam (Pira) 400 mg/kg, *i.p.* was used as a standard drug.

Values are in mean ± SEM. (n=6)

✸✸✸ denotes $p<0.001$ as compared to control group of young rats.

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■■ denotes $p<0.01$ as compared to diazepam (Dia) alone.

■■■ denotes $p<0.001$ as compared to diazepam (Dia) alone.

(One-way ANOVA followed by Dunnett's t-test and Student's unpaired t-test)

Therefore, we were motivated to explore the new approach in Indian traditional system to manage this deadly disease (AD). In the present study, we have focused upon exploring the potential of an Indian Ayurvedic poly-herbal formulation 'Abana' in reversing the memory deficits. Amnesia was induced in rats by intraperitoneal injection of scopolamine or diazepam, in addition to ageing induced amnesia (a natural process). Abana successfully reversed scopolamine, diazepam or ageing-induced amnesia, when administered for 15 days.

From literature, *Acorus calamu* (14), *Celastrus paniculatus* (15), *Centella Asiatic* (16), *Crocus sativus* (17), *Eclipta alba* (18), *Glycyrrhiza glabra* (19), *Nardostachys jatamansi* (20), *Ocimum sanctum* (21), *Piper longum* (22), *Zingiber officinale* (23) and *Withania somnifera* (24) were proved posses memory enhancing effect that present in Abana may involved in the reversal of memory deficit by Abana in this present investigations.

Immunohistochemical studies suggested that existence of chronic inflammation in certain regions of the brain in Alzheimer's disease patients. Since inflammation can be damaging to host tissue, it was hypothesized that anti-inflammatory drugs might be inhibiting both the onset and the progression of Alzheimer's disease. This hypothesis is supported by the observation that indomethacin (NSAID) halted the progressive memory loss seen in Alzheimer's disease patients. Moreover, it has also been observed that elderly patients suffering from Alzheimer's disease showed reduction in symptoms of Alzheimer's disease upon chronic use of anti-inflammatory drugs (25). Indomethacin, a non-steroidal anti-inflammatory drug exhibited a memory protective effect against electroconvulsive shock-induced retrograde amnesia and also against amyloid deposits in the brain (26,27). *Foeniculum vulgare* (28), *Boerhaavia diffusa* (29), *Celastrus paniculatus* (30), *Centella asiatica* (31), *Cyperus rotundus* (32), *Eclipta alba* (33), *Elettaria cardamomum* (34), *Phyllanthus emblica* (35), *Glycyrrhiza glabra* (36), *Ocimum* sanctum (37), *Piper longum* (38), *Zingiber officianale* (39) and *Withania somnifera* (40) have been proved as anti-inflammatory agents that might product inflammatory lesions in brain and involved memory improvement activity.

Oxygen free-radicals are implicated in the process of age-related decline in cognitive performance and may be responsible for the development of Alzheimer's disease in elderly persons (41-45). Oxygen-free radicals and other byproducts of oxidative metabolism have been shown to be neurotoxic and antioxidant rich diets improved cerebellar physiology and motor learning in aged-rats (46-48). *Acorus calamus* (49), *Asparagus racemosus* (50), *Foeniculum vulgare* (28), *Celastrus paniculatus* (15), *Centella asiatica* (51), *Crocus sativus* (52), *Cyperus rotundus* (53), *Elettaria cardamomum* (54), *Phyllanthus Emblica* (55), *Glycyrrhiza glabra* (56), *Nardostachys jatamansi* (57), *Ocimum sanctus* (37), *Piper longum* (58), *Terminalia chebula* (59), *Zingiber officinales* (60) and *Withania somnifera* (61) are ingredient of polyherbal product Abana, have been reported to possess antioxidant property,

which susceptible brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function. Thus, a combination of anti-inflammatory, antioxidant and neuroprotective role could all be leading to the net memory-enhancing effect of Abana.

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References

1. Vasudevan M, Parle M. Pharmacological actions of *Thespesia populnea* relevant to Alzheimer's disease. Phytomedicine 2006; 13: 677-687.
2. Dhingra D, Parle M, Kulkarni SK. Genetic basis of Alzheimer's disease. Indian J Pharm Sci 2005; 67: 409-413.
3. Wood AJJ. Drug therapy: Alzheimer's disease. New Engl J Med 2004; 351: 56-67.
4. Dadkar VN, Tahiliani RR, Jaguste VS, Damle VB, Dhar HL. Double-blind comparative trial of Abana and methyl dopa for immunotherapy of hypertension in Indian patients. Jpn Heart J 1990; 31: 193-199.
5. Rao R. Abana in cardiac disease and cardiac neurosis. Probe 1988; 27: 274-279.
6. Tiwari AK, Shukla SS, Agarwal A, Dubey GP. Lowering of serum total cholesterol to high density lipoprotein cholesterol ratios in hypercholesterolaemic patients by Abana: possible cardioprotective action. Altern Med 1990; 3: 145-148.
7. Wahal PK. A preliminary report on the inhibitory effect of Abana on platelet aggregation and adhesiveness in cases of coronary heart disease and hypertension. Probe 1991; 30: 312-315.
8. Talib SH, Khan ZH. Evaluation of Abana therapy in anxiety complex syndrome with special reference to vanilyll mandelic acid (VMA) as marker of assessment. Probe 1986; 25: 147-150.

9. Itoh J, Nabeshima T, Kameyama T. Utility of an elevated plus maze for evaluation of nootripics, scopolamine and electroconvulsive shock. Psychopharmacol 1990; 101: 27-33.
10. Reddy DS, Kulkarni SK. Possible role of nitric oxide in the nootropic and antiamnesic effects of neurosteroids on aging and dizocilpine-induced learning impairment. Brain Res 1998; 799: 215-229.
11. Parle M, Vasudevan M, Singh N. Swim everyday to keep dementia away. J Sport Sci Med 2005; 4: 37-46.
12. Parle M, Singh N. Animal models for testing memory. Asia Pacific J Pharmacol 2004; 16: 101-120.
13. Parle M, Dhingra D, Kulkarni SK. Neuromodulators of learning and memory. Asia Pacific J Pharmacol 2004; 16: 89-99.
14. Nishiyama N, Zhou Y, Saito H. Beneficial effects of DX-9386, a traditional Chinese prescription, on memory disorder produced by lesioning the amygdale in mice. Biol Pharm Bull 1994; 17: 1679–1681.
15. Kumar MHV, Gupta YK. Antioxidant property of *Celastrus paniculatus* Willd.: a possible mechanism in enhancing cognition. Phytomedicine 2002; 9: 302–311.
16. Sulochana B, Rao M, Chetana P, Devi U. *Centella asiatica* treatment during postnatal period enhances learning and memory in mice. Physiol Behav 2005; 86: 449 – 457.
17. Abe K, Saito H. Effects of saffron and its constituent crocin on learning behavior and long-term potentiation. Phytother Res 2000; 14: 149–152.
18. Thakur VD, Mengi SA. Neuropharmacological profile of *Eclipta alba* (Linn.) Hassk. J Ethnopharmacol 2005; 102: 23–31.
19. Dhingra D, Parle M, Kulkarni SK. Memory enhancing activity of *Glycyrrhiza glabra* in mice. J Ethnopharmacol 2004; 91: 361-365.
20. Joshi H, Parle M. *Nardostachys jatamansi* improves learning and memory in mice. J Med Food 2006; 9: 113-118.
21. Joshi H, Parle M. Evaluation of nootropic potential of *Ocimum sanctum* Linn. in mice. Indian J Exp Bio 2006; 44, 133-136.

22. Joshi H, Parle M. Effect of piperine on memory and behavior mediated via monoamine neurotransmitters. J Trad Med 2005; 23: 39-43.
23. Joshi H, Parle M. *Zingiber officinale*: Evaluation of its nootropic effect in mice. Afr J Trad CAM 2006; 3: 64-74.
24. Schliebs R, Liebmann A, Bhattacharya SK, et al. Systemic administration of defined extracts from *Withania somnifera* (Indian Ginseng) and shilajit differentially affects cholinergic but not glutamatergic and gabaergic markers in rat brain. Neurochem Int 1997; 30: 181-190.
25. McGeer EG, McGeer PL. Brain inflammation and the therapeutic implications. Curr Pharm Design 1999; 5: 821-836.
26. Rao SK, Andrade C, Reddy K, et al. Memory protective effect of indomethacin against electroconvulsive shock-induced retrograde amnesia in rats. Biol Psychiat 2002; 51: 770-773.
27. Stephan A, Laroche S, Davis S. Learning deficits and dysfunctional synaptic plasticity induced by aggregated amyloid deposits in the dentate gyrus are rescued by chronic treatment with indomethacin. Eur J Neurosci 2003; 17: 1921-1927.
28. Choi E, Hwang J. Anti-inflammatory, analgesic and antioxidant activities of the fruit of *Foeniculum vulgare*. Fitoterapia 2004; 75: 557– 565.
29. Bhalla TN, Gupta MB, Bhavgava KP. Anti-inflammatory activity of *Boerhaavia diffusa* L. J Indian Med Res 1971; 6: 11–15.
30. Ahmad F, Khan RA, Rasheed S. Preliminary screening of methanolic extracts of *Celastrus paniculatus* and *Tacomelia undulate* for analgesic and anti-inflammatory activities. J Ethnopharmacol 1994; 42: 193–198.
31. Ramaswamy AS, Periyasamy SM, Basu N. Pharmacological studies on *Centella asiatica* Linn. (*Brahma manduki*) (n.o. Umbelliferae). J Res Industrial Med 1970; 4: 160–175.
32. Jagtap AG, Shirke SS, Phadke AS. Effect of polyherbal formulation on experimental models of inflammatory bowel diseases. J Ethnopharmacol 2004; 90: 195–204.
33. Leal LK, Ferreira AA, Bezerr GA, Matos FJ, Viana GS. Antinociceptive, anti-inflammatory and bronchodilator activities of Brazilian medicinal plants containing coumarin: a comparative study. J Ethnopharmacol 2000; 70: 151–159.

34. Al-Zuhair H, El-Sayeh B, Ameen HA, Al-Shoora H. Pharmacological studies of cardamom oil in animals. Pharmacol Res 1996; 34: 79–82.
35. Asmawi MZ, Kankaanranta H, Moilanen E, Vapaatalo H. Anti-inflammatory activities of *Emblica officinalis* Gaertn. leaf extracts. J Pharm Pharmacol 1993; 45: 581– 584.
36. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from liquorice extracts on melanogenesis and inflammation. Pigm Cell Res 1998; 11: 355–361.
37. Kelm MA, Nair MG, Strasburg GM, De Witt DL. Antioxidant and COX inhibitory phenolic compounds from *Ocimum sanctum* Linn. Phytomedicine 2000; 7: 7–13.
38. Majumdar AM, Dhuley JN, Deshmukh VH, Raman PH, Naik SR. Anti-inflammatory activity of piperine. Jap J Med Sci Biol 1990; 43: 95-100.
39. Thomson M, Al-Qattan KK, Al-Sawan SM, et al. The use of ginger (*Zingiber officinale* Rosc.) as a potential anti-inflammatory and antithrombotic agent. Prostag Leukotr Ess 2002; 67: 475-478.
40. Agarwal R, Diwanay S, Patki P, Patwardhan B. Studies on immunomodulatory activity of *Withania somnifera* (Ashwagandha) extracts in experimental immune inflammation. J Ethnopharmacol 1999; 67: 27–35.
41. Sinclair AJ, Bayer AJ, Johnston J, Warner C, Maxwell SR. Altered plasma antioxidant status in subjects with Alzheimer's disease and vascular dementia. Int J Geriatr Psychiatry 1998; 13: 840-855.
42. Berr C. Oxidative stress and cognitive impairment in the elderly. J Nutr Health Aging 2002; 6: 261-266.
43. Butterfield DA, Lauderback CM. Lipid peroxidation and protein oxidation in Alzheimer's disease: potential causes and consequences involving amyloid-beta peptide-associated free radical oxidative stress. Free Radical Bio Med 2002; 32: 1050-1060.
44. Floyd RA, Hensley K. Oxidative stress in brain aging. Implications for therapeutics of neurodegenerative disease. Neurobiol Aging 2002; 23: 795-807.
45. Perry G, Cash AD, Smith MA. Alzheimer disease and oxidative stress. J Biomed Biotech 2002; 2: 120-123.

46. Sayre LM, Zagorski MG, Surewicz WK, Krafft GA, Perry G. Mechanisms of neurotoxicity associated with amyloid beta deposition and the role of free radicals in the pathogenesis of Alzheimer's disease: a critical appraisal. Chem Res Toxicol 1997; 336: 1216-1222.
47. Rogers EJ, Milhalik S, Ortiz D, Shea TB. Apple juice prevents oxidative stress and impaired cognitive performance caused by genetic and dietary deficiencies in mice. J Nutr Health Aging 2003; 7: 1-6.
48. Bickford PC, Gould T, Briederick L, et al. Antioxidants-rich diets improve cerebellar physiology and motor learning in aged rats. Brain Res 2000; 886: 211-217.
49. Manikandan S, Devi RS. Antioxidant property of α-asarone against noise-stress-induced changes in different regions of rat brain. Pharmacol Res 2005; 52: 467–474.
50. Kamat JP, Boloor KK, Devasagayam TPA, Venkatachalam SR. Antioxidant properties of *Asparagus racemosus* against damage induced by γ-radiation in rat liver mitochondria. J Ethnopharmacol 2000; 71: 425–435.
51. Subathra M, Shila S, Devi MA, Panneerselvam C. Emerging role of *Centella asiatica* in improving age-related neurological antioxidant status. Exp Gerontol 2005; 40: 707–715.
52. Chatterjee S, Poduval TB, Tilak JC, Devasagayam TPA. A modified, economic, sensitive method for measuring total antioxidant capacities of human plasma and natural compounds using Indian saffron (*Crocus sativus*). Clinica. Chimica Acta 2005; 352: 155–163.
53. Seo WG, Pae HO, Oh GS, et al. Inhibitory effects of methanol extract of *Cyperus rotundus* rhizomes on nitric oxide and superoxide productions by murine macrophage cell line, RAW 264.7 cells. J Ethnopharmacol 2001; 76: 59–64.
54. Hinneburg I, Dorman HJD, Hiltunen R. Antioxidant activities of extracts from selected culinary herbs and spices. Food Chem 2006; 97: 122–129.
55. Bhattacharya A, Chatterjee A, Ghosal S, Bhattacharya SK. Antioxidant activity of active tannoid principles of *Emblica officinalis* (amla). Indian J Exp Biol 1999; 37: 676–680.

56. Fukai T, Satoh K, Nombra T, Sakagamic H. Preliminary evaluation of antinephritis and radical scavenging activities of glabridin from *Glycyrrhiza glabra*. Fitoterapia 2003; 74: 624–629.
57. Tripathi YB, Tripathi E, Upadhyay A. Antilipid peroxidative property of *Nardostachys jatamansi*. Indian J Exp Biol 1996; 34: 1150–1151.
58. Khajuria A, Thusu N, Zutshi U, Bedi KL. Piperine modulation of carcinogen induced oxidative stress in intestinal mucosa. Mol cell Biochem 1998; 189: 113–118.
59. Naika GH, Priyadarsinia KI, Naika DB, Gangabhagirathib T, Mohana H. Studies on the aqueous extract of *Terminalia chebula* as a potent antioxidant and a probable radioprotector. Phytomedicine 2004; 11: 530–538.
60. Ahmed RS, Seth V, Pasha ST, Banerjee BD. Influence of dietary ginger (*Zingiber officinales* Rosc) on oxidative stress induced by malathion in rats. Food Chem Toxicol 2000; 38: 443–450.
61. Kaur K, Rani G, Widodo N, et al. Evaluation of the anti-proliferative and anti-oxidative activities of leaf extract from *in vivo* and *in vitro* raised Ashwagandha. Food Chem Toxicol 2004; 42; 2015–2020.