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KUSHMANDA GHRITA IN COGNITIVE DECLINE IN AGEING - AN OBSERVATIONAL CLINICAL STUDY

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ABSTRACT:

Background: Cognitive decline in ageing has been considered as a problematic mental illness in ageing since antiquity. Various treatment modalities are used to treat Cognitive decline in ageing. The use of Medhya Rasayana drugs in Ayurveda is a unique method of treatment mentioned for Cognitive decline.

Objective: Effect of Kushmanda Ghrita on Cognitive decline in ageing.

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Design: The use of Kushmanda (Benincasa hispida) is one of the Medhya Rasayana as described by Bhav Mishra. Ghrita is one of the best Medhya Rasayana considered by almost all Acharayas. Keeping this in mind Kushmanada Ghrita has been selected as a trial drug to treat patients of cognitive decline in ageing.

Participants: The study was carried out on 35 clinically diagnosed cases of Cognitive decline by using Addenbrooke's Cognitive Examination (ACE III). All patients were given 20 ml of Kushmanda Ghrita in two divided schedules Rasayana kala and Udana kala with 40 ml of lukewarm water for a period of two months.

Results: It has shown statistically significant results with ACE III total score (before treatment the score was 88 and after treatment, the score was 93) the p-value is $p< 0.001$. The value of WBI score was also improved from 19 to 22 and p-value is also less than 0.001 and has a significant result. It suggests that Kushmanda Ghrita has effective in age-associated cognitive decline.

Conclusion: Significant result of Kushmanda Ghrita was observed in memory, attention & orientation, fluency domain in cognitive decline in aging. Improvement in WBI and ADL scores was observed. The research study implicates that the Kushmanda Ghrita can be used as Medhya, Vataghna, Nidrakar, Pushtikar.

Keywords: Cognitive decline, Aging, Diabetes mellitus.

1.**Introduction: -** The world's population of older people is growing at the fastest rate ever. According to the population Census 2011 there are nearly 104 million elderly persons (aged 60 years or above) in India [1]. A report released by the United Nations Population suggests that the number of elderly persons is expected to grow to 173 million by 2026[2]. Cognitive decline in elderly is associated with physiological, functional and pathological changes which are concerned with the loss of physical ability and mental acuity. Clinically, a progression of cognitive decline is seen, which begins with mild memory loss and ends with severe cognitive and behavioral deterioration.

The rate of brain shrinkage or atrophy increases with age and is a major factor in early cognitive decline. Age associated changes in the brain like cortical atrophy, loss of myelin integrity, accumulation of neurofibrillary tangles impaired acetylcholine, dopamine receptor binding, and signaling etc. are causes of the cognitive decline. Cognitive decline is seen in higher-level brain functions like memory, language, visual perception, attention and orientation, and planning problem-solving sing. Most of time cognitive decline is taken for granted. Progressive cognitive

decline which usually becomes noticeable on middle age, has been ignored mightily as a part of getting old, as many people age into their 90s only with a modest loss of mental skills and abilities. In the elderly individual showing measurable cognitive decline, if not treated properly may find distressing; as remarkably declined cognitive performance in the sixth decade has been connected to increased risk of dementia and Alzheimer ‘s disease [3].

This condition can be correlated with Jaravastha janya Smritibhramsha mentioned in Charaka vimanasthana. And if the hetusevan persists it may progress to Smritinasha, Buddhinasha[4]. According to Acharya Sharangdhara decline of medha starts after 40 years of age, which may be consider as a warning signal for decline in buddhi, smriti in the successive years where Medhya Rasayana is advised to halt or revert these changes. Age associated cognitive decline is not mentioned as a disease entity in separate chapters in Ayurvedic classics but references about its symptoms gets scattered in the classics.

There is a paucity of modern drugs/ agents facilitating acquisition, retention, and retrieval of information and knowledge. Nootropic agents such as Piracetam, cholinesterase inhibitors like Donepezil are being primarily used to improve memory, mood and behavior. However, the resulting adverse effects associated with these agents have limited their use and it is worthwhile to explore the utility of traditional medicines in the treatment of various cognitive disorders [5].

Rasayana treatment can be a great solution for brain ageing as it is helpful in retardation of necrobiosis, cytokinesis and bio division of cell. Rasayana control the flow, distribution of consumption of finite supplies of Rasa and sneha to brain, thus improving the basic metabolic function of the brain tissue [6].

According to Acharya Sharangadhara decline of Medha starts after 40 yrs of age, which may be considered as a warning signal for decline in buddhi, smriti in the successive years where Medhya Rasayana is advised to halt or revert these changes. Research in this area also has proved the effectiveness of Medhya Rasayana in cognitive decline, dementia. Kushmanda Ghrita is mentioned as Medhya Rasayana in Bhaisajyaratnawali 25/34[7].

Kushmanda Ghrita pacifies the aggravated Dosha by its nature and enhances cognition with its Prabhav.

The ingredients of Kushmanda Ghrita are Kushmanda, Yastimadhu and Goghrita. All ingredients are Madhura Rasa, Sheeta veerya, Madhura vipaka, Snigdha guna yukta and Vatapittashamaka in nature.

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The major constituents of Kushmanda fruit were Volatile oil, flavonoids, glycosides, Beta sitosterol, Uronic acid, Linoleic acid, Palmitic acid, Oxalic acid, Ascorbic acid and Tryptophan etc. Also pharmacological research reveals Kushmanda‘s anti amnesic action.

Yastimadhu is traditionally much valued plant one among the four medhya Rasayana mentioned in Charaka Samhita. The major constituents of Yastimadhu are Glycyrrhizine, Glabridin, glabrol, licoricone etc.

Clinical trials of Kushmanda Ghrita in human being as Medhya, Smritikar in a cognitive decline is either not conducted till date nor published reports are not available. Hence this drug was selected for research study. This study is conducted to evaluate the Medhya action of Kushmanda Ghrita in cognitive decline in ageing.

1.**Materials and Methods:** All the raw drugs were purchased from authentified vendor. After Authentification and Standardization of all the raw drugs Kushmanda Ghrita was prepared by sneha kalpana vidhi in which Yashtimadhu kalka 1 part, Goghrita 4 parts and Kushmanda Swarasa 16 parts was taken and subjected to mild heat till the ghrita paka siddhi lakshanas was seen. Prepared Kushmanda Ghrita was stored in a glass container for maintaining hygienic condition. It was dispensed to the patients in glass container only. It was administered orally in the dose of, 20 ml twice daily in Rasayana and Udana kala with Luke warm water up to a 2-month period.

2.1 Study Design: - This study was clinical, observational and interventional. The study protocol was approved by Institutional ethical committee. The study was conducted at Bharati Vidyapeeth (Deemed to be) University, College of Ayurveda and hospital, Kayachikitsa Indoor and Outdoor Department. Informed consent was obtained from the participants. Any other medications other than Kushmsanda Ghrita for cognitive decline were not given to the patients as they were not on any allopathic or ayurvedic treatment. All patients included were of mild cases with ACE R score was as not less as said to be dementia.

Patients were enrolled from OPDs and IPDs of Kaya chikitsa department based on inclusion criteria and exclusion criteria. Total 30 elderly patients of cognitive decline who was under the inclusion criteria were taken for the study.

2.2 Parameters of assessment: - • ACE III Scale Hindi Version (Addenbrooke’s cognitive examination) (Hodges, J.R. and Larner A.J.2017) [8] • Wellbeing Index score (WBI score: WHO ‘s) [9]

2.3 Sample selection: Individuals above the age of 60 years and having memory complaints were recruited randomly from areas of nearby institute, through the oral interview. Those individuals who discontinued the two consecutive follow-up visits and those who discontinued the trial drug for more than 3 days for any reason were excluded from the trial. The remaining individuals who completed the trial were analyzed statistically.

2.4 Inclusion Criteria and Exclusion Criteria:- Patients who were having Alzheimer's disease and any other vascular dementia, evidence of Parkinson's disease, Depression, Diabetes mellitus, Hypertension of more than 5 years, Acute Liver disease, Pulmonary disease, HIV infection, Chronic alcoholic patients and History of Stroke, Transient Ischemic attack in last years, and on regular use of any medication that affect cognitive function were excluded from study.

Patients age above 60 years, irrespective of work and socioeconomic status and having symptoms of cognitive decline by applying MMSE scale score between 22 to 27(Indo: US cross national Dementia Epidemiology Study) were included in the study.

2.5 Statistical analysis: - • Paired t-test • Wilcoxon matched-pairs signed ranks test

3.Observation and Result: - As exact rate of incidence and prevalence of age associated cognitive decline in India or in Maharashtra was not available by the authentic sources; and since this is a comparatively new clinical condition in Ayurvedic research area, thirty completed sample size was decided as per ethical committee 's suggestion. Total 73 patients were screened, excluding 37 because of low education, chronic alcoholism, chain-smoking, uncontrolled diabetes mellitus, and history of stroke. Uncontrolled diabetes mellitus patient was excluded because of risk of cognitive decline due to vascular changes 36 was registered and 30 patients completed the trial. 6 patients dropped out because of irregular follow-up and discontinued interventions.

All patients were informed to contact immediately to us if any adverse drug reaction noted after taking Kushmanda Ghrita.

3.1.1. The mean MMSE score was 24.97 with very marginal variation.

Figure No.1. Showing MMSE score

Parameter	**MMSE Score**
Sample Size (n)	30
Mean ± SD	24.97 ± 0.93

Median (Min – Max)	25 24: 27)

The median ACE Total score improved after treatment with Kushmanda Ghrita. The improvement was statistically significant as compared to the baseline score.

Figure No. 2. Showing ACE score before and after treatment

Parameter	**ACE Total Score**		
	Before Treatment	**After Treatment**	**Difference**
Mean ± SD	88.00±1.31	92.63 ± 1.75	4.63 ± 0.76
Median (Min – Max)	88(86: 91)	93(89:96)	5 (3: 6)
Test of Significance	Wilcoxon matched: pairs signed: ranks test		
p Value, Inference	< 0.001, Significant		

The median attention score also improved significantly after treatment with Kushmanda Ghrita.

Figure No. 3. Showing Attention assessment before and after treatment

Parameter	**Attention**		
	Before Treatment	After Treatment	Difference
Mean ± SD	16.07 ± 0.45	17.97 ± 0.56	1.90 ± 0.66
Median (Min – Max)	16 (15: 17)	18 (17 :19)	2 (1: 3)
Test of Significance	Wilcoxon matched pairs signed ranks test		
p Value, Inference	< 0.001, Significant		

There was improvement in the median memory score after treatment, this treatment was statically significant as compared to baseline.

Figure No. 4. Showing Memory score before and after treatment

Parameter	**Memory**		
	Before Treatment	**After Treatment**	**Difference**
Mean ± SD	23.30 ± 0.47	25.37 ± 0.72	2.07 ± 0.58
Median (Min – Max)	23 (23 :24)	25 (25: 27)	2 (1 :3)
Test of Significance	Wilcoxon matched: pairs signed: ranks test		
P Value, Inference	< 0.001, Significant		

There was slight improvement seen in case of fluency, which however could not reach to statistical significance.

Figure No. 5. Showing Fluency score before and after treatment

Parameter	**Fluency**		
	Before Treatment	**After Treatment**	**Difference**
Mean ± SD	9.83 ± 0.53	10.90 ± 0.80	1.07 ± 0.87
Median (Min – Max)	10 (9:11)	11 (9:13)	01 (01 to 03)
Test of Significance	Wilcoxon matched pairs signed ranks test		
p Value, Inference	< 0.001, Significant		

The other 2 components of ACE viz. language and visuospatial memory remained unaltered after treatment.

Figure no. 6. Showing Language score before and after treatment

Parameter	**Language**

	Before Treatment	After Treatment	Difference
Mean ± SD	24.03 ± 0.85	23.83 ± 0.87	0.20 ± 0.66
Median (Min – Max)	24 (23:26)	24 (23:26)	00 (02 to 02)
Test of Significance	Wilcoxon matched: pairs signed: ranks test		
p Value, Inference	0.1484, Not Significant		

Figure No. 7 Showing Visuospatial score before and after treatment

Parameters	Visuospatial		
	Before Treatment	After Treatment	Difference
Mean ± SD	14.50 ± 0.68	14.47 ± 0.94	0.03 ± 0.56
Median (Min – Max)	15 (13: 15)	15 (11: 16)	00 (02 to 01)
Test of Significance	Wilcoxon matched: pairs signed: ranks test		
p Value, Inference	0.8438, Not Significant		

The median Well Being Index score improved from 19 to 22. This increase was significant statistically.

Figure No. 8 Showing WBI score before and after treatment

Parameter	WBI Score		
	Before Treatment	After Treatment	Difference
Mean ± SD	18.77 ± 0.86	22.40 ± 0.89	3.63 ± 0.56
Median (Min – Max)	19 (17 to 20)	22 (21 to 24)	04 (03 to 05)
Test of Significance	Wilcoxon matched pairs signed ranks test		
p Value, Inference	< 0.001, Significant		

The Activity of Daily Living (ADL) score also showed significant improvement after treatment with Kushmanda Ghrita.

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Parameter	ADL Score		
	Before Treatment	After Treatment	Difference
Mean ± SD	6.80 ± 1.67	5.03 ± 1.25	1.77 ± 0.57
Median (Min – Max)	7 (4:10)	5 (3:8)	2 (1:3)
Test of Significance	Wilcoxon matched pairs signed ranks test		
p Value, Inference	< 0.001, Significant		

Figure No. 9 Showing ADL score before and after treatment

1.Discussion: Age-associated cognitive decline is the clinical manifestation disturbing the elderly population. Several elderly individuals complain of impaired memory and perform less well than the younger ones in various cognitive jobs, predominantly those jobs that assess cognition and memory. These findings suggest that memory complaints are ubiquitous in our aging population [10]. Though it is so, still this is very much ignored or neglected issue in society as well as by the doctor's fraternity. Even though many individuals with mild age-associated cognitive decline complains of memory decline, impairments in other cognitive domains also take place.

No effective treatment is available to correct the persistent degeneration and deterioration of this condition. This condition can be correlated with Jaravastha janya Smritibhramsha mentioned in Charaka vimanasthana. If the hetusevan persists it may progress to Smritinasha, Buddhinasha. Though age-associated cognitive decline is not mentioned as a disease entity in separate chapters in Ayurvedic classics, references to its symptoms get scattered in the classics. Hence age-associated cognitive decline can be understood by understanding concepts of Jara, jara lakshana and its pathogenesis, Indriya, Medha, Buddhi, Smriti, the process of Gyanotpatti etc.

Research studies show that disturbance in Acetylcholine, Dopamine, BDNF, Serotonin, GABA enzymes, neuronal degeneration and loss, neurofibrillary tangles, and amyloid plaques are the main causes for cognitive decline in ageing. [11]

Medhya Rasayana has been mentioned in the classics for the management of neuropsychological disorders. But considering a heterogeneous etiopathogenesis and complication in the pathology of age-associated cognitive decline, the involvement of multiple factors in a cognitive decline in aging, a multi targeting combination of the drugs rather than a single drug was selected.

Various drug formulations are mentioned in the classics for such conditions. Out of which Kushmanda Ghrita was selected for the following reasons: Kushmanda Ghrita is a good memory enhancer and is mentioned in the classics for psychological disorders management. All ingredients of Kushmanda Ghrita are proven Medhya drugs and are

easily available. Pharmacological and preclinical research of Kushmanda Ghrita shows that it has nootropic activity, antioxidant, anti-inflammatory, memory enhancing effect, and anti-depressant activity. Also, no trials are conducted on Kushmanda Ghrita in mild cognitive impairment till today or published papers are not available. Considering all the above things Kushmanda Ghrita was selected for intervention in patients with age-associated cognitive decline.
The dose of the trial drug given was as mentioned by the classics itself ie.20ml in Rasayan kala and 20ml in Udana kala. The other Anupama may hamper the effects of the drug so simple lukewarm water was given as Anupama. There are no such confirmatory pathological investigations available for the diagnosis of age-associated cognitive decline. So basic laboratory investigations like Haemogram, Urine Routine: Microscopic, Random blood sugar levels, Blood urea level, Serum creatinine were done prior to inclusion purpose.

1.1. ACE III score: For ACE-III scale, the memory domain has P value of less than 0.001, the attention and orientation domain has P value 0.001 and the fluency domain has P value of less than 0001. It suggests that Kushmanda Ghrita has significant results in age-associated cognitive decline.

1.2. WBI score: For WBI score effect was observed with P value less than 0. 001.It suggests that Kushmanda Ghrita is Manovikar nashak, a cognitive enhancer. It has anxiolytic, and antioxidant activities.

1.3. ADL score: For ADL score effect was observed with P value less than 0.001. This suggests that Kushmanda Ghrita helps in improving activities of daily living. Kushmanda Ghrita is a good analgesic and anti–inflammatory, patient got good results in arthritis symptoms leading to a decrease in ADL score.

1.1. Probable mode of action of Kushmanda Ghrita: Medha can be understood by Grahana Shakti for which proper functioning of smriti and buddhi is a vital essentiality. Medha has been said as the function of Pitta. The balanced state of Pitta is responsible for proper functioning of Medha. The dominant rasa of Kushmanda Ghrita is Madhura rasa. Madhura rasa is said to be Sadindriya prasadaniya (Nourishing five sense organs Mind) and therefore has a direct effect over the site of these Indriyas (Sense organs) i.e., Shira (Head). Madhura rasa, sheeta virya and Madhura Vipaka of all ingredients of Kushmanda Ghrita pacifies Pitta. By Guru, Snigdha Guna and Madhura Vipaka, it controls the Chala Guna of Vata. Vata is the controller and stimulator of the Mind. As Medha is closely related to Manas, the factors affecting Manas will affect Medha too. Thus, it can be a drug of choice in patients suffering from smritibhramsh and Smriti nasha. Kushmanda Ghrita all ingredients having Madhura rasa, Guru, Snigdha guna, SheetaVirya and Madhura Vipaka,

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possesses Balya, Chakshushya, Vatapittahara, Raktaprasadana properties. Medhya effect is regarded as its Prabhava. Since Kushmanda Ghrita has antioxidant nootropics, as well as ACH inhibition, and tissue-protective action it helps in improving cognition in age-associated cognitive decline. Also, Ghrita is having lipophilic action the drug constituent reaches brain tissue fast and actively increasing cognition.

1.Conclusion:- On the basis of similar signs and symptoms, we can correlate cognitive decline in aging with Jara avasthajanya Smritibhramsha. A significant result of Kushmanda Ghrita was observed in cognitive decline in aging. A significant result of Kushmanda was observed in memory, attention & orientation, and fluency domain in cognitive decline in aging. Improvement in the well-being and quality of life of the patients was observed. Improvement in WBI and ADL scores was observed.

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