

The Emergency of Nutraceutical Compounds in the Preventive Medicine Scenario. Potential for Treatment of Alzheimer's Disease and Other Chronic Disorders

Victor Andrade¹, Leonardo Guzmán-Martínez¹, Nicole Cortés¹, Andrea González¹, Gonzalo Fariás² and Ricardo B Maccioni^{1,2*}

¹Laboratory of Neurosciences, Faculty of Sciences, University of Chile & International Center for Biomedicine (ICC), Santiago, Chile

²Department of Neurology and Neuroscience, Faculty of Medicine, University of Chile, Chile

Abstract

Evidence-based Nutraceutical Compounds (EBNC), containing bioactive principles of demonstrated efficacy and health security are opening solutions for a modern preventive medicine, and as potential solutions for many chronic diseases of the human beings. EBNC contain bioactive components of the human diet that can be used for the prevention or treatment of a disease. They are obtained through rigorous processes of extraction from natural resources and Good Manufacturing Practices (GMP) regulations, and exhibit sound preclinical studies published in high impact medical journals, and double-blind placebo-controlled clinical trials. Are these compounds significantly more effective than alternative medicines? EBNC rely on some of the major advances in molecular genetics, epitranscriptomics, molecular biology and modern pharmacology. They are certainly opening a solid pathway in benefit of human health and the welfare of mankind.

Keywords: Nutraceutical compounds; Bioactive molecules; FOSHU category; Preventive medicine; Integrated health condition; Treatment approaches for chronic diseases; Evidence-based nutraceuticals

Introduction

The progressive increase in the life expectancy of human beings, associated with a dramatic rearrangement in the pyramid of age distributions, has demanded significant efforts of the medical community and pharmaceutical industry toward research of novel compounds with efficiency for treating health disorders in the aging population, with low level of adverse effects. Medicine has grown significantly. In this context, significant advances in the search of new drugs and therapeutic strategies supported by clinical trials, have been critical for the treatments of a series of chronic diseases, including neurodegenerative disorders, diabetes, autoimmune disorders and cancer among other ailments. No doubt that these achievements in medical research, together with the enormous increase in health information to improve life styles, have been determinant for the current status of life expectancy and longevity. Nowadays, in the occidental world the subpopulation of individual older than 65 years old is reaching around 15%-20% of the entire population. Thus, age-related diseases are becoming the new target of the 21st century [1].

Despite major advances in the search of disease-controlling drugs, two major problems arise: 1) That for many chronic diseases no novel drugs have been generated, in some cases no pharmacological therapies have been demonstrated efficiency during the past 2-3 decades. For Alzheimer's Disease (AD) the last drug being used as treatment is memantine, which has only palliative effects on the disease, and it was launched 25 years ago. Since then, more than 400 compounds have been tested without success [2]; 2) The major adverse effects of the many drugs used in medical therapies, despite the many variants of the molecular structures that have been developed have not been solved. In this context a new scenario of EBNC appears to be a potential pathway.

During centuries human beings have been searching in plants and the oceans for substances that promise a cure for many diseases. Ayurvedic medicine has provided a powerful avenue, but this has been mainly regionally focused, being used in India, Nepal and surrounding communities but not as a main stream in the occident. Certainly, it has

been the basis for several medical approaches based on active principles from plants. On the other hand, a new paradigm has emerged in the past few years: nutraceuticals [3,4]. These are advanced products with nutritional value derived from functional food, with a beneficial impact in human health. Nutraceuticals are essential for preventive medicine and the human attempts to avoid diseases, but they can also help in the treatment of many health disorders. They have been considered as part of complementary medicine, however there is a new category of advanced nutraceutical formulae that can be incorporated into therapeutic approaches in specific diseases on the basis of the preclinical research support and also sustained by double-blind medical trials.

Nutraceuticals in the Prevention and Treatment of Alzheimer's Disease

Many substances that become bioavailable after digestion offer extra-nutritional beneficial properties; these substances are called "bioactive". The properties of such compounds include antioxidant, anti-inflammatory, antimicrobial, antihypertensive, and anticancer activities as well as regulatory roles for intra- and extracellular signaling pathways. The nutraceutical market has grown in the last decade due to increase consumer knowledge of these compounds and for the relevance on the prevention and therapy of several diseases. In this context, in 2007, the nutraceutical market reached \$117.3 billion, and it is proposed that the worldwide nutraceuticals market is expanding and would reach US \$250 billion by 2018 [5]. AD, as a growing world-

***Corresponding author:** Ricardo B Maccioni, International Center for Biomedicine, Avda. Vitacura 3568, D513, Vitacura, Santiago, Chile, Tel: +56229536362; E-mail: rmaccion@manquehue.net

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wide health problem, became a notorious focus for the evaluation of new nutraceutical products, mainly considering the slow advances in the search of new pharmacological therapies during the last decade, together with the promising actions of some nutraceuticals in the prevention and treatment of age-related diseases.

Thus, natural alternatives have emerged as possible solutions, supported by clinical research. Nowadays, there are 121 trials in order to evaluate a potential treatment for AD, among them, there are a few number of natural compounds accepted by the US Food and Drug Administration (FDA) [6]. Among the clinical studies to control progression of this pathology, novel strategies are being implemented to prevent AD based on dietary changes and nutritional supplements, functional foods and natural compounds. We have postulated that the onset of AD is a consequence of the response of microglial cells to “damage signals” or tau oligomers, which triggers a neuro-inflammatory response, promoting the misfolding of the cytoskeleton structure [7-9]. Innovative treatments are essential to improve the life quality and ameliorate the symptoms of affected subjects. However, pharmaceutical industry has failed in developing new drugs of efficacy to control AD. In this context, major attention has been given to nutraceuticals and novel bioactive compounds, such as the Andean Compound (or Andean Shilajit), endemic of Chile and obtained from areas in the north of Chilean desertic mountains and, its new formulation, Brain Up-10^R, supplemented with B vitamins complex [10,11]. Preliminary studies suggest that this compound achieves effectiveness, in order to control the disease or serve as a co-adjuvant for an effective treatment [10,11]. Phase 1 studies demonstrated the lack of adverse effects. Intensive work toward the elucidation of the molecular mechanisms of action of this compound is being carried out [12]. The most relevant finding was the action of this compound, and also fulvic acid, a main component of this substance, in disassembling preformed tau oligomers and filaments, and exerting inhibition of their assembly [13]. In addition, an advanced second phase clinical trial is actually being developed.

Another bioactive compound is the Indian Shilajit, commonly used on traditional indian ayurvedic medicine [14]. This plant, found at high altitudes, among its main components have fulvic acid and humic substances [14]. It has been reported a potential pro-cognitive properties [11], as well as antipsychotic and antiepileptic properties [15]. Administration of Shilajit extract for 7 days to winstar rats down-

regulates the acetyl-cholinesterase activity and enhanced muscarine 1 (M1) receptor binding [16]. The latter suggest that the memory enhance associated with Shilajit is related to the Cholinergic, but not GABAergic or Glutamatergic pathways, as none of them was affected when Shilajit was administrated [16].

In general, important efforts have been recently made to find natural compounds for effective and non-invasive treatment against AD. These include quercetin, a flavonoid able to reduce astrocyte activation, thus reducing neuroinflammation and improving memory in SAMP8 accelerated senescence mice. The animals were treated with an oral formulation of quercetin encapsulated in nanoparticles [17]. Another flavonoid compound with potential for AD treatment is apigenin, which can be found, among other sources, in chamomile and grapefruit. This compound is able to inhibit microglia-mediated release of IL-6 and TNF- α , the prostaglandin and Nitric Oxide (NO) production by inhibiting Cyclooxygenase (COX-2) and *inducible Nitric Oxide Synthase* (iNOS) enzymatic activities respectively, and also inhibits the nuclear factor κ B (NF- κ B) signaling pathway [18]. However, the most promising natural compound for anti-inflammatory treatment of AD is curcumin [19], a polyphenol isolated from rhizomes of curcuma, which reduces the expression of COX-2 and iNOS, impairs interleukina-6 (IL-6), NF- κ B and Mitogen-activated Protein Kinase (MAPK) signaling pathways, reduces astroglial activation [18]. In another context, studies have also demonstrated that curcumin enhances neurite outgrowth in cultured neuronal cells and also prevents and reverts tau aggregation *in vitro* [19]. These data suggests that this compound could be used in AD patients with cognitive impairment. Moreover, it has the same effects in animal models and humans, which presents this compound as an attractive alternative for further studies and, also to develop new natural or synthetic anti-inflammatory and anti-aggregative formulations to treat AD [18].

New compounds are currently being proposed to treat effectively AD, most of them, without success in clinical trials. Most of them, enhance by their antioxidant, anti-inflammatory, or metabolic properties [20,21], and have diverse natural origins (Table 1). They are at different stages in trials and present high potential to continue scaling in the cure or treatment of AD.

The 3-carboxy-3-oxopropanoic acid (OAA), is a natural chemical

Active Agent	Main component	Mechanism	Ref.
Apigenin	Apigenin	Reduction of expression of COX and iNOS	[18]
Curcumin	Curcumin	Reduction of the expression of COX-2, iNOS Impairment of IL-6, NF- κ B and MAPK signaling pathways	[18,19]
Quercetin	Quercetin	Reduction of levels of IL-6 and TNF- α	[82]
<i>Ginkgo biloba</i> ®	Terpenoids, flavonol glycosides and proanthocyanidins	Increases production of nitric oxide in blood vessels. Inhibits the platelet-activating factor	[64,65]
Oxalacetate	Oxalacetate	Mitochondrial metabolism	[28,29]
S-qual	7-hydroxy-3-(4'-hydroxyphenyl)-chroman	Mitochondrial metabolism	[32,33]
L-serine	2-amino-3-hydroxypropanoic acid	Neuroprotector	[37]
MLC901	Preparation of nine herbal compounds, that include tanshinone IIA and others.	Neuroprotector	[20,45]
Meganatural-az	Polyphenols	Tau Anti-aggregative	[20,48]
Resveratrol®	3,5,4'-trihydroxy-trans-stilbene	SIRT1 activator	[21,53]
Omega 3	Omega-3	Anti-oxidant and anti-inflammatory	[48,60]
Brain – Up10	Several bioactive organic compounds, selenium and minerals	Reduces tau aggregation and increases neurogenesis	[10]
<i>Moringa oleifera</i>	Essential aminoacid, Omega-3 and several bioactive compounds	Reduces homocysteine-induced AD-like pathology. Improves cognitive responses. Antioxidant and anti-inflammatory.	[71-74]
<i>Zizyphus jujuba</i>	Several bioactive compounds	Attenuates Alzheimer’s diseases associated hippocampal synaptic deficiencies. Improves memory and learning.	[79,80]

Table 1: Active natural compounds or nutraceuticals for AD therapy.

that participates in Krebs's cycle and acts as a glutamate scavenger [22]. It is found in blueberries, blackberries, tangerines and plums, and in vegetables as spinaches, beets and quinoa [23-26]. Besides, legumes and nuts also have great content of OAA [27]. Due to its bioenergetic, anti-inflammatory and neurogenetic properties, OAA has been postulated as a possible treatment for AD [28]. An incipient phase 1, non-randomized clinical trial is now recruiting subjects with diagnosis of probable AD to verify the safety and tolerance (Table 1). In a previous study, very modest cohort of 6 participants, showed that daily treatment of twice of 100 mg of OAA for 4 weeks, was safe and well tolerated [29]. Another natural compound related to mitochondria metabolism, is S-qual (7-hydroxy-3-(4'-hydroxyphenyl)-chroman). It is an Estrogen Receptor β (ER β) agonist, present predominantly in soy [30,31]. It has been found in AD patient's brains, evidence of a decrease in mitochondria activity by dysfunction [32,33]. S-qual has been proposed as a potential treatment for this pathology. A phase 2, randomized, double blind trial, is recruiting AD subjects to evaluate safety and tolerability, besides of mitochondrial activity and cognitive functions (Table 1).

Several others natural compounds already overcome the first stage of clinical trials, researching the efficacy and side effects on AD subjects. Among them, L-serine (2-amino-3-hydroxypropanoic acid), is a naturally occurring non-essential amino acid, with diverse biological functions, key in cellular metabolism and maintenance of Central Nervous System (CNS), and enhancing its role by phosphorylation [34,35]. It is present in eggs, soy and its derivatives, also in meat, fish and cheese. Moreover, it has been considered by the FDA as a Generally Recognized as Safe (GRAS) product. L-serine is synthesized by astrocytes and neurons in CNS [36], and showed to be neuroprotector in Amyotrophic Lateral Sclerosis (ALS) [37,38]. Besides, L-serine was capable of attenuate the density of Neurofibrillary Tangles (NFT) and Senile Plaques (SP) in brains of primates that exhibit these traits [37]. Based on the previous data and its importance in CNS; a Phase 2, randomized, double-blind, placebo-controlled study is recruiting AD patients at early stages of disease, to assay the effects of L-serine over tolerability and cognitive skills of subjects (Table 1). MLC901 is a group of natural herbs, used traditionally in Chinese medicine [39]. It is the simplified version of MLC601, which contain besides the plants components, substances coming from animals [39,40]. MLC901 has been previously used to improve recovery after stroke [41-43] and, has showed protective properties in cognitive tasks in mice models, improving neurogenesis [44]. Besides, MLC901 is capable to induce a significant decrease in tau phosphorylation levels in a cellular model of tauopathies [20,45]. Considering all these reports, a randomized, double blind, placebo-controlled trial, is recruiting subjects with mild to moderate AD to assay the safety and efficacy of MLC901, besides cognitive and functional skills (Table 1).

Meganatural-az (MN) corresponds to a group of polyphenolic extracts derived from grape seeds [20]. Is a blood pressure stabilizer [46]. MN ameliorates the cognitive damage and decrease amyloid beta (A β) oligomerization in brains of mice model of AD [47]. As well, there is evidence of neuroprotective properties, by disassembly of tau protein aggregates [20,48]. A phase 2, randomized, clinical trial is recruiting AD subjects to assess safety and pharmacokinetics. Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural polyphenol, capable of penetrating blood-brain barrier efficiently [49]. Is present in multiple plants, mainly in grape seed and is abundant in red wine [50,51]. It has beneficial properties in different pathological contexts, such as diabetes, cancer, and cardiovascular diseases [52]. Its mechanism is attributed as regulator of Sirtuin 1 (SIRT), a protein involved in cell cycle, metabolic and inflammatory function [53]. In regard to AD,

pre-clinical research presents this compound as a potential treatment agent, because it has the capacity to ameliorate A β in cellular lines and, to decrease the levels of A β and p-tau in serum of induced AD rats [54,55]. In addition, due to its antioxidant power, it has shown to be protective in diverse neurodegenerative disease models, both in cell lines and animals [21,56]. In humans, resveratrol has been beneficial in these disorders [57], and recently, it has shown to be a regulator of inflammation in subjects with mild to moderate AD, reducing the expression of proinflammatory agents and improving cognitive skills in comparison to placebo patients, in a randomized, phase 2-double blind trial [58]. These results do not show a decrease of modified tau levels.

Omega-3 is predominant in fishes and algae. In the same context of oxidative stress and inflammation, polyunsaturated fatty acids, such as Omega-3, are essential for proper brain and neuronal function. These compounds are key components of the plasma membrane and modulate important processes such as inflammation and oxidative stress [41]. Omega-3 are classified mainly into 3 fatty acids, alpha-linolenic acid, Docosahexaenoic acid (DHA) and Eicosapentaenoic Acid (EPA). Although DHA and EPA can be synthesized endogenously from α -linolenic acid (18:3n-3), the conversion rate in humans is very low; therefore, the main source of both fatty acids is the diet [43,44]. In the brain, studies have reported that docosahexaenoic acid protects against oxidative and inflammatory processes, which are involved in the etiopathogenesis of AD [48]. In fact, healthy adults who receive a supplement of this fatty acid have decreased serum levels of proinflammatory cytokines after 4 years of treatment [59]. It is known that a DHA derivative, neuroprotectin D1, represses the activation of the proinflammatory gene triggered by A β 42 in human neuronal cells. It has been shown that the levels of DHA and neuroprotectin D1 in the hippocampus are low in the brains of patients with AD [48,60]. DHA also increases the activity of glutathione reductase, and decreases the levels of Reactive Oxygen Species (ROS), and proapoptotic components in the cortex and in the hippocampus [61]. Currently, a series of longitudinal studies have been conducted in the general population, which have shown that a higher intake of these fatty acids in the diet is associated with a lower risk of suffering dementia [62,63]. In addition, the risk of developing Mild Cognitive Impairment (MCI) may be lowered with a high dietary intake of Omega-3 [6].

Ginkgo biloba is among the most widely used natural compounds worldwide for the prevention and treatment of neurodegenerative diseases such as AD [46]. The extract from the leaves of this tree contains mainly terpenoids, flavonol glycosides and proanthocyanidins. It is thought, that the active components of ginkgo act mainly, at brain level, by increasing cerebral blood flow, by inhibiting the platelet activating factor and increasing the production of nitric oxide in the blood vessels. In turn, it produces modification of the monoamine neurotransmitter systems: it shows a free radical scavenger activity and has neuroprotective and antiapoptotic properties, and also potentiates neurogenesis [64,65]. In clinical trials that seek the prevention of dementia in participants without cognitive impairment, they have used the standardized extract of Ginkgo EGb761 during 4 to 6 years of follow-up at a dose of 240 mg/day. Despite all the beneficial effects of the extracts, no decrease in the incidence of dementia was observed in the participants treated with the active compound, versus the placebo group in the GuidAge trial (2854 participants) [66]. In summary, until now there is no concrete evidence that Ginkgo biloba extract reduces the incidence of dementia, and there are inconsistent data on its effects on cognition [12]. The heterogeneity of types of extracts used in the studies may account for these inconsistencies.

In the neuroimmunomodulatory context, vitamins are important. ROS are intrinsically associated with microglial activation, by stimulating the inflammatory cascade. This activation of the microglia is strongly associated with neuronal damage in AD during neuroinflammatory processes. Several studies have investigated the possible therapeutic and/or protective effects of the antioxidant agents present in some foods and also in supplements in relation to AD. Among the antioxidants investigated are: i) α -tocopherol (vitamin E), ii) ascorbic acid (vitamin C) and iii) carotenes (vitamin A). In *in vitro* studies, it has been observed that α -tocopherol decreases lipid peroxidation induced by A β and oxidative stress and, also suppresses the cascades of inflammation signaling. Ascorbic acid by reduces nitrites and blocks the creation of them and may also affect the synthesis of catecholamines, while carotenes affect lipid peroxidation [51].

Moringa oleifera (MO) is a multipurpose tree found mainly in India, and almost all over the Asian and African countries and its fruit and leaves are consumed as food [67]. Several bioactive compounds such as polyphenols, carotenoids, flavonoids, isothiocyanates, tannins, phenolic acids and saponins can be found in different parts of the plant including leaves, flowers, fruits seed and seed oils among others, with high nutritional and medicinal effects [68-70]. Moringa compounds also contain important levels of essential aminoacids. Among its medicinal effects, MO was found to have antimicrobial, antidiabetic, anti-inflammatory and antioxidant properties [71-74]. It has been demonstrated that MO flowers have strong anti-inflammatory and anti-oxidant properties *in vitro* [72].

In AD, MO had a nootropic effect by improving colchicine-induced dysregulated lipid peroxidation and by downregulating the enzymes catalase, superoxide dismutase, among others [75]. Also, it restored monoamines in brain almost to control level [67], improved cognition and prevented neurodegeneration *in vivo*, on a mice model of age-related dementia [75]. Fortunately, there is a highly purified product generated with GMP standards, and available for research purposes (Zija International). And more recently, it has been demonstrated that MO alleviates homocysteine-induced tau hyperphosphorylation [76]. In addition to that, it has been demonstrated that MO is safe even at high doses. Leaves extract has been proven to be safe even at high dose of 2000 mg/kg/body weight, where an enhancement of learning and memory was observed [77]. And MO extracts showed no adverse reactions or pathological changes after a single dose of 5000 mg/kg/body weight or a 14 days administration of 1000 mg/kg/body weight [78].

Zizyphus jujuba is a plant that bears seeds and fruits employed for medicinal purposes in traditional oriental medicine [79]. It was shown that extracts of this plant improves memory and learning after bilateral brain lesions in rats [80]. More recently, it was demonstrated that the seeds of this plant attenuate the AD associated hippocampal synaptic deficiencies through the BDNF/Trk pathway [79].

At present, there is a growing number of studies with different methodological approaches related to antioxidant consumption and cognitive deterioration [27]; most controlled clinical trials include observational cross-sectional design studies and some prospective community cohorts [52-56]. In turn, there is variability in the source of vitamin administered, where some studies assess the daily consumption of vitamins through diet, while other studies use vitamin supplements. Finally, other approaches consider their results only at plasma vitamin levels [27]. In observational studies there is some evidence of an association between the dietary intake of antioxidants and a reduced risk of stroke, however, controlled clinical trials with antioxidant

supplements have not shown this decrease in the risk of suffering a stroke [23,43,81,82]. A recent meta-analysis evaluated the effect of dietary intake of α -tocopherol, ascorbic acid and β -carotene on the risk of developing AD. Li and co-workers found that the relative risk reduction for cognitive impairment was similar for the three vitamins, concluding that the dietary intakes of the three antioxidants can reduce the risk of AD, and vitamin E exhibits the most pronounced protective effect [23]. However, in controlled trials they have shown contradictory results [26,52,53,55]. According to the history of these vitamins, it is believed that ascorbic acid is the most effective antioxidant in plasma, partly due to its solubility in water and the wide range of ROS that it can eliminate. This is because ROS and oxidative stress trigger the neuroimmune response, which is related to the pathophysiology of AD [30]. In studies conducted by Kennard, it is showed that in an animal model of AD (A β PP/PSEN1 mice), a single dose of intravenous vitamin C (125 mg/kg, iv) improved short-term spatial memory in middle-aged mice (9 months) [31].

In turn, vitamins may also have a neuroprotective function by eliminating toxic compounds such as homocysteine, which is related to an increased risk of cerebrovascular events [43]. Lack of vitamins have been associated with poor cognitive performance in addition to the factors that promote vascular risk [33], which are also associated with an increased cognitive impairment and AD [32]. Homocysteine is active in the brain tissue and could contribute to the AD pathway through vascular mechanisms or as a neurotoxin [51]. Vitamins B6, B9 (folic acid) and B12 can safely reduce homocysteine by daily intake [43]. Folate and vitamin B12 are necessary for the conversion of homocysteine to methionine, in turn, vitamin B6 for the conversion of homocysteine to cysteine. There is contradictory evidence about the benefits of daily consumption of these three vitamins (B6, B9 and B12). A recent meta-analysis evaluates the effects of supplementation with vitamins B12, B6 and folic acid in cognitive deterioration, concluding there is insufficient evidence of its reduction [42] in patients with or without previous cognitive impairment, or who have suffered some type of trauma. However, there are studies that reported an improvement in cognitive abilities with the administration of B9 and B12, but only in patients with high total homocysteine. There is significant progress in a VITACOG trial, evaluating patients with mild cognitive impairment and high homocysteine levels. The treatment is a combination of 0.8 mg/day of folic acid, 0.5 mg/day of vitamin B12 and 20 mg/day of vitamin B6 for 24 months. The dose of vitamin B12 was up to 300 times higher than the recommended daily amount in most countries, to try to counteract enteric absorption difficulties in poorer older people. The results showed that the rate of brain atrophy is significantly lower in those who received treatment, and that there is a significant interaction of treatment with basal levels of homocysteine. Among patients with a basal homocysteine level greater than 13 μ mol/L, brain atrophy decreased by 53% with treatment [36]. In the FACIT trial, subjects (55-70 years old) with elevated levels of plasma homocysteine and normal levels of vitamin B12 received a folic acid supplement for 3 years. Significantly improving memory and information processing speed [40]. All previous reports, suggest the incredible potential of these supplements to daily diet, proposing new formulas or dietary regimes in order to improve cognitive performance.

Conclusion

All the former studies highlight the importance of the development of novel therapies based on nutraceutical compounds, for age-related pathologies. Nutraceuticals are currently an emerging industry with high potential as there are currently clinical trials for some of them, in

which their efficiency for some pathologies as well as safety in regards of the doses employed have been demonstrated. Thus, this would be an attractive field to make further investigations in order to develop novel therapies for age-related diseases, such as AD.

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