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Nonpharmacological treatment options for Alzheimer's disease: from animal testing to clinical studies

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Abstract: Despite extensive pharmacological approaches, there is no curative therapy for Alzheimer's disease (AD) or other types of dementias. While current pharmacological options alleviate some symptoms of AD, they can lead to various adverse effects. Hence, nonpharmacological treatment options for AD are often considered with the assumption that they are safe, effective, and economic in managing patients. Furthermore, studies on animal models have suggested that environmental exposures like diet, music, or reward-related actions can stimulate neuronal regeneration and differentiation without using any pharmacological factors. The aim of this review is to provide a summary of nonpharmacological treatment options for the management of cognitive, emotional, and behavioral symptoms of AD. In addition, this review provides an overview of the challenging and encouraging experiences and recent studies and problems in cognitive training related to animal models. Nonpharmacological studies of AD are discussed in this literature review in terms of animal models, physical activity, brain stimulation, and the role of social communication.

Key words: Alzheimer's disease, nonpharmacological, animal models, therapy, treatment options

1. Introduction

In 2014, the World Council for Dementia (WDC) asked the Alzheimer's Association (AA) to assess the state of evidence of cognitive decline and dementia for modifiable risk factors. Interestingly, in contrast to some preclinical results, the AA declared that there was not sufficient evidence supporting the links between various modifiable risk factors including regular physical activity, healthy diet, smoking, obesity, and lifelong learning/cognitive training or stimulation and cognitive decline at the 2014 WDC meeting in London (Baumgart et al., 2015). Although there is no definitive relationship between individual demographic information and Alzheimer's disease (AD) treatments, better patient investigations can be achieved by integrating a comprehensive assortment of patient information based on sex, age, education, lifestyle, medical history, and environmental exposures. Also, this demographic analysis can be used to ameliorate AD symptoms by diversification of the patient's lifestyle in nonpharmacological directions. Nonpharmacological treatment options involve prevention strategies as the best medicine since there are limited numbers of approaches available for AD therapy. Therefore, it is common to try to treat AD in its early stages, with or without medication. Nonpharmacological strategies may be based on physical activity, brain stimulation, social communication, and diet-chemical substances (Peng et al., 2016).

2. Nonpharmacological studies on animal models

Most information comes from animal studies for the positive effects of a physically and cognitively positive lifestyle on AD. Studies on the effects of environmental enrichment (EE), including residences with increased opportunities for physical activity and cognitive status, were conducted in various transgenic mouse models of AD, partially inconsistent, but predominantly yielding positive results on behavior and nerve pathology (Nithianantharajah and Hannan, 2006). EE appears to affect AD-like pathology through multiple mechanical pathways, including hippocampal neurogenesis, amyloid plaques, glial pathology, formation neurotrophic factors, and AD-related factors (Ambrée et al., 2006; Wolf et al., 2006; Herring et al., 2009; Beauquis et al., 2013). Recent findings on animal models suggest that early exposure to

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EE is more effective in reducing AD-related psychological deficiencies than late onset of amyloidogenesis and indicates long-term protective effects (Verret et al., 2013). The effects of EE also depend on the severity and the direction of the disease. In a rapid degeneration of the APP/PS1KI mouse model, EE did not enhance most behavioral and physiological markers of pathology (Cotel et al., 2012). According to these investigations, animal models are very useful and varied to study nonpharmacological aspects of AD, while other studies have shown that this diversity can make studies more complex and irrelevant when an inappropriate model organism is selected.

3. Physical activity

Clinical studies showed that physical activities (PAs) such as 40 min of ergo-cycling, running in place, and stair-climbing for 12 consecutive weeks improved neurogenesis by enhancing cerebral blood flow in brain areas related to the pathogenesis of AD (Chen et al., 2016). Recent findings have revealed that PA leads to improvement in cognitive function via several Aβ-dependent and independent mechanisms, such as reducing the levels of beta-amyloid (especially $A\beta_{1-42}$), amyloid precursor protein (APP), beta-site APP-cleaving enzyme 1 (BACE1), presenilin (PS) 1, and apolipoprotein E (APOE), or increasing the activities of neprilysin (NEP) and insulin-degrading enzyme (IDE) (Ebrahimi et al., 2017). Moreover, experimental analysis put forth that the maintenance of PA, mainly aerobic exercise and descending a ladder, modulated the symptomatic progression of AD (Soni et al., 2019). The frequency, intensity, or duration of PA was reported to be responsible for raising brain-derived neurotrophic factor (BDNF) signaling and altering small noncoding RNAs (Nigam et al., 2017; Silva et al., 2017; Stephen et al., 2017). PA improved brain blood flow, enlarged hippocampal volume, and improved neurogenesis. Therefore, PA has been considered to exhibit fewer side effects and better adherence in comparison to medication-based applications (Cass, 2017).

The suggested molecular mechanisms underlying the prevention of AD development are based on different pathways. The first is related to the interaction between PA and the *APOE* ε4 allele. The *APOE* ε4 allele is considered as the most significant genetic risk factor that may lead to vascular damage and impaired cholesterol transport. A recent study revealed that *APOE* ε4 allele-carrying patients benefitted more from PA intervention than noncarriers in terms of cognitive and neuropsychiatric functions as well as physical measures (Jensen et al., 2019b). The second is associated with the modulation of neuroinflammation in AD. With that, the main mediators of neuroinflammation such as interleukin-6 (IL-6) and soluble trigger receptor expressed from myeloid cells 2 (sTREM2) were modulated in AD patients after 16 weeks of PA (Jensen et al., 2019a). Third, PA provided protection of cognitive functions against Aβ-induced memory deficits associated with the formation of oxidative stress and hippocampal cellular disorganization (Rossi Dare et al., 2019). Fourth, PA consisting of aerobic and resistance exercises decreases acetylcholinesterase (AChE), thus improving cognition and memory functions of patients with AD (Farzi et al., 2019).

4. Brain stimulation

A number of noninvasive brain stimulation practices have been suggested for AD patients and healthy older adults to improve cognitive impairments associated with physiological and pathological aging. The most effective approaches for stimulating the brain are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) techniques. While rTMS delivers strong magnetic pulses to the cortex via the scalp, tDCS delivers weak electrical currents to the scalp for modulating neuronal transmembrane potential towards hyperpolarization or depolarization. However, due to adverse effects and failure to provide measurable differences between patients and placebo conditions 3 months after stimulation, the results of brain stimulation have been ambiguous (Cotelli et al., 2014; Eliasova et al., 2014; Khedr et al., 2014; Hsu et al., 2015).

5. Social communication

Hallucinatory experiences, social isolation, and loneliness are more common in AD patients than in healthy individuals (El Haj et al., 2016). Autopsy studies of 89 brains of AD patients showed that larger social networks were associated with decreased negative effects on cognition (Jedrziewski et al., 2014). Music and theater therapies exert positive impacts on cognition in patients with AD (Riello and Frisoni, 2001; Van Dijk et al., 2012a, 2012b). Listening to preferred music led to the activation of the supplementary motor area, which is concerned with memory. Moreover, listening to preferred music stimulated corticocortical and corticocerebellar networks that affect brain function (King et al., 2019). Likewise, AD patients who joined a living-room theater activity offered by professional actors recalled more memories and exhibited less socially isolated behavior (van Dijk et al., 2012a, 2012b).

6. Diet and disease relationships

Recent findings of epidemiological investigations established that diet and nutrition are the main modifiable risk factors for AD development. Different research showed that diet can even change animal behaviors and population habitat in nature. In consequence,

supplementations of antioxidants, certain vitamins, polyphenols, and polyunsaturated fatty acids in the daily diet along with eating fish, fruits, vegetables, and coffee reduce the risk of AD. Adhering to a healthy diet, such as Japanese, Argentinian, and Mediterranean diets, is closely related to a reduced risk of AD (Hu et al., 2013). Therefore, the combination of Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, called MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay), has become prominent in reducing AD risk. A recent cohort study revealed that the MIND diet might radically alleviate the cognitive decline due to age-related neurodegenerative diseases such as AD or other dementia types. This combined diet encourages the consumption of brain-healthy foods like green leafy vegetables, berries, beans, whole grains, olive oil, fish, and poultry. The MIND diet also limits the consumption of animal-based foods and foods high in saturated fat (Table 1) (Morris et al., 2015a, 2015b). Also, heavy metal accumulation negatively affects not only human brain functions but also animal physiology.

A growing number of experimental studies have revealed that oxidative stress plays a key role in both initiation and progression of AD via lipid oxidation, DNA oxidation, and glycoxidation, eventually leading to mitochondrial defects. Therefore, antioxidant-based therapeutics are assessed as promising tools for the treatment of AD (Feng and Wang, 2012; Moneim, 2015).

Ascorbic acid, also known as vitamin C, has shown therapeutic benefits against AD-related pathological conditions in experimental animal studies. The mechanisms behind the beneficial effects include scavenging free radicals, inhibiting membrane lipid peroxidation, modulating neuronal bioenergetics, and antiproteolytic properties (Olajide et al., 2017). Moreover, it was reported that vitamin D supplementation improved the Mini-Mental State Exam (MMSE) score for cognitive impairments in AD (Annweiler, 2014). On the other hand, a high intake of vitamin E via diets is associated with the incidence of AD. In contrast to this, randomized controlled trials determined that treatment with vitamin E suspended functional decline in patients with mild to moderate AD, but vitamin E did not exhibit cognitive benefits in patients or in generally healthy older individuals (Shinohara and Yamada, 2015). The intake of probiotics was also suggested as another type of nutrition-based nonpharmacological treatment option due to their efficacy of modulating proinflammatory cytokines related to gut microbiota alterations with aging (Mendiola-Precoma et al., 2016).

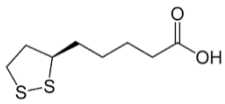
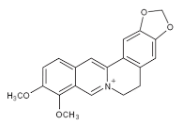
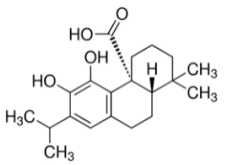
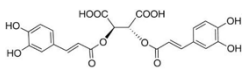
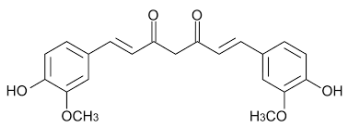
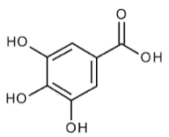
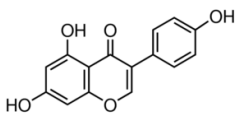
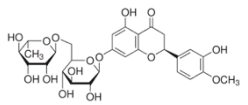
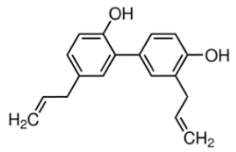
Several polyphenolic compounds obtained from fruits, vegetables, herbs, and nuts also have neuroprotective properties against AD and these naturally occurring phytocompounds support memory and cognitive function. The possible molecular mechanisms behind their therapeutic potentials are generally associated with alleviation of oxidative stress-mediated damage, protein folding, and neuroinflammation (Essa et al., 2012; Shal et al., 2018). The common phytocompounds and their specific functions in AD therapy are summarized in Table 2.

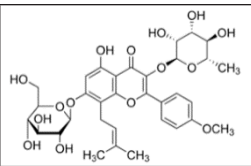
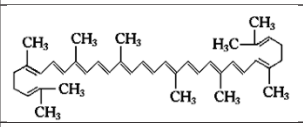
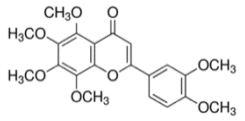
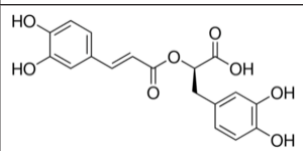
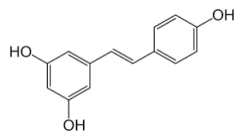
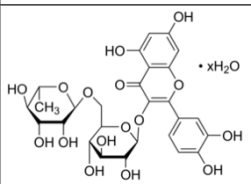
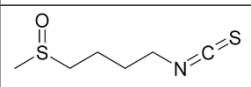
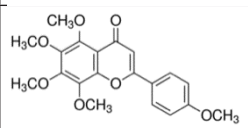
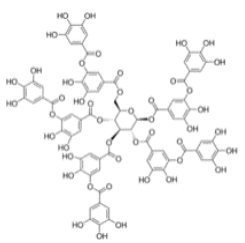
It is still unclear how phytocompounds reach the brain. Also, neither the quantity nor the biologically active form that is required for exerting therapeutic actions is known (Albarracin et al., 2012). About 500 years ago, the Swiss scientist Paracelsus stated that "Poison is in everything, and nothing is without poison. The dosage determines it either a poison or a remedy". Accordingly, at relatively higher doses or under certain conditions antioxidant-containing functional food ingredients including carotenoids, vitamins C and E, and polyphenols, like flavonoids, show prooxidant activities (Terada et al., 1999; Rietjens et al., 2002). Lipoic acids (LAs) and their derivatives, known as anti-Alzheimer molecules that prevent beta amyloid accumulation, can be found in different plants such as spinach, broccoli, and potatoes. In addition, phenol-lipoyl hybrids are synthesized from LA derivatives and these molecules are shown to be effective against AD

Table 1. Dietary components of the MIND diet.

Healthy	Unhealthy
Green leafy vegetables; ≥6 servings/week Other vegetables; ≥1 serving/day Nuts; ≥5 servings/week Berries; ≥2 servings/week Beans; >3 meals/week Whole grains; ≥3 servings/day Fish; ≥1 meal/week Poultry; ≥2 meals/week Olive oil; as primarily used oil Wine; 1 glass/day	Red meats; <4 meals/week Butter and stick margarine; <1 time/day Cheese; <1 serving/week Pastries and sweets; <5 servings/week Fried or fast foods; <1 time/week

Table 2. Protection mechanisms by certain phytocompounds against various neurotoxic insults in AD.

Antioxidant	Chemical structure	Anti-AD action	Reference
Alpha-lipoic acid		Modulating Aβ-induced AChE activity and oxidative stress	(Marinelli et al., 2017a)
Berberine		Ameliorating tau hyperphosphorylation	(Liu et al., 2014)
Carnosic acid		Protecting against neurodegeneration in the hippocampus by Aβ induction	(Azad et al., 2011)
Chicoric acid		Reducing Aβ1-42 accumulation and levels of APP, inhibiting BACE1 activity	(Liu et al., 2017)
Curcumin		Activating neuronal nitric oxide pathway	(Yu et al., 2013)
Caffeic acid		Blocking Aβ formation and aggregation	(Habtemariam, 2016)
Epigallocatechin		Modulating the enzymes involved in APP processing and reducing the formation of Aβ	(Rezai-Zadeh, 2005)
Ferulic acid		Exerting antiinflammatory actions	(Ghosh et al., 2017)
Gallic acid		Preventing fibril formation by Aβ peptide	(Liu et al., 2013)
Genistein		Modulating neuroinflammation, Aβ deposition, and tau hyperphosphorylation	(Park et al., 2016)
Hesperidin		Exhibiting high-affinity BACE1 inhibitor, preventing Aβ fibril formation	(Chakraborty et al., 2016)
Honokiol		Modulating excitotoxicity associated with the blockade of glutamate receptors and reducing neuroinflammation	(Talarek et al., 2017)

Icariin		Preventing Aβ1-42 aggregation	(Liu et al., 2015)
Leucomicin		Preventing Aβ1-42 induced oxidative stress	(Türkez, 2018)
Lycopene		Inhibiting NF-κB activity and regulating neuroinflammatory cytokines	(Sachdeva and Chopra, 2015)
Naringenin		Alleviating Aβ-induced impairments, lipid peroxidation, and apoptosis via the estrogenic pathway.	(Ghofrani et al., 2015)
Nobiletin		Reducing Aβ plaques, NFTs, and cognitive impairments	(Nakajima et al., 2015)
Oleuropein		Counteracting amyloid-β peptide and tau aggregation	(Martorell et al., 2016)
Quercetin		Minimizing Aβ1-40 and Aβ1-42 amounts, decreasing BACE1-mediated cleavage of APP	(Sabogal-Guáqueta et al., 2015)
Rosmarinic acid		Preventing Aβ-sheet assembly	(Cornejo et al., 2017)
Resveratrol		Promoting the removal of Aβ peptides and antiinflammatory content	(Braidy et al., 2016)
Rutin		Inhibiting Aβ aggregation, supporting antioxidant SOD, CAT, and GSH-Px enzyme activities	(Yu et al., 2015)
Sulforaphane		Reducing cholinergic neuron loss	(Zhang et al., 2014)
Tangeretin		Alleviating cholinergic deficits, reducing Aβ accumulation, inhibiting tau hyperphosphorylation and increasing NEP levels	(Braidy et al., 2017a)
Tannic acid		Inhibiting BACE1 activity and aggregation of tau, disrupting Aβ fibrils	(Braidy et al., 2017b)

symptoms with synergistic effects due to their antioxidant and antiamyloid properties (Cacciatore et al., 2016; Pagoni et al., 2020). Another synthesized derivative of LA is LA-GPE (R-α-lipoyl-Gly-l-Pro-l-Glu dimethyl ester), which has antioxidant and enzyme inhibitory features. LA-GPE molecules effectively ameliorate side effects of AD by inhibiting AChE enzyme activity, increasing antioxidant status, and preventing necrotic cell death (Marinelli et al., 2017).

Therefore, the uptake of one kind of antioxidant substance in overdose leads to detrimental conditions. Due to this, the application of only one antioxidative-containing compound against AD is not rational or advantageous. The effectiveness of antioxidant therapy is also allied with the optimum starting period of treatment. As oxidative stress comes into existence very early in the progression of AD, it is obvious that antioxidant therapy will be helpful if started early before other harmful and irreversible conditions arise (Persson et al., 2014).

7. Conclusion

About 110 years after the first description of AD, neuroscientists have still not determined an exact therapeutic approach against AD progression. Meanwhile, the number of elderly people with AD is increasing all over the world. In addition, the costs for fighting AD are stressing the economies of even developed countries. Unfortunately, many global drug companies are reluctant to invest in the development of novel anti-AD formulations and the current pharmacological or etiological treatment options provide limited and insufficient results without the exact cure of AD. Moreover, these existing pharmacological applications exhibit side effects in patients. At this point, nonpharmacological options involving regular physical activity, brain stimulation, improving social communication abilities, and altering nutrition style present effective, safe, and economic prevention and treatment opportunities to moderate AD. However, the above-mentioned options seem to be not exclusive and may be considered as complementary. The uses of nonpharmacological options for patients with AD have revealed clear potential benefits for quality of life. Therefore, the efficacy of nonpharmacological treatment approaches needs to be further investigated. For their translation to clinical application, more standardized trials with larger patient sizes are urgently required. In addition, the integration of animal models in these studies can ensure that results be obtained quickly and safely. Also, using model organisms can reduce expenses and eliminate many ethical issues associated with nonpharmacological studies. This review has summarized 20 years of literature studies that investigate nonpharmacological treatment of AD related to nutritional habits, living conditions, and social status.

Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this paper.

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