

Neuroprotective strategies using vegetal compounds in the treatment of Alzheimer's disease

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Keywords: Alzheimer's disease, neuroprotective vegetal compounds, antioxidants

ABSTRACT. Lately, different therapy strategies for treating or slowing the progression of Alzheimer's disease are being analyzed. Moreover, the last two decades have seen a considerable research effort directed towards discovering the causes of Alzheimer's disease with the ultimate hope of developing safe and effective pharmacological treatments. In addition to the therapeutic strategies based on targeted drugs, the regimens will require the simultaneous application of neuroprotective drugs. Therefore, although there is currently no "cure" for Alzheimer's disease, a large number of potential therapeutic strategies emerged lately. In this small mini-review we will selectively describe some of the compounds derived from plants that could have a great potential in the treatment of various diseases, including Alzheimer's disease. In this way, there are many plant species that have been traditionally used for memory disorders. The differentiated results and powerful activity of these extracts are making these neuroprotective strategies to be somehow plausible for the treatment of Alzheimer's disease. In addition, these plants can be examined in order to isolate and identify their active ingredients and this can serve as a starting point to find safer and more effective agents for therapeutic use. On thing is certain: as the effective treatment options are limited, there is a demand for new drugs. Thus, plant extracts or vegetal compounds could represent an important part in this equation.

1. INTRODUCTION

It's been a century since Alois Alzheimer first diagnosed a patient with a disorder that continues to raise serious problems of medicine. The fact that Dr. Alzheimer's first patient developed a combined form of Alzheimer's disease and Parkinson's was a prediction for the subsequent findings that Alzheimer's disease is part of a spectrum of neurodegenerative disorders with many intermediate and combined forms.

Alzheimer's disease is a neurodegenerative disorder of the brain tissue which causes the progressive and irreversible loss of mental functions, and in particularly of memory. It is the most common and most important degenerative brain disorder [1]. Also, dementia caused by Alzheimer's disease is the most common type, accounting for about 60% of all patients with dementia. Regarding the link between age and disease, it is estimated that 5% of the people over 65 years old have Alzheimer's dementia, while in those over 85 years old the percentage rises to 25% [2].

In case of an early onset, before the age of 65, - as in the first reported case of case of Alzheimer's - the term of pre-senile dementia is used, while the concept of senile dementia is used in the late cases occurring in the elderly over 70 years [3].

Currently there is no effective treatment for the disorder progression. In this way, the proposed interventions are mainly palliative and have only a limited effect on the symptoms. Of course, given

the prevalence of the disease, the pharmaceutical companies make significant efforts to discover drugs that would stop the neurodegenerative processes.

Moreover, although the exact causes of Alzheimer's disease remain poorly understood, it is assumed that both genetic and environment factors contribute to its appearance. The genetic mutations that were found in early-onset family cases, counted for less than 5% of the patients affected by Alzheimer's disease. For the most common form of the disorder, the so-called "sporadic" form, the alleles of several genes (of apolipoprotein E gene in particular), increase the risk of developing the disease [1].

Given the evolutionary trends of Alzheimer's disease that correlate with aging and gradual increase in the number of illnesses, it is estimated that, in the first decades of this millennium, Alzheimer's dementia will become the number one public health problem, by surpassing cardiovascular diseases, cancer and traffic accidents, as the main cause of morbidity, disability and mortality [4].

Also, the pathogenesis of Alzheimer's disease is complex. Genetic factors, free radicals, neurotoxins, neurotrophic support can all contribute to the onset of the pathogenic cascade leading to the neurotransmitters insufficiency and the formation of amyloid plaques and neurofibrillary deposits [2]. In fact, generally these two effects are representing the target of the actual therapy.

2. THERAPEUTIC AND NEUROPROTECTIVE STRATEGIES

In this way, while the symptomatic therapy seeks to replace the deficient neurotransmitters, the new drugs are being produced in order to stop the depositing of amyloid beta 42. The amyloid plaques are neurotoxic and are actively involved in the neurodegeneration that occurs in Alzheimer's disease [5]. As a result, the modulation of their toxicity is seen as an important therapeutic approach to control the onset of Alzheimer's disease [6].

As already mentioned, despite the significant increasing discoveries regarding the pathogenesis in Alzheimer's disease, the therapeutic strategies are still very limited and aim only to relieve symptoms.

Thus, immunohistochemical and ultrastructural studies are indicating that in Alzheimer's disease, an early pathogenic event refers to the hippocampal synaptic losses followed by similar events in the frontal, temporal, parietal, and cingulate cortex [7]. This anatomic pattern of early loss of synapses is combined with the fact that the synapses correlates with the levels of Abeta 42, but not with the amyloid plaques. Also, synaptic loss is significantly related to the cognitive deficit [8].

Also, regarding the possibility of preventing Alzheimer's disease, some studies such as the one of Pinder et al. from 2008 [9], are emphasizing the role of the diet, finding a lower incidence of the disorder in the societies consuming mediterranean food such as fish, fruit, vegetables, olive oil etc. Also, it seems that a moderate lifelong consumption of wine reduces the risk of developing dementia, compared with both abstainers and chronic drinkers [10]. It seems that this effect is determined by the properties of the polyphenols present in wine [11].

Thus, the patients with Alzheimer's disease suffer from a significant decrease in the function of cholinergic neurons in those brain areas responsible for the higher mental functions, which are deficient in the day-to-day activities of life [12]. As AChE deficiency is one of the characteristics of Alzheimer's disease and is responsible for most of the disorder's symptoms, such as the patients decline in memory and cognition, the AChE inhibitors such as tacrine, donepezil, rivastigmine and galantamine are the current drugs against Alzheimer's disease on the market [13]. However, the side effects of these drugs are including various aspects of toxicity, tolerability and loss of efficiency, which suggested a deeper look into the natural alternative medicines [4].

In this way, natural products have offered an alternative therapeutic strategy in Alzheimer's disease, as they are usually safe and have fewer side effects than synthetic chemical drugs [14]. In fact, plants have a long history as a rich source of bioactive compounds for new drugs and, as regarding efficacy, they may have many advantages, as we will describe below.

Moreover, recent findings have shown that natural products have the potential not only to decrease the Abeta toxicity, but also to prevent the production of Abeta [15]. For example, resveratrol (a derivative from red grapes), curcumin (derived from turmeric) and epigallocatechin-3-gallate (derived from green tea) have been reported to reduce the effect of Abeta in the brain cortex. In addition, curcumin is reported to have the ability to block the Abeta aggregation [14,15].

In South Africa, some 3,500 plant species are used as traditional drugs [16]. These plants contain chemical compounds with various pharmacological effects and many are used to treat neurological disorders [16]. In a previous study, a number of plants, including *Ziziphus mucronata* (roots), *Lannea schweinfurthii* (roots), *Terminalia sericea* (roots) and *Crin bulbispermum* (Amaryllidaceae) (roots and bulbs), have been shown to have the ability to inhibit the acetylcholinesterase and provide antioxidant capacity [17], indicating their potential in the treatment of neurodegenerative disorders.

Also, extracts belonging to the species of *Peganum harmala* and *Adhatoda vasica*, which are both β -carboline alkaloid containing plants, demonstrated potent activity against AChE [18]. Thus, it is believed that the major biological activity showed by both of the extracts could be attributed to the dominant compounds in each extract. In this way, *Peganum harmala*'s major constituent is harmaline, and the vasicine *Adhatoda vasica* respectively, which possess various pharmacological activities, serving as a sedative, hypnotic, anxiolytic, anticonvulsant, anti-tumor, anti-thrombotic, anti-parasitic, antimicrobial and antiviral agents [18].

As mentioned before, increased oxidative stress could cause serious damages at the proteins, lipids and DNA levels [19]. The elevated levels of reactive oxygen species (ROS) are also associated with increased deposits of amyloid, which is of course a hallmark in detecting the outbreak of Alzheimer's disease, as we mentioned above. In this way, if ROS levels are exceeding the basic level of cellular protection mechanisms, this will result in cell death [3]. Therefore, plant extracts that have strong free radical scavenging properties (such as *Terminalia chebula*, *Terminalia arjuna* and *Emblica officinalis*) could have a key role in reducing oxidative stress and this may explain their use in traditional medicine against aging, Alzheimer's disease and related disorders [20].

Also, since previous studies have shown that the oxidative damage is present in the brain of patients with Alzheimer's disease [3,19] the use of antioxidants in the treatment of Alzheimer's disease has gained increased popularity lately and there is enough epidemiological data to suggest that antioxidants may be associated with a lower incidence of Alzheimer's disease.

In this way, a large-scale clinical trial which was conducted on patients with moderate Alzheimer's disease, previously showed that vitamin E and selegiline were effective in delaying the progression of moderate Alzheimer's disease [21]. We should also mention that some of these single positive studies with vitamin E should be interpreted also in the context of several meta-analyses regarding the vitamin E, indicating that daily doses of 400 IU or more lead to an increased death risk of vascular causes [22,23]. Anyway, perhaps the side effects results regarding vitamin E are caused by the fact that the pharmaceutical preparations contain only one isoform of vitamin E from the eight existing in nature [21].

Also, *Cassia fistula*, a plant of Southeast Asia, which is widely spread in Egypt, as an ornamental tree, have its seeds well known in the traditional medicine, and recently, the effects of these seeds extracts against aging associated diseases was studied. In this way, the ethanolic extract from the seeds of *Cassia obtusifolia* (*Cassia fistula*) was found to significantly attenuate memory impairment induced by scopolamine by inhibiting acetylcholinesterase. Moreover, the extract was a good neuroprotective agent against mitochondrial toxin 3-NP [24].

There is also a variety of plants which were previously cited for their possible implications in AD pathology. From these, we can mention *Emblica officinalis* (Amla) which grows in the tropical and subtropical parts of East Asia, and has been cultivated in Egypt in recent years for its economic value and it is used as tonic for the heart and brain in Unani medicine. In this way, the extract

obtained from *E. officinalis* has the ability to improve or enhance memory due to antioxidant, anti-inflammatory and neuroprotective properties [25].

The same applies to *Nerium oleander*, which is widely cultivated as a garden plant and has shown anticancer activity, while the anti-aging properties of this plant extract were investigated recently, and polysaccharides isolated from oleander flowers showed neuroprotective activity against neuronal cells death in Alzheimer's disease [15].

In the same time, other research groups have studied Black pepper (*Piper nigrum*) which has been cited to have a possible relevance for the treatment of Alzheimer's disease. In this way, it is known to possess several pharmacological actions such as antimicrobial, antifungal, anti-inflammatory and antioxidant effects [26]. In fact, piperine, the compound obtained from *Piper nigrum* in vitro was demonstrated to have a protective role against oxidative damage by inhibiting the free radicals and the reactive oxygen species (ROS) [27].

Also, the resulting oil from *Nigella sativa*, which is cultivated for its seeds and used as spice in Egypt and other Arab countries, showed some neuroprotective effect with promising perspectives in Alzheimer's disease [28], while also the cocoa beans of the *Theobroma cacao* were cited in similar ways [29,30]. In addition, the recent literature [31] described the compounds present in cocoa and chocolate as exercising many beneficial effects on the brain, improving cognition in both animals and humans. The health promoting properties of cocoa powder were attributed mainly to the polyphenolic compounds.

But which are the products from these plant extracts that could explain their neuroprotective effects? We can mention here the polyphenols (mainly catechins, epicatechins and procyanidins), which are in fact the major source of antioxidants in the cocoa bean, as we already mentioned above. In this way, polyphenols are natural substances that are present in fruits and vegetables, including olive oil, red wine and tea. Also, the flavonoids are the largest group of polyphenols with over 2,000 individual flavonoids being described.

In fact, the capacity of flavonoids to act as antioxidants depends on their molecular structure, the position of the hydroxyl group and other constituents. They also have several important biological properties, such as anti-inflammatory, anticancer, antiviral, antimicrobial, vasorelaxant and anticoagulant manifestations [32]. In general, the antioxidant properties of catechins are more powerful than those of the α -tocopherol or vitamin C and E [33]. In addition, the catechins exert their antioxidant activity by chelating metal ions such as iron (Fe^{2+}) and copper (Cu^{2+}), and prevent the generation of free radicals [34].

Moreover, the flavonoids in cocoa beans are also known for their antioxidant effect, with defense role [35].

Also, recent studies have shown the role of the compounds from natural sources regarding the inhibition of A β plaques in vitro and in vivo [36]. However, gathering the evidence for the ability of vegetal compounds to inhibit the A β oligomerization in vivo remains a challenge. For example, in the case of *Cinnamomum zeylanicum*, which is a traditional medicinal product, it is believed that the protective effects of cinnamon are due to its various components, such as cinnamaldehyde, eugenol, linalool, cinnamyl alcohol and a wide range of volatile substances including safrole, coumarin or cinnamic acid esters [37]. Moreover, cinnamon has also other important properties, such as controlling blood glucose [38], antioxidant, anti-inflammatory [39] and antimicrobial effects [40]. It was additionally shown to inhibit the aggregation of tau proteins in Alzheimer's disease [41] and to be efficient in the treatment of type II diabetes [37]. The potentially toxic compounds from cinnamon bark, highlighted by some studies, are mainly lipid soluble fractions that are present only in very small quantities in the soluble extracts of cinnamon [42]. Also, while studies have indicated the presence of polyphenols in the cinnamon extract [42], while polyphenols seem to exert an effect in inhibiting the aggregation of the various amyloidogenic peptides [43].

3. CONCLUSIONS

The findings of this study indicate that the compounds derived from plants could yield a great potential in the treatment of various diseases, including Alzheimer's disease and their properties targeted against the acetylcholinesterase, introduce them as promising candidates for further in vitro and in vivo studies. There are many plant species that have been traditionally used for memory disorders that show the variability of the ways to protect against Alzheimer's disease. The differentiated results and powerful activity of the extracts possessing unique bioactive components make these neuroprotective strategies to be somehow plausible for the treatment of Alzheimer's disease. In addition, these plants can be examined in order to isolate and identify the active ingredients and this can serve as a basis to find safer and more effective agents for therapeutic use.

ACKNOWLEDGMENTS

Ciobica Alin is supported by an internal grant GI-2014-01 from Alexandru Ioan Cuza University, Iasi. Radu Lefter is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/I5911.5151133675. The other authors declare that they have no potential conflicts of interest to disclose.

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