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Short Communication

Monoclonal Antibodies or Natural Products will be the Ideal Medicines for Different Stages of Alzheimer's Disease

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Cognitive decline and dementia are among leading chronic conditions undermining the quality of life in our aging population. Dementia is a term used to describe a variety of diseases in which the normal function of the brain gets impaired due to irreversible loss of neurons. According to expert prediction of Alzheimer Disease International-ADI-, the number of dementia patients all over the world would grow from 47 million in 2015 to 74 million in 2030 and then to 131 million by 2050 [1]. This means that in the next 30 - 40 years, almost each person would be affected by dementia throughout the life cycle either as a patient or as a caregiver.

Despite the enormous financial expenses (about $600 billion was spent for AD research in the USA in 2015) and the effort of world scientific and medical community, a 30-year period of active research into the neuro-biology and neuro-pharmacology of AD did not result in the development of a therapy. Indeed, these therapies would not merely mitigate the severity of clinical symptoms, but would also reliably modify the course of the disease, i.e. stop or clearly retard its progression. In the skilled professional's opinion, a key reason for this little progress in the treatment of AD may be the late start of therapy.

Furthermore, AD is first diagnosed and, hence, the therapy starts only when a patient has developed a dementia syndrome, indicating that the cerebral compensatory reserves have been exhausted because of extensive neurodegeneration. Inhibition of the enzyme acetylcholinesterase (AChE) or butyrylcholinesterase (BuChE) is considered as one of the major therapeutic strategies offering only symptomatic relief and moderate disease-modifying effect. As two of licensed drugs (cholinesterase inhibitors [ChEIs]) are naturally derived (galantamine and rivastigmine), the potential for plants to yield new therapeutic agents has stimulated extensive research to discover new ChEIs together with plant extracts, phytochemicals and their derivatives with other mechanistic effects relevant to dementia treatment. These drugs, such as galantamine and rivastigmine, attenuate the decline in the cholinergic system but, as the alkaloids occupy the most dangerous end of the phytochemical spectrum (indeed they function as feeding deterrents and poisons to other organisms within the plant itself), they are often associated with unpleasant side effects [2]. In addition, these cholinesterase inhibiting alkaloids target only one system in a disorder, which is typified by multifactorial deficits.

Therefore, currently it is highly demanded to diagnose AD in early, predementia or, perhaps, pre-symptomatic stage of the neurodegenerative process. According to estimates, this stage may last for at least 10 - 15 years. Once more, equally critical task is to search for viable methods for pharmacological interventions able to stop or substantially slow down the development of neurodegenerative process and thus to prevent the appearance of dementia or delay it for several years without side effects. Without solving this problem, any "super" early diagnosis of AD and/or another progressive neurodegenerative disease causing the dementia becomes a purely scholastic action that is not only unable to help a patient, but can also bring harm, being the source of chronic psychological stress and depression, which are the risk factors for AD development.

With an aging population and no cure for dementia on the horizon, risk factor modification prior to disease onset is an urgent health priority. With over 150 unsuccessful compounds tested and a cure for dementia yet to be discovered, identifying modifiable risk factors towards disease prevention is a high priority. Non-cholinergic therapeutic approaches include antioxidant and vitamin therapy, stem

cell therapy, hormonal therapy, use of antihypertensive or lipid-lowering medications and selective phosphodiesterase (PDE) inhibitors, inhibition of β-secretase and γ-secretase and Aβ aggregation, inhibition of tau hyperphosphorylation and intracellular NFT, use of non-steroidal anti-inflammatory drugs (NSAIDs), transition metal chelators, insulin resistance drugs, etanercept, brain-derived neurotrophic factor (BDNF) etc. But all these medications have only one target and this target is late in the progression of the disease. Also the modern therapies utilized for AD treatment have many adverse effects, driving the quest for more safe and effective medications. With the social and financial burden of this disease increasing every year, the onus is now on the field of AD researchers to investigate alternative ideas to deliver outcomes for patients. AD appears to be a complex and multifactorial disorder. The etiology of AD and its underlying mechanism are still not clear. Both environmental and hereditary factors are believed to be involved in the pathogenesis of AD. Among the most common pathogenic factors are: 1. Accumulation of insoluble deposits of beta amyloidal plaques outside the neurons. 2. intracellular neurofibrillary tangles due to hyperphosphorylated tau protein (NFTs) - tau protein missorting, 3. loss of synapses, 4. brain inflammation, 5. neuronal loss, 6. altered cholesterol metabolism, 7. formation of reactive oxygen species (ROS) due to oxidative stress, 8. presence of metal ions and eventual brain shrinkage, 9. depletion of neurotransmitter - acetylcholine at synapses by the over expression of acetylcholinesterase enzyme -, 10. mitochondrial dysfunction, 11. protein glycation, 12. Apolipoprotein E polymorphic allele risk, 13. Aging also has a strong influence on AD development. The progression of the above events leading to cell death and neurodegeneration in AD is yet not known. So the progress in understanding the disease etiology demands a multiple-site-targeted therapy.

Efforts to develop new therapies to combat Alzheimer's disease suffer from high failure rates that make it difficult to justify continued investment in the field. One possible explanation is the possibility that treatments aimed at a single pathologic process will be ineffective. For example the most popular, the first (see above) and dominant hypotheses in the area of AD is the amyloid hypothesis, which posits that either the overproduction and/or the under clearance of amyloid β (Aβ) is a proximate cause of AD. Research into clearance mechanisms of Aβ suggested that either active or passive immunization approaches could be potentially useful to reduce the amount of Aβ in the brain and thereby prevent, delay or even possibly reverse the cognitive, behavioral and functional decline in AD. However the results of all phase 3 studies with bapineuzumab and solanezumab were negative. The second of the currently popular explanations for these failures is that treating AD patients when they are demented is too late and that, to modify the natural course of the disease, one needs to intervene when persons are cognitively intact or very mildly affected, although it is not known just how early one would need to start treatment [3].

So we need treatments in very early stages, even before persons have any symptoms, these medications have to present no side effects, have as targets as many pathogenetic mechanisms of AD as possible, and healthy elderly people will be willing to take them, even they have no symptoms.

Hippocrates many centuries before said: "Food should be your medicine and if you need medicine, take it from food".

Natural products have provided an invaluable source of inspiration in the drug discovery pipeline. Functional foods to prevent and/or treat many conditions, including neurodegenerative diseases, represent a promising field of study currently gaining attention. Many dietary components, including different types of fruits, vegetables, spices, drinks, beverages and marine products as well as a Mediterranean diet, are a good source of antioxidants - are effective at inhibiting stress- and have anti-inflammatory properties, with many showing substantial potential against AD pathogenesis such as Aβ accumulation and toxicity, and tau phosphorylation. Associations with reductions in other pathophysiological conditions of AD while improving memory, learning ability, cognitive function and protecting against neuronal cell death were also reported for these dietary components [4].

Polyphenols have been associated to pleiotropic biological effects: they are known to behave as potent antioxidants, as direct radical scavengers in the lipid peroxidation, and to interact with a number of signaling targets involved in biological processes, such as carcinogenesis and inflammation. Previously also identified lifestyle risk factors have been attributed to half the cases of dementia, and should

inform clinical intervention towards preventing or delaying cognitive decline in aging. Emerging evidence suggests, for example, that vitamin D deficiency is an important marker of cognitive decline.

Another problem the clinicians have to solve is the side effects by synthetic drugs. The side effects and toxicity exhibited by synthetic drugs and various other therapeutic strategies have led to an increased demand of plant derived herbal medicines which are either approved or are in different stages of clinical trials for a number of diseases in the last few decades. Although synthetic chemistry dominates the present scenario of drug discovery and manufacturing, still the contribution of plant-derived compounds for treatment and prevention of various diseases could not be ignored. Plant products being natural, are often considered as safe, though some side effects have also been reported for some plant products. Such adverse effects of plant derived natural products may include allergic reactions, toxicity and plant pharmaceutical interactions with synthetic/semi synthetic drugs. In spite of these side effects of some of the natural products, these plant derived natural products have been considered to be less toxic and relatively safer substitutes to synthetic drugs against a number of precarious diseases, including AD. Moreover, a number of plant-derived natural compounds have been shown to provide better patient safety and tolerance and increase in the chances of acceptance by the patient [5].

In the recent years use of complementary medicine like herbs has increased in the management of chronic disorder. Herbs are the source of most drugs which plays the role in the development of drug. Several traditional Chinese medicine (TCM) formulas have been well-documented in the Chinese literature as medicines for dementia. Based on the principles of TCM, these formulas address not only modifying the disease symptoms but also restoring and sustaining the body's homeostasis. Also other medicinal plants have been reported for possible anti-AD activity in a number of preclinical and clinical trials. Natural products are currently considered as an alternative strategy for the discovery of novel multipotent drugs against AD. Ethnobotany, being popular in China and in the Far East and possibly less emphasized in Europe, plays a substantial role in the discovery of anti-AD agents from botanicals. Chinese Material Medica (CMM) involving Chinese medicinal plants has been used traditionally in China in the treatment of AD. Ayurveda has already provided numerous lead compounds in drug discovery and many of these are also undergoing clinical investigations. A number of medicinal plants either in their crude forms or as isolated compounds have exhibited to reduce the pathological features associated with AD.

Many clinical studies with natural products have been published recent years. The vast majority of them use only one natural product for example curcumin either for AD patients, or healthy controls or patients with Mild Cognitive Impairment. Bauman., *et al.* gave curcumin 1 or 4 gr/day to 34 patients with probable or possible AD more than 50 years old. The results showed that there were no significant differences between curcumin and PL after 6 months both in efficacy and adverse events [6]. Rainey-Smith., *et al.* gave Biocurcumax™ 1500 mg/day (1320 mg/day curcuminoids) to 160 health elderly 40 - 90 years old for 12 months. Their target was to show the prevention of cognitive decline. Unfortunately they found no changes in cognitive performance and they recorded gastrointestinal complaints in 23 subjects [7]. Cox., *et al.* gave Longvida® Optimized Curcumin 400 mg (80 mg curcumin) to 60 healthy elderly 60 - 85 years old for 4 weeks. Their results showed an improvement of cognitive functions and the product was well tolerated [8]. As one can understand there are controversies, because there are different methodologies, different populations and different size of the samples.

There are only some clinical studies which use two or three natural products for healthy elderly people without using any biomarkers in blood or CSF. Witte., *et al.* gave resveratrol 200 mg/day in a formula with quercetin to 46 healthy overweight 50 - 80 years for 26 weeks to investigate the ability to enhance cognitive performance. They noticed significant retention of memory, significant increase of hippocampal functional connectivity, and improvement of glucose metabolism. Adverse effects were not assessed [9]. Wightman., *et al.* used trans-resveratrol 250 mg/day or trans-resveratrol 250 mg/day with 20 mg piperine in 23 healthy 19-34 years old for 21 days. Six healthy men underwent bioavailability assessment. The results showed that piperine enhances the effect of resveratrol on cerebral blood flow but not the cognitive performance and bioavailability [10].

Perhaps the solution will be a combination, a cocktail of some natural products which have the probability to target all the pathogenetic mechanisms which has to be examined first in neuron cultures, then in transgenic mice and finally in Patients with Mild Cognitive Impairments with positive and negative biological markers for AD.

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