Act of Phytochemical-Based Antioxidants in Neurodegenerative Disorders Utilizing Indian Medicinal Plants

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Abstract: Neurodegenerative diseases are multifactorial nervous system deteriorating conditions that concern over 30 million aging populations worldwide. The effect of protein malfunction or defective trafficking is neurodegenerative disease, such as Alzheimer disease [AD], Parkinson's disease [PD], Huntington's and Amyotrophic lateral sclerosis disorders. Furthermore, mitochondrial dysfunction, oxidative stress / age-linked environmental factors have also been involved. Prolonged use of synthetic medications could lead to adverse side effects for these illnesses. Henceforth herbal therapy attracts much attention rather than a pharmaceutical therapy is favoured. Indeed, several research studies have identified use of medicinal plants and their components for drug production, and recently more than 100 new medicines are now being established clinically. Accumulative data shows that nutraceuticals property is critical for cognition optimisation and risk mitigation. The study explores the role of phytochemical based antioxidants in cognitive and adverse signal transduction events, with a special focus on the Mediterranean diet [MeDi] comprising bioactive compounds like - xanthophyll carotenoids and omega-3 fatty acids. These phytochemical compounds are capable of improving cognition, considering their selective brain involvement and their specifically oxidative damage and inflammation. The objective of this study is to detail the molecular mechanisms of some Ayurvedic plants signal transduction and locations of operation. It is hoped that this review further helps to examine a new therapeutic recommendations and further research in clinical trials on the use of poly-herbal Ayurvedic medicine for the treatment and prevention of dementia. It is expected to increase the ease in the usage of Ayurveda-based knowledge base combined with combined scientific and high-performance screening strategies in the drug research and development campaign, while offering new practical guidelines for neurosurgical diseases linked to age.

Keywords: Neurodegenerative, protein malfunction, oxidative stress, MeDi, Bioactive compounds, omega-3-FA, cognition, AD, PD, Medicinal plants.

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I. INTRODUCTION

Chiefly neurodegenerative diseases are a significant threat to human health. Such age-dependent conditions are becoming more common, resultantly due to the adverse effects of neurodegenerative processes that occur in elderly^{1,2}. Etymologically, the term consists of prefix "Neuro", refers to nerve cells (i.e. neurons) and "degeneration", and refers to a phase of losing structure/function in the case of tissues or organs³. Thus, neurodegeneration refers to any pathological condition that mainly affects neurons in the strict sense of the term. In fact, a wide group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomical structures constitute neurodegenerative diseases; they occur in a relentless way for unexplained reasons and development. Neurons, which include the brain and spinal cord, are the building blocks of the nervous system. Normally, neurons do not replicate or replace themselves, so they will not be replaced by the body when they become injured or die.⁴ Incurable and disabling disorders resulting in gradual degeneration / death of nerve cells or neurons in the human brain are neurodegenerative diseases. This causes movement disorders (called ataxias) or mental functioning issues (called dementias).⁴ Proposed investigation highlights the impact of neuro-protective effects of Indian medicinal plants promising to reverse the pathology of Alzheimer's and Parkinson's. finding explains the importance of herbal medicine plants in relation to neuro-protective activity and mechanisms of their action^{4,5}. Etiology with respect to the onset of disease inclination has its own molecules mechanism and clinical manifestations, in various pathogenic cascades, certain general pathways may be recognised. Disease progressions and vulnerability manifests with protein miss-folding and aggregation, oxidative stress and free radicals formation, metal dyshomeostasis, mitochondrial dysfunction, and impaired phosphorylation all occurring simultaneously, are included.⁶

1.1 AGING

The complex physiological mechanism of morphological and biochemical modifications that gradually occur is recognised in aging⁷. The modifications include the CNS, shrinking of telomere, the hormonal and reproductive systems, the cardiovascular system. With the exception of family forms that can be determined to affect people younger than 60,

ageing remains the greatest risk issue for NDs.^{7,8,9}. In recent decades' human life expectancy has increased particularly in developing countries, and age-related neurodegenerative, including Alzheimer disease and Parkinson disease, have become more prevalent as the population of the world grows older^{8,10}. Although neuronal cell death is not always planned to occur at a selected age, ageing-related cell and molecular changes communicate with genes and environmental components to determine which cells are effectively ageing and on the road to neurodegeneration⁹. Mitochondrial dysfunction, multiple loose radical development and oxidative stress, microglia dysfunction, decreased chaperone output, decreased synaptic density, blood-brain barrier disturbance, and low range of neurogenesis are correlated with ageing^{9,10}. In addition to practical degradation of neuronal effects in age-related genetic disorders, the accumulation of mitochondrial DNA deletions in the ageing process¹¹. The decline in antioxidant enzyme synthesis and function is also associated with oxidative neuronal damage within the ageing mind. Oxidative damage to mitochondrial DNA is thought to be due to free radicals of mitochondrial origin. Moreover, growing older comes with a transition in the composition of the fatty acids of the mobile membrane. Like arachidonic acids, PUFA is prevalent in the ageing of the brain and particularly susceptible to oxidative damage such as lipid peroxidation¹². Histopathological transition also takes place in the neuro-inflammatory brain with microglia morphology and pass time. Older microglia are also less mobile, less mobile and more somatic in younger organisms than microglia¹². Microglial phagocytosis is also seen to shift within an elderly brain¹³, and the aged micro glyphs show enlarged phagosomal / lysosomal marker expression associated with this. Cognitive dysfunction, as well as some types of common neurodegenerative diseases such as AD¹⁴, are also being shown to be an ordinary method for biologically active ageing since choline interest in key brain areas is being lost or declined.

1.2 CLASSIFICATION OF NEURODEGENERATIVE DISEASES

To date, the lion's share of focus has been paid towards understanding the onset of various neurodegenerative diseases, including AD, PD, HD and amyotrophic lateral sclerosis(ALS)³ as shown in Fig 1.

Fig 1: Classification of neurodegenerative diseases³⁹

1.3 MULTIFACTORIAL FACTORS ASSOCIATED WITH NEURODEGENERATIVE DISEASE

Neurodegenerative disorder comprises a series of pathological disorders occurring in the selected areas of the nervous system which are distinguished by sluggish progressions and permanent dysfunction and neuron depletion, defining clinical appearance and direction. multifactorial causes of hereditary, environmental and endogenous influences related to aging are known to be the main fundamental process contributing to neurodegenerative^{3,6}.

1.4 COMMON PATHOGENIC MECHANISMS UNDERLYING MANY NEURODEGENERATIVE DISEASES INCLUDE

- Abnormal protein misfolding, proteasomal dysfunction and aggregation.
- Oxidative stress and formation of reactive oxygen species [ROS].
- Impaired bioenergetics, mitochondrial dysfunction and DNA damage.
- Fragmentation of neuronal Golgi apparatus.
- Dysfunction of neurotrophins. [NTFs]
- Neuro-inflammatory process.

Fig 2: Genetic factors and environmental factors associated with neurodegenerative diseases⁶

a) **DYS-FUNCTIONING OF MITOCHONDRIA IN ND-**

Mitochondria are important cell survival regulators, death and mitochondrial power dysfunctions contributing to reduced ATP production, decreased calcium tamponing and increased reactive oxygen generation. Several research indicates that mitochondria plays a crucial function in ageing^{15,16}. Energy metabolism and mitochondrial respiratory defects in AD are features of neurodegeneration-impaired brain tissue but also in AD patient peripheral cells. Biochemical research has been shown for/disrupting processes in the post-mortem AD brains in three main enzymes: the dehydrogenase complex of pyruvate (PDHC), the mitochondrial cycle of α -ketoglutarate dehydrogenase complex (KGDHC)¹⁷.

b) **PROTEIN MISFOLDING AND AGGREGATION IN ND-**

Protein aggregates do not accumulate in stressed stable neurons owing, in part, to cell-like 'quality control machines;' molecular chaperones, for example, can have a toxicity defence mechanism because chaperones can inhibit and facilitate the refilling of proteins that have misfolded proteins in and between polypeptides. In addition to the regulation of the content of proteins produced by molecular chaperones, the defective or aberrant proteins are obvious from the framework of ubiquitin-proteasome system [UPS], and autophagy/lysosomal degradation. If the chaperones cannot fix misfolded proteins, they can be tagged for degradation by the proteasome with the addition of poly-ubiquitin chains. In ND conditions, the brain is expected to accumulate intra- or extracellular protein aggregates because of the reduction in molecular chaperone activity¹⁸.

c) **OXIDATIVE STRESS IN ND-**

As a part of the cellular metabolism, the reactive oxygen species are usually generated in the cell of living organisms and are important to cellular homeostasis maintenance. Low to modest ROS concentrations function in mechanisms such as immune response, inflammation, synaptic plasticity, learning and memory in physiological settings¹⁹. The excess of the ROS production can be risky, creating adverse oxidative changes to the cell portion as the primary targets for ROS-induced disruption, including mitochondrial structures²⁰. The human body, however, has a number of antioxidants, such as [SOD] and glutathione systems, which counterbalance the effect of oxidants²¹. In the event of an imbalance between free radical development and detoxification, the production of ROS will overwhelm antioxidant resistance, leading to a noxious condition known as oxidant stress, and in general cellular degradation^{22,23} as shown in Fig 2.

1.5 **FUNCTIONAL ROLE OF MEDICINAL PLANTS AND ITS PHYTOCONSTITUENTS IN NEURODEGENERATION**

The use in dementia therapy of complementary drugs, such as plant extracts, differs according to various cultural practises. Neuro-endocrine-immune systems are modulated by Ayurvedic medicinal herbs and these are rich sources of compounds like antioxidants and anti-inflammatory^{14,24}. It is assumed that they boost memory and rejuvenate cognitive functions²⁵⁻²⁷. Numerous Ayurveda medicinal herbs have been used in control and treatment of chronic and acute neurological disorders.

Table 1: Medicinal plants used in neurodegenerative diseases³⁸

Medicinal Plants	Phytoconstituents	Mode of action
Acorus calamus	Alpha & beta asarone	Inhibits the acetylcholinesterase.
Allium sativum	S-allylcysteine	Improves locomotor function associated with increased production of dopamine, decreased production of lipid peroxidation & superoxide and improves SOD operation
Bacopa monnieri	Bacoside, bacoside-A, mannitol, b-sitosterol, betulinic acid	Inhibits the degeneration of cholinergic and has cognitive enhancement effects in rats.
Centella asiatica	Asiatic acid and asiaticoside	Inhibits beta-amyloid cell death in vitro.
Convolvulus pluricaulis	Convoline, convolidine, convolvine, confoline, convozine, kaempferol & steroids phytosterol.	In the hippocampal areas associated with memory/learning functions, there has been a dose-related increase of AchE activity in the CA1 & CA3 region.
Curcuma longa	Essential oils, curcumin, polyphenol	
Ginkgo biloba	Ginkgolides A,B,C,J & bilobalide, bi-flavones, poly-prenols	It functions to various degrees as free radical cells that are used to minimise membrane fluidity and impaired cells observed with AD in view of excessive fluid peroxidation mediators.
Glycyrrhiza glabra	Glycyrrhizin, glycyrrhizic & 2 molecules of glucuronic acid.	Inhibition of viral fixation and replication of cell membranes and intervention in cell signal transduction
Withania somnifera	Withanolide-A to Y, withasomniferols A to C, withaferin A & withanone.	It has been shown to be free radicals formed by withaniamides during initiation and progression of AD. Withaniamides avoided the mortality of neuronal cells from amyloid plaques

Emerging evidence indicates that healthy lifestyles during life can reduce the likelihood of cognitive impairment in later life, or postpone the onset as shown in Table 1. A small one-year delay in AD onset by some form of lifestyle intervention is expected to result in 9.2 million fewer people with AD globally by 2050^{28,29}. Indeed, a third of AD cases may be prevented through lifestyle changes, it has been suggested^{29,30}. Food is not only the source of food & energy,

but there is a complementary treatment that can also offer health benefits. The use of functional foods and nutraceuticals as therapeutics allows diet therapy to be a safe method³¹. It has recently been suggested that a combination of nine risk factors is responsible for around 35 percent of dementia cases^{29,32}. This includes early childhood education (up to 12 years), mid-life hypertension, mid-life obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, and

group isolation. Namely carotenoids and omega-3 FA, which are key nutritional components of MeDi, this nutrition components role on cognition and AD is discussed below²⁹.

1.6 MEDITERRANEAN DIET- AS A THERAPEUTIC DIET REGIME

Whole grains, fruits, vegetables, legumes, nuts, yoghurt, fish & white meat as sources of protein are part of the Mediterranean conventional diet. The fruit & vegetable-rich diet is associated with a low incidence of chronic degenerative disorder and decreases the risk of cancer, cardiovascular disease, relative to other countries in the Mediterranean population^{31,33}. The neuro-protection fundamental mechanism provided by MeDi is yet to be understood. This diet provides you a rich source of antioxidants, unsaturated fatty acids and vitamins. Therefore, this MeDi has to be suggested as different nutritional components that operate synergistically and dose dependently to reduce or decrease the risk factors associated with AD^{29,34}.

1.7 CAROTENOIDS AND ITS NEURO-PROTECTIVE PROPERTIES

Carotenoids are plant pigments which are naturally ubiquitous and photosynthetic species that occur naturally (plants, algae, cyanobacteria) and certain non-photosynthetic organisms synthesise de novo. The lipid-soluble C40 compounds are carotenoids and are known as carotenes or xanthophyll. Importantly, they must derive from the diet mainly from the leaves of edible plants that are dark green, yellow, orange and red in colour, where humans cannot synthesise carotenoids de novo^{29,35}. The basic mechanisms that underlie the relationship between carotenoids and cognitive health and function have not been thoroughly explained yet. Due to their chemical structure and localization within biological membranes, carotenoids are believed to be neuro-protective, thus providing antioxidant and anti-inflammatory properties at their storage locations. The processes involved in neurodegeneration can be mitigated by these properties, namely oxidative stress and inflammation^{29,36}.

1.8 NEURO-PROTECTIVE PROPERTIES OF OMEGA-3-FA

Fats and oils are an important part of the diet (and a significant component of MeDi) in addition to carotenoids since they provide energy storage FAs and design the biological membranes of cells and their organelles. FAs are non-branched carbon, hydrogen, and acid molecules on one end. They may be completely saturated in their composition or have one or more saturations (double bonds). In its name and classification, the FA's number of carbons and unsaturations must be specified. It is not yet completely known the precise biochemical processes by which ω -3 FAs transmit cognitive benefits. However, it has been suggested that their

properties may lead to the reduction of AD pathogenesis processes like inflammation. As described above, neuro inflammation is inflammation occurring within a CNS which can trigger neuronal death and synaptic dysfunction. Hence, it has been put forward that DHA played an important function in neuro-inflammation regulation and resolution.^{29,37} Herbal treatment, as a whole, offers potential solutions to current treatments for neurodegenerative diseases. Alternative medicine has been used since ancient times, and various extracts of medicinal plants and herbal formulas have shown promise for use in Neurodegenerative Diseases. Because of the presence of numerous chemical constituents and their ability to function on various biological targets, medicinal plants offer a fertile ground for new drug development⁴⁰. Medicinal plants and natural compounds, such as Withania somnifera (ashwagandha), Ginseng, curcumin, resveratrol, Baccopa monnieri, Ginkgo biloba, Tinospora cordifolia, Convolvulus pluricaulis and Wolfberry have been applied to prevent or alleviate neurological diseases and relief of neurological symptoms.

2. CONCLUSION

With recent accomplishments in AD and PD, HD and ALS in view, neurodegenerative disorders tend to share many similar degenerative multifactorial mechanisms. Due to these multifactorial and clinical features, the platforms of gene expression analysis is commonly used to examine the altered pathways during degeneration and to classify possible biomarkers and drug goals. As a forum for the ancient Ayurvedic Medicine method, inclusive descriptions of plants used for neuroscience therapy have been offered in the latest study. The different phyto-constituents of various plants demonstrated the protective effect for Neurodegenerative diseases. Thus, the existences of bioactive chemicals are mostly responsible for the treatment, conducted over the last two decades that nutraceuticals are important to brains and can have a beneficial influence on cognition. It is proven that phytochemical constituents are important as a preventive measure for the optimization of cognition and neurologic disorders. Yet conformity with proper foods and access to good diets such as MeDi are one huge obstacle. With respect to MeDi, there is clear proof that it may play a beneficial effect on the cognitive health of healthy people and decrease the likelihood of contracting neurological disorders by following or adhering to this trend.

3. AUTHORS CONTRIBUTION STATEMENT

Navya Raj MP (NR) and Sushma BV(SBV) conceptualized the study. Navya Raj MP, Pooja G Singh (PS) and Sushma BV(SBV) drafted the manuscript and necessary inputs were given towards designing the Manuscript and helped with the discussion.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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