

“AN APPROACH TOWARDS GERIATRIC NEURODEGENERATIVE DISORDERS THROUGH AYURVEDA”**Dr. Pallavi Ghadage¹, Dr. Pawan Lekurwale², Dr. S. G. Shrikhande³, Dr. G. S. Jayaraman⁴**

1. Associate Professor, Dept. of Kayachikitsa, LN Ayurved College & Hospital, Bhopal, MP
2. Professor, Dept. of Kayachikitsa, LN Ayurved College & Hospital, Bhopal, MP
3. Assistant Professor, Dept. of Kriyashareer, LN Ayurved College & Hospital, Bhopal, MP
4. Associate Professor, Dept. of Shalya Tantra, Sri Sairam Ayurveda Medical College and Research Centre, Chennai, Tamilnadu.

ABSTRACT:

While one cannot avoid the natural process of aging, it is possible to enhance one's quality of life. Age is a major risk factor for neurodegenerative maladies like dementia, Parkinson's disease, etc., which are key challenges for clinicians all the time. People often misunderstand dementia as 'normal ageing' due to the similarities between ageing and neurodegenerative diseases. The effect of molecular and cellular damage over time leads to a gradual decrease in physical and mental capability, a growing risk of disease, and eventually death. There are few or no effective treatments available for aging-related neurodegenerative diseases, which tend to progress in an irreversible manner and are associated with large socioeconomic and personal costs. Ayurveda offers a holistic approach to treatment, as well as several nootropic herbs with multidimensional bioactivities for various disorders. Researchers have widely admired medicinal plants due to their natural sources and fewer side effects, leading to a recent surge in global interest in Ayurveda. People are increasingly approaching Ayurvedic clinicians, making it crucial to understand the disease condition from an Ayurvedic perspective and manage it effectively.

This article reviews the Ayurvedic drugs with potential in the treatment of age-related neurodegenerative disorders.

KEY WORDS :- Ayurveda, Ageing, Neurodegenerative diseases, cellular, Epigenetic**Corresponding Details:****Dr. Pallavi Ashok Ghadage**

Room No 14, F Block, JK Hospital Campus, Kolar Road, Bhopal

Mobile No. 8975325824

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INTRODUCTION

Ageing is the natural process of becoming older though one cannot avoid it but quality of life can be enriched. Ageing increases the risk of human diseases [1]. Of the roughly 150,000 people who die each day worldwide, about two-thirds die from age-related causes. [2] Age is a major risk factor for neurodegenerative maladies like Dementia, Parkinson's disease etc. which are key challenges to clinicians all the time. Ageing and neurodegenerative disease shares similar processes, so dementia is misunderstood as 'normal ageing'. The effect of molecular and cellular damage over time leads to a gradual decrease in physical and mental capability, a growing risk of disease and eventually death. Few or no effective treatments are available for ageing related neurodegenerative disease, which tend to progress in an irreversible manner and are associated with large socioeconomic and personal costs. Ayurveda, being fundamentally the science of life and longevity, seems to have addressed these issues in a unique holistic manner involving not merely the biological care, rather also encompassing the psychological and spiritual dimensions. Ayurveda considers ageing as the Swabhava of life. In other words, senescence is the swabhava or inherent nature of living being, because the life is time bound and it is inherently mortal. Jara also called as Vardhakya (aging) is defined as that which has become old by the act of wearing out. According to Ayurveda, Jara/ aging is not a disease but a natural phenomenon like hunger, thirst or sleep. In the theory of natural destructions (Swabhavoparama vada), Charaka describes that there is a causative factor for the manifestation of a being but there is no cause for the cessation of this manifestation, since death following birth is a state of natural flow. [3] [4] Ayurveda provides a holistic approach to treatment along with several nootropic herbs having multidimensional bioactivities in various disorders. Researchers have widely admired medicinal plants due to their natural sources and fewer side effects, leading to a recent surge in global interest in Ayurveda. People are increasingly approaching Ayurvedic clinicians, making it crucial to understand the disease condition from an Ayurvedic perspective and manage it effectively.

MATERIALS AND METHODS

Information from Ayurveda texts and review articles from NIIMH, Pubmed and Google scholar was used for the completion of the study.

RESULT AND DISCUSSION

In order to develop successful interventions, it is important to consider the basic mechanisms of ageing and their role in the onset of progression of neurodegenerative disease.

The biology of ageing and relation with neurodegeneration

1. Ageing is an inevitable and irreversible process associated with readily identifiable and characteristic changes in the individual organism's physical appearance and function. Studies have defined molecular and cellular processes and biomarkers that

are associated with aging in diverse mammalian species and may be linked to the basic biological mechanisms underlying human aging. We identified 10 so-called hallmarks of ageing and categorised them into primary, antagonistic, and integrative hallmarks. Onistic, and integrative hallmarks. hallmarks. [6] The primary hallmarks are genomic instability, telomere attrition, epiMitochondrial dysfunction, cellular senescence, and deregulated nutrient sensing are the antagonistic hallmarks. The integrative hallmarks include stem cell exhaustion, altered intercellular communication, and chronic inflammation. exhaustion, altered intercellular communication, communication, and chronic inflammation.

2. **Genomic instability:** It can be defined as an increased probability in accumulating genome damage, acquired either through a defect in the repair of such damage or an accumulation of inductive triggers. Oxidative DNA damage from endogenous reactive oxygen species (ROS) can increase inflammation, accelerate ageing and increase susceptibility to cancer and neurodegenerative diseases. DNA damage promotes cellular senescence and inflammation which together exacerbate ageing related neurodegeneration.
3. **Telomere attrition:** Telomeres shortening has been pointed to as the main factor that speeds up telomeres ageing and promotes degenerative process with each DNA replication the telomeres are progressively shortened, leading to the appearance of critically shorter telomeres. Telomerase is the key enzyme involved in the chromosomes ends protection and repair from shortening during replication, consequently preventing catastrophic DNA loss and promoting the maintenance of healthy cell function.
4. **Epigenetic alteration:** The epigenetic modifications including chromosome modification, DNA methylation and changes in regulatory RNAs are having a great impact on neurodegenerative disorders as well as memory over time various factors affect the epigenetic modification for example cigarette shocking, food habits, exercise etc. these epigenetic changes might cause death of neurons thus leading to various neurodegenerative disorders.[7]
5. **Loss of proteostasis:** The balance between protein synthesis and degradation creates a steady state known as proteostasis. Increased protein misfolding, aggregation and deposition are observed in many neurodegenerative disorders.[8]
6. **Mitochondrial dysfunction and mitophagy:** The production of ROS is amplified in damaged mitochondria and is implicated in the normal ageing process and in a majority of known neurodegenerative diseases.[9] Besides ATP production

mitochondria also have key role in several intercellular pathways, including lipids biosynthesis, calcium signaling and cell apoptosis, all of which are central processes in the development of neurodegenerative disease.[10]

7. **Cellular senescence:** It is hemostatic process that reduces proliferation and helps to prevent the propagation of damaged cells. Some of the factors that trigger senescence in pathological conditions are oxidative SIPs, mitochondrial dysfunction, DNA damage, telomere attrition, aberrant gene activation, epigenetic modifications and impaired autophagy. Ageing increases the number of senescent cells and the loss of neurons compromising brain function and triggering or aggravating a neurodegenerative disease. [11]
8. **Deregulated nutrient sensing and altered metabolism:** Major nutrient sensing pathways and molecules include insulin, insulin like factor 1 (IGF1) mechanistic target of Rapamycin (mTOR), AMP activate protein kinase (AMPK) and sirtuins. [12] mTOR, AMPK and Sirtuins are being explored as therapeutic targets for neurodegenerative diseases. Metabolic dysfunction is frequently observed in patients with neurological disease and might correlate with low NAD⁺ abundance, mitochondrial dysfunction and oxidative stress. [13]
9. **Stem cell exhaustion:** Functional stem cells are needed for optimal health in later life. However, stem cell function and proliferative capacity decline over an organism's lifespan. This functional loss can be caused by age related high levels of DNA damage, low DNA repair capacity, defects ion proteostasis, epigenetic deregulation, mitochondrial dysfunction, telomere inactivation or cell senescence. [14]
10. **Altered intercellular communication and immune function:** Alterations in levels of hormones such as leptine, ghrelin, insulin, adiponectine and IGF1 regulate neuronal damage and neurodegeneration. The immune system is essential for shaping the brain during development and both the neurons system and the immune system change withage, so the loss of regulation of immune responses in the brain is likely to be a factor neurodegeneration. [15]
11. **Chronic inflammation:** Inflammation, a fundamental protective event in response to any insult, becomes upregulated with advanced age. Uncontrolled and sustained inflammation can be harmful and result in age related chronic neurodegenerative disease.[16] Chronic inflammation, persistent activation of microglia, sustained

elevation of pro-inflammatory mediators and increased oxidative stress are associated with age related neurodegenerative disease.[17] Other factors reported to contribute to the inflammatory response and pathogenesis of neurodegenerative disorders include age related sex steroid hormone deficiency,[18] defective proteasome and autophagy degradation systems,[19] cellular senescence,[20] increased oxidative DNA damage and impaired DNA repair,[21] decreased innate and adaptive immune system responses [22] and environmental stressors.[23] Neuro-inflammation is a major pathophysiological feature of neurodegenerative disorders. Targeting of these neuro-inflammatory processes might be beneficial in age related neurodegenerative diseases.

AYURVEDA

Ayurveda take a holistic approach toward the maintenance of Dhatusamya, for which various principles have been described. Ageing is considered as a disease that may be manifested timely or untimely.

Rasayana specially deals with the science of nutrition, geriatric care and rejuvenation. Rasayana signifies not a single drug or medication rather refers to a rejuvenative regimen which of course uses rejuvenative remedies or drugs, dietetics and overall healthy life-style and positive psychological conduct. The use of Rasayana measures and remedies produces best qualities of Dhatus, i.e. body tissues by acting through one or all of the following three levels of biological system with net result of improved nutritional status leading, in turn, to better qualities of tissues, longevity, immunity, resistance against disease and improved mental faculties. The primary levels/ modes of Rasayana effect are: [24][25][26]

- At the level of Rasa (Promoting directly the nutrient value of plasma).
- At the level of Agni (Promoting biofire system responsible for digestion and metabolism).
- At the level of Srotas (Promoting microcirculation and tissue perfusion).

Ayurvedic medicines, having historical roots more than 5000 years ago, have been increasingly searched for worldwide for multiple purposes. For instance, several Ayurvedic medicinal herbs and formulations, traditionally known as Rasayana, have been shown to markedly promote health, immunity, vigor, vitality and longevity at same time as protecting from stress. Drugs like **Ashwagandha**, **Musta**, **Guduchi**, **Mandukaparni**, **Brahmi**, **Shankhapushpi**, **Yashtimadhu**, **Vacha**, **Tulsi**, **Haridra**, **Amalaki**, **Medhya** Rasayana,

Bramha Rasayana claim to facilitate healthy ageing, arrest degenerative changes and have rejuvenating potential at cell and tissue level.

In this sense, here we briefly **discuss the evidence - based** perspectives of some of these anti-ageing drugs, considering their role in the prevention and management of NDDs.

Effect of Ashwagandha [*Withania somnifera* (L.) Dunal], aka Indian ginseng, is a flagship rejuvenating and adaptogen Ayurvedic herb, traditionally used as an anti-ageing agent. In human HeLa cell lines, Ashwagandha root extract, tested at various concentrations, led to an enhancement in telomerase activity.[27] Ashwagandha extract also exhibited anti-genotoxic effects against H₂O₂- induced DNA damage in human peripheral blood lymphocytes.[28] Withanolide A exhibited neurotropic properties in AD models.[29]

Studies on the antithrombotic properties of secondary metabolites appear to be limited. However recent reviews have highlighted that carvacrol, alpha cyperone and nootkatone; terpene compounds from the essential oils of **Musta** [*Cyperus rotundus*].[30]

Effect of Guduchi [*Tinospora cardifolia* (Wild) Hook. F. & Thomson] is a celebrated Rasayana herb of Ayurveda. It is used at several dosage forms to treat inflammation, arthritis, allergy, diabetes and as an anti-ageing and rejuvenating tonic.[31] A study found that extracts from Guduchi markedly enhances the rate of cell survival and protected against radiation induced cytotoxicity and DNA damage in PC12 cells. Another study using ethanolic Guduchi stem extracts reported DNA protective ability on sodium arsenite – induced genotoxicity in lymphocytes from Swiss Albino mice using the Comet assay.[32]

Effect of Mandukaparni [*Centella asiatica* (L.) Urban] is renowned Ayurvedic herb effectively used to improve memory and for rejuvenation in traditional practices. In a study it is found that Mandukaparni extracts was able to trigger an almost nine fold increases in telomerase activity compared to untreated human peripheral blood mononuclear cells.[33] Interestingly, in rodent models, treatment with Mandukaparni extracts showed improvement in cognitive functions through improving mitochondrial and antioxidant gene expression in the brain and liver.[34] The plant extracts also have been shown to promote wound healing (possibly attributed to the presence of triterpenoid saponins) via the facilitation of new skin cell growth, increasing skin tensile strength and resilience, and inhibiting bacterial growth.[35]

Castasterone, a Mandukaparni leaf derived phytoconstituent, was also able to inhibit H₂O₂ induced DNA damage in a single cell gel electrophoresis assay (comet assay).[36] In study it is showed that, asiatic acid from Mandukaparni reduced ROS generation.[37]

Asiatic acid attenuated mitochondrial dysfunction, and naringenin was observed to upregulate endogenous antioxidant enzymes.[38]

Effect of Brahmi [*Bacopa Monnieri* (L.) Wettst. In Eng. And Prantl] is another Ayurvedic plant traditionally used as a nootropic and tonic agent. A study performed on Brahmi extracts reported an extraordinary adaptogenic potential and role in scavenging superoxide anion and hydroxyl radicals and in inducing H₂O₂- induced cytotoxicity and DNA damage in human fibroblast cells.[39] In another study Brahmi ethano extracts also demonstrated a marked protective activity against H₂O₂- induced cytotoxicity and DNA damage in human non-immortalized fibroblast. Another investigation reported a significant antioxidant and DNA damage preventing effect. In a further investigation, Brahmi extract displayed protective effects against sodium nitroprusside (SNP) - induced DNA damage. For bacosides, bioactive constituents of Brahmi, remarkable potentialities have been reported in terms of scavenging free radicals and protecting neural cells from cytotoxicity and DNA damage in Alzheimer's disease.

Effect of Shankhapushpi (*Convolvulus pluricaulis* Choisy) is another Indian traditional plant widely used for its effective nootropic effects. A study evaluated the neuroprotective potential of Shankhapushpi ethanol extract and it was found to possess antioxidant and anti-apoptotic properties and to protect from H₂O₂- induced cytotoxicity and plasmid DNA damage.

Effect of Yashtimadhu (*Glycyrrhiza glabra* L.), aka Mulethi or Jethimadhu in traditional practice, is rich in glycyrrhizin (a triterpene saponin), and its root extract have been reported to increase DNA resistance from CdCl₂ induced genetic and oxidative damages in human lymphocytes. In vitro, such extracts also protected plasmid pBR322 DNA and microsomal membranes from gamma radiation induced strand breaks.[40]

Effect of Vacha (*Acorus calamus* Linn.), is another Ayurvedic plant with potent antioxidant and cytoprotective abilities, being able to effectively protect DNA from gamma radiation induced strand breaks and to enhance DNA repair process in vitro.[41]

Effect of Tulsi (*Ocimum basilicum* L.) essential oil has been shown to raise the apparent telomeres length in cell culture and to down regulate the telomeric repeat binding factor 1 (TTERF-1) telomere length suppressor.[42] It is also found that bioactive compounds present in seed extracts from another Tulsi variety, i.e., *Ocimum tenuiflorum* L., exerted a prominent antioxidant potential and conferred DNA protection in a plasmid DNA pBR322 model.[43]

Effect of Haridra (*Curcuma longa* L.) is also an extensively used medicinal herb and soul of Indian Kitchen. Haridra aqueous extracts and its main constituent, Curcumin, are found to be protective against lipid peroxide- induced DNA damage.[44] A recent study in a mouse model with carboplatin- induced myelosuppression suggested that curcumin promotes the FNA repair pathway in bone marrow.[45] The curcumin interaction with Kelch- like ECH-associated protein 1 (Keap 1), the nuclear factor E2- related factor 2 (Nrf2) is released, which regulates antioxidant enzymes, anti-inflammatory responses proteins, and DNA repair enzymes.[46] Curcumin also stabilizes A beta aggregates and promotes disaggregation of existing A beta deposits.[47] The secondary metabolites with reported protective against synucleinopathy in PD include aegeline an alkaloid-amide from curcumin.[48] It is also found that curcumin prevented seizure- induced mitochondrial dysfunction and damage of the mitochondrial ultrastructure in cortical and hippocampal neurons.[49]

Crocin, the principle carotenoid from Saffron (*Crocus sativus*) inhibited tau hyperphosphorylation in the cerebral cortex of a rodent model of AD.[50]

Effect of Amalaki (*Emblica officinalis* Gaertn.) fruits, is a time tested Ayurvedic Rasayana drug, widely used for the prevention or even treatment of various age- related health conditions. In study it is revealed that Amalaki helped maintain the length of DNA telomers, structures located at the ends of chromosomes to protect from damage.[51] Intake of Amalaki Rasayanaby aged individuals showed stable maintenance of DNA strand break repair without toxic effects. However, there was no change in nucleotide and base excision repair activities.[52]

Effect of Medhya Rasayana, a memory enhancer formulation prepared from a mixture of selected plants and their extracts, has a great ability to promote brain rejuvenation, triggering a marginal but sustained increase in constitutive DNA base excision repair in brain tissues of adult rats.[53]

Effect of Bramha Rasayana, another formulation, is a health promoting formulation, increased constitutive DNA base excision repair and reduced clastogenicity.[54] **Effect of Chyawanprasha** is also a popular health supplement traditionally used for rejuvenation and displays cytoprotective and genoprotective effects.[55]

Not only ayurvedic herbs but panchakarma procedures like **Virechana karma**[56] also showed effect on gene expression.

Yoga[57] is known reliever of stress, stress causes several physiological changes one of that is increase in oxidative molecules. DNA damage is increases due to constant exposure with stress hormones (Cortisol and catecholamine). In study it is found that, a holistic yoga intervention showed highly significant impact on DNA damage

CONCLUSION

Increasing ageing population and associated risk of developing neurodegenerative disorders are matter of significance because of its impact on studies to develop evidence-based treatment strategies. But neither highly effective treatment nor potent protective approaches have yet been identified. Ayurveda being the science of life and longevity, offers a treasure of geriatric care. Rasayana medicines explained in Ayurveda are extensively researched and proven to exert antioxidant, adaptogenic, immunomodulatory, immunostimulant, cytoprotective and rejuvenating properties, underlines the hope that Ayurveda can provide promising anti-ageing drugs which will focus on the ten hallmarks of ageing, most of which show associations with neurogenerative disorders. Though this is only a conceptual study, but the information provided can be utilized in various experimental and clinical studies.

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