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Review

Protective effects of flavonoids against Alzheimer's disease-related neural dysfunctions

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ABSTRACT

Senile ages of human life is mostly associated with developmental of several neurological complicated conditions including decreased cognition and reasoning, increased memory loss and impaired language performance. Alzheimer's disease (AD) is the most prevalent neural disorder associated with dementia, consisting of about 70% of dementia reported cases. Failure of currently approved chemical anti-AD therapeutic agents has once again brought up the idea of administering naturally occurring compounds as effective alternative and/or complementary regimens in AD treatment. Polyphenol structured neuroprotecting agents are group of biologically active compounds abundantly found in plants with significant protecting effects against neural injuries and degeneration. As a subclass of this family, Flavonoids are potent anti-oxidant, anti-inflammatory and signalling pathways modulatory agents. Phosphatidylinositol 3-kinase (PI3K)/AKT and mitogen activated protein kinase (MAPK) pathways are both affected by Flavonoids. Regulation of pro-survival transcription factors and induction of specific genes expression in hippocampus are other important anti AD therapeutic activities of Flavonoids. These agents are also capable of inhibiting specific enzymes involved in phosphorylation of tau proteins including β-secretases, cyclin dependent kinase 5 and glycogen synthase. Other significant anti AD effects of Flavonoids include neural rehabilitation and lost cognitive performance recovery. In this review, first we briefly describe the pathophysiology and important pathways involved in pathology of AD and then describe the most important mechanisms through which Flavonoids demonstrate their significant neuroprotective effects in AD therapy.

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1. Introduction

Later part of human life is mostly associated with developmental of several neurological complicated conditions including decreased cognitive abilities and reasoning, increased memory loss and impaired language. Prolonged state of these symptoms together with loss of function and development of cognitive deficit in elderly people is commonly referred as dementia. Today, Alarming upsurge in prevalence of dementia has become the main concern of many governments and health care providers. It is predicted that prevalence of dementia among the U.S. oldest-old will be increased from 1.35 million in the year 2015 up to 4.72 million in 2050 [1,2]. Alzheimer's disease (AD) is the most prevalent neural disorder associated with dementia, comprising about 70% of all dementia reported cases. The most bothering complication associated with AD is incapacitation in performing routine daily functions. Additionally, failure of currently existing therapeutic regimens in treatment of AD, strongly points out the need for development of new generation of therapies to enhance cognitive performance or at least diminish the rate of progression of it. Although the pathways involved in neurodegeneration has not been completely understood yet, several genetical and environmental factors, together with vascular pathology have recently been shown to take part in development and progression of AD [3].

AD is mostly diagnosed by detection of largely deposited amyloid plaques consisting form Amyloid β (Aβ) aggregates outside of neural cells. Intracellular hyper-phosphorylated Tau proteins together with neurofibrillary tangles (NFTs) are other hallmarks of AD [4]. Early stages of AD begins with mild decline in mental function, continues with decline in memory state and rational abilities and ends with alteration in personality and failure in maintaining routine physical functions [5]. Several theories have been proposed to explain mechanisms and pathways involved in initiation of AD some of which include hyper phosphorylation of the microtubule-associated protein tau, Amyloid β plaque formation and loss of the cholinergic system function. However, none of them completely describes the pathophysiology observed during recognition, perhaps due to poor clinical and experimental outcomes [6]. "Inflammation" has proposed to be one of the main contributing factors in development of AD. Findings consistent with this theory include elevated levels of pro-inflammatory cytokines expressed by activated microglial cells and reactive astrocytes in AD. Furthermore, epidemiological studies have also shown that long-term consumption of NSAIDs can reduce symptoms and delay the onset of AD [7]. Analyzing brain samples of affected patients have also demonstrated rising levels of inflammatory cytokines in the initial stages of disease [8]. Genomic studies also demonstrate overexpression of genes responsible in dissemination of inflammation during AD [9]. Current evaluations have also demonstrated that oxidative stress significantly attributes in pathogenesis of AD. These studies have claimed that oxidative stress is a central event preceding occurrence of neurofibrillary tangles and senile plaques formation [10].

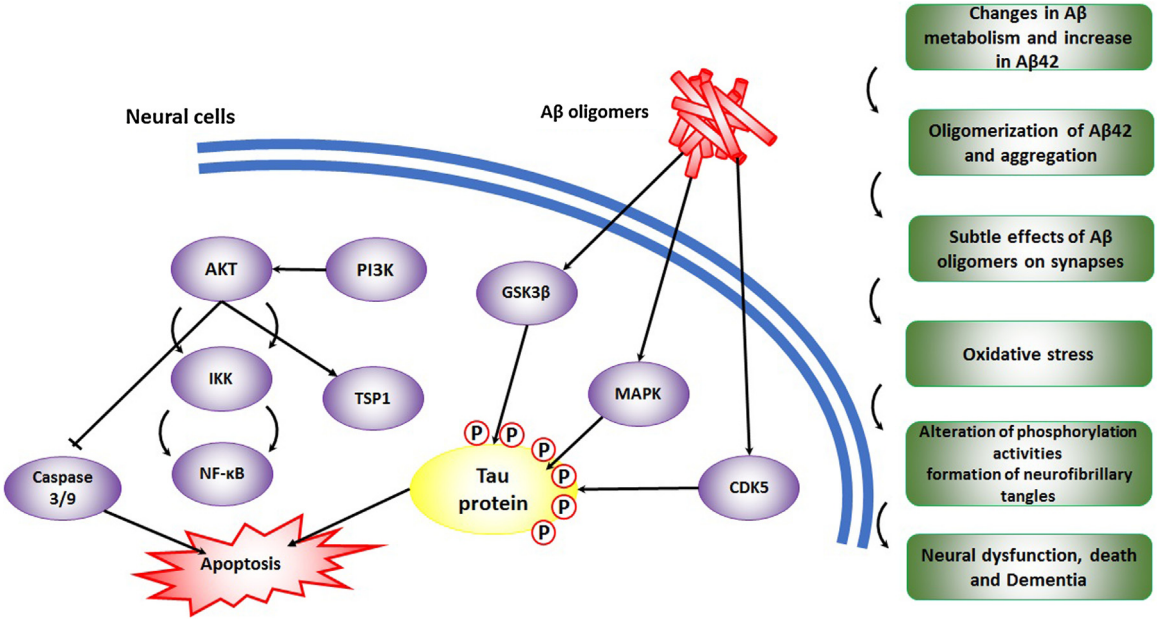

Fig. 1. signaling pathways and different steps involved in neuronal cells apoptosis and induction of Alzheimer's disease.