ROLE OF NIRGUṆDI KALPA IN MILD COGNITIVE IMPAIRMENT (MCI) W.S.R.TO AMNESIC MCI

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "Role of Nirguṇdi Kalpa in Mild Cognitive Impairment (MCI) w.s.r.to amnesic MCI" for the degree of 'Āyurveda Vāridhi' Doctor of Philosophy' in the subject of Kayachikitsa under the faculty of Ayurved has been carried out by Dr. Madhavi Prabhakar Mahajan in the Department of Kayachikitsa, Bharati Vidyapeeth Deemed University, College of Ayurved, Pune during the period from August 2010 to August 2016 under the guidance of Dr. Anand V.Joshi.

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I hereby declare that the thesis entitled "Role of Nirguṇdi Kalpa in Mild Cognitive Impairment (MCI) w.s.r.to amnesic MCI" submitted by me to the Bharati Vidyapeeth University, Pune for the degree of Doctor of 'Āyurveda Vāridhi' Philosophy (Ph.D) in Kayachikitsa under the Faculty of Ayurved is original piece of work carried out by me under the supervision of Dr. Anand V. Joshi. I further declare that it has not been submitted to this or any other University or Institution for the award of any Degree or Diploma.

I also confirm that all the material which I have borrowed from other sources and incorporated in this thesis is duly acknowledged. If any material is not duly acknowledged and found incorporated in this thesis, it is entirely my responsibility. I am fully aware of the implications of any such act which might have been committed by me advertently or inadvertently

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KEY TO TRANSLITERATION

A	a, A	k\	k K	T	ṭa	Ba	bha
Aa	ā, Ā	K	Ka	z	ṭha	म	ma
[	i, I	K\	Kh	D	ḍa	Ya	ya
[-	ī, Ī	K	Kha	Z	ḍha	र	Ra
]	u, U	ga\	g	Na	ṇ Ṇ	ल	La
}	ū, Ū	ग	ga	t	ta	व	Va
?	ṛ ,Ṛ	Ga	gha	qa	tha	Sa	Śa
ए	e, E	=	ṅa,Ṅa	d	da	Ya	Ṣa
ऐ	ai, Ai	च	Ca	Qa	dha	स	Sa
Aao	o, O	C	Cha	na	na	h	Ha
AaO	au, Au	ज	ja	p	pa	xa	kṣa
AM	ṃ, Ṃ	Ja	jha	f	pha	~	Tra
A:	aḥ ,AḤ	Ha	ña,Ña	ba	ba	&	Jña

ABBREVIATIONS

Short Form	Full Form
Su.	Sutra Sthāna
Vi	Vimāna Sthāna
Śā.	Śarira Sthāna
Ni.	Nidāna Sthāna
In.	Indriya Sthāna
Ci.	Cikitsā Sthāna
Si.	Siddhi Sthāna
VN	Vitex Negundo
Ca.Sam.	Carak Samhitā
A.H.	Aṣtānga hṛdaya
MCI	Mild cognitive impairment
aMCI	Amnesic mild cognitive impairment
naMCI	Non amnesic mild cognitive impairment
AD	Alzheimer's disease.
WHO	World Health Organization
%	Percentage
Yrs.	Years
CNS	Central nervous system
SOD	Superoxide dismutase
ROS	Reactive oxygen species
NADPH	Nicotinamide adenine dinucleotide phosphate
DNA	Deoxyribo Nucleic Acid.
Ach	Acetylcholine
GABA	Gamma-Amino Butyric Acid
RNS	Reactive nitrogen species
OS	Oxidative stress
BBB	Blood-brain barrier

IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
IL-18	Interleukin 18
TNF-α	tumor necrosis factor alpha
BDNF	Brain-derived Neurotrophic Factor
APOE	Apolipoprotein E
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
NCI	no cognitive impairment
HC	Hippocampus
NFT	Neurofibrillary tangles
ADNI	Alzheimer's Disease Neuroimaging Initiative
CIND.	Cognitive imparment no dementia
ChAT	Choline acetyltransferase
GDNF	Glial Cell Line-derived Neurotrophic Factor
NGF	Nerve Growth Factor
CSF	Cerebro spinal fluid
ACER	Addenbrooke’s Cognitive Examination Revised
CERAD-NB	Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Battery
NIMHANS	National Institute of Mental Health &Neuro Sciences
ADL	Activities of Daily Living
WBI	Wellbeing index
GERRI	Geriatric Evaluation by Relatives Rating Scale Instrument
CT	Computed tomography CT
MRI	Magnetic resonance imaging

PET	Positron emission tomography
SPECT	Single-photon emission computed tomography
QEEG	Quantitative Electroencephalography
NSAID	Nonsteroidal anti-inflammatory drugs
CAMCOG	Cambridge Cognitive Examination
GDS	Geriatric Depression scale
MMSE	Mini mental state examination
DM	Diabetes mellitus
HTN	Hypertension
CRF	Case report format
ICMR	Indian Council of Medical Research
Vol.	Volume

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ABSTRACT

Objective: To evaluate the efficacy of Nirgundi kalpa in MCI w.s.r. to amnesic MCI.

Background: Mild cognitive impairment (MCI) in elderly person is related with an augmented risk of developing dementia. This clinically significant evident dementia can be prevented if treatment procedures are invented for MCI. There remain, as yet, no globally accepted pharmaceutical interventions for MCI, aMCI. Ayurvedic medicines have an extensive history of use for cognitive impairments and many of them have been proved cognitive enhancer, neuroprotectors in experimental studies. Nirgundi Kalpa is one of the drug which is theoretically proved cognitive, memory enhancer.

Methods: Elderly subjects meeting current criteria for aMCI were identified and assessed with a standardized neuropsychological examination and battery like ACE-R, WHO's wellbeing index (WBI), GERRI. Total seventy five subjects were provided with Nirgundi kalpa for three months and observed for further six months. Amongst fifty subjects completed the trial.

Results: Patients presented statistically significant improved cognitive function in domains like memory, fluency and attention and orientation. Especially the improvement in WBI score and ADL scores was significant

Conclusion: Nirgundi kalpa was found to be useful in aMCI by increasing memory. Attention and orientation and fluency.

.Key words: aMCI, Cognitive decline, Vitex negundo, Memory, Smruti

INTRODUCTION

1. INTRODUCTION

The problem of ageing is global in nature as it is experienced by all the countries. In India life expectancy is going up with improved health care facilities and standard of living. It has risen from 57 yrs. in 1990 to 65yrs. at present. The present no. of senior citizens in India is 65 million but is soon expected to cross 177 million by the year 2025. It is apparent that as people age they show decline in tasks that are markers of fluid intelligence, although differences in the course of age related decline are observed across different studies, it is clear that even healthy adult experience some decline in fluid abilities with advancing age, although the age at which deflection occurs is a variable commodity.[1.2]

Ageing has a series of continuous degeneratin and deterioration of progressive deterioration of physiological functions with age, including a decline in productivity[3]

Since long, age associated cognitive decline has been a subject of interest between the researchers.Cognitive decline is seen in higher level brain functions like memory, language, visual perception, attention and orientation, planning and problem solving.Most of the 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 risks of dementia.

Mild cognitive impairment describes a transitional stage between normal ageing and dementia[4] and reveals the clinical state where a person has memory complaints to a greter extent than one would expect for age with objective evidence of cognitive impairment but no evidence of dementia.

Various different tags have been attributed over the years to what are approximately speaking the similar concepts. Many disorders may show memory disturbances as part of their exhibition; like delirium, anxiety, depression, chronic drug

and alcohol consumption, some physical illness and these conditions should be excluded while diagnosing MCI. Subject of MCI will progress to Alzheimer's in their lifetime is not always true, but these individuals are more prone to it.Amnesic MCI and non amnesic MCI are two types of MCI, which may progress to dementia, Alzheimer's disease.Criteria for amnesic MCI includes impaired memory function for age and education, preferably informed by caretaker, preserved general cognitive function, intact activities of daily living and no dementia.[4] Mild cognitive impairment is important to diagnose as it recognise memory decline in elderly, identify the persons at high risk of developing dementia and may benefit the people from preventive strategies.

Estimates of the prevalence of MCI (and related conditions) vary from 17% to 34%.There is no prospective study whatsoever of aMCI in India. But the researchers have shown that MCI occurs in almost about 20% of elderly individuals. One research study shows that overall prevalence of MCI is 14.89%.[5] Tivari et al., in their study showed the prevalence of MCI near Varanasi was 2.74%. [6] It is proven and known fact that as age increases there is decline in cognitive ability and memory.[7] Annual rates of conversion from MCI to dementia range from 4% to 25%.[8] But maximum other studies have prevalence rates between 10% and 15%.[9]

There is no long-established evidence currently that MCI is approachable and quick responsive to treatment but some agents used to treat AD are being tested in MCI.[10]

Available treatment is majorly neurotransmitter-replacement treatments. But the treatments which reverse or delay deposition of abnormal phosphorylation of tau protein and amyloid plaques would be of great importence in inhibiting the progression of the MCI.

The role of Āyurvedic drugs to lessen cognitive disabilities in patients with memory problems should not be forgotten as Āyurveda has mentioned numerous drugs for cognitive impairement, which are also proved pharmacologically.

Āyurveda mentions that decline in Medhā starts at the 4th decade of life.Level of cognition also depends upon prakṛti, sāra, satva of the person. Ageing is related to decline in cognition. aMCI may be considered Smṛtibhraṃśa which is related to ageing. This cognitive decline can be treated, prevented with some special type of medicine i.e.

Rasāyan, rejuvenation therapy, Medhya Rasāyana.[11] Some drugs having medhya action are illustrated in Āyurveda. Among these, many drugs have been assessed for antidepressant, stimulant and antioxidant, sedative and tranquilizing effect both experimentally and chemically, and have been shown satisfactory results. Medhya Rasāyana is a broad and wide concept having direct action on psychological as well as cognitive functioning and they are beneficial for the promotion of Medhā, Smṛti.

There are multiple evidences suggesting that older adults retain considerable neural plasticity and thus the ability to enhance neural, brain functions as a result of specific experiences or interventions in middle to old age.[12]Considering the above finding as the truth, the Medhya rasāyana treatment becomes more important as far as medical interventions for the mentioned problem is concerned.

Nirguṇdi (VN) is one of the classical Medhya rasāyana drug as stated in the Bhāvprakāśā nighaṇtu, is used in diseases related Manas i.e. Apasmāra, Unmāda etc. And mentioned as Smṛtidā (memory enhancer) in the classic.[13]

Nirguṇdi kalpa consisting Nirguṇdi, Madhu, Goghṛta, has been stated as manovikārnā śāk in Kākcandiśāvarakalpatantraṃ.[14]

In aMCI a Rasāyana which normalizes the function of disturbed Doṣa and Manas, is necessary for desired results. Nirguṇdi kalpa pacify the aggravated Doṣa by its nature and enhance cognition with its Prabhāv.Also pharmacological research reveals Nirguṇdi's antiamnesic action.But clinical trials of Nirguṇdi kalpa as Medhya Smṛtikar in aMCI is either not conducted till date nor published results are not available. Hence this drug was selected for the research study.

Need of the study:

Average life expectancy has been increased which has resulted in a considerable increase in the number of individuals aged 65 years and above. Memory impairment is the common consequence of the ageing process in the elderly. Mild cognitive impairment is a condition characterized by significant cognitive impairment in the absence of dementia. It primarily affects memory but it might cause changes in daily instrumental functions in subtle ways. Memory changes from MCI are not part of normal ageing they are more than what would have been expected as per age.If this

cognitive impairement progresses may affect social, functional, and occupational activities. aMCI can be a marker of Alzheimer's disease and dementia.

The prevalence of MCI is about four-times greater than dementia. It is estimated that MCI incidence in the developing world will increase by 100% between 2001 and 2040.[15]

Hence, India being a developing country with rapidly developing demographic ageing, it is a priority to identify the individuals at the risk of developing dementia at early stages to target preventive interventions. MCI is an intermediate phase between dementia and normal ageing-related cognitive decline; therefore, the recognition of MCI plays an important role in early intervention, prevention and proper treatments.

No any concrete therapy in modern medicine has been practiced in MCI or aMCI. The drugs which are in use have shown efficacy but with associated various side effects.

Āyurveda plays important role in preventive as well as treatment aspect of cognitive disorders. But it is the need of the time to clinically study the theoretically proved Medhya rasāyana in Mild cognitive impairement

Hence Nirguṇdi Kalpa was planned in MCI with special reference to aMCI, to relieve the sign, symptoms.

Hypothesis:

Being Medhya, Smṛtikar Nirguṇdi kalpa will be useful in amnesic MCI.

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REVIEW OF LITERATURE

2. REVIEW OF LITERATURE

2.1 - Review of aMCI – Āyurvedic approach:

Ageing is a process of physical, psychological and social change in multidimensional aspects. The world population of the elderly is increasing extensively, and by the year 2050, adults older than 65 years will involve 1/5th of the global population. 3.8% population are older than 65 years age in India. Approximately the number of elderly people in India by 2016 will be around 113 millions.[1, 2]

Heart diseases, Respiratory diseases, Cancer and Stroke are the leading causes of mortality among aged people. Considerable causes of morbidity among this group is chronic inflammatory and degenerative conditions such as Arthritis, Diabetes, Osteoporosis, Alzheimer's disease, psychiatric disorders, Parkinson's disease, Depression and age related urinary problems. Research studies in pre-dementia syndromes, particularly aMCI, reveals that the aMCI is a prodromal phase of dementia, particularly the AD type.

Mild cognitive impairment (MCI), most simplistically refers to the cognitive changes in the absence of dementia. It is the intermediate stage between normalcy and dementia. The rates of MCI prevalence vary from 3 to 17%, it being 3% at 60 years to 15% at the age of 75. In fact, the rate of development of MCI was about 5.3% per year (3.5% in the seventh decade of life and 7.2% in the eighth decade.)[3, 4]

As per Āyurveda, cognition come into view under the concept of Jñānotpatti, Medhā, Buddhī and Smṛti. Jñānotpatti occupy gross objects Indriya, Indriyārtha, Buddhī, Manas and Ātmā.Though MCI is not mentioned as a disease moety in separate chapters in Āyurvedic classics, references about its symptoms gets scattered in the classics.Hence MCI, aMCI can be understood by understanding following things.

Āyurveda has given utmost importance to Jarāvasthā and a separate branch of Āyurveda called Rasāyana was specially structured so as to postpone the declining effects of ageing.

2.1.1 - Paribhāṣā of Jarā:

Jarā – derived from the root 'Jruśā vayohānou' elucidated as:

'Vayaḥ kṛta Ślathamāṃsādyāvasthā Viseśā'

Means loosening of muscle and other tissues underneath the influence of ageing.

- In Śābda kaustubha, the word "Jarā" has been defined as 'Śāithilya āpadakāvasthā' also conveying the same meaning.

Ageing is defined in Āyurveda as an inseparable bondage of four aspects viz. Śārīra, Indriya, Satva and Ātmā which is the result of constant biological activities throughout the life. Although ageing is limited to physical body, the other features are important factors and give qualitative meaning for life. Therefore, along with many physiological functions activity, self determination, desire, inspiration, memory, intellect are the signs of living organism. When these signs become extinct, the body will then be confirmed dead.

Definition of Vaya:

'Kāla pramāṇa viśeṣa apekṣini hi śārirāvasthā vaya iti abhidhīyate'

Aruṇdatta explains the age (Vaya) as a factor dependent on Kāla pramāṇa viśeṣa – quantum of time duration. Vaya can be denoted as time bound changes occurring in the body.

Śābda kalpadṛma has explained vaya as 'Vayate veti ajāti iti vā ' – All meaning to move. So, ageing is a continuous process which never stops.

Classification of Vaya:

Counting the chronological age from the time of birth, Āyurvedic classics divide human life span into three main categories - Bālaya, Madhya and Vṛddha.There is some difference of opinion regarding this amongst our ancient scholars.

From the classics, it can be seen that revered Ācāryās had great observation of body changes happening during old age. They clearly distinguished somatic changes (including pathological conditions) from psychic variations. Somatic changes like Tvak pāruṣya, Ślatha sāra, Ślatha Māṃsa, Ślatha sandhī, Ślatha asthi, Dhātu kṣaya , Indriya hāni, Prabhā hāni,Agnisāda,Kāyasya avanamana,Vepathu, Khālitya, Vali, Pālitya, Kāsa and Śvāsa are clearly observed. Mental variations include Grahaṇa,Dhāraṇa,Smaraṇa (perception, retention and retrieval abilities),Vacana,Vijñan hāni along with Pauruṣa, Parākrama , Utsāha kṣaya.[5,6]

Vāgbhata again mentions the gradual decline in the Dhātus (tissues) and functions of Indriyas (sense organs) and motor organs with Agnisāda in aged people, which refers to the diminution of Jatharāgni and Dhātvāgni.This changed metabolism or slowing down of metabolism is one of the most important causes of ageing as per Āyurvedic perspectives.[7]

By the fall of all these vital functions, person gradually suffers the decline till the age of 100 years.[5] From all the above lines, one can infer that all Ācāryās had more or less the same opinion regarding different milestones of life.

Table: 1 Classification of Vaya.

Vaya	Carak Saṃhitā	Suśruta Saṃhitā	Kāśyapa Saṃhitā	Hārit Saṃhitā
Garbha	Foetal life	-------	-----	-------
Bālaya	Up to 30yrs.	Up to 16yrs.	Up to 1yrs.	Up to 16yrs.
Kumāra	-------	------	1 to 16yrs.	
Yuvāna	----	----------	16 to 34yrs.	16 to 25yrs.
Madhyama	30 to 60yrs.	16 to 70yrs.	34 to 70yrs.	25 to 70yrs.
Vṛddha	>60 yrs.	>70 yrs.	>70 yrs.	>70 yrs.

Concept of decade wise ageing according to Ācāryās:

It is very difficult to know the exact cause of Ageing and its exact mechānism. However, the process of Ageing is now known to be controlled largely by genetic, immune and endocrine mechanisms, in addition many other allied contributing factors with the scope of developing positive interventions. Āyurveda considers ageing as the Swabhāva or nature of the living being which is considered to be a time-bound entity and it biologically ceases to exist through senescence and death. However, in this school of thought death is limited to physical body only, the subtle energetic body survives death and is claimed to be capable of rebirth. [8]

Śārangdhara and Vāgbhata explain the time-bound sequential biological human ageing in terms of sequential loss of certain biological qualities of life specific to different decades of life as described in the following table. [9]

Table: 2 Sequential loss of biological qualities in every decade of life.

Decades	Aṣṭānga Saṃgraha	Śārangdhara
1	Childhood(Bālya)	Childhood(Bālya)
2	Growth (Vṛddhī)	Growth (Vṛddhī)
3	Complexion (Prabhā)	Complexion (Prabhā)
4	Intellect (Medhā)	Intellect (Medhā)
5	Skin (Tvak)	Skin (Tvak)
6	Reproduction (Śukra)	Vision (Akṣi)
7	Vision (Akṣi)	Reproduction (Śukra)
8	Hearing (Śruti)	Valour (Virya)
9	Mind(Manas)	Reasoning (Buddhī)
10	Sensory & motor organs(Sarva indriyāṇi)	Motor organs (Karmendriya)
11	-	Mind (Manas)
12	-	Life (Āyu)

It is obvious from the above mentioned that ageing is a slow and continuous process, which affects various body tissues and other factors at the different times. Some may doubt whether Prabhā is to be included in ageing process, but, there is no two opinion about the inclusion of declining in Medhā as the part of ageing. In this way the process of ageing according to Āyurveda definitely begins in the fourth decade of life. The effect of ageing is more noticeable in the fifth decade of life when the properties of skin elude. Therefore, the process enhances and affects one by one the functions of vital tissues and organs like vision, Śukra, Buddhī, hearing, motor organs, mind and other sense organs.

Types of ageing:

Ageing is of two types:

a) Natural ageing (Kālaja) which occurs at or after the proper age i.e. 60 years, even after following the daily and seasonal routines explained in Svasthavṛtta (social and preventive medicine) and use of purification treatments at proper time. This type of ageing progresses slowly, it is of low intensity and not very

troublesome. It is not curable and considered to be palliative (Yāpya) with treatment modalities like Rasāyana.

b) Premature ageing (Akālaja Jarā) occurs before the age of 60 and due to inappropriate practice of personal hygiene and purification.Also stressors are increasing in all the field of life so ageing starts very early. It is of greater intensity and rapidly progressive and said to be curable with Rasāyana drugs according to the Doṣa and accompaniment of the diseases or the stage of ageing. Some of the symptoms of ageing are also seen in 3rd to 4th decade of life.

Is ageing reversible??

The question come up here is that whether the ageing process is reversible or not? In this concern following facts mentioned in Āyurveda may be taken in consideration.Ageing (Jarā) is a naturally occurring disease.Caraka has considered it as "Svabhāvoniṣpratikriyaḥ" i.e. by nature they are incurable .Though it is niṣpratikriyaḥ Cakrapāṇi while commenting on these words states that the word"Niṣpratikriyaḥ" means ordinary treatment has got no effect on ageing. Rasāyana is the special treatment of Jarā as it has been clearly mentioned in Caraka that the old Cyavan ṛṣi became young after the use of Rasāyana.Dalhaṇa opines that the Kālaja Jarā is incurable and Akālaja Jarā can be treated with Rasāyana treatment.In Su. Sthāna, while describing the best Bhāva, Caraka has mentioned Jarā as Yāpya. Means a person lives with the disorder without cure but without disturbed by the diseases if appropriate treatment is taken. The disease recurs immediately after the treatment is withdrawn in Yāpya stage. This explanation is similar with the Cakrapāṇi's commentary as mentioned above. From above facts it can be said that, a timely senescence can be controled with proper dietics and Rasāyana, so that its unwell effects are prohibited. Rasāyan can just delay the process of ageing for some time, but it cannot be retarded and as soon as the effect of Rasāyana finishes ageing process accelarates.And premature ageing can be cured by direct encounter with underlying pathology. Process of ageing starts again to march to the forward so Rasāyana is not the complete treatment for Jarā.This can be easily explicable by following example.

By using Cyavanaprāśā (a Rasāyana Yoga) in proper way and dosage, very old saint 'Cyavana'turned young.[10]In addition it is said that consumption of Cyavanaprāśā not only abolish the signs of old age but also provide the young appearance.

Factors influencing the ageing process:

In Āyurveda classics no specific etiology of ageing process has been described. But, there are some major and minor factors mentioned in the classics, which can be considered favorable in this view. Only when these factors act in tandem with each other, ageing occurs.

- Kāla (Time factor):

For the onset of ageing process Kāla is the crucial and important factor to be considered from Āyurvedic standpoint.[11, 12]

While mentioning Śāriravṛuddhīkara bhāvas, Ācāryā Caraka has given due importance to Kāla, ahead of Svabhāva saṃsiddhī, Āhāra sauṣthava and Avighāta.

After reaching certain phase, ageing process (here degenerative process) starts which may be slow or fast depending upon the environment, habits,diet and other allied factors of an individual.

Modern scientists also agree with the influence of time factor on ageing process. They opine that ageing is a process of unfavorable progressive change usually correlated with the passage of time, becoming apparent after maturity and terminating invariably in death of the individual.

- Svabhāva Vāda (Theory of Natural phenomenon):

Svabhāva means the 'inherent property' or 'natural constitution'.The birth of an individual and development of foetus occurs by itself.[13, 14] The body tissues are very minute and innumerable. Their union and disunion are under the control of Vāta as well as Svabhāva (natural property) to combine or separate. Cakrapāṇi says that combination of Paramāṇu is responsible for Śārirāraṃbha' (growth of the body) and their separation for Śāriravināśā (degradation of body tissue). [15]

Thus, Svabhāva also plays a major role in the causation of ageing process but it also depends on the time factor.

- Vāta:

All the Doṣa can never function or be active alone. Vāta is the major amongst the three Doṣa as it controls the other two, Pitta and Kapha. For the sustenance of life, all the Doṣa, Dhātu and Mala should be in equilibrium. Still Vāta is needed which

dominates the formation of total body structure and functions. Vāta acts not only at microscopic cellular level but also at macroscopic organic level.The body tissues are very minute and innumerable. Their union and disunion are under the control of Vāta which is responsible for ageing process. [15]

- Svabhāvoparama vāda (Theory of Natural destruction):

There is a causative factor for the formation of beings, but no cause is found for their eradication. i.e., the destruction of any beings is automatic. [16] This theory can be applied from the Madhyama vaya onwards where in the process of catabolism dominates the process of ageing.It may be assumed that there is a cause for growth and when it becomes ineffective or stops functioning, process of degeneration or ageing process starts. However, this Svabhāvoparama vāda was not accepted much by Āyurveda.

- Sati Virodhaka bhāva:

Cakrapāṇi while commenting on ageing mentioned that absence of an opposing factor leads to Vṛuddhī of any substance.[17]He mentions that a wholesome diet should increase the body tissue elements of an old man as per Sāmānya siddhānta and if it is so, the person never becomes old and die ; he should have become 'Ajarāmara'. But that is not the case. Even though a wholesome diet is consumed which increase body tissues, an individual reaches different stage of life, like old age because of the presence of a factor called Virodhaka bhāva. Here Virodhaka bhāva supercedes the result of wholesome diet and thereby the growth of body tissue elements. This is nothing but the inclination in catabolic activity with advancing age.Until puberty stage, anabolic activity is more so that growth and development occurs. After that, as the age advances, preponderance of catabolism delay the growth and causes deterioration of body, ultimately landing in death.

- Deśa:

Though these are not the major etiological factors of ageing process, they do contribute for that. A person will be strong enough if his birth has taken place in an

environment which is conducive to increase the strength of any people. The people of such area will have good immunity naturally and thereby ageing process becomes slow.

- Āhāra sauṣthava:

It has been mentioned that Āhāra sauṣthava contribute the development of body.[18] Āhāra sauṣthava means the excellence of properties of food i.e., Āhārasaṃpat.The development of body tissues depends upon the nutrients present in the food consumed. The adequet and overall food supply is the most important extrinsic factor affecting the growth. So, the total development of an individual is dependent on the nutritive values of the food consumed and hence the ageing process is directly proportion to the nutritive values of the food ingested.

- Avighāta:

Absence of inhibiting factors such as excessive indulgence in exercise and stressful conditions.Modern scientists have also proved this i.e., stress speeds up the ageing process by excessively generating free radicals.

- Prakṛti:

The word "Prakṛti" here indicate both to the nature of a particular species and nature of an individual within that particular species. For example, onset of ageing process differs from one species to another. Similarly, within the species also, the nature of an individual varies according to Deśa, Kāla, Prakṛti, Āhāra, etc. and consequently ageing process may initiate early, timely or late.

It is observed that all the above-mentioned factors play vital role in ageing process,

Doṣavasthā during ageing:

As increase and drop in the levels of Doṣa occur around the time cycle, and by the nature of activities & food ingestion of individuals, Doṣa are highly unsteady in living body. The classics have mentioned that in the late life predominance of Vāta doṣa occurs. The predominance of Doṣa can be understood in two ways: (a) the elevated levels of Doṣa reflecting altered physiological mechanisms and (b) increased frequency of related Doṣa pradhan diseases, the susceptibility for which may or may not stem

from the altered physiology. In the former condition Vāta is a secondary during ageing whereas in the latter it is a part of essential pathological consequence.

Also the senescence mechanism possibly has tendency towards the qualities of Vāta doṣa. Further, Suśruta's stress upon this point is very clear - 'Bhuyiṣthaṃ Vardhate Vāyuaḥ' i.e. a surplus increase in the Vāta occurs during senile state. A nearer perusal of these statement convey us that the predominance in Vāta during old age does not seem to be merely a secondary effect.The initial increase of Vāta does occur as 'periodical clock' during the life cycle. The virtue of its qualities apt to initiate the mechanism of ageing. The succession of ageing with Dhātu kṣaya again add to the increase in the Vāta doṣa. This viscious cycle forms the base of progressive old age. The status of Pitta and Kapha doṣa during the old age are not clearly stated in the texts. However, substantial decrease in Kapha is apparent in old age as we go through the feature of senility.The texts have included depletion of Dhātu, loss of virility and Bala as the important feature of old age.

Dhātu avasthā during ageing:

The classical texts do not specify and a particular Dhātu as taking chief role in the ageing pathology.The important measures of ageing seems to act at the level of different Dhātus. However gradual decline in the Dhātu is universally noted by all Ācāryās. Carak and Suśruta opines that the period of old age is marked with day by day breakdown and qualitative and quantitative decrease in Dhātu.[6,5] Bhela saṃhitā further explains that in Vṛdhāpya, the capacity for viveka i.e. descretion of assimilized nutrients into Dhātu becomes hampered possibly due to Parikṣaya of Dhātu.

Therefore, the replacement of Dhātus is also reduced as a consequence of already existing vitiation. Production of the particular Dhātu with low quality is again another possibility out of such Paripāka. By stating such a significant aspect, Bhela ācārya has apparently referred the incapacitation of Dhātu. Caraka has considered gradual decline in the qualities of Dhātu as a sign of senescence.[5]

Manas & indriya during ageing:

For the onset and progression of ageing pathology mental and physical reasons are equally responsible because of intricate relation between mind and body in health and disease.On observing the collective feature noted for Jarāvasthā, one can see the

clear note of all the ancient scholars in considering Manas and all Indriya's functions are affected by ageing. However, the involvement of mind and sensory system seems to start from the fourth decade of life.

Indriya:

Carak and Suśruta has mentioned day by day decrease, decline (Hrīyamāna) in the Indriya, during Vṛddhāpya.[6, 5] Vāgbhat has mentioned gradual decline in Indriya guṇa which calls for further clarification and interpretation. Decline in these Jñānendriya meaning reduced function of these system occurs viz. reduced sight, reduced sense or smell, reduced taste, hearing & reduced skin sensory abilities. Caraka has mentioned that Indriya functioning system has five components viz. Indriya tattva, Indriya dravya, Indriyārtha, Indriya buddhī and Indriya adhīshthāna. These are essential components of every Indriya. But 'Indriya Guṇa' as such is not found mentioned anywhere. Thus 'Guṇa' as noted by Vṛddha Vāgbhata does not mean a component of Indriya rather literarily referred to quality the functional ability. So one has to assume an old individual though does not complain of incapacitation of Indriya, there definitely exists an 'altered functioning' as an effect of ageing.

Manas:

Cintan(think),Ūhyaṃ(infer) ,Vicāryaṃ (rationalize), Dhyeyaṃ (determination) & Sankalpa (decesiveness) are the the normal function of Manas . Smṛti (memory) and Buddhī (intellect) are the closely associated entities of Manas. This decline in Manas has to be viewed along with these functions also. Particularly, texts have mentioned decrease in Utsāha (enthusiasm), Pauruṣa and Parākrama (valour) as the signs of ageing. The last two also need the efficiency of physical performances. Thus, aspect of mind which is related with somatic activity seems to be affected in the aged from Āyurvedic perspects. Āyurveda also have noted decrease in Grahaṇa, Dhāraṇa, Smaraṇa, Vacana and Vijñana as one of the features of Vṛddhapya .[5] Grahaṇa meaning the cognitive abilities which calls for attention of mind & sensory system efficiency. Dhāraṇa means the retentive ability which involves the coding of memory & analysis of subject matter.Smaraṇa means the memory retrieval. Dhāraṇa and Smaraṇa are both functions of basal ganglia cells (hippocampus) and many researches support the role of acetyl choline in the memory functions. The term Vacana may not merely refer articular speech here but rather the capacity for 'power of expression' of mental concepts and

seems to relate with memory. Memory function is comparatively well preserved in older adults who have high verbal skill level .Similarly Vijñana refers to capacity for learning and analysis of the fact. These components depicting psychoneurophysiology is a noteworthy observation made by Caraka at the context of ageing.

A variety of mental factors affect not only health but also plays major role in disease formation. Considering this fact Caraka has described various Mānsika bhāva and their methods of examination to assess the mental status of an individual.
It can be divided in positive & negative emotions.[19] Positive bhāvas like Harśā, Priti, Medhā, Virya, Dhairya, Dhṛti, Śraddhā, Vijñana, Śila, Saṃgyā & Smṛti. Negative bhāvas like Bhaya, Śoka, Krodha, Moha, Cintā, Dveṣa, Rāga, Viṣāda etc.

In Āyurveda the etiology and symptomatology of many diseases emphasize the importance of Mānsika bhāva. When they are in physiological limit described as Mānsika bhāva but when it crosses the physiological range, they are named as Mānsika vikāra.

At the level of psyche, the Rajas and Tamas are considered to be Doṣa. In view of their susceptibility to vitiation leading to the imbalance, stress and difference of various kinds which may manifest in the form of Ichhā, Kāma, Krodha, Lobha, Mada, Moha, Bhaya etc.

2.1.2 - Concept of Medhā and Manas:

Mind and intellect are among the phenomena on which man failed all the times to derive into a definite conclusion. Now it is the requirement of time to interpret and conclude those ancient concepts of Medhā and Manas in terms of modern medical and psychological sciences. For the successful survival of man in this competitive world there is a need for promotion of mental health and management of various psychological and psychosomatic problems along with physical health.

Śārira and Manas both is the seat of disease. Same way definition of Svastha put emphasis on spiritual, psychological and physical well being of metaphysical faculty in which Manas is regulator and most important factor. The term ‘Āyu’ stands for the undividable concomitance of the Śārira (body), Indriya (sense organs), Satva (mind) and Ātmā (soul). Medhā affects the pleasure or misery of the Āyu and is essential for completion of the motive of Āyurveda. It prevents an individual from

indulging into Prajñaparādha. Longevity without Medhā is a sort of burden on society and for man too. Hence promotion of Medhā is desired and essential for everyone. Ācāryās have given much emphasis to promotion of Medhā. Now a day's also scientists are busy with the experiments to achieve high intellect and powerful mind.

Āyurveda has mentioned several naturally occurring medicinal plants under the category 'Medhya'. The drugs promoting Medhā (intellect) are termed as 'Medhya' drugs. Several medicinal plants mentioned as Rasāyana drugs in Āyurveda are primarily claimed as 'Medhya' as they have high caliber of inducing mental upliftment as major influence. In addition there is a special class of some Rasāyana drugs called Medhya Rasāyana which is supposed to be having specific influence on higher brain functions.

The mental health of the individual plays a significant role in the well being of a person. WHO also defines health as 'physical, mental and social wellbeing.[20] A recent study conducted by WHO has predicted that in terms of disease burden; by the year 2020 depressive illness will become the number two disease in the world overriding Diabetes, Cancer, Arthritis etc.[21]

During the past two decades awareness and research in the field of mental health and disorders have developed rapidly. The widely described concept of prākṛt and vikṛta can be correlated with psychology and psychiatry of this era. The modern concept of Manas is somewhat different from the ancient concept but the main part is going parallel. According to Āyurveda, Manas is said to be Antaḥkaraṇās while in other doctrines Manas, Buddhī and Ahaṃkāra are described as Trividha Antaḥkaraṇās. Thus, it can be easily understood that Āyurvedic concept of Manas include Buddhī and Ahaṃkāra too.

In Bhagavad Gitā elaborative description of human psychology is presented and in short it can be confidently said that it is a complete psychology. According to Bhagavad Gitā the senses and the objects constantly blast the Manas. At this point it is said that the self is like the lord of the chariot and the body is his chariot. The intellect is the charioteer and the Manas the reins. The senses are the horses; the objects of the senses are the roads. The senses (horses) are to be controlled by the Buddhī (the charioteer) through the reins, the Manas. The Manas restrained or unrestrained by the Buddhī leading to the region of dazzling joy or the cycle of birth and rebirth respectively.

In Śābdartha Cintāmani Kośā definitions of Medhā has been mentioned as that:

- Which retains the knowledge for long time after its perception through any sense organ.
- Power to retain the knowledge of various texts. Means it keeps the whole knowledge of various kinds of texts by reading, listening, repeating and practicing.
- To recall the subject after short or long period which was experienced in past. Though the Ācāryās have not defined it in the main text, but the commentators have explained it elaborately.

Śābdakalpadṛma and Amarkoṣa explained Medhā as one type of Buddhī which has the power of retaining the knowledge for a long period. Owing to Medhā, a person becomes able to obtain the knowledge of existing objects and hence he becomes learned.Vācaspatyaṃ and Śābda stomomahānidhī has given its same meaning.[22] It is that type of knowledge which is retained for a long period and will not be forgotten. According to Caraka, Dhī means the perception of true knowledge, while Dhṛti refers to the power of controlling mind and Smṛti refers to recalling the past experiences. Cakrapāṇi on commentary of Caraka Saṃhitā mentioned that it is a type of Dhī having the power of retention of knowledge.

Ācārya Dalhaṇa has commented it as in the meaning of perception and retention power of knowledge of the text. Also Dalhaṇa says"Grantha avadhāraṇa śākti medhā" which indicates that it is a power of grasping of subject. According to Ācārya Suśruta, Medhā is meaning of perception and retention power of knowledge.In Śābdārtha Cintāmaṇi also Medhā has been defined in same way. Ācārya Dalhaṇa and Hemadri have also commented upon Medhā as unobstructed, subtle and very deep knowledge gained by all the senses. Aruṇdutta has mentioned Medhā as that which is a faculty of Buddhī.

In Monnier William's dictionary the Medhā is understood by the meaning mental vigour or power, intelligence or prudence, wisdom, retention of knowledge for long period residue of which cannot be further expressed in proper time. According to Rasa Vaiśeṣika the Medhā is concern with Prabhāva (effect) i.e. Achintya Śākti. Practically the word Medhā is used to denote high intellect.

The word 'Medhāvi' is used for the person who has the knowledge of various Śāstras (literature) and having Pratyutpanna mati. According to Āyurveda, it shows just

one phase of the memorizing process. In nutshell it can be said that Medhā is the faculty of Buddhī which has the power to retain the experiences or knowledge and when needed it recalls that retained knowledge as it is. Relative word to Medhā is 'Medhya' which is derived from word 'Medhā' adding 'ya' suffix meaning

- Which is beneficial to Medhā.
- Which produces Medhā.
- Which promotes the retention power.

Factors affecting the Medhā:

The individual difference in Medhā is due to the difference in the development of brain. But still there are other factors also which influence on Medhā. These external factors are,

- Abhiruci (interest) – Each and every person has its own field of interest. Accordingly understanding of the subject becomes easier, hence grasping takes place without much effort. i.e. A mathematician can solve the mathematics puzzle easily compare to a common man, on the other hand he may not understand the chemistry as well.
- Saṃbandha (Association) – The new thing comes to contact may be similar or related to the previously learnt one. If not then also brain tries to associate it with any known subject, because association facilitates the categorization of new subject to retain it for longer time.
- Praṇidhāna (concentration or attention) – The popular concept of concentration involves that there is an intense application of the mind to a restricted area of the environment (an object, an idea etc.) to the exclusion of all extraneous thoughts that have no bearing on the focus of attention. Thus the width of the area on which attention is focussed is thus narrowed down, leads to deeper encoding of grasped subject.

- Abhyāsa (repetition) – The subject which is experienced repeatedly makes a deep imprint in the brain. The thing heard or read once may remember or may not but one book or versa if repeated frequently then whole thing can be remembered. It is the common experience of students. In primeval teaching

methodology our ancestors paid much emphasis on repetition. Guru used to teach next lesson only when Śiṣya remember the previous one.

Moreover, individual difference in the registration or encoding process also plays a major role in the retention power. So, it can be said that registration phase is more important than the retention power. Because only those subjects will be retain which has been gone through the encoding process. It is mere impossible to recall the knowledge which has not been retain. But it is not essential that the knowledge which has not been recalled is not passed through the retention process. Because many times person seems incapable to recall such things on time which he could recall at any time before. The same thing comes into mind easily after the person gets tired by recalling it. If it was not retained then how does it recall?

In spite of fundamental resemblance in the mankind as a whole, differentiation find from individual to individual. The factors of this differentiation are multifarious and they together exert effects on the constitutional, temperamental, psychological and spiritual make up of each individual. It reflects the inner dynamical characteristic of an individual which is a portrait of his important dimensions of behavior.

Manas play important role in the individual behaviors having potential and also affliction of psychological disorders. Hence a brief description about Manas is given further. Āyurveda refers learning and memory to Jñānotpatti, which is said to be Mānaslakṣaṇa. To make the understanding of various stages of the Jñānotpatti, its pathways and factors involved in it easier a schematic representation of it is given below.

Mechanism of knowledge generation or Jñānotpatti:

Carak has narrated the whole phenomena and termination or conversion of the knowledge into action in the context of describing the function of Manas.[23]

The first stage is the perception of Indriyārtha through the Jñānendriya associated with the Manas and this has been correlated with the Indriyabhigraha as well as the Ūhya. The functions of Indriyabhigraha and Svanigraha are important at this phase both for perceiving object of one single Indriya with due concentration and for selecting the right kind of object for perception. There is a constant backup of Dhī, Dhṛti and Smṛti during all the stages of the genesis of knowledge.

The second stage deals with the Kalpanā, i.e. consideration of merits and the demerits and this integrate the Vicāra function of the Manas and in the third stage, the production of "Niscyātmikā buddhī" occurs. At this stage a final decision of indulgence or non-indulgence into the object is taken.

The last stage is the transformation or termination of knowledge into action and regarding this transformation or termination, Caraka says that on the basis of the decision arrived at through the "Adhyavasāya", a living organism indulges in the bodily action or the vocal action. The whole process of perception, genesis of knowledge is an inclusive description of higher order of cognition. And this is a determinant of the behavior of the individual.[24, 25, 26]

Factors influencing the physiology of Manas:

- At metaphysical level:

Ātmā: It is Ātmā which gives Cetanātva to the Manas, by which Manas attains its Kartṛtva.

- At intellectual level:

Buddhī, the characteristic of Ātmā, influences Manas through its 3 dimensions viz.

Dhī: Proper judgement

Dhṛti: Controlling power

Smṛti: Recall or memory

Functional dimensions of Manas; Satva - knowledge, Rajas -action and Tamas - regulation also influence the mind physiology at intellectual level.

- At physical level:

<u>Doṣa:</u>

Vāta:

Vāta control Manas and stimulation of Manas is under the influence of Vāta.[27]

Prāṇa: Buddhī Hṛdayendriya Cittadhṛk.[28]

The function ascribed to the Prāṇa is to hold or direct the Citta and Hṛdaya.

Udāna: Udāno..... Smṛti Kriyā. [29]

Udāna is responsible for the recollection of past experience i.e.the memory thus it helps the Manas to analyse the entire perception and action projected to Karmendriya.

Vyāna: Vyāno Hṛdi Sthitaḥ.....Gati.....

Stability and concentration of Manas is dependent upon the normal condition of Vyāna.[30]

Pitta:

Sādhaka : Sādhaka Hṛdgataṃ Pittaṃ.....

..... Buddhī Medhā Abhimānādyai……[31]

Sādhaka pitta is responsible for Medhā.

Kapha :

Normal mental functions like tolerance, concentration, endurance are under the control of normal functioning of Kapha.[32] Avalambaka kapha and Tarpaka kapha are very much related with Manas.

Dhātu:

Rasa: Cintyānām Ca Aticintanāt.[33]

Rakta: Kriyānām Apratighātaṃ

Rakta is responsible for Normal mental function and these normal functions are:-

Amohaṃ Buddhī Karmānāṃ…

I.e Knowledge, perception and action stimulation.

Māṃsa: Akṣaglāni

Meda: Sukhābhiṣanga, Ālasya, Dṛdhatā [34]

Asthi: Śrama, 35 Dhāraṇa, Sankṣobha [36]

Majjā: Bala, [37, 38] Bhrama, Murcchā, Tamodarśāna [39, 40]

Śukra: Harṣa, Saṃkalpa, Kāma, Ānanda

Tvaca: Tatraikaṃ sparśānendriya cetah samavāyi..... cetāh . [41]

Ojas: It is the media through which mind and body are related.

Ojovṛddhī leads to Tuṣti-mental satisfaction. Ojokṣaya is caused by Krodha, Śoka, etc [42]Among the seven Dhātu the best qualities of Rasa, Rakta, Māṃsa , Śukra and Oja improve the functions of the faculties of Medhā. Rasa Dhātu nourishes the Buddhī whereas the best quality of Rakta is responsible for the promotion of the Medhā. Māṃsa sāratā indicates strong Dhṛti, likewise the Śukra of best quality is stated to strengthen the same i.e. Dhāraṇa śākti and Dhṛti. [43]Ojas has direct relationship with all the faculties of Buddhī, as it is held responsible for their nourishment.[44] Caraka highlighted the

relation between Śārira and Manas in this way: Both Śārira and Manas interact with one another in all spheres of activity. Subtle mind requires same factors for its activity in the gross body.Manas is said to have specific karma.

Origin of Manas:

Manas is in the latent form in the Garbhāvasthā (embryonic stage) and during 5th month it is capable of exhibiting the desire through the longings of the mother and later by 6th month the intellect is established. The Bhāva / factors which are responsible in the growth and development of foetus are. Mātṛja, Pitṛja, Ātmāja, Satvaja, Rasaja, Sātmyaja, Satvaja bhāva refers to the latent mind which plays an important role in the development of foetal factor like Śāouca (Cleanliness), Ruci / Bhakti (Devotion), Aāstikya (Divine), Śukla dharma (Transparency), Mati / Buddhī (Intellect).

Guṇa of Manas:

Satva, Rajas and Tamas are the triguṇas. Amongst Rajas and Tamas are termed as Manas Doṣa, which hamper the functional ability of Manas and Satva is Manas guṇa, which promotes the normal functioning of the Manas.

Functions of Manas:

The production of Buddhī is not a one step phenomenon, but involves a sequence of various intermediary events. Indriya abhigraha (controlling sensory and motor organs), Svanigraha (controlling itself) Ūhya, Vicāra and Buddhī pravṛtti have been described as the functions of Manas by Caraka. Although each of these functions seems to be separate and independent, still when the complete event of 'Jñānotpatti' (production of knowledge) is closely studied, each of these functions appears to be intermediate steps finally leading to knowledge.

The functions of Manas can be arranged under following sequence –

Cognitive function – Jñānapradhāna vyāpāra

Conative function – Ceṣṭapradhāna vyāpāra

Affective function – Bhāvanāpradhāna vyāpāra

- Cognitive function- Cognitive means to perceive. Manas send the impulses and inspiration to the cognitive senses facilitates them for the perception of objects.

- Conative function- Manas stimulates the Karmendriya to perform their functions.
- Affective function- Various emotions and feelings are the manifestation of Manas only.

These all functions of cognition are possible only when the Manas is normal. In case of lack of attention and concentration (mano anavasthānāt), Jñānotpatti is not possible.

Manas and its faculties:

Sensory faculty and motor faculties are two types of faculties. The faculties are not perceptible. They are only inferable. There are five sensory faculties (Jñānendriyas) and five motor faculties (Karmendriyas).

The five sensory faculties:
Ghrāṇendriya (Olfactory faculty), Rasanendriya (Gustatory faculty), Cakṣurendriya (Visual faculty), Sparśānendriya (Tactile faculty), Śravaṇendriya (Auditory faculty).

The motor faculties:
Pāda (faculty for Locomotion), Pāṇi (faculty for Grasping and holding), Pāyu (faculty for Excretion), Upastha (faculty for Reproduction) and Vāk (faculty for Communication).

Mind is dual faculty. It has sensory and motor functions. As a sensory faculty its object is anything, that is thinkable.

Multiplicity of Manas:

Although there is only one mind in person, we think that there is multiplicity of mind in one person itself due to the various factors. This is because of the union of mind with various objects including its own objects and disposition of mind as to the modes created by the universal attributes.[45]

Influence of Doṣa on Manas:

Āyu is the combination between Śārīra (body), Indriya (sensory organs), Satva (mind) and Ātmā (soul). The living body for its subsistence requires continuous physiological activity to take place.The total body physiology can be divided in two categories by Āyurveda i.e.Saṃyoga-formation,Viyoga-destruction. In between these two stages there is intermediate action i.e. Rupāntara (modification). So the physiology according to Āyurveda comes under three stages – Saṃyoga, Rupāntara and Viyoga. Doṣa are the factors responsible for these three different activities. The three Doṣa have their unique functions.

Kapha – Saṃyoga

Pitta – Rupāntara

Vāta – Viyoga

Doṣa maintain the integrity during normalcy. Abnormally increased or decreased Doṣa destroy the body. Doṣa can vitiate other principles of body and Manas is not apart from it.Satva, Rajas and Tamas are the triguṇas among which Satva is Manas guṇa and Rajas and Tamas are Manas Doṣa. The tridoṣa have the intimate relationship with the triguṇas. Vātadoṣa is rājasika in nature. Pitta during normalcy is sātvika but becomes Rājasika when abnormally increased. Kapha is sātvika in normal limits but turns to tāmasika when increased abnormally. Even though Vāta is rajoguṇātmaka, it is essential in regulating the activity of Manas.

Sex in relation with Manas:

Sex is also related with Buddhī. If a person indulges in sex considering all factors of nirupadrava, viśālā yoni, taking proper Vājikaraṇa his life span will increase with healthy state of body and mind.[46] But an unwise indulges in sex without proper judgment that will led to several psychological imbalance viz. depression,inferiority complex, short temperness etc.

2.1.3 - Concept of Smṛti (memory):

Impairment in memory and other cognitive attributes are the basis for mild cognitive impairment. The major function of Buddhī is to identity or differentiate between the Hita and Ahita and it is practicable only if the person has already experienced the Hita and Ahita earlier. It is also essential that a person's capacity to recollect is unafflicted. Therefore, Smṛti is a part of mental functions and this quality

of Manas i.e. Mind is attributed to Ātmā in Āyurveda.[47] It is the capacity of the human mind to recollect the Saṃskāra through experiences. These experiences are expressed at a proper time through Smṛti when it is stimulated by same factors.

According to Tarka Saṃgraha, Buddhī has two components viz. Smṛti and Anubhāva.

Smṛti: which can be useful for remembering the literature.

Anubhāva: which can be useful for remembering past experience acquired by sense organs like eye, ear etc.

Definition of Smṛti:

Different Ācāryās have given different definitions of Smṛti which are as follows:

- Capacity to recollect the past experienced knowledge is called Smṛti. (Vācaspatyaṃ)
- Unforgetfullnes (Asaṃpramoha) of the internal impression in the mind about the moments of the past is called Smṛti.
- Smṛti is the product of the traits of internal impressions produced by the union of experiences of the soul and the mind.
- Smṛti is the mass product of the knowledge gained by the impression gathered in the mind.
- Caraka says that recollection of things directly perceived, heard or experienced earlier is called Smṛti.[48]
- Suśruta has mentioned Smṛti as Bhutārtha Vijñāna i.e. knowledge of past experience. [49]
- Vijayarkṣita has mentioned that remembrance of past experience is called Smṛti.

Smṛti is used to denote memory .While describing the therapeutic appliation of Ghṛta, it has been advocated by Caraka as best suited for those who seek Smṛti, Medhā, Agni, Buddhī, and Indriya Bala. Smṛti indicates ability to recollect and to be well versed in Śāstra and to acquire mastery in higher sciences.[50] Smṛti does not stand for mere recollection but for the whole process involved in the formation of the faculty of memory. No definite cause of Smṛtibhraṃśa has been described, but Carakācārya has explained aids to attain a good memory and other 8 important causative factors that bring about a good memory.[51]

Aids to attain a good Smṛti:

The following serve as means for the attainment of Mokṣa:

- Due devotion to noble souls.
- Shunning of the company of the wicked.
- Observing sacred vows and fast.
- Pursuit of the rules of good conduct.
- Compliance with scriptural prescriptions.
- Scriptual knowledge.
- Liking for lonely living.
- Detachment from the object of senses.
- Striving for salvation.
- Complete mental control.
- Abstinence from the performance of acts leading to good and sinful effects.
- Anihilation to the effects of past actions.
- Desire to get away from the worldly trap.
- Absence of egoistic disposition.
- Being afraid of contacts of the soul, mind and body.
- Concentration of the mind and intellect in the soul.
- Review of spiritual facts.

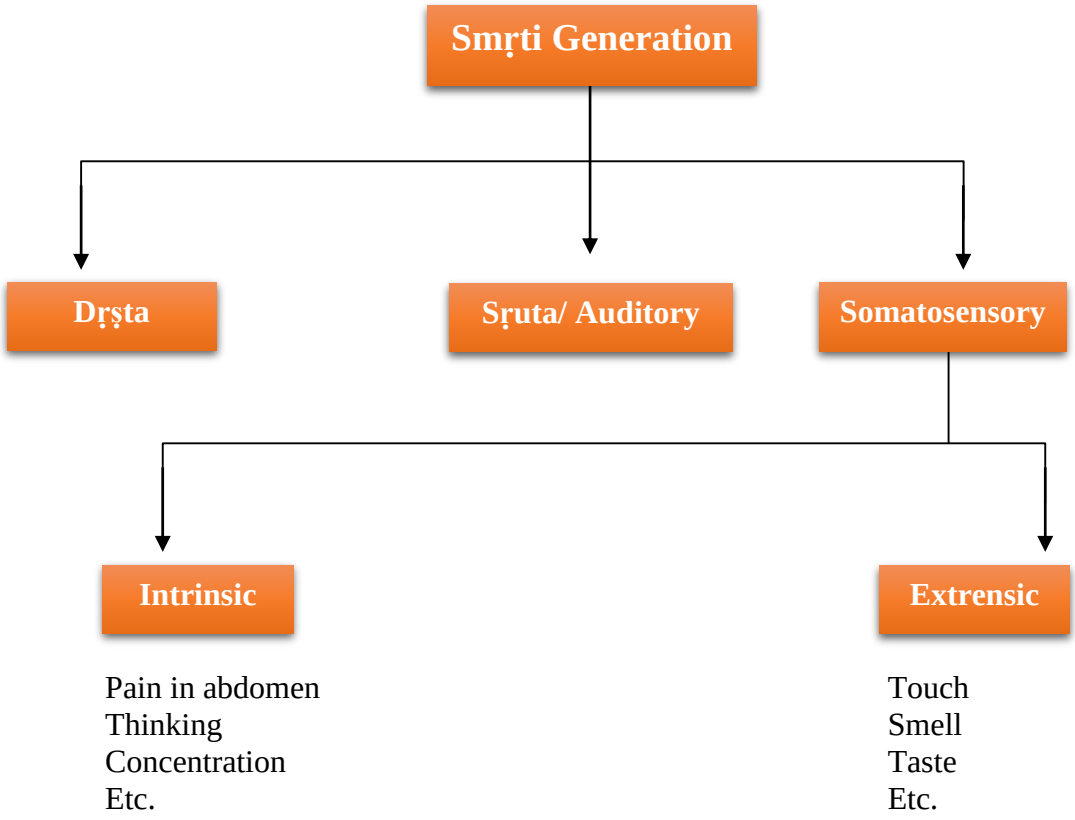
The regime prescribed in the verses above, beginning with devotion to the noble persons with absolute mental control serve as an aid to good memory. If one only remembers the real nature of things, he gets rid of miseries.

Causative factors for good Smṛti: [52]

- Nimitta: For Smṛti, knowledge of cause and effect is very helpful. According to Cakrapāṇi one remembers Kārya (effect) by noticing Kāraṇa i.e.cause. While prescribing Guggulu tiktaka ghṛta to the patient, remembering a Rakta vikāra like pruritus and urticarial.
- Rupa grahaṇāt: Knowledge of form is also helpful in Smṛti. By looking the urticarial rashes remembering Guggulu toxicity, penicilline reaction, allergic urticaria etc.

- Sādraśāyāt: Knowledge of similarity is also helpful for Smṛti, e.g.on seeing a son, one remembers that his father is having similar features.
- Saviparyāyāt: Knowledge of contrast is another factor of the Smṛti e.g.clinical assessment of Kṣaya of one Guṇa(Snigdha kṣaya) by looking the Vṛuddhī of opposite Guṇa (Rukṣyadhīkya) is one such Smṛti utilization
- Satvānubaṃdha: It is the process of acquiring knowledge by immense concentration of mind. In this method active memory is taking place. Here the person deliberately recalling and recognizing the object by concentrating to an object. It is a method of memorizing rather than stimulus.
- Abhyāsa: This is the knowledge and memory acquisition by repetition method. This is also a method of memorization.Recitation method-the mental repetition of something is called recitation. ('Arthaṃ Abhyāsa Balādeva smarati…..') Cakrapāṇi told it is a method of active memory.
- Jñana Yoga: Attainment of metaphysical knowledge may be called as Jñana yoga, which is also Tattva jñana yoga. This Tatva jñana yoga is attributed to be one of the cause of the recollection of the past. Nobody could challenge these people who are having this sort of memory.eg. Āpta.[50]According to modern educational psychology the children come under this group are termed as 'Gifted children'. Many studies have been conducted to identify the normal from 'gifted. In these studies it was observed that a large number of gifted children belong to the families of unusual ability and attainment. They are intellectually far superior to the average population.
- Punaḥśrutāt: Subsequent partial communication also helps in better Smṛti. For instance, when a thing has passed away from the memory, then even if slight hint or previous reference is given, it helps in memorizing that thing. It is said that memory is derived from Ātmā and Satva, two of the bhāvas responsible for the formation of foetus. Moreover, it is also the function of the intellect and the mind. Caraka clearly explains that memory is impaired due to a person being overcome by Rajas and Tamas. [53]

Fig.1 Smṛti Generation



If the factors, mentioned above for a good Smṛti are followed in one's lifestyle, some of the possible etiological factors affecting one's cognition could be prevented thus reducing the risk of the dementia. Decline of Medhā during the 4th decade of life has been described in the classics. If Rasāyana drugs are administered before this age, several degenerative disorders can be delayed.

Among all sense organs for knowledge perception most important are visual and auditory knowledge. Without having either of these perceptions normally one couldn't acquire proper knowledge according to a functional MRI study. Three occipito temporal areas in the ventral object of vision pathway had mostly transient response to stimuli, indicating their predominant role in perceptual processing. Possibly may be due to these reasons Ācāryās made stress upon these two perceptions i.e.visual and auditory specifically. In modern science if we are considering sensory cortical areas of brain it performs mainly on the basis of three perceptions as our Ācāryās told.Primary sensory

areas detect only specific sensation i.e. visual, auditory or somatic-transmitted to the brain. Secondary areas also makes out of the signals in the primary areas.

Applied aspect of Smṛti in Āyurveda:

Descriptions of a good number of psychic and somatic diseases are there in Āyurvedic classics in which Smṛti is getting affected worse.Eg.In Unmāda the Vibhrama is happening to Smṛti.[54] Here either the patient cannot remember the things or remember in an altered manner. In Apasmāra, Apagamana of Smṛti is taking place for short time. Here transiently the decline or complete loss of memory is happening. In various therapeutics a large number of formulations are mentioned in texts which promotes Smṛti in diseased as well as in healthy.

Buddhī and Smṛti have to be analyzed in paralances like -

Doṣa siddhānta (More functional aspects).

Dhātu and Mala siddhānta (More structural aspects).

Srotosiddhānta.

Ācāryās were very practical in this regard and most of the times Buddhī and Smṛti are explained under clinical entities for their applied Śārir adhyāyana.Existence of a special Srotas for the Manokarmā is still controversial as this entity of Manovahasrotas is not specifically mentioned under the Srotoadhīkāra by any of Ācāryās. However Ācārya Cakrapāṇi, Dalhaṇa and Hārāṇachandra explained the Manovaha srotas for certain explanations like Svapna. But in this context Cakrapāṇi emphasized that the Manovaha srotas should be considered as ten Dhamani of Hṛdaya.

In the area of Unmāda and Apasmāra diseases also, Ācāryās quoted this terminology as

"Manovahāni srotāmsyavritya janayanti Unmādaṃ…

Srotāmsy adhīṣatyā manovahāni pramohantyāśu narasya cetā"

But here also the basic pathogenesis is taking place at the somatic level in Hṛdaya. From all these descriptions it can be concluded that-

The Buddhī and Smṛti are the functions of Manovaha srotas.

From the clinical point of view Manovaha srotas should be considered in somatic level especially while dealing with Dravya cikitsā.

Rasa- Rakta vaha srotas in connection with Manas karma:

On analyzing different classical references related to Nidānas and Lakśāṇās of different somatic, psychic and psycho somatic diseases it can be seen that main Doṣa duṣti is taking place in Rasa and Rakta vaha srotasa. It can be apparent from the following examples.

In the Saṃprāpti of Mada, Murcchā and Sanyāsa the former two are mainly occurring due to the duṣti of Rasa and Rakta vaha srotas.

In the saṃprāpti of Vyānaga and Neelikā, due to the exclusive Manonidāna like Śoka and Krodha the prime vitiation takes place in the main seat of Rasa dhātu i.e Tvak.

For the Duṣti of Rasavaha srotas one among the several reasons is psychological.

While describing the etiologies of Rakta duṣti in Caraka saṃhitā Vidhīśonitīya adhyāya 'Krodha' is found to be responsible for Manovikāra.[55]

Following lakśāṇās of Rasa Rakta dhātu vikāra indicate its relation with the mental faculties.

Arocaka – Rasavṛuddhī

Hṛdayadrava - Rasakṣaya

Hṛullāsa – Rasa vṛuddhī

Svadu dveṣa, – Rasa vṛuddhī

Tamapraveśā - Rakta vṛuddhī

Śitābhilāṣā - Raktakṣaya

Śābdāsahatva - Rasakṣaya

This may be the reason by which most of the psychosomatic diseases are manifesting at the sites of Rasa and Rakta vaha srotasa.

Eg. Asthma- 'Śāvāsaṃ amāśāya samudbhāvaṃ ….'

Or otherwise it can be said that for the occurrence of a psychosomatic disease Rasa or Rakta (or both) Vaha srotoduṣti is inevitable. So the treatments to the psychosomatic diseases should be directed to this angle of Rasa rakta duṣti. From all these references and postulations we can derive following hypothesis. Buddhī and Smṛti are functioning through Rasa and Raktavaha srotas, of these Rasavaha srotas bears prime importance for the mental functions. Buddhī Smṛti like Manokarmas can be attributed to minute units of human body like cell and is present in every system. This may be due to the Sarva vyāpitva of Manas or Rasa dhātu. Buddhī Smṛti disturbances can be occurring even from the cellular level to the entire system.

As Smṛtibhraṃśa comprises of two words 'Smṛti' and 'Bhraṃśā', the general aspects of Bhraṃśā is considered herewith.

Bhraṃśā:

Falling or slipping down or off.

Decline, decrease, decay,

Ruin, fall, destruction, running away.

Straying or deviating from, abandonment

Disappearance, loss, cessation.

Deprivation of …..

These are the various meanings of Bhraṃśā word from various dictionaries, śabdakoṣa Thus in a nutshell, Smṛtibhraṃśa means decline of memory.

Inter relation with Buddhī, Medhā and Smṛti:

After critical evaluation of Buddhī, Medhā and Smṛti it can be pointed out that these are the steps of same process. One is incomplete without the other. The process of recollection takes place properly only and only after the Buddhī, Medhā and Smṛti unites. So in this sense they are unseperable. This could be understood well by comparing the cognition process with computer. While using computer the important data is first entered, stored and after some days, months or even after many years also it can be recollected just as it was stored.

Human brain is too, a one kind of computer. Only main difference is that computer is Acetana it cannot think itself, whereas human being is Cetana (conscious) with the presence of Ātmā (soul) and all the actions performed by the conjugation of Manas. For the cognition, sense objects conjoins with senses and senses with Manas. Buddhī vyāpāra (discrimination) follows just after it. Buddhī works on it by reasoning and logic and reacts accordingly.Gained knowledge gets stored for further use if there is no action to be taken. Retention of cognition takes place under the area of Medhā. When any stimulant comes against, those stored knowledge comes in mind. With the help of Smṛti recollection happens. If preserved in improper way, then all the efforts of recalling would be in vain. So, Smṛti needs systematic interpretation and retention. Like this Smṛti produced when encoding, retention and recollection of the experiences unites. In which Buddhī helps in encoding, Medhā in retention and Smṛti facilitate recollection. In short encoding is must in Smṛti, only those subject could be recalled

which has been encoded before. The same way if retained knowledge is not recollected it is of no use. Hence, Buddhī, Medhā and Smṛti are having different meanings and functions but they cannot work independently. Medhā can be subdivided into the following faculties.

Viveka Śākti (power of discrimination)

Grahaṇa Śākti (power of grasping)

Dhāraṇ Śākti (power of retention)

Smaraṇa Śākti (power of recollection)

Relation between Tridoṣa and Medhā:

Vāta: Prāṇa vāta is responsible to controll the functions of Buddhī and Manas. 'Buddhī citta indriya dhṛk', while Udāna vāta helps in recalling the past experiences.[28, 29]

Pitta: Function of Pitta is to promote Medhā, but Sādhaka pitta is mainly responsible for good Medhā, Buddhī and abhimana.[31]

Kapha: Tarpaka and avalambaka kapha in their normal state confer the knowledge and intelligence. Kapha is also responsible for the best qualities of Dhṛti.[56] So that it is understandable that Buddhī, Medhā, and Prajñā are the words used interchangeable and depende on Doṣa condition.

Manas doṣa:

Rajas doṣa:

It is the mediator between Tamas and Satva. It is responsible for vigor, expression of emotions and motivation.The egoistic type of emotions like fear, anger, hope, envy, prudent, pride etc.are due to Rajas Guṇa.

Tamas Doṣa:

It is known as Avaranātmāka and has Mohānśā i.e. it has got characteristics of covering or concealing and is Viṣādātmāka i.e. depressive in nature. The unawareness, effortlessness are due to Tamas doṣa. But due to its heaviness, some amount of Tamas doṣa is required for enduring stability to Manas.

Sleep in relation with Medhā:

Sleep has great role in proper functioning of Jñānendriya and Medhā and other Manasabhāva.Sleep also plays an important role in repairing the breakdown of tissues

but in Caraka saṃhitā while describing the benefits of nidrā, explained that Sukha, Dukha,Puṣti, Bala, Abala, Kārśya, klibatā, Jñāna and ajñāna are dependent upon sleep.

Relation between Medhā and food:

In Āyurvedic classics certain code of dietetics has been mentioned. If one takes Āhāra in this described manner, the food undergoes proper digestion and in turn maintains the healthy state of Manas, Buddhī and Medhā.

Relation between Śārira prakṛti and Medhā:

In Āyurveda, the term 'Prakṛti' has been used in the sense of personality. These are the Vāta, Pitta and Kapha. While Manas prakṛti is known as Triguṇātmāka typology as it is based on the fundamental postules of three constituents of Manas. These are Satva, Rajas and Tamas. It is a reality that human organism behaves in a wholesome complex manner and cannot be isolated physical and psychological factors of Prakṛti on different and independent substratum and so these two biases are just based on the predominance and specification of fields otherwise they are immediately related.

Vāta prakṛti – In the characteristics of Vāta prakṛti by its Aṃśāmśā, Ācārya Caraka has mentioned that Vāta prakṛti people due to the Śighra guṇa of Vāta seems quick in understanding (grasping) but weak in recalling things,means they have good short term memory but poor long term memory.[57] While Ācārya Suśruta has said that they have lack of patience and less discriminative power. According to Ācārya Vāgbhata they are unsteady in respect of Dhṛti, Smṛti, Buddhī and movement. [58]

Pitta prakṛti – According to Ācārya Suśruta Pitta prakṛti person is highly intelligent, clever and loves to monopolize the conversation.[59]

Kapha prakṛti – Kapha prakṛti person is endowed with self control and having strong faith in Śāstras. He is intelligent, taking more time to grasp any subject but after that possessed with good memory. [60]

Relation berween Vaya and Medhā:

Āyurveda has divided the life span into three parts. Bāla, Madhya and Jirṇa. Bāla vaya covers the age upto 30 and is subdivided into two parts. The initial one is

from 1 to 16 years and later stage is from 16 to 30 years. Madhya avasthā covers the age upto 60 years. Vṛddha avasthā starts after 60 upto 100 years. Medhā, Buddhī and Smṛti vary according to Vaya. In Bālayāvasthā there is good grasping power and retention also but due to undetermined psychic disposition there is lack of reasoning and logic at the level of Buddhī.

Ācārya Caraka says that in Madhya avasthā Medhā, Buddhī etc. psychic faculties remains balanced, because it is a stage of predominance of Pitta doṣa which is mainly responsible for Medhā.[5] Due to well determine psychic disposition a person is having good discriminative power. So it helps to understand the subject better and initiates retention for a long time. Above qualities begin to decline as the elements of the body disintegrate in Vṛddha avasthā. Psyche becomes unstable due to predominant Vāta. So it becomes difficult to discriminate the thing properly hence retention and recollection of new experiences decrease with increasing age.

Relation between Agni and Medhā:

In living being the Agni is one among the twelve Prāṇas. It is the key factor for any kind of transformation occurs in the environment as well as in the body. Agni works on ingested Āhāra and converts it into Āhāra rasa which is the nutrient of whole body. Āyu Upacaya, Varṇa, Bala, Svāsthya, Utsāha, Tejas, Prabhā, Ojas all these factors are depended on Agni. [61]

Pācaka pitta is said to be the seat of Agni. It controls the rest of the Pittas to perform their action. Sādhaka pitta which is responsible for good Medhā, also gets nourishment from it. Balanced state of Dhātvāgni provides the proper nourishment to all Dhātu. Healthy state of Dhātu ultimately represents good quality of Medhā as seen before.[31]

Role of Medhā in health and diseases:

Medhā is related with Manas and Manas being an important constituent of the living being, Medhā also attains an important position. Caraka has pointed out that Icchā, Dveṣa, Sukha, Dukha, Prayatna, Ceṣṭā, Dhṛti, Buddhī, Smṛuti and Ahaṃkāra are the indicators of Puruṣa and they can be witnessed only in a living human being. [47] Svastha Puruṣa is one who has Prasanna ātmā, Prasanna Manas and Prasanna indriya. [62] According to Cakrapāṇi, Prasanna Ātmā indicates the vikāra rahita and absence of

Dukha; these Dukha may caused by vaiṣamya. This explanation shows the interring relationship between the Śārīra and other components of life. Whereas on the other hand it explains that components other than Śārīra are also liable to be influenced by different abnormalities and as such it is absolutely essential that apart from the body other three constituents should also be free from any imbalance or derangement.

In Āyurveda more importance is given to the functional entity (Manas) rather than structural entity (Mastiṣaka, Hṛdaya). Very few references are available about Mastiṣka (brain) where as more references are available about Manas during healthy and diseased conditions. Ācārya Caraka stated that a person whose Dhī, Dhṛti and Smṛti are impaired, subjects himself to intellectual depravity by virtue of his bad action .[53]It is called Prajñāparādha which further aggravates all the Doṣa. In Caraka saṃhitā Śārirasthāna, it is mentioned that if something Nitya (eternal) is viewed as Anitya (ephemeral) and something Ahita (harmful) as Hita (useful) and vice versa, it is indicative of the impairment of intellect (Buddhī).

When Manas becomes dominated by Satva guṇa, a person's Medhā or Buddhī will be very clear; he will be capable of thinking on proper lines. Certain psychological disorders like depression, impaired cognition will be absent in the person having good Medhā or Buddhī. So, all these references directly or indirectly establish a relationship between health and Medhā.

Decline and derangement of Medhā:

ĀcāryaVāgbhata and Śārangdhara have given the decade wise Hrāsa krama (order of decline) of psycho-physiological measures. At their time average life span was of 100 years. So they have put forward this opinion considering 100 years of age. Balyāvashtha ends up after 10 years, growth after 20 years, and lusture after 30 years and decline of Medhā starts after 40 years. Both Ācāryās have accepted it in one voice. This shows the declination order seen in the normal (healthy) person. This is the age related natural phenomena occurs due to Kāraṇa daurbalya hence cannot be avoided upto much extent. That's why it should be nourished by extraneous substances which promotes its normal functioning. There are some diseased conditions also in which derangement of Medhā found before its natural time of decline. In most of the psychological diseases alteration of Medhā, Buddhī, Smṛti, Dhī, Dhṛti seen due to

vitiation of Manovaha Srotas by Manas bhāvas.For ex. Unmād, Apasmāra, Atatvābhinivesh etc. [54, 63, 64]

Medhya diets and regimens in saṃhitās:

"Medhāyuskāmaya Rasāyana cikitsā" is the separate chapter described by Suśruta in which he clearly indicates the importance of Medhā in that period also. In this chapter he has mentioned various Medhya drugs. At the end of this chapter Medhākara gaṇa has been mentioned. [65] Constant study, discussions (on philosophical and scientific topics), discussions in other subjects and residence with professors or men learned in the respective branches of knowledge, are the best means for improving memory and expanding one's intellect. These are some Āhāra-auṣaadha having Medhya properties mentioned in Bṛhattrayī.

Abhayā , kāśmarya , Mātulunga, Rasona, Vāstuka, Śātāvari, Bhallātaka kṣira ,Palāndu, Tāla phala,Yava, Gagaṇambu, Kṣira, Navanita, Ghṛta, Mahāghṛta, Taila, Eranda taila, Yavatikta taila, Gomutra, Kushmāndaka, Kurma and Mayura māṃsa, Sarpa māṃsa, Krakara māṃsa, Tittira māṃsa etc.

2.1.4 – Nidāna (Etiology):

As separate detailed description of Jarā avasthājanya Smṛtibhraṃśa has not been described in any of the classics, only indirect and scattered information about the etiology of this disease can be found.
As it is stated:

"Setikartavyatāko Rogotpādaka Heturnidānaṃ.'
According to one of the definition of Nidāna, any thing which can vitiate Manas doṣa and make them capable of causing manifestable mental morbidity is Nidāna of Manasa roga.Since imbalance state of Doṣa is disease condition. As Śārir doṣa leads to physical disease consequently in the same way imbalance of two Manasa doṣa i.e. Rajas and Tamas is considered as Manasa roga. Commonly it is addressed by all classics that vitiation regarding Vṛuddhī of Doṣa is Rogakaraka. So vitiation of Rajas and Tamas in terms of Vṛuddhī is Manas roga kāraka. Hence anything which will vitiate Rajas and

Tamas, so as to increase them, and by "Arthāpatti" too, on the contrary everything which will decrease Satva Guṇa will be potent causative factor of Manasa roga.

A wide spectrum of Nidāna of Manasa roga is available which can be classified under various categories for a better understanding as follows:

Tridoṣa duṣtikara

Āhāra, Vihāra and ManasĀtmāka.

Prajñāparādha, Asātmyaindriyārtha Saṃyoga, Kāla etc.

After Hīna-Mithyātiyoga of Kāla-Artha-Karma.

Potency to disturb the controlling levels of Manas viz. Ātmā, Buddhī, Indriya and physical factors.

Occasionally some traumas also have causative value like "Marmaviddha lak śāṇās" of Simanta marma.

Distribution of available and possible Nidānas is interconnecting to each other between above said five categories. So it is good to follow Āhāra, Vihāra, Manasātmāka distribution which covers other aspects.

- Āhāraja:

Food articles do have their effect on Manas owing to "Sarvaṃ Dravyaṃ Pāncabhautikaṃ "[66] thus effect of Āhāra on Manas is evident. Caraka emphasize that Āhāra has prime role in well being and morbid condition of life.[67] Out of this obviously Rājasika and Tāmasika Āhāra should be considered as Nidāna of Mānsika roga. Moreover the food articles which directly can influence Manas in hazzardous style,are to be considered as Nidāna such as Madya, Viṣa, Upaviṣa, Duṣiviṣa etc. and on the same line in current period, the drug abuse,narcotics, tranquilizers also can be included in this category along with nonvege food owing to over ruling of principle of Ahiṃsā and Bhutadayā.

- Vihāraja :

Vihāra include all the movements concern with Śārira, Vāṇi and Manasa too.Adaptation of Hīna, Mithyā, and Atiyoga of these karmās leads to various disease. [68] Effect of Kāyika and Vācika karma on Manas are not that much distinct although it

does not indicate that both of them do not have any influence regarding Manasa roga. Undoubtedly, Manasa karmās will be having direct influence on Manas. As stated by Vāgbhata any thing which comes under the term Pāpa (sin) is nidāna of Manasa rogas.[69] Also the term Vihāra comprises of whole of the "Svasthavṛitta".But regarding nidāna of Manasa roga; one must concentrate more significantly on Sadvṛtta and the conducts postulated in "Acāra rasāyana". [70] Over ruling of them is directly referred as Nidāna of Manasa roga.

The entire set of "Prajñāparādha" which is elaborately described in Caraka saṃhitā is indicative of Nidāna of Manasa roga.The Prajñāparādha is defined as the derangement of the three components of Prajñā, viz. Dhī, Dhṛti and Smṛti. [71] These can be summarised as under. Dhī is called derangement of understanding where by the eternal and the non eternal (Nityānitya) , good and evil (Hitāhite) are mistaken one for the other, for true understanding always perceive rightly.[72] In the event of the derangement of the will i.e. Dhṛti the psyche (Sattva) which is always reaching out for its objects, is incapable of being restrained from undersirable objects,as Dhṛti is the controller.[73] When on account of the psyche (Manas) being clouded with passion and delusion i.e. Rajomohāvṛtāt Manas, the retention of true knowledge is shattered, i.e. called the derangement of Memory ; for indeed the memorable abodes in the memory.[74] Misconception by the intellect and misconduct are to be understood as volitional misconduct i.e. Prajñāparādha because they come under the sin of the mind (Manas) .[75] Various illeffects by Bhutābhiṣanga ,Grahās as well as Kṛtya, Abhicāra, Śāpa, Nakṣatra bādha etc. do come under the term Vihāra, which is responsible for Manas rogas. Under influence of non-existing entities like Deva, Asura, Gṃdharva, Pitra, Piśāca etc. Unexplained and irrelivent manifestation of mental disorders of behavior takes place.Result of "Purvakṛta Pāpakarma" is dependent on favourite and unfavourite times of life which are called as Daiva, or bad luck etc. These can cause Manasa roga.

- Manas:

Emotional disturbances are the strongest cause of Manas roga. Abrupt rise or sudden regress in any emotion can directly lead to various mental disorders.All kinds of mental imbalance take place out of the disassociation of mind from what is desired and its involvement with what is undesired.[76] On that consideration positives like - Icchāpurti, Kirti, Dhanlābha, Harṣa, Priti, Sukha, Yaśā, Mahtvākamkṣā, Dambha, Mana and Garva as well as negative emotions like –

Śoka, Bhaya, Dukha, Parājaya, Apamāna, Cintā, Krodhā, Irṣyā, Matsar, Dveṣa, and Moha all these if present in a risky manner or like sudden out break they may prone direct and Samvāyi causes of Manasarogas.

- Miscellaneous:

Some of the more nidānas are described under Unmāda and Apasmāra which can be taken as nidāna of all Manasa rogas.

Such as:

Misbehaviours with noble persons such as saints, Brahmanās, teachers or God.

Performing sexual acts during dusk (Saṃdhyākāla and Parvasandhī i.e. Aṣtami, Amāvasyā, Purnimā etc.)

Being isolated and salitary i.e. Ekāntavāsa.

Delivery periods of pregnant women is also considered in the regards.

Overruling of religious conducts e.g. Yajña, Bramhacarya etc.

Being completely nude allways.

Sexual intercourse with a women during menstrual period.

Effect of moon movements on manifestation and self ceasation of periodic attacks of Manasa roga.

Excessive ingestion of any one particular rasa leads to various disorders some of which are at the level of psyche.[77]

Lavaṇa atisevana –

Over ingestion of Lavaṇa rasa leads to hindrance to the functioning of Indriyas and causes Moha.

Katu rasa atisevana – causes moha, tama and bhrama.

Tikta rasa atisevana – causes moha, bhrama.

Therefore the consumption of any one rasa in excessive amounts has been condemned by the classics.

- Rogaja:

Physical diseases have direct influence on psychopathology e.g. Śvitra, Kuṣtha, Jvara, Arśā, Amlapitta etc. This covers a brief yet all covering account of Samavāyi karaṇā i.e.Nidāna of Manasaroga.

Physical influence in Manasroga:

Reciprocal effects are transferred on body and mind to each and other. Many of the bodily factors are having their direct influence regarding various disorders of Manas. Prominant of them are Rasa, Rakta, Ojas, Prāṇa, Udāna and Vyāna vāta, Sādhakāgni, Avalambaka and Tarpaka kapha and also Tvaca. Some of the physical function like food intake (hunger / thrust), the sleep pattern and style of sexual act also influence the psychopathology upto significant extent also be considered as Manas roga nidāna if found abnormal. Vāta is the controller and motivator of the mind. Particularly Prāṇa, Udāna and Vyāna are directly involved with the activities of the Manas, the functions described of the Prāṇa are Cittahṛdayendriyadhṛka.This means that it is accountable for the perception and conduction of the stimuli to the Manas and its interpretation and orientation accordingly. It controls all the functions of Manas also.Udāna is responsible for recollection of the past experiences i.e. the memory. Thus, it helps the Manas to analyze the entire perception and concepts formed on the basis of the part experiences and thus to orient the attitude and action to be projected to karmendriyas. As Vyāna is responsible for Gati.Stability and concentration of Manas is dependent upon the normal conditions of Vyāna.[30]

Hence, the factors which provocate the Vāta, especially the Prāṇa, Udāna and Vyāna are also the causative factors of cognitive decline or Smṛtibhraṃśa. The factors which increase the Rukṣatā i.e.heavy exercise, starvation, excessive walking, trauma, suppression of urges are the etiological factors which provocates the Vāta in general and Prāṇavāta in particular.[78] Suppression of the urges like sleep, sneezing, vomiting and belching, heavy weight lifting, excessive crying and laughing vitiate the Udāna in particular .Likewise, excessive thinking, excess travelling, ununctous and Rukṣa diet, excessive joy or objection etc.vitiate the Vyāna. Many of these factors like starvation, excessive eating, thinking, grief, fear, suppression of urges, Rukṣa etc. and many others like indigestion Guru, Sīta and Asātmyabhojan etc. vitiate the Agni.[79]. This vitiation has also got an impact on the Sādhakāgni and Sādhaka pitta causing a derangement in its functions. The functions of Sādhakāgni like memory (Smṛti), intelligence (Buddhī, Medhā) , consciousness, to enable one to achieve ones aspirations and a number of emotional stimulations like excitement, fear, etc. are derranged.[31] The nutrition of the mind is also dependent on the diet.However, its nutrient action is dependent on the normalcy of the Agni, because from the undigested food the body elements cannot be found or nourished.[61] Thus, the impairment in the functions of the Agni directly affect

the nutrition and make it susceptible to the diseases. The unfavourable diet also vitiates the mind as it is nourished by the properties present in the Pāncabhautika āhāra.

The normal functions of Tarpaka kapha is also to nourish the Indriyas. Hence, the factors which vitiate the Kapha should also be taken into consideration. Hṛdaya is the Cetanāsthāna and it is the seat of the mind. It is made up of the pure or clarified part of the Kapha, Rakta and Meda, consequently the vitiating factors of these three basic substances may also lead to Jarā avasthājanya Smṛtibhraṃśa. Disturbance in the function of Śukra and Ojas may lead to Smṛtibhraṃśa due to ageing. Therefore, fear, anger ,worries, grief, suppression of natural urges, exertion, habitual sexual abstinance etc.may develop Smṛtibhraṃśa and ageing too.[80]Likewise, Cintā, Bhaya, Śoka etc. Mānsika bhāvas which may vitiate the Rajas and Tamas, and Rukṣādi sevana are the causes of Ojokṣaya which ultimately lead to Smṛtibhraṃśa and ageing .[81]

Among the seven Dhātus, Dhṛti is also described to the best qualities of Māṃsa. Likewise Indriyaprasāda and Manapriti are said to be the functions of normal Rasadhātu.[82] Good quality of Medhā is said to be due to Rakta and Māṃsa.So disturbances in these dhātu also may sometimes lead to Smṛti decline.

This etiology can be divided into 5 divisions as follows:

- Āhāraja - i.e. Food related
  Tāmasika and Rājasika Āhāra
  Duṣta Āhāra
  Kapha vṛuddhīkara Āhāra
  Anabhiṣta Āhāra etc

- Vihāraja i.e. related to activities
  Tāmasika and Rājasika activities
  Antisocial activities
  Unwanted activities
  Uncontrolled activities

- Rogaja i.e. disease induced
  Vāta dominant diseases
  Kapha dominant diseases
  Psychosomatic disease etc.

- Mānsika kāraṇajanya i.e.Psychological factors
  Śoka, Bhaya, Krodha, Dukha, Irṣā, Cintā, Dveṣa, Atipritī, Moha etc.
  Mānsika abhighāta
  Financial problem
  Abnormal sexual acts
  Family and social problem

- Purvakṛita pāpa karma i.e. Daiva, Niyati etc.

2.1.5 - Probable saṃprāpti of Jarā avasthājanya Smṛtibhraṃśa:

After referring classics it can be said that Jarāvasthā and Smṛtibhraṃśa both are dominated by aggravated Vāta doṣa. It can be said that Smṛtibhraṃśa is a disease of the mind developed due to provoked Vāta. The above mentioned etiological factors have polymodal effect in the pathogenesis. Hīna satva, Rajas predominant prakṛti and the person whose mind is weakened by all the stressful conditions are more prone to develop Smṛtibhraṃśa in Jarāvasthā. Again, as discussed earlier in the Nidāna, the regular consumption of diet dominant in Tamas and Rajas guṇas increase the Tamas and Rajas doṣa in the mind. The increased Rajas supports the Tamas to develop Smṛtibhraṃśa. Moreover, the Rajas diet depreciates the Dhṛti.[83]To control the functions of the Manas is the main function of Dhṛti. The mind depreciated or lacking in Dhṛti cannot restrain itself (Svasyanigraha) and yet indulges in excess thinking, looses confidence, fails to achieve the decided goal and thus the person lags behind. At the biological level, Vāta, Pitta and Kapha are stated to represent predominantly of Rājasika, Satvika and Tāmasika nature. Hence, the factors provocating the respective doṣa also provocate the respective Manasadoṣa viz. the provoked Vāta will vitiate the Rajas doṣa and the provoked Kapha will vitiate the Tamas doṣa of the mind.

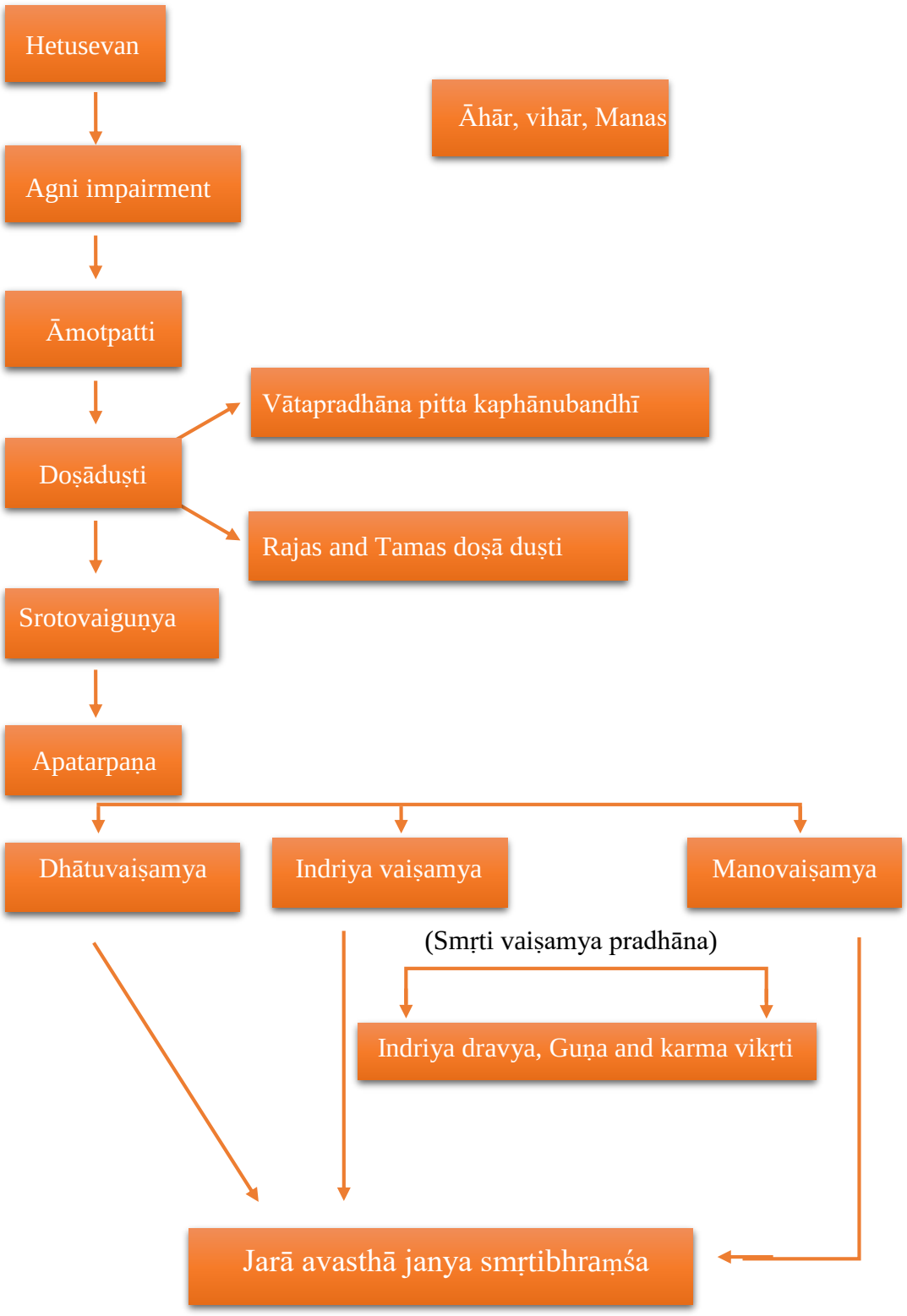
Due to the etiological factors agniduṣti takes place leading to Āmotpatti. This leads to Doṣaduṣti (Vātapradhānakaphapittānubandhī) along with Manas doṣa duṣti (Rajas and Tamas).All these process leads to Srotovaiguṇya leading to Apatarpaṇa or degenerative changes in the body. These pathological changes causes Dhātu vaiguṇya,

Indriya vaiṣamya and Manovaiṣamya (Smṛti vaiguṇya pradhāna). All this degenerative or apatarpanottha pathology results into declined nutrition of Indriyas casing Indriya vikṛti, Indriya dravya and Indriya guṇa hāni. Above pathology leads to declined functions of Indriya i.e.Grahaṇa, Dhāraṇa, Smaraṇa.And ultimately Jarāvasthā or ageing process –Smṛtibhraṃśa pradhāna.

In a nut shell the vitiated Prāṇa, Udāna and Vyāna, Sādhakapitta, Avalambaka and Tarpakakapha and Rajas and Tama doṣa are regarded as the factors involved in the pathogenesis of Smṛtibhraṃśa and all the symptoms are produced due to these factors.

Probable Saṃprāpti of aMCI - Āyurvedic view

Fig. 2 Probable Saṃprāpti of aMCI - Āyurvedic view



Saṃprāpti ghatak:

Doṣa: Manas doṣa, Rajas and Tamas

Śāririka doṣa: Vāta: Prāṇa, Udāna, and Vyāna

Pitta: Sādhaka

Kapha: Tarpaka,Avalambak

Duṣya: Rasa, Rakta, Majjā

Srotas: Manovaha, Rasa- Raktavaha, Majjāvaha

Agni: Manda, Viṣama

Udbhava sthāna: Manas

Adhīsthāna: Mastiṣaka

Vyaktisthāna: Manas, Indriya

Purvarupa: Alpa vyakta laksana

Rupa: Impaired Dhī, Dhṛti, Smṛti

Upaśāya: Abhyāsa, Medhya and Rasāyana dravya

Anup Śāya: Hetusevan

Sādhyaāsādhyatva: Kṛcchrasādhya / Yāpya

Rogamārga: Madhyama

Symptomatology –

The symptom complex of Jarā avasthājanya Smṛtibhraṃśa comprise psychological symptoms. Since its incidence rates in ancient times might be low, the importance for its detailed description and treatment methods would not have been found essential by our Ācāryās. Hṛdaya is the āśraya of Manas.Along with Hṛdaya, the other Āśrayi of Hṛdaya viz. Prāṇa, Udāna, Vyāna vāta, Sādhaka pitta and Avalambaka kapha gets vitiated leading to vitiation of Śārira dhātu, Mala, and Srotas.The symptoms of Jarā avasthājanya Smṛtibhraṃśa are related to mind. So symptoms like Krodha, Udvega, Moha, Cintā, Bhaya etc. can be seen also at minimal.Major symptom is memory decline or Dhī, Smṛtibhrṃśā. When the disease runs for a chronic course, the above symptoms may associate with physical symptoms due to Doṣa duṣya duṣti.

Though aMCI is not mentioned as a disease moety in separate chapter in Āyurveda classics, however decline in cognition; especially memory in aMCI can be correlated with Smṛtibhraṃśa in ageing or Jarāvasthā; which has been described by

Carakācārya in Vimānsthāna. Since Smṛti is closely interrelated with Buddhī. Derangement in Buddhī leads to disturbance in Smṛti. Considering references related to Jarā avasthājanya Smṛtibhraṃśa and aMCI, we have tried to find out similarities in both the conditions as follows:

Table. 3 Similarity between aMCI and Jarāvasthājanya Smṛtibhraṃśa

aMCI	Jarā Avasthājanya Smṛtibhraṃśa
A clinical condition	A clinical condition
Occurs in old age	Occurs in old age
Degenerative in nature	Degenerative in nature
Memory decline is the first symptom to know	Smṛtibhraṃśa relatively first symptom to know
Impairment may be in other cognitive domains also	Grahaṇa,Dhāraṇa vikṛti also
Progressive condition	Progressive condition
May progress to dementia	May progress to Smṛtināśa
Activities of daily living not hampered due to memory impairment	Activities of daily living not hampered due to memory impairment
Not demented	Not demented

2.1.6 - Management:

As Smṛtibhraṃśa is mainly related with ageing and due to impairment of Buddhī, Smṛti management by Medhya Rasāyana drugs would be the appropriate line of treatment.

The treatment for Manasa roga may be classified into 4 groups.

- General line of management:

In Sutrasthāna Vāgbhata mentions that Dhī (intellect), Dhairya (will power) and Ātmādivijñāna (self orientation) are all said to be the measures to have healthy mind.

- Pancakarma treatment:

In the exhibition of mental diseases the srotases are obstructed either partially or completely. To treat the diseases these channels should be cleaned. Additionally in order to achieve the maximum result of Śāmana cikitsā, it is preferred to do śodhan cikitsā before administration of śāmana cikitsā.

- Palliative Therapy:

After the classical Pancakarma therapy if the disease is not relieved completely, the following initiative techniques may be employed. Also Rasāyan drugs are the important line of treatment.

- Behavioral treatment:

  Sāntvana (Consoling words)

  Bhaya (Frightening)

  Tādana (Beating)

  Tarjana (Scolding)

  Tamogṛhapraveśā (Isolation in dark room)

  Harśāna (Cheering up)

  Trāśāna (Shocking)

  Abhyanga (Oil Massage)

  Pradeha (Appling irritant to the body)

  Dāna (Donate)

  Vismaya (Astonishing)

  Vināśākathana (Conveying bad news)

- Therapeutica Measures:

  Anjana (Collyrium)

  Nasya (Inhalation)

  Śeka (Irrigation)

  Dhupana (Fumigation)

  Dhumapāna (Inhalation of smoke)

- Diet:

  Food and habits which increase intelligence (Medhya āhār vihāra)

- Aśvāsana treatment: Consoling words (Āśvāsana) to the patients.

- Preventive measures:

Once relieved of mental diseases, the person should not be informed of his activities during illness. He should be allowed to rejoice with the objects of his own choice to facilitate the normalcy of his mind. Sadvṛtta pālana by every individual of the community for prevention of mental illness.Apart from therapeutic measures following measures will facilitate in rising Buddhī , Medhā.

Satata Adhyāyana - Constant study.

Vāda - Interaction

Paratantra avalokana – Referring to other allied subjects.

Tadvidyā saṃbhāṣā - Debate and seminars.

Ācārya sevā - Obedience to the teachers.

Wholesome regimen: Food substances like Wheat, rice, green gram, milk & leafy vegetables.

Unwholesome regimen: Food substances that are incompatible contaminated, unhealthy and unacquainted are proscribed. Excessive consumption of food is also unwholesome.

Concept of Rasāyana:

Rasāyana tantra is one of the eight major clinical disciplines of Aṣatānga Āyurveda. It is a multi-angled approach not only taking care of the body but also the mind and spirit, thus aiming at the overall well being of an individual. Rasāyana therapy offers a comprehensive physiologic and metabolic restoration as is evident from the fundamental statement of Caraka i.e.

"Lābhopāyo Hi Śāstānāṃ Rasādināṃ Rasāyanaṃ"

The intention of Rasāyana is to prevent diseases and delay ageing process. In all the classical literatures of Āyurveda, a comprehensive description of Rasāyana is available which indicates the proficiency of medical knowledge in the field of geriatrics. A number of Rasāyana drugs have been prescribed which have the property of keeping the balance of the bodily dhātus.

In Harśā carita, Rasāyana is used for "Vṛddha graham" which is responsible for enhancing ageing process. Mārkandey purāṇ and Vāyu purāṇ says that in order to overcome the ageing process, Rasāyana was promoted and this has been illustrated with the story of Cyavana and Sukanyā.In Bhagavad gitā, Vāyu puraṇ and Upaniśādās some scattered references are available regarding Rasāyana as a protective measure. Later on, Rasāyana tantra has developed in a more systematic manner by development of immune-modulator, psychotropic and noo-tropic drugs which improve body immunity, mental and intellectual faculties by reducing anxiety, stress and by enhancing mental power.

In Kāśyapa sṃhitā, Āhāra, Jala, Māṃsa and Kṣira have been considered for their best Rasāyana effects. In Bhela saṃhitā, the concept of Rasāyana therapy is described in an independent chapter known as "Dirghāyuṣayopāya" in which the methods of enhancing the longevity are discussed. Chakradutta has prescribed various mineral and herbo-mineral preparations for the prevention and management of diseases.

- Definition of Rasāyana:

The different definitions of Rasāyana given in the Āyurvedic texts are as follows:

Rasāyana therapy is the therapy which establishes the age (Vayasthāpana), increases the life span, intelligence (Medhā) and strength (Bala) and enables one to prevent the diseases.[84] Dalhaṇa while commenting on the above definition of Suśruta gives two meanings of Vayasthāpana. First meaning is enabling a person to live his normal period of life. For second meaning is that Rasāyana prevents the Jarā, so that young age is established for a longer period.Also Rasāyana is a theapy which provides nourishment to Rasa, Rakta etc. dhātu.Rasāyana is a way by which the Rasa, Virya, Vipāka and Prabhāva of the used drug provides Āyu, Bala, Virya and firmness and causes prevention of ageing. [85]

- Properties of Rasāyana:

As the action of Rasāyana takes place in the whole body, changes occurs at both, physical and mental level.

Improvement in mental qualities:

Caraka mentions that Rasāyana improves intelligence, power of recollection, power of sense organs and perfection in speech.Moreover, Medhya rasāyana can specially act on Medhā as it can cause improvement in mental capacity.

Improvement in the physical qualities:

Rasāyana also helps to regain youthfulness, longevity, strength, voice, complexion etc. and cures excess sleep, fatigue and intolerance. Rasāyana is Tridoṣa śāmaka, Agni dīpana and helps in the proper formation of bodily tissues. [86]

- Special qualities and mode of action of Rasāyana:

By its action Rasāyana removes the impurities (Mālā) located in the tissue elements (Dhātu) causing the enhancement of Agni in each Dhātu. Enhanced Agni causes restoration of respective Dhātus in quality and their improved quality leads to perfect health and longevity in the human being.There are mainly two opinions regarding the mode of action of Rasāyana i.e .Rasāyana works by: Controlling the formation of tissue elements (Dhātupāka) and by removing the vitiation from different channels.

Tissue formation:

Formation of new elements and destruction of old elements is the continuous process in the body.This process mainly depends upon the amount of food taken and the condition of Agni of each tissue elements. Role of Agni is very important as the bodily elements get deteriorated when the Agni is increased. This destructive process is very rapid during the old age, even if the subject takes enough food leading to weakness of the body. At such a stage, if a Rasāyana drug is used, it controls the Dhātupāka. Thus, Rasāyana maintains the proper Dhātupaka and brings back the lost vitality of the body.

Removing vitiation from different channels:

Srotas has two functions:

Absorbed food materials carrying to the site of metabolism through Srotas.

Ejection of waste products resulted due to the process of metabolism.

Through these two functions, Srotas play an important role in maintaining the proper health of the body, when it is not afflicted by vitiated Doṣa.In the process of saṃprāpti, aggravated Doṣa are circulated in the body and produce the disease. When it gets obstructed by a vitiated Srotas, then such an obstruction is also responsible for lowering the resistance power of the body which leads to the improper formation of tissue elements and weakens the body. So in any disease, Srotovaiguṇya is common.

Treatment should be done to remove this Srotovaiguṇya. This can be achieved by administering Rasāyana therapy. The term 'Rasāyana' itself indicates that it is a substance which helps in the free circulation of Rasa through its channels without any obstruction. So it can be said that Rasāyana is doing a dual role in removing the obstructions in the pathways and taking the nutrient materials to the respected Dhātus leading to the regaining of the lost resistance power of the body.

- Concept of Medhya rasāyana in Āyurveda:

Since Medhā is a type of Buddhī, it’s a ‘Ātmā guṇa’which is manifested by its conjugation with Manas. Since it is the Guṇa of Ātmā, Buddhī lies in Samavāya saṃbandha with Ātmā.

Regarding this context, if one thinks about Medhya dravya, it’s clearly seen that, if this kind of Medhya dravya effects at a subtle level, they can be beneficial for Medhā.

According to the modern view, intellect (Buddhī) doesn't develop after a certain age in child, means it (Buddhī) can't be increased after that particular age. According to Āyurvedic view, Buddhī is a 'Ātmāja guṇa, so it is mostly impossible to change it.Here it is said to be 'mostly impossible' instead of terming it to be'completely impossible'; as Āyurveda is a theistic science, which gives importance to Daiva and Tapa (Penance), Karma (fate) and Karmaphala. So it may also be possible that Buddhī-Medhā can be rarely developed by the grace of God or Tapa (Penance)-Varadāna (Boon) and Karma (fate).

Medhya Rasāyanas are described abundantly in all classics of Āyurveda. In Caraka Saṃhitā, description of Medhya Rasāyana can be found in Rasāyana adhyāya, while in Suśruta Saṃhitā, a separate Adhyāya is allotted for it. Moreover, while narrating Jātakarma sṃskāra of child, Suvarṇa prāśāna has been mentioned to obtain Medhā. Acquisition of 'Medhā', as the result of Suvarṇa. Ghṛta, Madhu prāśna is also said in Leha Adhyāya of Kāśyapa saṃhitā. One question arises here that if Medhā which is a Ātmā guṇa, is subtle, how will a Medhya dravya work?

This question can be answered in two ways, like (a) by removing the obstacle or hurdle affecting the process of Medhā, which is mentioned earlier. Drugs like Jyotiṣmati or Vacā, which are Uṣṇa and Tikṣṇa by nature, removes the obstruction made by Kapha, Āma or Tamas guṇa in Manovaha strotas, by their Guṇa or Karma.By purification of Manovaha strotas, the contact of Manas with the objects can occur more efficiently (Manas connects with Indriya by its strotas as commented by Cakrapāṇi and Gangādhara). By this, Viṣaya grahaṇa (Grasping) and its encoding by Manas occurs in a better way, which results in the production of Medhā.

(b) As the supporting factor of evolution process of Medhā the Medhya Dravyās like Yaṣtimadhu, Śānkhapuṣpi, Brāmhi are mainly Sīta virya and Madhura-Tikta-Kaṣāya Rasa dominant. These types of drugs are helpful in Viṣaya grahaṇa and process of Manas by their Guṇas like Indriya prasādana (i.e. Madhura Rasa is Indriya prasādana). This type of Dravya increases the stability of Manas by their Guṇa, Virya etc. Because of this, Manas inspite of being always in motion connects with the Indriya for some more time which results in better retention and as a result, it seems that Medhā is increasing.

By keeping into consideration the Rasādi guṇa of dravyās and Āyurvedic process of Dravyā's absorption, digestion; it can be postulated that Medhya dravya work at the subtle level after Bhutāgni pāka, not after normal Jātharāgni pāka. So, it can

be said regarding the mode of action of Medhya dravya that they sharpens the Buddhī-Medhā which already exists in every individual.

Caraka says that due to the vitiation of Rajas and Tamas activity, the recollection of any knowledge of reality is impaired and this is because of derangement in memory function. Though all the Rasāyana drugs are known to promote intellect, Medhya rasāyanas form an important part of Rasāyana discipline. Medhya rasāyana drugs have been claimed to exert pronounced effect on the mental capability of a person. A number of plant-based pharmacological agents have been used since centuries with an object to improve Dhī (intellect), Dhṛti (retention) and Smṛti (recall) or to minimize the decline of cognitive functions among the individuals with some neurological abnormalities. In modern conventional treatment schedule, a number of drugs with a wide range of their therapeutic actions like stimulation of CNS, cerebral blood flow modifiers, stimulation of cerebral protein synthesis including non-specific arousal of cerebral functions associated with enhancing the learning and memory performance are being used. In recent times many other drugs specially herbal, those grouped under 'nootropic agents' with their specific properties in the improvement of cognitive deficits (particularly memory) have been used out in the clinical practice and such agents are claimed to be free from adverse reactions even on long term use.

Āyurveda has already described several medicinal plants under the concept of Medhya rasāyana which refers to the agents acting on higher brain function by interacting on ability or power of acquisition (intelligence), ability or power of retention and ability or power of recall of memory by amelioration of Medhā of the individuals. In Āyurveda, several Medhya rasāyana drugs are kept under the category of Medhya which are responsible for facilitating learning and memory. In Caraka saṃhitā, four prime Medhya Rasāyana drugs have been advocated i.e., Mandukaparṇi, Śānkhapuṣpi, Guduci and Yaṣtimadhu.

- Geriatrics & Rasāyana:

The foremost aim of Geriatrics is to study the changes in the tissues during the ageing process and attempt to make the lives of old persons comfortable. If we compare Rasāyana with gerontology we can find the major difference between them. In addition to prevention of ageing, Rasāyana is aimed for longevity; maintenance of positive health; the improvement in mental faculties like intelligence, perservence and memory; and resistance against disease. Rasāyana essentially referes to the acceleration of the

process of nutrition for the correct condition of the body tissue. The Rasāyana treatment is also a prophylactic measures against the process of ageing.

Thus we notice that the aim and scope of Rasāyana treatment is far wider than that of gerontology, which at present is limited to the care of old persons. With the development of the subject when the process of decadence of the various tissue of the body will be clear at the ultra structural level it may be sought to take the ageing process at every phase of life. Then it may include the other aim of Rasāyana therapy also.

Some contemporary technical terms used for Rasāyana drugs:

Antioxidant
Adaptogenic
Antistress
Humoral Immunity enhancer
Immunomodulator
Bonemarrow proliferator
Mental Agility enhancer
Reductants
Cidal constituents
Tissue protectors
Nephro protectors etc.

- Anti oxidant defence mechanism:

Approximately 20 million molecules of free radicals are produced everyday. If these free radicals attack altogether, then living organism fails to exist. Each cell protects itself from damage by producing free radical scavengers such as enzymes that neutralise free radical. Hence, balance is maintained between free radical production and scavenging activity of enzymes. This is known as Antioxidant defense system. Antioxidants are defined as 'substances whose presence in relatively low concentrations significantly inhibits the rate of oxidation of targets'. Being present in serum, these antioxidants circumvent the damage caused by oxygen free radical. They consist of substances that provide the much needed stability to the free radical by allowing the pairing of electrons. Thus, they counteract the free radical attack.

Types of antioxidant activity:

It may be accomplished by three different mechanisms:

By directly scavenging the free radicals by means of anti radical scavenging enzymes such as SOD, catalase and glutathione peroxidase.

By inhibiting the generation of ROS.

By raising endogenous antioxidant defenses i.e. unregulated expressions of the genes encode the enzymes SOD, catalase.

This antioxidant defense system is basically of two types.

Primary defense:

Antioxidant nutrients:

Antioxidant defenses rely heavily on vitamins and minerals from the diet. These include beta carotene (precursor of Vit. A),Vitamin E (tocopherol), vitamin C (ascorbic acid), selenium, zinc,manganese and copper.

Antioxidant scavenging enzymes:

SOD, Catalase, Heme peroxisases, Glutathione peroxidase

Secondary Defense:

In addition to the primary defense against ROS by antioxidant enzymes,secondary defense against ROS is also offered by small molecules- the ‘Scavengers’, which react with radicals to produce another radical compound.When these scavengers produce a lesser harmful radical species, they are called 'antioxidants' -tocopherol, ascorbate and reduced glutathione (GSH) may act in combination to act as cellular antioxidants. Tocopherol, present in the cell membrane and plasma lipoproteins functions as a chain breaking antioxidant.Once the tocopherol radical is formed, it can migrate to the membrane surface and is reconverted to tocopherol by reaction with ascorbate or GSH. The resulting ascorbate radical can regenerate ascorbate by reduction with GSH, which can alsodirectly scavenge ROS and the resulting GSSG can regenerate GSH through NADPH glutathione reductase system.Since ROS mediated oxidative stress is now regarded as the major factor causing ageing and age related neuro-degenerative diseases, suitable antioxidant therapies to control these processes have already attracted worldwide attention in recent years. The pineal hormone, melatonin, having potent antioxidant activity is a potentially promising candidate for the control of ageing and other ROS mediated pathogenesis.

Restricting the caloric intake has also been shown to delay ageing through -

Decreased production of mitochondrial O2 and H2O2 and

Increased production of antioxidant defenses, leading thereby to decreased production of oxidative damaged proteins, lipids and DNA. Caloric restriction may thus decrease the oxidative stress and damage and may prolong life in humans.

Isolation of an antioxidant factor which is specific in its action, is nontoxic and shows antistress property, from the natural sources such as plants and the therapeutic application of such an antioxidant factor would perhaps be one of the better approaches to control the ROS mediated pathogenesis.

- Adaptogens & Rasāyana:

Majority of Rasāyana drugs were proved to have immunomodulatory property, anabolic effect and antioxidant properties. Recent advancement in the medical science is pointing toward another activity of such drugs and these are called Adaptogenic property.A Russian Scientist, Lazarev, coined the concept of 'Adaptogen' in 1947.Adaptogen is a substances meant to put the organism into a state of non specific heightened resistance in order to resist stresses and adapt to extraordinary challenges.

In general, Adaptogens are a group of medically effective substances that normalise body functions, strengthen systems and functions compromised by stress and have a protective effect against a wide variety of environmental and emotional stresses. General Adaptive Syndrome (GAS), formulated by Selye is a consistent, nonspecific response of the organism to stressful influences of totally diverse types, the adaptive reaction enables the body to heighten its power or resistance towards stresses and to adapt to external conditions .Though difficult to differentiate adaptogenic effect from other remedies of related action, there are number of criteria which allow a formal arrangement of these other drugs in immunostimulants, nootropics, anabolics, tonics and geriatric acids. Rasāyana is certainly having any one or more of these activities.Immune stimulants are substances, which bring about a heightened resistance through the stimulation of non-specific defensive processes, which are largely independent of antigens.

Nootropics (cognition enhances) are effective psychopharmacological agents, which are said to improve the higher integrative brain functions, such as memory, learning, understanding, thinking and the capacity for concentration. No specific

mechanisms are known. It is assumed that nootropics stimulate existing neural synapses to optimum performance (adaptive capacity) and also for damageing influences, such as disturbances of the energy and neurotransmitter metabolism or ischaemia (protective capacity).

Anabolics are substances, which activate the anabolic metabolism. They promote the synthesis of nucleic acids and protein metabolism, thereby in general growth. Tonics and geriatric remedies fall into the category of wellness enhancers.
Though a precise conceptual definition can not be given for both, tonics are defined in a much generalised way as substances which mitigate conditions of weakness or lack of tone within the entire organism, or in particular organs. Being Adaptogenic, like all the others, generally, Adaptogens raise ones capacity, as a result may also be included by the group of tonics.

Geriatric remedies are substances serving as a preventive treatment of old age diseases. Stiffness and age-conditioned rigidity are possibly the outer manifestations of diminished or lacking ability to adapt.
Brekhman, in 1958, summarised the concept Adaptogen as follows:

It must show a nonspecific effect (raising the power of resistance to toxins of a physical, chemical or biological nature).

It is to normalise, independent of the type of pathological condition.

It must be harmless and disturb the body functions as little as possible.

Accordingly, Adaptogens are to strengthen the nonspecific powers of resistance to noninfectious stresses, raise the general performance capacity during stress situations and thereby prevent diseases that could develop due to overstressing the organism. It is seen as characteristic of Adaptogens that their anti stress effect towards stresses of a noninfectious variety, always stands in the foreground.

Although in so called Adaptogens, immune stimulating, Nootropic or metabolic effects have also been proved.By going through the aforesaid pages, it is certain that adaptogens show the similar qualities of Rasāyana i.e., Dhātuvṛdhīkara, Medhya, Puṣtikara, Balya, Dehendriya dṛdhīkaraṇās, Bṛhāniya, Jivaniya etc. and thus help improve body's defense system.

- “Purve vayasi madhyevā….” – Scientific Evidence.

As all those of middle age who have ever fumbled for a name to fit a face will believe, the brain begins to lose Śārpness of memory and powers of reasoning and understanding not from 60 as previously thought, but from as early as 45, scientists says. Over the decade, there was a 3.6% decline in the mental reasoning of men and of women aged 45 to 49.[87]

The process appeared to have speeded up in the older age groups. Men aged 65 to 70 have a decline of 9.6% while women fared a little better, at 7.4%. It matters, say the scientists, because those whose brains appear to deteriorate fastest may be more likely to develop dementia in later life and because if there is any chance of slowing that process, those at highest risk may need to be detected and treated at an early stage, before Alzheimer's or another form of dementia becomes apparent.

The scientists' conclusion is that deterioration of the brain sets in earlier than most of us would have hoped, but there are things that can be done about it. People with high blood pressure, obesity and high cholesterol who are at high risk of heart problems, are also at higher risk of dementia, studies show. For some of these risk factors, such as obesity, hypertension, and hypercholesterolemia, it is mid-life levels that seem to be more important than those measured at older ages.[88]These gives us a logical picture and confirm the fact that our Ācāryās have put forth hundreds of years ago that Rasāyana should be adopted in younger and middle age groups to delay the deteriorating effects of ageing and the above researches further support the same.

- Probable mode of action of Medhya rasāyana in Jarā:

Āyurveda is full of evidences regarding use of single drugs or formulations in age related cognitive decline. The drugs either mentioned as Medhya rasāyanas specifically or other having Medhya activity can be potentially used for prevention and management of age related cognitive decline or cognitive decline due to some disease. Intactness of Prāṇa, Udāna vāta, Sādhaka pitta, Avalambaka & Tarpaka kapha, Rasa, Rakta, Māṃsa, Śukra dhātu and Ojas are responsible for optimum functioning of Medhā and the vitiation of these reflect ill-effects on Medhā. Medhya drugs act as Medhākara by improving Dhī, Dhṛti and Smṛti. Dhī, Dhṛti and Smṛti are related to Manas and Manas responds to Medhya drugs. Medhya Rasāyanas have specific effects

on mental performance, higher CNS functions and have beneficial effects on anxiety, stress, and depression.

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2.2 aMCI review: Modern medicine approach

The mental process by which knowledge is gained and comprehended is known as cognition. Cognition consists of higher level functions of brain such as knowing, judging, thinking, memory and problem-solving. These functions incorporates language, imagination, perception and planning.

Three basic elements of cognition are, the union of earlier experience; the capacity to make judgment, evaluations and decisions; the third one is the capability to identify silent features in specific circumstances. These features are directly proportional to each other. Everyday innumerable cognitive tasks are performed by the person effortlessly. Mental abilities keep on changing as per age. May be as a result of brain maturation then ageing of brain cells and their complex interconnections. Many people shows decline in some cognitive functions during ageing while some elderly may not show any cognitive decline. Though there is difference between cognition of elderly and young person, the changes are very subtle. The most constant change is cognitive slow down. Age hampers attention, especially when it is necessary for multitasking. Also processing information rapidly and dividing attention effectively slows down in elderly. Memory decline in ageing is very common but exact nature of decline depends upon the particular type of memory.

Amnesic MCI is a condition in which people have memory problems more sever than normal for age and education,but not serious enough to affect daily life.It may occur as a transitional stage between normal ageing and dementia. Although MCI can present with a variety of symptoms, when memory loss is the predominant symptom it is termed "amnesic MCI" and is frequently seen as a prodromal stage of Alzheimer's disease.

Mild cognitive impairment (MCI) was first defined in 1999 as a pathological brain condition. Despite its name, the degree of cognitive impairment in MCI is not so mild. The subgroup of MCI with memory impairment, termed amnesic MCI or aMCI, carries very high risk for progression to dementia.The degree of memory impairment in aMCI marginally interferes with daily productivity and quality of life and borders on

mild AD. Amnesic mild cognitive impairment (aMCI) patients have an increased risk of developing AD; however, not all aMCI patients develop AD, as some may remain stable over time, revert to a normal cognitive state, or progress to another type of dementia. It is thus crucial to identify those aMCI patients that will convert to AD.Amnesic MCI results in AD neuropathology. Petersen et al. reported that of 15 autopsied brains from aMCI individuals showed temporal lobe abnormalities consistent with considerable memory impairment and other pathology, on the continuum between ageing and very early AD.

The totality of evidence supports aMCI as a precursor of AD. However, since progression from aMCI to AD is not inevitable, it is possible early intervention at the MCI stage could slow or halt progression toward AD. Number of people develop noticeable cognitive decline with age, characterize by a dementia state. On the other hand there are some aged individuals who suffer nearly very mild change in their cognitive abilities with age, even into the tenth decade of their life. Clinical researchers have differentiated persons who show a moderate impairment with progressing age, in one or more cognitive domains that influence the ability to carry out activities of daily living but does not achieve the mark of a classical dementia state. This class is classified by several as “Mild cognitive impairment” (MCI). Before understanding MCI, it is essential to understand about ageing and age related changes in body and brain specially.

2.2.1 - Ageing:

In the widest sense, ageing reflects all the changes that occur over the course of life. One grow, develop and reach maturity. Though ageing and senescence are relative terms and used as synonyms many times, but Charles Mobbs gives different views that “Ageing is a process of gradual and natural changes, resulting in maturation through childhood, puberty and young adulthood and then declines through middle and late age”.While in the process of senescence the capacity for cell division, growth and function is lost over time, ultimately leading to an incompatibility with life i.e. the process of senescence terminates in death.

All changes that happens with age or in late age are not harmful (e.g. grey hair, baladness), some may even be desirable (e.g. increased wisdom and experience).

Normal ageing have normal pattern of impairments and diseases that represent several elderly while healthy ageing is associated with a process by which harmful effects are minimized, reducing the undesired effects of ageing,protecting function until senescence make continued life impossible.

The human body has two different ages; a chronological age and a biological age. Chronological age refers to the actual time a human has been alive, while biological age refers to how old that human seems. Anatomical and physiological changes with ageing are described in almost every body system. Ageing changes occur to molecules, to cells and to organs and system. They mostly become apparent in early or middle adult life, but their magnitude and practical significance vary considerably. Significant and progressive alterations in average body composition appear in the fifth decade of life.

Diseases of old age (diseases which increase in frequency with age, such as Arthritis, Heart disease, Osteoporosis, Alzheimer's disease, etc.) are often distinguished from ageing.

Table 4.Selected age-related changes and their consequences (source google images)

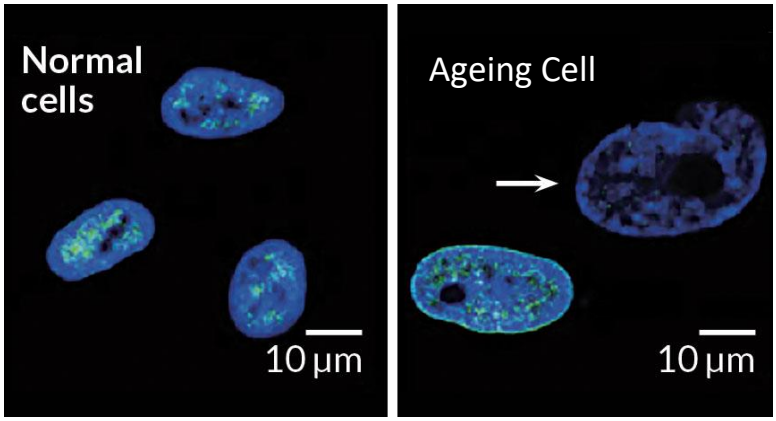
Organ/system	Age related physiologic changes	Consequences of age related physiologic change	Consequences of diseases ,not age
General	↑Body fat	↑Volume of distribution of soluble drugs	Obesity
	↑Total body water	↓Volume of distribution of water-soluble drugs	Anorexia
Eyes/ears	Presbyopia	↓Accommodation	
	Lens opacification	↑Susceptibility to glare	Blindness
		Need for increased illumination	
	↓High- frequency acuity	Difficulty discriminating words if background	
		Noise is present	

Endocrine	Impaired glucose homeostasis	↑Glucose level in response to acute illness	Diabetes mellitus
	↓Thyroxin clearance [and production]	↑T dose required in hypothyroidism	Thyroid dysfunction
	↓ADH, ↓Renin, and ↓Aldosterone		Na+,↑K+
	↓TESTESTERONE		Impotence
	↓Vitamin D absorption and activation	osteopenia	Osteomalecia, Fracture
Respiratory	↓Lung elasticity and chest wall stiffness	Ventilating/perfusion mismatch and ↓P_{02}	Dyspnea, Hypoxia
Cardiovascular	↓Arterial compliance and ↑systolic BP→LVH	Hypotensive response t ↑ HR, volume depletion, or loss of arterial contraction	Syncope
	↓β- adrenergic responsiveness	Cardiac output and HR response to stress	Heart failure
	↓Baroreceptor sensitivity and ↓ SA node atomicity	Impaired blood pressure response to standing volume depletion	Heart block
Gastrointestinal	↓Hepatic function	Delayed metabolism of some drugs	Cirrhosis
	↓Gastric acidity	↓Ca^{2+} absorption on empty stomach	Osteoporosis,B12 deficiency
	↓colonic motility	constipation	Fecal impaction
	↓Anorectal function		Fecal incontinence
Hematological / Immune system	↓Bone marrow reserve (?)		Anemia
	↓T cell function	False –negative PP response	
	↑Autoantibodies	False-positive rheumatoid factor, antinuclear antibody	Auto immune disease
Renal	↓GFR	Impaired excretion of some drugs	↓Serum creatinine
	↓Urine concentration (see also “Endocrine”)	Delayed response to salt or fluid restriction / overload, noctuia	↓Na^2

Genitourinary	Vaginal/Urethral mucosal atrophy	Dyspareunia, Bacteriuria	
	Prostate enlargement	↑Residual urine volume	Urinary incontinence, urinary retention
Musculoskeletal	↓Lean body mass, muscle		Functional impairment
	↓Bone density	osteopenia	Hip fracture
Nervous system	Brain catechol synthesis	Benign senescent forgetfulness	Dementias, Delirium
	↓Brain catechol synthesis		Depression
	↓Brain dopaminergic synthesis	Stiffer gait	Parkinson's disease
	↓Righting reflexes	↑Body sway	Falls
	↓Stage 4 sleep	Early wakening, insomnia	Sleep apnea
Organ/System	Age related physiologic change	Consequences of age related physiological change	Consequences of Disease, not Age
General	↑Body fat	↑volume of distribution for soluble drugs	Obesity
	↓Total body water	↓Volume of distribution of water soluble drugs	Anorexia
Eyes / ears	Presbyopia	↓Accommodation	
	Lens opacification	↑Susceptibility to glare	Blindness
		Need for increased illumination	
	↓High- frequency acuity	Difficulty discriminating words if background	
		Noise is present	
Endocrine	Impaired glucose homeostasis	↑Glucose level in response to acute illness	Diabetes mellitus
	↓Thyroxin clearance (and production)	↑T dose required in hypothyroidism	Thyroid dysfunction
	↓ADH, ↓renin, and ↓aldosterone		↓Na^+,↑K^+
	↓Testosterone		Impotence
	↓Vitamin D absorption and activation	Osteopenia	Osteomalecia, fracture

Respiratory	↓Lung elasticity and ↑chest wall stiffness	Ventilation/perfusion mismatch and P_{O2}	Dyspnoea, hypoxia
Cardiovascular	↓Arterial compliance and ↑systolic BP→LVH	Hypotensive response t↑ HR, volume depletion, or loss of arterial contraction	Syncope
	↓β-adrenergic ode responsiveness	↓cardiac output and HR response to stress	Heart failure
	↓Baroreceptor sensitivity and ↓ SA node automaticity	Impaired blood pressure response to standing volume depletion	Heart block
Gastrointestinal	↓Hepatic function	Delayed metabolism of some drugs	Cirrhosis
	↓Gastric acidity	↓Ca^{2+} absorption on empty stomach	Osteoporosis, B12 deficiency
	↓Colonic motility	constipation	Fecal impaction
	↓Anorectal function		Fecal incontinence
Hematologic / Immune system	↓Bone marrow reserve (?)		Anemia
	↓T cell function	False-negative PP response	
	↑Autoantibodies	False-positive rheumatoid factor, antinuclear antibody	Autoimmune disease
Renal	↓GFR	Impaired excretion of some drugs	↓Serum creatinine
	↓Urine concentration (see also “Endocrine”)	Delayed response to salt or fluid restriction / overload, nocturia	↓Na^{+}

Fig. 3 Ageing Cell(source google images)



Theories of ageing:

Theories proposed for explaining ageing can be divided in to two categories, one is programmed theories and the other one is error theories. Though it is so, none of them can satisfactorily explain process of ageing.[1]

Programmed theory of ageing states that all cells are programmed to divide and death in specific time and functional changes in those cells is responsible for ageing of that individual. According to this theory gene mechanism is responsible for maintenance, restoration and preventive responses in the body and this progress to deterioration ultimately leads to death.

The error theories put emphasis on external or environmental forces which gradually provoke collective damage of cells and organs at different levels leading to ageing and finally death. Both these theories are interlinked with each other in a complex way for the process of ageing.

The programmed theory includes:

- Programmed senescence theory:

Certain genes plays great role in programmed senescence of cells. Means period of cell ageing for each individual is already programmed in to the genes. Theory says that rejuvenation in the life of the cells is already preset.

- Immunological theory:

Immunological theory reveals that the speed of ageing, which is an extremely complex sequence of various processes, is mostly controlled by the immune system. During ageing, the numbers of critical cells in the immune system reduces. The immune system become less functional .Means this system is programmed to decline as per ageing .It protects against external infectious organisms, not only this it also facilitate to identify and remove toxins and cancer cells from the body. As one ages, the potential for these elements to cause damage in our bodies increases in ageing increasing the vulnerability to infectious diseases and thus ageing and death.

- Endocrine theory:

It has been observed that the production of some of the hormones declines with age. Like growth hormone levels, estrogen and testosterone, melatonin and thyroxin declines with age. Hormones control the target organs and organize the speed of ageing. Some research studies reports that insulin/ IGF-1 signaling pathway plays a major role in the hormonal regulation of ageing

Error theory:

- Wear and tear theory:

This theory of ageing propose that ageing is merely the consequence of general deteriorative processes that takes place in every cell and tissue, in any organized system. Vital parts of the cells and tissues wear out ensuing in ageing.

- Rate of living theory:

The theory propose that individuals life span is inversely proportional to the rate of oxygen basal metabolism, the shorter the life span greater the rate of oxygen basal metabolism

- Free radicals theory:

Theory postulates that the inborn method of ageing takes place by increasing oxidative damage to cells by free radicals .These free radicals are produced throughout the aerobic respiration. Cellular levels of free radical damage increases with age. - Damage at cellular levels by free radical increases with age gradually resulting to cell senescence and death.[2]

- Cross - linking theory:

Theory reveals that cells and tissues get damaged by accumulated of cross-linked proteins slow down bodily processes resulting in to ageing. Binding of glucose to protein causes various problems. Protein becomes impaired after binding and becomes unable to perform even normal function effectively and increasing cell ageing faster.

- Somatic DNA damage theory:

DNA damages takes place continuously in the living cell. While the majority of these damages are repaired, some are accumulated and not corrected. These high levels of DNA damage may speed up physiological decline and the development of age-related disorders.[3]

As per to current discoveries,cellular ageing is dependent on the cell division and the total cellular life span is measured by the number of population doublings or cell generations not by chronological time.Telomeres are stretches of DNA at the ends of chromosomes.The progressive loss of telomeres eventually induce anti-proliferative signals that result in cellular senescence i.e. telomere sequences shorten each time the DNA replicates, reach a critically short length and cells show signs of genomic instability and eventually stop dividing causing cellular ageing.

2.2.2 - Ageing and cognitive decline:

Age related cognitive decline or mild cognitive impairment is a term reserved for abnormal cognitive function less severe than dementia in person older than 50. It is measured as a prior condition to senile dementia. Dementia has severe cognitive decline so as individual is markedly impaired in social and occupational functioning.As a result that person becomes dependent.

Degeneration of the cerebral neurons is one of the commonest and important causes of dementia with increasing age which leads to deterioration of quality of life in elderly. According to World Health Organization, it is estimated that 5% of men and 6% of women of above 60 years of age affected with Alzheimer's type of dementia worldwide. According to Alzheimer's disease International society there are 35.6 million people living with dementia worldwide in 2010, increasing to 65.7 million by 2030 and 115.4 million by 2050. Hence to control this development of cognitive decline before it crosses the doorstep to dementia is very important.[4]

Age-related changes in brain:

Structural changes:

During ageing number of changes takes place in the body whether physical, chemical or biological. Hence, it is logical to assume that the brain is no exception to this phenomenon. It is found that the cerebral ventricles expand as a function of age, and this progression is known as ventriculomegaly. More current studies have reported age-related regional decreases in cerebral volume.[5]This regional volume decline is not homogeneous; some brain regions shrink at a rate of up to 1% per year, whereas others remain comparatively stable until the end of the lifetime. The brain is very complex organ and is composed of many different areas and kind of tissue or matter. The different functions of different tissues in the brain may be more or less susceptible to age-induced changes.

Thinning of the cortex:

There is decrease in grey matter volume between middle age and old age, while white matter volume was found to be increased from age 19-40, and decline after this age. [6] Studies using Voxel-based morphometry have identified areas such as the insula and superior parietal gyri are especially vulnerable to age-related losses in grey matter of older adults. The first six decades of an individual's life were correlated with the most rapid decreases in grey matter density, and this takes place over dorsal, frontal, and parietal lobes on both interhemispheric and lateral brain surfaces. Certain language functions such as word retrieval and production were found to be located to more anterior language cortices, and deteriorate as a function of age. These anterior language cortices were found to mature and decline earlier than the more posterior language cortices. It has also been found that the width of sulcus not only increases with age, but also with cognitive decline in the elderly.[7]

Loss of neural circuits and brain plasticity:

Brain's ability to change structure and function is known as brain plasticity.[8]A proposed mechanism for the observed age-related plasticity deficits in animals is the result of age-induced alterations in calcium regulation. Alteration in the abilities to handle calcium ultimately influence neuronal firing and the ability to spread action potentials, This action potential in turn will affect the ability of the brain to alter its

structure or function (i.e.its plastic nature).Hence it is necessary to keep the brain functioning always.

Due to the structural and functional complexity of the brain it is reasonable to assume that some areas are more vulnerable to ageing than others. Two circuits, hippocampal and neocortical circuits are more prone for this. It has been recommended that age-related cognitive decline is not due to neuronal death only but because of synaptic alterations also. Research study also supports this idea from that the cognitive deficit is due to functional and biochemical factors like changes in chemical messengers, enzymatic activity or gene expression in cortical circuits.[9]

Chemical changes:

Along with the structural changes the brain shows some biochemical changes with age. Information is received, processed, and transmited by specialized nerve cell called Neuron.These Neurons are communicated with each other via specialized chemical messengers called neurotransmitters. These neurons cells communicate with one another with the help of neurotransmitters into the synapse, where they are then taken up by specific receptors on neighboring cells. There are various types of neurotransmitters in the brain which are produced inside a neuron, released into the synapse, and then cause an excitatory or inhibitory effect on receptor cells, helping to propagate or downgrade action potentials.

So far, more than 60 different neurotransmitters in the human brain have been recognized by scientists and expecting to find more in the future. Neurotransmitters like, dopamine, serotonin, glutamate, acetylcholine, GABA, norepinephrine and others have important roles in human cognition and behavior. As it is thought and converse often that it neurotransmitters have a single role or function, neuroscientists are finding that neurotransmitters are multi-faceted, complex, and interact with one another in a variety of different ways. For example, it is considered since long that dopamine is the neurotransmitter involved with reward processing. However new research suggests that the release of acetylcholine results in the release of dopamine and ultimately, both influence reward processing and learning.[10]

Following neurotransmitters play a significant role in mental health:

- Acetylcholine:

Acetylcholine (ACh) was the first neurotransmitter to be identified. It is a small-molecule neurotransmitter that works primarily at the neuromuscular junction, translating intention into action between the neuron and the muscle fiber. But it has also been linked to cortical neuroplasticity and attention.[11]For voluntary movement, learning, memory, and sleep involvement of acetylcholine is important. Excess acetylcholine is associated with depression and too little in the hippocampus is associated with dementia.

- Dopamine:

Significant age-related decline in dopamine synthesis, notably in the striatum and extrastriatal regions (excluding the midbrain) is seen in research studies using positron emission tomography in living human beings.Age-related decreases in dopamine receptors D1, D2, and D3 is significantly noted. Commonly decrease in D1 and D2 receptors is seen, and specially a decrease of D1 and D2 receptor binding in the caudate nucleus and putamen.[12]Considerable age-related declines in dopamine receptors, D2 and D3 were detected in the frontal cortex, anterior cingulate cortex, lateral temporal cortex, hippocampus,amygdala, medial temporal cortex, medial and lateral thalamus. [13]Loss of dopamine with age is responsible for many neurological symptoms that increase in frequency with age, such as decreased arm swing and increased rigidity. Changes in dopamine levels may also cause age-related changes in cognitive flexibility. Dopamine is correlated with movement, attention, and learning. Excess dopamine is associated with schizophrenia, and too little is associated with some forms of depression as well as the muscular rigidity and tremors found in Parkinson's disease. Dopamine is also involved with motivation, decision-making, movements, reward processing, attention, working memory and learning.[14]

- Serotonin:

It plays a role in sleep, mood, impulsive and aggressive behavior and appetite. Very less serotonin is associated with depression and anxiety disorder. With increased age, decrease in levels of different serotonin receptors and the serotonin transporter, 5-HTT occurs. Studies conducted on humans, in vivo, show that levels of the S2 receptor

in the caudate nucleus, putamen, and frontal cerebral cortex, decline with age. With increased age decreased binding capacity of the 5-HTT receptor in the frontal cortex, as well as a decreased binding capacity of the serotonin transporter, 5-HTT, in the thalamus and the midbrain is found. Lack of Serotonin is linked to depression and related neuropsychiatric disorders. But 5HT has also been concerned in appetite, memory, sleep, and, most recently, decision making behaviors.[15]

- Glutamate:

Glutamate is another neurotransmitter that decreases with age. Research studies have shown that in older individuals there is low glutamate concentration in the motor cortex compared to younger subjects. A significant age-related decline particularly in the parietal gray matter, basal ganglia, and to a lesser degree, the frontal white matter, has also been noted. Glutamate also plays an important role in learning and memory, long term potentiation; the molecular process believed to help form memories, occurs in glutamatergic neurons in the hippocampus and cortex.[16]

- GABA (Gamma-Amino Butyric Acid):

In mammalian central nervous system GABA is the main inhibitory neurotransmitter in the brain GABA is found at inhibitory synapses. In synaptic neuronal processes it binds to specific transmembrane receptors in the plasma membrane.In Alzheimer's individual neurotransmitter GABA is unusually and abundantly produced, which causes impairment in synaptic transmission, plasticity and memory. If there is a trouble with the GABA in our brains, the neurons fire more and more, increasing the speed of the processes in the brain.

GABA inhibits excitation and anxiety. Low quantity GABA is associated with anxiety and anxiety disorders. This neurotransmitter also plays an important role in brain development. GABA works to inhibit action potentials in the brain and has been associated to seizure and other pathologies. Due to change in GABA polarity stimulating immature neurons, could help lay down essential brain circuits in early development.[17]

- Epinephrine:

Epinephrine is a hormone which is released from the adrenal medulla in response to stress.It is supportive in enhancing memory. Epinephrine does not readily cross the blood-brain barrier, the hormone mainly improves memory by modifying brain functions with the help of engaging peripheral mechānisms. Glucose is released from the liver as a result of circulating epinephrine ultimately leading to memory enhancement. So release of epinephrine and elevated blood sugar levels helps to up regulate brain functions responsible for formation of new memories.

- Nor epinephrine:

Nor epinephrine is both a hormone and a neurotransmitter. Nor epinephrine when released in cerebellum it activates the β-adrenergic receptor which is vital for cerebellar motor learning consolidation variation in nor epinephrine have long been known to be associated to stress, cognitive, mood and neuropsychiatric symptoms .Low levels are linked with a poor memory ,loss of alertness and depression.

- Endorphins:

Endorphins have anti-ageing effect by removing Superoxide. By facilitating the production of Superoxide Dismutase endorphins can remove this harmful Superoxide. This is possible because the endorphins can keep the brain cells young and healthy. Superoxide dismutase; the enzyme which neutralized the toxicity of the harmful Superoxide. Hence endorphins have anti-ageing and memory and learning enhancing effect. Other neurotransmitters, neurochemicals like oxytocin and vasopressin, hormones like estrogen and testosterone are also efficient in enhancing cognition.

Neuronal morphology:

Process of ageing is linked with numerous structural, chemical, as well as functional transformation in the brain. Research studies have states that the cerebral ventricles enlarge as a person ages. However current MRI research studies showed uninformed regional decline in cerebral volume in ageing.[18]Posterior language cortices maturation and functional decline takes place slowly than anterior language cortices, as a result word retrieval and production decline early in ageing.Synaptic alterations are

more responsible than neuronal death for cognitive decline in ageing. Alteration in enzymatic activity, chemical messengers, or expression of gene in cortical circuits are some functional and biochemical factors which are responsible for cognitive decline.[19]However, increasingly, research studies have verified that cerebral changes with normal ageing are mainly due to restructuring of cortical connectivity patterns rather than by regional alterations.[20]

- Neurofibrillary tangles:

Normal pattern of ageing is bit difficult to differentiate from neuro-pathologies of the conditions such as AD, Arterioscelrosis, Diabetes, Parkinson's disease etc. Neurofibrillary tangles are buildup of proteins.Neuron microtubules transports nutrients and other essential materials from the cell body to axonal tip.Tau proteins keep these microtubules paraellel and together. In conditions like ageing, MCI, AD etc. due to disaggregation of this protein filaments formation takes place which forms the tangels. Because of this, neuron microtubule cannot remain straight and transport the essential material for the survival of neurons.As a result axonal tip starts degenerating due to poor nourishment. Consequently the complete neuron get degenerated resulting in the reduction of neuronal communication in the circuit.

Though neurofibrillary tangles are the characteristic of AD, they too can takes place in non demented healthy ageing. Tangles may be found intensely around the hippocampus in persons over the age of 55.Tangles are present in all brains over the age of 55, intense in specific structures around the hippocampus and their number increases with ageing, severity of AD,MCI and other dementias. But the location of tangles changes according to disease condition than normal ageing. As the healthy non-demented person ages, increase in the density of tangles is commonly found, but no major difference in the location of tangles found.

Two pathological lesions, neurofibrilllary tangles and amyloid plaques are commonly found in AD pathology. Plaques are found between the neurons and tangles are found inside the neurons. Plaques consist of small dense deposits of beta amyloid proteins which are chemically adhesive.Hence they gradually stick to each other to form plaques. However, plaques are not a constant feature of ageing brain like tangles.

- Role of oxidative stress:

Microvasculature changes in cerebrum, oxidative stress and inflammatory reactions are mainly responsible for cognitive impairment.Brain has enormous phospholipids in it which prone to oxidative damage, also it consumes almost 20% of oxygen required by the entire body. Hence brain is more susceptible to oxidative damage. This results in the raise in damaged DNA and lipids because of oxidation during ageing. Eventually neuronal death takes place due to this free radicals damage. This process also takes place in healthy non demented adult individual and is important thing in neurodegenerative diseases and brain ageing, ischemic disorders.

According to Merriam-Webster Medical Dictionary oxidative stress is, "physiological stress on the body that is caused by the cumulative damage done by free radicals inadequately neutralized by antioxidants and that is to be associated with ageing." Oxidative stress, is the result of the difference among the production and detoxification of reactive oxygen and nitrogen species (ROS/RNS) dysfunction of proteins, nucleic acids, and lipids starts due to excess amount of ROS/RNS molecules. But only selected groupss of neurons are susceptible for this oxidative stress. These susceptible neurons are the primary indicator of the functional decline and cellular death in ageing or neurodegenerative diseases. Protein aggregation, calcium dysfunction, mitochondrial dysfunction, glutamate-induced excitotoxicity, accumulation of OS and genomic instability collectively are the neuro degenerating factors. Oxidative stress is the factor which unites all above factors .Various researches shows that oxidative stress is one of the important and very much controllable factor for MCI and AD pathology.[21]

- Inflammation:

Multiple factors influence ability to think and remember as we age. Chronic inflammation, vascular diseases is one of them.The concept of cognitive decline due to inflammation is relatively new, but it shows to be constant with the increasing thought of the injury or damage of chronic inflammation which can be assessed by C-reactive protein or interleukin-6 levels. Numerous studies have observed the correlation between inflammation and mild cognitive impairment specially inflammation, metabolic syndrome and MCI.[22] In brain inflammatory process is restricted with the help of the blood-brain barrier(BBB) mechānism during healthy circumstances. So with

the help of this mechānism inflammatory agents are prevented and permits only selected nutrients and small molecules into the central nervous system .On the other hand, chronic systemic inflammation disturbs the integrity of the BBB, permitting irritants to enter the brain encourageing the production of inflammatory cytokines, such as IL-1β, IL-6 and IL-18. Some cytokines impair neurogenesis while some like IL-1β, IL-6 and TNF-α damage and destroy existing neurons disrupt neural circuits involved in cognition and memory.[23]Acute decline in spatial memory was found after inducing systemic inflammation in humans by Salmonella typhi vaccine.[24]

A research study related to inflammatory markers showed that individuals having high CRP levels have poor cognitive performance in some domains, in AD patients as well as in cognitively healthy individuals.[25]

Neuropsychological changes:

In normal ageing, cognitive abilities tend to decline more slowly and to a lesser degree than do physical abilities. Despite this resilience, some level of cognitive impairment is expected as ageing progresses, relative to performance levels at younger ages.

- Changes in orientation:

Awareness of own identity in relation to one's surroundings is known as orientation. Orientation is inspected by an individuals a sense of time, place, and person. Orientation may get hampered by almost all neuropsychological disturbances. Some research says that ageing is associated with mild orientation decline while some research doesn't agree with this.[26]

- Changes in attention:

The ability to concentrate and focus on specific point is known as attention .Simple attention span or immediate memory does not show much decline in ageing.On the contrary more visible effect in ageing is seen on complex attention tasks, for example selective and divided attention.[27] Research studies have reported that older adults need more time encoding and retrieving information when their attention is

divided or switched from one task to another.[28]Sensory deficits also have impact on ability of attention in elderly.

- Changes in memory:

Change in memory is one of the most common cognitive complaints between elderly individuals. The consequence of ageing is not equal in all aspect of memory.[29]Long term memory remains comparatively conserved in old age. Short term memory or the development of new memories, is more affected in ageing. Healthy ageing can not be held responsible for disorder of memory by itself on the contrary it is related with general debility in neural and cognitive systems.

During ageing the neuronal connections and synapses starts weakening or deteriorating, which affects the retrival of memories.Because of the ageing white matter starts degenerating due to reduced blood flow with reduction in neurotransmitters. Both of these results in decline in thinking ability and memory.

Formation of neurofibrillary tangles, beta amyloid plaques and neurochemical changes during ageing is responsible for memory decline. According to decline theory it can be said that if memory is not retrieved or exercised often, it get deteriorated .Environmental factors such as exposure to toxins, faulty life styles helps in accelerating memory decline. Pathology of some age related disorders as well as few drugs like beta blockers, statins etc.used for the treatment of these diseases can cause memory decline.

These age-related memory changes also can be connected to slow processing speed.[30] Ability to get distracted fast, diminished activity to ignore irrelevant things, rapidly decreased use of strategies to improve learning and memory, reduced ability to ignore irrelevant information. [31]

Genetic changes:

Though the individuals intelligence is most of the time genetic, but along with genetic factors environmental factors play impotent role in deciding whether that person would be dazzling, smart or not. With the help of genetic research one can look for genetic as well as environmental role to healthy cognitive ageing. Research studies on cognitive ability and genetics has reported that genetics plays a major role in cognitive

ageing.[32,33] Researchers have identified few genetic markers which are associated with cognitive functions in elderly as well as with demented individuals.

These markers are:

Apolipoprotein E (APOE) , Cathecol-O-Methyltransferase (COMT), Kidney and Brain-expressed protein (KIBRA), Calsyntenin (CLSTN), Brain-derived Neurotrophic Factor (BDNF)

During ageing rise in certain type of genes is seen specifically APOE gene Interaction among the genes determines the cognitive ability in elderly.[34]Recognizing genetic variant will found to be a great help finding the most effective ways for treatment and prevent ion of diseases like AD.

Ageing and cognitive abilities:

Changes in structure and function of brain differ across the whole brain. They are also not uniform in all individuals and in all cognitive domains. As a result of diminished sensory capacities perception also declines. Along with this memory and attention are the domains where ageing affects more.Processing speed also get affected due to ageing. Higher-level cognitive functions like language processing, decision making may also be affected in ageing. Because of this individual may not perform cognitive tasks well in ageing.

Normal ageing and neuronal viability:

Until recently, it was widely accepted that neuron death was an inevitable result of normal ageing. This conviction was spawned primarily by a few influential papers from as early as the 1950s that demonstrated significant neuron death in aged humans in the absence of AD, as well as in nonhuman primates and rodents. These studies reported disparate results with respect to degree of neuron loss, but as a group, their data suggested that most neocortical areas and certain hippocampal subfields lose 25 to 50% of their resident neurons with age. There is no neuron loss in nondemented elderly humans in the EC or CA1, the two hippocampal regions most directly implicated in

memory function, but there is some age-related neuron loss in the hilus of the dentate gyrus and the subiculum.

Fig. 4 Young vs Old Brain (Image source - Google images)

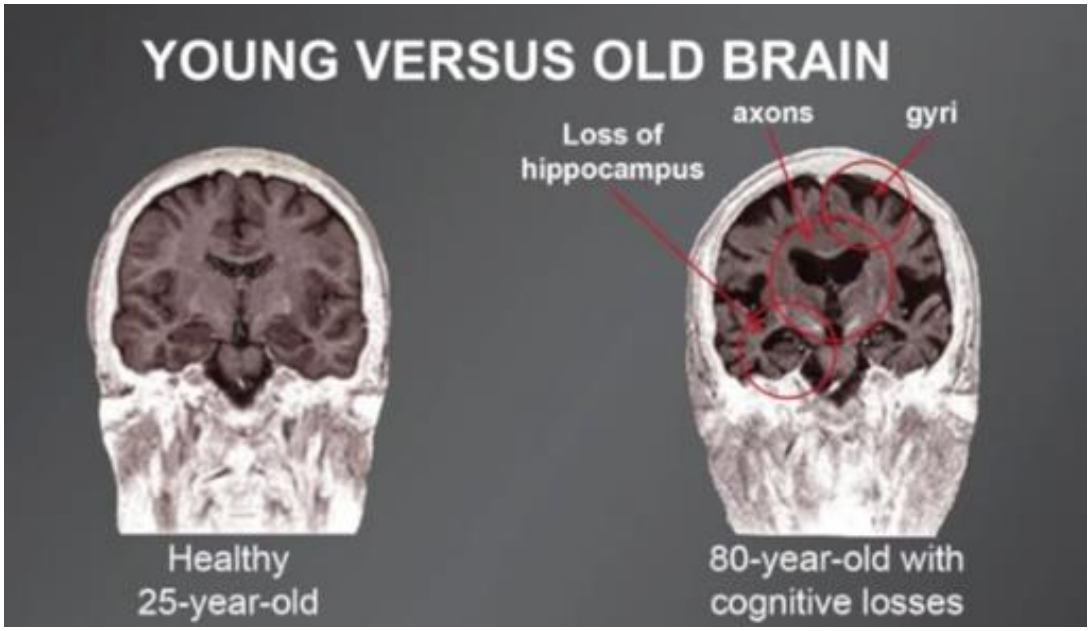
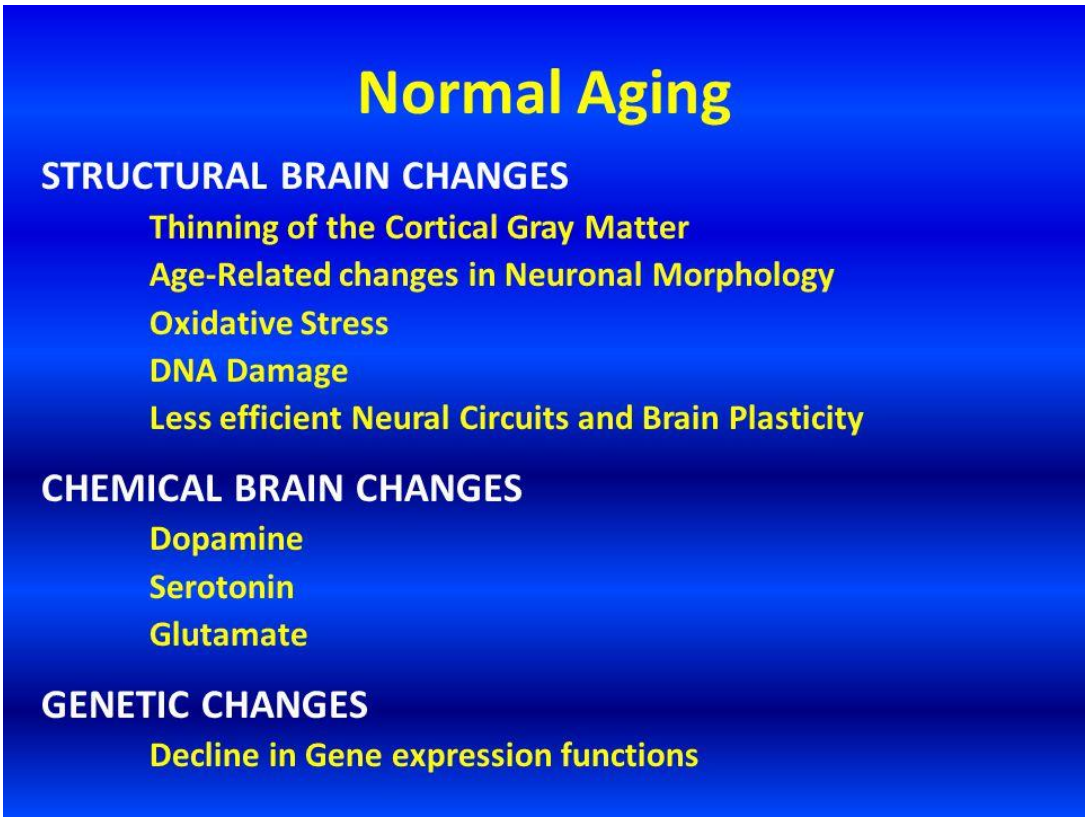


Table 5. Normal ageing changes in Brain



2.2.3 - Mild cognitive impairment (MCI):

The field of ageing and dementia is focusing on the characterization of the initial stages of cognitive impairment. Researchers have identified a transitional stage between the cognitive changes of normal ageing and Alzheimer's disease (AD) known as "Mild cognitive impairment" (MCI).Individuals having mild memory problems, less severe than dementia were evaluated in memory clinics for long time period.The concept of MCI was developed from this evaluation study only.It was observed by doctors in memory clinics that elderly individuals suffering from mild cognitive decline did not fit into the "two cognitive domains impaired" criteria required for an NINDS/ADRDA diagnosis of AD , hence such cases were quoted as MCI.[35,36]

Amnesic MCI (aMCI) was the most common type of MCI found in the epidemiological study.Understanding the complete neuropathological status of individuals with MCI will be essential for appropriate therapeutic interventions and realistic expectations for slowing or stopping the clinical decline.

Average life expectancy has been extended with the improvements in health care over the past 50 years, which in turn resulted in a substantial increase in the numbers of individuals over 65 years of age. Many elderly people complain of impaired memory and perform less well than the younger one in various cognitive tasks, particularly those tasks that assess memory; these findings suggest that memory impairments are a common consequence of the ageing process.[37]

One of the research reported that 14% elderly person above the age of 70 yrs. had dementia[38] and almost same number of individuals had unambiguous mild cognitive impairment which did not meet the dementia criteria.[39] Persons with moderate to severe dementia are generally brought to medical center because their care needs attention.[40] Milder forms of cognitive impairment, however, present alarming conceptual and practical challenges in detection, by primary care physicians.Research also shows that to a large extent, the age-related cognitive decline reveals the inclusion of persons with incipient dementia.[41] The concept incipient dementia which is common among aged persons is further supported by neuropathological studies that inform evidence of AD years prior to the clinical symptoms.[42,43]

To identify early signs and symptoms for early diagnosis of dementia and related disorders ,much effort were put in the field of research in the last decade so as to identify prognostic markers of disease development.Early identification would allow the execution of research to verify whether and which interventions at the early stages can alter the natural history of the disorder.On the other hand AD pathology is much common in persons with memory impairment but no dementia.Research studies reveals that elderly individuals with memory impairment gets converted to AD more rapidly, the conversion rate is as high as 15% per year. Such evidences suggests that considerable memory impairment, no dementia and frequently indicated as MCI , in elderly people may be a transition phase between the normal ageing process and AD.[44,45]

Even though many individuals with MCI complains of memory decline, impairments in other cognitive domains also takes place and not all MCI patients progress on to convert in to AD.[46] Recognition of MCI suggest possibilities for early diagnosis and possible treatment with the intention of delaying the onset or preventing dementia.[47]The thought of ageing effects against disease is not new; in 1962, Kral bring in the view of “benign” versus “malignant” senescent forgetfulness to identify differences between stable memory complaints of elderly people and those that potentially point out early disease.[48]

The term MCI was introduced in 1980s by Reisberg and colleagues to differentiate individuals at the transient stage between ageing and dementia. After detailed observational study of ageing, in 1999 Petersen et al. extended this concept further with proposed criteria.This development helps to create clinical awareness and stimuletion about the concept of cognitive impairment as well as dementia in health professionals and public also.Extension of the concept and criterias internationally, from earlier versions took place in 2003.

This new international criteria was designed after many clinical trials and so broadly developed that it could include all the cases at intermediate state of cognitive decline at any stage and clinical and research effectiveness. This helps in undertaking several clinical, pharmacological, epidemiological trials on this subject resulting in acceptance of concept and awareness creation among the people and medical professionals.[49]

Definition of MCI:

Research and clinical findings reveals that dementia may have a prolonged prodromal phase which has directed the clinicians for meticulous investigation of persons having cognitive impairment but no dementia. Hence thorough work in this field has created many definitions.[50.51]

Petersen and colleagues have used the term MCI to define "individuals with symptomatic and progressive memory impairment that shares many features with early AD''[52]

Initially an MCI was defined(by Mayo clinic) as decline in memory and cognitive performance along with objective episodic memory decline with no dementia and with preserved activities of daily living. This very first definition was more concentrating on memory issues observed as prodromal symptoms of AD. Decline in other domains was not considered here.As MCI has heterogenous etiology and not all MCI leads to AD, a definition with broader view considering all domains was needed here and was put forward.

Recently critrias for DSM-5 including mild neurocognitive domains are released which resembles closely to MCI in following way; [53]

i. Clinical concern raised by the patient or an informer, or observations made by the clinician

ii. Cognitive impairment in one or more cognitive domains preferably relative to appropriate normative data for that individual.

iii. Functional independence preservation.

iv. No dementia.[54]

After evaluation of these available definitions it can be concluded that, in general definitions can be divided into definitions focusing predominantly on memory impairment and other that include various degrees of impairment within all cognitive domains.

Prevalence of MCI:

An increasing number of studies have been conducted during the last decade in an attempt to estimate the prevalence of MCI in the common people. In the beginning the frequency of MCI in the population was taken too lightly, as well as its incidence amongst persons with healthy cognitive functioning. Certainly, the first round of epidemiological investigations of MCI accepted the original Mayo clinic MCI criteria which were restricted to isolated memory impairment. In further studies the expanded MCI criteria have been used, creating considerably higher estimates. The main population-based research studies using the expanded Mayo Clinic criteria shows the average prevalence of MCI is 18.9%.[55]

Research studies put forward that these individuals tend to progress to probable AD at a rate of around 10% to 15% per year. As per 'Alzheimer's disease International' there are 35.6 million individuals living with dementia globaly in 2010, increasing to 65.7 million by 2030 and 115.4 million by 2050. Thus it is most important to control this progress of cognitive decline before it crosses the doorstep to dementia

Prescribed researches of the prevalence of memory complaints within the community differ greatly, from 22% to 56%.This variation is related to questionnaire used and to the average age of the population studied .Other factors such as sex, education, other diseases appear significant as well.[56] Regardless of the influence these variable definitions may have the exact prevalence of MCI among elderly people.All the definitions have two main features. First one, the age-specific prevalence of MCI is greater than that of dementia, and MCI is about four times more common than dementia when considered on population assessment of non-institutionalized individuals.Next, in spite of the wide range of definitions used, older individuals with any cognitive impairment are at considerably greater risk of future conversion to dementia. Present evidence suggests that even within a cautiously defined syndrome such as amnesic MCI, there might be both clinical and pathological heterogeneity.[57] Studies reports that the rates of MCI vary from 3 to 17%, it being 3% at 60 years to 17% at the age of 75. One research study says that the rate of development of MCI was about 5.3% per year.[58.59]

A community-based study in Kolkata, India, determined the rates of prevalence of aMCI to be 6.04% and that of multiple-domain subtype to be at 8.85%, with males having a predominance of aMCI and female having multiple-domain MCI. 15 per cent prevalence MCI among individuals aged 50 yrs. and older, multiple-domain MCI being the major prevalent subtype (8.9%) is revealed by a cross-sectional study in India.These findings are similar to the reports from studies performed in developed countries, and were shown to be significantly associated with increasing age, hypertension, and diabetes mellitus.[60]

Pathophysiology of MCI:

Inspite of many advances in clinical definitions of MCI, diagnosis of MCI or NCI on the basis of brain autopsy is still challenging.Despite of the continuous efforts placed on recognizing the candidates of MCI and its progression to AD, very few is known about its pathology and pathophysiology.The results from recent study by Yan et al. showed decreased effective connectivity among the hippocampus (HC), middle temporal gyrus and fusiform gyrus, as well as between the precuneus / posterior cingulate cortex and HC in patients with amnesic MCI.[61] Sulcal widening in the superior frontal and superior temporal sulci is accelerated in MCI patients.[62] Current evidence shows that neurofibrillary tangles (NFT) density is also greater in MCI than in normal cognitive ageing, even though no variation in the density of amyloid plaques were observed. Density of NFTs in temporal lobe has strong association with memory dysfunction.[63] NFTs distribution is initially largely restricted to the hippocampus and entorhīnal cortex and slowly spreads with disease progression.[64]

Nho et al., in a research study, observed strong associations between AD Neuroimaging Initiative (ADNI) topography of memory and atrophy of lateral and medial temporal lobe. Reduced ADNI-Exec. scores were associated with advanced GM and cortical atrophy across broadly distributed regions, especially in the bilateral parietal and temporallobes.[65] Individuals having executive dysfunction MCI shows thinning in posterior cingulate cortices and bilateral dorsolateral prefrontal.Various diseases can lead to cognitive impairment in the absence of dementia, principally when cognitive impairment is defined as CIND.

MCI and AD:

MCI has motivated rigorous investigation of the pathological processes that could lead to this state of cognitive impairment. Although there was a lot interest in the prodromal phases of AD even before MCI was firmly defined. Studies suggest that age-related increase in the density of neurofibrillary tangles in the hippocampus and entorhīnal cortex are a feature of normal ageing.[66] Some studies shows that senile plaque density and neuron loss are the most important features that differentiate healthy ageing from dementia. Morris and Price in their study on 46 subjects with clinical dementia rating scores of 0·5 (called "very mild AD" by the investigators but similar to MCI) had signs of pathology of a severity between the patients in the early stages of AD and normal elderly individuals. These findings suggest direct correlation between amnesic MCI and early AD pathology.[67]All this observation have been done from the group of patients who had no or minimal cerebrovascular disease or other systemic illness. Additionally Nuns Study supports for the above relation. The study shows that the relation between clinical symptoms and neurofibrillary-tangle pathology was firm in the memory impaired group, prove the relation between AD pathology and amnesic MCI.

MCI and Cerebrovascular Disease:

Cerebrovascular disease are highly prevalent among elderly people and the evidence suggesting that, it may contribute strongly to dementia. Cerebrovascular disease on cognitive impairment among elderly people has been explored by several studies.[68]Many studies showed that individuals having MCI showed considerably increased incidences of vascular risk factors and evidence of vascular brain injury. These outcomes suggest that cerebrovascular disease is significant to memory impairment.

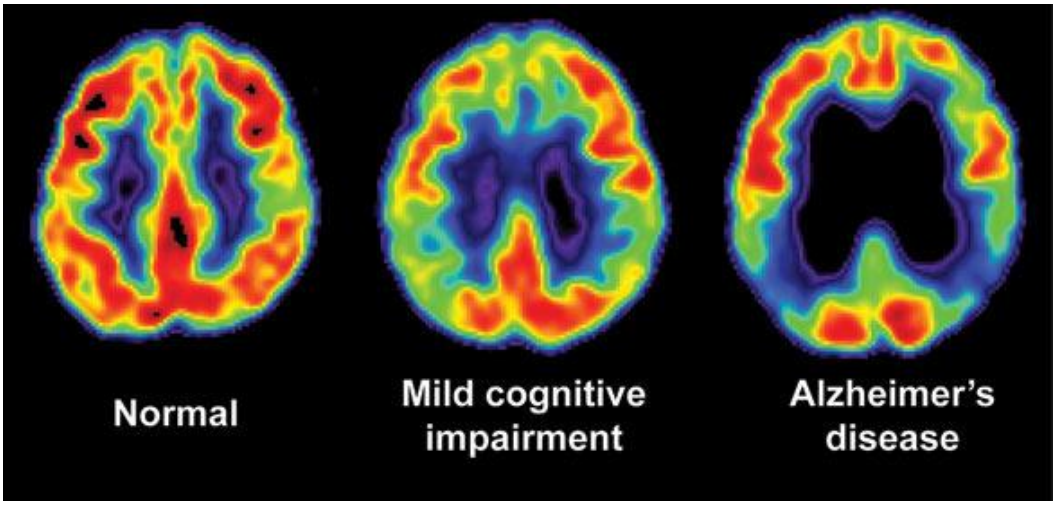
In the absence of macroscopic infarctions also, persons with confirmed severe atherosclerotic disease in the circle of Willis were at considerably greater risk (relative risk >3) of memory- related MCI. Because white-matter-hyper intensity volumes are linked with extracranial carotid-artery illness.[69] These findings support the assumed pathophysiological link between clinical and imaging evidence of cerebrovascular

disease and the etiology of the related cognitive impairment.Even though it is assumed that a number of diseases cause CIND in the general population, pathological heterogeneity amongst cognitively impaired aged populace is even apparent within carefully identified subgroups of individuals eg, those with amnesic MCI.

Gross pathological changes in MCI:

Neurotic plaques and neurofibrillary tangles (particularly in the entorrhīnal cortex and hippocampus) along with amyloid deposition are the gross pathological changes in MCI.

Fig. 5 Brain changes -normal / MCI /AD(Image source –Google images)



Gross morphological features of MCI:

Widening of sulci, such as the ventral ramus of the lateral fissure is found in aMCI and mild AD.In the end stage of AD these morphological changes are exaggerated and extended to additional cortical regions

Amyloid pathology in MCI:

Amyloid beta (Aβ) plaques in brain, are a characteristic lesion of individuals having clinical diagnosis of MCI. Gradually the distribution of Aβ deposits changes and spreads.[70] Subjects having dementia rating (CDR) scores of 0.5 (questionable dementia/MCI) showes significant rise in the diffuse plaque density in temporal cortex. As the severity of the disease increased the proportion of plaques shifted from diffuse to neuritic with increase in density.[71]

Neuronal loss in MCI:

Various studies have observed the change in number of neurons in MCI.Due to neuronal loss reduction in the number of synapses takes place. In very mild AD or can say in MCI where CDR is 0 to 0.5 ,neuronal numbers were significantly decreased in the entorhīnal cortex and hippocampal CA1 subfield.This suggest that atrophy of neurons and their death already starts at a time as individuals starts to notice clinical symptoms .[72]

Neurofibrillary Tangels in MCI:

When hyperphosphorylated forms of the protein tau are aggregated neurofibrillary tangles are composed.These tangles are argyrophilic revealing the beta fibular configuration .Broadly it can be said that neurofibrillary tangles are notably increased in the entorhīnal cortex, amygdala, subiculum and the inferior parietal cortex in MCI than the normal individuals signifying that these tangels are significant for the evolution to MCI.[73]

- Structural Changes in Medial Temporal Lobe:

In early aMCI, atrophied entorhīnal cortex and hippocampus was seen more than seen in cognitively healthy subjects.[74]Research shows a considerable loss in synaptic contacts in the inferior temporal cortex in aMCI as compared to healthy persons.[75]

- Synaptodegeneration In The Hippocampus:

Considerable decline in the plasticity found, which is related to post-synaptic density protein in the hippocampus; a vital component of a trisynaptic memory circuit in aMCI with no Dementia.[76] F-actin and drebrin are the postsynaptic binding protein

involved in synaptic plasticity. These proteins are found to be decreased in the hippocampus of MCI patients.[77]

Fig.6 Healthy vs Damaged Neurons (Image source-Google images)

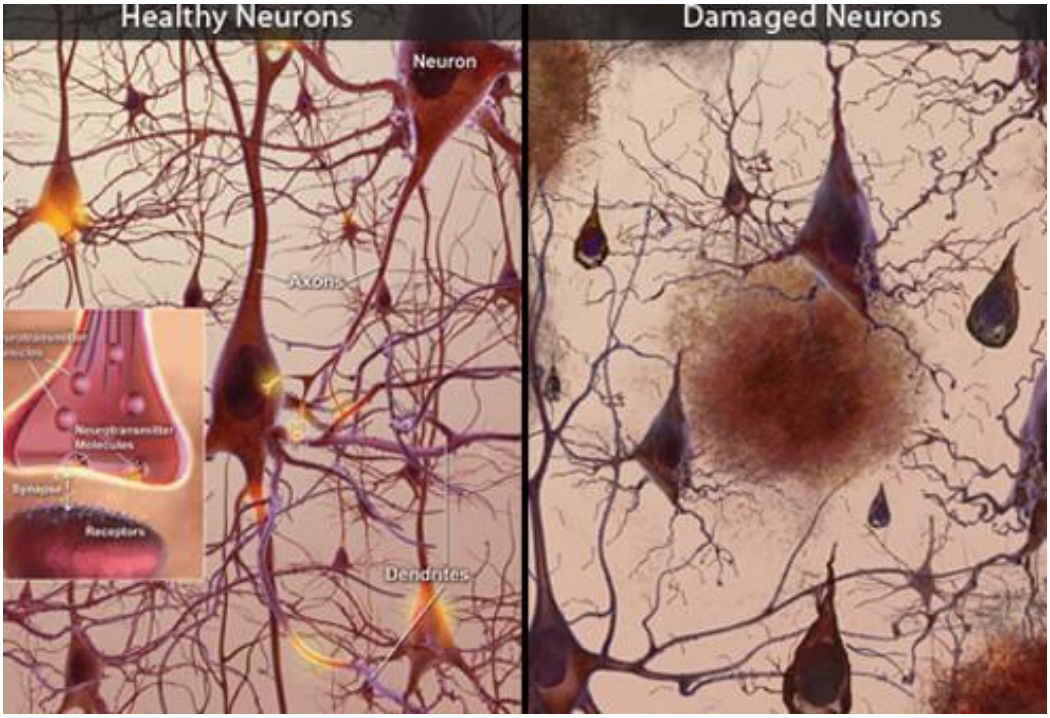
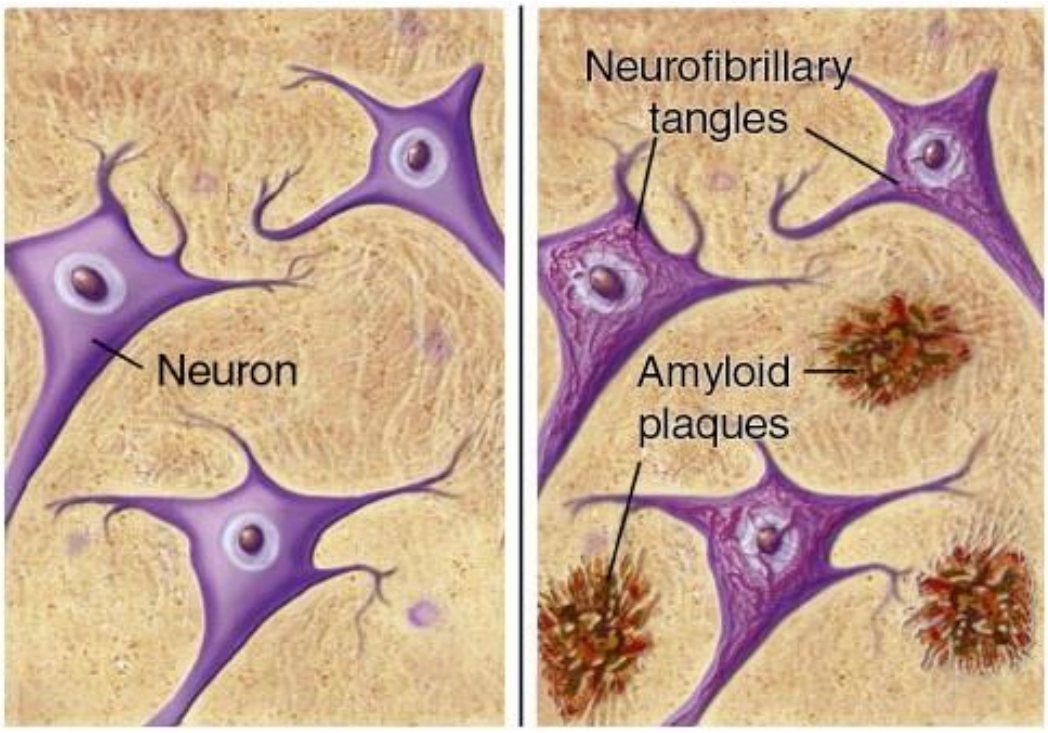


Fig. 7 Healthy vs MCI Neurons (Image source-Google images)



- Cholinotrophic basal forebrain system in MCI:

Sizeable neocortical deficits in the enzyme accountable for the synthesis of acetylcholine (ACh), choline acetyltransferase (ChAT) is found in the individuals of AD. This was followed by the report of reduced ACh release and choline uptake, loss of cholinergic perikarya from the nucleus basalis of Meynert. From the above research it was proposed that the related loss of cholinergic neurotransmission in the cerebral cortex and other areas contributed appreciably to the decline in cognitive function seen in patient of AD. Not only this, some finding also showed eleveted ChAT activity in the superior frontal cortex and hippocampus in MCI individuals.[78]

- Neurotrophic abnormalities in MCI:

Abnormal levels of neurotrophic factors (BDNF, NGF, and GDNF) at baseline predict the transition from MCI to dementia. Decreased neurotrophic support results in AD, including its prodromal stages.Research showed considerably lower serum concentrations of BDNF, NGF and GDNF in cognitively impaired persons i.e., MCI and AD as compared to healthy controls.[79]

- Oxidative stress in MCI:

Oxidative stress is extensively involved in the pathology of degenerative Alzheimer's and other dementias even in the early stages of the diseases. Not only in typical AD subjects but also in individuals with MCI, CSF Aβ42 levels are significantly reduced in comparison with healthy adults. This reveals abnormal amyloid metabolism, signifying the development of some tiny amyloid plaques in the cortex and the hippocampus. Simultaneously or afterward, total tau levels; particularly p-tau levels found predominantly increases in AD patients comparing to healthy controls.

Incidentally, numerous research studies indicate that endosomal and oxidative stress dysregulation are amongst the initial pathological changes observed in hippocampal CA1 pyramidal, cortical and NB CBF neurons.[80]Before clinical symptoms these dysregulations appear earlier to substantial deposition of cerebral amyloid, vascular amyloid and tau pathology in AD.[81]

Biological markers:

As MCI is clinically and pathologically heterogeneous, biomarkers may be particularly useful for recognizing subtypes. The use and study of biological markers will improve diagnosis and early detection of underlying neuropathology as well as offers tool for the evaluation of treatment benefits. In this background, the ideal biomarker would provide at least two intentions.

- Biomarker would allow early diagnosis, which relates to early recognition of pathophysiology for early intervention and disease modification.
- Biomarker should enable evaluation of objective treatment benefit to adjust the therapeutic regimen according to patient response.

Biomarkers of Alzheimer's disease can also be useful for MCI:

Presence of Alzheimer's disease (AD) pathology and AD-associated neuronal injury in vivo is indicated by number of biomarkers.These biomarkers may be highly usefull in etiology determination, looking after disease progression and prediction of disease prognosis in clinical use as well as in research field. These are the Biomarkers of brain amyloid pathology: amyloid imaging, Cerebrospinal fluid Aβ42 levels, Biomarkers of neuronal injury: CSF tau & phosphorylated tau levels, Volumetric MRI, Fluorodeoxyglucose - PET.

To find out whether MCI is due to AD pathology, biomarkers are currently suggested only for academic, medical research studies. In this background, biomarker support can be used to create likelihood that MCI takes place from AD pathophysiology, with three levels of certainty: MCI is very possibly to be due to AD when both classes of biomarker data are positive; MCI has transitional possiblity of underlying AD when only one class of data is positive and the other is not possitive; MCI is not likely to be due to AD when both classes are negative. Contradictory biomarker evidence is measured uninformative on etiology.

Progression of CIND definitely:

Rate of memory impairment and progression to dementia is variable. The variation in rates of conversion to dementia for persons in the clinical trials performed till today; may be due to selection bias, since study groups are more likely to include subjects with early AD.

Though it is so evidences suggest that individuals having memory impairment specially age associated, have possibility of future dementia.This association may, on the other hand, reveal inclusion of subgroups of person who are both cognitively and genetically alike to persons with amnesic MCI. Very little research work has been done on non-demented persons considered to have cognitive impairment due to cerebrovascular disease. Preliminary evidence, however, in the Canadian Study of Health and ageing suggests 50%individuals having vascular pathology progressed to dementia. This percentage is almost equal to that for individuals with amnesic MCI.Also not all CIND person progress to dementia.

Predictors of progression:

Elevated systolic blood pressure and increased cholesterol levels,[82]impairments of memory and executive function,[83]white-matter lesions on magnetic resonance scans[84]and the possession of the apolipoprotein e4 allele are the factors which predict the progress of dementia in the normal population.[85]Numerous studies have observe clinical and imaging predictors that can improve the ability to detect individuals at the risk of conversion to dementia within 1–3 years of diagnosis of aMCI.[86] Quantitative MRI studies with MCI persons suggests that hippocampal atrophy is present before dementia onset and progresses with conversion to clinically noticeable disease.[87]

A double blind, placebo controlled clinical trial on aMCI found that percentage of persons progressing to Dementia within 5 yrs.was 4 times the normal individuals; when size of hippocampus was 2.5 standard deviations below standards described for age and sex.[88] From this very concise evaluation of imaging and clinical predictors of transmition from aMCI to dementia various studies suggests that if the individuals' cognitive ability, brain imaging, and genetic susceptibility are more close to AD, the more possiblity of them to progress rapidly to dementia, especially if the cognitive

complaints are informed by family.[89] These clarifications support the concept that this particular form of MCI indicates early AD.

Predictors of conversion from vascular MCI to dementia have been studied less. But research data suggests that corroboration of features linked with AD in the vascular-MCI group can be a stronger predictor of conversion to dementia than associated measures of vascular disease.It has been reported that increased rates of progression to dementia for those individuals with extensive abnormalities of cerebral white matter. More careful longitudinal study of the effect of vascular disease across the cognitive domains reveals that measures of brain and hippocampal atrophy are more strongly related to progressive cognitive decline than lacunar infarcts or abnormalities of cerebral white matter.These data suggest that corroboration of features associated with AD in the vascular-MCI group may be a stronger predictor of conversion to dementia than associated measures of vascular disease.[90]

Etiology of MCI:

The causes of mild cognitive impairment are however not fully understood. Expert consider that not all but many cases result from brain changes occurring in the very early stages of AD or other dementias.Various different causes are responsible for MCI. Some of theme is treatable and some are not.Existing data indicates that MCI frequently, but not always, occurs from a minor degree of the same types of brain changes seen in AD or other types of dementia. With the help of autopsy studies of people with MCI some of these changes have been recognized. These changes comprise:

- Abnormal cluster of beta-amyloid protein (plaques) and microscopic protein bunch of tau characteristic of AD.
- Lewy bodies, the microscopic cluster of another protein associated with Parkinson's disease, Lewy bodies and some cases of AD.
- Reduced blood flow through blood vessels of brain or small strokes.

Brain-imaging studies show that the consequent changes may be linked with MCI:

Shrinkage of the hippocampus, enlargement of the brain's ventricles, and reduced use of glucose, which is the primary source of energy for cells.MCI can also have a different, often treatable causes. This can be consisting of anxiety, depression or stress. Some physical illness, poor eyesight or hearing, vitamin or thyroid deficiencies or the side effect of some medications.

In older persons, AD is the most common cause of MCI and mild dementia. Amnesic impairment is most usual for AD whether in the MCI or mild dementia stage. With advancing age cerebrovascular disease causes brain infarctions and happen to be more common as well. The frontotemporal degenerations are rearest degenerative dementias, but they also can create an MCI syndrome. Use of multiple medications and adverse effects of drugs can sometimes produce cognitive impairment.

Diagnosis:

MCI is a "clinical" diagnosis characterizing a physician's finest professional judgment regarding the explanation for an individual's symptoms. CSF test, brain imaging tests and other biomarkers test may be carried out in case of confusion in diagnosis.

Following points found useful to reach the diagnosis of MCI:

Meticulous medical history, Contribution from a family member or friend to give additional information about development and change in symptoms.Assessment of independent function and daily activities, Evaluation of mental status.Neurological and psychological examination specially examination of mood. Neuropsychological tests, laboratory tests like some hematological and radiological investigations.

The diagnostic criteria for MCI holds memory complaint, abnormal memory function as compared to what is predictable based on age and education, preserved general cognitive function, intact activities of daily living and absence of dementia.[91] To differentiate between normal ageing and mild cognitive impairment Neuropsychological assessment has proved sensitive.[92]

For the diagnosis of MCI following signs, symptoms are essential.

- In comparison with the person's previous level change in cognition, observed by family or nearer.
- Objective evidence of decline in performance in one or more cognitive domains which is more than expected for the age and education of individual.
- Daily activities are not interfered considerably, even though complex functional activities such as paying bills, preparing a food or shopping, may require more time or may be executed less competently. With minimum aid support independence in daily living is preserved.
- Can not explained by dementia or delirium or prime psychiatric disorder.[93.94]

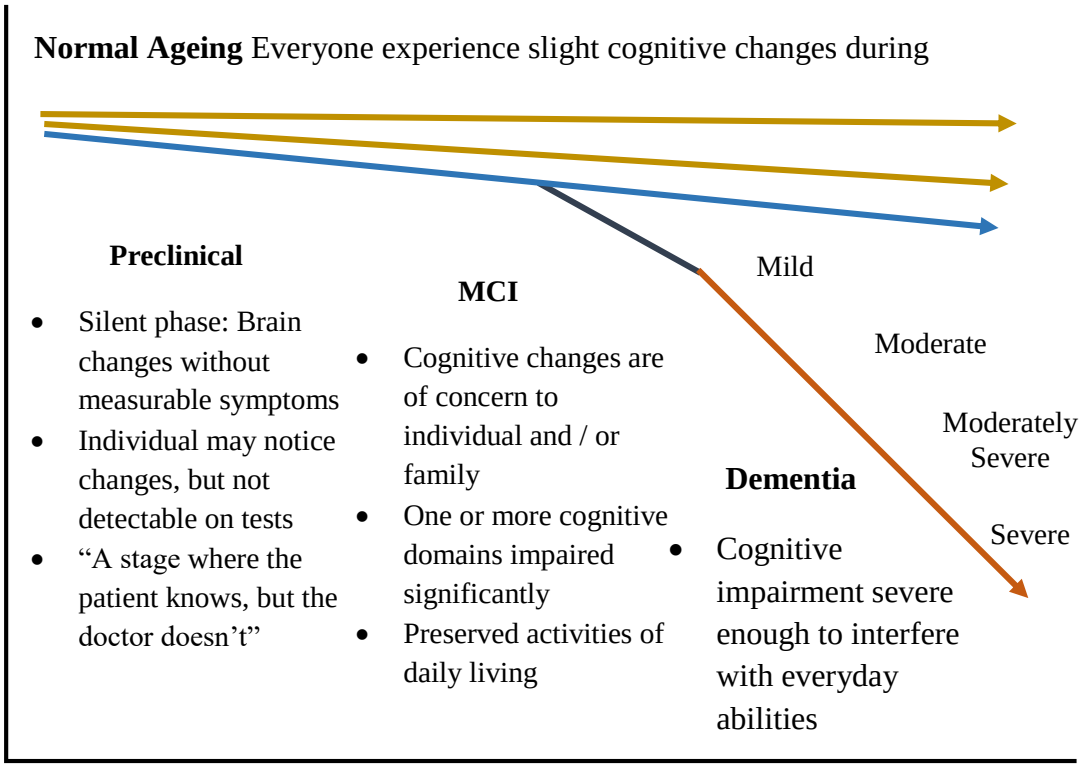
Cognitive functioning is typically characterized into these domains: learning and memory, language, visuospatial, executive and psychomotor. These domains have a coarse connection with their cerebral localization. Only one of these areas have to be impaired for a diagnosing MCI, whereas a diagnosis of dementia requires that more than one domain must be impaired. Involvement of domain can be obtained from meticulous physical, psychoneurological history and examination.

However, when events of forgetfulness or misplacing become frequent, suspicion should be high that there is more than just normal forgetting. Similarly, frequent re-asking of questions is much more likely to indicate substantial memory impairment.[95]The commonest most primitive symptom of pathologic cognitive impairment in the elderly is declining efficiency of memory, often represented by re-asking of questions. The most common earliest manifestation of pathologic cognitive impairment in the elderly is declining efficiency of memory, often exemplified by re-asking of questions.To understand the boundry between normal and abnormal in the specific subject ,is the challenge for the doctors.

In naMCI, finding words and difficulties in speech, disturbed orientation, impaired visual perception and impaired mental alertness are the features. Risk of progression to dementia is higher in multi domain MCI than MCI having only word finding or memory problems.

For diagnosis of MCI medical history and mental status exam are the utmost important tools.A general neurologic examination is necessary to understand the cause of the cognitive decline.A meticulous history from the care taker is essential for judgement and diagnosis.In addition to this, medication history is very important as many drugs; their interaction,; their adverse effects have potential to impair cognitive functions. Clinical judgment is required to integrate information from the various sources. Radiological investigations and blood tests are of importance as they help to evaluate the patient. Though laboratory blood tests have minimal role in diagnosis, but they can be useful in detecting the etiology of cognitive decline. For the diagnosis of MCI the American Academy of Neurology suggested a easy set of laboratory tests and a brain imaging study.[96] Like Serum B12, thyrotropin levels, MRI or CT to rule out evidence of cerebrovascular disease, subdural haematoma, brain tumors etc.or the side effects of some medication. Of course above all this, clinical judgment is essential to integrate information from the sources.

Fig. 8 Cognitive changes in normal ageing, MCI, Dementia



Types of MCI: [97]

Based on cognitive features

This can be further divided into:

Amnesic MCI (aMCI):

Memory domain aMCI-Memory only impaired.

Multiple-domain aMCI- Memory & another domain also impaired.

Non-amnesic MCI (naMCI):

Single non-memory domain impaired

Multiple non-memory domains impaired

Based on etiopathology:

Neurodegenerative: (MCI, Pre-Alzheimer's, Lewy Body, Fronto-temporal or focal atrophy)

Vascular: Vascular dementia and mixed dementia.

Dysthymia or dysphoria (anxious and/or depressed states)

Fig. 9. MCI Types

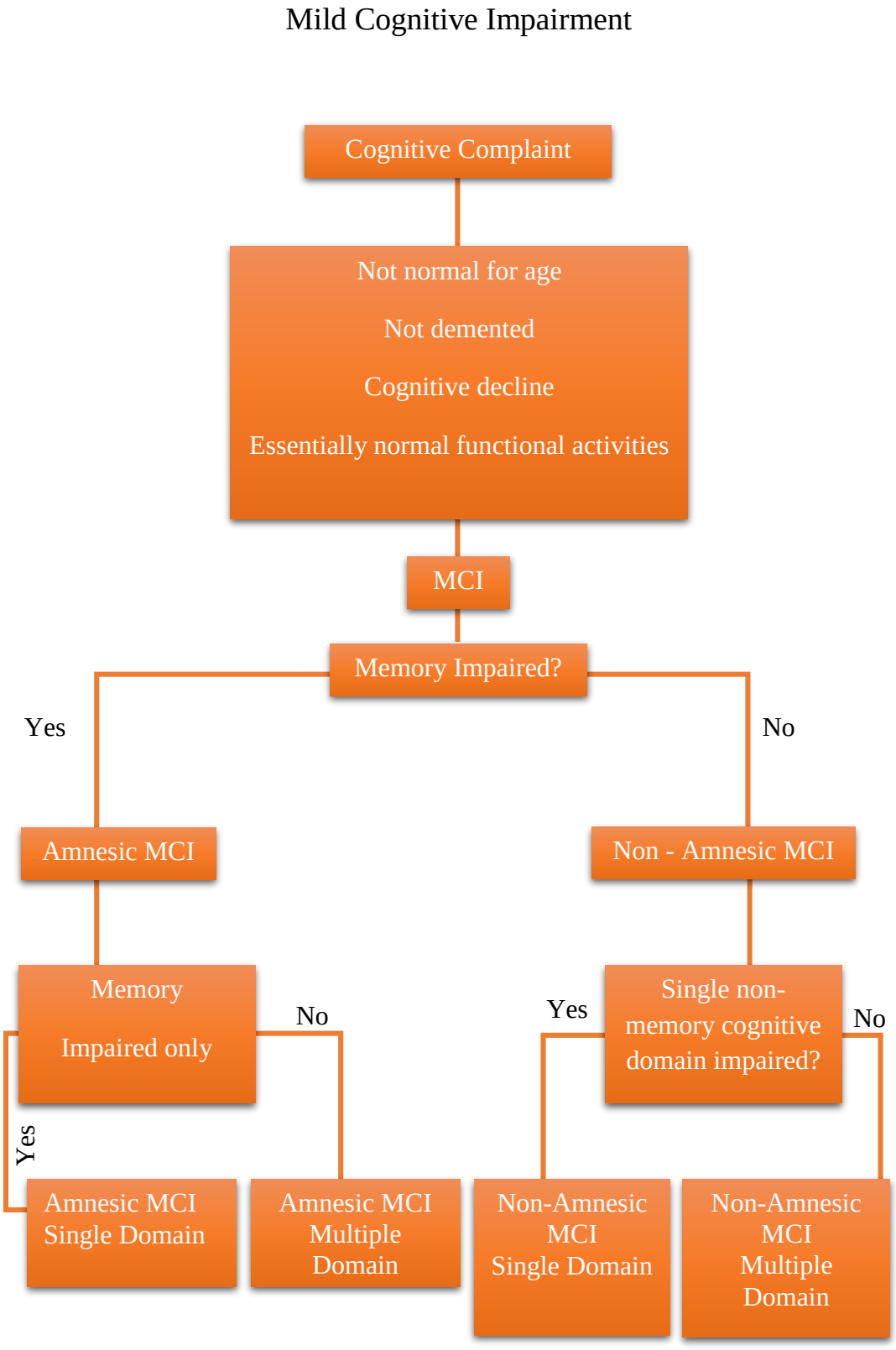


Fig. 10 Grouping of MCI subtypes with etiology.A-aMCI,B-naMCI

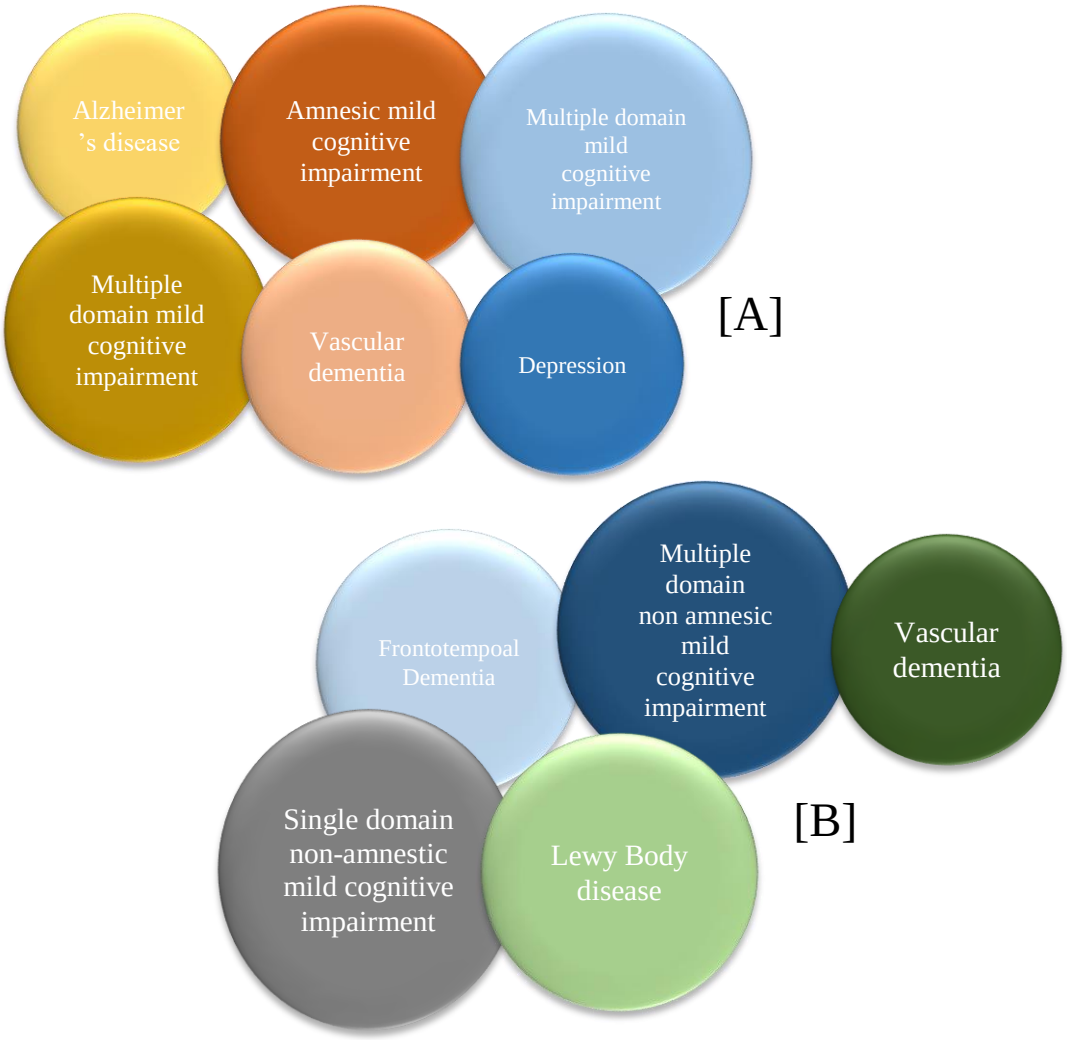


Table 6. aMCI & naMCI(Image source-Google images)

Variable	aMCI	naMCI
Etiology	Neurodegenerative disease	Vascular damage
	APOE ε4	Cerebrovascular disease
Pathology	Neurodegenerative	Cerebrovascular
	Amyloid β plaques	Cortical infarctions
	Neurofibrillary tangles	Subcortical infarctions
	Hippocampal atrophy	White matter hyper intensities
	Reduced brain volume	
Presentation	Memory impairment present	Impairment in non-memory domains Preferably
Long term outcomes	Alzheimer's dementia (AD)	Non-Alzheimer dementias: Vascular dementia
		Lewy body, Frontotemporal

Absence of memory impairment along with existence of impairment in one or more non-memory cognitive domains comprising executive function,attention, language and visouspatial skills domains is characterized as non-amnesic MCI (naMCI) while the clinical presentation with memory impairment is characterized as amnesic MCI (aMCI).

MCI may have impairment in a single cognitive domain or multiple cognitive domains. To understand the degree of the underlying brain pathology, disease severity and possibility of progression to dementia, the number of affected domains has important inference. If there is an underlying degenerative etiology single or multiple domain MCI is assume to progress to AD. In contrast, naMCI may develop non AD dementias such as fronto-temporal dementia when single domain is affected or Lewy bodies' dementia in multiple domains affection with a degenerative etiology.

Petersen et al. defined aMCI criteria are as follows.[98.99]

- Subjective memory complaint, if possible notified by an informant.
- Memory impairment relative to age and education matched normal subjects.
- Comparatively normal general cognitive function.
- Essentialy intact activities of daily living (ADL). IADL may get hampered little.
- Not demented.

Signs & symptoms of mild cognitive impairment (MCI):

Characteristically, memory complaints include trouble remembering the names of people they met recently, difficulty remembering the flow and topic of a conversation and an increased tendency to misplace things or problems likewise. Individuals may forget things more frequently. Or forget essential events such as appointments or social engagements. They may lose the chain of thoughts or the flow of dialogue, books etc. May feel increasingly disturbed by making small decisions, scheduling steps to carry out a job or understanding instructions. Subjects may have troublesome feeling to find the way about familiar environments. One may become more spontaneous or

demonstrate increasingly poor judgment. Family and friends of the patients may notice any of these changes.

Many times, the individual may be fairly aware of these troubles and may compensate with the habit of increased dependence on notes and calendars and diaries. These findings reflects the picture of AD, but less severe than the neuropsychological symptoms related with Alzheimer's disease.

Assesment of MCI:

For the verification, if a person is merely ageing in a healthy way or if he is on the way to AD cognitive assessment is necessary. One can depend on the family, friends to detect changes in mental health, but an objective evaluation(Memory and cognitive performance advances) must be applied to decide about the areas of cognitive function impaired and upto what extent. Considering this, several assessment batteries are available to determine the globala level of cognitive decline.

For assessment of mild cognitive decline the screening test should be sensitive, specific and validated.However the test which is standardized, reliable and valid, which can be used in busy clinical practice is not still available.[100] MMSE has been very commonly used since 1975 in clinical practice as short and reliable cognitive screening test.[101]However, a meta-analysis about the accuracy of MMSE in screening of MCI, revealed its limition for accurate screening.[102]

Various screening batteries such as Three Word Recall, Abbreviated Mental Test, Brief Cognitive Scale, Cognitive Abilities Screening Instrument, Cognitive Assessment Screening Test, and Clock drawing test, Mini-Cog, Short test of mental status and Rapid Dementia Screening Test etc. were developed and tried for MCI screening. Some were found useful some not.

Addenbrooke's Cognitive Examination (ACE) [103]and its revised version (ACE-R) [104] were developed as a brief test of cognitive functions sensitive to the early stage of dementia. In addition to detection of dementia, the ACE and ACE-R are reported to be useful for detecting MCI and predicting conversion of MCI to dementia.[105]To date, many different language versions of ACE-R have been validated.[106]

Review study shows that there is scarcity of standardized indigenous neuropsychological measures for cognitive assessment of older Indian adults. However, Hindi Mental State Examination[107] and ACE in Indian language [108] have been adapted as screening battery in some studies. Ganguli and colleagues adapted and modified "Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Battery (CERAD-NB)" for Indian participants short in education. [109]But the Indian adaptation of CERAD-NB includes measures of memory and construction and unable to assess some key cognitive functions like attention, executive functioning,working memory well.Despite of its limitation it has been used to evaluate cognitive function of urban elderly people and also to estimate the MCI prevalence.[110] In recent times, for older Indian adults NIMHANS Neuropsychological Battery for the Elderly has been developed and standardized and validated.[111]

To know individual's ability to carry out normal Activities of Daily Living (ADL) is a necessary part of the overall assessment of the individual with cognitive decline, especially dementia and it is vital in determining the diagnosis and in evaluating change. Apart from diagnosis, the extent of ADL performance allows the measurement of treatment effects, care-giver trouble; the targeting of interventions and the clarification of the connection between cognition and everyday functional ability .For this purpose ADL assessment battery should be used in MCI as well as dementia.

To compare quality of life and well-being in relation with every treatment follow up in subjects of MCI, WHO Well being index may be used. Quality of life based on vigor, mood, and general interest is measured with the help of this scale.[112] The WHO-5 Well-Being Index is a valid questionnaire with the aim of measuring current mental well-being .[113]

In addition to evaluating the patient, the caregiver stress can also be evaluated to assess the treatment effects. There are many scales that can be used for this evaluation.Like Caregiving Burden Scale, Caregiver Burden Inventory, Caregiver Activity Survey etc. GERRI is mentioned as effective scale in assessing caretaker's burden and improvement in patient's cognition, mood and social life.

Laboratory investigation and diagnosis:

There is no specific test to confirm a diagnosis of mild cognitive impairment. Clinician has to decide whether MCI is the most likely cause of symptoms, based on the information provided and results of various tests that can help clarify the diagnosis. Blood tests can help rule out physical problems that can affect memory, such as a vitamin B-12 deficiency or an underactive thyroid gland etc. MRI, Diffusion weighted imageing, Functional MRI, PET, SPECT may help in diagnosis, assessing type of MCI and its prognosis.

Structural MRI and CT, SPECT, PET and QEEG are the most frequently studied imaging measures in studies focusing on MCI. There were significant deviation in demographical and clinical characteristics amongst studies.[114]

Structural changes in MCI and early AD seem to be pronounced in medial temporal lobe structures, particularly in the entorhīnal cortex and hippocampus. The earliest functional changes seem to involve the posterior cingulate cortex, the hippocampal formation and temporoparietal association areas. The most important EEG change seems to be an increase in theta frequency.

Considerable reduction in volume of hippocampas and entorhīnal cortex was constantly found in individuals with MCI in comparison with cognitively healthy controls. And also a risk factors for the progress to AD.Research of existing studies shows that neuroimaging techniques may become a valuable tool in MCI and early AD diagnosis. On the other hand factors like easy practicability, cost effectivity, use in regular practice, and larger study with follow up should also be considered.[115]

Treatment of MCI:

As MCI does not trouble the individual greatly, many times question arises that whether to treat MCI or not. But if the symptoms of MCI is distressing somebody, treatment which is safe; tolerable should be given. Though the level of concern varies from person to person, at least symptomatic treatment can be given.Other reason to treat MCI is to prevent future progress to dementia.Since MCI is high risk state for dementia. Another reason to treat MCI is that, many MCI patient already have developed early

AD pathology. And with time the subject may pogress to AD. Hence at this stage treatment is essential to modify and slow down the disease process at its earliest.

Treatment of patients with MCI and mild dementia must consist of encouragement for physical, mental and social activeness.

Nonpharmacological treatment:

- Computer-assisted cognitive training:

Better memory and verbal activity is related with the engagement of individual in stimulating cognitive activities. Several studies have shown that cognitive training improves memory. Though the results are encouraging, still more research study on large groups is essential.

- Long-term group psychological interventions:

The plan may included remembrance, psychomotor and recreational jobs, multisensory stimulation and social communication and interaction along with some daily home work with the involvement of family members.Clinical research showed improvement in global cognition after twenty sessions of memory training, cognitive stimulation, reminiscence, psychomotor recreation and social interaction.[116]

- Exercise:

Exercise has positive effects on neuronal survival and neuronal function, inflammation of nurons, development of new blood vessels, brain amyloid burden and endocrinal response to stress. Exercise also improve cardiovascular strength, which is related with cognitive health.Studies shows the effect of physical exercise on cognition improvent.But there are some studies which failed to show positive effect on cognitive decline.

Even though an analysis of nonpharmacological interventions in MCI or dementia states weak evidences it is believed that mental and physical stimulation should be encouraged for healthy cognitive life.

- Treatment of aggravated and co morbid condition:

Many other disease conditions also can aggravate memory loss in MCI or produce MCI in a healthy person like diabetes mellitus, hypertension etc.These conditions should be treated properly.For example stress, via cortisol levels directly acts on hippocampus as a toxin, which is capable of increase disease related hippocampal memory dysfunction .Long standing depression shows to be a cause for AD.[117] So attempt to reduce stress level in MCI appear to be reasonable goal for the treatment.

- Diet:

Dietary intervention is possible in the treatment of MCI, either for prevention or treatment. Healthy diet helps preventing hypertention, diabetes, stroke like risk factors .Thus helps in prevention of MCI. Increased homocystene levels are responsible for decline in memory. However diet rich with B6, B12 and folic acid decrease the homocystene levels and prevent MCI and dementia and further progress to the disease dementia. Patients having OMEGA 3 fatty acid in diet has shown good results on MCI and dementia. Evidence shows that diet rich in Omega 3 speciallyDocosahexainoic acit shows better performense on cognitive levels.[118]So these techniques also can help in treating and preventing MCI and dementia.

Pharmacological treatment:

The suitable target for pharmacological intervention should be directly related to patient-relevant result of clinical treatment trials. The aim of the treatment should be to improve subjective and more significantly objectively assessable cognitive performance. An additional important objective of the treatment is to prevent the progression of cognitive decline and eventually to delay the conversion of MCI to dementia. It must be noted that prevention of conversion to dementia or even the stabilization of the cognitive status must be consider as achievement in treatment.

It is assumed that most of the MCI patients specially aMCI patients have an AD underlying pathology.Hence it is logical to examine whether drug treatment approach for AD might be useful in the treatment of MCI .Up till now a variety of substances that

have been hypothesized to be effective in AD, have been evaluated in randomized controlled trials, for example non steroidal anti-inflammatory drugs, platelet aggregation inhibitors, statins, insulin,antioxidants.

Some drugs usefull in the treatment of AD are being tested in MCI as there is no perfect drug found for complete treatment of MCI.[119]However in the treatment of various cognitive impairments detection of the exact etiology for the cognitive deficite is essential to achieve appropriate strategy.

Following are the pharmacological agents used in the treatment:

- Acetylcholinesterase – Inhibitors:

Cholinesterase is the enzymes which catalyzes the hydrolysis of the neurotransmitter acetylcholine (ACh) into choline and acetic acid.This reaction is essential to allow a cholinergic neuron to return to its inactive condition after activation.

Acetylcholinesterase AChE is mainly found at cholinergic brain synapses and neuromuscular junctions. It terminates the impulse transmission at cholinergic synapses through quick hydrolysis of the neurotransmitter ACh to acetate and choline.

It is mainly intricately concerned with functions of memory storage, consolidation and recall to transmit signals to each other AChE act as a chemical messenger. Optimal levels of Acetylcholine are responsible for better working of memory, better fluid intelligence, logical thinking ability, reasoning, creative thought, executive function, attention control, more brilliant dreams at night. Low levels of Acetylcholine results in memory disorders like AD and other forms of mental impairments.

At the time of releasing a neurotransmitter like acetylcholine by a single neuron other connected neurons also get excited. Too little excitement and person may suffer from low brain activity. But too much excitement is equally bad, potentially leading to over-stimulation and something called excitotoxicity. Acetylcholinesterase control cholinergic excitement occurred in the brain by breaking down excessive acetylcholine in between neural synapses. This excess acetylcholine in the synaptic cleft needs to be removed .Either it can be taken up again by the neurons or can be wrecked down by an enzyme such as Acetylcholinesterase to prevent the neuronal receptors.

During ageing acetylcholine starts declining naturally leading to a loss of brain plasticity and difficulty learning. Among patients of AD Acetylcholine neurons degenerates faster and level of ACh are decreased.[120]Anti-cholinesterases inhibit the cholinesterase enzyme from breaking down ACh, increasing the level and duration of the neurotransmitter action.

Inhibition of brain AChE is the major therapeutic target in the AD treatment.[121] Reversible AChE inhibitors, given in the therapy, treat symptoms associated to memory, thinking, judgment, language and other thought processes. These drugs maintain ACh level by decreasing its breakdown rate. Consequently, they enhance cholinergic neurotransmission in forebrain regions and functioning brain cells loss is compensated.

So far no drug has a confirmed indication for delaying or halting the progression of MCI.[122] Research is still going on. Donepezil, Rivastigmine and Galantamine as reversible AChE inhibitors, are medications presently approved by U.S. Food and Drug Administration and the European Medicines Agency to treat the cognitive manifestations of AD, MCI and improve the quality of life of the patients.[123]

- Donepezil:

Donepezil is a selective, reversible AChE inhibitor that binds to the peripheral anionic site exerting symptomatic effects in the AD treatment as well as delaying the deposition of amyloid plaque.[124.125]Although its principal therapeutic use is in the palliative treatment of mild to moderate AD. Mild improvement in cognitive functions was seen in the patients receiving the higher dose. However the higher drug dose showed the increased incidence of cholinergic side effects like abdominal pain, nausea, diarrhoea, anorexia and bradycardia.[126]Some research trial showed that Donepezil improves global cognition.[127]

- Galantamine:

It is an alkaloid isolated from the plant Galanthus woronowii. It is a selective, rapidly-reversible, competitive AChE inhibitor. It enhances the activity of nicotinic receptors. Since the severity of cognitive impairment in AD associates with loss of nicotinic receptors, this effect shows to be helpful for the treatment.[128]

Side effects of the drugs are mainly with gastrointestinal symptoms. Galantamine is less tolerated than other AD drugs. It affects not only cholinergic transmission but other neurotransmitter systems too, such as monoamines, γ-aminobutyric acid (GABA), glutamate, through its allosteric mechanism.[129]

In a clinical trial, 232 MCI patients were administered galantamine combined with memantine, galantamine only and a placebo.[130] Cognitive changes and progress to dementia were assessed. Despite some methodological issues, the aMCI subgroup getting galantamine and memantine demonstrated a significant positive result on cognition

- Rivastigmine:

It is a powerful, slow-reversible carbamate inhibitor which blocks cholinesterase activity by binding at the esteratic part of the active site. Rivastigmine inhibits both BuChE and AChE. In 60 countries it has received approval for the treatment of mild-to-moderate AD.

Adverse events include nausea, vomiting, diarrhea, abdominal pain, headache, anorexia, syncope, and dizziness. The side effects can be reduced using transdermal patch delivering rivastigmine. Beside AD and MCI , rivastigmine can be useful in the treatment of Lewy bodies' and Parkinson's disease dementia.[131]Cholinesterase inhibitors have consistently shown symptomatic benefits and are now recognized as the standard treatments in patients with mild-to-moderate AD.[132]

- Memantine:

It has antioxidant and free radical-scavenging activities. Founds effective in AD but no reliable data from an RCT is yet available.Can be used in MCI.

- Gingko Biloba:

For many years Ginkgo Biloba is being used to improve cognitive functioning in elderly individuals. It has a modest effect on the cognitive function in AD,that is comparable to that of AChE inhibitor or memantine, with fewer side effects.[133]

But according to the Cochrane Library, evidence that Ginkgo Biloba has predicted for MCI and AD are inconsistent and unreliable.[134]

- Anti-inflammatory drugs:

Non-steroidal anti-inflammatory drugs reduce brain neurotoxic inflammatory responses, so could improve cognition .[135]Any firm conclusion on the use of NSAIDs in MCI can not be drawn as the findings of research till today are insufficient and some studies on NSAID are still going on.

But Bruno P. Imbimbol in his study says "chronic use of NSAIDs may be beneficial only in the very early stages of the AD process in coincidence of initial Adeposition, microglia activation and consequent release of pro-inflammatory mediators. When the deposition process is already started, NSAIDs are no longer effective and may even be detrimental because of their inhibitory activity on chronically activated microglia" [136]

- Piracetam:

Piracetam is a cyclic derivative of gamma-aminobutyric acid (GABA) and seems useful in the treatment of brain disorders.One year multi-centric study has been conducted to study efficcy of piracetam on MCI.[137]While the study confirmed the relatively good tolerability of piracetam.

- Antioxidents:

Due to high polyunsaturated fatty acids, maximum oxygen use by brain tissues and relatively little antioxidents levels in its tissues, brain is more vulnerable to oxidative stress. Association between antioxidant, memory and cognition, as well as protective effect of antioxidents against cognitive decline in the aged is clearly reported by many researchers.[138]Contribution of oxidative stress in AD pathology is well known fact.

One of the research study reports that the compound curcumin, derivative of the Curcuma Long Lin, contains antioxidant properties and slow down Aβ aggregation. [139]Another study reports that Resveratrol is found in the black grapes protects brain cells from the destruction by free radicals.[140]

There are many treatments with antioxidants showing good results in MCI. On the other hand, results of many studies are not significant or unsatisfactory. This may be because of a variety of reasons. One of the reason may be that one single antioxidant

would not be much helpful to break the pathophysiology of AD. Second important reason may be that, intervention at late stage of AD.As oxidative stress starts very early before the clinical symptoms of AD appears, antioxidents should have been started very early to get good results.

While working on antioxidents, oxidative stress markers, it should be remember that whether that drug crosses the blood-brain barrier or not. As results may vary depending on the applied investigation.

- Platelet aggregation inhibitors:

Platelet aggregation inhibitors has antiplatelet and anti-inflammatory effect.Hence it may act as a potential preventive medicine for MCI.[141]

- Vitamin B:

High homocysteine plasma levels impairs methylation resulting to signaling between nerve cell in the brain.This ultimately results in to decline of cognition.Decreased vitamine B levels increases homocystein concentration in the plasma.Several research trials reports that teatment with Vitamine B showed good results in some cognitive domains and executive functions of the brain.[142]

- Other Substances:

Along with the above mentioned drugs many other drugs have been investigated and used in MCI. Such as melatonin, insulin, omega-3 fatty acids, ampakines, testosterone, metformin, oestrogen, Vitamin E etc.All these drug showed inconsistent results.

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2.3 - Drug Review

MCI many times is the earliear stage of of dementia, has demonstrated itself the difficult clinical disorder to be treated pharmacologically.Due to its increasing significance in society, it is one of the active areas of basic neurobiological research and of drug development. However, so far, only 2 drugs have been accepted by the (Federal Drug Administration) FDA for the treatment of cognitive deficits, mild cognitive deficits. Donapezil and Tacrine. These drugs are acetylcholinesterase inhibitors, which increase the effectiveness of cholinergic neurotransmission, which in turn leads to a modest improvement in memory.

As the concept of decline of cognition and Smṛti in ageing is well known fact in Āyurveda but a new approach in the research field. Though aMCI can be correlated with decline of Smṛti in ageing it can be considered as a primordial stage of dementia. As Smṛtibhraṃśa due to ageing involves multiple causes for cognitive deficits, single drug formulations might cover only a fraction of the treatment, hence the search for a group of drugs, particularly, such a group of drugs which is having Medhya and Rasāyana properties and other multimodal pharmacological actions might be greatly beneficial.

2.3.1 - Selection of drug:

Nirguṇdi (VN) is one of the classical Medhya rasāyan drug as stated in the Bhāvprakāśa nighaṇtu,is used in diseases related Manas i.e. Apasmāra ,Unmāda etc. and mentioned as Smṛtidā (memory enhancer) in the classic. Anti-amnesic activity of Nirguṇdi is already proved in animal study. Antioxident, antiamnesic properties of Goghṛta and Madhu are well known. Nirguṇdi kalpa has been stated as manovikārnāśāk in Kākcandiśāvarakalpatantraṃ. Moreover, considering the etiopathogenesis of this clinical condition, the drug Nirguṇdi kalpa was planned. Because of easy availability, cost effectivity, theoretical and research background of raw drugs of Nirguṇdi kalpa as effective cognitive enhancer, Nirguṇdi kalpa was selected for study. Also no trials are conducted or published on Nirguṇdi kalpa till today, hence this drug was selected for the clinical trials. Nirguṇdi kalpa contains Nirguṇdi, Madhu and Goghṛta.

Though Nirguṇdi has been repeatedly mentioned and appreciated for its ‘Vātaghna, Śulaghna’ effects in Āyurvedic classical texts, but screening for its medhya effect in human being remains untouched.

2.3.2 - Nirguṇdi kalpa:[1]

Ingredients:

Nirguṇdi (Vitex Negundo) (Part used root)

Goghṛta (Cow’s ghee)

Madhu (Honey)

Table 7. Nirguṇdi Kalpa Ingredients

Ingredient	Rasa	7Virya	Vipāka	Doṣaghnata	Guṇa	Karma
Nirguṇdi	Tikta, Katu, Kaṣāya	Uṣṇa	Katu	Vātakap hāra, Pittakara	Rukṣa, Laghu, Uṣṇa,	Medhya, Smṛtidā, Rasāyan, Pācan, Agnidipan Kledaharaṇa
Madhu	Madhur, Kaṣāya	Śīta	Katu	Kapha-pitta nāśak	Rukṣa, Guru, Śīta	Medhya, Rasāyan, Pachan, KledĀhāran
Goghṛta	Madhur	Śīta	Madhur	Pitta Vāta nāśaka	Snigdha , Guru, Sīta	Rasāyana, Medhya, Bṛhaṇa, Snehan, Agnidipan, Viṣa nāśaka

Table 8. Organoleptic characters of Nirguṇdi kalpa

Parameters	Colour	Odour	Touch	Taste
Nirguṇdi kalpa	Greenish brown	Strong	Slight oily	Bitter astringent

2.3.3- Nirguṇdi (Vitex Negundo):

This review gives a bird's eye view mainly on the pharmacognostic characteristics, traditional uses, phytochemistry and pharmacological actions of Nirguṇdi.

Classification of VN[2]:

Kingdom: Planate
Subkingdom: Tracheobionta – Vascular plants
Super division: Spermatophytes – Seed plants
Division: Magnoliophyta – Flowering plants
Class: Magnoliopsida – Dicotyledons
Subclass: Asteridae
Order: Lamiales
Family: Verbenaceae
Genus: Vitex
Species-negundo
VN plant is shown
Sanskṛut name: Nirguṇdi
Latin name: Vitex Negundo
English name: Three or five leaved chaste
Synonym: Sindhuvāraka, Suvahā, Śefāli, Bhutkeśi, Nīlakeśi, Nīlamanjiri, Indrasurasā etc.
Parts used: Leaves, root, seeds, stem, flower

Fig. 11. Nirgundi Plant

Fig. 12. Nirgundi Roots

Pharmacodynamics of Nirguṇdi.[3]

Rasa	: Tikta, Katu, Kaṣāya
Guṇa	: Laghu, Rukṣa
Vipāka	: Katu
Virya	: Uṣṇa
Doṣa	: Vāta-Kapha śāmaka, Pittakar

Botanical description:

VN is a woody, aromatic shrub growing to a small tree. It commonly bears tri- or penta-foliate leaves on quadrangular branches, which give rise to bluish-purple coloured flowers in branched to mentose cymes. It thrives in humid places or along water courses in wastelands and mixed open forests.It is grown commercially as a crop in parts of Asia, Europe, North America and the West Indies. Though Vitex Negundo also finds use as a food crop and a source of timber, this review deals only with the medicinal importance and other related attributes of the plant.

Leaves: Petiolate, shorter opposite, ex-stipulated, digitātely, three to five foliate.

Leaflets: Shortly petiolulate, narrow, lanceolate, acute or acuminate, base acute, entire or rarely crenate, glabrous, above and pale whitish green and covered with a fine white tomentam beneath.

Flower: Bracteate, bract 1.4- 2.5 mm long. Lanceolate and canducous, bisexual, zygomorphic bluish purple or white in color symmetrical.

Root: Roots are woody, quite thick, 7-10 cm in diameter; brownish externally, rough due to the presence of a small rootlets and longitudinal fissures. The bark is very thin, can be scrapped off effortlessly. Transverse section shows outer cork consisting of 12- 20 rows of nearly cubical to rectangular cells, the cells of peripheral rows being thick walled but not lignified.

Habitat and distribution: Nirguṇdi is found all over India especially in hot and temperature region. In Orissā, Punjāb, Bengāl, Mahāraśtra, Gujarāt, Madhyapradeśā, Southern part of India. It is also found in Nepal, Sri Lanka, Japan, Phillipines, North Australia, Afghanistan, Africa .[4,5.6]

Composition of Nirguṇdi:

The Pancamahābhautikatva of Nirguṇdi on the basis of Rasa, Guṇa, Virya, and Vipāka can be assumed as follows – As the drug Nirguṇdi possesses Uṣṇa, Tikṣṇa, Laghu guṇa, Uṣṇa virya, Katu vipāk, rasa Tikta, Katu. It must be composed of Agnimahābhuta in dominance followed by Vāyu, Nabhas, Prithvi and Jala in descending order.

Phytochemical constituents of different plant parts of VN[7].

Leaves:

hydroxy-3,6,7,3′,4′-pentamethoxyflavone, 6′-p-hydroxybenzoyl mussaenosidic acid; 2′-p-hydroxybenzoyl mussaenosidic acid,5,3′-dihydroxy-7,8,4′-trimethoxyf Lavaṇa one; 5,3′-dihydroxy-6,7,4′- trimethoxyfLavaṇa one, viridiflorol; β-caryophyllene; sabinene; 4-terpineol; gamma-terpinene; caryophyllene oxide; 1-oceten-3-ol; globulol, betulinic acid (3β-hydroxylup-20-(29)-en-28-oic acid); ursolic acid (2β -hydroxyurs-12-en-28-oic acid); n-hentriacontanol; β- sitosterol; p-hydroxybenzoic acid, protocatechuic acid; oleanolic acid; flavonoids , angusid; casticin; vitamin-C; nishindine; gluco-nonitol; p-hydroxybenzoic acid; sitosterol

Roots:

2β, 3α-diacetoxyoleana-5,12-dien-28-oic acid; 2α,3α-dihydroxyoleana-5,12-dien-28-oic acid; 2α,3β -diacetoxy-18-hydroxyoleana-5,12-dien-28-oic acid; vitexin and isovitexin , negundin-A; negundin-B; (+)-diasyringaresinol; (+)-lyoniresinol; vitrofolal-E and vitrofolal-F , acetyl oleanolic acid; sitosterol; 3-formyl-4.5-dimethyl-8- oxo-5H-6,7- dihydronaphtho (2,3-b)furan [8, 9,10,11,12]

Seeds:

3β -acetoxyolean-12-en-27-oic acid; 2α, 3α-dihydroxyoleana-5,12-dien-28-oic acid; 2β,3α diacetoxyoleana-5,12-dien-28-oic acid; 2α, 3β-diacetoxy-18-hydroxyoleana-5,12-dien-28-oic acid , vitedoin-A; vitedoin-B; a phenylnaphthalene-type lignan alkaloid, vitedoamine-A; five other lignan derivatives , 6-hydroxy-4-(4-hydroxy-3- methoxy-phenyl)-3-hydroxymethyl-7-methoxy-3, 4- dihydro-2-naphthaldehyde , β-sitosterol; p-hydroxybenzoic acid; 5-oxyisophthalic acid; n-tritriacontane, n- hentriacontane; n-pentatriacontane; n-nonacosane

Essential oil of fresh leaves, flowers and dried fruits:

δ-guaiene; guaia-3,7-dienecaryophyllene epoxide; ethyl-hexadecenoate; α-selinene; germacren-4-ol; caryophyllene epoxide; (E)-nerolidol; β-selinene; α-cedrene; germacrene D; hexadecanoic acid; p-cymene and valencene.

History:

In Vedic literature Viṣanudharma and Pāniniya sutra, Vātikā gaṇa patha, the drug Nirguṇdi and Śephāli are quoted respectively. In Saṃhitā kāla this drug was commonly used in medicine. In Caraka saṃhitā, the drug is classified under the Viṣaghna and Kṛmighna Mahākaśāya. It was used in Yonivyāpada cikitsā for Kṣira vaivarṇya, Kṛmināśā, Viṣa cikitsā etc.

In Suśruta saṃhitā, Suśruta opines that there are two types of Nirguṇdi. a) Nirguṇdi b) Sitāsindhuvāra.Dalhaṇa says that Nirguṇdi means Nilapuṣpa, while Sitasindhuvāra means Śveta flower variety. Here the former drug is listed in Surasādi gaṇa, and later in Śvāsaghana, Rakṣoghna and Vraṇa Śodhana. Vāgbhata has similar view as the previous Saṃhitās.

Nighaṇtu Kāla:

Nirguṇdi is described in Karvirādi Varga with its two type's viz. Sindhuvāra and Śaephālika in Dhanvantari nighaṇtu. Madanphala nighaṇtu has added this drug under the Abhyādi varga. Rāj Nighaṇtu has described the drug under the Śatāvhādi varga and has given three varieties. Kaiyadeva nighaṇtu has counted the drug in Auśādhī varga and has given its five type. Bhāvaprakaśa nighaṇtu has included the drug in Guducyādi varga. The recent text Dravyaguṇa Vijñāna by Śrī Yādavaji Trikamji – states synonyms, vernacular names, guṇa, karma, family character, drug characters, uses like saṃhitākārās and also of opinion about the drug in Unani science. While in the text of Prof. P.V.Śārmā, the effect of the drug on various body system separately are mentioned and has included the drug in Vedanāsthāpana varga and Rasāyana also.

Therapeutic Uses:

In saṃhitā Nirguṇdi has been used for various purpose. In Caraka saṃhitā, it has been chiefly mentioned in Vātavyādhī treatment as inflammatory and analgesic. In Viṣa cikitsā for preparing Mṛtasanjivani agada, used for Nasya, Lepa dhāraṇa in Sarpa danśā, Bhuta Preta Prabhāva etc.Krimi cikitsā etc.

Suśruta saṃhitā for treatment of Apaci Granthi, Galaganda, Kaphaja Kāsa etc. Aṣatānga Hṛdaya and saṃhitā have used Nirguṇdi in Granthi, Apaci, Arbuda, Kāsa, Ślipada, Nādi, Muṣāka alarka, Viṣa pratiṣedha in Kuṣtha treatment

The most of the Nighaṇtu has used the Nirguṇdi in treating disorder like:

Kuṣtha, Kandu, Gulma, Aruci, Kāsa, Śopha, Sandhīvāta, Medoroga, Gudavāta, Jvara, Gṛdhrasi, Pratishyāya, Śvāsa etc.

Compounds of Nirguṇdi:

Various Kaśāya kalpanā, Nirguṇdi Taila, Svarasa, Ghṛta, Vati, Lepa, Kvātha, Mashi etc.

Formulations Containing Nirguṇdi:

Nirguṇdi kalka, Nirguṇdi ghṛta, Nirguṇdi kvātha, Vranaśodhana taila, Agastya Haritaki Rasāyana ,Viṣagarbha taila ,Vacādi tail, Rāsnādi tail,Jātyādi tail, Nirguṇdi tail , Dāśāmoola taila ,Viṣatinduk taila, Aṣtavargakāṣāya ,Vātagajankuśa , Mahāvātavidhvansa rasa ,Yakrutpleehāri louha ,Trivikram rasa , Mānasa mitra vātaka, Dantyādyāriṣta , Bilvādi leha , Amritāriṣta, Liv. 52, Pilex, V-Gel, Himcolin gel, Rumālāya gel, Acne-n-Pimple cream and Muscle & Joint Rub etc.

Pharmacological and clinical researches:

In various fields like chemistry, pharmacology, pharmacognosy, therapeutics; the research works have been carried out and published. Extensive research is going on, on the different parts of the plant. The available literary information is compiled and psesented here. However, very less number of studies were conducted to investigate the effect of VN extract against cognitive impairment in-vivo.

The effectiveness of Vitex negundo (VN) has been scientifically reported for various activities such as:

- Anti-amnesic activity: [13]

VN has been studied for its antiamnesic activity in animals by many scientist but no studies have been conducted or published so far found to explore its effect on human beings.

Otari et al., carried out in vitro research with the aqueous extract of VN to see its anti amnesic activity.VN found to reduce oxidative stress by reducing lipid peroxidation and enhancing endogenous antioxidant enzymes in the brain and decreasing brain acetyl-cholinesterase activity.[14]Azhar et al,(2004) studied antiamnesic activity of VN.They reported that the VN extract has acetylcholinetrase (AChE) inhibiting activity. VN has lignans derivative, which is responsible for inhibiting AChE anh BChE activity.[15]This activity tends to allow the more retention of acetylcholine in the brain, which is important for the cognitive functions, learning and memory.Increasing antioxidant activity in brain also results in cognition improvement.

- Anti-inflammatory and analgesic activity:

Telang et al., (1999) studied analgesic and anti-inflammatory action of VN leaf extract. The findings suggested VN holds antiinflammatory activity which is more efective on subacute inflammation rather than acute one. VN also may act as an analgesic, both centraly and peripheraly.These action of VN can be credited to its flavonoid contents, which inhibit prostaglandin biosynthesis. HenceVN can be useful in relieving both the visceral and integumental pain. VN also potentiate the effects of certain analgesics anti-inflammatory drugs.[16]

Dharmasiri et al., (2003) studied anti-inflammatory and analgesic activities of VN leaves. Their observations gave evidence for the anti-inflammatory and analgesic properties of leaves of VN.[17]

Zheng et al., (2009).verified the analgesic activity of the acetoacetate fraction of VN seeds in the test models of nociception induced by chemical stimuli.From the observation they reported the evidence for analgesic property of VN seeds which could be explained the analgesic effect of VN seed decoction in Arthritis.[18]

- Effect on oxidative stress

VN is well known for its antioxidant properties.It has been proved through in vitro as well as in-vivo research.

Renuka et al.,(2007) studied the effecacy of VN on the levels of enzymic and non-enzymic antioxidants in the adjuvant induced arthritic (AIA) rats. Observation reveals significant decrease in enzymic antioxidant – SOD, CAT, GPx, G6PD and non-enzymic antioxidant-GSH, Vit-C in AIA rats against the normal rats suggesting antioxidant activity of VN.[19]

Tasduq et al., (2008) found negundoside and an irridiod glycoside from leaves of VN. Negundoside (NG) provide protection against carbon tetra chloride induced toxicity and oxidative stress. Hence concluded antioxidant activity of VN.[20]

Agnelarul et al., (2010) conducted a study to reveal the gastroprotective activity of water extract of VN against the aspirin induced gastric mucosal damage in albino rats. The gastroprotective effect of VN was observed at an oral dose of 200mg/kg body weight administered for 18 days before ulcer induction. VN offers gastric protection against aspirin induced ulcer by significantly blocking lipid peroxidation which is proved by the reduced levels of lipid peroxide. . In histological study, VN pretreatment showed not only the maintenance but also the regeneration of gastric mucosa in the damaged region. Presence of flavonoids, which shows anti-ulcerogenic and gastroprotective activities .This indicates that the gastroprotection by VN, as observed in the present investigation, may be due to the presence of flavonoids.[21]

- Effect on reproductive potential:

Hu et al., (2007) studied VN ethanolic extracts and reported that VN posseses estrogen-like activity and suggested its use in hormone replacement therapy in female. [22]

- Potentiating effect of other drugs:

VN has shown potentiated effect of certain analgesic anti-inflammatory drugs like ibuprofen, aspirin. It also potentiate the effect of pentobarbitone, diazepam, morphine and pethidine, diphenylhydantoin and valporic acid [23.24, 25.26]

- Anticonvulsant activity:

Tandon et al., (2005) studied effect of anticonvulsant activity of VN in pentylenetetarazole (PTZ) induced convulsion. They reported that VN possesses anticonvulsant activity. Additionally, they said that VN if given with modern standard

anticonvulsant drugs, it potentiate the standard drugs activity and also decrease the dose of standard drugs like diphenylhydantoin and valporic acid.[27]

- Anthelmintic activity:

Ahirrao et al., (2009) reported anthelmintic activity of leaves of VN and Jatropha curcas. Both the leaves show good anthelmintic activity. But Jatropha curcas leaves found more potent antihelmentic than VN.[28]

- Anxiolytic Activity:

Adnaik et al.,(2009) studied anxiolytic effect of VN the elevated plus-maze animal model.They reported that VN posseses anxiolytic effects.VN increase the level of GABA, leading to anxiolytic effect .[29]

- Antipyretic Activity:

Rama et al.,(2010) assessed the antipyretic action of VN.They reported that the VN leaf extract causes a considerable antipyretic effect in yeast provoked elevation of body temperature in comparison with the effect of paracetamol.[30]

- Anti-hyperglycemic activity:

Villasenor et al.,(2006) studied anti hyperglycemic activity of VN along with other drugs like Eucalyptus tereticornis as antidiabetic agents using the oral glucose tolerance test . VN exhibited greater antihyperglycemic activity than Eucalyptus tereticornis. Both showed a significant decrease in Blood Glucose Levels at 60 min but at alpha=0.05 for VN and at alpha=0.07 for Eucalyptus tereticornis. [31]

- Anti pigmentation activity:

Haq et al., (2006) found tyrosinase inhibitory lignans in the methanol extract of the roots of VN .They evaluated its effect concluded that the lignans compounds found from the VN roots, can inhibit tyrosinase enzyme and can be used for the treatment of hyperpigmentation associated with the high production of melanocytes in various skin diseases.[32]

- Antitussive and antihistaminic activity:

Nair et al., (1994) studied antitussive effects of the n-butanol fraction of VN on sulphur dioxide-induced cough in mice. They observed that VN extract confirmed a considerable inhibition of cough reflex in a dose dependent manner. Not only has this it had antihistaminic, mast cell stabilizing, smooth muscle relaxing activity. This results suggests the use of VN in respiratory tract infection.[33]

- Hepatoprotective activity:

Mahalakshmi et al.,2010) studied the hepatoprotective activity of VN leaves ethanolic extract in ibuprofen induced hepatotoxicity in Wistar Albino male rats .The results suggested that VN having the hepatoprotective activity, that support the hepatic cells protection .[34]

Tandon et al., (2008) concluded research work that VN posseses hepatoprotective activity against anti-tubercular drugs induced hepatotoxicity and proved the hepatoprotective propertb of VN.[35]

- Antifungal and antibacterial activity:

Sathiamoorthy et al., (2007) studied antifungal property of VN. During their study the found and isolated new antifungal flavonoid glycoside from VN. They isolated new flavonoid glycoside and five compounds like (1) 5'-hydroxy–3',4',3,6,7-pentamethoxyflavone (2) agnuside (3) luteolin (4) negundoside (5) iso-orientin from VN.This proves the antifungal action of VN.[36]

- Anti snake venom activity:

Alama et al., (2003) examined snake venom neutralization by VN root extracts. This results reported that VN extracts hold potent snake venom neutralizing capability. This indicates the relation with SarpaViṣaghna activity of VN mentioned in classics.[37]

Acute toxicity study:

Acute toxicity study of ethanolic leaf extract was carried out by Tandon et al., Results revealed that VN is nearlly nontoxic, as its LD50 dose recorded was 7.5 g/kg/wt.[38]

2.3.4 - Goghṛta:

Haviṣa, sarpiṣa and Ājya are the synonyma of Ghṛta .The ‘Ṛgveda’ contains numerous references on Ghṛta, presenting it’s importance in diet as well as medicine which provides various health benefits.It is prepared by heating butter or cream to just over 100 C to remove water content . Goghṛta is the best and the choice of food nutrient for diet and medicinal purposes.

Ghṛta is the best Ajasrika Rasāyanas. It is Āyu vardhak, Balavardhak, Vayasthāpak, Ojovardhak, Dhātupośāk and is utmost in Snehana dravyas. With the help of Saṃskāranuvartan property, as per its ingredients the medicated Ghṛta will be achieving properties without leaving its own properties.It is Yogavāhi so it carries active principles of the drugs reach to finest parts of the tissue fast.

Properties of Goghṛta –[39]

English name -- Clarified butter.

Rasa- Madhur

Virya- Śīta

Vipātk -Madhur

Guṇa -- Mṛdu, Ślakṣaṇa, Guru

Doṣaghnatā -Vātaghna & Pittaghna

Table 9. Pharmacodynamics of Goghṛta:

Nighaṇtu	Varga	Rasa	Guṇa	Virya	Vipāka
Dhanavantari	Suvarṇādi	-	-	Śīta	Madhura
Kaiyadeva	Ghṛtavarga	Madhura	Guru, Mridu Ślakshna	Śīta	Madhura
Rāj	Kṣirādi	Madhura	Snigdha, Guru	Śīta	Madhura
Bhāvāprakāśa	GhṛtaVarga	Madhura	Guru	Śīta	Madhura
DravyaGuṇaVijñāna	Snehavarga	Madhura	Guru, Snigdha	Śīta	Madhura

Table 10. Karma or properties of Goghrta:

Karma	C. S.	S. S.	A. H.
Agnivardhaka	+	-	-
Rasavardhak	+	-	-
Balya	+	+	+
Ojavardhaka	+	-	-
Kāntivardhaka	+	-	+
Smṛtivardhaka	+	+	+
Indriya Balavṛddhak	+	-	-
Buddhi Vardhaka	+	+	+
Vayasthāpana	+	+	+
Unmādahar	+	+	+
Apsmārhar	-	+	-
Viṣanāśka	+	+	+
Medhāvardhaka	+	+	+

It pacifies Vāta by snigdha propety, pitta by madhura rasa and śīta property and kapha by processing with kaphahara drugs. It should be taken in small quantities for longer duration to pacify pitta and in large amounts to pacify Vāta. Ghṛta is indicated in persons suffering from conditions like rukṣatā, kṣatā, Vāta vikāra, Pitta vikāra, Unmāda, Mada, Apasmāra, Murcchā, Śiroroga, Akṣiroga, Vrana, Śoṣa, Kuṣtha, Jvara, Dāha, smṛtinaśa and Angimāndya, and persons who are Vṛddha, Bāla and those who are desirous of Āyu, Bala, Varna, Svara, Puṣti, Prajā, Saukumārya, Buddhī, Smṛuti, and Indriya and clearness of voice.

The most important property that makes it different from Taila, Vasā or Majjā is its action on higher mental functions in mastiṣkajanya vikāra. Snehana especially by Ghṛta is very much important in Mastiṣakajanya vikāras or neurological disorders, due to the similarity of mastulunga sneha dravyas.[40]So it has targeted action on intellectual and cognitive functions. Goghṛta has a remarkable efficacy in crossing BBB (Blood Brain Barrier) which is very much needed for treating mental anomalies.[41]

Bhāvaprakāśa mentiones that Goghṛta is Rasāyana, Aruci nāśak, good for eyes, Dipan, Kānti vardhak, Smṛti vardhak (enhances memory) and Balavardhak, promotes longevity and protects the body from diseases. Other properties of Goghṛta include cooling and softening effect on the body, enhancing clarity of voice and complexion. It is conducive for Rasa dhātu, Śukra dhātu and Ojus .[42]

Many Āyurvedic formulations are prepared with Goghṛta. Digestion, absorption and delivery to a target organ system is vital in obtaining the maximum benefits from any formulation. These actions are facilitated by Goghṛta. Lipophilic action of Goghṛta facilitates transportation to a target organ and final delivery inside the cell, as cell membrane also contains lipid. This lipophilic nature of Goghṛta facilitates entry of the formulation into the cell and its delivery to the mitochondrion, microsome and nuclear membrane. When herbs are mixed with Goghṛta, their activity and utility is potentate many times.

Goghṛta consists of Snigdha and Guru Guṇas which helps in Vāta doṣa Śamana and maintaining kapha doṣa, which is useful in myalgia, fatigue in old age. Goghṛta has madhura rasa which is saptadhātu vardhaka, indriya prasādaka, hence necessary in decreased sensorial function of old age. Goghṛta is Rasāyana, Smṛti, Buddhī, Agni,

Śukra and Oja vardhaka which are useful in resisting age related development, eg.impaired memory, sexual dysfunction etc. in ageing.

Modern view about Goghṛta:

Clarified cow milk fat or butter fat is known as Ghṛta (ghee). It is prepared by heating butter or cream to just over 100ºC to remove water content by evaporation. The residue is filtered out as pure Goghṛta. The composition of Goghṛta residue obtained from Indian cow is as follows:

The color of Goghṛta is yellow to white depending upon the carotene content. Goghṛta contains approximately 8% lower saturated fatty acid which makes it easily digestible. These lower saturated fatty acids are the most edible fat and which are not found in any other edible oil or fat.

Composition of Goghṛta.[43]

Tri-glycerides	97.098%
Di- glycerides	0.25 - 1.4%
Monoglycerides	0.16 - 0.038 %
Ketoacid glycerides	0.015-0.018 %
Glycerylesters	0.011-0.05%
Free fatty acids	0.1-0.44%
Phospholipids	0.2 -1.0%
Sterols	0.22-0.41%
Vitamin – A	2500 I.U (per 100 gm)
Vitamin – D	8.5x 10.7gm (per 100 gm)
Vitamin – E	24x10.3gm (per 100 gm)

Vitamin – K	1x10.4gm (per 100 gm)
Butric acid	4.5 -6.0 %
Caporic acid	1.0-1.36%
Caprylic acid	0.9-1%
Capric acid	1.5-1.8%
Lauric acid	6-7%
Myristic acid	21-23%
Palmitic acid	19-19.5%
Stearic acid	11-11.5%
Arachidic acid	0.5-0.8%
Oleic acid	27-27.5% F.

Analytical parameters of Goghṛta.

The Physico-Chemical Properties of Goghṛta is mentioned below .[44]

Loss on drying	0.15%
Ash content	0.10%
Acid insoluble ash	0.0009%
Fat content	99.83%
Saponification value	222.9
Iodine value	34.6
Specific gravity	0.935
Acid value	2.52
Refractive value	1.456
Unsaponifiable matter	0.31

Goghṛta also contains Vitamin A, D, E and K. Vitamins A and E are antioxidant and are helpful in preventing oxidative injury to the body. No other edible fat or oil contains Vitamin A except fish oil. Vitamin A keeps epithelial tissue of the body intact; keeps the outer lining of the eyeball moist and prevents blindness. Goghṛta also contains 4-5% linoleic acid, an essential fatty acid, which promotes proper growth of human body. Due to Lipophilic action of Goghṛta, they easily facilitate transportation to a target organ and final delivery, inside the cell, because cell membrane also contains lipid. This lipophilic nature of Goghṛta facilitates entry of the formulation into the cell and its delivery to the mitochondria, microsome and nuclear membrane.

In the process of evaluating the activities of natural compounds, it has been found by means of sophisticated research that when herbs are mixed with Goghṛta, their activity and utility is potentiated, many times.Goghṛta contains anti oxidants beta-carotene and Vitamin E. It is predicted that 80% to 90% of degenerative disorders related to excessive production of free radicals of reactive oxygen species. When free radicals are in excess, they try to latch on to whatever is available in their surrounding area, and this is how the lipids in the blood and cell membranes are oxidized. The oxidized lipids or the lipid peroxides are injurious to the system. As we know, they trigger the process of atherosclerosis. The reactive oxygen species also cause damage to the DNA in the cells. Excessive free radicals have been associated with ageing and many other diseases. The efficiency of many Āyurvedic drugs is due to potent anti-oxidant properties of removing of scavenging free radicals.

Pharmacological and clinical researches:

The distribution of drug in blood is chiefly influenced by its lipid solubility, ionization, differences in the regional blood flow etc. A water soluble drug is usually distributed in the extracellular spaces and it may not readily diffuse in to CSF and other body cavities, while the lipid soluble drugs are rapidly distributed throughout the intra and extra cellular spaces. The drugs that are rapidly absorbed from the gut because of their lipid solubility are known to readily diffuse into the CSF and the brain. That is why drugs given in the form of a ghṛta are rapidly absorbed and distributed in the target areas of the body like the nervous system in this case. The main reason behind this is the molecular structure of the blood brain barrier. This membrane separating the CNS

tissue and the circulating blood is lipophilic in nature. Thus it selectively allows the passage of lipids and lipid soluble drugs across it. Therefore any drug given in the form of ghṛta will not only be digested and absorbed fast, but will also be able to reach some of the most distant and difficult to reach areas of body like the CNS. This explains the better efficacy of various psychotropic drugs given in the form of siddha Goghṛta in CNS diseases. And also tallies with the qualities of Goghṛta which were discussed earlier like Buddhī and Smṛtivardhaka. Also its antioxidant properties prevent the oxidative damage of brain and other tissues of the nervous system, thus providing protection from various degenerative diseases.

Goghṛta is one of the easily digestible and assailable food which provides essential nutrients and critical anti oxidants or free radical scavengers to human body for its protection and growth.

While evaluating the activities of natural compounds, it is found that when herbs are processed or mixed with Goghṛta, their activity, utility and rate of absorption is potentiated[45]. In one of the study conducted by Kumār et al (2000) Goghṛta was observed to improve the growth rate and digestion.[46]

Begum et al., (2008) reported that Goghṛta carries the therapeutic properties of herbs to all the body'stissue .As the lipophilic action of Goghṛta facilitates transportation to a target organ and final delivery inside the cell since the cell membra ne also contains lipid. Goghṛta can also be used as a bio enhancer for the drugs having poor bioavailability.[47]

Brain is the fattest organ in our body and may consist of at least 60 percent fat. [48]Fatty acids form important structural components of each nerve cells. Fatty membranes also form the blood-brain-barrier which protects the brain and controls passage of substances. Fatty tissue, by nature, is a good carrier of many subtances; it is also very susceptible to oxidative degeneration. For this reason, Āyurvedic therapies use oils in treatment of most diseases, especially those affecting the brain.

Sharma et al., (2010) says that Goghṛta is a good carriers for toxins out of the body as well as good carriers of medicine. Goghṛta is commonly used as a carrier for medicinal herbs like Brāmhi. Goghṛta has been shown to improve lipid (cholesterol) metabolism in the body, it also has a protective effect against oxidation of lipids in the

body. [49] When given as Bacopa-medicated Goghṛta (Brāhmi Ghṛta), it is beneficial for promoting learning and memory in amnesia.[50]

Achliya et al., (2004) conducted a in vitro study to evaluate nootropic activity of medicated Ghṛta i.e.Brāmhi Ghṛta.They reported that the formulation proved the Nootropic and memory enhancer properties.[51]

FibiMol in an open clinical trial to study the efficacy of Pancagavya Ghṛta on cognitive domain in Down's syndrome. Found significant improvement in cognition. [52]

2.3.5 - Madhu (Honey):

Madhu is a valuable product of nature since ancient times. Various ingredients of honey have helped it to become not only a sweet liquid, but also a natural product with high nutritional and medicinal value.Madhu is an invaluable natural substance with many diverse usages. It strengthens the immunity and helps to maintain the health by preventing various types of diseases but it must be pure and genuine.

Madhu is also known as Pushpāsava, Pushparasa, Mādhvika, Kṣaoudra,

Biological sources:

Madhu is a sugary secretion deposited by the honey bees, Apis mellifera linn and other species of Apis in the honey comb. It must be free from foreign substances such as parts of insects and leaves, but may contain pollen grains.[53]

Properties according to modern science:

Various experiments and studies on Madhu have shown that it has antiseptic, antimicrobial, anti-inflammatory, sedative, mild laxative, healing and cleansing properties.

Characteristics:

Madhu is thick, syrupy, translucent liquid when fresh. The color is pale yellow or reddish - brown and it possesses pleasant odor and sweet taste which is dependent upon the floral source of the product. On storage it becomes opaque and granular due to the crystallization of dextrose.The average pH of honey is 3.9, but ranges from 3.4 to 6.1.

According to Carak, Vāgbhata Madhu is of four types. Bhramara, Poutrika, Mākṣaika, Kṣaoudra. Bhāvaprakāśā, Suśruta has mentioned eight types of Madhu

Properties:

It is Madhur and Kaṣāya in rasa (Madhur is predominat rasa and Kaṣāya is anurasa), Rukṣa,Laghu in guṇa, Śīta in virya.Guru according to Caraka,Laghu according to Suśruta.It is Picchila, Sukṣama margānusāri (enters minute pores), Yogavāhi, Grāhi,Viṣada.Immature Madhu leads to aggravations of Tridoṣa and mature honey restore these three Doṣa in its equilibrium state. Newly formed Madhu increases the body weight and old Madhu decreases the body fat and thus body weight.

It is Vāta vardhak, Kapha-Pittanāśāk, Srotovisodhana, Sandhānkṛta, Śodhana, Chedana, Yogavāhi, Agnidipan, Lekhana, and Hṛdya. Bhāvprakāśā mentions that Madhu is Sandhānakar (helps regeneration of cells), Ropaṇa (healing), Sangrāhi (improves better absorption), Prasādana (nurtures body).

Table 11. Pharmacodynamics of Madhu according to different Ācāryās:[54-60]

	C.S. Su.	S.S. Su.	A.S. Su.	A.H. Su.	M.P.N. Ikshukādi varga	B.P.N. Madhu varga	K.N. Aushdhi Varga
Rasa	Madhur, Kaṣāya	Madhura	Madhura, Kaṣāya	Madhura, Kaṣāya -	--	Madhura	Madhura
Anurasa	-	Kaṣāya	- - -	- - -	- - -	Kaṣāya	Kaṣāya a
Guṇa	Guru, Rukṣa	Laghu, Rukṣa, Picchīla	Guru, Rukṣa	Rukṣa	Laghu, Rukṣ, Viṣad	Laghu, Rukṣa, Viṣad, Sukṣama	Laghu, Rukṣa, Viṣad, Sukṣama
Virya	Sīta	Sīta	Sīta		Sīta	Sīta	Sīta
Vipāka -	- - -	- - -	- Katu	- - -	- - -	- - -	- - -
Doṣghantā	Vāta kārak, Kaph pitta nāśak	Tridoṣnāśak	Vātakārak, Kaph pitta nāśak	Vāta kārak, Kaph pitta nāśak	Vāta karak, Kaph pitta nāśak	Alpa vātlaṃ, Kaph pitta nāśak	Vāta kārak, Kaph pitta nāśak

Therapeutic uses:

Madhu is Raktapitta nāśak,Vraṇaśodhaka,Kāsanāśāka, Medoroga nāśāka ,Kṛmihara ,Prameha nāśāka , Kuṣtha nāśāka ,Viṣanāśāka,Hikka -Śvāsa -Kāsa nāśāka, Atisāra nāśāka,Cakṣuṣya,

Table 12. Composition of Madhu. [61--63]

Constituents	Average percentage
Water	17.2
Fructose	38.19
Glucose	31.28
Sucrose	1.31
Diasacarides (usually maltose)	7.31
Higher sugars	1.5
Free acid as gluconic	0.43
Gluconolactone	0.14
Total acid as gluconic	0.57
Ash	0.169
Nitrogen	0.041
Minerals	0.20
Proteins	0.30
pH value	3.9

Though the composition and physicochemical properties of honey are variable depending on its floral source and often named according to the proportion of the sugar content, geographical location some common properties are as followes:

Chemical composition of honey:

The precise value of the honey varies according to the plant source, season and production method.Storage condition also may influence final composition. But the

main constituents are same in all the honeys. Naturally darker honey has greater antioxidant properties. Acetic, Butanoic, Formic, Citric, Succinic, Lactic, Malic, Pyroglutamic, Gluconic acids and a number of aromatic acids are found in Madhu.

Chemical constituents:

It consists chiefly of fructose (40-50%), glucose (30-40%), and small amounts of sucrose (0.1-10%), dextrin, formic acid, volatile oil and pollen grains. In addition to these, traces of enzymes, vitamins, proteins, maltose, melezitose, pentosans, gums, trace elements, amino acids, and coloring matter are also present.

Other contents:

Vitamin B6, vitamin C, thiamin, niacin, riboflavin, pantothenic acid.

Minerals calcium, copper, iron, magnesium, manganese, phosphorus, potassium, sodium, zinc.

Amino acids,Antioxidants, Chrysin, pinobanksin, vitamin C, catalase, pinocembrin

Pharmacological, clinical research on honey:

Within last decade, studies have been conducted using regional honey to investigate effects on learning and memory. Al-Himyari et al. conducted a five-year pilot study involving cognitively intact subjects and with mild cognitive impairment aged 65 and older. They were randomized and provided either one tablespoon honey or placebo daily. They found that only 95 subjects who received honey compared to 394 who received placebo developed dementia. So the study concluded that honey act as natural preventive therapy for both cognitive decline and dementia.[64]

Othman et al.,(2011)conducted clinical trials on postmenopausal women.Learning and memory is always affected by a decline or loss of estrogen (as in a case of postmenopausal women or ovariectomized rats), resulting in decreased cognitive function .[65] Considering this, a study using Tualang honey was planed and

conducted on 102 healthy postmenopausal women .[66] The participants' memory and oxidative stress status were assessed pre- and post itervention.Women who received Tualang honey showed improvement in their immediate memory but not in immediate memory after interference and delayed recall.

Heitkamp et al.,(1984) in one of the in vitro study showed reduced concentrations of ACh and increased AChE in the brain homogenates of stressed OVX rats compared with nonstressed Sam-operated controls and the effects were reversed after treatment with honey. Honey has been reported to contain choline, ACh, naringenin and chlorogenic acid .[67]

Chepulis et al., (2009) in their animal study concluded that early introduction of honey diet is beneficial and can improve memory loss and cognitive decline associated with ageing. While it is possible that the learning and memory improvement following honey supplementation is due to the sugar content in honey, these investigators controlled for this effect using sucrose. [68]

Al-Rahbi et al., (2014) performed an animal study on honey. The rats' memory performance was assessed pre and post trial. They administered honey to 40 ovariectomised (OVX) and 20 Sam-operated female Sprague-Dawley rats. Tualang honey treatment improved both short-term and long-term memory, and enhanced the neuronal proliferation of hippocampal CA2, CA3 and DG regions compared to untreated groups.[69]

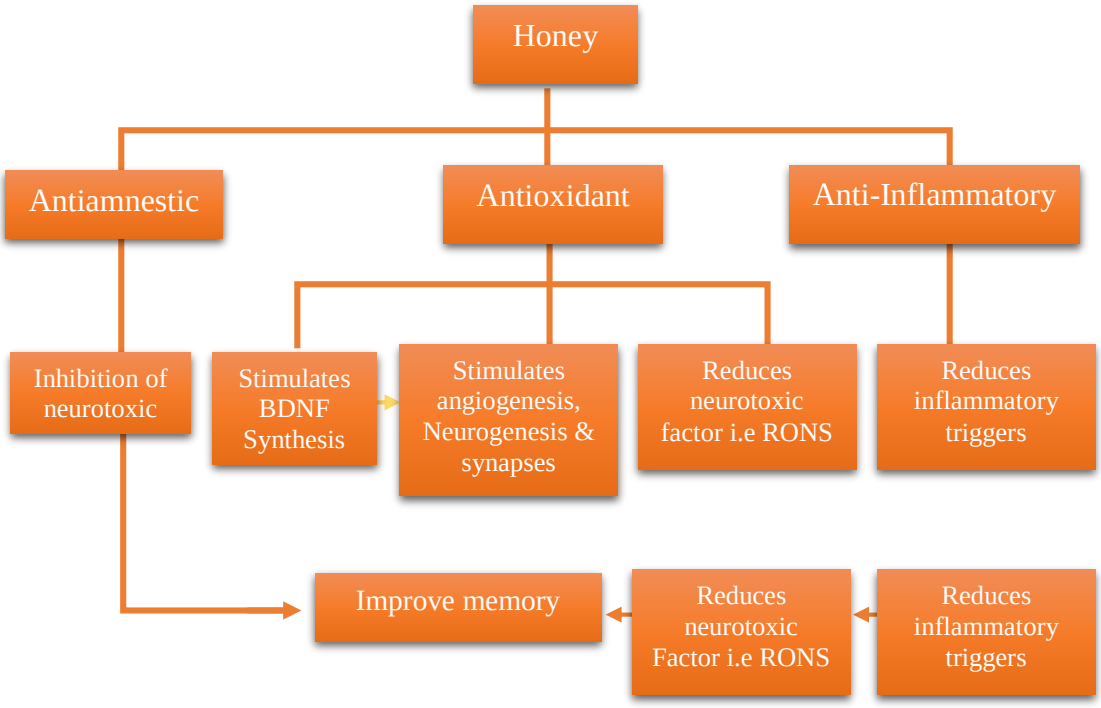
Oyefuga et al.,(2012) in a study found that both short (3 wks.)and long term (12 weeks), honey supplementations at a dose of 250 mg/kg body weight may increase the brain protein and CAT activities of brain cells, suggesting a significant increase in antioxidant capacity thus enhancing defenses against, cell injury, oxidative cell damage and the degenerative process of cell components. The positive effect on rat brain is probably partly due to the antioxidant properties found in Tualang honey such as flavonoids (catechin, kaempferol, naringenin, luteolin and apigenin) and phenolic acids (gallic, syringic, benzoic, trans-cinnamic, p-coumaric, and caffeic acids).[70]

Al-Rahbi et al.,(2014) in their study found that for hippocampal atrophy and neuronal loss in experimental animals decreased expression of BDNF is also responsible.In stressed OVX rats BDNF concentration is significantly decreased,

compared to other experimental groups and the concentration is restored to normal following honey treatment.[71]

It has very good wound healing property .Honey also has the capacity to inhibit the triggering of neuroinflammatory and microglial activation. Its anti-inflammatory role may help in increasing memory.

Fig. 13. Probable Action of Honey on MCI



2.3.6 - Probable action of Nirguṇḍi kalpa on aMCI:

It has been mentioned in classics that Nirguṇḍi kalpa contributes to reduce the psychological disorders, memory impairement.

On the basis of Rasapancaka, the pharmacotherapeutic properties reveals that Nirguṇḍi kalpa may contains Tikta, Katu and Madhura rasa and Katu vipāka , Uṣṇa virya.

While normalizing the body physiology, by pacifying tridoṣa; correcting Agni (digestion and metabolism) and nourishing Rasa dhātu in a proper way, Nirguṇdi kalpa releases its Medhya property to correct mental health. And also helps in minimizing age related degenerative changes.

Ingredients of Nirguṇdi Kalpa are well known Rasāyan and Medhya drugs. The Medhya Rasāyanas are special Āyurvedic neuro nutraceuticals which are specific to brain and nervous system. They are claimed to promote cognitive function of the brain. Nirguṇdi by its Tikta, Katu rasa and Katu vipāka, Uṣṇa virya helps in correcting Agni impairment, Āmotpatti and srotoavarodha. Resulting in enhancement in nutrition of body and brain.The influence of drug on brain is not explainable in the terms of rasapancaka and tridoṣasiddhānta only.

As Nirguṇdi kalpa is a Medhya rasāyana drug, it mainly act by its Acintya Virya i.e. Prabhāva. The effect of Medhya rasāyana is also different at different levels such as at level of Rasa, Agni, and Srotasa. At the level of Agni these drug performe by stimulating and recovering the function of Agni. At level of Srotsa, these drugs improve the circulation of Rasa by opening and cleaning the micro channel and then eventually improve the function of Medhā. These drugs have beneficial effect on body as well as on mind. On the basis of Rasa it can be said that, Tikta Rasa has direct action on the promotion of Medhā. It executes their function with its Laghu property and Dīpana-Pācana and Srotośodhaka action. Madhura rasa also acts by promoting the formation of Oja, nourishes five sense, mind and Medhā. Hence Nirguṇdi kalpa being Medhya rasāyana drug it also acts as above.

In Āyurveda, it is clearly emphasized that Smṛtibhraṃśa or decline in memory results due to Rajas and Tamas doṣa in the mind. These doṣa are responsible for creating Āvaraṇa over the mind.Vāta doṣa influences the Rajas and there by causes the Manasa doṣa vikṛtis. Smṛuti, depends upon the state of balance of Vāta doṣa.

Therefore balancing of Vāta is essential in management of Smṛtibhraṃśa.Nirguṇdi kalpa does the Vātahara action. Hence it may help in promoting the Medhya properties.

In this study the relief from the chief symptoms has been found to be statistically significant. These observations reveal that the drug might have counteracted or

pacified Rajas and Tamas doṣa, so Āvaraṇa of mind was removed and the disease was subsided or controlled.

Here the Nirguṇdi kalpa is having the Tikta pradhan rasa and Katu vipak,Uṣṇa virya so we can predict that the Nirguṇdi kalpa helps in the enhancement of Grahaṇa śākti and Smaraṇ śākti.

Snigdha, sukṣama, anuloman property of Goghṛta in Nirguṇdi kalpa increases the permeability of cell membrane and become helpful in elimination of Doṣa and Mala.

Pharmacological study reports of ingredients of Nirguṇdi kalpa also supports this efficacy of Nirguṇdi kalpa.Memory impairment in the patients during ageing results from a deficiency in cholinergic function in the brain.

The role of acetylcholinesterase inhibitors and butyrylcholinesterase (BChE) inhibitiors is to improve the endogenous levels of acetylcholine in the brains of the patients and thereby to improve cholinergic neurotransmission.Therefore, inhibition of AChE and BChE is the most effective therapeutic approach to treat the memory decline.

VN has compounds like lyoniresinol, vitrofolal E and vitrofolal and other two lignans, which inhibits AChE.Vitrofolal E strongly inhibit BChE, leading to memory improvement. [15] Also in-vitro study has been revealed an anti amnesic property of the VN.[14]

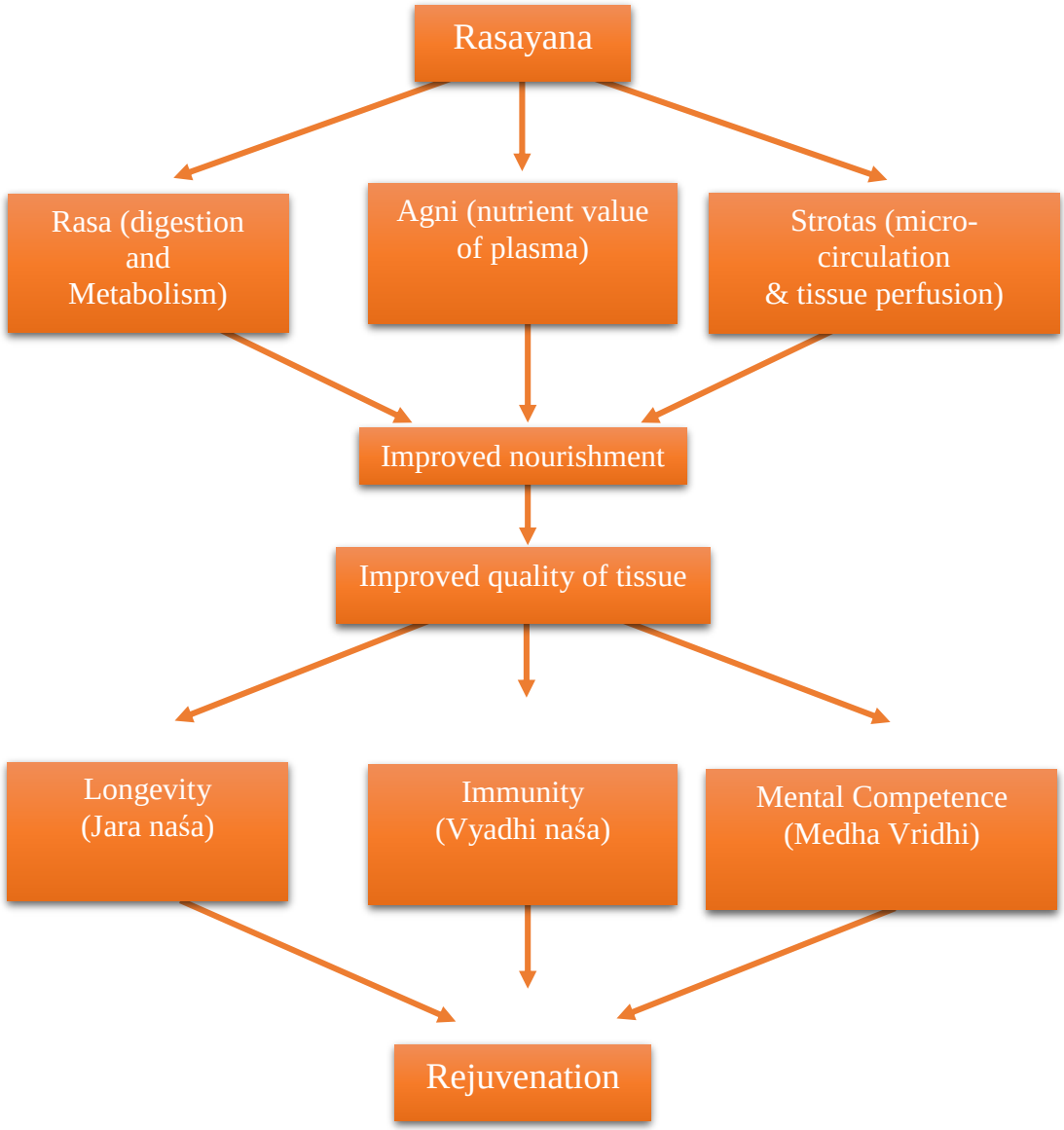
Nirguṇdi kalpa's antioxidant properties prevent the oxidative damage of brain and other tissues of the nervous system, thus providing protection from degeneration.

As Nirguṇdi and Madhu are processed with Goghṛta, their activity, utility and rate of absorption is potentiated.[45]The lipophilic action of Goghṛta facilitates transportation to the target organ and final delivery inside the cell since the cell memb rane also contains lipid and may help to cross blood brain barrier.

For hippocampal atrophy and neuronal loss BDNF is responsible factor. Madhu restores normal concentration of BDNF.[71]It also enhances the neuronal proliferation of hippocampus region. [69]This property, antioxidant property and high sugar contents of Madhu improves cognition and memory.

All the ingredients in Nirguṇdi kalpa have antioxidant, immunomodulatory, adaptogenic and memory enhancing properties. Therefore in addition to Rasāyan effect on other systems of body, Nirguṇdi kalpa has good effect on Manas bhāva also.

Fig. 14. Action of Rasāyana



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2.4 - Previous research work done on MCI and the trial drug:

Efforts in the field of ageing and dementia has been pointed towards finding out early signs symptoms for early diagnosis of dementia creating conditions. Which could be used to find out predictive markers of disease development and early intervention may help further progress of the dementing condition.MCI is the clinical condition between normal ageing and dementia, on which lot of literary, clinical, pharmacological research has been going on.Although various research studies are performed on MCI, aMCI, its patophysiology, treatment; very few studies were done or results published on MCI and its Āyurvedic aspects.

Tripathi et.al.in their study, examined diagnostic correctness of various neuropsychological procedures in individuals with MCI. They found that individuals with MCI showed decline in memory and executive functioning. Measures of episodic memory and word list more particularly come into view as sensitive tool for identification of MCI and possibly would be used as potential cognitive marker for MCI.[1]

Sallaway S. et al. proved that the 6-month donepezil RCT has shown a statistically significant but small improvement in cognitive levels of the MCI patients. Side effects like diarrhoea, nausea and vomiting and abnormal dreams were predominantly noted.[2]

The preference to delay conversion from aMCI to AD has major importence in dementia research. Niels D et al., studied activity of galantamine in patients with MCI compared to placebo drug.The individuals on galantamine group showed a lower rate of whole brain atrophy, over a 24-month treatment period in APOE ϵ4 carriers,in comparison with those people treated with placebo. Demonstrating that galantamine may help to delay progress of MCI to AD.[3]

Various studies have been conducted on effect of Āyurvedic drugs in cognitive, memory decline .Amongs human trials are few.All these studies are conducted not under the title MCI always, but some related terms are also used like age associated cognitive disorder, senile dementia, age associated memory decline etc.Our intention is

to present an overview of evidences of a range of Āyurvedic drugs which can be used for the prevention and minimization of age associated cognitive decline or MCI.

Raghav et al.,conducted a double-blind, placebo-controlled randomized study to assess the effect of standardized Bacopa monniera extract on learning ,memory.The subjects were provided with either standardized Bacopa monniera extract or placebo for a period of 3 months, followed by a placebo period of another 4 weeks. The study revealed that standardized Bacopa monniera extract produced significant improvement on mental control, logical memory and learning activity.[4]

Kulatunga et al., demonstrated the effects of Guducyādi Medhya rasāyana therapy in Senile Memory Impairment. Guducyādi Medhya rasāyana found to be statistically highly significant; $P<0.001$, on short memory impairment and long term memory impairment in senile memory impairment. Guducyādi Medhya rasāyana has shown memory enhancing, antidepressant, anti-stress, and anxiolytic potential. Guducyādi Medhya rasāyana also found to be ACh enhancer.[5]

A study was carried on 61 aged subjects of both sexes aged 62-75 years. Out of 61 persons 28 had cognitive deficits particularly the memory loss whereas 21 were normal. The subject of both group were treated with organic extract of Bacopa monnieri in effective doses continuously for six months and evaluated on various neuropsychological parameters. The results obtained at the end of six months revealed beneficial effect in improving memory, attention span and behavioral problems among demented elderly people. The neurochemical loss was checked and enhanced in senile dementia cases. Result showed that the test drug has potential to improve memory and other cognitive deficits among the aged persons suffering from dementia and associated behavioural problems. [6]

Shende K. et al., performed clinical trials on Śivā gutika with Sārasvatāriṣta in age associated mild cognitive impairment for 3 months. Cognitive impairement was assessed using CAMCOG scale. Results founded were significant with no adverse effects.[7]

Agrawal et al., conducted clinical research on the proprietary Āyurvedic mixture Mentat in cognitive decline conditions. A double-blind, placebo-controlled

study of 50 adult students for 3 months was conducted.The results showed improvement in memory,attention,and anxiety reduction.[8]

Meng R. et al., in the randomized controlled trial clinical observation and mechānism study on treatment of senile dementia with Naohuandan ,mentiones that the chinese herbal preparation Naohuandan could be used for improving cognitive function in a senile dementia ,as it gives good results compared to piracetam.[9]

Andrade C et al., conducted the Clinical research on the herbal formulation Memorin.It was evaluated for 3-month in randomized, double-blind, placebo-controlled study in age-related cognitive decline. All subjects completed a battery of neuropsychological tests that assessed visual and verbal memory, visuospatial skills, and perceptuomotor functioning.

In the Memorin group, significant improvement was seen on most functions like visual and verbal memory, perceptuomotor functioning test. Age did not significantly influence the results.[10]

Achliya et al., conducted in vitro research on Brāmhi Ghṛta.As literary study mentions positively about memory enhancing activities of Brāmhi Ghṛta.Their study reports significant effects as cognitive enhancer in rodents. And stated that Brāmhi Ghṛta may be useful as supportive treatment in neurodegenerative disorders where memory is impaired.[11]

V. Kumar et al., studied the effect of various doses of aqueous extract of Centella asiatica for 21 days.The drug was investigated in i.c.v. STZ-induced cognitive impairment and oxidative stress in male Winster rats. Cognitive behavior was assessed on the days 13, 14 and 21. These rats showed a dose dependent increase in cognitive behavior. A significant decrease in MDA and an increase in glutathione and catalase levels were observed only in rats treated with higher dose of Centella asiatica .Hence the results concluded that aqueous extract of Centella asiatica is effective in preventing the cognitive deficits and oxidative stress, caused by i.c.v. STZ in rats. [12]

Parle M et al.,studied cognitive effects of Glycyrrhiza glabras on mice.The study revealed that Glycyrrhiza glabras significantly improved learning and memory.Also the amnesia induced by diazepam , scopolamine and ethanol in mice was

reversed by Glycyrrhiza glabras. This cognitive enhancement could be because of facilitation of cholinergic transmission in brain.[13]

Singh N. et al., in their study showed Celastrus paniculatus significantly increase in learning and memory and also regulates the serum biochemistry.[14]

Like this a variety of plant showed their cognitive enhancing activities relevant to use in the neurodegenerative disorders.A good number research studies are on antioxidant properties ,cholinergic modulation, role of biogenic amines.

The review of studies regarding Āyurvedic drugs reveals that these drugs can be used for both prevention and management of age related cognitive deficits and progress to senile dementia can be halted. Thus it can be concluded that based on these evidences these drugs have potential to check the cognitive decline in elderly and can be used to improve their quality of life and enjoy an independent socially productive life.

No research trial reports were found on Nirguṇdi kalpa or its effect on aMCI. But various research reports of its ingredients are found and could be helpful to assess the action of Nirguṇdi kalpa on aMCI.

Otari et al.,in their study demonstrated and reveled the hydroalcoholic extract of VN leaves in normal as well as in scopolamine- induced cognitive deficit mice .And found out the probable efficacy of hydroalcoholic extract of VN in poor learners to meet cognitive demand as well as in age, stress, emotions, etc. induced cognitive dysfunction. The result showed cognitive enhancing activity of VN.

The scientists again reveled that, the effect may possibly due to AChE inhibition, antioxidant effect, and increase in cholinergic transmission by the extract.Lignans, flavonoids, phenolic acid, triterpenoids etc.in the VN may be accountable for the nootropic activity.[15]

Antioxident, antiamnesic properties of Goghṛta and Madhu are well known.Though antiamnesic activity of Goghṛta alone are not studied, its nootropic activity along with other medhya drugs are proved.[16,17]

Al-Himyari et al., conducted a five-year pilot study involving cognitively intact subjects and patients with mild cognitive impairment aged 65 and older. They were

randomized and provided either one tablespoon honey or placebo daily. They found that only 95 subjects who received honey compared to 394 who received placebo developed dementia. So the study concluded that honey acts as a natural preventive therapy for both cognitive decline and dementia. [18]

Al-Rahbi et al.,(2014) performed an animal study on honey. The rats' memory performance was assessed pre and post trial. They administered honey to 40 ovar iectomised and 20 Śām-operated female Sprague-Dawley rats. Tualang honey treatment improved both short-term and long-term memory and enhanced the neuronal proliferation of hippocampal CA2, CA3 and DG regions compared to untreated groups.[19]

Summary:

Review of research literature on MCI found ample of research reports published on MCI and aMCI in foreign countries.While researches from India are very few. Also research studies on incidence and prevalence rate of aMCI in India are very few.

The review of research studies concerning Āyurvedic drugs reveals that these drugs can be used for management of age related cognitive decline and prevention of its progress to senile dementia .These drugs have shown and proved potential to improve the cognitive decline in elderly leading to improve their quality of life .But most of the studies on these area are animal trials. Very few scientific clinical human studies are performed .However, there is a clear and urgent need for large scale independent clinical trials on well described patient cohorts, using thoroughly applied design criteria and well established end-points.

Though lot of pharmacological and clinical research work is performed on Nirguṇdi,it is related to its analgesic and anti-inflammatory effects.No clinical research was conducted to study its antiemnestic activity.No published or unpublished data found on Nirguṇdi Kālpa.

Hence, modest efforts have been made in this study to generate scientific evidence for the efficacy and safety of the Nirguṇdi kalpa in aMCI.

This review sums up clinical and experimental studies to illustrate evidences regarding the indication for use of these drugs in cognitive decline and thereby improving their quality of life and making them socially accepted.

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AIMS AND OBJECTIVES

3. AIMS AND OBJECTIVES

- Aim:

To study the efficacy of Nirguṇdi kalpa in MCI with special reference to amnesic MCI

- Objectives:
    - To review the literature of mild cognitive impairment, jarā and ageing as per modern science and Āyurveda.
    - To observe side effects of the drug if any.
    - To assess overall wellbeing effect of the drug.
    - To try to establish Āyurvedic parameters for assessment of cognition, Smṛuti.

MATERIAL AND METHODS

4. MATERIAL AND METHODS

Material:

Trial drug

Patients

4.1 - Trial Drug - Nirguṇdi kalpa:

Standardization, preparation of Nirguṇdi kalpa:

- Collection & authentification of raw materials:

Nirguṇdi tree was identified and roots were collected, from the farm near Khed Shivapur, Pune district as per guidelines mentioned in Āyurvedic classics. The place was hygienic. Help of botanist and Dravyaguṇa Śāstra masters was taken during this for identification of the plant.

Madhu was collected from authentic source in Pune.

Goghṛta was purchased and collected from authentic source in Pune.

The raw materials were properly examined for adulterants and foreign matter like sand, insect, rodent contamination which was found to be in specified limit as per Āyurvedic Pharmacopoeia of India.

- Authentication of raw materials:

Authentication of raw materials was carried out at Department of Botany, Pune University. Pune

The authentication certificate of raw materials are mentioned in annexure.

After drying of Nirguṇdi roots, size reduction was done. Size separation was done using 80 mesh size sieve

- Organoleptic Parameters:

Organoleptic parameters like colour, odour and taste were carried out for all raw materials. These parameters helped in visual identification of raw materials.(Refer annexure).

- Standerdization of raw drugs:

Standard guidelines given by WHO and API Methods and Āyurvedic guidelines(mentioned by Carka saṃhitā & Kākacandeśvarakalpatantraṃ) were followed for pharmacognostic and physiochemical standardization of raw material i.e. ingredients of Nirguṇdi kalpa.

Heavy metal analysis of Nirguṇdi was performed.The permissible limit for Heavy Metal content was mentioned in Āyurvedic Pharmacopoeia of India.

Standardization of raw material was done at Late prin.B.V.Bhide Foundation, S.P.College road,Tilak road,Pune 411030.(Refer annexure.)

- Trial drug preparation:

Standard operating procedure (SOP) for Nirguṇdi kalpa:

i. Nirguṇdi root was properly cleaned, shed dried and powdered. It was sieved by 80 mesh sieve to obtain fine powder.

ii. Nirguṇdi powder was mixed with Madhu and Goghṛta thoroughly to get homogenous mixture in following proportion

Nirguṇdi:	Madhu:	Goghṛta
1	: 0.9	: 0.66

iii. In the above given proportion, the combination Nirguṇdi kalpa was prepared.

iv. As per textual guidance it was kept in a clean, dry earthen vessel, coated internally by Goghṛta.

v. The container was sealed with a paste of fuller earth and water and cotton cloth.

vi. The earthen vessel was emmersed in Dhanya rashi (A sac full of wheat) and kept for one month.

vii. After one month the seal of the vessel was opened and the Nirguṇdi kalpa was taken out of it and stored in clean glass container with tight lid.

Drug was prepared at GMP certified lab.

- Standardization of trial drug:

The final product standardization was done as per IP guidelines. Determination of physicochemical parameters done. Heavy metal analysis was performed.The permissible limit for Heavy Metal content was mentioned in Āyurvedic Pharmacopoeia of India. Microbial Limit Test Microbial analysis was carried out as per standard procedure (Indian Pharmacopoeia, 2010.) (Refer annexure) Standardization of Nirguṇdi kalpa was done at Late prin.B.V.Bhide Foundation, S.P.College road, Tilak road, Pune 411030

Toxicity Study:

All the raw drugs of Nirguṇdi kalpa are found to be non toxic in literary search and are in day to day use.

Acute toxicity study of ethanolic leaf extract was carried out. Results revealed that VN is nearlly nontoxic, as its LD50 dose recorded was 7.5 g/kg/wt.

Considering these points and after discussion with ethical committee, toxicity study of Nirguṇdi kalpa was not performed.

Fig. 15. Nirgundi Root Powder

Fig. 16. Madhu

Fig 17. Goghruta

Fig. 18. Drug prepared in Earthan Pot

Fig 19. Nirgundi Kalpa

Fig. 20 Packets of Nirgundi Kalpa

Administration of drug:

Dosage -10 gms.once in a day.

Route of administration- Oral

Kāla- Rasāyan kāla.

Anupan- Luke warm water

Dosage period- 3 months.

10 grams of drug was administered orally in Rasāyana Kāla with Luke warm water for three months.

- Packaging and dispensing of study drug -

Nirguṇdi kalpa was prepared in bulk quantity and was stored in proper condition with care.150 grams was packed in plastic bag and dispensed to the patient for each 15 days. Drug was given by investigator to the patient directly.

- Accounting procedure:

Raw material was tested for confirming of standards established in project. Nirguṇdi kalpa was manufactured once i.e., before trials and standardized.

4.2 Patients:

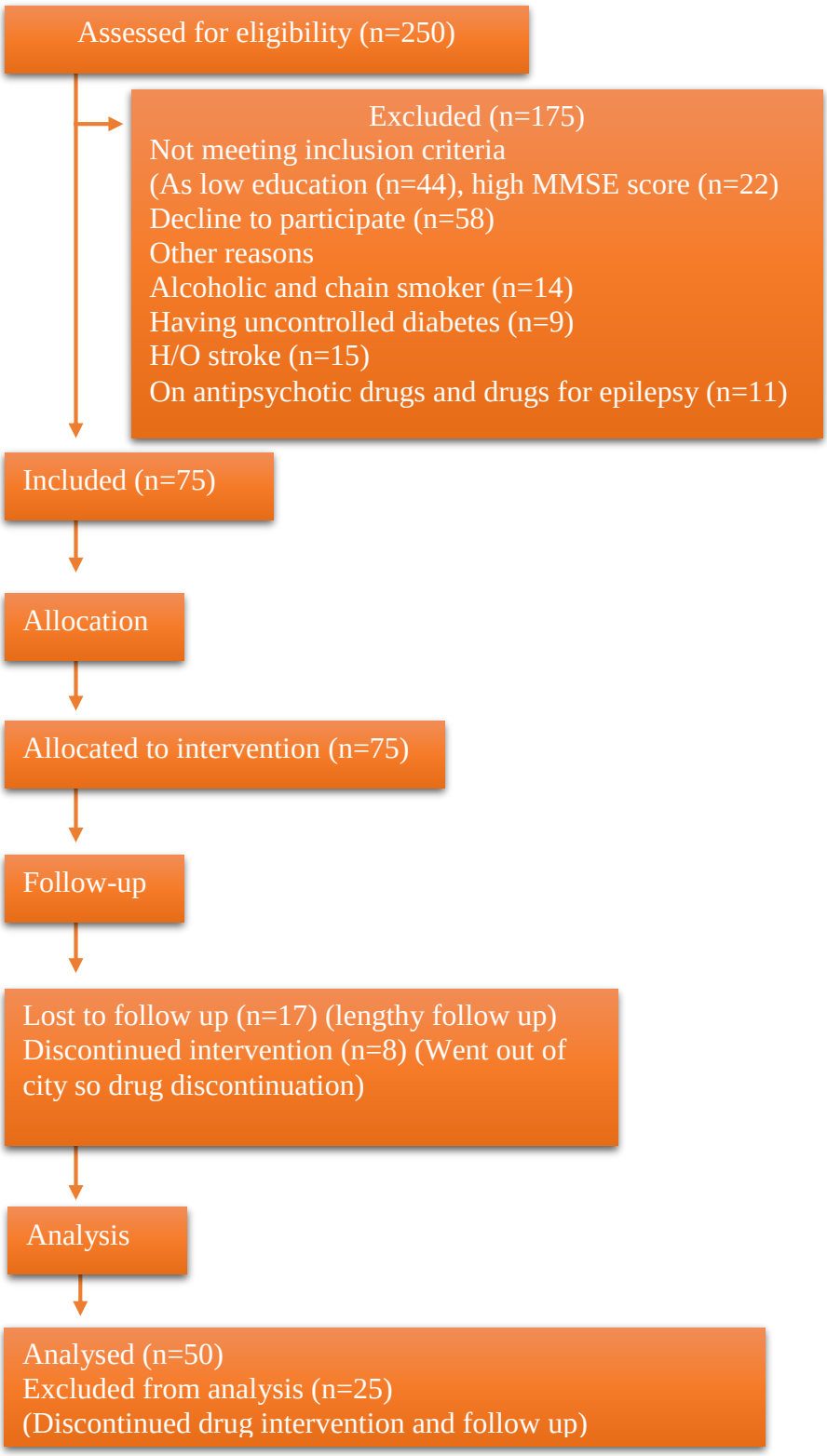
Total 50 complete patients of aMCI were taken. Patients were screened and included and assessed in the trial according to criteria mentioned in methodology.
Sample selection:

Participants were selected from the Bharati Vidyapeeth Deemed University college of Ayurveda Hospital, Pune.Individuals coming to Bharati Vidyapeeth Deemed University college of Ayurveda Hospital, above the age of 40 years and having memory complainets were recruited randomly from areas of near by Katraj Dhankawadi,Pune, India , through the oral interview. Participants were excluded if they did not meet the inclusion criteria. Like low education level and high score of MMSE. If they declined

to participate in the study. Also they were excluded, as suffering from uncontrolled Diabetes mellitus,or taking antipsychotic and anti epileptic medication,having history of stroke,or individual was heavy alcoholic or chain smoker.

Those who were not excluded were included in the trial were allocated and intervened with the trial drug.Those individuals who discontinede 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. Remaining individuals who completed the trial were analysed statistically.

Fig. 21. Sample Selection



Subject recruitment and screening

Patients above 40 yrs. of age having memory complaint were screened for the signs and symptoms of aMCI and if MMSE score was 22-27 ,GDS score was normal or showing mild depression were sent for pathological investigations mentioned in the protocol. After this if he fits in to the inclusion criteria of the study he was selected for trial after lingual and written consent. Trial drug was given for further 3 months by the investigator. Patient was kept under observation for further six months.

4. 3 - Methodology:

- Type of study:

Randomized clinical study

- Place of study:

Bharati Vidyapeeth Deemed University, College of Ayurved and hospital, Kayachikitsa dept.IPD and OPD, Pune- 411043.

- Sample size - complete 50 patients

Inclusion and exclusion criteria of study participants-

Inclusion criteria:

i. Patients having clinical complaints of aMCI having their age above 40 yrs. Irrespective of gender, work and socio economical status.

ii. Patient having memory complaint more than 6 months, whose score on MMSE is 22-27, and who are not depressed or mildly depressed on GDS scale.

iii. Patients whose minimal education is 7th standard.

Exclusion criteria:

i. Patients having major psychological or major neurological problems.

ii. HIV infected patients /AIDS.

iii. Malignancy.

iv. Hypothyroidism, uncontrolled DM and uncontrolled HTN

v. Alcoholic, chain smoker.

Investigations:

Lab tests - Haemogram, Urine Routine, Microscopic, Blood Sugar Levels-Fasting and Postprandial, Blood Urea levels, Serum creatinin, Tridot for HIV.Electro cardio gram was done prior to inclusion in the trial.

Assessment criteria:

i. Clinical examination.

A detailed history and case was taken and physical examination performed after the verbal consent of patients as per the proforma prepared for this purpose.

ii. MMSE score - Mini mental state examination.[1]

This is a 30 point scale and answer is awarded one score.After thorough literary study and considering opinions of peers in this field cut off was decided.Hence patients whose score was in between 22-27 were selected for inclusion in the trial.

iii. GDS score. [2]

Yesavage Geriatric Depression Scale (short – version) was used to screen the subjects for depression. It contains 15 questions and each "depressed'' answer is awarded one score. According to its norms, the scoring above 5 indicates depression, while 7±2 scores indicate mild depression and scoring 1±2 indicates severe depression.

iv. ACE-R score. [3]

Addenbrook's cognitive examination, final revised version,2005 was used.The ACE-R is scored out of 100. Cut off scores of either 88(sen.=94%, sp.=89%) or 82(sen.= 84%, sp.=100%) are for Dementia .The cut off-score for aMCI has not been clearly determined in ACE-R.After the thorough literary study and considering opinions of peers in this field the cut -off score for this study decided was lower 85/100 and higher 92/100.

v. Wellbeing index by WHO score.(WBI) [4]

This is the scale used to assess overall psychological wellbeing of the patients.It is a 25 questions scale. Raw score: total the figures of the 5 answers - 0 to 25. Raw score: 0 represents worst possible quality of life and 25 represents best possible quality of life.A score below 13 indicates poor well-being and an indication for testing for depression .Hence patients showing such score were not included in the trial

vi. GERRI test score.[5]

Geriatric Evaluation by Relatives Rating Instrument (GERRI).

GERRI profile for patient's elderly relative, which indicates the level of cognitive, social and emotional deterioration of the patients. No standard score for aMCI is mentioned the, but pre and post trial score comparison can give idea about cognitive, social and emotional well being.Information is to be obtained from patients caregiver, relatives.

Subjective/objective parameter:

Memory complaints with special reference to decline of memory by application gradation scales

Early withdrawal of subjects:

Patient was withdrawn from the trial if there is occurrence of serious adverse events the investigator felt that the protocol had been violated or the patient had become uncooperative or patient was not willing to continue the trial during course of treatment. Even though subjects were withdrawn prematurely from the study data of these subjects is kept.

Primary study endpoints:

Improvement in scores of ACER scale according to standardized age, education norms

Secondary study endpoints:

Improvement in score of WHO Wellbeing Index (WBI score)

Improvement in score of care taker interview (GERRI score).

Study procedures:

The evaluation schedule was as followed:

VISIT 0 : Screening visit (informed consent date)

VISIT 1 : Baseline visit, start day of therapy

VISIT 2 to visit 7 : Treatment phase (visit once in 15 days)

VISIT 8 : Follow up phase

VISIT 9 : Follow up (observation) phase

VISIT 10 : Follow up (observation) phase and end of study

Table 13. Study procedure

	Screening	Treatment and evaluation phase									End of study
Visit	V0	V1	V2	V3	V 4	V 5	V 6	V 7	V8	V9	V10
Days	D0	D 1	D 15	D 30	D 45	D 60	D 75	D 90	D 91	D 180	D 270
Informed consent		√									
Inclusion /exclusion criteria	√										
Treatment		√	√	√	√	√	√	√			
Assessment MMSE, GDS	√										
	√										
ACER Clinical exam		√			√		√		√	√	√
	√	√	√	√	√	√	√	√	√	√	√
WBI		√	√	√	√	√	√	√	√	√	√
GERRI		√									√
Safety laboratories, parameters	√	√	√	√	√	√	√	√	√	√	√
Adverse events		√	√	√	√	√	√	√	√	√	√

Medication and treatment permitted during drug trial:

Treatment of minor element requiring medication for less than a week was permitted. Any ongoing treatment of Hypertension, Diabetes Mellitus and Arthritis etc. which didn't interfere the trial drug effect were continued.

Treatment not permitted before and during trial:

Self-medication, internal steroids, tranquillizers, psychotropic or anti cholinergic drugs were not permitted during trial.

Statistical plan:

Statistical method

For comparison of score visit wise t-test was applied, we have observed that, p-value for t-test is less than 0.05.It can be concluded that there is significant effect observed after visit wise score. Observations in each domain and WBI score and ADL score and GERRI score are quantitative so t-test was used.

Subject populations for analysis:

The subject population whose data was subjected to the study analysis-both for the primary analysis and any applicable secondary analysis was kept. Missing data was kept as missing along with explanation of probable cause of missing data.

Adverse events:

No serious adverse event during the study were seen.

Adverse events monitoring safety parameter:

- Blood pressure
- Blood sugar levels-fasting and postpradial

The treatment was stopped or the patients was withdrawn from the trial if, occurrence of serious adverse events, the investigator felts that the protocol has been violated or the patient has become uncooperative, patient was not willing to continue the trial or to follow the assessment schedule.

Confidentiality, record keeping:

Information about study subjects was kept confidential.Documents were kept and maintained carefully by the investigator. Special CRF was prepared for the study

Ethical considerations:

BVDUCOA's human ethical committee approval was taken prior to the study.

The formal consent (ICMR guideline) of a subject, using the ethical committee approved consent form, were signed by the subject and the investigator.

Termination of trial:

Trial was terminated at the end of the followup period of the last subject included in the trial.

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2) Yesavage JA et al., 1982 Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res.17 (1):37-49

3) Mioshi, E et al., 2006 The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. International Journal of Geriatric Psychiatry, 21, 1078–1085

4)WHO-5Questionnaires.https://www.psykiatri-regionh.dk/who-5/about-the-who-5/Pages/default.aspx

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OBSERVATIONS AND RESULTS

5. OBSERVATIONS AND RESULTS

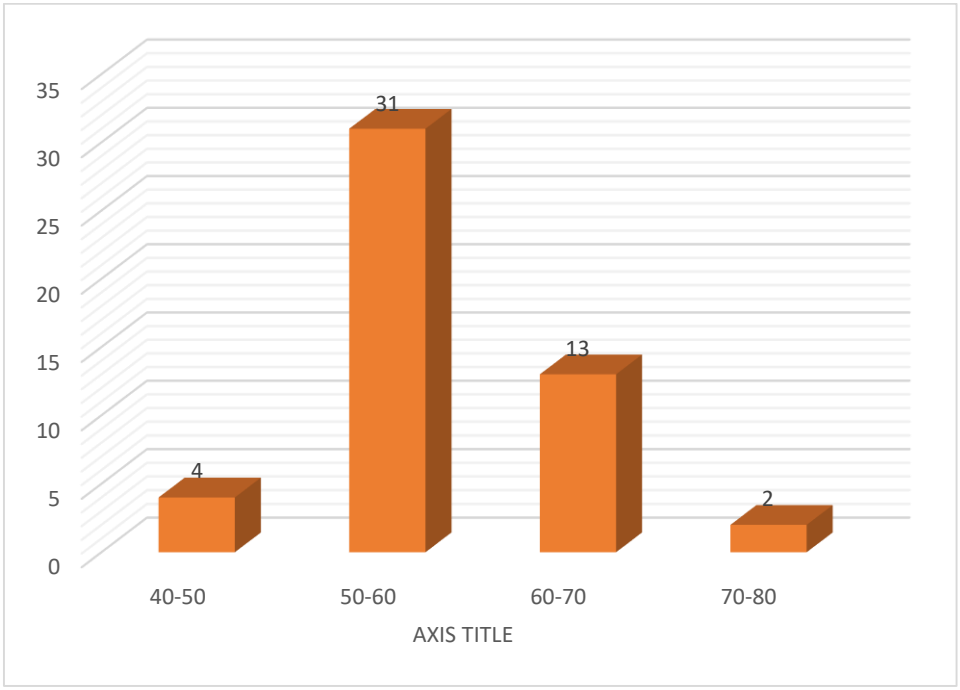
Demographic data and results of 50 completed patients is being presented here.

Age wise distribution of patients:

Table.14

Age	40-50yrs.	50-60yrs.	60-70y	70-80yrs
No.	4	31	13	2
No.in %	8	62	26	4

Graph-1



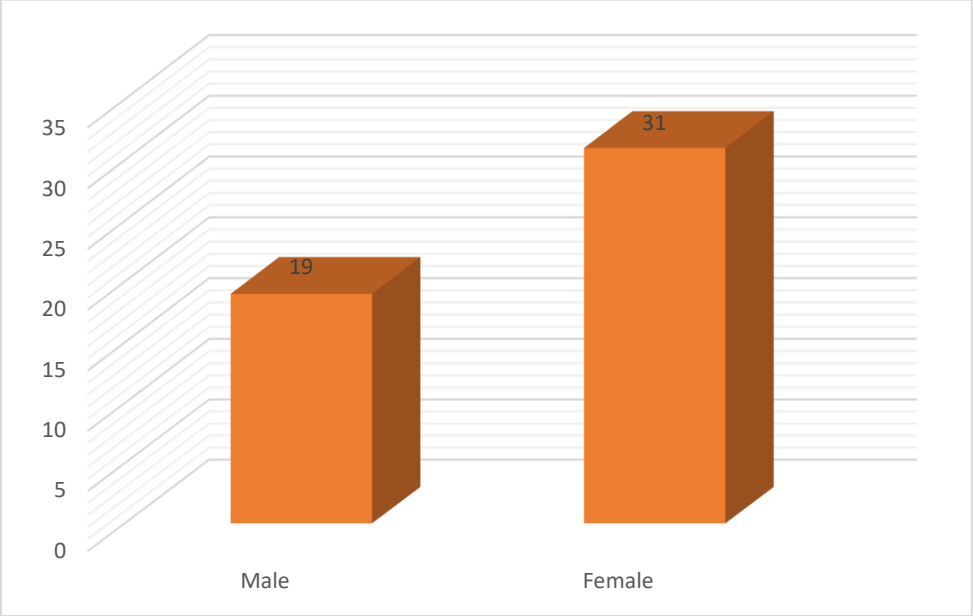
Maximum number i.e. 62%patients were in the age group of 50-60 yrs., followed by 26% patients in the age group of 60-70 yrs., 8% in 40-50 yrs. and 4% in 70-80 yrs. of age group.

Gender wise distribution of patients:

Table.15

Gender	Male	Female
No.of patients	19	31
No.of patient in %	38	62

Graph.2



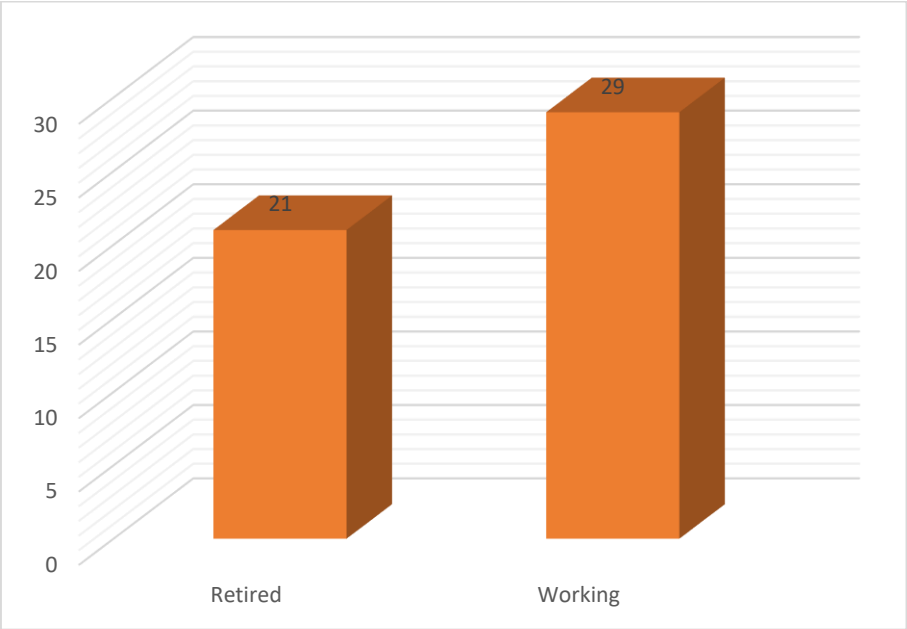
Maximum i.e. 62% of total patients were female and 38% were male

Distribution of the patients according to work condition:

Table.16

Working status	Working	Retired from work
No.of patients	29	21
No.of patients in %	58	42

Graph.3



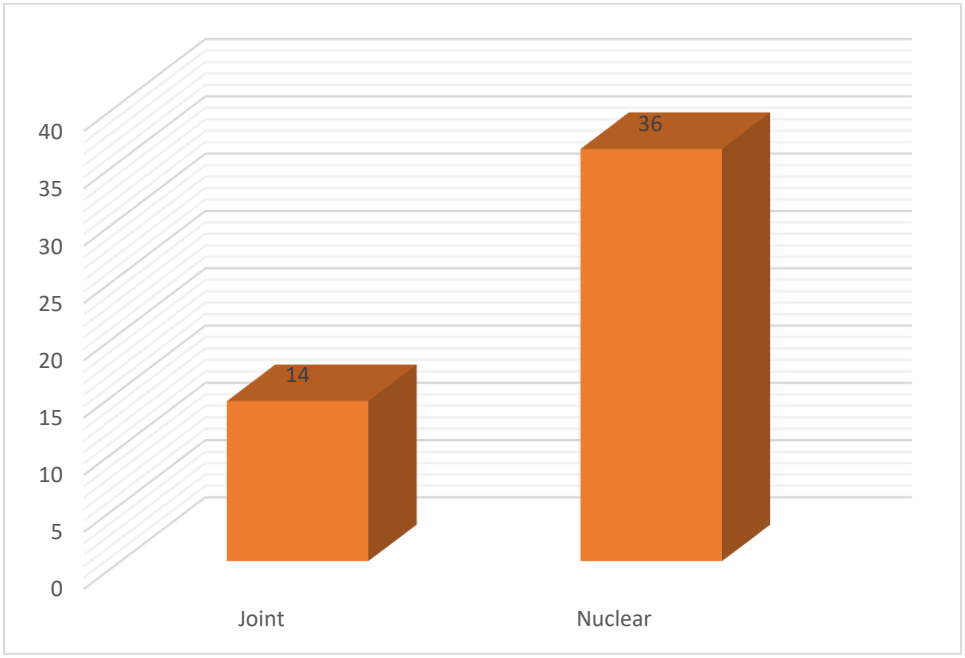
58% patients were working, whereas 42% patients were retired from the work

Distribution of patients according to joint or nuclear family status:

Table 17

Family status	Joint family	Nuclear family
No.of patients	14	36
No.of patients%	28	72

Graph. 4



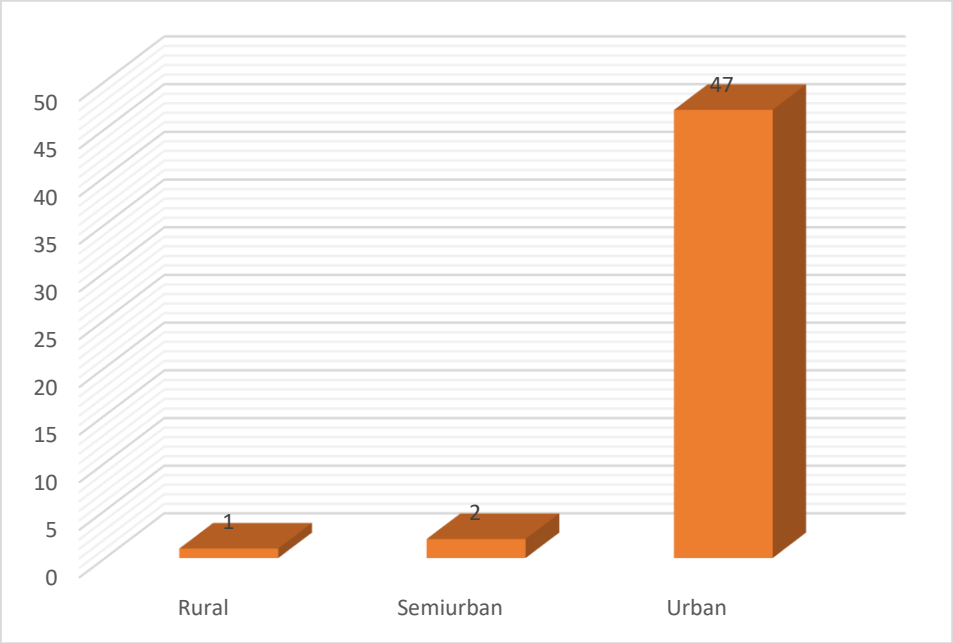
72% patients were from nuclear family while 28% patients were from joint family

Living area wise distribution of patients:

Table.18

Area	Urban	Semiurban	Rural
No.of patients	47	2	1
No.of patients in %	94	4	2

Graph 5



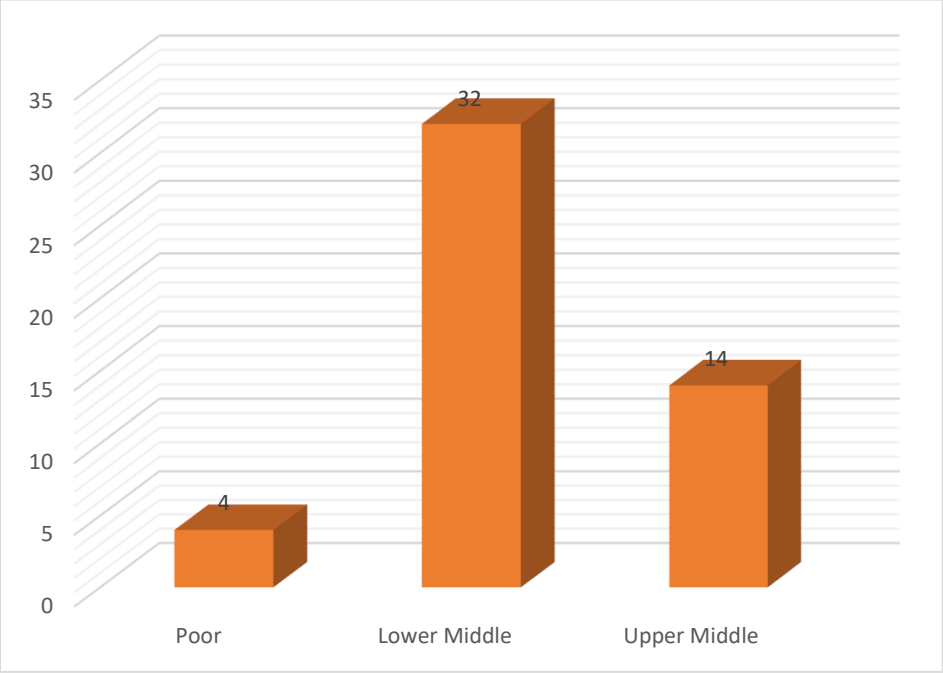
94% patients were from urban area, 4% from semiurban area and 2% patient from rural area.

Socio economic class wise distribution of patients:

Table 19

Socio economic class	upper middle class	lower middle class	poor class
No.of patients	14	32	4
No.of patients in%	28	64	8

Graph 6



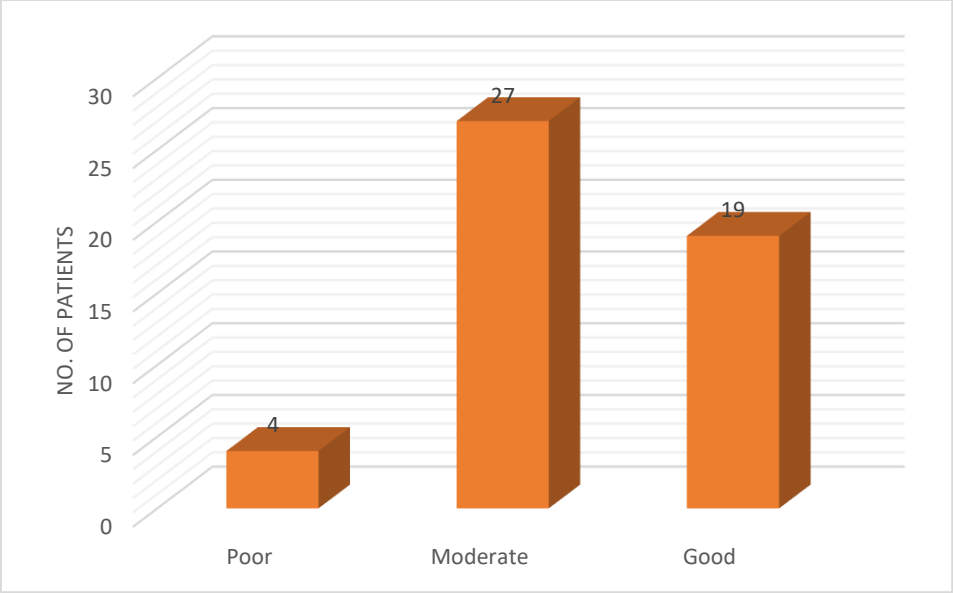
64%patients belonged to lower middle class, 28% from upper middle class and 8% patients were from poor class.

Housing condition wise distribution of the patients:

Table .20

Housing condition	Good	Moderate	Poor
No.of patients	19	27	4
No.of patients in %	38	54	8

Graph 7



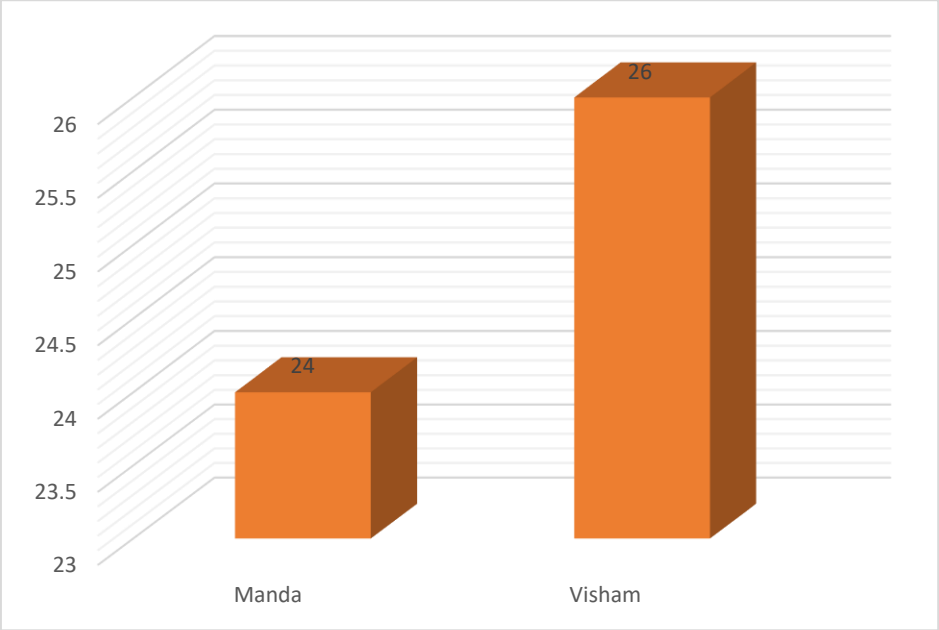
54% patients had moderate housing condition, 38% had good housing condition and 8% had poor housing condition

Jātharāgni condition wise distribution of the patients:

Table 21

Jātharāgni condition	Manda	Viśām
No.of patients	24	26
No.of patients in %	48	52

Graph 8



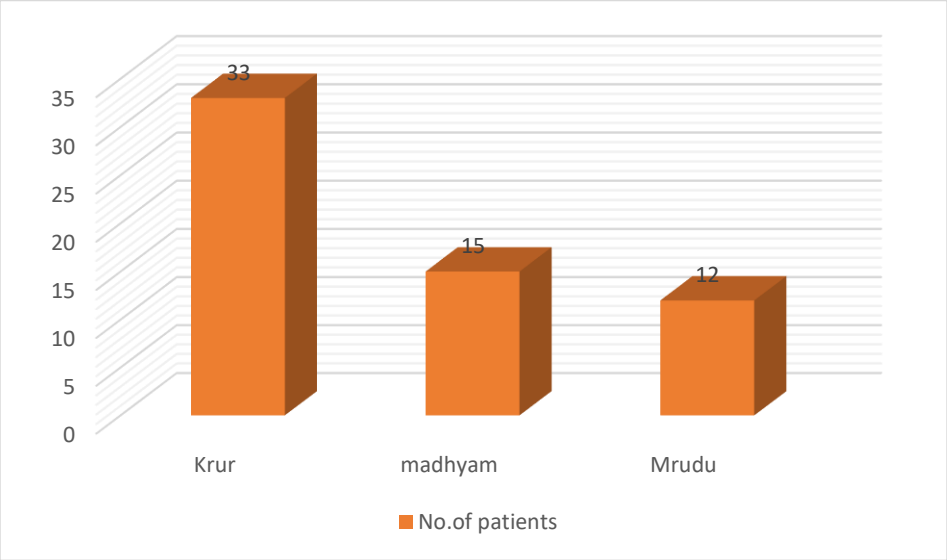
52% patients had Viśām agni while 48% had Manda agni

Kośtha wise distribution of the patients:

Table.22

Kośtha	Kṛra	Madhyam	Mṛdu
No.of patients	33	15	12
No.of patients in %	66	30	24

Graph.9



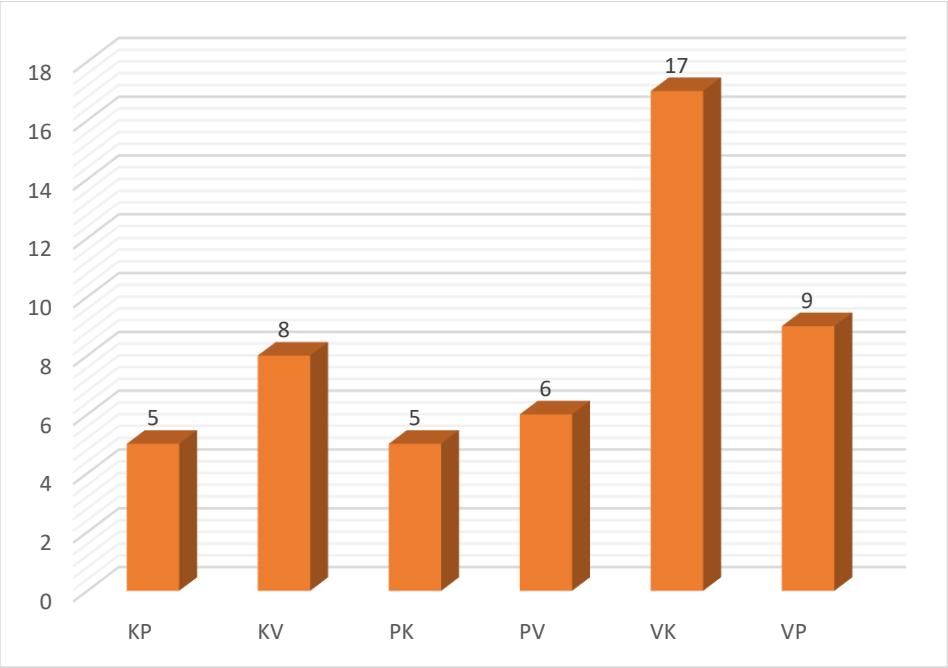
66% patients had Kṛra kośtha followed by 30% of madhyam kośtha and 24% had mṛdu kośtha.

Prakṛti wise distribution of the patients:

Table.23

Prakṛti	KP	KV	PK	PV	VK	VP
No.of patients	5	8	5	6	17	9
No.of patients in %	10	16	10	12	34	10

Graph 10



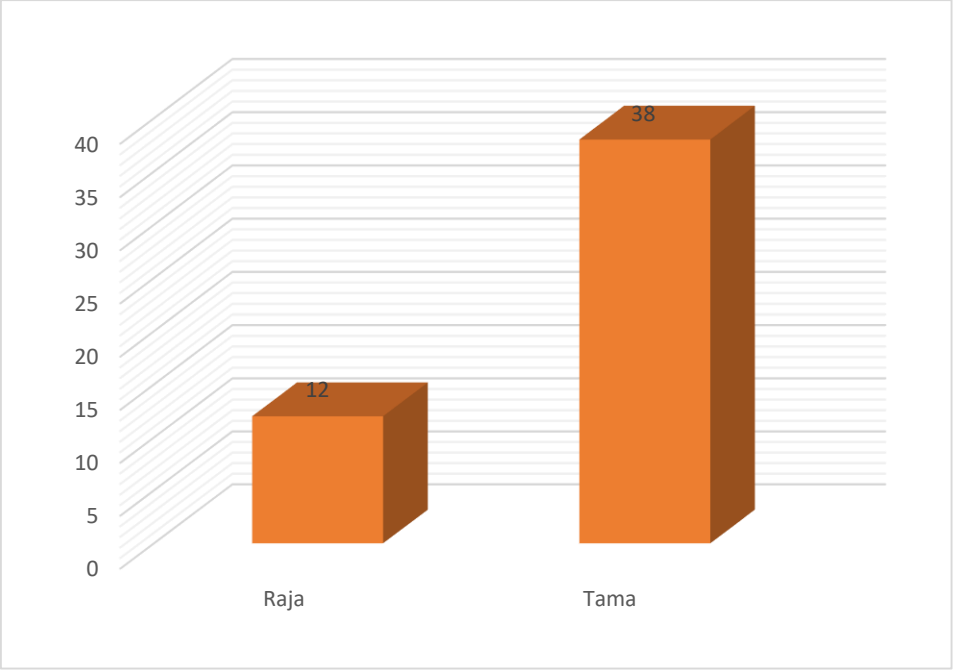
34% of patients had Vātakapha prakṛti followed by 18% of the patients who had Vātapitta prakṛti,followed by 16% patients of Kapha Vāta prakṛti.12% had Pitta Vāta,10% each in Pitta kapha and Kapha pitta prakṛti.

Manas prakṛti wise distribution of the patients:

Table 24

Manas prakṛti	Rajas pradhān	Tamas pradhān
No.of patients	12	38
No.of patients in %	12	76

Graph 11



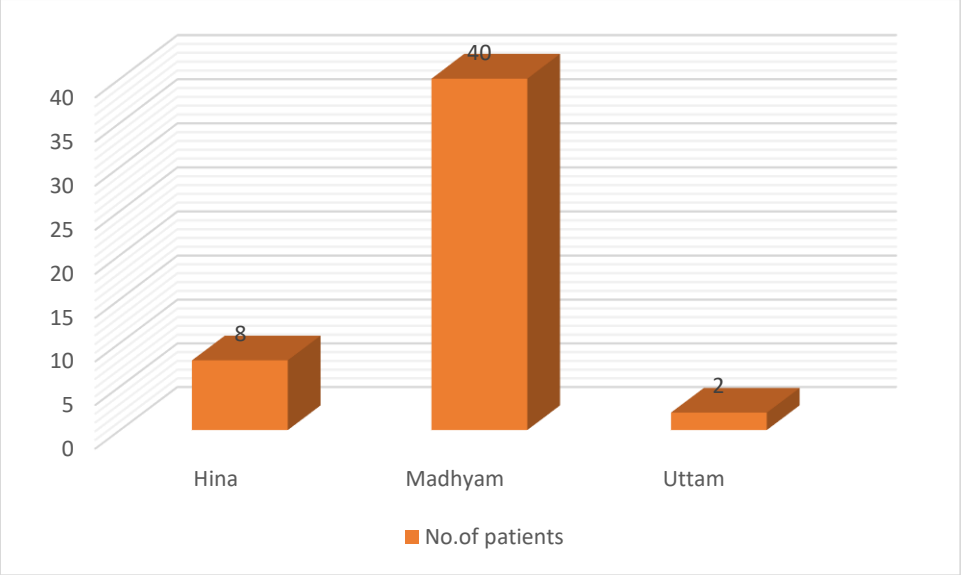
76% patients had Tamas pradhāna manas prakṛti,24% had Rajas pradhāna manas prakṛti.

Satva wise distribution of patients:

Table 25

Satva	Hina	Madhyam	Uttam
No.of patients	8	40	2
No.of patients in %	16	80	4

Graph 12



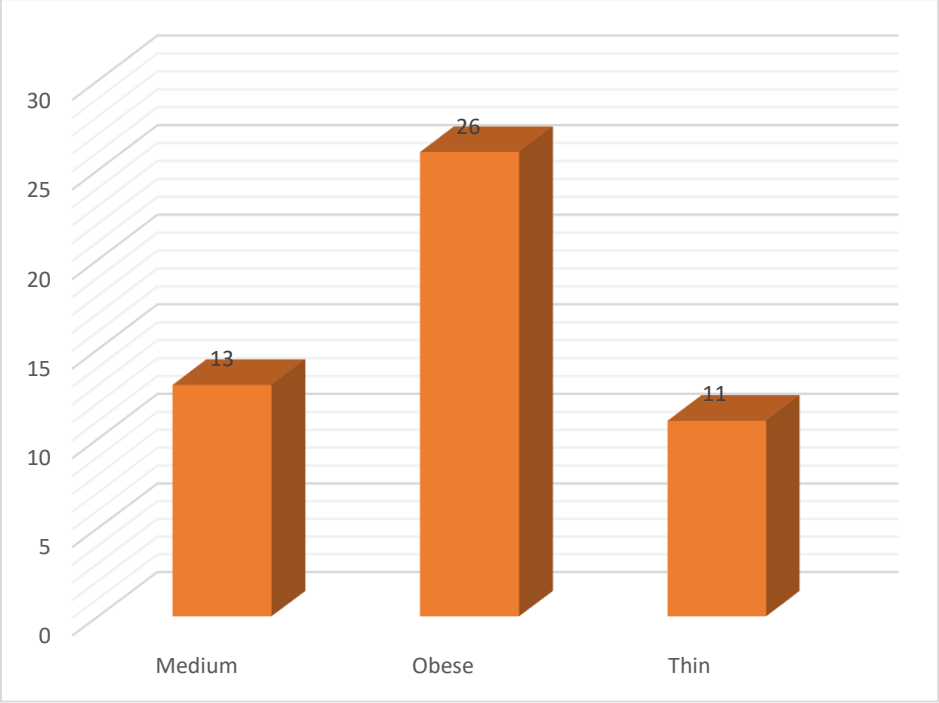
80% patients had Madhyam satva, 16% had Hina satva and 4% were having Uttam satva.

Distribution of the patients as per body built:

Table 26

Built	Thin built	Medium built	Obese
No.of patients	11	13	26
No.of patients in %	22	26	52

Graph 13



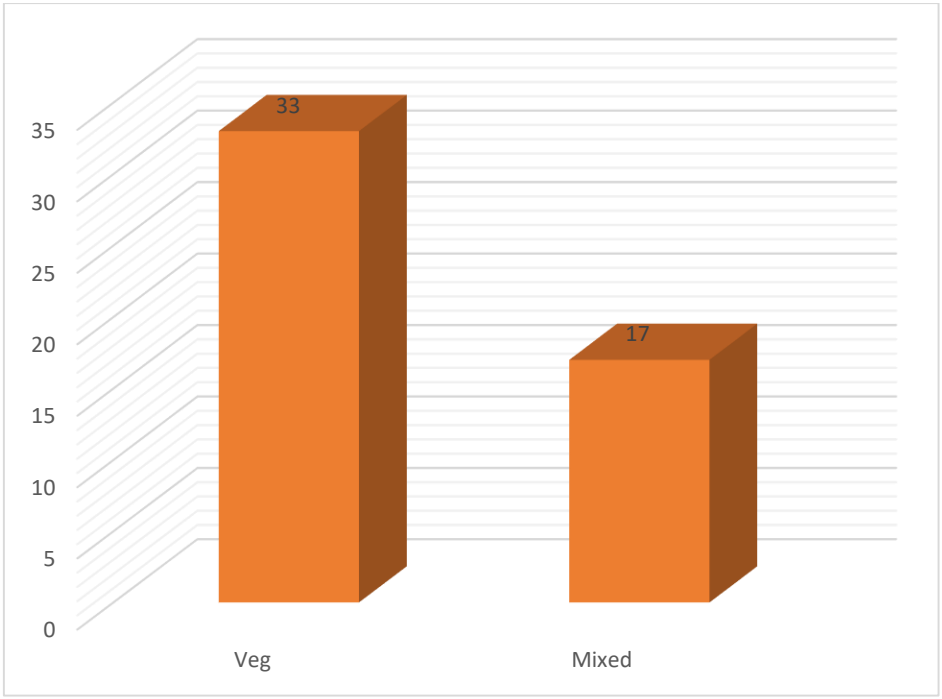
52% patients were obese while 26% patients were having medium built.22% patients were having thin built.

Diet wise distribution of the patients:

Table 27

Diet	Mixed diet	Vegetarrian
No.of patients	17	33
No.of patients in %	34	66

Graph 14



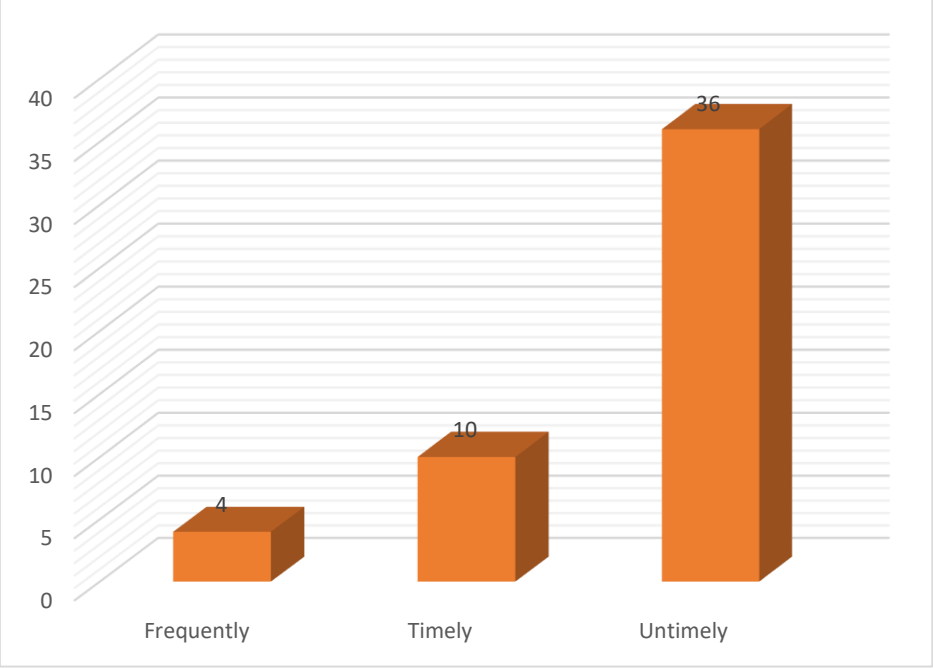
66% patients were taking vegetarian diet while 34% patients were taking mix diet.

Distribution of the patients according to meals timing:

Table 28

Meals timing	Timely	Untimely	Frequently
No.of patients	10	36	4
No.of patients in %	20	72	8

Graph 15



72% patients were taking meals irregularly and untimely,10% were taking meals on regular times and 8% patients needed frequent meals in a day.

Distribution of Female patients with and without menstruation:

Table 29

Menstrual condition	Regular Menstruation	Menopause
No.of patients	1	30
No.of patients in %	2	60

Graph 16

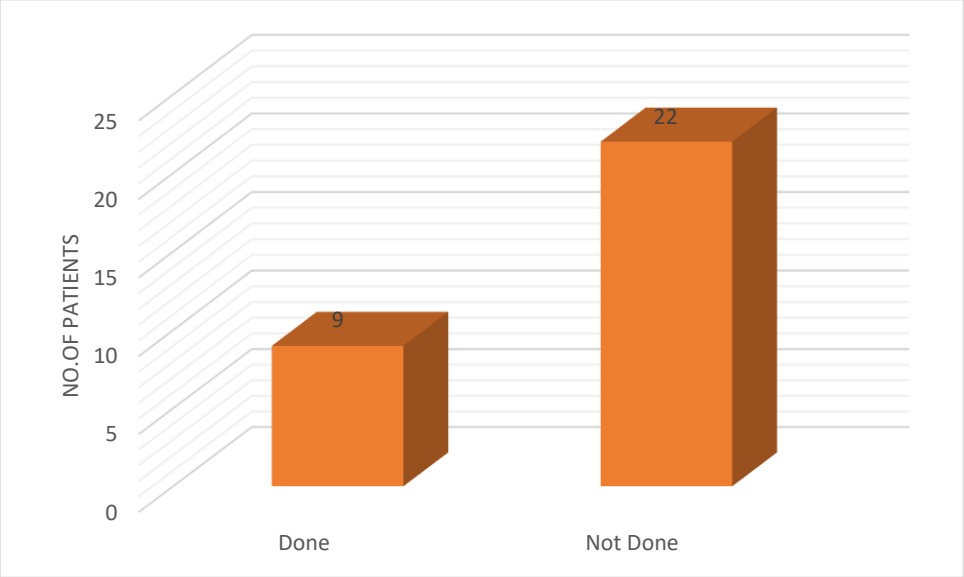
60% female patients were having menopause and 2% patients had regular menstruation

Distribution of female patients according to surgical and nonsurgical menopause:

Table 30

Surgical menopause	Hysterectomy surgery done	Hysterectomy not done
No.of patients	9	22
No.of patients in %	18	44

Graph 17



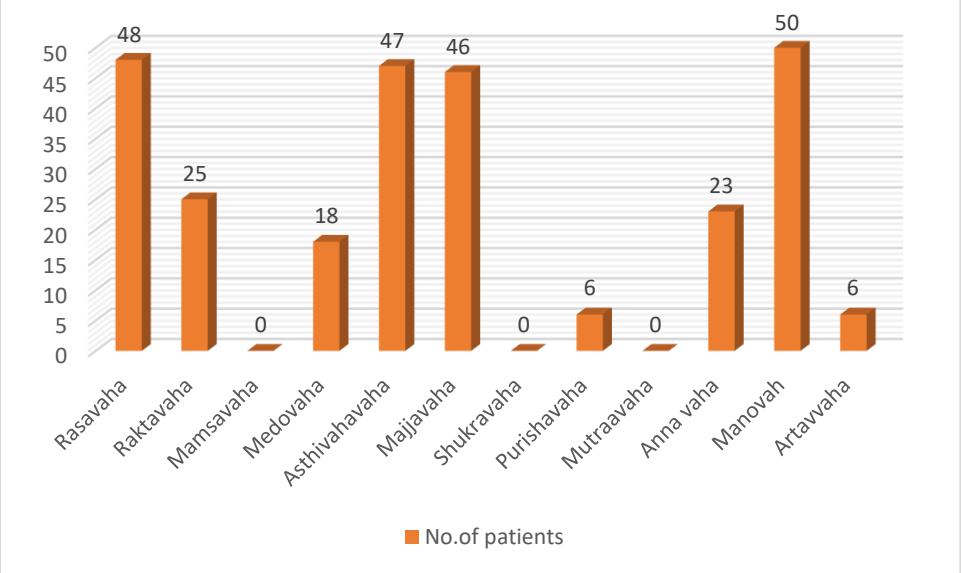
Among 30 menopausal patients 18% patients had undergone hysterectomy surgery while 44% had normal menopause.

Distribution of the patients according to Srotas dusti:

Table 31

Srotas dusti	Rasavaha	Raktavaha	Māṃsavaha	Medovaha	Asthivaha	Majjāvaha	Śukravaha	Purisavaha	Mutravaha	Annavaha	Manovah	Ārtavvaha
No.of patients	48	25	0	18	47	46	0	6	0	23	50	6
No.of patients in %	96	50	0	36	94	92	0	12	0	46	100	12

Graph 18



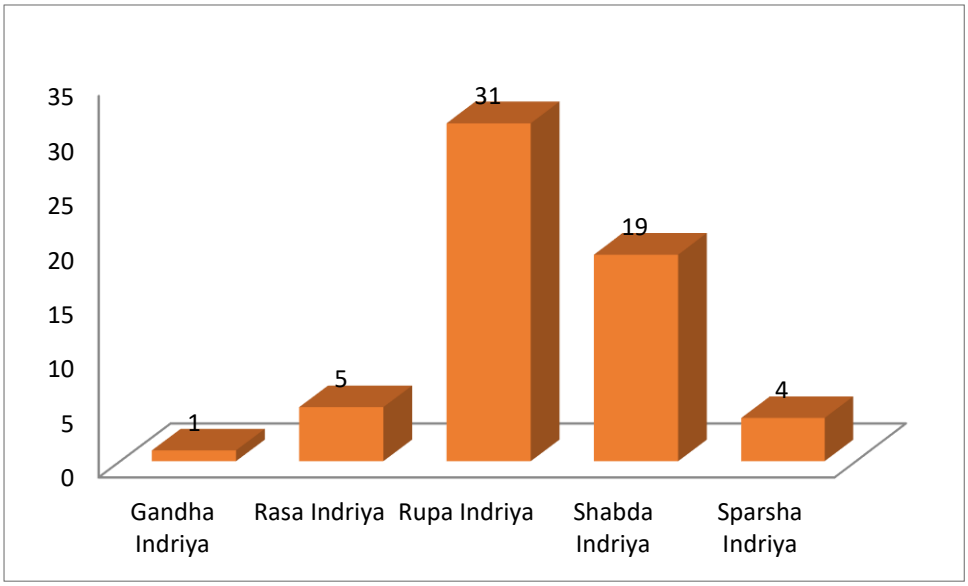
96% patients had Rasavaha srotas affected,50% had Raktavaha srotas affected also,Asthivaha srotas dusti in 94% patients, Majjāvaha srotas dusti in 92% patients,Medovaha srotas dusti in 36%,Annavaha srotas dusti in 46%,Purisāvaha srotas dusti in 12% ,Ārtavvaha srotas dusti in 12% patients found.All patients had Manovaha srotodusti.

Indriya duṣti wise distribution of patients:

Table 32

Indriya	Śabda	Sparśā	Rupa	Rasa	Gandha
No.of patients	19	4	31	5	1
No.of patients in %	38	8	62	10	2

Graph 19



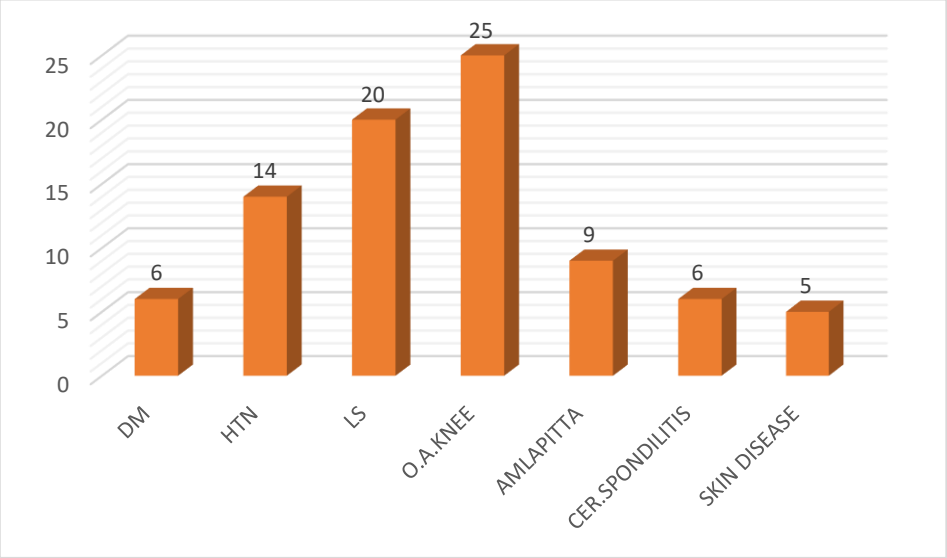
62% patients had Rupa indriya duṣti i.e.impaired vision,38% had Śābda indriya duṣti or mild hearing impairment 8% patients had,Sparśanendriya duṣti,10% had Rasanendriya duṣti , while2% patient showed duṣti of Gandha or ghrāṇendriya.

Other associated diseases in the patients of aMCI:

Table 33

Disease	DM	HTN	L.S	O.A knee	Amlapitta	Cer.S	Skin disease
No.of patients	6	14	20	25	9	6	5
No.of patients in %	12	28	40	50	18	12	10

Graph.20



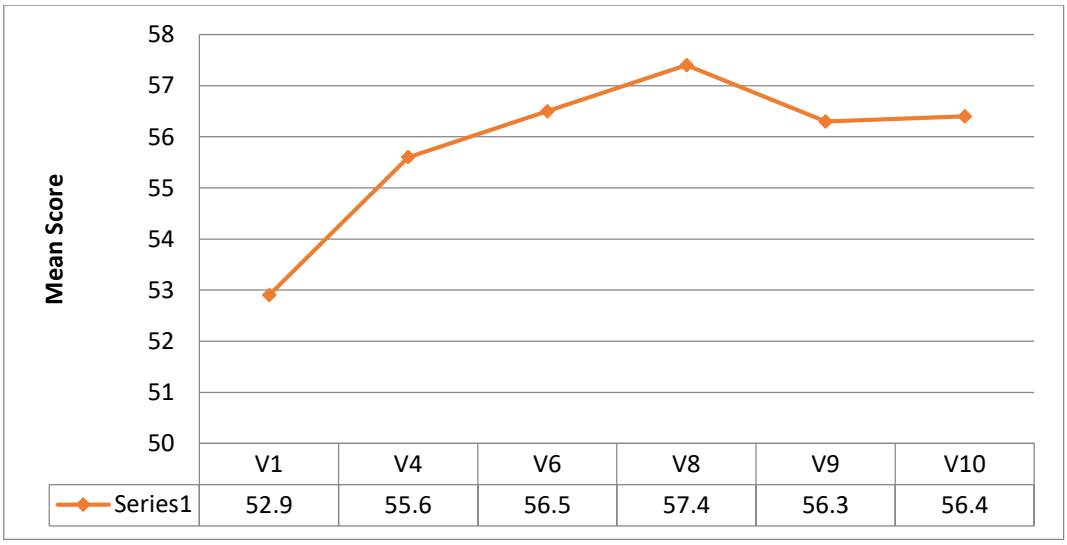
50% patients were suffering from Osteoarthritis of knee (O.A knee), 40% from Lumbar spondilitis (L.S),12% from Cervical spondilitis (Cer.S), 28% were suffering from Hypertension (HTN).12% patients were suffering from Diabetes mellitus (DM),10% from skin diseases and 18% patients were suffering from Amlapitta.

ACER score in patients of aMCI- pre and post treatment:

Table. 34

Visits	V1	V8	V9	V10
ACER score	52.9	57.4	56.3	56.4

Graph 21



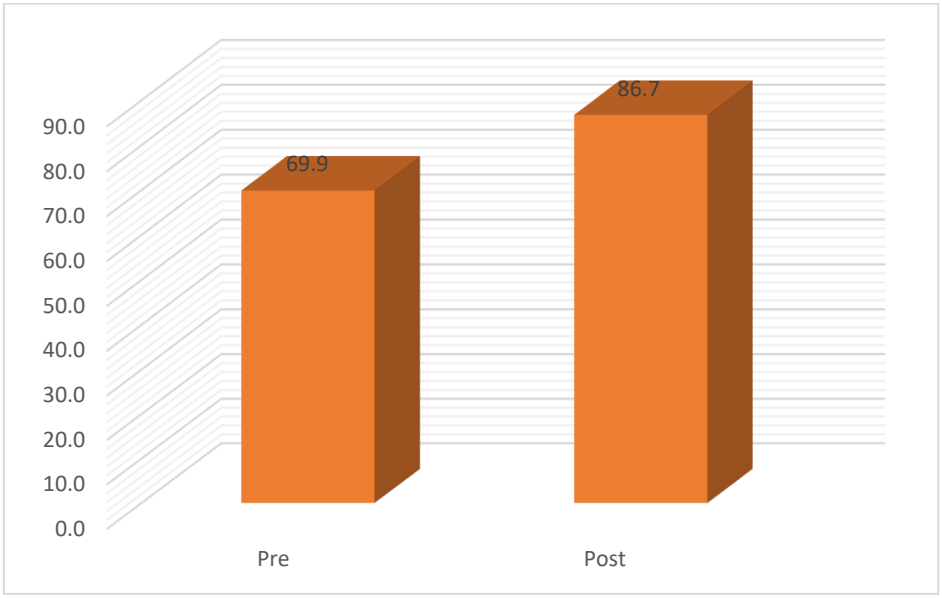
At Visit 1 average score was 52.9 it went on increasing up to 57.4 till visit 8 then it decreases to 56.3 at visit 9 and it seems unchanged 56.4 at visit 10.

WBI score inpatients of aMCI- pre and post treatment:

Table 35

	Pre treatment	Post treatment
WBI score	69.9	86.7

Graph22



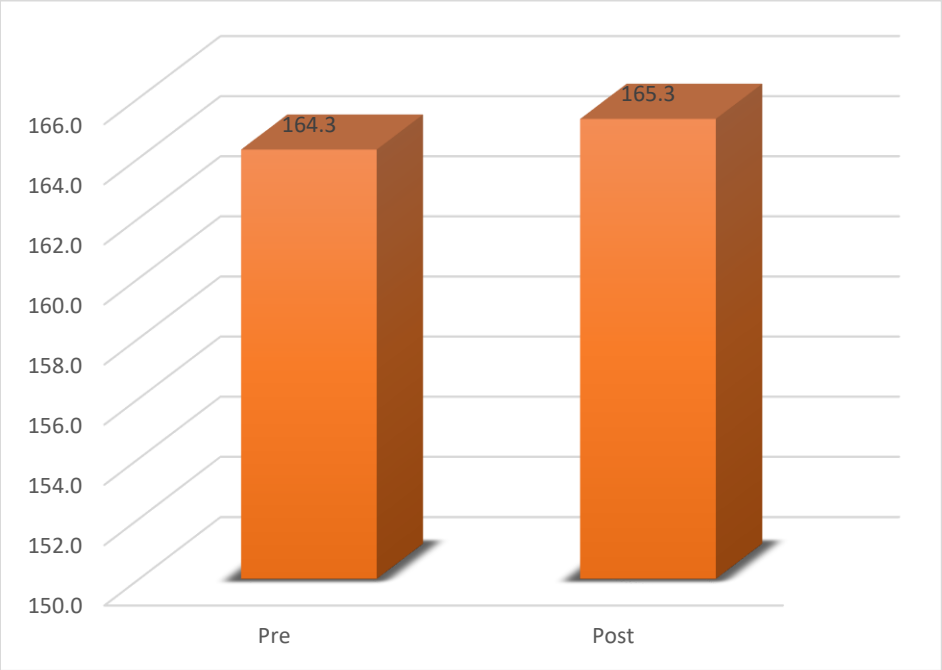
Pre treatment the WBI score was 69.9 and after treatment it became 87.7

GERRI score in aMCI patients- pre and post treatment:

Table 36

	Pre treatment	Post treatment
GERRI score	164.3	165.3

Graph 23



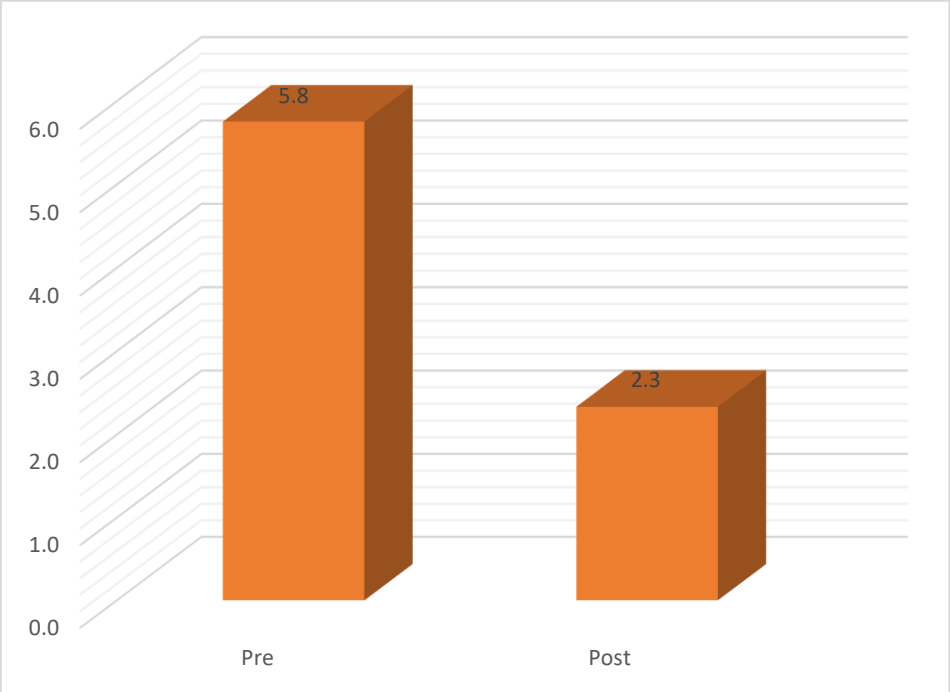
Pre treatment score was 164.3 and after treatment it became 165.3

ADL score in aMCI patients- pre and post treatment:

Table 37

	Pre treatment	Post treatment
ADL score	5.8	2.3

Graph 24



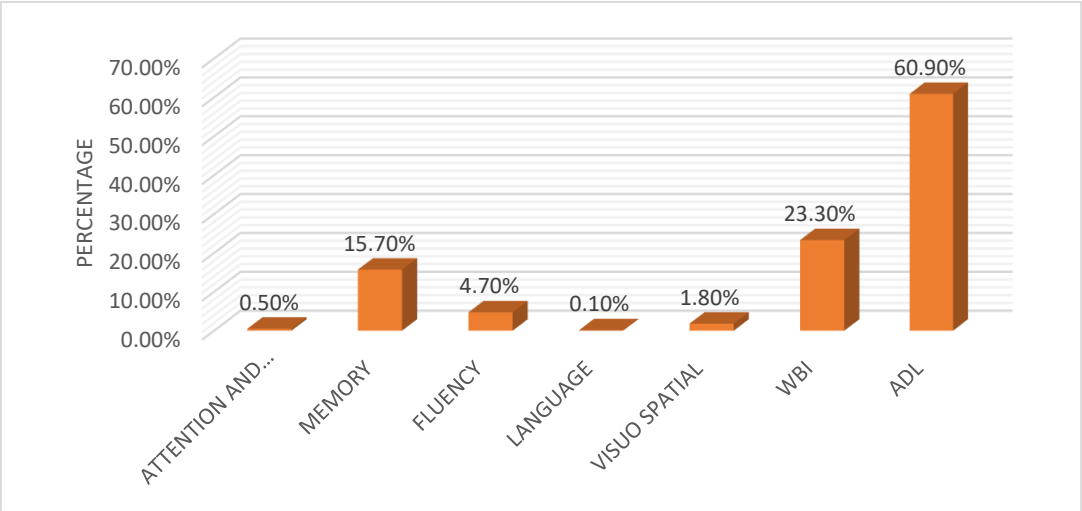
Pre treatment ADL score was 5.3 after treatment it became 2.6.

% effect in each cognitive domain, WBI index and ADL score:

Table 38

	Mean			Difference at V8	Difference at V10	% Effect at V8	% Effect at v10	P-Value
	V1	V8	V10					
ATTENTION AND ORIENTATION	16.7	17.2	16.8	0.6	0.1	3.3%	0.5%	<0.05
MEMORY	20.4	24.2	23.6	3.8	3.2	18.5%	15.7%	<0.05
FLUENCY	11.7	12.0	12.2	0.3	0.6	2.4%	4.7%	<0.05
LANGUAGE	24.1	24.1	24.1	0.1	0.0	0.3%	0.1%	>0.05
VISUO SPATIAL	14.9	15.0	15.1	0.1	0.3	0.8%	1.8%	>0.05
WBI	17.7		21.8		4.1	0.0%	23.3%	<0.05
ADL	5.5		2.2		3.4	0.0%	60.9%	<0.05

Graph 25



Since the observations are quantitative, we have used t-test. From above table we can observe that, Difference at visit 8 for attention and orientation was 3.3% with P-Value less than 0.05. For memory the percentage effect at visit 8 was 18.5% with P-Value less than 0.05, For Fluency there was change in mean at visit 8 about 2.4% with P-Value less than 0.05. For WBI score effect was observed at visit 10 about 23.3% with P-Value less than 0.05 and for ADL score effect at visit 10 was observed about 60.9% with P-Value less than 0.05. While P-Value for Language and Visuo Spatial were greater than 0.05. Hence we conclude that, Effect observed in Memory, Attention and Orientation, Fluency, WBI and ADL was significant.

Overall effect of the treatment:

Table 39

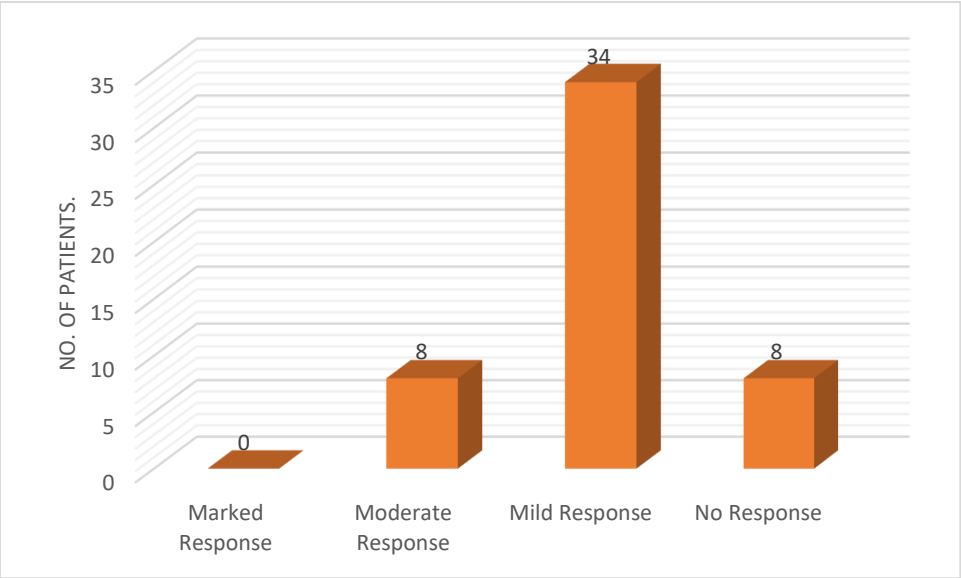
Above 75% Improvement	Marked response
50%-75% Improvement	Moderate response
25%-50% Improvement	Mild response
Below 25% Improvement	No response

%wise overall effect of the treatment:

Table 40

	No. of Patients	Percentage
Marked response	0	0
Moderate response	8	16
Mild response	34	68
No response	8	16
TOTAL	50	100

Graph 26



From above table we can observe that, 8 patients out of 50 observed moderate response. Mild response observed in 34 (68%) patients and no response was observed in 8 (16%) patients.

DISCUSSION

6. DISCUSSION

Cognitive decline or memory decline is a burning problem in today's era. Life expectancy has increased because of development in medical science. Consequence of this is increase in elderly population. Which is exerting a lot of medical, social burden on the society. Hence there is a requirement to tackle their problems as early as possible.

Discussion on literature review:

Mild Cognitive Impairment (MCI) is the clinical manifestations disturbing the elderly population. This is the transitional stage between the cognitive declines of normal ageing. Several elderly individuals complains of impaired memory, and perform less well than the younger one in various cognitive jobs, predominantly those jobs that assess memory; these findings suggest that memory impairment is a frequent consequence of the ageing process. Though it is so, still this is very much ignored or neglected issue in the society.

Even though many individuals with MCI complains of memory decline, impairments in other cognitive domains also takes place but not all MCI patients progress on to convert in to AD.Research studies in pre-dementia syndromes, particularly aMCI, reveal that the aMCI is a prodromal phase of dementia, particularly the AD type.

Though prevalence rate of MCI, aMCI is constantly varying, the rate is continuously increasing.

Disturbance in ACh, Dopamine, BDNF, Serotonine, GABA enzymes, neuronal loss, neurofibrillay tangels and amyloid plaques are the main reasons for aMCI.Large research is going on on MCI in other countries as compared to India. Prevalence of AD and other dementia also increasing in India.

At the present time, no effective treatment is available to correct the persistent degeneration and deterioration of the disease. The rate of adverse events are in the higher side too. Due to progression in serious disorder, MCI is a clinical condition whose identification and monitoring is suggested. As early diagnosis and treatment turn out to be a major factor in the prevention of successive disability like dementia.

In this research work on aMCI an attempt has been made to find a clinical correlation between aMCI and Jarāvasthā janya Smṛtibhraṃśā.

Though MCI is not mentioned as a disease moety in separate chapters in Āyurvedic classics, references about its symptoms gets scattered in the classics .Hence MCI,aMCI can be understood by understanding concepts of Jarā,jarā lakṣaṇ and its pathogenesis, Indriya, Medhā ,Buddhi ,Smṛti,process of Jñānotpatti etc.

The term "Smṛtibhraṃśā" jarājanya has been adopted because a direct reference of Smṛtibhraṃśā has been mentioned in Ca.śā. 1/101, though no etiopathogenesis is described. Besides, the term Smṛtinaśā, denotes complete loss of memory which more or less means an irreversible progress in Smṛti decline has taken place. In addition, it means that a treatment aimed, can not show any improvement in memory. While by using the term Bhraṃśā, it can be considered that, still positive changes in memory decline can be expected with the help of Rasāyan therapy.

Collecting and considering the references in Āyurvedic classics a probable samprapti of aMCI is described in Review of literature chapter.

Medhya Rasāyana has been mentioned in the classics for the management of neuropsychological disorders.But considering a heterogenous etiopathogenesis and complication in pathology of aMCI ,involvement of multiple factors in aMCI;a multitargetting combination of the drugs rather than a single drug, was selected. Various drugs formulations are mentioned in the classics for such condition. Nirguṇdi kalpa was selected for following reasons:

- Nirguṇdi kalpa mentioned in the classics as usefull in psychological disorders.
- Nirguṇdi mentioned in the classice as memory enhancer
- Other ingredients are also theoretically proved Medhya drugs.
- Easy availability of all the ingrediants
- Cost effectivity
- Also no trials are conducted on Nirguṇdi kalpa on aMCI till today or published papers are not available.

Considering all the above things Nirguṇdi kalpa was selected for intervention in the patients of aMCI.

Discussion on material and methods:

As exact rate of incidence and prevalence of aMCI or MCI in India or in Maharashtra was not available by the authentic sources; and since this is a comparatively new clinical condition in Āyurvedic research area, fifty completed sample size was decided as per ethical committee’s suggestion.

Type of trial was randomized trial. As rate of prevalence of aMCI in Maharashtra or India was not available so sample size selected was small.Also no published results are available about research on any Āyurvedia drug on aMCI .So for comparison, proved results of any Āyurvedic drug in aMCI were not available.Considering these points and Ethical committee's suggestion randomized trials were conducted.

Total 250 patients were screened, 75 were registered and 50 patients completed the trial. 25 patients were dropped out. Drop out rate was more .May be because of ignorance or granted ness towards this symptom as it does not affect largely the individual's daily activities of living. Second reason found for this was lengthy follow up.

Actual chronological ageing starts from the age of sixty as per Carka saṃhitā. But now a day's signs of ageing are commonly seen in early age. Medhā starts declining from the 4^{th} decade of the life as per mentioned in Śārangdharasaṃhitā. Research studies also suggested that cognition starts declining from 50 yrs. of the life. Hence considering these points and considering subject experts opinion, patients above 40 years of age were included in the trial. But very few patients of aMCI found in the age group 40-50 yrs.in the trial. 62 %patients belonged to age group 50-60 yrs.

Dose of trial drug given was as mentioned by the classics it self ie.one Karṣa(apprx.10 grams) in Rasāyan kāla i.e.empty stomach in the early morning. As other anupān may hamper the effects of drug so simple lukewarm water was given as anupān. Drug duration is not exactly mentioned in the reference book of Nirguṇdi kalpa. Bhaiśājya ratnāvali has mentioned the same formulation with little difference in quantity of ingredients. There the duration of drug intake for manovikār has been mentioned as two months. Considering this and the discussion with well known psychiatrists and neurologists in Pune the drug duration was kept for three months. Follow up period for further six months was decided by ethical committee subject experts. So as to find out whether the drug effect lasts for further period or not.

Special CRF was prepared for this trial. Which include both physical as well psychological neurological examination from the Āyurveda as well as modern point of view.Special consent form was also prepared according ICMR guidelines.

There are various neuropsychiatric batteries available for the assessment of cognitive decline and memory decline.Most of them are derived in the foreign countries

and for the population there. Many of them are highly paid scales and not easily available. Some scales are not valid enough to use. Some consume very long time for assessment which is not practical in busy clinical work. Some scales are computerized and need special technological and financial assistance.There is no detailed information available for the cognition, memory assessment in Āyurveda classics. Few people have taken efforts to convert the original English scale in local Indian language. Some have tried to formulate a new scale for this purpose eg.NIMHANS Banglore has formulated a cognitive assessment scale for elderly, which is very highly paid scale. But validity of these version was again a major problem. So considering above things, after discussion with psychiatrists and psychologists in Pune the scales which are valid, reliable, easily used, and less time consuming, relatively suitable for Indian population and easily available were selected for the assessment purpose.

For designing each point in the CRF peer's advice was considered. As education may have impact on cognition of the person, to avoid the bios; minimum education criteria was decided. Where patient will be enough learned to read and write. But because of education criteria it became tough to get patients above 75 years of age for inclusion in this trial.As these patients did not completed the education criteria.

As depression may result in to cognitive impairement; which is quite different entity from MCI. So to avoid the bias patients were initially screened by GDS scale to exclude them from the trial.

MMSE test was selected for screening only; as it does not give the complete detailed information about the cognitive domain affected. But it is a good test for initial diagnosis of MCI and consumes less time. For detailed assessment ACER was selected. As it gives complete information about all affected domains, takes around 20-25 minutes for assessment, easy availability and easy applicability.(Details of ACER,GDS,MMSE,GERRI,WHO Wellbeing index are enclosed in annexure)

Major psychiatric disorders may have impact on memory which may give wrong diagnosis of MCI. Psychotropic drugs also disturbs memory and can not be stopped suddenly as it may increase the disease pathology,so such patients were excluded from the trial.

Most of the patients had memory complaint more than one year prior to the registration in the study.

There are no such confirmatory pathological investigations available for the diagnosis of aMCI. So basic laboratory investigations like Haemogram, Urine Routine-

Microscopic, Blood sugar levels, Blood urea level, Serum creatinin, Tridot for HIV, Electro cardiogram were done prior to inclusion in the trial; more or less for exclusion purpose, confirmation of other associated disease.Haemogram, Urine Routine-Microscopic, Blood sugar levels, Blood urea level, Serum creatinine were done post treatment as per requirement to observe any adverse effects of the drug during the trial.

Raw Nirguṇdi roots had very mild aroma but after drug preparation aroma converted into strong odor.

Asātmyaindriyārthasaṃyog, prajñāparādh, pariṇām were the causes found for aMCI in the trial. Among them excessive intake of Katu, tikta, amla, lavaṇ rasa, rukśā, laghu, Uṣṇa guṇa, untimely meals, paryuṣitānna sevan were more commonly seen causes.

Bhaya, śoka, moha, krodha were the Manas hetus found responsible for aMCI.

Discussion on observation and results:

Medhā starts declining in fourth decade of the life. Out of the 50 patients of aMCI studied in this study, among 40-50 yrs.age group patients were less. 50-60 age group patients were 62%. This observation also supports the research statement in modern sciences that cognition starts declining after 50 year of age. This age group denotes the initial stage of Vāta predominance. Rajas is mainly related with Vāta, this might play an active role in the pathogenesis of memory decline in aMCI.

Only 4% patients were from 70-80 yrs. age group. This was may be because, at this age, these memory complaints are either taken granted or ignored.

Most of the patients had more than1 year chronicity in the cognitive symptoms.

Number of female patients were more i.e. 62%. As sample size was small, nothing concrete can be concluded about gender differences in a MCI.

94% patients were from urban area. Patients coming at our hospital were from nearby area which is urban area, also due to frequent follow up visits patients from nearby area were selected.

Maximum, 72% patients were from nuclear family. As sample size was small nothing concrete can be concluded about family background differences in aMCI.

42% were retired from work. 58% patients were working. Difference in this percentage is little so no firm conclusion can be drawn.

64% were from lower middle class, 28% patients were from upper middle class and 8% patients from poor economical class. 54%patients had moderate housing condition, 38% patients were from good housing condition and 8% were from poor

housing condition. Due to small sample size and difference, can not conclude firmly about relation between financial condition and aMCI.

Maximum no. of patients i.e.52 % patients had Viśāmāgni.This suggests Vāta vṛddhi during this period or old age.

100% patients were literate. It was one of the criteria of inclusion.

66% patients had Kṛra koṣtha. Kṛra koṣtha is suggestive of Vāta doṣa dominance which is the prime causative factor for all neuropsychological disturbances.

Maximum i.e.34% patients were of Vātakaphaprakṛti followed by 18% patients of Vātapittaprakṛti. This indicates dominance of Vātadoṣa in prakṛti. Which is responsible for early cognitive decline. Also this gives evidence that Vātakapha prakṛti patients are more at risk for developing aMCI.

76% patients had Tamas pradhān prakṛti while 24% patients had Rajas pradhān prakṛti. Though Rajas is responsible for Vāta vikruti and acceleration of ageing; Tamas dominance is responsible for Smṛti decline.

96.8% female patients were at menopausal stage and 3.2% were having menstrual cycle regularly. Most of the patients had early menopause and hysterectomy done. This observation suggests that early menopause may be one of the responsible factor for cognitive decline.

18% patients had complaint of Amlapitta. All these patients were having chronic Amlapitta. Research studies have already revealed the relationship between MCI and Acid reflux syndrome.Ghrelin is the enzyme which is negatively correlated with cognitive domains, attention, verbal memory, working memory, and naming. Increased ghrelin levels are related to lower cognitive function. Ghreline levels get disturbed due to chronic gastro intestinal diseases. Hence chronic Amlapitta may contribute in the aMCI samprāpti. [1]

12% of patients had complaint of Diabetes mellitus. It is proved that MCI takes place twice more frequently in individuals with Diabetes mellitus type 2. Number of studies have evaluated the cognitive function in individuals with diabetes or pre-diabetes, and revealed that poor glucose regulation is related with global cognitive decline especially memory domain, but the deficits in other cognitive domains is

weak.[2]In this study number of patients found with this association are few. So can not claim any confirmed relationship between aMCI and diabetes mellitus.

28% had complaint of Hypertension. Hypertension can reduce cerebral blood flow and metaboloism i.e glucose utilization to gain energy, particularly in specific brain regions such as frontal and temporal lobes. Age and hypertension leads to damage the endothelium of the cerebral arteries. Which results in disturbed blood brain barrier allowing the entry of toxic substances. Atheroscelorosis due to an age and hypertension also reduces microcirculation to white matter.All these factore may help in declining cognitive function in elderly.[3]

50%of patients had complaints of specially knee joint osteoarthritis and 40% had complaint of lumbar spondilitis. 12% had cervical spondilitis. Means number of patients suffering from degenerative arthritis type in patients of aMCI was more.

Initially it was said that there is no association between Osteoarthritis and MCI or cognitive decline. But some clinical research studies have proved that peripheral inflammation may be related with increased risk for neurodegenerative disorders like AD. Also there is a link between serum levels of pro-inflammatory cytokines and other markers,like IL-6 , (IL)-1β , tumor necrosis factor (TNF)α , C-reactive protein etc. with increased risk for dementia .

Cunningham C, et al: found release of proinflammatory factors in the central nervous system that exacerbated neurodegeneration, when acute systemic inflammation was experimentally induced in animal models of neurodegeneration. [4.5]

Significant evidence prove the responsibility of proinflammatory cytokines, including IL-1β, as mediators in Arthritis development. [6,7]

Localized induction of osteoarthritis in the young adult APP/PS1 mouse model of neurodegenerative cognitive decline condition leads to activation of glial cells as well as speeding up the neuroinflammation and exacerbation of AD plaque pathology.

Clinical and animal research reports in the earlier period showed an increase in serum circulating pro-inflammatory cytokines in patients suffering from arthritis [8.]

Hence it can be said that there is confirmed relationship between peripheral and brain inflammation in neurodegenerative disorders and cognitive decline. aMCI has the

same or nearby equal pathological changes as AD and may progress to AD. So in this study it can be said that Osteoarthritis pathology may progress the cognitive decline.Off course old age is the common factor for the conditions, aMCI and Osteoarthritis.

Treatment approach which reduce peripheral inflammation or has link between peripheral inflammation and the central nervous system could be beneficial in reducing aMCI as well as Arthritis.Nirguṇdi kalpa acts like this only and hence found useful in aMCI.

In this study maximum that is 52% patients were obese .Decrease in dendritic spine density on pyramidal neurons and reduction in synaptic protein levels in the prefrontal cortex and perirhinal cortex is seen in obesity. These brain changes are responsible for decreased levels of circulating corticosterone and elevated levels of circulating leptin leading to cognitive impairment. However many research studies repots association between obesity and MCI but whether that changes are due to obesity itself or from metabolic syndrome or diabetes is not clear.[9]

At Visit 1 average ACE-R score was 52.9 it goes on increasing till 57.4 on visit 8 then it decreases to 56.4 at visit 10. It suggests that effect of drug was continued till the drug was continued. But after that in observation visits score comes little down. It can be said from above results that Nirguṇdi kalpa definitely have significant results in aMCI,but should be given for long period for sustainable results.

It was observed that, difference at visit 8 for attention and orientation was 3.3% with P-Value less than 0.05. For memory the percentage effect at visit 8 was 18.5% with P-Value less than 0.05, For Fluency there was change in mean at visit 8 about 2.4% with P-Value less than 0.05. Hence we conclude that, Effect observed in Memory, Attention and Orientation, Fluency. Nirguṇdi kalpa showed more significant action on memory domain. May be because the main drug in Nirguṇdi kalpa, Nirguṇdi is potent Smṛtidā or memory enhancer in action.Goghṛta and Madhu also enhances this action.

For WBI score effect was observed at visit 10 about 23.3% with P-Value less than 0.05.It suggests that Nirguṇdi kalpa is Manovikār naśak, cognitive enhancer.It has antiamnesic activity along with anxiolytic, antioxidant activities.

GERRI score did not showed any improvement pre and post treatment.This score depends upon patient’s caretakers or family member’s observation, seriousness

about the patient's cognitive condition. Since aMCI is not life threatening condition and its symptoms do not interfere much in activities of daily life, family also was not paying much attention on this, which reflected in GERRI score.

For ADL score, effect at visit 10 was observed about 60.9% with P-Value less than 0.05.This suggests that Nirguṇdi kalpa definitely helps in improving activities of daily living.This difference was more because most of the patients had Arthritis in association with aMCI.Nirguṇdi being good analgesic anti-inflammatory, patients got good results in arthritis symptoms leading to decrease in ADL score.

It was found in the study that patients started getting results in arthritic pain and swelling after the two weeks of drug administration. And after one and half months of drug intake symptoms were strongly decreased. Till the end of nine months of study, symptoms of arthritis were not aggrevated.

Common age related physiological problems found along with aMCI were Arthritis,Hypertension ,Diabetes mellitus,Amlapitta,visual,hearing impairment.Among them Arthritis and visual impairement were found most commonly in this study.Out of those Arthritis is most common cause for dependency in elderly.Nirguṇdi kalpa along with antiamnesic activity showed very good analgesic and anti-inflammatory activity. Also rate of consumption of NSAID for this reason was found to be reduced a lot.

From obtained data it can be observed that, 8 patients out of 50, observed moderate response. Mild response observed in 34 (68%) patients and no response was observed in 8 (16%) patients

It is found that the individuals with Amnesic mild cognitive impairment mostly had Obesity and HTN also along with faulty dietary and lifestyle pointing towards the change in diet and life style along with medication.

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SUMMARY

7. SUMMARY

The study was carried out at Bharati Vidyapeeth Deemed University College of Ayurveda and hospital, Pune, Maharashtra. Subjects with Mild cognitive impairment were screened and selected. 75 patients of were given Nirguṇdikalpa at the dose of 10g once daily with water for a period of 3 months and observed for further 6 months. There were 25 drop outs. In the study, mean score significantly differed after treatment for memory, attention & orientation, fluency in language, WBI and ADL score. Also the P-Values for above observations were less than 0.05 hence it can be concluded that there is significant result observed in memory, attention & orientation, fluency domain,WBI and ADL scores. The significant effect of therapy was observe in ACER, ADL, WBI score.Nirguṇdi kalpa significantly showed improvement in parameters such as memory, orientation and attention and fluency domain.

Main action of Medhya drugs is classified as Grahaṇa, Dhāraṇa and Smṛti vardhaka or enhancer.

Here the Nirguṇdi kalpa is having the Tikta, Katupradhān rasa and vipāk, Uṣṇavirya and it can be said that the Nirguṇdi kalpa helps in the Grahaṇaśākti and Smaraṇaśākti enhancing action resulting to enhancement of Smṛti.Katu rasa and vipāk and Uṣṇavirya help in removing srotorodh. Snigdha property of Goghṛta in it increases the permeability of cell membrane and become helpful in elimination of doṣa and mala. The influence of drug on brain is not explainable in the terms of rasapancaka and tridoṣa siddhānta only. The medhya action is a multi-system effect. Because of all these characteristics of Nirguṇdi kalpa it is useful in aMCI

As the Nirguṇdi kalpa is predominantly Vātahara hence it balances Vātadoṣa which normalise the Rajas doṣa of Manas and there by cures the Manasa vikṛtis. Smṛti, depends upon the state of balance of Vātadoṣa .Therefore balancing of Vāta is essential in management of Smṛtibhraṃśa in Jarāvasthā.

CONCLUSION

8. CONCLUSION

In the conceptual study of aMCI, I tried my level best to rearrange the conceptual study of aMCI with Āyurvedic point of view and reoriented with practical approach.

On the basis of similar signs and symptoms I can corelate aMCI to Jarā a\cvCER score after treatment.

I found that memory symptom showed significant relief and its level of significance as per statistical analysis is p value less than 0.05.

I found significant relief in attention & orientation domain and its level of significance as per statistical analysis is p value less than 0.05.

Significant relief in fluency domain found and its level of significance as per statistical analysis is p value less than 0.05

Significant improvement in WBI score found and its level of significance as per statistical analysis is p value less than 0.05

Significant improvement in ADL score found and its level of significance as per statistical analysis is p value less than 0.05

Significant improvement in GERRI score its level of significance as per statistical analysis is p value more than 0.05

I found very good results of Nirguṇdi kalpa in reducing Arthritis signs and symptoms along with aMCI.

Āyurvedic parameters for assessment of cognition, Smṛti, could not be established.

No toxicity or adverse effects of Nirguṇdi kalpa observed through out the study. The study confirms the efficacy of Nirguṇdi kalpa as cognitive, memory enhancer in aMCI.

Outcome of the study:

Significant result of Nirguṇdi kalpa was observed in aMCI. Significant result of Nirguṇdi kalpa was observed in memory, attention & orientation, fluency domain in aMCI. Nirguṇdi kalpa increases memory in aMCI. Improvement in well being and quality of life of the patients was observed. Improvement in WBI and ADL scores was

observe. Study drug being Medhya as well asVātaghna, antiarthritic, anti-inflammatory and analgesic; this improvement was seen.

Limitations of the study:

Small sample size and less drug duration of the study were the limitations in the study. Lengthy follow up and negligence of the patients towards the symptoms leading to more number of drop-outs and difficulty in finding cases in a clinical setup because of negligence by the patients and relatives towards the symptoms of MCI, were the hurdles faced in the study

Future avenues:

Longer study duration with a larger sample size should be done. Effect of use of Medhya Rasāyana from young or middle age should be studied.

More diagnostic methods could be used in the diagnosis of aMCI such as neuro-imaging, genetic markers should be researched upon.

Study of histopathological changes, neuro-chemical changes in detail should be carried out to further understand the nature of this condition.

Frequent cognitive screening of all the adults beyond the age 50 years should be done to detect Mild cognitive impairment so as to prevent further loss of the cognitive parameters and to thereby prevent the onset of deteriorating conditions like Alzheimer's' disease and dementia.

Further studies are desirable to explore the role of drug transporters in restricting or permitting the brain penetration of various active ingredients of Nirguṇdi kalpa. Bioavailability of glucose at brain level helps in its nourishment and proper functioning. A study suggested that presence of optimal level of glucose in brain plays a vital role in learning and memory. Nirguṇdi kalpa contains Madhu in large quantity which is the natural source of glucose. Hence a suitable clinical study to evaluate the change in glucose level in brain after administration of Nirguṇdi kalpa and its role in cognition and memory in healthy and diseased subjects would be an important milestone.

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ANNEXURE - A

WRITTEN INFORMED CONSENT

Role of Nirgundi kalpa in Mild Cognitive Impairment (MCI) w.s.r.to amnesic MCI

Name of the Subject:

Date of Birth:

Age / Sex:

Full Address:

Telephone Number:

I) PURPOSE OF THE TRIAL :-

1. To study the efficacy of Nirgundi kalpa in amnesic MCI

2. Study the clinical improvement in signs & symptoms of amnesic mild cognitive impairment.

II) PROCEDURES TO BE FOLLOWED : -

In this trial you will be examined by Dr. Madhavi Mahajan at regular intervals as per research protocol. Physical examination and other investigations will be done before and end.

IIII) RISK :-

If any adverse reaction occurs and become intolerable, the dose will be reduced or stopped.

IV) BENEFITS :-

The Medicine is being studied as a potential treatment of neuropsychological diseases. It may improve your condition. Of Course, this can't be guaranteed or promised and you may not receive the active experimental treatment. Your participation in this trial will contribute in the enhancement of medical sciences and will help in providing scientific knowledge for the betterment of mankind.

V) CONFIDENTIAL & RECORDS : -

Your medical records are related to your trial will be maintained in confidentiality.

VI) IF ANY PROBLEM DEVELOPS YOU CAN CONTACT : -

If any serious problem develops, please contact Dr.Madhavi Mahajan, on mob.no.9860124248 you will receive prompt and appropriate medical attention.

VII) OBTAINING INFORMATION:-

You are encouraged to ask any questions that occur to you at this time or to questions at any time during your participation in the trial. You will be given a copy

of this agreement. If you desire more information at a later date you may ask Dr. Madhavi Mahajan.

VIII) <u>WITHDRAWAL:-</u>

I am fully aware of my right to withdraw from the study at any time without giving any reasons for doing so and it will not affect the further management of my disease in any way in future.

Format of informed consent form for Subjects participating in a clinical trial.

Informed Consent form to participate in a clinical trial.

Study Title:

Study Number:

Subject's Initials: Subject's Name:

Date of Birth / Age:

(i) I confirm that I have read and understood the information sheet [ ]
dated for the above study and have had the Opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that [ ]
I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

(iii) I understand that the Sponsor of the clinical trials, others working on the [ ]
Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trail. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of data or results that arise from this [ ]
study provided such a use is only for scientific purpose (s).

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject / Legally Acceptable.

Representative :

Date : / /

Signatory’s Name :

Signature Investigator :

Date : / /

Study Investigator’s Name :

Signature Witness :

Date : / /

Name of the Witness :

DOCUMENTATION OF INFORMAED CONSENT

Role of Nirgundi kalpa in Mild Cognitive Impairment (MCI) w.s.r.to amnesic MCI

I have read the above information and have had an opportunity to ask any questions and all of my questions have been answered. I consent to take the medication called Nirgudi kalpa.

I fully understand that it is used in humans and its safety and effectiveness have been fully established. I have been given a copy of this consent form.

Name : -

Signature : -

I the undersigned have fully explained in local language the relevant details of this trial to the patient named above and or the person authorized to take the consent for the patient. I am qualified to perform this role.

Signature

Dr. Madhavi Mahajan

Date :-

Witness :-

Signature :-

Relationship with the subject

Address of Witness

संमतीपत्र

माझ्या आजारचे निदान, स्वरूप, प्रकल्पाचे महत्त्व या गोष्टी संबंधित डॉक्टरांनी मला समजावून सांगितल्या आहेत. तसचे अपेक्षित परिणाम दुष्परिणाम मला संबंधित डॉक्टरांनी समजावून सांगितले आहेत. मला सर्व प्रश्न विचारण्याची संधी आहे. मी प्रकल्पाचा दरम्यान कोणत्याही वेळी डॉक्टरांना प्रश्न विचारू शकतो. या प्रकल्पात सहभागी होण्याचा निर्णय घेण्यासाठी मला पुरेसा अवधी दिलेला आहे.

या प्रकल्पात सहभागी झाल्यावर देखील कोणत्याही क्षणी कारणाशिवाय प्रकल्पातून वाहेर पडण्याचा माझा अधिकार अवाधित आहे. मला पूर्ण कल्पना आहे की, प्रकल्पाव्यतिरिक्त कोणतीही वैद्यकीय चिकित्सा मी संबंधित डॉक्टरांच्या सल्ल्याशिवाय घेऊ शकणार नाही (आत्ययिक अवस्थे व्यतिरिक्त) सदर चिकित्सेमुळे कोणाताही दुष्परिणाम उद्भवल्यास त्याची माहिती त्वरीत संबंधित डॉक्टरांना देणे वंधनकारक आहे. तसेच त्या दुष्परिणामांसाठी योग्य ती उपाययोजना सदर हॉस्पिटलमध्ये उपलव्ध असून ती पूर्णत: मोफत आहे. प्रकल्पातील सर्व माहिती नियामक अधिकारी, प्रायोजक यांना उपलव्ध करून देणे माझ्यावर वंधनकारक आहे.

सदर प्रकल्पातील औषध प्रायोगिक स्वरूपात आहेत याची मला पूर्ण कल्पना आहे. ही सर्व माहिती मला मी जाणत असलेल्या भाषेत समजावून सांगितली आहे. तसेच संबंधित पत्रकाची प्रत देखील मला दिलेली आहे. हे सर्व लक्षात घेवून मगच मी स्वत: सदर संशोधन प्रकल्पामध्ये स्वेच्छेने सहभागी होत आहे.

रूग्ण :
नांव :
सही : तारीख :

रूग्णाचा कायदेशीर प्रतिनिधी / साक्षीदार
नांव :
सही : तारीख :

संमतीपत्र चर्चा करणारी संबंधित व्यक्ती
नावं :
सही : तारीख :

❖ **सदर अभ्यासाठी माझा खर्च किती होईल ?**

सदर अभ्यासाठी चिकित्सा पूर्णत: मोफत आहे. या अभ्यासामध्ये सहभागी होण्याचे कोणतेही मानधन तुम्हाला मिळणार नाही. सदर औषधामुळे किंवा इतर कारणांनी प्रकल्प कालावधीत काही दुष्परिणाम जाणवल्यास तुम्हाला त्वरित उपाययोजना मोफत उपलब्ध होईल.

❖ **सदर प्रकल्पात स्वयंसेवक म्हणून माझे हक्क काय आहेत ?**

या प्रकल्पातील तुमचा सहभाग संपूर्णत : स्वसंमत असेल. तुम्ही या प्रकल्पासंदर्भात पूर्ण माहिती संबंधितांकडून घेऊ शकता. आम्ही पूर्णत: अश्वासन देतो की, संमतीपत्रावर सही केल्यावर तुमच्या कोणत्याही कायदेशीर हक्कांची पायमल्ली होणार नाही. या प्रकल्पाच्या संदर्भात काही बदल झाल्यास किंवा नवीन माहिती उपलब्ध झाल्यास तुम्हाला, तुमच्या पालकांना किंवा कायदेशीर प्रतिनिधींना त्याची पूर्ण कल्पना दिली जाईल.

❖ **माझी गोपनीयत कशी असेल ?**

प्रकल्पातील सर्व माहिती गोपनीय ठेवली जाईल व ती सार्वजनिक केली जाणार नाही. पण सदर माहितीं नियामक अधिकारी, हॉस्पिटलची समिती, प्रायोजक यांना उपलब्ध असेल जर हा अभ्यास प्रकाशित झाला तर तुमची वैयक्तिक माहिती गोपनीय ठेवली जाईल.

❖ **संबंधित डॉक्टर मला या प्रकल्पातून कमी करण्याचा सल्ला देऊ शकतात का ?**

हो जर संबंधित डॉक्टरांना असे वाटले की, सदर चिकित्सा तुमच्यासाठी उपयुक्त नाही किंवा ही चिकित्सा तुमच्यासाठी दुष्परिणामकारक आहे किंवा नवीन मिळालेल्या माहिती नुसार ही चिकित्सा तुमच्यासाठी योग्य नाही तर संबंधित डॉक्टर तुम्हाला या प्रकल्पातुन कमी करून योग्य ती चिकित्सा करतील.

❖ **या प्रकल्पाच्या कालावधीत मी इतर कोणते औषधोपचार घेऊ शकतो का ?**

मानसिक आजाराशी संबंधित नसलेल्या इतर चिकित्सा (उदा: औषधे, आहार इ.) तुम्ही संबंधित डॉक्टरांच्या सल्ल्याने घेऊ शकता. मानसिक आजाराशी संबंधित औषधे मात्र तुम्ही या कालावधीत घेऊ शकत नाही. सदर कालावधीत कोणतीही चिकित्सा किंवा औषधे घेतल्यास त्वरीत संबंधित डॉक्टरांना कळवावे.

❖ **आत्याथीक अवस्थेत (इमरजन्सी निघाल्यास) मी कोणाशी संपर्क साधावा ?**

जर तुम्हाला प्रकल्पातील सहभागा बद्दल काही प्रश्न असतील किंवा तुम्हाला अचानक तीव्र त्रास सुरू झाला तर खालील डॉक्टरांना त्वरीत संपर्क साधावा.

CASE – PAPER

Sec A

Case No. OPD No. IPD No.

Name –

Age - Sex –

Religion –

Date of commencement - Date of Completion

Education – Literate/ Illiterate

Lower primary / Higher primary / high school/

Diploma / graduation / P.G.

Occupation – Present – Retired life / working

Past-

Habitat - Rural / urban / semi urban

Address -

Present Complaint -

Past History –

1) Any major illness in the past Y/N

IF Yes a) Disease

b) Treatment taken

2) Are you under the Rx of any disease at present?

a) Disease

b) Rx

Family History –

a) Joint / Nuclear
b) Housing Condition – Poor / Moderate / good / very good

Personal History –

a) Residence – Lives with family / alone / in old age home
b) Marital status – Unmarried / married / divorced / Widow
c) No. of children – Male - Female -
d) Socio economic status – Upper class / upper middle / lower middle poor
e) Food – Veg / Non-veg / mixed

Rasa -

Guna –

Timely consumption / untimely / consumption / frequent food intake

f) Agni – Sama / vishama / manda / tikshna
g) Kostha – Mrudu / Madhya / krura

Sec – B

Hreeyamana Indriya (Diminution in perception)

1) Shabda (Hearing) Y/N

2)	Sparsha (Tactile)		Y/N
3)	Roopa (Vision)	Y/N	
4)	Rasa (Taste)		Y/N
5)	Gandha (smell)	Y/N	

Mini :- Mental State Examination (MMSE)

(1 point for each correct Ans.)

Orientation :- What is

1) Time -
2) Date –
3) Day –
4) Month –
5) Year –

What is the name of this

a) Ward –
b) Hospital
c) District
d) Town
e) Country

Registration –

a) Name 3 objects or identify 3 objects by name & ask the patient to Repeat.
   Total points – 3

   Obtained score –

   [Score 1, 2, 3, points according to how many are repeated Resubmit list until patient is ward perfect in order to use this for a later test of recall score only 1st attempt.]

b) Attention & calculation

How the point subtract 7 from 100 & then again from the result, a total of 5 times score 1 point for each.

Correct subtraction –

Obtained score –

c) Recall – Ask for 3 objects used in registration test, 1 point being awarded for each correct answer

(Total points - 3)

(Obtained score -)

d) Language –

One point each for 2 objects correctly named

(e.g. pencil, watch)

(Total points - 2)

(Obtained score -)

One point for correct for repetition of 'No. IFS, AND'S or BUT'S

(Total points - 1)

(Obtained score -)

3 points if 3 stage commands correctly obeyed

1) Take this piece of paper in your Right hand.\
2) Fold it half
3) Place it on the floor

(Total points - 3)

(Obtained score -)

One point for correct for response to a written command such as

"Close Your eyes"

(Total points - 1)

(Obtained score -)

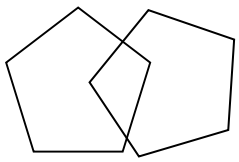
Have the patient write a sentence

(A ward 1 point if the sentence is meaningful has verb & a subject)

(Total points - 1)

(Obtained score -)

Test the patient's ability to copy a complex diagram of 2 intersected pentagons



(Total points - 1)

(Obtained score -)

Total score obtained - ---/Total score = 30 (normal)

Score will be defined according to age and education

Yesavages Geriatric Depression Scale (Short form)(GDS)

1. Are you basically satisfied with your life ?	No
2. Have you dropped many of your activities & interests ?	Yes
3. Do you feel that your life is empty ?	Yes
4. Do you often get bored ?	Yes
5. Are you in good spirits most of the time ?	No
6. Are you afraid that something bad is going to happen to you ?	Yes
7. Do you feel happy most of the time ?	No
8. Do you often feel helpless ?	Yes
9. Do you prefer to study home at night, rather than go out & do new things ?	Yes
10. Do you feel that you have more problems with memory than most ?	Yes
11.Do you feel it is wonderful to be alive how ?	No
12. Do you feel pretty worthless the way you are now.	Yes
13. Do you feel full of energy?	No
14. Do you feel that your situation is hopeless?	Yes
15. Do you think that most persons are better off than you are ?	Yes

Scores - 3 ± 2 = Normal

7 ± 3 = Mildly depressed

12 ± 2 = Very depressed

Sec – C

Interviewers observation

Appearance

Behavior

Speech

Level of consciousness.

Sec – D

I) Samanya pariksha

Netra –

Nakha –

Nadi –

Raktachapa -

Shwas gati –

Dehoshma –

Lasika granthi –

Dehabhara –

II) Vishesha Pareeksha

Prakruti –

Sara –

Samhanana –

Pramana -

Satmya –

Satwa –

Ahara Shakti – I) Abhyavaharana Shakti

II) Jarana Shakti

III´Vyayam Shakti –

III) Strotas Parikshana –

1) Rasa vaha -

2) Rakta vaha –

3) Mansa vaha –

4) Meda vaha –

5) Asthi vaha –

6) Majja vaha –

7) Shukra vaha –

8) Prana vaha –

9) Anna vaha –

10) Udak vaha –

IV)

I] Sarva Kriya su cha Asamarthata – Physical disability (Modified Barthel's index of ADL)

a) Bowel –	Continent	0
	Occasional incontinent	1
	Incontinent	2
b) Bladder -	Continent	0
	Occasional incontinent	1
	Incontinent	2
c) Toilet using -		
	Independent without difficulty	0
	with mild difficulty in sitting & getting up	1
	with moderate difficulty in sitting & getting up	2
	with marked difficulty in sitting & getting up	3
	Needs Support	4
d) Bathing -		
	Independent without difficulty in bathing	0

with mild difficulty in bathing	1
with moderate difficulty in bathing	2
with marked difficulty in bathing	3
Needs Support	4

e) Dressing -

Independent without difficulty in dressing	0
with mild difficulty in dressing	1
with moderate difficulty in dressing	2
with marked difficulty in dressing	3
Needs Support	4

f) Grooming -

Independent without difficulty in grooming	0
with mild difficulty in grooming	1
with moderate difficulty in grooming	2
with marked difficulty in grooming	3
Needs Support	4

g) Walking -

without difficulty in walking	0
with mild difficulty in walking	1
with moderate difficulty in walking	2
with marked difficulty in walking	3
Needs Support	4

h) Transfer -

without difficulty in walking	0
Fatigue after covering big distance	1
Fatigue after covering moderate distance	2
Fatigue after covering marked distance	3
Needs other help to travel	4

i) Feeding -

without difficulty in feeding	0
mild difficulty in feeding	1
moderate difficulty in feeding	2
marked difficulty in feeding	3
Needs others help	4

j) Stairs -

with difficulty in climbing	0
mild difficulty in climbing	1
moderate difficulty in climbing	2
marked difficulty in climbing	3
Needs support in climbing steps	4

II] Shlatha asara Sandhi – Flabbiness of joints

[Leg Mobility test - LMT]

Leg Mobility assessed by asking the patient to perform a simple test the point sitting on chair

1) Ask to get up 2) Walk 20 ft. 3) Return to chair & sit down

Normal LMT □ □15 sec, Abnormal > LMT 15 sec

III] Nidra Nasha (Insomnia)

a) Disturbance during sleep

No disturbance	0
1 – 2 hrs. disturbance	1
2 – 4 hrs. disturbance	2
4 – 6 hrs. disturbance	3
6 – 8 hrs. disturbance	4
> 8 hrs. disturbance	5

b) Difficulty in initiating sleep

No difficulty	0
½ - 2 hrs difficulty	1
2 – 3 hrs difficulty	2
3 – 4 hrs difficulty	3
4 – 5 hrs difficulty	4
> 5 hrs difficulty	5

c) Sleep time / Duration at sleep

Total sleep hours (8 hrs.)	0
4 – 6 hrs sleep	1
2 – 3.9 hrs sleep	2
	3
	4
	5

_____

Total score obtained

Sec E

Lab Investigations

Haemogram	Hb :	TLC
	DLC	
Urine	R	
	M	
BUL		
Sr. Creat		
BSL	F	
	PP	

Tridot for HIV

ECG

Others-

Sec F

Medication

Nirgundi kalpa, Dose-

FOLLOW UP PAPER

Sub :

Patients Name

OPD À IPD No.

Date

Daignosis

Complaints of

1) Samanya Pariksha

Netra

Nakna

Nadi

Raktachapa

Shwasagati

Dehoshma

Lasikagranthi

Deha bhara

2) Improvement in the scales:

i) ACE-R

ii) WHO wellbeing index

iii)GERRI

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2005)

Name :
Date of birth :
Hospital no. :

Addressograph

Date of testing: ..... /..... /.....
Tester's name: .....
Age at leaving full-time education: .....
Occupation: .....
Handedness: .....

ORIENTATION

➢ Ask: What is the	Day	Date	Month	Year	Season	[Score 0-5]
	.....	.....	.....	.....	.....	
➢ Ask: Which	Building	Floor	Town	County	Country	[Score 0-5]
	.....	.....	.....	.....	.....	

REGISTRATION

➢ Tell: 'I'm going to give you three words and i'd like you to repeat after me: lemon, key and ball'. After subject repeats, say 'Try to remember them because i'm going to ask you later'. Score only the first trial (repeat 3 times if necessary).

Register number of trials .....

[Score 0-3]

ATTENTION & CONCENTRATION

➢ Ask the subject: ' could you take 7 away from a 100? After the subject responds, ask him or her to take away another 7 to a total of 5 subtractions. If subject make a mistake, carry on and check the subsequent answer (i.e. 93, 84, 77, 70, 63 -score 4)

Stop after five subtractions (93, 86, 79, 72, 65). ....

[Score 0-5]
(for the best performed task)

➢ Ask: 'could you please spell **WORLD** for me? Then ask him/her to spell it backwards:

....

MEMORY - Recall

➢ Ask: 'Which 3 words did I ask you to repeat and remember?'

....

[Score 0-3]

MEMORY - Anterograde Memory

➢ Tell: ' I'm going to give you a name and address and I'd like you to repeat after me. We'll be doing that 3 times, so you have a chance to learn it. I'll be asking you later'

Score only the third trial

[Score 0-7]

	1st Trial	2nd Trial	3rd Trial
Harry Barnes	....	....	....
73 Orchard Close	....	....	....
Kingsbridge	.....	.....	.....
Devon	.....	.....	.....

MEMORY - Retrograde Memory

[Score 0 -4]

➢ Name of current Prime Minister .....
➢ Name of the woman who was Prime Minister .....
➢ Name of the USA president .....
➢ Name of the USA president who was assassinated in the 1960's .....

ATTENTION&ORIENTATION MEMORY

VERBAL FLUENCY - Letter 'P' and animals

➢ **Letters**

Say: 'I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. Are you ready? You've got a minute and the letter is P'

[Score 0 - 7] ☐

				>17	7
				14-17	6
				11-13	5
				8-10	4
				6-7	3
				4-5	2
				2-3	1
				<2	0
				total	correct

➢ **Animals**

Say: 'Now can you name as many animals as possible, beginning with any letter?

[Score 0 - 7] ☐

				>21	7
				17-21	6
				14-16	5
				11-13	4
				9-10	3
				7-8	2
				5-6	1
				<5	0
				total	correct

FLUENCY

LANGUAGE - Comprehension

➢ Show written instruction: [Score 0-1] ☐ ☐

Close your eyes

➢ 3 stage command:
'Take the paper in your right hand. Fold the paper in half. Put the paper on the floor'

[Score 0-3] ☐ ☐

LANGUAGE - Writing

➢ Ask the subject to make up a sentence and write it in the space below:
Score 1 if sentence contains a subject and a verb (see guide for examples)

[Score 0-1] ☐ ☐

LANGUAGE

LANGUAGE - Repetition

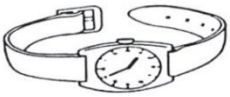
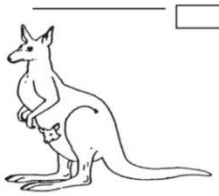
➢ Ask the subject to repeat:**' hippopotamus'; 'eccentricity; 'unintelligible'; 'statistician'**
Score 2 if all correct; 1 if 3 correct; 0 if 2 or less. [Score 0-2]

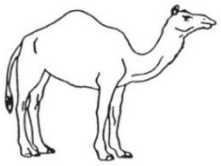
➢ Ask the subject to repeat: **'Above, beyond and below'** [Score 0-1]

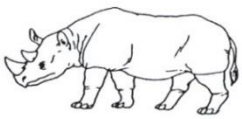
➢ Ask the subject to repeat: **'No ifs, ands or buts'** [Score 0-1]

LANGUAGE - Naming

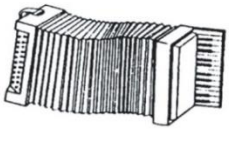
➢ Ask the subject to name the following pictures: [Score 0-2] pencil + watch







[Score 0-10]

LANGUAGE - Comprehension

➢ Using the pictures above, ask the subject to: [Score 0-4]

- Point to the one which is associated with the monarchy _____
- Point to the one which is a marsupial _____
- Point to the one which is found in the Antarctic _____
- Point to the one which has a nautical connection _____

LANGUAGE

LANGUAGE - Reading

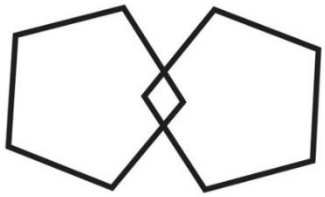
➢ Ask the subject to read the following words: [Score 1 only if all correct] [Score 0-1]

sew
pint
soot
dough
height

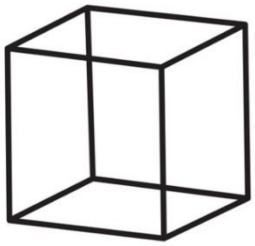
LANGUAGE

VISUOSPATIAL ABILITIES

➢ Overlapping pentagons: Ask the subject to copy this diagram: [Score 0-1]



➢ Wire cube : Ask the subject to copy this drawing (for scoring, see instructions guide) [Score 0-2]



➢ Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (for scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct) [Score 0-5]

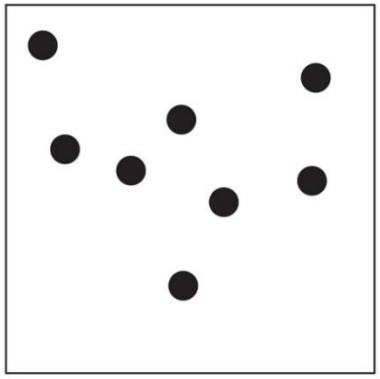
VISUOSPATIAL

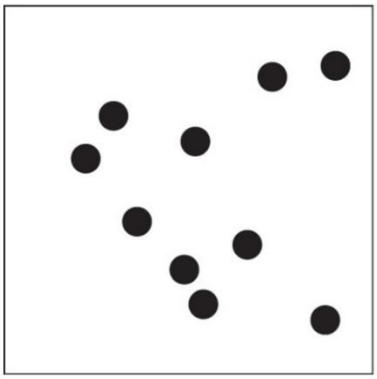
PERCEPTUAL ABILITIES

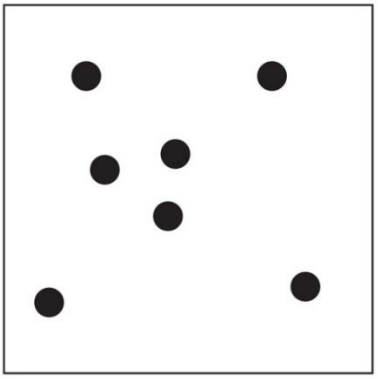
VISUOSPATIAL

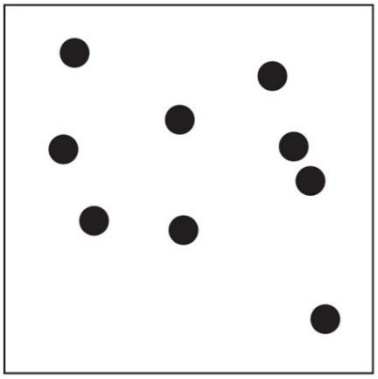
➢ Ask the subject to count the dots without pointing them

[Score 0-4]







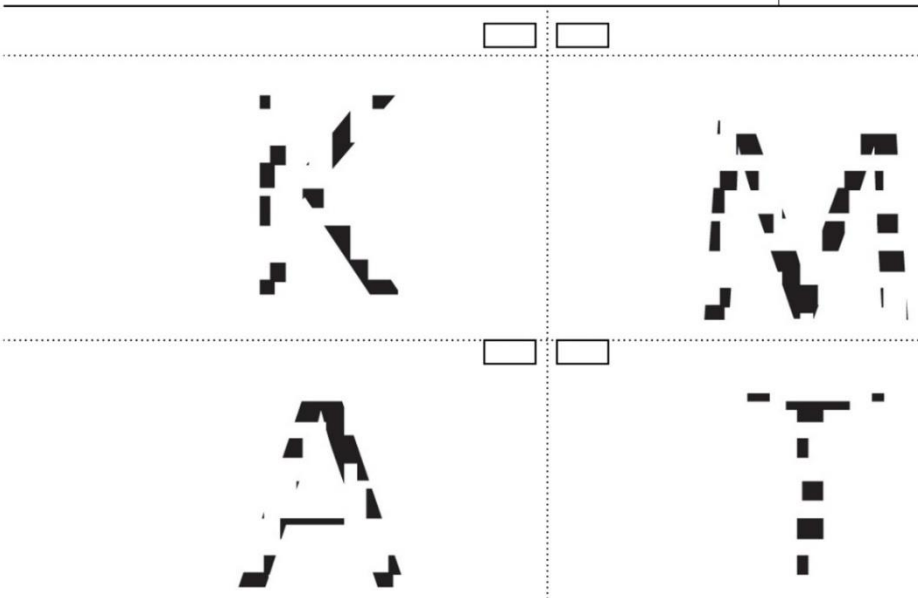


ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2005)

PERCEPTUAL ABILITIES

➢ Ask the subject to identify the letters [Score 0-4]



RECALL

➢ Ask "Now tell me what you remember of that name and address we were repeating at the beginning'"

		[Score 0-7]
Harry Barnes	....	
73 Orchard Close	....	
Kingsbridge	.....	
Devon	.....	

RECOGNITION

➢ This test should be done if subject failed to recall one or more items. If all items were recalled, skip the test and score 5. If only part is recalled start by ticking items recalled in the shadowed column on the right hand side. Then test not recalled items by telling "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point which is added to the point gained by recalling. [Score 0-5]

Jerry Barnes		Harry Barnes		Harry Bradford		recalled	
37		73		76		recalled	
Orchard Place		Oak Close		Orchard Close		recalled	
Oakhampton		Kingsbridge		Dartington		recalled	
Devon		Dorset		Somerset		recalled	

General Scores

MMSE	/30
ACE-R	/100

Subscores

Attention and Orientation	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

VISUOSPATIAL MEMORY SCORE

Normative values based on 63 controls aged 52-75 and 142 dementia patients aged 46-86

Cut-off <88 gives 94% senstivity and 89% specificity for dementia
Cut-off <82 gives 84% sensitivity and 100% specificity for dementia

Psychiatric Research Unit
WHO Collaborating Centre in Mental Health

WHO (Five) Well-Being Index (1998 version)

Please indicate for each of the five statements which is closest to how you have been feeling over the last two weeks. Notice that higher numbers mean better well-being.

Example: If you have felt cheerful and in good spirits more than half of the time during the last two weeks, put a tick in the box with the number 3 in the upper right corner.

	Over the last two weeks	All of the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
1	**I have felt cheerful and in good spirits**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2	**I have felt calm and relaxed**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3	**I have felt active and vigorous**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4	**I woke up feeling fresh and rested**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5	**My daily life has been filled with things that interest me**	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

Scoring:

The raw score is calculated by totalling the figures of the five answers. The raw score ranges from 0 to 25, 0 representing worst possible and 25 representing best possible quality of life.

To obtain a percentage score ranging from 0 to 100, the raw score is multiplied by 4. A percentage score of 0 represents worst possible, whereas a score of 100 represents best possible quality of life.

for caretake

Geriatric Evaluation by Relative's Rating Instrument (GERRI)

1. Remembers name of spouse/children living with him/her. C
2. Shaves or puts on makeup, combs hair without help. S
3. Prepares coffee, tea, or simple meals for self when necessary. S
4. Remembers where small items, such as keys, jewelry, or wallets are placed. C
5. Reports he/she feels sad. M
6. Appears restless and fidgety. M
7. Pays bills with checks. S
8. Remembers familiar phone numbers. C
9. Grasps point of newspaper articles, news broadcasts, etc. C
10. Reports feeling of hopelessness about the future. M
11. Forgets names of common objects. C
12. Handles incoming calls. S
13. Gets lost — leaves house and does not know where he/she lives. C
14. Remembers point in conversation after interruption. C
15. Handles money shopping for simple grocery items or newspaper or cigarettes. S
16. Reports feeling worthless. M
17. Continues to work on some favorite hobby. S
18. Does not recognize familiar people. C
19. Repeats same point in conversation over and over. C
20. Appears tearful. M
21. Leaves clothes soiled. S
22. Physically dirty or sloppy in appearance. S
23. Mood changes from day to day, happy one day, sad the other. M
24. Forgets the day of the week. C
25. Goes out inappropriately dressed. S
26. Embarrassing behavior. S
27. Forgets what he/she is looking for in the house. C
28. Forgets appointments. C
29. Remembers names of close friends. C
30. Acts childish. S
31. Continues to watch or "follow" favorite TV or radio program. C
32. When asked questions, seems quarrelsome and irritable. M
33. Does not pursue every day activities. S
34. Overquick or "jumpy" reaction to sudden noises or sights. M
35. Has difficulty concentrating or paying attention. C
36. Does not socialize with friends. S
37. Has fluctuations in memory — good one day, bad the next. C
38. Remembers where clothes are placed. C
39. Wants to have things his/her own way. S
40. Irregular eating habits, misses meals or eats meals consecutively. S
41. Remembers to lock door when leaving the house. C
42. Initiates phone contacts with friends. S
43. Appears to be easily annoyed or angered. M
44. Remembers to take medication. C
45. Reports feeling optimistic about future. M
46. Appears to be cheerful. M
47. Forgets to turn off stove. C
48. Appears friendly and positive in conversations with family members. S
49. Behaves stubbornly, such as refuses to take medication. S

C = Cognitive functioning
S = Social functioning
M = Mood

Score:
1 = Almost all the time
2 = Most of the time
3 = Often
4 = Sometimes
5 = Almost never
6 = Does not apply

ANNEXURE - B

॥ पुष्पं पुष्पं विचिन्वीत मूलच्छेद न कारयेत्॥

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संदर्भ : वनस्पतिशास्त्र/
Ref.No. : Bot/ 416/2010-11

दिनांक :
Date : 16/8/2011

AUTHENTIC CERTIFICATE

This is to certify that **Dr. Madhavi Prabhakar Mahajan Student** of Bharati Vidyapeeth College of Ayurveda Pune- 411 043. She has selected research topic for her Ph.D. degree which is as given below:

'ROLE OF NIRGUNDI KALPA IN MILD COGNITIVE IMPAIRMENT (MCI) W.S.R.T. AMNESIC MCI'

Under this study the specimens which she has been submitted to me for the botanical standardization and authentication was identified and confirmed as given below:

	Botanical name	Family	Plant part used
Nirgundi	*Vitex negundo* Linn.	Verbenaceae	Roots
Madhu	----------As it is----------		
Goghruta	----------As it is----------		

The drug samples were submitted in an organ form and as it is. These are identified as above. This is for information and necessary action.

Department of Botany PUNE 411 007 University of Pune

Dr. S. S. DEOKULE
PROFESSOR & HEAD
Department of Botany
University of Pune,
PUNE-411 007.

A. S. Bhave
Hon. Director

Shikshana Prasaraka Mandali's
Late Prin. B. V. Bhide Foundation
For Education & Research In Chemistry, Ayurveda & Allied Sciences
S. P. College Campus, Tilak Road, PUNE - 411030. India
Tel. : 020 - 24324324. Email : bhidefoundation@rediffmail.com

Date : 29/12/11

To,

Dr. Madhavi Mahajan

Bharati Vidyapeeth deemed university Ayurvedic College.

Katraj

Pune

Subject: Report of Analysis of the **Nirgundi root Powder sample** provided by you.

Dear Madam,

This has a reference to the subject matter. The given sample was analyzed as per your Requirement and the results obtained are as follows:

Sr. No.	Name of the test	Results	Standard Values from API
1	Loss on Drying @ 110^0 C	6.48%	Not Available
2	Foreign Matter	0.36%	NMT 1 %
3	Ash Content	2.84%	NMT 3%
4	Acid Insoluble ash	0.11%	NMT 0.2%
5	Water Soluble Extractive	10.24%	NLT 9 %
6	Alcohol Soluble Extractive	6.48%	NLT 5

(*NMT= Not Less Than *NLT= Not More Than)

In case of any queries regarding the results please feel free to contact us back.

For Late prin. B. V. Bhide Foundation

Mangesh Tembhurne

Late Prin. B.V. Bhide Foundation
for Education and Research
in Chemistry

A. S. Bhave
Hon. Director

Shikshana Prasaraka Mandali's
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Date : २९|१२|११

To,
Dr. Madhavi Mahajan
Bharati Vidyapeeth deemed university Ayurvedic College.
Katraj
Pune

Thin Layer Chromatography

Sample Preparation: alcoholic extract of the sample was prepared.

Solvent system used: ethyl acetate: chloroform: methanol

Rf Values: 0.14, 0.34, 0.64, 0.84, 0.95 etc.

For Late prin. B. V. Bhide Foundation
Mangesh Tembhurne.
Late Prin BV Bhide Foundation
for Education and Research
in Chemistry

A. S. Bhave
Hon. Director

Shikshana Prasaraka Mandali's
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Date : २१/१२/११

To,
Dr. Madhavi Mahajan
Bharati Vidyapeeth deemed university Ayurvedic College.
Katraj
Pune

Subject: Report of Analysis of the **Ghee** sample provided by you.

Dear Madam,
This has a reference to the subject matter. The given sample was analyzed as per your Requirement and the results obtained are as follows:

Sr.No	Test	Result	Standard as per PFA
1	Total fat content	85.41%	Not less than 85%
2	Total ash content	0.69%	Not available
3	Saponification Value	232.14	225-235
4	Iodine Value	53.28	50-55
5	Acid Value	0.34	NMT 0.5
6	Refractive Index	1.446	1.453-1.456
7	Adulteration of Vanaspati ghee	Negative	Negative

In case of any queries regarding the results please feel free to contact us back.

For Late prin. B. V. Bhide Foundation
Tembhurne
Mangesh Tembhurne

Late Prin BV Bhide Foundation
for Education and Research
in Chemistry

A. S. Bhave
Hon. Director

Shikshana Prasaraka Mandali's
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Tel. : 020 - 24324324. Email : bhidefoundation@rediffmail.com

Date : 29/12/11

To,
Dr. Madhavi Mahajan
Bharati Vidyapeeth deemed university Ayurvedic College.
Katraj
Pune

Subject: Report of Analysis of the **Honey** sample provided by you.

Dear Madam,
This has a reference to the subject matter. The given sample was analyzed as per your Requirement and the results obtained are as follows:

Sr.No	Test	Result	Standard as per PFA
1	Moisture content	21.76%	Not more than 25%
2	Total acidity	0.38%	Not more than 0.5%
3	Total ash content	0.59%	Not available
4	Specific gravity at 27°C	1.3201	Not less than 1.35
5	Total reducing sugars	66.79%	Not less than 65%
6	Total sucrose content	3.84%	Not more than 5%
7	F/G ratio	0.76%	Not less than 0.95%
8	Fiehe's test	Negative	Negative
9	Aniline chloride test	Negative	Negative

In case of any queries regarding the results please feel free to contact us back.

For Late prin. B. V. Bhide Foundation
Tembhurne
Mangesh Tembhurne

Late Prin BV Bhide Foundation
for Education and Research
in Chemistry

A. S. Bhave
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S. P. College Campus, Tilak Road, PUNE - 411030. India
Tel. : 020 - 24324324. Email : bhidefoundation@rediffmail.com

Date : 15/3/12

To,

Dr. Madhavi Mahajan

Bharati Vidyapeeth deemed university Ayurvedic College.

Katraj

Pune

Subject: Report of Analysis of the **Nirgundi Kalp** sample provided by you.

Dear Madam,

This has a reference to the subject matter. The given sample was analyzed as per your Requirement and the results obtained are as follows:

Sr.No	Test	Result
1	Moisture Content	12.61%
2	Total Ash Content	2.34%
3	Acid Insoluble Ash	0.16%
4	Water Soluble Extractive	8.68%
5	Alcohol Soluble Extractive	9.72%
6	Total Reducing Sugars	22.64%
7	Total Sucrose Content	1.24%
8	Total Fat Content	20.18%

In case of any queries regarding the results please feel free to contact us back.

For Late prin. B. V. Bhide Foundation

Tembhurne.

Mangesh Tembhurne

Late Prin BV Bhide Foundation
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In Chemistry