Neuroprotective Natural Products for AD

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Submitted by: Xin Chen

Definition

Neuroprotective natural products, for exmaple, the cholinesterase inhibitor galantamine, have effects on neurovegetative diseases. Rivastigmine is also a semi-synthetic derivative of a natural product called physostigmine. Mixtures or extracts of natural products might have advantages compared to individual natural compounds, as they have multiple simultaneous target approaches, which could be a novel treatment option for Alzheimer's disease (AD), considering the complexity of its pathophysiology. Mounting evidence has suggested that herbs or herbal formulations, together with mixtures obtained from other natural sources, may provide cognitive benefits to AD patients. Consequently, various natural sources and their extracts are extensively employed in animal models and AD patients.

1. Introduction

With the substantial amount of evidence indicating that the primary causative factor in the pathogenesis of AD is the accumulation of Aβ [1], decreasing Aβ has become the major strategy in developing new therapeutics for AD [2]. However, successful AD therapeutic regimens may require multiple neuroprotective agents being used concomitantly. Through careful examination of the pathophysiological processes occurring in AD, several molecular targets have been identified as mediating these processes. These targets could aid in the development of potentially high-yield neuroprotective strategies [3]. Possible neuroprotective mechanisms focus on the inhibition of deleterious intraneuronal mechanisms triggered by Aβ and other toxic stimuli through specific interaction with various neuronal targets [4]. Practical neuroprotective approaches for managing AD include the discovery of small molecules to block Aβ interactions with its extracellular and intracellular targets [5], to minimize stress kinase signaling cascades [6], to prevent caspase activation [7] and pro-apoptotic protein expression [8], to inhibit excessive tau protein phosphorylation [9], to counteract cholinergic function loss [10], to promote the trophic state and neuron plasticity [11], to hinder reactive oxygen species accumulation [12], to suppress neuroinflammation [13] and to block excitotoxicity [14]. It is worth mentioning that some of the neuroprotective agents exhibit their effects through more than one approach. This is especially true with mixtures and extracts of natural products that contain more than one bioactive compound. Therefore, the neuroprotective effects from mixtures and extracts of natural products are always multidimensional and offer an advantage for the treatment of AD compared to single compound. Furthermore, the additive or synergistic action of crude extracts or mixtures can eliminate some of the side effects associated with the predominance of a single xenobiotic compound, providing a more comprehensive spectrum of activity, and minimizing the chances of pathogens developing resistance [15].

Neuroprotective Effects from Natural Products

Natural products have been shown to play neuroprotective roles through almost all of the different molecular mechanisms mentioned above (Figure 1). When focusing on the mixtures and extracts of natural products, the observed neuroprotective effects have typically been recognized as being obtained through anti-oxidative or anti-neuroinflammatory activities, preventing the aggregation of Aβ and tau protein as well as through enhancing cholinergic signaling. It is reasonable to speculate that the onset and progression of AD could be slowed down or even prevented by natural products working on multiple pathological targets [16].

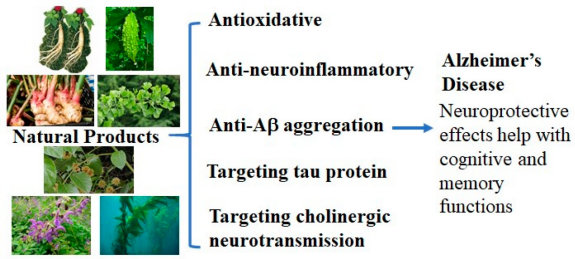

Figure 1. Neuroprotective effects from natural products for AD.

2. Neuroprotective Natural Products for AD

When going through all the possible neuroprotective mechanisms that natural products may have to treat AD, it is clear that most of the individual natural compounds may exert their neuroprotective activity through more than one mechanism. One excellent example is the polyphenol flavonoid resveratrol whose neuroprotective potential consists of antioxidant activity [17], anti-neuroinflammatory activity [18], promoting the clearance of Aβ peptides [18], inhibition of GSK3β, and decreased brain levels of phosphorylated tau [19], as well as increasing cholinergic neurotransmission [20] and BDNF expression [21]. On the other hand, natural product mixtures or extracts, containing numerous individual compounds, may possess better neuroprotective potential as some of these compounds can work synergistically to present more profound effects on preventing neurotoxicity [22]. Moreover, extracts or mixtures of natural products directly obtained from their origins are more affordable therapeutic options with fewer side effects. In fact, some of these natural product mixtures or extracts have shown very promising neuroprotective activities in vitro and in vivo with quite a few being evaluated in clinical trials for AD right now. Here, we summarize the information about natural product mixtures or extracts with their neuroprotective activities for AD.

Neuroprotective Natural Products from Medicinal Plants for AD

Medicinal plants have been discovered to be able to decrease AD progress and symptoms [23]. Both the extracts and the active individual compounds from medicinal plants have been intensively investigated for their effects on AD [24]. The active compounds isolated from medicinal plants, such as phenolic lignans, flavonoids, tannins, and polyphenols, as well as triterpenes, sterols, and alkaloids, have exhibited various beneficial neuroprotective functions, including antioxidant, anti-neuroinflammatory, anti-amyloidogenic, anti-tau aggregation, and anticholinesterase activities [23]. Some of these active compounds, either as single components like curcumin, melatonin, resveratrol, and vitamins C and E, or as herbal extracts such as aged garlic extract, Ginkgo biloba extract, and green tea have been evaluated in AD patients with positive results [25].

3. Conclusions

Mounting evidence has demonstrated the great neuroprotective potentials of natural products and natural bioactive compounds in AD treatment with few harmful side effects. Although not fully understood, the pathological process associated with AD is believed to be multifactorial. Neuroprotective strategies involving multiple mechanisms of action are important for the prevention and treatment of AD. Natural product mixtures or extracts, with multiple bioactive compounds and the ability to exert multiple neuroprotective mechanisms, are preferable in AD drug discovery. With more practical and comprehensive quality control guidelines developed to ensure the safety and efficacy of natural product therapies, as well as new approaches and strategies to help promote the CNS access of these neuroprotective agents, such as the incorporation of nanotechnology in the delivery of natural products, natural product therapy could play an essential role in the prevention and treatment of AD.

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Keywords

Alzheimer's disease (AD);neurodegenerative;neuroprotective;natural products;antioxidant;anti-neuroinflammatory;amyloid β peptide (Aβ);neurofibrillary tangles (NFTs)