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REVIEWS: CURRENT TOPICS

The protective role of plant biophenols in mechanisms of Alzheimer's disease☆

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Abstract

Self-assembly of amyloid beta peptide (Aβ) into the neurotoxic oligomers followed by fibrillar aggregates is a defining characteristic of Alzheimer's disease (AD). Several lines of proposed hypotheses have suggested the mechanism of AD pathology, though the exact pathophysiological mechanism is not yet elucidated. The poor understanding of AD and multitude of adverse responses reported from the current synthetic drugs are the leading cause of failure in the drug development to treat or halt the progression of AD and mandate the search for safer and more efficient alternatives. A number of natural compounds have shown the ability to prevent the formation of the toxic oligomers and disrupt the aggregates, thus attracted much attention. Referable to the abundancy and multitude of pharmacological activities of the plant active constituents, biophenols that distinguish them from the other phytochemicals as a natural weapon against the neurodegenerative disorders. This review provides a critical assessment of the current literature on *in vitro* and *in vivo* mechanistic activities of biophenols associated with the prevention and treatment of AD. We have contended the need for more comprehensive approaches to evaluate the anti-AD activity of biophenols at various pathologic levels and to assess the current evidences. Consequently, we highlighted the various problems and challenges confronting the AD research, and offer recommendations for future research.

Keywords: Alzheimer's disease; Amyloid beta; Biophenols; Phytochemicals; Neurodegenerative disorders

1. Introduction

Aging is characterized by multiple physiological phenomena, progressive accumulation of nonfunctional cellular components owing to oxidative damage and a decline in turnover rates and fitness [1]. The accumulated evidences in the last 20 years indicate that the oxidative stress may play a significant role in both aging and age-related maladies, while there is no agreed-upon paradigm for the cause and theory of aging [2,3]. The decline in physiological function upon aging gives rise to a plethora of age-related disorders such as cardiovascular diseases, cancer, arthritis, osteoporosis, benign prostatic hyperplasia, late-onset diabetes, macular degeneration and neurodegenerative diseases [4]. Neurodegenerative diseases are defined as hereditary and sporadic conditions characterized by gradual and progressive loss of neural cells, leading to nervous system dysfunction [5]. Alzheimer's disease (AD) is the most common form of dementia and prevailing neurodegenerative disorder in the world, becoming an imperative public health concern because of no real cure.

Hitherto, AD-approved medications are dreadfully limited in their numbers and efficacy. Scientists in various fields have embarked on a "holy mission" for discovering new possibilities for the treatment and prevention of AD. There is accumulating evidence that diet can play an important role in maintaining brain health [6]. Dietary guidelines for the prevention of AD and healthy brain aging recommend generous consumption of vegetables, whole grains, legumes, fruit, nuts and seeds on a daily basis [7]. Although there is no certainty that any particular nutritional component causes or prevents AD, dietary components with antioxidant properties are attracting increasing scientific and commercial interest to take advantage of a burgeoning market. During last few decades, there has been a "tidal wave" of proposals linking aging and age-related disorders to oxidative stress.

Reactive oxygen and nitrogen species (RONS) are generated during normal physiological processes. They play a pivotal role in the immune response and cell signaling. Our body is endowed with an endogenous antioxidant defense system that keeps the RONS levels within the physiologically beneficial limits. Oxidative stress is characterized by an imbalance between RONS production and elimination. Hypothetically, the intake of antioxidant-rich substances can supplement the endogenous antioxidant defense system, counteract oxidative stress and arrest or even reverse subsequent cellular damage [8]. Dietary antioxidants are generally considered the bioactive principles of fruits and vegetables. They include

☆ Chemical compounds studied in this article: Caffeic acid (PubChem CID: 689043); Gallic acid (PubChem CID: 370); Hydroxytyrosol (PubChem CID: 82755); Quercetin (PubChem CID: 5280343); Rutin (PubChem CID: 5280805); Luteolin (PubChem CID: 5280445); Resveratrol (PubChem CID: 445154); EGCG (PubChem CID: 65064); Curcumin (PubChem CID: 969516); Oleuropein (PubChem CID: 5281544).

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vitamins like ascorbic acid, tocopherols and carotenoids and nonvitamins such as biophenols. Research on biophenols' anti-AD activities has been more promising and rapidly growing [9]. There have been a number of attempts to review biophenols and their role in AD [10–12]. However, none has offered a holistic approach to help assessing the current evidence and introducing new researchers to this vibrant multidisciplinary area of research. In this review, we have tried to systematically evaluate the evidence generated from *in vitro*, animal and clinical experiments, with critical appraisal of the strengths and limitations of various bioassays so as to stress the necessity of adopting a holistic paradigm to investigate anti-AD of biophenols.

2. Biophenols

Biophenols are secondary metabolites ubiquitous in the plant kingdom. The term *biophenol* was introduced to replace the more commonly used but less chemically accurate term *polyphenol*. The prefix *poly* creates an inappropriate impression of polymeric nature or multiple hydroxyl groups. Recently, biophenols were defined as "*Phenolic compounds isolated from plant tissues or products that are derived from shikimate-phenylpropanoid and/or polyketide pathway(s) including their derivatives, conjugates, degradation products and metabolites*" [8]. Generally, biophenols can be divided into four different groups: phenolic acids and alcohols, flavonoids, lignans and secoiridoids. The major sources of biophenols in the human diet are fruits and vegetables, though it is even debatable whether biophenols are the cause behind the reduced morbidities related to consumption of fruits and vegetables [8,13]. Biophenols are the most frequently investigated plant secondary metabolites [8]. This surge in biophenol research is mainly fuelled by their unique antioxidant properties and the wide spectrum of pharmacological activities, which may be employed to counteract oxidative stress [9].

3. Alzheimer's disease

AD is a progressive neurodegenerative disorder and the most common form of dementia amongst the elderly in the western world. Dementia is a syndrome of multiple disturbances in higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment [14]. To date, there is no prevention or treatment for AD. The United States Food and Drug Administration (FDA) has approved two classes of medications: cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. These drugs can offer modest symptomatic relief in a limited number of patients and only during early stages of AD [15]. In 2009, caprylic triglyceride was approved as a medical food by FDA for the dietary management of mild-to-moderate AD. It may provide an alternative energy source for brain cells that have lost their ability to use glucose [16].

3.1. Pathophysiology of AD

During the last two decades, epidemiological and clinical studies have suggested a heterogeneous etiology, and identified two key risk factors for AD: primarily, aging and secondary, genetic predisposition [17]. The exact pathophysiology of AD is not fully understood but based on the present diagnostic biomarkers; the causes are excessive deposition of extraneuronal senile beta-amyloid (Aβ) plaques and intraneuronal tau (τ) protein neurofibrillary tangles (NFT). What causes this is unclear, but there are a number of hypotheses that have been put forward.

3.1.1. The amyloid cascade and modified amyloid hypothesis

The most commonly accepted hypothesis is known as the amyloid hypothesis, which invokes the participation of amyloid precursor protein (APP) in neuronal cell death (Fig. 1). It postulates that the deposition of partially aggregated soluble Aβ (39–43 peptide residues) triggers a neurotoxic cascade, thereby causing neurodegeneration and AD [18]. In support of this hypothesis, there is a correlation between memory deficits, Aβ elevation and amyloid plaques in AD transgenic mice models and in humans [19–21]. The extracellular nonfibrillar Aβ does not seem to cause overt damage to adjacent neurons or to induce formation of neurofibrillary tangles (NFTs) [22]. Over time, this hypothesis has undergone modification, and it is now proposed that the primary contributor to the etiology of AD lies within the cytoplasmic domain of APP [23], and the emphasis switched to the oligomeric, rather than fibrillar forms of Aβ [24,25] supporting the view that intracellular Aβ oligomers are more neurotoxic than extracellular Aβ deposits.

However, due to an unexplained causal link between Aβ and NFTs by Aβ hypothesis, a few studies have suggested that the amyloid hypothesis is unjustified [26,27]. They consider Aβ as an inconsequential bystander or even a beneficial mediator of cellular responses [28]. Furthermore, it was also suggested that Aβ is an artifact of cell culture conditions and that it does not reflect any *in vivo* or diseased conditions [29]. On the basis of numerous supportive results, however, the amyloid hypothesis still remains the best-defined and most widely accepted theory for AD.

3.1.2. Cholinergic hypothesis

The major neurotransmitter in the cholinergic system is acetylcholine (ACh) which plays an important role in memory and learning. It was proposed that the cholinergic system is strongly involved in the functional processes that lead to the AD [30]. As memory impairment and dementia are primary symptoms of AD, this led to the emergence of "cholinergic hypothesis," which essentially states that a loss of cholinergic function in the central nervous system contributes significantly to the cognitive decline associated with advanced age and AD [31,32]. Ach is synthesized by choline acetyltransferase, and its pharmacological action is terminated by cholinesterase. Vertebrates possess two isoforms of cholinesterase: acetylcholinesterase (AChE), which is principally associated with neurons and axons, and butyrylcholinesterase (BChE), which is secreted by glial cells within the brain [33]. The classical action of these enzymes is the catalytic hydrolysis of ACh within cholinergic synapses of the nervous system. AChE is highly selective for the hydrolysis of ACh, while BChE is able to metabolize other molecules [34]. The majority of cholinesterase activity in healthy human brain is AChE because of its higher availability (4:1) compared to BChE [35]. In the late stages of AD, levels of AChE decline by up to 85%, while BchE increases by up to twofold to be the predominant cholinesterase in the brain [35,36].

Cholinesterase inhibitors prevent the breakdown of ACh and promote an increase in ACh concentration and duration of action, contributing benefits to the patients [37]. In addition, results from clinical trials and noninvasive functional imaging research [38,39] suggested that cholinesterase inhibitors might alter APP processing and therefore provide some degree of neuroprotection [40,41].

3.1.3. Mitochondrial cascade hypothesis

Mitochondria are dynamic eukaryotic organelles, which have several roles. They are the primary site of ATP production by oxidative phosphorylation. They maintain calcium homeostasis, participate in calcium signaling and regulate intrinsic apoptosis. It is generally accepted that mitochondrial function declines with age [42]. Mitochondrial dysfunction has been described in the brain [43,44], fibroblasts and blood cells [45,46] of AD patients, in transgenic mouse models of AD [47,48], as well as in cell lines expressing mutant APP or treated with Aβ [49]. All these events led to the "mitochondrial cascade hypothesis," which asserts that inheritance determines mitochondrial baseline function and durability. Mitochondrial durability influences how mitochondrial function changes with age. AD histopathology and symptoms ensue when mitochondrial changes reach a threshold [50]. In AD, there is a severe reduction of many mitochondrial enzyme activities [51], which causes defects in electron