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Neurodegenerative diseases: From available treatments to prospective herbal therapy

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ABSTRACT

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and many others represent a relevant health problem with age worldwide. Efforts have been made in recent years to discover the mechanism of neurodegenerative diseases and prospective therapy that can help to slow down the effects of the aging and prevent these diseases. Since pathogenesis of these diseases involves multiple factors therefore the important task for neuroscientists is to identify such multiple factors and prevent age-associated neurodegenerative diseases. For these neurodegenerative diseases yet we have only palliative therapies and none of them significantly capable to slow down or halt the underlying pathology. Polyphenolic compounds such as flavonoids present in vegetables and fruits are believed to have anti-aging properties and reduce the risk of neurodegenerative diseases. Despite their abundance, investigations into the benefits of these polyphenolic compounds in human health have only recently begun. Preclinical and clinical studies have demonstrated the potential beneficial effects of flavonoids in neurons. Although clinical trials on the effectiveness of dietary flavonoids to treat human diseases are limited but various animal models and cell culture studies have shown a great promise in developing these compounds as suitable therapeutic targets. In this review, we elaborate the neuroprotective properties of flavonoids especially their applications in prevention and intervention of different neurodegenerative diseases. Their multi-target properties may allow them to be potential dietary supplement in prevention and treatment of the age-associated neurodegenerative diseases.

Contents

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; DA, dopamine agonist; IFN, interferon; EGCG, epigallo catechin 3-gallate; Aβ, amyloid beta; BDNF, brain derived neurotrophic factor; MPTP, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxy dopamine; 3-NP, 3-nitropropionic acid; Nrf2, NF-E2-related factor 2; HO-1, heme oxygenase-1; NF-kB, nuclear factor kappa B; iNOS, inducible nitric oxide; IL, interleukin; TNF- α, tumor necrosis factor α; ROS, reactive oxygen species; PI3K/Akt, phosphatidylinositol-3 kinase/Akt; ERK1/2, extracellular signal-regulated protein kinase; PKC, protein kinase C; JNK, c-Jun N-terminal kinase; CREB, cAMP response element binding protein; NO, nitric oxide; NADPH, nicotinamide adenine dinucleotide phosphate; MAPK, mitogen activated protein kinases; LPS, lipopolysaccharide; H_2O_2, hydrogen peroxide; RNS, reactive nitrogen species; STAT1, signal transducer and activator of transcription-1; AP-1, activated protein-1.

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1. Introduction

Neurodegeneration is the slow and progressive neuronal dysfunction characterized by the progressive loss of neurons in the central nervous system that leads to either functional loss (ataxia) or sensory dysfunction (dementia). Manifestation of neuronal loss or degeneration comes out in the form of memory impairment, locomotory dysfunction, cognitive defects, emotional and behavioral problems. Neuronal degeneration is the main pathological feature of various age-related neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) (Amor et al., 2010; Jellinger, 2001). The main causes of the neuronal degeneration in these diseases along with environmental factors, genetic mutations and brain aging, are several cellular and molecular events such as increase in oxidative stress, impaired mitochondrial functions, deposition of aggregated proteins, inflammatory response, activation of neuronal apoptosis, altered cell signalling and gene expression (Jellinger, 2001; Parihar et al., 2008). These factors play an important role in the etiology of common neurodegenerative diseases. Currently, neuroscientists are trying to fully exploit the data obtained from the mechanisms of these factors in order to explore the therapeutic interventions directed towards treatment of neurodegenerative diseases. Although in last decade neurodegenerative diseases had received the utmost attention through research, still these diseases have only palliative therapies and none of them are significantly capable to slow or halt the underlying pathology of these diseases. However, the question still remains constant that if there is no available cure then whether there is another way to prevent or halt these neurodegenerative diseases. As most of the neurodegenerative diseases begin very early in life and remain asymptomatic for most of the phases, hence the therapies initiated in advance stage of the disease have limited value to patients. Therefore, the early therapeutic interventions that may restore neuronal functions by reducing or eliminating the primary stressor are necessary to stop the progression of such disease and the suffering of people.

Naturally occurring compounds have been proposed as an alternative form of treatment for the prevention of age-related neurodegenerative diseases. Many polyphenolic compounds and vitamins such as C and E may contribute to this prevention. Epidemiological evidences have shown that the Mediterranean diet, which is rich in polyphenolic compounds, is effective in the prevention of age-related diseases such as AD (Scarmeas et al., 2006; Sofi et al., 2010). Flavonoids are naturally occurring polyphenolic compounds that perform neuroprotective function via the enhancement of existing neuronal function or by stimulating neuronal regeneration (Vauzour et al., 2008). In addition, flavonoids protect neuronal cells by reducing oxidation of proteins, lipid peroxidation and prevent generation of reactive oxygen species (ROS), thus act as upstream therapy to neurodegeneration. Flavonoids are ubiquitously present in daily dietary fruits and vegetables and they are available to patients much more rapidly than new prescription drugs thus they can be considered as the better options for the prevention and treatment of neurodegenerative diseases. This review explains the potential role of flavonoids in neuroprotection via modulation of various signalling pathways. Due to their clinical efficacy over available palliative therapies, flavonoids can be the key compounds for the development of a new generation of therapeutics in prevention of neurodegenerative diseases.

2. Available treatments

Neurodegenerative diseases involve multiple factors including environmental, genetic, cellular and molecular. These factors initiate their contribution very early in life of a person with neurodegenerative diseases. The available clinical therapies do not target multiple sites and neither arrest disease progression but mainly help in keeping patients from getting worse for a limited period of time. The few clinically relevant medicines and therapies available for the neurodegenerative diseases like AD, PD, HD, ALS and MS are listed below (Table 1):

AD is a late-onset, progressive, age-dependent neurodegenerative disease which is clinically characterized by insidious onset of memory and cognition impairment. Presence of amyloid plaques, neuritic plaques and neurofibrillary tangles, that are the main hallmarks of AD, formed due to accumulation of amyloid beta (Aβ) and abnormal tau proteins (Castellani et al., 2010). Cognitive impairment in AD is caused by decreased acetylcholine in the presynapse, thus increase in acetylcholine level by inhibiting its cholinesterase activity may improve the memory and cognitive impairment. A few clinically active cholinesterase inhibitors such as donepezil, galantamine, rivastigmine, Huperzine A are available that provide only a modest effect, and can be variable among patients (Hong-Qi et al., 2012). In AD abnormal levels of glutamate is also one of the factors for neuronal dysfunction so the drug such as memantine and namzaric can be valuable for AD patients for prevention of N-methyl-D-aspartate (NMDA) receptor overstimulation (Roberson and Mucke, 2006). Axona (caprylidene) is another medical drug that increases the concentration of ketone bodies that serve as an alternative source of energy for neurons and represents the most recent treatment for AD (Sharma et al., 2014).

PD is the second most common neurodegenerative disease recognized by resting tremor, rigidity, bradykinesia and postural instability. PD patients show continual degeneration of neurons, especially the dopamine producing neurons in the substantia nigra pars compacta region of the striatum (Dauer and Przedborski, 2003). Current treatments for PD include drug course of therapy and surgery. The current drug treatment for PD is supply of levodopa that control PD symptoms, particularly those related to bradykinesia (Jankovic, 2002). Catechol-o-methyl-transferase (COMT) inhibitor such as tolcapone (tasmar) is dopamine agonist (DA) which is also found to increase the plasma concentration of levodopa (Kaakkola et al., 1994). DA such as ropinirole has been shown as effective drug in early stages of PD (Korczyn et al., 1999). Apomorphine hydrochloride is a water soluble DA suitable for intravenous, subcutaneous, sublingual or intranasal administration

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