Efficacy and Safety of an Ashwagandha in Memory and Cognitive Function

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Original Article

Efficacy and Safety of an Ashwagandha (*Withania somnifera*) Root Extract in Improving Memory and Selected Cognitive Functions

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Abstract

Background and Objective: Ashwagandha has been recommended in traditional Ayurveda for improving memory. This study aims to evaluate the efficacy and safety of Ashwagandha toward improving memory and certain aspects of cognitive functioning.

Material and methods: A prospective, randomized, double-blind, placebo-controlled study was conducted in 50 healthy adults. Subjects were treated with either oral Ashwagandha root extract (300 mg capsule) or placebo BID for eight weeks. The primary efficacy parameters were improvements in immediate memory, general memory and working memory as assessed through the Wechsler Memory Scale III (WMS-III^{IND}). The secondary efficacy outcomes were improvements in visuo-spatial processing/response, executive function, attention and information processing speed, as assessed through WMS-III^{IND} subtest scores for Visual Reproduction I & II, Shepard's mental rotation task, Erikson Flanker task, Wisconsin Card Sort test, Trail Making Test part A and Mackworth's sustained attention test. Safety was evaluated by recording adverse events.

Results: At baseline, no significant difference in cognitive impairment, subjective complaints and vital parameters was seen across the two groups. The Ashwagandha group showed greater improvement than the placebo group for immediate memory and general memory, evidenced in greater improvement in the subtest scores for Logical Memory I ($p = 0.007$), Verbal Paired Associates I ($p=0.043$), Faces I ($p=0.020$), Family Pictures I ($p=0.006$) and Logical Memory II ($p = 0.006$), Verbal Paired Associates II ($p=0.031$), Faces II ($p=0.014$), Family Pictures II ($p=0.006$). However, there was only mixed evidence for improvement in working memory. The Ashwagandha group showed greater improvement than the placebo group also for executive function, attention and information processing speed, through greater improvement on the Erikson Flanker task ($p=0.002$), Wisconsin Card Sort test ($p=0.014$), Trail Making Test part A ($p=0.006$) and Mackworth's sustained attention test ($p=0.009$). However, no significant improvement was observed for visuo-spatial processing and response.

Conclusion: Ashwagandha (*Withania somnifera*) can be effective in improving immediate memory and general memory. and in improving executive function, attention and information processing speed without any side effects.

Key words: Ashwagandha (*Withania somnifera*), memory, cognition, efficacy, safety

Introduction and Background:

Withania somnifera, also known as Ashwagandha, Indian Ginseng or Winter Cherry has a long history in the Indian Ayurvedic system of medicine and is a central herb in Ayurveda. The dominant mode of use of the herb in health or functional applications is by drying the plant's root in the shade, powdering it and then ingesting it or its extract in small doses. The Ayurveda complementary medicine literatures, both traditional and modern, enumerate several benefits of ashwagandha under the rubrics of anti-stress effects, neuroprotective effects, immunomodulatory effects, and rejuvenating effects, via the herb's interplay with the nervous system, the endocrine system, the cardiopulmonary system, the energy production system and the immune system. Among the varied uses of ashwagandha, the focus of this research is on the subset of uses related to ashwagandha for the improvement of memory and certain aspects of cognitive functioning: visuo-spatial processing/response, executive function and attention and information processing speed. A principal contribution of this research is that it is the first to present the results of a randomized, double-blind, placebo-controlled clinical study on ashwagandha root extract's effects on memory and cognitive functioning using a wide range of modern neuro-assessment instruments. There being so few studies examining the effect of ashwagandha on memory and cognitive functioning constitutes a noteworthy gap in the modern scientific literature, because traditional Ayurveda prominently identifies the application of ashwagandha in improving memory.

Materials & Methods:

In this prospective, randomized, double-blind, placebo-controlled study, 50 healthy adults over 35 years of age with MCI [screening Mini-Mental State Examination (MMSE) score of ≥19][6] were enrolled if they were willing to sign informed consent. Patients with screening MMSE score of <19 (moderate and severe memory impairment), known neuropsychiatric conditions, receiving psychotropic drugs, alcohol or any other drugs or alternative medicines for enhancement of memory were excluded from the study. Similarly, patients with persistent endocrine disorders, uncontrolled hypertension or diabetes mellitus, drug dependence or severe co-morbid medical conditions were excluded. Pregnant and lactating women and subjects with known hypersensitivity to Ashwagandha were also not enrolled in the study. Nootropic agents, central anticholinesterase drugs to enhance the memory and cognition were prohibited during the study. The subjects were randomized by PC based software (Rando version 1.2©, R.Raveendran 2004) into two groups to receive either oral Ashwagandha root extract 300 mg capsule (KSM-66 Ashwagandha, Ixoreal Biomed, Los Angeles, California, USA) or identical placebo twice daily for eight weeks. The subjects were evaluated at baseline, after four and eight weeks.

The efficacy parameters were the improvement in the scores of Wechsler Memory Scale III (WMS-III^{IND})[7] for certain memory and cognition domains. The memory domain included the subsets of immediate memory (logical Memory I, Verbal Paired Associates I, Faces I and Family Pictures I), general memory (Logical Memory II, Verbal Paired Associates II, Faces II and Family Pictures II), and working memory (Letter Number Sequencing and Spatial Span). The cognition domain included the WMS-III^{IND} subsets related to visuo-spatial processing and response (Visual reproduction I, Visual reproduction II) and also Shepard's mental rotation task[8], executive function (Wisconsin Card Sort test[9] and Erikson Flanker task[10]), and attention and information processing speed (Trail Making Test part A and Mackworth's sustained attention test[11]).

Safety was evaluated by recording adverse events. Global Assessment of Tolerability to Therapy (PGATT) was assessed on a 5-point scale; "excellent" (no adverse effects & patient able to tolerate the drug), "good" (minimal side effects not interfering with patients daily activities), "moderate" (some side effects and minimal interference in patients daily activities), "poor" (significant side effects & Significant interference in patients daily activities) and "worst" (patient not able to tolerate the drug at all due to adverse effects). The study was conducted in accordance with the ethical principles of declaration of Helsinki and Good Clinical Practice Guidelines. The study protocol was approved by the ethics committee.

Statistical analysis:

This being an exploratory study, 50 subjects (25 in each treatment arm) were enrolled. Measurement data is expressed as means with SD; categorical data and discrete data is expressed as numbers with percentages. Ranking data and scores are presented as means with SD. Since there were no dropouts/exclusion of patients from the study, all analysis is done on per-protocol (PP) dataset using MedCalc Statistical Software version 14.8.1. The two groups are compared for measurement data for demography and vital parameters using one-way analysis of variance (ANOVA). Similarly, the two groups are compared for scores at all visits and changes from baseline in the scores using one-way analysis of variance (ANOVA).Baseline scores are compared to post-treatment scores using Friedman test followed by post-hoc individual comparisons using Wilcoxon test. All testing is done using two-sided tests at alpha 0.05 (95% confidence level).

Results:

At baseline, demographic parameters and cognitive impairment as determined by MMSE was similar in both the groups (table 1). Subjective symptoms before treatment were also similar in both the groups. The comment symptoms reported by the subjects were: forget things more often (all patients in both groups), forget important events such as appointments or social engagements (88% in both groups), lose train of thought or the thread of conversations, books or movies (64% vs 48%; p=0.254), feel increasingly overwhelmed by making decisions, planning steps to accomplish a task or interpreting instructions (32 vs 40% p=0.556), start to have trouble finding your way around familiar environments (20 in both groups). No significant difference was seen in the vital parameters at baseline.

Memory: The mean baseline and change from baseline for the scores in the subsets in memory domain are presented in tables 2, 3 and 4. The improvement (change from baseline) in the immediate memory subsets was greater ($p<0.05$) with Ashwagandha treatment compared to placebo at eight weeks; however, the difference was not significant at four weeks. (Table 2)

Similarly, the improvement (change from baseline) in the general memory subsets was greater with Ashwagandha treatment compared to placebo at both four and eight weeks. The difference was not significant at four weeks ($p>0.05$), but was significant at 8 four weeks ($p<0.05$). (Table 3)

There was mixed evidence for Ashwagandha improving working memory even at 8 weeks. There was significant improvement for spatial span at 8 weeks ($p<0.05$) but not for letter number sequencing (Table 4).

Cognitive Functioning: The mean baseline and change from baseline for the scores in the subsets in cognition domain are presented in tables 5, 6 and 7. The mean scores are similar with Ashwagandha and placebo for all three subsets at baseline.

Visuo-spatial processing/response was assessed through WMS-III^{IND} subtest scores for Visual Reproduction I & II and Shepard's mental rotation task.. The improvement (change from baseline) in the scores for all three subsets was greater with Ashwagandha treatment compared to placebo at four and eight weeks; however, the differences were not statistically significant ($p>0.05$). (Table 5)

Executive function was assessed through Wisconsin card sort test and the Erikson Flanker Task. The mean values are similar with Ashwagandha and placebo for the Wisconsin card sort test and the number of correct responses for Erikson Flanker task at baseline ($p>0.05$). The improvement (change from baseline) in the sub-set scores and responses was greater with Ashwagandha treatment with p-values of $p=0.014$ and $p=0.002$ respectively (Table 6).

Attention and information processing speed were assessed through Trail Making Test part A and Mackworth's sustained attention test. The mean values are similar with Ashwagandha and placebo for the tests in the attention and information processing speed subsets at baseline ($p>0.05$). The improvement (change from baseline) in the sub-set scores were significantly greater with Ashwagandha treatment at both 4 and 8 weeks after therapy ($p<0.05$) (Table 7). In Trail Making Test, the time taken for the test was significantly reduced by a greater extent with Ashwagandha treatment compared to placebo at week 4 ($p=0.021$) and 8 weeks ($p=0.009$).

After treatment for 4 or 8 weeks, the vital parameters (systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate) were similar with Ashwagandha treatment as placebo (ANOVA; $p>0.05$ for all). The study medication was very well tolerated by the study subjects. No adverse event was reported by any subject in either of the study arms. As per the patient's global assessment of tolerability to therapy (PGATT), all subjects in both group reported an "excellent" tolerability. No significant difference was seen on the vital parameters i.e. blood pressure, pulse rate, respiratory rate and temperature between Ashwagandha and placebo. All patients in both treatment groups were compliant to the study therapy.

Discussion:

Memory and cognitive functioning are critical for everyday life in the modern knowledge worker economy. Memory and cognitive functioning tend to decline with age past a person's prime. Various experimental treatments have been studied for preventing cognitive impairment; however, many have failed to provide meaningful results.[12] Herbal medicines have also been invested in the treatment of cognitive deficit disorders, but they also have limitations for their use. For example, many of the clinical trials with Ginkgo are conducted with unsatisfactory methods. Two Cochrane reviews (2007 and 2007) have concluded that the use of ginkgo biloba for improvement in cognitive function is unconvincing.[13,14]

Ashwagandha has been used as a traditional medicine from the time of Ayurveda because of its varied actions including aphrodisiac, GABA like activity, anti-inflammatory agent, astringent, antioxidant, anti-carcinogenic, anti-aging and immunomodulatory activity.[15] Withania somnifera has been discussed as one of the therapies in Alzheimer's disease.[16] Animal study has shown potential of Withania somnifera in reversing the pathology in Alzheimer's disease.

In our study, Ashwagandha treatment resulted in memory and cognitive improvement as measured on various parameters. The Ashwagandha group showed greater improvement than the placebo group for immediate memory and general memory, evidenced in greater improvement the subtest scores for Logical Memory I ($p = 0.007$), Verbal Paired Associates I ($p=0.042$), Faces I ($p=0.020$), Family Pictures I ($p=0.006$) and Logical Memory II ($p = 0.006$), Verbal Paired Associates II ($p=0.031$), Faces II ($p=0.014$), Family Pictures II ($p=0.006$). However, there was only mixed evidence for improvement in working memory. The Ashwagandha group showed greater improvement than the placebo group also for executive function, attention and information processing speed, through greater improvement on the Erikson Flanker task ($p=0.002$), Wisconsin card sort test ($p=0.014$), Trail Making Test part A ($p=0.006$) and Mackworth's sustained attention test ($p=0.009$). However, no significant improvement was observed for visuo-spatial processing and response.

At baseline, there was no significant difference in the cognitive impairment, symptoms or other parameters in both groups; hence all these observed differences can directly be attributed to Ashwagandha.

No adverse event in any of the subjects demonstrates placebo like safety profile of the study medication. Ashwagandha did not result in any significant alteration of vital parameters including systolic and diastolic blood pressure, pulse rate, respiratory rate or temperature. The subjective assessment of tolerability was also excellent in all subjects. These all findings confirm s the excellent tolerability of Ashwagandha in healthy subjects.

The study has few limitations. First, the sample size of the study is very small; however, as this was an exploratory study, it was decided to enroll 25 subjects in each group. The duration of treatment was short. The large clinical trial with longer follow up is required to confirm the results of this study.

Conclusion:

Ashwagandha (*Withania somnifera*) can be effective in improving immediate memory and general memory. and in improving executive function, attention and information processing speed without any side effects.

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Table 1: Baseline characteristics

	Ashwagandha (n=25) Mean (SD)	Placebo (n=25) Mean (SD)	't' test 'p' (t)
Age (yrs.)	50 (7.33)	51 (7.98)	0.647 (0.213)
Weight (kg.)	61.36 (6.8)	57.84 (6.34)	0.060 (3.711)
BMI (kg/m^2)	25.01 (2.68)	24.09 (2.64)	0.125 (2.284)
MMSE total score	23.2 (2.04)	24.56 (2.24)	0.093 (2.944)

Table 2: Wechsler Memory Scale (WMS-III^{IND}): Immediate memory subset

	Ashwagandha (n=25)		Placebo (n=25)		
	Mean	*SD*	*Mean*	*SD*	*p*
Logical memory I					
• Baseline	8.62	2.04	9.00	2.56	0.057
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	2.71	2.51	1.42	2.77	0.092
• Change at 8 wks.	4.12	2.69	2.04	2.55	0.007
Verbal paired associates I	*Mean*	*SD*	*Mean*	*SD*	*p*
• Baseline	8.50	3.30	8.65	3.78	0.879
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	1.58	2.69	0.38	2.52	0.111
• Change at 8 wks.	2.38	2.53	1.04	1.93	0.043
Faces I	*Mean*	*SD*	*Mean*	*SD*	*P*
• Baseline	10.38	2.78	10.73	2.93	0.662
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	2.38	2.46	1.15	2.52	0.090
• Change at 8 wks.	3.50	2.52	1.85	2.33	0.020
Family pictures I	*Mean*	*SD*	*Mean*	*SD*	*P*
• Baseline	11.04	3.21	11.65	3.50	0.522
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	2.29	2.10	0.81	2.58	0.030
• Change at 8 wks.	2.92	1.79	1.35	2.06	0.006

Table 3: Wechsler Memory Scale (WMS-III^{IND}): General memory subset

	Ashwagandha (n=25)		Placebo (n=25)		
	Mean	*SD*	*Mean*	*SD*	*p*
Logical memory II					
• Baseline	7.50	2.73	7.73	2.86	0.772
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	2.79	2.89	1.35	2.77	0.078
• Change at 8 wks.	3.88	2.56	1.77	2.58	0.006
Verbal paired associates II	*Mean*	*SD*	*Mean*	*SD*	Sig.
• Baseline	9.21	3.16	8.65	2.67	0.508
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	1.00	1.79	0.23	1.95	0.152
• Change at 8 wks.	1.58	1.67	0.54	1.65	0.031
Faces II	*Mean*	*SD*	*Mean*	*SD*	Sig.
• Baseline	9.92	2.45	9.08	2.02	0.195
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	2.42	2.00	1.65	2.10	0.194
• Change at 8 wks.	3.46	1.84	2.15	1.76	0.014
Family pictures II	*Mean*	*SD*	*Mean*	*SD*	Sig.
• Baseline	11.29	2.82	11.19	2.73	0.900
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	2.38	1.64	1.27	1.71	0.024
• Change at 8 wks.	3.17	1.93	1.77	1.42	0.006

Table 4: Wechsler Memory Scale (WMS-III^{IND}): Working memory subset

	Ashwagandha (n=25)		Placebo (n=25)		
	Mean	*SD*	*Mean*	*SD*	*p*
Letter number sequencing					
• Baseline	11.88	2.86	12.85	2.15	0.185
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	0.46	2.21	-0.04	1.75	0.386
• Change at 8 wks.	1.00	1.74	0.23	2.01	0.154
Spatial span	*Mean*	*SD*	*Mean*	*SD*	Sig.
• Baseline	12.12	3.31	11.65	3.54	0.629
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	0.71	2.37	-0.23	1.90	0.131
• Change at 8 wks.	1.00	1.69	0.04	1.59	0.044

Table 5: Visuo-spatial processing and response

	Ashwagandha (n=25)		Placebo (n=25)		
	Mean	*SD*	*Mean*	*SD*	*p*
WMS-III[IND] **Visual reproduction I**					
• Baseline	12.71	3.43	12.65	2.84	0.952
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	0.33	2.04	0.08	2.21	0.671
• Change at 8 wks.	0.79	1.84	0.08	1.72	0.163
WMS-III[IND] **Visual reproduction II**	Mean	SD	Mean	SD	Sig.
• Baseline	11.83	3.07	11.69	2.84	0.867
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	0.58	1.89	-0.08	1.62	0.193
• Change at 8 wks.	0.83	1.46	0.08	1.72	0.100
Shepard's mental rotation task (correct)	Mean	SD	Mean	SD	Sig.
• Baseline	4.04	1.40	4.23	1.58	0.656
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	0.33	1.46	0.46	1.68	0.774
• Change at 8 wks.	0.88	1.54	0.42	1.60	0.315

Table 6: Executive function

	Ashwagandha (n=25)		Placebo (n=25)		
	Mean	*SD*	*Mean*	*SD*	*p*
Wilconsin card sort test					
• Baseline	48.92	22.19	51.23	16.40	0.679
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	-6.42	5.94	-2.54	6.30	0.030
• Change at 8 wks.	-7.96	5.24	-4.15	5.29	0.014
Erikson Flanker task (#correct)	Mean	SD	Mean	SD	Sig.
• Baseline	5.62	2.12	5.65	2.26	0.963
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	0.50	0.88	-0.04	0.60	0.017
• Change at 8 wks.	0.75	0.79	0.08	0.63	0.002

Table 7: Attention and Information Processing Speed

	Ashwagandha (n=25)		Placebo (n=25)		
	Mean	*SD*	*Mean*	*SD*	*p*
Trail making test part A (time required)					
• Baseline	68.17	21.59	62.19	26.70	0.387
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	-4.92	4.56	-2.50	3.30	0.039
• Change at 8 wks.	-6.38	4.15	-3.46	2.66	0.006
Mackworth's sustained attention test (#correct)	Mean	SD	Mean	SD	
• Baseline	8.88	2.03	9.12	1.68	0.652
Change from baseline	*Mean ch.*	*SD*	*Mean ch.*	*SD*	
• Change at 4 wks.	0.67	0.92	0.00	1.06	0.021
• Change at 8 wks.	0.88	1.08	0.04	1.08	0.009