

# Personalized treatment interventions: nonpharmacological and natural treatment strategies in Alzheimer's disease

---

Šagud, Marina; Tudor, Lucija; Pivac, Nela

Source / Izvornik: **Expert Review of Neurotherapeutics, 2021, 21, 571 - 589**

Journal article, Accepted version

Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

<https://doi.org/10.1080/14737175.2021.1906223>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:914722>

Rights / Prava: [In copyright](#)/[Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-12-23**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine  
Digital Repository](#)



Marina Sagud, Lucija Tudor, Nela Pivac (2021) Personalized treatment interventions: nonpharmacological and natural treatment strategies in Alzheimer's disease Exp Rev Neurotherapeutics doi:10.1080/14737175.2021.1906223.

<sup>1</sup>Department of Psychiatry, Clinical Hospital Centre, Zagreb, Croatia

<sup>2</sup>School of Medicine, University of Zagreb, Zagreb, Croatia

<sup>3</sup>Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia

Correspondence: Professor Nela Pivac, PhD

Bijenicka cesta 54, 10000 Zagreb

Tel: +385 1 4571 207

Fax: +385 1 4561 010

Email: npivac@irb.hr

## **Abstract:**

### Introduction

Alzheimer's disease (AD) is a slow, irreversible, progressive, complex, and fatal neurodegenerative disorder. Available pharmacological treatment, known for almost two decades, does not cure the disease, but only alleviates the symptoms, with various efficacy and different side-effects. Therefore, there is an unmet need to find other person-centered or personalized approaches to treat AD.

### Areas covered

This article describes the application of precision medicine-like approaches utilizing non-pharmacological treatment strategies and the use of natural products in personalized care for patients with AD.

### Expert opinion

Due to the heterogeneity of disease symptoms, somatic conditions, and patient preferences, there is definitely no „one size fits all “intervention. Therefore, individualized treatment choice is based on dementia stage, medical and psychiatric comorbidity, leading symptoms, patient preferences, and remaining capacity of the patient. In the absence of disease-modifying agents, a patient-centered, multidisciplinary team approach appears to be the best option to alleviate the heavy symptomatic burden in this unfortunate population. Hence, appropriate interventions can be offered along the AD continuum, while a better understanding of personal characteristics might help in establishing optimal individualized treatment, as well as its duration and intensity, to deliver interventions in the most effective ways.

**Keywords:** dementia, exercise, musicotherapy, sensory and multi-sensory stimulation interventions, vitamins, natural compounds

**Highlights:**

- personalized treatment interventions (nonpharmacological treatment and effects of natural products) in Alzheimer’s disease (AD) are described
- current pharmacological treatments do not cure or stop AD
- use of physical activity, acupuncture, animal-assisted, bright light, horticultural, music, visual art and massage therapy might improve behavioral symptoms in AD
- natural products and vitamins improve the effectiveness of existing AD treatments
- combination of pharmaco- and nonpharmacological treatments and natural products might offer person-centered approaches to treat AD

**1. Introduction**

Alzheimer’s disease (AD) is the most frequent cause of the dementia syndrome [1]. AD is the most frequent form of dementia, or major neurocognitive impairment. It is a chronic neurodegenerative disorder characterized by global and progressive deterioration of cognitive ability despite the preservation of consciousness. The most affected cognitive functions are those of memory, learning, abstract thinking, orientation, and visual-spatial relationships.

AD is a slow, irreversible, complex, and multifactorial neurodegenerative disorder that is classified as a major health problem and fatal worldwide epidemic [2]. It is characterized by progressive cognitive decline, disorientation, behavioral changes, and death. After the development of neurocognitive disruptions, such as deficits in episodic memory, executive functioning, perceptual speed, visuospatial skills, verbal ability, attention, thinking and learning [3,4], these symptoms cannot be stopped or significantly improved. Consequently, these losses contribute to a complete failure in the fulfillment of basic social, moral, and working duties. The first sign of AD is a gradual worsening of the ability to remember new information. Cognitive disturbances affect different cognitive domains, including universal domains such as attention, working memory, executive function, procedural learning and memory, speed of processing, fear-extinction learning and semantic memory, and higher domains that include episodic memory, social cognition, theory of mind, verbal learning, memory and language (use and understanding) [2,3,5]. Cognitive decline is characterized by a dynamic process of neurocognitive changes from normal cognition and has several stages: 1) Preclinical stage with minimal or no clinical symptoms, but with positive biomarkers, which can last for years (possibly even decades) and is usually identified only in research settings. 2) Mild cognitive impairment (MCI), or prodromal phase, which may or may not progress to dementia, and is characterized by mild changes in memory and thinking ability. 3) Dementia of Alzheimer's type (AD), which is often diagnosed in the mild dementia stage, with the gradual progression to moderate and severe stages.

AD represents an enormous public burden [6] and elicits stress to family members and caregivers. The treatment includes pharmacological and nonpharmacological interventions. So far, the only pharmacological treatments for cognitive dysfunction in AD are acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine, and galantamine) and N-methyl-D-aspartate (NMDA) antagonist memantine. Disappointingly, no new drug has been approved by the FDA since 2003 [7]. All currently available pharmacologic treatments are easing rather than curing cognitive deterioration and progression of AD is inevitable. Trials of monotherapy with antidementia drugs have small effect sizes, equivalent to an approximately 3-month delay of cognitive decline [8]. While their combination may offer some additional benefits to cognition, the clinical relevance is

unclear [9]. Antidementia drugs are also associated with adverse events, such as weight loss induced by AChE inhibitors [7,10]. New treatments for AD fail in randomized clinical trials in the Phase II/III [7].

Namely, an individual with AD is unique in his/her disease stage, levels of pathology, risk factors, different comorbidities, dietary and physical activity habits, lifestyle and personality and psychological traits [11]. Therefore, efforts are needed to provide a “precision medicine” approach using specific genetic, neuroimaging, biochemical, and neuropsychological approaches that would remove risk factors, focus on the treatment of comorbid diseases, target underlying medical conditions, and offer personalized advice for lifestyle modification [7].

Cognitive deficits in AD almost never exist in isolation and are intertwined with a range of neuropsychiatric symptoms, or behavioral and psychological symptoms of dementia, such as depression, sleep difficulties, hallucinations, delusions, anxiety, agitation, aggression, appetite disturbance, apathy, irritability, disinhibition, motor disturbance and elation. Treatment of those symptoms is often limited by the poor efficacy of psychotropic drugs, their tolerability, and significant side-effects. Moreover, for the preclinical stage and MCI, there is currently no medication approved for postponing the progression to dementia [7,8,9].

Personalized treatment of AD includes a personalized or individualized approach that is concentrated on the individual patient; it should target prevention, treatment, and reduction of adverse effects [5]. A personalized approach is constructed on the better understanding of the biological and genetic underpinning of AD, its cognitive and behavioral and psychological symptoms characteristics, and is based on the genomic, transcriptomic, epigenomic, proteomic, metabolomic, and lipidomic data and biomarkers associated with heterogeneous pathways altered in AD that are responsible for the diverse symptoms related to different stages of AD [1].

In this review, we have summarized the available research and data on the use of natural products and vitamins and other nonpharmacological treatments (use of acupuncture, animal-assisted, bright light, horticultural, music, visual art and massage therapy and physical activity) that can positively influence cognition and behavioral and psychological symptoms of dementia and mood.

## **2. Nonpharmacological treatment of AD**

Nonpharmacological treatment of AD has gained attention in recent years, primarily as an alternative first-line approach, or an additional intervention to treat behavioral symptoms [12], but some interventions may exert beneficial effects on cognition. The umbrella term „nonpharmacological treatment“ covers numerous treatment approaches [13], starting from simple activities such as walking or puzzle-solving, to implementation of high technology-assistance, such as computer-assisted training and robots. A validated taxonomy of these interventions is lacking in the literature [12]. The aim of such interventions is to postpone patient deterioration, including cognitive decline, alleviate psychiatric symptoms, and improve overall health and quality of life. The largest body of evidence exists for cognitive training, physical exercise, and music-based therapy [13].

Given that patients diagnosed with AD already develop severe and irreversible brain damage, the key question is whether they still exhibit sufficient brain plasticity to respond to any kind of treatment. If the answer is yes, then the aim of such treatment might not be only to improve the patients' behavioral symptoms, but also to boost cognitive functions. The next inquiry is the effectiveness of those methods throughout different disease stages. Understanding the differential efficacy of complementary interventions for patients at different stages of the illness is crucial.

### **2.1. Physical activity**

While physical activity includes “any body movement produced by skeletal muscles that requires energy expenditure”, exercise training specifically refers to structured activity, either aerobic exercise or strength training. Any physical activity affects almost every organ, including brain [14]. It can induce brain neural plasticity across lifetime. Probably unlike any other treatment, it might affect brain health decades prior to the onset of cognitive impairment. For example, among adolescents, apolipoprotein e4 (ApoE4) carriers with low physical fitness had lowered cortico-cortical communication during intelligence test, in contrast to those with high fitness, who had similar results to non-ApoE carriers [15]. In older age, physical activity was associated with

decreased risk of transition from non-impaired to mildly impaired cognitive function, and from mild to severe cognitive impairment [16]. Even simple activities such as walking may delay cognitive decline and improve activities of daily living in people with dementia [17]. Systematic review of existing meta-analyses confirmed the beneficial potential of physical activity (such as aerobic exercise, cycle ergometer exercise or brisk walking) for general cognition in AD patients [18]. Regular physical activity also improved executive function, working memory and cognitive flexibility [19]. However, such advantages of physical activity on cognition in people with AD were not universal across studies (reviewed in [20]), probably owing to heterogeneous samples and methodologies, and the lack of standardized protocols.

The mechanisms behind the therapeutic effects of physical activity in AD are incompletely understood but are far beyond managing energy balance and body weight [14]. Beneficial effects of physical activity on at least some aspects of cognition were also consistently reported in rodent AD/dementia models [21-27]. There is strong evidence on the preventive effects of physical activity against dementia-induced brain changes, such as the decrease in AChE activity and lipid peroxidation in the rat hippocampus [27] by strength training, and against the progression of amyloid beta (A $\beta$ ) plaque burden [22,28] and neuro-inflammation, mitochondrial dysfunction in the hippocampus and cerebral cortex [22] by treadmill running. Physical activity also influenced the brain already affected by plaques and tangles. For example, treadmill exercise prevented inflammatory events triggered by A $\beta$  in mice hippocampus [29] and was associated with fewer cortical A $\beta$  deposits [30], increased number of proliferating neuronal stem cells in the dentate gyrus, reduced hippocampal volume occupied by amyloid plaques [31], reversed the lipid peroxidation increase and restored the reduction in AChE activity [26], compared to sedentary controls. Both interval and continued exercise decreased the levels of hippocampal A $\beta$ 40 and A $\beta$ 42 levels, reduced lipid peroxidation and enhanced antioxidant defenses [23]. However, free running did not alleviate microvascular dysfunction [31], while, in another study voluntary exercise increased tissue oxygenation, which supports the metabolic demand of neurons [30]. Moreover, voluntary physical exercise mitigated the neurodegenerative changes in the brain such as

disintegration of the pyramidal layer structure, neuronal loss, severe pericellular edema and accumulation of amyloid and cerebral amyloid angiopathy [21].

One of the mechanisms behind the exercise-induced reduction of amyloid pathology might occur by increasing its clearance, rather than affecting its influx in the brain. The A $\beta$  output from the brain into the circulation is regulated by the low-density lipoprotein receptor-related protein 1 (LRP1) and P-glycoprotein [32]. Exercise increased the level of LRP1 in the mice cortex [30], while aerobic training increased the mRNA expression of ATP-binding cassette transporter G-1 (ABCA1) in the rat hippocampus, even after the intra-hippocampal injection of A $\beta$ 1-42 [24]. However, it did not influence the level of Receptor for advanced glycation end products (RAGE) [30], which facilitates the influx of circulating A $\beta$  into the brain [32].

Despite compelling evidence from animal models, clinical data of physical activity's influence on AD biomarkers are not that encouraging, along the cognitive continuum. In older adults who were clinically normal on the baseline, the intensity of self-reported physical activity did not modulate the rate of cerebrospinal fluid A $\beta$ 42 decrease, p-tau181, and total-tau increase, or the cortical A $\beta$  accumulation [33]. In agreement, among clinically normal older participants, objectively measured physical activity was not associated with A $\beta$  burden, although greater engagement in physical activity was prospectively associated with slower A $\beta$ -related cognitive decline and gray matter volume loss [34]. In participants with mild AD, 16 weeks of moderate- to high-intensity aerobic exercise, did not modify cortical A $\beta$  levels [35]. In patients with mild to moderate AD, a 3-month, individualized, moderate-intensity aerobic training had no effect on whole brain blood flow, or regional perfusion in the frontal precuneus, cerebrospinal fluid (CSF) A $\beta$  species, total tau, phosphorylated tau, and soluble amyloid precursor proteins, despite improvements in cardiorespiratory fitness [36], neuropsychiatric symptoms, physical performance [37] and cognition, at least in a subgroup of patients exercising with high attendance and intensity [38]. Those data collectively suggest that physical activity, while not affecting the A $\beta$  deposits in humans [39], might still be protective against A $\beta$ -related cognitive decline and neurodegeneration. This might be explained by the decreased neuroinflammation, increased fibronectin type III domain-containing protein 5/irisin and the upregulation of neuroprotective



signaling molecules, and reduced oxidative stress [21], and the increase of resting glucose uptake in parietal and temporal regions [40] induced by physical activity. It also appears that exercise had a stronger impact on cognitively healthy than on impaired individuals. In the former group, its effects were demonstrated over the whole temporal lobe, whereas in subjects with MCI or AD, more regional changes were detected [39]. Moreover, older individuals had impaired cerebrovascular response to moderate-intensity exercise, compared to young individuals [41]. Likewise, in a preclinical trial, the effects of physical activity were also reduced through the aging process, at least the magnitude of change in the transcriptome of the cortex and hippocampus in response to running [42]. Smaller physical activity's effects in those with amyloid plaques might be due to lower exercise-induced brain blood flow, and the negative impact of beta-amyloid accumulation on cerebrovascular function [43].

Discrepant results of the physical activity effects on AD biomarkers may result from different methodologies, ie different types, frequency, intensity and duration of physical activity or dementia stage (MCI, mild or advanced AD). For example, only strength exercising prevented deficits in long-term memory and decrease in AChE activity, whereas only running exercise prevented the increase of free radicals, and the decline in total antioxidant capacity in  $\beta$ -amyloid characterizing an AD-like condition in rats [27]. Moreover, continuous aerobic training had the greatest effects on soluble A $\beta$ 1-42 reduction in the rat hippocampus than non-training or non-continuous training [24]. In patients with AD, high frequency interventions had no greater effects on cognition than low frequency intervention [44]. In fact, the effect of lower intensity physical activity was better for executive functions and higher intensity physical activity for working memory, in patients with AD [19].

While studies have shown different effects of physical activity on different cognitive, behavioral, biochemical and neuroimaging outcomes, ranging from none to minimal and to pronounced, all of them suggested at least some advantages, that might be utilized across AD stages. However, getting AD patients to exercise is challenging especially due to physical disabilities, and medical comorbidities, and carries increased risk of falls and injuries. Sometimes, chair exercises could be used. Therefore, type, intensity and frequency of physical activity need to be adjusted to

patient mobility, stability, cardiovascular status, overall fitness, and carried out under the closed supervision. Some effects of the increased physical activity and increased physical fitness on the brain of patient with AD are shown in Figure 1. These beneficial effects include increased resting glucose uptake, decreased A $\beta$ -induced cognitive decline, reduced inflammation, decreased level of oxidative stress, and consequently grey matter volume loss.

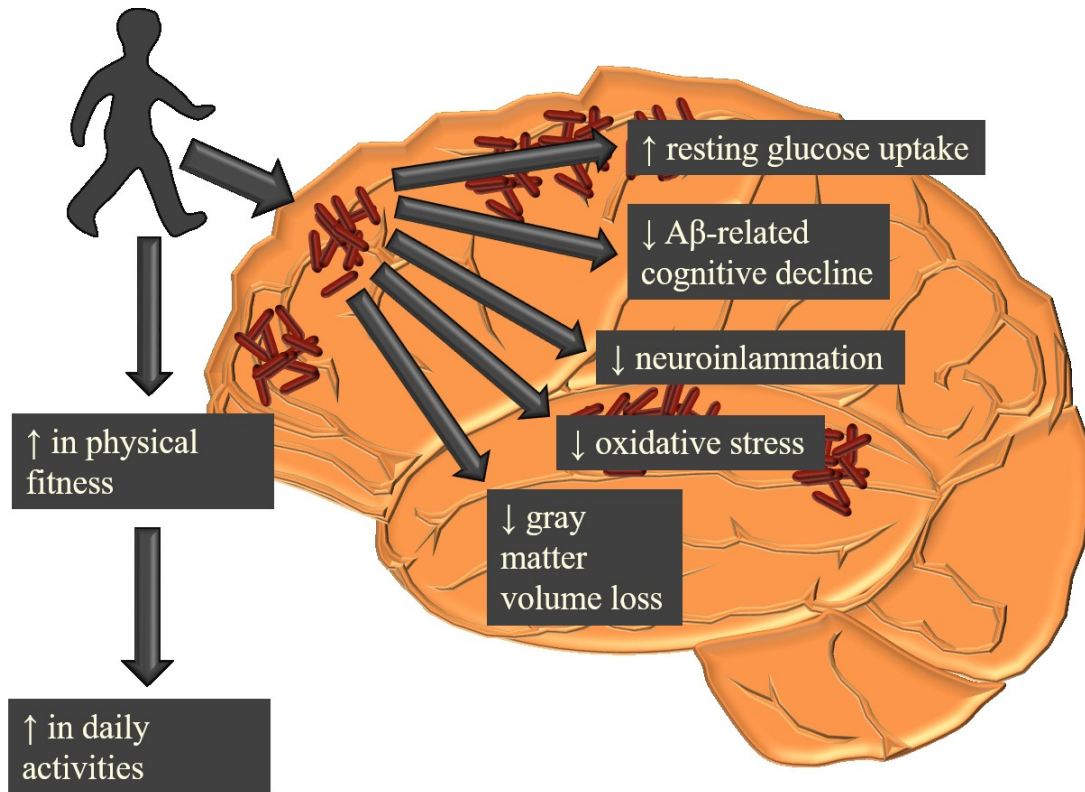


Figure 1. Schematic representation of the effects of increased physical activity and physical fitness on the AD brain.

## 2.2. Cognitive interventions

Cognitive interventions are usually classified as cognitive stimulation, cognitive training, cognitive rehabilitation and reminiscence therapy. Cognitive stimulation involves a variety of activities, such as word games, puzzles, music, cooking and discussing past and present events, to counteract the confusion, based on reality orientation, and is carried out by trained personnel within small

groups, on a regular basis [12]. It has significant effects on quality of life [45]. Cognitive training interventions are designed to attenuate cognitive decline in dementia, while training basic functions using standardized tasks, to improve or maintain non-verbal and verbal memory, language, visual-spatial skills, concept formation and reasoning [46]. In general, cognitive training induced at least moderate improvement in cognitive test performance in both MCI and patients with mild to moderate AD, and this achievement was maintained over a short or medium period [13]. This method also prevented cognitive decline among older people at risk for dementia, in terms of reducing the incidence of MCI or dementia [47]. Reminiscence therapy encourages the discussion of past experiences, using materials such as photographs, books, old newspapers and familiar items from the past [12], although some studies applied modern technology such as personalized digital memory book, mobile application, and a computer-aided programs [48] to evoke memories and facilitate sharing their experiences. This kind of therapy is applied in a small group of patients with the mild-to-moderate AD severity, and has shown to make progress in cognition, reduce depression, improve quality of life [48] and decrease anxiety [45]. Cognitive interventions in general had benefits on cognition, but did not improve activities of daily living [18]. Cognitive rehabilitation is a problem-solving behavioral therapy, aimed to improve functional disability [13].

While numerous preclinical and clinical trials demonstrated some beneficial effects of different types of physical exercise on AD biomarkers, the data on the effects of cognitive interventions are scarce. Among participants with MCI or healthy elderly people, who participated in computerized cognitive stimulation during 20 sessions, those with the higher vascular burden (regarding the volume of white matter hyperintensities) had a decreased neuroplastic response (assessed as upregulation in functional connectivity within the brain default mode network) to this intervention [49]. In a rat model, physical or cognitive exercise reversed the decrease in hippocampal lipid peroxidation, and restored A $\beta$  infusion-impaired hippocampal AChE activity, and hippocampal tissue disorganization, but did not improve lowered total antioxidant capacity [26]. Strikingly, in another animal model, cognitive exercise had similar effects on the reversal of memory deficits and A $\beta$ -induced brain changes to those of physical activity (running exercise) [26].

### **2.3. Sensory-based interventions**

These procedures are based on advantageous stimulation of one (uni-sensory) or more (multi-sensory) sensory systems (such as smell, sight, hearing, or touch), producing favorable effects on behavioral and psychological symptoms [50]. While cognitive function deteriorates, the world is experienced at a sensory level, with an impoverished ability to integrate sensory experiences to understand the surroundings. Thus, people with dementia are very sensitive to sensory experiences, and their living environment needs to be managed carefully to make it understandable and comfortable [50]. Since sensory organs can be stimulated even in the advanced dementia stages, sensory stimulation is the only person-centered approach that may be provided for people with severe dementia in nursing homes [51].

#### **2.3.1. Animal-assisted therapy (AAT)**

This treatment involves the participation of highly trained animals, such as dogs and cats, to address the physical and emotional needs of patients. Dogs were the most commonly used animals [52], due to their natural friendliness and ability to interact with people and engage individuals in pleasurable activities [53,54]. Other animals included were cats, horses, rabbits, budgerigars and guinea pigs, or substitutes for animals in the forms of toys, video stimulation or seal-like robotic pet called PARO [52]. Unlike many other complimentary interventions, animal-assisted therapy may be utilized in different degrees of dementia severity, but only in patients who prefer this kind of treatment [55], and preferably in patients who had earlier pleasant experiences with animals [56]. Even in nursing-home residents with moderate to severe dementia, this approach increased periods of positive emotions and social interactions [57], elicited specific emotions and behavior, such as feelings of calmness, closeness, joy and tenderness, and created specific relationship with a dog [56] and improved communication, including initiative, liking, humor, and interest [54]. The therapeutic effects are achieved via multimodal stimulation and relaxation. Animal interventions were associated with improvements in nutritional intake, social interactions, verbalizations and mood, compared to control without animals, with the larger benefits observed with live animals than with robotic/stuffed animals [58].

#### **2.3.2. Manual massage therapy (MMT)**

Massage, as a tactile sensory stimulation, improves primarily sleep and agitation. Touch provides a non-verbal communication. When a patient with dementia has lost the cognitive function to comprehend a verbal message, touch might be the only way to identify that he/she is receiving attention and recognition from others [50]. Massage, primarily administered to the hands, arms or back, appears to be the most effective sensory-based intervention [58]. It primarily improved behavioral and psychological symptoms, but not cognitive deficits [59]. The co-administration of aromatherapy may have an additional therapeutic value through the link between smells and emotion [50]. It might be easily applied in all dementia stages, and, importantly, might decrease the use of psychotropic drugs. Among the sensory-related activities, those related to touch were shown to have influence into the very latest stages of AD [60].

### **2.3.3. Music therapy (MT)**

Music has a primordial effect, especially a rhythmic beat, because patients with advanced dementia respond to rhythm even when other basic skills no longer exist [60]. Music therapy can also be used from the early stage of the disease, and it may elicit strong emotional and physiological response, which through the stimulus of limbic system and cortical networks, manages to preserve language, cognition and learning, and alters mood [61-63]. Music therapy might be active, such as songwriting, singing, and playing musical instruments, or receptive, such as listening, or both, delivered to individuals or groups, with or without a music therapist. Music therapy was also effective in MCI patients [64]. Though targeting multiple symptom domains seems promising, there has been disagreement between published meta-analyses whether active or receptive treatments have similar effects on specific outcomes [13]. Notwithstanding those dilemmas, the individual choice of music is of utmost importance. Namely, pleasant and unpleasant music have been found to elicit different emotional responses [65], and to activate different parts of the brain [61].

**2.3.4.** Music produced notable effects on normal brain function but the music styles and individual musical forms may have a different impact. Namely, while stimulating songs enhanced attention, depressive songs actually reduced it, at least in healthy students [66]. In healthy young women, relaxing music reduced stress levels much

faster than silence, while the opposite was detected for rap music [67]. Moreover, listening to classical music in musically experienced participants resulted in the differential expression of genes related to dopamine release and signaling, synaptic function, cognition, neurogenesis, long-term potentiation, dephosphorylation, ATP synthase-coupled proton transport, cytolysis, and positive regulation of caspase, peptidase, and endopeptidase activities [68]. While there was a clear trend showing increased peripheral oxytocin and decreased cortisol levels in participants actively engaged in music performance (reviewed in [69]), more research is needed to reveal the effects induced by different music forms, ie familiar vs non-familiar, public vs private performance, or arousing vs relaxing music. **Acupuncture therapy (AT)**

This method is based on acupoint selection and their combination used to stimulate specific parts of the body, while electroacupuncture induces stimulation by a pulsating electrical current through acupuncture needles [70]. Acupuncture stimulation at certain cognitive-related acupoints(s) activates the brain area via neuro-endocrine-humoral regulatory networks [71]. Meta-analytic evidence reported that acupuncture improved cognitive functions in rodent models [72]. Beneficial effects of acupuncture on cognition in clinical trials have also been detected, such as in patients with MCI [64] or in mild, moderate, and severe AD [73]. In the latter population, while acupuncture did not have superior effects compared with drug therapy, acupuncture in combination with pharmacotherapy was beneficial on general cognitive function and activities in daily living [18]. Acupuncture produces various physiological effects, through releasing different neuropeptides and neurotransmitters and influencing brain functional connectivity and glucose metabolism, depending on the various combined acupoints, and intensity, frequency, and duration of its application [71,74]. In addition, acupuncture increased prefrontal processing efficiency in MCI patients [75].

However, acupuncture treatment carries several limitations. It is a sophisticated treatment, with different acupoint selections, session duration, and frequency, so current protocols for cognitively impaired patients need standardization and optimization given that current research evidence is relatively insufficient to establish clinical guidelines [76]. Acupuncture may also produce focal

adverse events, such as subcutaneous hematoma, numbness, and in some studies, intolerable pain in elderly patients with MCI [77].

### **2.3.5. Horticultural therapy (HT)**

Participatory horticultural therapy provides multisensory stimulation and increases social activities. While participatory horticultural therapy includes plant cultivating, ornamental horticultural therapy is restricted to garden tours or viewing pictures of nature, and those two types have shown different outcomes. In fact, a meta-analysis reported positive effects of participatory horticultural therapy on cognition, agitation, positive emotion, and engagement, while ornamental therapy did not affect agitation and positive emotion [78]. In another meta-analysis, horticultural therapy also decreased the time of „doing nothing“ [30]. It was studied in patients with dementia, including AD, of all severities.

### **2.3.6. Bright light therapy (BLT)**

Exposure to artificial light, greater than 2500 lux, is supposed to stimulate sunlight and produce a cascade of biological effects [79]. Light therapy is primarily used to treat sleep and circadian disturbances, with some effects on cognition, while the effects on depression and agitation were inconsistent [80]. It was applied in all dementia stages, although it is unclear which disease stages are associated with the best outcomes. While some authors reported better results in mild to moderate stages, others noticed its higher effectiveness in advanced phases (reviewed in [81]).

### **2.3.7. Visual art therapy (VAT)**

This treatment in AD is based on painting, sculpting, or coloring, which helps patients to express their feelings and share their stories [82]. While patients with cognitive difficulties gradually lose their ability to verbalize their thinking and feelings, basic visual and motor skills remain for a longer time. Similar to other complementary treatments, visual art therapy has different modalities. While in structural form the therapist establishes tools and themes, in non-structural, the client has an initiative for choice, which increases creativity. The former modality is appropriate for more advanced dementia stages [82]. Therefore, with the appropriate modifications, art therapy is suitable for all dementia phases.

### **2.3.8. Multisensory stimulation**

This kind of treatment involves the stimulation of multiple senses by the patient's exploration of an environment including light effects, calming sounds, smells, and tactile stimulation [50]. A key feature of Snoezelen, a specially designed, multi-sensory-room for therapeutic purposes, is the interactivity and the environmental response to the patient's actions. Patients with dementia are likely to not have much control over their environment and therefore this sense of control may improve their self-esteem and confidence [60].

Clinical data demonstrated the efficacy of a multisensory environment on mood, behavior, and reduction in heart rate; however, the effects on cognition were not superior to other treatments [83]. Multi-sensory stimulation in animal models improved neurological function and BDNF expression in an ischemic mouse model [84].

#### **Treatment in different AD stages**

The aim of intervention for MCI is to decrease the rate of conversion from MCI to AD [85]. Strikingly, in MCI, music therapy had the highest probability of being the best treatment for global cognition, followed by acupuncture and then exercise, among potential pharmacological (including AChE inhibitors) and nonpharmacological treatments, but cognitive interventions were not included [64]. On the other hand, computerized cognitive training had moderate effects on most memory and learning domains in people with MCI, while its effects were much weaker in patients with dementia [46]. This evidence-based treatment in this stage is encouraged to prevent disease progression, given that there still exists neuronal plasticity. In these early stages, physical activity, horticulture, and cognitive stimulation might be used to promote neuroplasticity, as well as psychoeducation, to increase confidence [63].

The aim of the treatment in the mild-to-moderate phase is to preserve cognition and delay disease progression as much as possible. For example, multicomponent cognitive stimulation in participants with mild stage dementia had not only positive effects on cognition and behavior, but also delayed disease progression for at least two years [85]. The combination of several modalities was also effective; for example, in individuals with predominantly mild AD, an integrated program focused on cognitive training, art therapy, and music therapy improved multiple domains such as cognition, depression, anxiety and activities of daily living [86]. The



largest benefit of visual art therapy was observed in patients with mild AD, compared to those with normal cognition or with other dementia types, though some differences existed between different artistic methods [87]. These findings suggest the presence of sufficient cognitive plasticity even in mild AD stages.

The recent overview of 14 systematic reviews of nonpharmacological interventions reported that cognitive stimulation therapy, music-based therapeutic interventions, and psychological treatments (mainly cognitive behavioral therapy) were the most promising interventions for people with moderate dementia [45]. In individuals with moderate to severe dementia, light therapy, acupuncture, massage, and animal-assisted interventions decreased night-time restlessness, improved nocturnal sleep duration, and continuation, while light therapy strengthened circadian rhythm [51]. The most common nonpharmacological, sensory-based interventions are presented in Table 1. The combination of different treatments, including regular daily exercise and reminiscence therapy, for several months, resulted in the slight improvement of global cognition, and also produced the change in resting-state brain activity, suggesting neuronal plasticity [88].

The framework for the more advanced dementia patient daycare program should focus on sensory-related experiences, meaningful human interaction, and one-on-one activities, rather than group programs [60]. In late-stage AD, the primary aim of complementary treatments is to sustain quality of life [60]. Multisensory stimulation environment in a Snoezelen room and receptive music therapy is based on individual preferences, relaxation, and feelings of happiness [89]. Along with receptive music therapy, active music therapy, such as clapping, singing, and dancing, might also improve emotional state in capable individuals [90]. Importantly, the danger of over-stimulating patients is as important as avoiding under-stimulation, since clients, particularly in late-stage dementia, may become agitated if the intervention time is extended [60].

An active lifestyle (including physical and social activity) is an important modifiable factor for brain function across dementia stages. Coronavirus disease 19 (COVID-19) infection represents a challenge in terms of wide-spread reduction of physical activity [91] and social contacts. Therefore, home-based workouts (including endurance, resistance, and balance exercises; app-based exercise training with online partners) and outdoor activities have been strongly

recommended during COVID-19 pandemic [91]. However, during restrictions for nursing home residents, they might become deprived of sunlight which might lead to sleep and behavioral problems. These difficulties might be overcome by indoor bright light therapy [79].

The applicability of nonpharmacological treatments (acupuncture therapy, animal-assisted therapy, bright light therapy, horticultural therapy, music therapy, and visual art therapy) in MCI and in different AD stages (mild, moderate, severe AD) is presented in the Figure 1. Possible mechanisms of action of these nonpharmacological treatment strategies are shown in Tables 1 and 2. Animal assisted therapy is associated with reduced cortisol levels [92] and release of endorphins, oxytocin, prolactin and dopamine [55]. Massage therapy is linked to decreased sympathetic and increased vagal activity, increased oxytocin and decreased cortisol levels, and improved circulation [93,94]. Music therapy is associated with elevated functional connectivity of sensory and attentional networks [96], activation of the dopaminergic mesolimbic pathway [61], decreased heart rate [89,90], and increased oxygen saturation [89]. Horticultural therapy is assumed to be associated with stimulation of multiple senses (sight, vision, hearing, smell and touch) [12], and gardening is associated with stress-reduction effects, such as lowered sympathetic arousal in other populations [99]. Bright light therapy may be related to an increase in activity of the suprachiasmatic hypothalamic nuclei, decreased melatonin levels, and restored sleep-wakefulness rhythm [79]. Acupuncture is associated with decreased oxidative stress, apoptosis and neuroinflammation, improved synaptic plasticity, increased brain glucose intake, decreased A $\beta$  levels [74], and various brain responses related to different acupoints [67]. All of these strategies may alleviate AD symptoms.

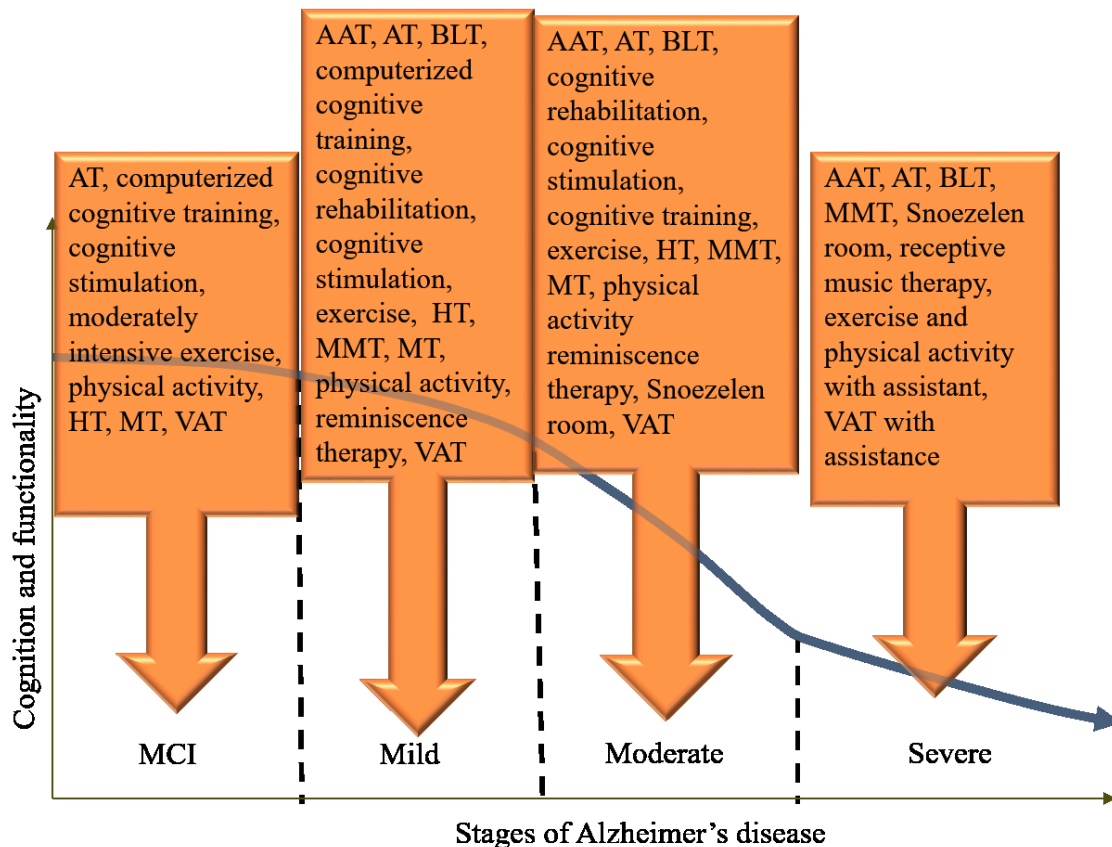


Figure 2. Schematic presentation of the nonpharmacological treatments across stages of Alzheimer's disease. AT= acupuncture therapy; AAT= animal-assisted therapy; BLT= bright light therapy; HT=horticultural therapy; MT=music therapy; VAT= visual art therapy; MCI= mild cognitive impairment; MMT= manual massage therapy.

Table 1 shows the most common sensory-based interventions (acupuncture therapy, animal-assisted therapy, bright light therapy, horticultural therapy, music therapy, visual art therapy and massage therapy) used in clinical practice, their potential benefits, as well as concerns.

**Table 1.** The most common sensory-based interventions used in clinical practice.

| Type of intervention          | Potential benefits   | Concerns   | Addressing concerns  |
|-------------------------------|--|--|--|
| Animal-assisted therapy (AAT) | Improvement in depression [52], positive impact on emotional status, small benefits on cognition | Protection of animal rights, safety of participants (potential animal bites, fear of animals, allergic | The use of certified dogs who completed a training course; excluding patients with fear of animals, use of robotic pets or puppets instead of live |

|  |   |   |   |
|--|---|---|---|
|  | [55]  | reactions, infection)   | animals   |
| Manual massage therapy (MMT)               | Alleviation of depression, agitation [59], and aggressive behavior [95], relaxation, pain reduction   | Not suitable for patients with deep vein thrombosis or muscular injury at massage parts   | Taking medical history and exploration of body parts prior to massage   |
| Music-based therapeutic interventions (MT) | Effective on general cognition [64], depression, anxiety and quality of life [45], reduction of apathy [97], facilitation of autobiographical memories [61], reduction of agitation and aggression [12] | Music with fast tempos may increase arousal and decrease enjoyment [98], adverse affective responses in vulnerable, depressed individuals [65]              | Selection of music with slow-to-moderate tempos [98], individual selection of music related to happy memories [65]  |
| Visual art therapy (VAT)                   | Beneficial effects on cognition in participants with cognitive decline, less clear in AD patients, alleviation of depression and anxiety [87]   | Patients without an art background must learn basic skills, some patients might have difficulties completing tasks, requiring sufficient hand function [82] | Optimal choice of type, duration and intensity of the intervention, knowledge of the patient's previous abilities and skills  |
| Horticultural therapy (HT)                 | Increase in engagement [30,78], decrease the time spent in inactivity [30], some effects on cognition [78], reduction of pain, improvement in attention, lessening of stress                            | Ingestion of toxic plants by advanced dementia residents, getting wet or become stuck during inclement weather [99]   | Excluding toxic plants and pesticides from the therapeutic garden, close supervision of participants, use of gardens designed specifically for the safety and benefit of residents with dementia, such as wander gardens [99] |
| Bright light therapy (BLT)                 | No effects on behavioral AD symptoms [12], but beneficial effects on sleep, the only therapy to strengthen the circadian rhythm [51]  | Individuals in earlier AD stages may be more sensitive to light and become agitated with high amounts of short wavelengths [81]                             | Scheduling administration time according to individual circadian rhythm; using more moderate light, levels, tailored on an individual basis, use with caution in agitated patients [80]                                       |
| Acupuncture therapy (AT)                   | Potential to improve cognition and activities of daily living [69], might be even more effective on some cognitive outcomes than conventional medicines [100]   | Local skin irritation or injury was the most common, nausea, vomiting, dizziness, tiredness** [101], fainting [64]  | Proper training in acupuncture, recognizing conditions that increase the risk of complications (such as treatment with anticoagulants or immuno-suppressive agents) [101]   |

AT= acupuncture therapy; AAT= animal-assisted therapy; BLT= bright light therapy;

HT=horticultural therapy; MT=music therapy; VAT= visual art therapy; MMT= manual massage

therapy; \*these effects have been studied only in populations other than dementia; \*\*the reports

of adverse events were inadequate in almost all studies addressing patients with AD [100]; therefore, adverse events are presented from the medical literature according to reference No. [101].

Table 2 shows preclinical and clinical findings of the most common sensory-based interventions (acupuncture therapy, animal-assisted therapy, bright light therapy, horticultural therapy, music therapy, visual art therapy and massage therapy) and possible biological mechanisms involved.

**Table 2.** Potential biological mechanisms of the most common sensory-based interventions used in clinical practice and in animal models.

| Type of intervention          | Preclinical findings  | Clinical findings  |
|-------------------------------|---|--|
| Animal-assisted therapy (AAT) | Preclinical studies not possible, but dogs involved in AAT had ↓ heart rate and tympanic membrane temperature post-session, suggesting a more relaxed state [102] | Gradual ↓ in saliva cortisol levels in patients with mild to moderate dementia, compared to controls, [92], ↑ salivary oxytocin after single session [103]*, ↑ blood β-endorphin, oxytocin, prolactin, and dopamine, ↓ blood cortisol after interaction with dog [104]*, ↓ in heart rate (only in healthy participants, but not in patients [105]*         |
| Manual massage therapy (MMT)  | ↓ blood pressure and heart rate, Reduction of muscle atrophy, modulation of gene expression and immune response in skeletal muscles [106]                         | ↓ in sympathetic and ↑ in vagal activity, ↑ oxytocin, ↓ cortisol levels, improvement in brain circulation parameters [reviewed in 93, 94]*   |
| Music-based therapy (MT)      | Rescuing stress-induced impairment in neuroplasticity by Mozart music, but no effects in non-stressed rats [107]*, ↑ BDNF/TrkB by Mozart music [108]              | ↑ in functional connectivity of sensory and attentional networks [96], ↑ of dopaminergic mesolimbic pathway, ↑ in oxygen saturation [89], mixed effects on salivary cortisol [109], effects on autonomic system based on music valence [61], ↑ with energizing music, and ↓ in sympathetic activity with calming music, ↑ parasympathetic activation [109] |
| Visual art therapy (VAT)      | No preclinical trials   | ↑ sensory evoked responses in visual areas [110]*, Simultaneous stimulation of several brain regions during creative task [111]*, activation of reward pathway, ↑ presence of alpha waves [112]*   |
| Horticultural therapy (HT)    | No preclinical trials   | Stimulation of multiple senses (sight, vision, hearing, smell and touch) [12], biological effects in AD patients have not yet been tested, but gardening was associated with stress-reduction  |

|                            |  |   |
|----------------------------|--|---|
|                            |  | effects, such as lowered sympathetic arousal [99]*, beneficial effects on peripheral BDNF levels [113, 114]*, ↓ in circulatory IL-6 [113]* in other populations   |
| Bright light therapy (BLT) | beneficial effects on circadian rhythm, blood glucose levels, glucose tolerance [115]*, ↑ BDNF and neurogenesis in hippocampus, similarly to exercise [116]*, reversal of reduced glucose metabolism in rat depression model, but no effects on neuroinflammation [117]*   | Delay in the melatonin midpoint, phase shift in peripheral circadian gene expression [118]*, ↑ steepness in evening melatonin rise, ↓ 24-hour urinary and evening salivatory cortisol [119]*, ↓ in plasma cortisol levels [120]*, ↑ in glucose uptake in the right olfactory bulb, but not in hippocampus [121]*, ↓ in brain MAO-A levels [122]*                            |
| Acupuncture therapy (AT)   | Electroacupuncture: ↓ of oxidative stress, apoptosis and neuroinflammation, ↑ in synaptic plasticity and brain glucose intake, ↓ of Aβ levels (reviewed in [74], ↑ cerebral blood flow [123], ↓ in cortisol, ↑ in dopamine, endorphins, oxytocin [reviewed in 124]* ↓ atherosclerotic changes in the common carotid artery [125] | Activations of brain regions vary with different acupoints, or their combinations [review of PET and fMRI studies in 71], Improvement of endothelin function, ↑ regional cerebral blood flow and connectivity, alterations in sympathetic and parasympathetic nerve activity [reviewed in 126]*, ↑ in blood BDNF [127]*, ↓ in plasma IL-6 and catecholamine levels [128].** |

AT=acupuncture therapy; AAT=animal-assisted therapy; BLT=bright light therapy; HT=horticultural therapy; MT=music therapy; VAT=visual art therapy; MMT>manual massage therapy; ↓=decrease; ↑=increase; \*these effects have been studied only in populations other than dementia; \*the reports of adverse events were inadequate in almost all studies addressing patients with AD [100], so presented are adverse events from the medical literature according to [101].

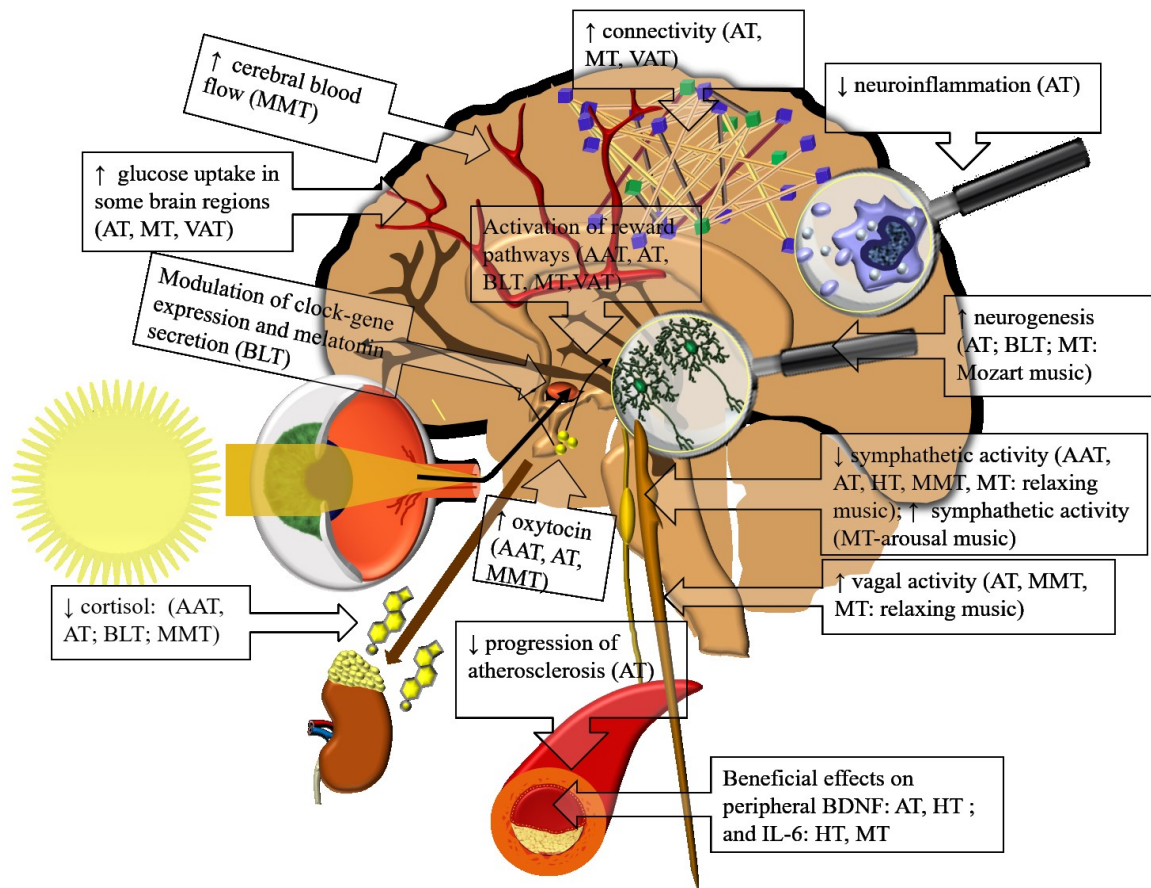


Figure 3. Schematic representation of the distinct physiological effects of different nonpharmacological treatments.

The proposed mechanisms (Figure 3) are simplified and very preliminary and should be taken with caution, given that studies on dementia patients or preclinical models of AD are scarce, and most studies are carried out on other populations or in animal models. Likewise, there was a considerable variation in the methodology across studies. Moreover, findings from healthy controls may not generalize to patients with advanced neurodegeneration.

The combination of multimodal nonpharmacological interventions might be beneficial for people with AD [129]. However, establishing the effectiveness of non-pharmacologic therapies can be difficult due to the large number of therapies, the diversity of therapeutic aims and targets [18] and different proportions of at-risk APOE4 carriers [130]. In addition, many studies focusing on

nonpharmacological treatment did not evaluate dementia severity [18 which is significant given that stages of AD and degree of severity affect response to treatment [1,7].

### **3. Natural products in treatment of AD**

Besides presence of insoluble A $\beta$  peptides and intracellular accumulation of hyperphosphorylated tau proteins (neurofibrillary tangles, NFT), decreased levels of ACh, reduced expression of ACh receptors in brain and increased activity of the AChE, involved in ACh degradation, represent molecular hallmarks of AD [131]. AD is also characterized by excessive production and accumulation of reactive oxygen (ROS) and nitrogen (RNS) species, that cause protein, DNA and tissue damage, activate microglia and astrocytes and immunological response, which lead to mitochondrial dysfunction, intracellular Ca<sup>2+</sup> influx, overexpression of glycogen synthase kinase-3b (GSK-3b) and  $\beta$ - and  $\gamma$ -secretases resulting in generation of protein aggregates such as A $\beta$  and NFT.  $\beta$ -secretase, also known as  $\beta$ -site amyloid precursor protein cleaving enzyme-1 (BACE-1) is over-expressed in AD brain and causes the reduction of neuroprotective proteins such as brain-derived neurotrophic factor (BDNF). Besides that, iron dysregulation, glutamate toxicity and disrupted process of neuronal autophagy contribute to mitochondrial and cell damage and formation of toxic protein aggregates [131,132].

Currently used treatments are based on AChE inhibitors and NMDA antagonist memantine, however these treatments do not stop the progression of the disease, but only ameliorate the symptoms. AD is a multifactorial disease and it has been well accepted that the multitarget therapy would be more beneficial than single target pharmaceuticals. Compounds that could simultaneously affect multiple targets would show better efficacy and milder side effects than one or several single target drugs. Most of the medicinal herbs and dietary products contain vitamins and numerous pharmacologically active compounds that could synergistically affect multiple targets in AD which is the reason why some of them have been major constituents of novel therapy designs [132].

#### **a. Vitamins in AD**

Some studies have shown that malnutrition, high fat diet and diet with high glycemic index could increase the neuronal damage, while a diet rich in vitamins (vitamins A, B, C, D and E),



Mediterranean and ketogenic diet, as well as caloric restriction, could have beneficial effect on the progression of AD and cognitive decline in patients with dementia by attenuating reactive radicals and A $\beta$  toxicity [133-135].

Vitamin A is antioxidant involved in differentiation of neural cells, gene expression and expression of neurotransmitters [136]. Its deficiency was associated with higher risk of MCI and worse clinical manifestations of AD [136,137]; however, while there are studies that showed reduced cognitive decline in subjects who received  $\beta$ -carotene supplements [138], not all studies confirmed its protective role.

B vitamins are diverse group of water-soluble vitamins included in metabolism of carbohydrates, lipids, proteins, including neurotransmitters, as well as in process of DNA methylation. Beneficial effect of vitamins B on cognition in MCI and AD is possibly associated with the metabolism of homocysteine, in which vitamin B12, B6 and folic acid play major role [139-141]. It has been shown that the deficiency of these vitamins impairs the process of homocysteine transformation to methionine, resulting in accumulation of homocysteine in the body, and consequently reduction of S-adenosylmethionine, which is a major methyl donor in the process of DNA methylation. Homocysteine buildup can contribute to development of AD and cognitive damage by affecting the DNA methylation and thus enabling overexpression of genes associated with AD and its progression [139-141]. Several studies reported positive effect of vitamin B12, B6 and folate supplementation on improving MCI and AD symptoms and preventing cognitive decline, although the recommendations of the dietary supplementation dosage and average serum levels required for protective effect of these vitamins have been indecisive [134,140,142].

Vitamin C and vitamin E are the strongest natural antioxidants. Vitamin C is free radical scavenger and metal chelator, while vitamin E has important role in reducing the lipid peroxidation and A $\beta$  deposition in brain, as well as regulating the homeostatic levels of presynaptic proteins [134]. Some studies reported the association of the vitamin C, vitamin E and their combined supplementation with better Mini Mental Scale Examination (MMSE) scores, verbal memory and cognitive functioning in patients with dementia and AD [143-145]. In

particular, vitamin E deficiency is being considered as a strong risk factor for development of AD and MCI and supplementation at higher doses has been recommended [146].

Vitamin D, in addition to being risk factor in development and progression of AD and other neurodegenerative diseases, was associated with decreased A $\beta$  formation and deposition and reduced neuroinflammation, possibly by maintaining homeostasis of Ca<sup>2+</sup> [147]. Low serum levels of vitamin D has been associated with increased the risk of AD and MCI [148] and cognitive impairment, while vitamin D supplementation in addition to memantine therapy showed improvement in cognition and memory in patients with mild and moderate AD [149,150].

Although there are several studies that did not confirm the association of vitamin deficiency with AD development and pathology and recommended supplementation dosage is still uncertain, there are promising findings that suggest that vitamins A, B, C, D, and especially vitamin E supplementation with higher doses could be beneficial in slowing the progression and attenuating the symptoms of AD [134].

#### **b. Natural compounds in treatment of AD**

Natural products and herbal extract have always been part of the traditional medicine and they still have a big impact in the modern drug development. Some of the naturally occurring compounds extensively studied in treatment of AD are curcumin, a diphenol found in *Curcuma longa* (turmeric), and resveratrol, a phenol found in mulberries, red wine and tea. Both are strong antioxidants with ability to disaggregate toxic A $\beta$  plaques, attenuate hyperphosphorylation of tau proteins and stimulate their degradation [151]. Curcumin can also affect glucose and cholesterol levels, microglial activity and inhibit AChE activity [151-153], while resveratrol shows neuroprotective effect by inducing neuronal autophagy, increasing Ca<sup>2+</sup> levels, and reducing the over-expression of proinflammatory miRNA [154]. Recent clinical trials reported association of resveratrol supplementation and reduced levels of A $\beta$ -40 in CSF and plasma in patients with mild and moderate AD [155] and better immune and cognitive response [156].

Extracts of *Ginkgo Biloba*, *Olea europea* and *Cannabis sativa* are also demonstrating strong antioxidant and immunomodulatory properties by downregulating the expression of proinflammatory cytokines such as tumor necrosis factor alpha (TNF1 $\alpha$ ), interleukin 6, interleukin

$1\beta$  (IL-6, IL- $1\beta$ ), nuclear factor kappa B (NF $\kappa$ B) and stimulating neuronal autophagy and expression of autophagy related genes [153,157,158]. It has been reported that Ginkgo extracts lower the neuronal damage in multicellular network model [159] and in animals [160]. Ginkgo is widely used dietary supplement for improving cognitive functioning in healthy individuals, but also in dementia and AD, where it is often used as additional therapy with memantine [161,162]. The synergistic effects of memantine and flavonoids, terpenoids and ginkgolic acid found in Ginkgo extracts are reported to have stronger therapeutic effect than memantine alone [158,163]. Oleuropein aglycone and oleocanthal, derivatives found in olive oil, are free radical scavengers, strong inhibitors of cyclooxygenases and inhibitors of toxic protein aggregation resulting in improved cognitive performance in transgenic mice [153,157]. In addition, olive oil is major constituent of Mediterranean diet, which has been associated with better cardiovascular, immune and cognitive state as well as with lower risk of MCI and AD [133,157]. Another promising and highly studied therapeutic candidates are cannabidiol (CBD) and  $\Delta$ 9-tetrahydrocannabinol (THC), major compounds of *Cannabis sativa*, with high antioxidant and neuroprotective properties. Phytocannabinoids have been associated with reduced levels of inducible nitric oxide synthase (iNOS), A $\beta$  senile plaques and NFT and their administration in mice resulted in improved memory and learning in animal models of AD [164] and shows potential in treating chronic pain and associated symptoms in patients with AD [165].

Several natural compounds could possibly be used in the treatment of AD due to their potential to regulate the levels of ACh. For example, ginsenosides, saponins derived from *Panax ginseng*, are shown to upregulate choline acetyltransferase [166], while huperzine A, ginger extracts (*Zingiber officinale*) and curcuma are natural inhibitors of AChE, which leads to increased ACh concentration [132,158]. Besides regulating the levels of ACh, ginsenosides have shown neuroprotective and anxiolytic effects by stimulating gamma aminobutyric acid (GABA-A) and glycine receptors, inhibiting N-methyl-D-aspartate (NMDA) receptors and degrading the A $\beta$ , along with variety of other beneficial pharmacological effects on immune system and general homeostasis [167]. Administration of Rg $_1$  and Rb $_1$  ginsenosides had beneficial effect on lowering the A $\beta$  toxicity, increasing the cortex thickness and synaptic density in vivo [167]. In vitro studies

showed that huperzine A, active compound found in *Huperzia serrata*, can attenuate cognitive decline and protect neurons against A $\beta$  toxicity by scavenging free radicals and upregulating the neural growth factor (NGF) [168], however, its effectiveness and lack of side effects in humans have not been confirmed. Major active components of ginger oil, 6-gingerol and 6-shogaol, besides having AChE inhibiting properties, showed strong neuroprotective and antioxidant effect in animal models of AD, by increasing the nerve growth factor (NGF) level, suppressing the inflammatory response and BACE-1 activity, decreasing the levels of A $\beta$ , and consequently improving learning and memory [169].

Another strong antioxidants and anti-inflammatory BACE-1 inhibitors are flavonoids such as myricetin and quercetin, found in abundance in *Punica granatum* (pomegranate), and monacolines, such as ankaflavin and monascin, found in red mold rice [132,170]. Quercetin and myricetin can both inhibit A $\beta$  fibril formation and, in that manner, protect neurons from A $\beta$  plaque induced toxicity. It has been shown that administration of pomegranate extracts can improve attention, memory and learning in humans [170]. Monacolins are natural statins that are used to improve the condition of cardiovascular and metabolic diseases. It has been suggested that ankaflavin and monascin, along with other secondary metabolites found in red mold rice can reduce the levels of ROS, attenuate the activity of BACE-1, lower the levels of ApoE, NFT and accumulated A $\beta$  and in that way used in treating AD [171].

The list of major plant extracts with their main active compounds and their benefit in treating AD with potential mechanism of actions is listed in Table 3.

Table 3. Major active phytochemicals and their role in treatment of AD

| <b>Natural therapeutic</b>      | <b>Main active compound(s)</b> | <b>Potential mechanism of action (in vitro and in vivo studies)</b>   | <b>Reported beneficial effect in animals and humans</b>   |
|---------------------------------|--------------------------------|---|---|
| <i>Curcuma longa</i> (turmeric) | Curcumin                       | <ul style="list-style-type: none"> <li>•antioxidant activity: metal chelation, reducing iNOS activity [151], promoting expression of antioxidant enzymes by activation of the Nrf2-Keap1 (Kelch-like ECH-associated protein 1) pathway [153,172]</li> <li>•anti-inflammatory properties: suppression of NF<math>\kappa</math>B, IL-6, IL-1B, TNF1A, inhibition of cyclooxygenases (COX-2) and lipoxygenase [151]</li> </ul> | <ul style="list-style-type: none"> <li>•enhanced memory functions and behavioral symptoms in animal models [175]</li> <li>•better cognitive performance (Mini-Mental State Examination, MMSE) in elderly [176]</li> </ul> |

|                           |  |  |   |
|---------------------------|--|--|---|
|                           |  | <ul style="list-style-type: none"> <li>•reducing accumulation of toxic aggregations: destabilization of A<math>\beta</math> plaques and NFT [173]</li> <li>•lowering glucose and cholesterol levels [151]</li> <li>•inhibition of AChE and MAO-B activity, increased the expression of glial cell-derived neurotrophic factor (GDNF) [174]</li> </ul>  |   |
| Mulberries, red wine, tea | Resveratrol  | <ul style="list-style-type: none"> <li>•antioxidant activity: reducing iNOS levels and increasing the expression of antioxidant enzymes [153]</li> <li>•reducing accumulation of toxic A<math>\beta</math> aggregations by activation of sirtuin 1 (Sirt-1), decreasing <math>\beta</math>-secretase expression, attenuating hyperphosphorylation of tau proteins [153]</li> <li>•antiapoptotic activity: inhibiting B-cell lymphoma xL (Bcl-xL) and Bax, activating Bcl-2, blocking the activation of <i>c-Jun</i> N-terminal kinase (JNK), activating phosphoinositide 3-kinase/Akt (PI3K/Akt) and ERK/cyclic AMP-response-binding element [153,175]</li> <li>•anti-inflammatory properties: reducing the over-expression of proinflammatory miRNA, reducing COX-2 levels suppressing the release of NF<math>\kappa</math>B, IL-6, IL-1B, TNF1A [154]</li> <li>•inhibition of mitochondria membrane permeability [153]</li> <li>•increasing Ca<sup>2+</sup> levels, suppressing MAO-B activity, increasing the expression of GDNF [174]</li> </ul> | <ul style="list-style-type: none"> <li>•reduced levels of A<math>\beta</math>-40 in CSF and plasma in patients with mild and moderate AD who received resveratrol supplementation [155] and better immune and cognitive response [156] (clinical trials).</li> </ul>  |
| <i>Ginkgo biloba</i>      | Flavonoids (quercetin, kaempferol), terpenoids (ginkgolides), ginkgolic acid | <ul style="list-style-type: none"> <li>•anti-inflammatory properties: downregulating the expression of proinflammatory molecules (TNF1<math>\alpha</math>, IL-6, IL-1<math>\beta</math>, prostaglandin E<sub>2</sub>) [157,158]</li> <li>•stimulating neuronal autophagy [157,158]</li> <li>•antiapoptotic properties: preventing mitochondrial release of cytochrome c, increasing the expression of Bcl-2-like protein, triggering PI3K/Akt and PKC signaling pathway [153]</li> <li>•suppressing MAO-A activity and triggering expression of BDNF [174]</li> </ul>  | <ul style="list-style-type: none"> <li>•lower neuronal damage in multicellular network model [159] and in animals [160],</li> <li>•stronger therapeutic effect memantine when administrated with Ginkgo extracts [161,162]</li> <li>•enhancement in cognitive function and neuropsychiatric symptoms in people with dementia [177,178]</li> </ul> |
| <i>Olea europea</i>       | Oleuropein aglycone  | <ul style="list-style-type: none"> <li>•free radical scavengers [157]</li> <li>•downregulating the expression of proinflammatory cytokines TNF1<math>\alpha</math>, IL-6, IL-1<math>\beta</math>, inhibition of COX-2 [153,157]</li> <li>•stimulating neuronal autophagy via</li> </ul>  | <ul style="list-style-type: none"> <li>•improved cognitive performance in transgenic mice [157]</li> <li>•ameliorated depressive symptoms in animal</li> </ul>  |

|                                      |   |   |  |
|--------------------------------------|---|---|--|
|                                      |   | <p>5'AMP-activated protein kinase (AMPK)/mTOR pathway [179]</p> <ul style="list-style-type: none"> <li>•inhibiting toxic protein aggregation [157]</li> <li>•increased expression of BDNF and tropomyosin-related kinase A (TrkA) and B (TrkB) [153,180]</li> </ul>   | models [180]   |
| <i>Cannabis sativa</i>               | cannabidiol (CBD), $\Delta^9$ -tetrahydrocannabinol (THC) | <ul style="list-style-type: none"> <li>•antioxidant properties: reducing levels of ROS/RNS, iNOS and caspase 3 activity [165]</li> <li>•downregulating the expression of proinflammatory cytokines such as TNF1<math>\alpha</math>, IL-6, IL-1<math>\beta</math> [158]</li> <li>•stimulating neuronal autophagy and expression of autophagy related genes [158]</li> <li>•reducing levels of A<math>\beta</math> senile plaques and tau hyperphosphorylation through reduction in phosphorylated p-GSK3<math>\beta</math> [153,165]</li> <li>•inhibiting AChE activity [158]</li> </ul> | <ul style="list-style-type: none"> <li>•improved memory and learning in animal models of AD [164].</li> <li>•management of chronic pain and associated neuropathology in AD [165]</li> </ul> |
| <i>Panax ginseng</i>                 | Ginsenosides  | <ul style="list-style-type: none"> <li>•upregulation of choline acetyltransferase, stimulation of GABA-A and glycine receptors, inhibition of NMDA receptors [158,167]</li> <li>•reducing pro-inflammatory mediators such as COX-2, TNF<math>\alpha</math>, and inducible nitric oxide synthase (iNOS) [153,167]</li> <li>•degrading the A<math>\beta</math> plaques by activating autophagy [158]</li> </ul>   | <ul style="list-style-type: none"> <li>•increased cortex thickness and synaptic density in vivo [167].</li> <li>•improved thinking and working memory in AD patients [181]</li> </ul>        |
| <i>Huperzia serrata</i>              | Huperzine A   | <ul style="list-style-type: none"> <li>•scavenging free radicals, activation of antioxidant enzymes [168]</li> <li>•upregulating the NGF [168]</li> <li>•enhanced activity of electron-transport chain, lowering the mitochondrial cytochrome c release [182]</li> <li>•antiapoptotic properties: attenuating the increase of caspase-3 activity [153]</li> <li>•inhibiting BACE-1 activity [132]</li> </ul>  | <ul style="list-style-type: none"> <li>•attenuated cognitive decline and better neuronal protection against A<math>\beta</math> toxicity in animal models [168]</li> </ul>                   |
| <i>Zingiber officinale</i> (ginger)  | 6-gingerol, 6-shogaol                                     | <ul style="list-style-type: none"> <li>•increasing the NGF levels, inhibiting AChE activity [169]</li> <li>•anti-inflammatory properties: suppressing BACE-1 activity [132]</li> <li>•decreasing the levels of A<math>\beta</math> [169]</li> </ul>   | <ul style="list-style-type: none"> <li>•improving learning and memory in rodents [169]</li> </ul>  |
| <i>Punica granatum</i> (pomegranate) | Myricetin, quercetin                                      | <ul style="list-style-type: none"> <li>•antioxidant activity: metal chelation, scavenging free radicals, increasing the activity of antioxidant enzymes [183]</li> <li>•antiapoptotic properties: inhibition of Bax and Bak and induction of Bcl-2 and Bcl-xL [183]</li> <li>•downregulating pro-inflammatory mediators (TNF1<math>\alpha</math>, IL-6, IL-1<math>\beta</math>, NF-<math>\kappa</math>B, iNOS) [153]</li> </ul>   | <ul style="list-style-type: none"> <li>•improved attention, memory and learning in humans [170]</li> </ul>   |

|               |                                    |   |   |
|---------------|------------------------------------|---|---|
|               |                                    | <ul style="list-style-type: none"> <li>•inhibiting the formation and destabilizing the structure of A<math>\beta</math> fibrils [153,183]</li> <li>•enhanced activity of electron-transport chain, inhibition of mitochondria membrane permeability, increasing the expression of AMPK [153]</li> </ul> |   |
| Red mold rice | Monacolines (ankaflavin, monascin) | <ul style="list-style-type: none"> <li>•reducing the ROS levels [170]</li> <li>•anti-inflammatory properties: attenuating the activity of BACE-1 [170]</li> <li>•decreasing the levels of ApoE, NFT and accumulated A<math>\beta</math> [171]</li> </ul>  | <ul style="list-style-type: none"> <li>•ameliorating the of memory impairment and increasing learning ability in rodents [184]</li> </ul> |

Although plant extracts contain active compounds that are synergistically aimed at multiple AD targets, a great challenge is represented by their low bioavailability and lack of precisely defined mechanisms of action. Many bioactive molecules and natural extracts are strong antioxidants and have anti-inflammatory and immunomodulatory properties. They often act through several biological mechanisms simultaneously, such as inhibition of AChE, BACE1,  $\gamma$ -secretase or monoamine oxidase (MAO) activity, metal chelation or prevention of formation and accumulation of A $\beta$  and NFT protein aggregates [153]. Moreover, it is not an easy task to identify key compound(s) in herbal extracts and replicate the synergistic effects to potentially be used on a larger scale. However, natural treatments have shown promising results in “in vitro” and “in vivo” studies and have been shown to improve the effect of existing AD treatments and thus represent strong candidates in ongoing and future clinical studies [132].

## 5. Expert Opinion

Alzheimer's disease (AD) is a devastating and fatal illness. Even more hurtful is that, despite the huge advances in diagnostic imaging and molecular tools, no treatment affecting underlying disease pathology is available, and cognitive deterioration is inevitable. Symptoms of this complex disease are far beyond memory and orientation difficulty, with a range of disturbing behavioral symptoms being more the rule than the exception. Even very low doses of psychotropic drugs may produce serious adverse events. Therefore, in the absence of effective disease-modifying, as well as safe pharmacological agents for behavioral symptoms, complementary treatment in this highly vulnerable population becomes even more important than

in any other field of psychiatry. This was reflected in numerous clinical trials, followed by reviews and meta-analyses. Nonpharmacological treatment in AD is an umbrella term, which covers a diversity of procedures, targeting different disease manifestations. The lack of standardized protocols, different methodologies, and treatment aims make the interpretation and generalization of these studies difficult. Interestingly, some practices, such as physical exercise, acupuncture, or cognitive training, demonstrated beneficial and/or preventive effects on brain neuropathology in preclinical models of dementia, although clinical data are not that encouraging. Some other interventions cannot be tested in animals, like visual art therapy, horticultural or animal-assisted therapy. There is a strong evidence that food supplements and natural products may mitigate some aspects of disease pathology and cognitive impairment, with potentially lower toxicity and less side-effects than classical pharmacological therapy. Natural treatments have shown promising results in ameliorating the AD symptoms and slowing down the progression of the disease in preclinical studies, and some of them improved the effect of existing AD therapy in humans, which is seen in rising number of filed patents for treatment and prevention of AD. However, extensive clinical trials confirming significant therapeutic effect of natural products on humans is still missing, alongside with ideal strategy of administration to overcome blood-brain barrier and increase bioavailability. Natural product formulations still require detailed studies of molecular mechanisms of action, however, their ability to affect several targets of AD simultaneously, as well as rapid development of drug delivery systems, could represent promising strategy in treating AD in the future.

Our opinion is, given some well-documented benefits of nonpharmacological treatments, that at least some of those interventions should be offered in all facilities taking care of patients with AD. While, for example, in acute wards procedures such as massage, exercising, music or light therapy may be delivered, in chronic settings patients may also participate in cognitive training, therapeutic gardens, or interact with therapy animals. The choice for each person is made upon the disease stage, leading behavioral symptoms, availability of certified staff, cognitive capacity, somatic fitness, and individual preferences. The purpose of nonpharmacological treatment is not limited to symptom alleviation. It may also decrease psychotropic drug consumption, improve



quality of life, bring some joy, stress relief, and relaxation, evoke pleasant memories, and make life more meaningful, even in people in more advanced dementia stages. The majority of procedures are easy to perform in different settings and are cost-effective. However, caution is needed to prevent injuries or overstimulation. State-of-the-art care for AD patients should always include teamwork. In the absence of curative treatment, the key to success is the alleviation of symptoms, a decrease of isolation and loneliness, and a maximal increase in time spent in pleasurable and, if possible, creative activities, which is best achieved by a personalized approach.

## **6. Conclusion**

Since current pharmacological treatments do not cure or stop AD, nonpharmacological strategies (such as physical activity, use of acupuncture, animal-assisted, bright light, horticultural, music, visual art, and massage therapy) might improve behavioral and cognitive symptoms in AD. In addition, natural products and vitamins improve the effectiveness of existing AD treatments. The combination of pharmacological and nonpharmacological treatments and natural products might offer person-centered approaches to treat AD. Namely, physical activity and cognitive training, combined with other nonpharmacological strategies improve neuroprotection, normalize and regulate cerebral blood flow, offer stress relief and hormone balance, and are associated with increased production of BDNF and other growth factors, resulting in elevated neurogenesis, neuroplasticity, and angiogenesis, and decreased cortisol secretion and reduced inflammation. Due to the heterogeneity of disease symptoms, somatic conditions, and patient preferences, there is definitely no „one size fits all“ intervention. Therefore, individualized treatment choice is based on dementia stage, medical and psychiatric comorbidity, leading symptoms, patient preferences, and remaining capacity of the patient. In the absence of disease-modifying agents, a patient-centered, multidisciplinary team approach appears to be the best option to alleviate the heavy symptomatic burden in this unfortunate population. Hence, appropriate interventions can be offered along the AD continuum, while a better understanding of personal characteristics might help in establishing optimal individualized treatment, as well as its duration and intensity, to deliver interventions in the most effective ways.

## **Funding**

This study was funded by the Croatian Science Foundation, project no. IP-2019-04-6100.

## **Disclosure**

The authors report no conflicts of interest in this work.

## **Declaration of Interest**

None. All authors declare that they have no personal interest, direct or indirect, in any matter that raises or may raise a conflict with their duty as authors of this text. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript.

## **Acknowledgements**

The authors are grateful to Milka Sagud, MSN, PMHNP, a native English speaker, for correcting the English language.

## **References**

1. Peng X, Xing P, Li X, et al. Towards personalized intervention for Alzheimer's Disease. *Genom Proteom Bioinformatics*. 2016; 14(5): 289–297. \*\*this review discusses personalized intervention at each of the disease stages, tailored toward the patients according to the demographic and in-depth information;
2. Hampel H, O'Bryant S, Durrleman S, et al. A Precision medicine initiative for Alzheimer's disease: the road ahead to biomarker-guided integrative disease modeling. *Climacteric*. 2017;20(2):107-118.
3. Nikolac Perkovic M, Svob Strac D, Tudor L et al. Catechol-O-methyltransferase, cognition and Alzheimer's disease. *Curr Alzheimer Res*. 2018;15:408-419.
4. Nikolac Perkovic M, Pivac N. Genetic markers of Alzheimer's Disease. *Adv Exp Med Biol*. 2019;1192:27-52.
5. Reitz C. Toward precision medicine in Alzheimer's disease. *Ann Transl Med*. 2016;4(6):107. \*\* this review discusses precision medicine approach in Alzheimer's disease

6. Marešová P, Dolejš J, Mohelska H, Bryan LK. Cost of treatment and care for people with Alzheimer's Disease: A Meta- Analysis. *Curr Alzheimer Res.* 2019;16(14):1245-1253.
7. Yiannopoulou KG, Papageorgiou SG. Current and future treatments in Alzheimer disease: an update. *J Cent Nerv Syst Dis.* 2020;12:1179573520907397.\*\* this review describes potential disease-modifying therapies for patients with AD.
8. Knight R, Khondoker M, Magill N, et al. A systematic review and meta-analysis of the effectiveness of acetylcholinesterase inhibitors and memantine in treating the cognitive symptoms of dementia. *Dement Geriatr Cogn Disord.* 2018;45(3-4):131-151.
9. Glinz D, Gloy VL, Monsch AU, et al. Acetylcholinesterase inhibitors combined with memantine for moderate to severe Alzheimer's disease: a meta-analysis. *Swiss Med Wkly.* 2019;149:w20093.
10. Vancampfort D, Solmi M, Firth J, et al. The impact of pharmacologic and nonpharmacologic interventions to improve physical health outcomes in people with dementia: A meta-review of meta-analyses of randomized controlled trials. *J Am Med Dir Assoc.* 2020;21(10):1410-1414.e2.
11. Galvin JE. Advancing personalized treatment of Alzheimer's disease: a call for the N-of-1 trial design. *Future Neurol.* 2018;13(3):151–160.
12. Abraha I, Rimland JM, Trotta FM, et al. Systematic review of systematic reviews of nonpharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. *BMJ Open.* 2017;7(3):e012759.\* this review describes that from the nonpharmacological treatments, music therapy and behavioral management techniques were effective for reducing BPSD.
13. Sikkes SAM, Tang Y, Jutten RJ, et al. Toward a theory-based specification of nonpharmacological treatments in aging and dementia: Focused reviews and methodological recommendations. *Alzheimers Dement.* 2020; [16]. doi:10.1002/alz.12188\*\* this review describes nonpharmacological treatment's benefits for dementia, supports cognitive training and music therapy and provides directions for future research.

14. Fuller OK, Whitham M, Mathivanan S, et al. The protective effect of exercise in neurodegenerative diseases: the potential role of extracellular vesicles. *Cells*. 2020;9(10):2182.
15. Tsai CL, Sun HS, Kuo YM, et al. The Role of Physical Fitness in Cognitive-Related Biomarkers in Persons at Genetic Risk of Familial Alzheimer's Disease. *J Clin Med*. 2019;8(10):1639.
16. Yoneda T, Lewis NA, Knight JE, et al. The Importance of Engaging in PA in Older Adulthood for Transitions between Cognitive Status Categories and Death: A Coordinated Analysis of Fourteen Longitudinal Studies. *J Gerontol A Biol Sci Med Sci*. 2020:glaa268.
17. de Almeida SIL, Gomes da Silva M, Marques ASPD. Home-based pa programs for people with dementia: systematic review and meta-analysis. *Gerontologist*. 2020;60(8):600-608.
18. Wang LY, Pei J, Zhan YJ, et al. Overview of meta-analyses of five nonpharmacological interventions for Alzheimer's Disease. *Front Aging Neurosci*. 2020;12:594432.
19. Zhu L, Li L, Wang L, et al. PA for executive function and activities of daily living in AD patients: a systematic review and meta-analysis. *Front Psychol*. 2020;11:560461.
20. Colovati MES, Novais IP, Zampol M, et al. Interaction between physical exercise and APOE gene polymorphism on cognitive function in older people. *Braz J Med Biol Res*. 2020;54(2):e10098.
21. Kurucz A, Bombicz M, Kiss R, et al. Heme Oxygenase-1 Activity as a Correlate to Exercise-Mediated Amelioration of Cognitive Decline and Neuropathological Alterations in an Aging Rat Model of Dementia. *Biomed Res Int*. 2018;2018:7212861.
22. Kim D, Cho J, Kang H. Protective effect of exercise training against the progression of Alzheimer's disease in 3xTg-AD mice. *Behav Brain Res*. 2019;374:112105.
23. Li B, Liang F, Ding X, et al. Interval and continuous exercise overcome memory deficits related to  $\beta$ -Amyloid accumulation through modulating mitochondrial dynamics. *Behav Brain Res*. 2019;376:112171.
24. Sarlak Z, Moazzami M, Attarzadeh Hosseini M, et al. The effects of aerobic training before and after the induction of Alzheimer's disease on ABCA1 and APOE mRNA expression and

- the level of soluble A $\beta$ 1-42 in the hippocampus of male Wistar rats. *Iran J Basic Med Sci.* 2019;22(4):399-406.
25. Belaya I, Ivanova M, Sorvari A, et al. Astrocyte remodeling in the beneficial effects of long-term voluntary exercise in Alzheimer's disease. *J Neuroinflammation.* 2020;17(1):271.
  26. Dare LR, Garcia A, Soares CB, et al. The Reversal of Memory Deficits in an Alzheimer's Disease Model Using Physical and Cognitive Exercise. *Front Behav Neurosci.* 2020;14:152.
  27. Schmidt HL, Carrazoni GS, Garcia A, et al. Strength training or green tea prevent memory deficits in a  $\beta$ -amyloid peptide-mediated Alzheimer's disease model. *Exp Gerontol.* 2020. Epub ahead of print.
  28. Dungan CM, Valentino T, Vechetti IJ Jr, et al. Exercise-mediated alteration of hippocampal Dicer mRNA and miRNAs is associated with lower BACE-1 gene expression and A $\beta$ 1-42 in female 3xTg-AD mice. *J Neurophysiol.* 2020 ;124(6):1571-1577. doi: 10.1152/jn.00503.2020.
  29. Rosa JM, Camargo A, Wolin IAV, et al. Physical exercise prevents amyloid  $\beta$ 1-40-induced disturbances in NLRP3 inflammasome pathway in the hippocampus of mice. *Metab Brain Dis.* 2021;36(2):351-359.
  30. Lu LC, Lan SH, Hsieh YP, et al. Horticultural therapy in patients with dementia: A systematic review and meta-analysis. *Am J Alzheimers Dis Other Demen.* 2020;35:1533317519883498.
  31. Falkenheim K, Ruiz-Urbe NE, Haft-Javaherian M, et al. A pilot study investigating the effects of voluntary exercise on capillary stalling and cerebral blood flow in the APP/PS1 mouse model of Alzheimer's disease. *PLoS One.* 2020;15(8):e0235691.
  32. Cai Z, Liu N, Wang C, et al. Role of RAGE in Alzheimer's Disease. *Cell Mol Neurobiol.* 2016;36(4):483-95.
  33. Stojanovic M, Jin Y, Fagan AM, et al. Physical exercise and longitudinal trajectories in Alzheimer disease biomarkers and cognitive functioning. *Alzheimer Dis Assoc Disord.* 2020;34(3):212-219.
  34. Rabin JS, Klein H, Kirn DR, et al. Associations of PA and  $\beta$ -Amyloid with longitudinal cognition and neurodegeneration in clinically normal older adults. *JAMA Neurol.* 2019;76(10):1203–10.

35. Frederiksen KS, Madsen K, Andersen BB, et al. Moderate- to high-intensity exercise does not modify cortical  $\beta$ -amyloid in Alzheimer's disease. *Alzheimers Dement (NY)*. 2019;5:208-215.
36. van der Kleij LA, Petersen ET, Siebner HR, et al. The effect of physical exercise on cerebral blood flow in Alzheimer's disease. *Neuroimage Clin*. 2018;20:650-654.
37. Sobol NA, Hoffmann K, Frederiksen KS, et al. Effect of aerobic exercise on physical performance in patients with Alzheimer's disease. *Alzheimers Dement*. 2016;12(12):1207-1215.
38. Hoffmann K, Sobol NA, Frederiksen KS, et al. Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: A randomized controlled trial. *J Alzheimers Dis*. 2016;50(2):443-53.
39. Haeger A, Costa AS, Schulz JB, et al. Cerebral changes improved by PA during cognitive decline: A systematic review on MRI studies. *Neuroimage Clin*. 2019;23:101933.
40. Robinson MM, Lowe VJ, Nair KS. Increased brain glucose uptake after 12 weeks of aerobic high-intensity interval training in young and older adults. *J Clin Endocrinol Metab*. 2018;103(1):221-227.
41. Ward JL, Craig JC, Liu Y, et al. Effect of healthy aging and sex on middle cerebral artery blood velocity dynamics during moderate-intensity exercise. *Am J Physiol Heart Circ Physiol*. 2018;315(3):H492-H501.
42. Foley KE, Yang HS, Graham LC, et al. Transcriptional profiling predicts running promotes cerebrovascular remodeling in young but not midlife mice. *BMC Genomics*. 2019;20(1):860.
43. Sisante JV, Vidoni ED, Kirkendoll K, et al. Blunted cerebrovascular response is associated with elevated beta-amyloid. *J Cereb Blood Flow Metab*. 2019;39(1):89-96.
44. Jia RX, Liang JH, Xu Y, et al. Effects of PA and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. *BMC Geriatr*. 2019;19(1):181.
45. Kishita N, Backhouse T, Mioshi E. Nonpharmacological interventions to improve depression, anxiety, and quality of life (QoL) in people with dementia: An overview of systematic reviews. *J Geriatr Psychiatry Neurol*. 2020;33(1):28-41.

46. Hill NT, Mowszowski L, Naismith SL, et al. Computerized cognitive training in older adults with mild cognitive impairment or dementia: A systematic review and meta-analysis. *Am J Psychiatry*. 2017;174(4):329-340.
47. Yao S, Liu Y, Zheng X, et al. Do nonpharmacological interventions prevent cognitive decline? a systematic review and meta-analysis. *Transl Psychiatry*. 2020;10(1):19.
48. Cuevas PEG, Davidson PM, Mejilla JL, et al. Reminiscence therapy for older adults with Alzheimer's disease: A literature review. *Int J Ment Health Nurs*. 2020;29(3):364-371.
49. Bentham C, De Marco M, Venneri A. The Modulatory effect of cerebrovascular burden in response to cognitive stimulation in healthy ageing and mild cognitive impairment. *Neural Plast*. 2019;2019:2305318.
50. Behrman S, Chouliaras L, Ebmeier KP. Considering the senses in the diagnosis and management of dementia. *Maturitas*. 2014;77(4):305-10.
51. Prins AJ, Scherder EJA, van Straten A, et al. Sensory stimulation for nursing-home residents: systematic review and meta-analysis of its effects on sleep quality and rest-activity rhythm in dementia. *Dement Geriatr Cogn Disord*. 2020;49(3):219-234.
52. Chang SJ, Lee J, An H, et al. Animal-assisted therapy as an intervention for older adults: a systematic review and meta-analysis to guide evidence-based practice. *Worldviews Evid Based Nurs*. 2020. doi:10.1111/wvn.12484
53. Peluso S, De Rosa A, De Lucia N, et al. Animal-assisted therapy in elderly patients: evidence and controversies in dementia and psychiatric disorders and future perspectives in other neurological diseases. *J Geriatr Psychiatry Neurol*. 2018;31(3):149-157.
54. Rodrigo-Claverol M, Malla-Clua B, Marquilles-Bonet C, et al. Animal-assisted therapy improves communication and mobility among institutionalized people with cognitive impairment. *Int J Environ Res Public Health*. 2020;17(16):5899.
55. Klimova B, Toman J, Kuca K. Effectiveness of the dog therapy for patients with dementia - a systematic review. *BMC Psychiatry*. 2019;19(1):276.

56. Swall A, Ebbeskog B, Lundh Hagelin C, et al. Stepping out of the shadows of Alzheimer's disease: a phenomenological hermeneutic study of older people with Alzheimer's disease caring for a therapy dog. *Int J Qual Stud Health Well-being*. 2017;12(1):1347013.
57. Wesenberg S, Mueller C, Nestmann F, et al. Effects of an animal-assisted intervention on social behaviour, emotions, and behavioural and psychological symptoms in nursing home residents with dementia. *Psychogeriatrics*. 2019;19(3):219-227.
58. Smith BC, D'Amico M. Sensory-based interventions for adults with dementia and alzheimer's disease: A scoping review. *Occup Ther Health Care*. 2020;34(3):171-201.
59. Margenfeld F, Klocke C, Joos S. Manual massage for persons living with dementia: A systematic review and meta-analysis. *Int J Nurs Stud*. 2019;96:132-142.
60. Abramowitz L. Working with advanced dementia patients in a day care setting. *J Gerontol Soc Work*. 2008;50(3-4):25-35.
61. Peck KJ, Girard TA, Russo FA, et al. Music and memory in Alzheimer's Disease and the potential underlying mechanisms. *J Alzheimers Dis*. 2016;51(4):949-59.
62. Clements-Cortes A, Bartel L. Are we doing more than we know? Possible mechanisms of response to music therapy. *Front Med (Lausanne)*. 2018;5:255.
63. Cocchiara RA, De Lucia F, Koci L, et al. Management of the early stage of Alzheimer's disease: a systematic review of literature over the past 10 years. *Clin Ter*. 2020;171(4):e357-e368.
64. Lai X, Wen H, Li Y, et al. The Comparative efficacy of multiple interventions for mild cognitive impairment in Alzheimer's disease: A bayesian network meta-analysis. *Front Aging Neurosci*. 2020;12:121.
65. Garrido S, Stevens CJ, Chang E, et al. Music and Dementia: Individual differences in response to personalized playlists. *J Alzheimers Dis*. 2018;64(3):933-941.
66. Begum MM, Uddin MS, Rithy JF, et al. Analyzing the impact of soft, stimulating and depressing songs on attention among undergraduate students: A cross-sectional pilot study in bangladesh. *Front Psychol*. 2019;10:161.



67. Paszkiel S, Dobrakowski P, Łysiak A. The impact of different sounds on stress level in the context of eeg, cardiac measures and subjective stress level: A pilot study. *Brain Sci.* 2020;10(10):728.
68. Harvey AR. Links between the neurobiology of oxytocin and human musicality. *Front Hum Neurosci.* 2020;14:350.
69. Kanduri C, Rajjas P, Ahvenainen M, et al. The effect of listening to music on human transcriptome. *PeerJ.* 2015;3:e830.
70. Xu A, Zeng Q, Tang Y, et al. Electroacupuncture protects cognition by regulating tau phosphorylation and glucose metabolism via the AKT/GSK3 $\beta$  signaling pathway in Alzheimer's disease model mice. *Front Neurosci.* 2020;14:585476.
71. Yu CC, Ma CY, Wang H, et al. Effects of acupuncture on Alzheimer's disease: Evidence from neuroimaging studies. *Chin J Integr Med.* 2019;25(8):631-640.
72. Zhao FY, Fu QQ, Zheng Z, et al. Verum- versus sham-acupuncture on Alzheimer's Disease (AD) in animal models: A preclinical systematic review and meta-analysis. *Biomed Res Int.* 2020B:5901573.
73. Wang YY, Yu SF, Xue HY, et al. Effectiveness and safety of acupuncture for the treatment of Alzheimer's disease: A systematic review and meta-analysis. *Front Aging Neurosci.* 2020;12:98.
74. Song YY, Xu WT, Zhang XC, et al. Mechanisms of electroacupuncture on Alzheimer's disease: A review of animal studies. *Chin J Integr Med.* 2020;26(6):473-480.
75. Ghafoor U, Lee JH, Hong KS, et al. Effects of acupuncture therapy on MCI patients using functional near-infrared spectroscopy. *Front Aging Neurosci.* 2019;11:237.
76. Su XT, Wang LQ, Li JL, Zhang N, Wang L, Shi GX, Yang JW, Liu CZ. Acupuncture therapy for cognitive impairment: A Delphi expert consensus survey. *Front Aging Neurosci.* 2020;12:596081.
77. Li W, Wang Q, Du S, Pu Y, Xu G. Acupuncture for mild cognitive impairment in elderly people: Systematic review and meta-analyses. *Medicine (Baltimore).* 2020 Sep 25;99(39):e22365.

78. Zhao Y, Liu Y, Wang Z. Effectiveness of horticultural therapy in people with dementia: A quantitative systematic review. *J Clin Nurs*. 2020. doi:10.1111/jocn.15204
79. Roccaro I, Smirni D. Fiat Lux: The light became therapy. an overview on the bright light therapy in Alzheimer's disease sleep disorders. *J Alzheimers Dis*. 2020;77(1):113-125.
80. Mitolo M, Tonon C, La Morgia C, et al. Effects of light treatment on sleep, cognition, mood, and behavior in Alzheimer's disease: A systematic review. *Dement Geriatr Cogn Disord*. 2018;46(5-6):371-384.
81. Hjetland GJ, Pallesen S, Thun E, et al. Light interventions and sleep, circadian, behavioral, and psychological disturbances in dementia: A systematic review of methods and outcomes. *Sleep Med Rev*. 2020;52:101310.
82. Wang YQ, Li DM. Advances in art therapy for patients with dementia. *Chinese Nursing Res*. 2016;105-108.
83. Lorusso LN, Bosch SJ. Impact of multisensory environments on behavior for people with dementia: A systematic literature review. *Gerontologist*. 2018;58(3):e168-e179.
84. Yu KW, Wang CJ, Wu Y, et al. An enriched environment increases the expression of fibronectin type III domain-containing protein 5 and brain-derived neurotrophic factor in the cerebral cortex of the ischemic mouse brain. *Neural Regen Res*. 2020;15(9):1671-1677.
85. Juárez-Cedillo T, Gutiérrez-Gutiérrez L, Sánchez-Hurtado LA, et al. Randomized controlled trial of multi-component cognitive stimulation therapy (SADEM) in community-dwelling demented adults. *J Alzheimers Dis*. 2020;78(3):1033-1045.
86. Jung YH, Lee S, Kim WJ, et al. Effect of integrated cognitive intervention therapy in patients with mild to moderate Alzheimer's disease. *Dement Neurocogn Disord*. 2020;19(3):86-95.
87. Masika GM, Yu DSF, Li PWC. Visual art therapy as a treatment option for cognitive decline among older adults. A systematic review and meta-analysis. *J Adv Nurs*. 2020. Online ahead of print.
88. Shigihara Y, Hoshi H, Shinada K, et al. Nonpharmacological treatment changes brain activity in patients with dementia. *Sci Rep*. 2020;10(1):6744.

89. Maseda A, Cibeira N, Lorenzo-López L, et al. Multisensory stimulation and individualized music sessions on older adults with severe dementia: effects on mood, behavior, and biomedical parameters. *J Alzheimers Dis.* 2018;63(4):1415-1425.
90. Sakamoto M, Ando H, Tsutou A. Comparing the effects of different individualized music interventions for elderly individuals with severe dementia. *Int Psychogeriatr.* 2013;25(5):775-84.
91. Müller P, Achraf A, Zou L, et al. COVID-19, physical (in-)activity, and dementia prevention. *Alzheimers Dement (N Y).* 2020;6(1):e12091.
92. Menna LF, Santaniello A, Gerardi F, et al. Efficacy of animal-assisted therapy adapted to reality orientation therapy: measurement of salivary cortisol. *Psychogeriatrics.* 2019;19(5):510-512.
93. Field T. Massage therapy research review. *Complement Ther Clin Pract.* 2014;20(4):224-9.
94. Tarsha MS, Park S, Tortora S. Body-centered interventions for psychopathological conditions: A review. *Front Psychol.* 2020;10:2907.
95. Wu J, Wang Y, Wang Z. The effectiveness of massage and touch on behavioural and psychological symptoms of dementia: A quantitative systematic review and meta-analysis. *J Adv Nurs.* 2017;73(10):2283-2295.
96. King JB, Jones KG, Goldberg E, et al. Increased functional connectivity after listening to favored music in adults with Alzheimer dementia. *J Prev Alzheimers Dis.* 2019;6(1):56-62.
97. Goris ED, Ansel KN, Schutte DL. Quantitative systematic review of the effects of nonpharmacological interventions on reducing apathy in persons with dementia. *J Adv Nurs.* 2016;72(11):2612-2628.
98. Garrido S, Stevens CJ, Chang E, et al. Musical features and affective responses to personalized playlists in people with probable dementia. *Am J Alzheimers Dis Other Demen.* 2019;34(4):247-253.
99. Detweiler MB, Sharma T, Detweiler JG, et al. What is the evidence to support the use of therapeutic gardens for the elderly? *Psychiatry Investig.* 2012;9(2):100-110.

100. Huang KY, Liang S, Yu ML, et al. A systematic review and meta-analysis of acupuncture for improving learning and memory ability in animals. *BMC Complement Altern Med.* 2016;16(1):297.
101. Chung A, Bui L, Mills E. Adverse effects of acupuncture. Which are clinically significant? *Can Fam Physician.* 2003;49:985-989.
102. Clark SD, Martin F, McGowan RTS, et al. Physiological state of therapy dogs during animal-assisted activities in an outpatient setting. *Animals (Basel).* 2020;10(5):819.
103. Clark S, Martin F, McGowan RTS, et al. The impact of a 20-minute animal-assisted activity session on the physiological and emotional states in patients with fibromyalgia. *Mayo Clin Proc.* 2020A;95(11):2442-2461.
104. Dendaal JS. Animal-assisted therapy - magic or medicine? *J Psychosom Res.* 2000;49(4):275-80.
105. Ein N, Li L, Vickers K. The effect of pet therapy on the physiological and subjective stress response: A meta-analysis. *Stress Health.* 2018;34(4):477-489.
106. Lima CR, Martins DF, Reed WR. Physiological responses induced by manual therapy in animal models: a scoping review. *Front Neurosci.* 2020;14:430.
107. Papadakakis A, Sidiropoulou K, Panagis G. Music exposure attenuates anxiety- and depression-like behaviors and increases hippocampal spine density in male rats. *Behav Brain Res.* 2019;372:112023.
108. Xing Y, Xia Y, Kendrick K, Liu X, Wang M, Wu D, Yang H, Jing W, Guo D, Yao D. Mozart, Mozart rhythm and retrograde Mozart Effects: evidences from behaviours and neurobiology bases. *Sci Rep.* 2016;6:18744.
109. Sittler MC, Worschech F, Wilz G, Fellgiebel A, Wuttke-Linnemann A. Psychobiological mechanisms underlying the health-beneficial effects of music in people living with dementia: A systematic review of the literature. *Physiol Behav.* 2021;233:113338.
110. Alain C, Moussard A, Singer J, Lee Y, Bidelman GM, Moreno S. Music and visual art training modulate brain activity in older adults. *Front Neurosci.* 2019;13:182.

111. De Pisapia N, Bacci F, Parrott D, Melcher D. Brain networks for visual creativity: a functional connectivity study of planning a visual artwork. *Sci Rep*. 2016;6:39185.
112. King JL, Kaimal G. Approaches to research in art therapy using imaging technologies. *Front Hum Neurosci*. 2019;13:159.
113. Ng KST, Sia A, Ng MKW, et al. Effects of horticultural therapy on asian older adults: a randomized controlled trial. *Int J Environ Res Public Health*. 2018;15(8):1705.
114. Park SA, Son SY, Lee AY, Park HG, Lee WL, Lee CH. Metabolite profiling revealed that a gardening activity program improves cognitive ability correlated with BDNF levels and serotonin metabolism in the elderly. *Int J Environ Res Public Health*. 2020;17(2):541.
115. Bilu C, Einat H, Zimmet P, et al. Beneficial effects of daytime high-intensity light exposure on daily rhythms, metabolic state and affect. *Sci Rep* 2020; 10(1): 19782.
116. Kwon SJ, Park J, Park SY, et al. Low-intensity treadmill exercise and/or bright light promote neurogenesis in adult rat brain. *Neural Regen Res*. 2013;8(10):922-9.
117. Liu Y, Wang L, Pan D, et al. PET evaluation of light-induced modulation of microglial activation and GLP-1R expression in depressive rats. *Transl Psychiatry*. 2021;11(1):26.
118. Kervezee L, Cuesta M, Cermakian N, Boivin DB. The Phase-Shifting effect of bright light exposure on circadian rhythmicity in the human transcriptome. *J Biol Rhythms*. 2019;34(1):84-97.
119. Leverse R, Van Someren EJ, Nielen MM, Uitdehaag BM, Smit JH, Hoogendijk WJ. Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. *Arch Gen Psychiatry*. 2011;68(1):61-70
120. Jung CM, Khalsa SB, Scheer FA, et al. Acute effects of bright light exposure on cortisol levels. *J Biol Rhythms*. 2010;25(3):208-16.
121. Kohno K, Terao T, Hatano K, et al. Post comparison of [(18) F]-fluorodeoxyglucose uptake in the brain after short-term bright light exposure and no intervention. *Acta Psychiatr Scand*. 2016;134(1):65-72.
122. Spies M, James GM, Vraka C, et al. Brain monoamine oxidase A in seasonal affective disorder and treatment with bright light therapy. *Transl Psychiatry*. 2018 ;8(1):198.

123. Ding N, Jiang J, Xu A, Tang Y, Li Z. Manual acupuncture regulates behavior and cerebral blood flow in the samp8 mouse model of Alzheimer's disease. *Front Neurosci.* 2019;13:37.
124. Su T, Pei L. Acupuncture and oxytocinergic system: The promising treatment for autism. *Transl Neurosci.* 2021;12(1):96-102.
125. Shen Y, Cheng ZD, Chen YG, et al. Electroacupuncture inhibits atherosclerosis through regulating intestinal flora and host metabolites in rabbit. *Evid Based Complement Alternat Med.* 2020;2020:5790275.
126. Sun J, Ashley J, Kellawan JM. Can acupuncture treatment of hypertension improve brain health? A Mini Review. *Front Aging Neurosci.* 2019;11:240
127. Tong T, Pei C, Chen J, Lv Q, Zhang F, Cheng Z. Efficacy of acupuncture therapy for chemotherapy-related cognitive impairment in breast cancer patients. *Med Sci Monit.* 2018;24:2919-2927.
128. Okada K, Kurita A, Takase B, et al. Effects of music therapy on autonomic nervous system activity, incidence of heart failure events, and plasma cytokine and catecholamine levels in elderly patients with cerebrovascular disease and dementia. *Int Heart J.* 2009;50(1):95-110.
129. Chalfont G, Milligan C, Simpson J. A mixed methods systematic review of multimodal nonpharmacological interventions to improve cognition for people with dementia. *Dementia.* 2020;19(4):1086–1130.
130. de Frutos-Lucas J, Frost N, Erickson KI, et al. Does APOE genotype moderate the relationship between PA, brain health and dementia risk? A systematic review. *Ageing Res Rev.* 2020;64:101173.
131. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. *Pharmacol Rep.* 2015;67(2):195-203.
132. Koynova R, Tenchov B. Natural Product Formulations for the Prevention and Treatment of Alzheimer's disease: A Patent Review. *Recent Pat Drug Deliv Formul.* 2018;12(1):23-39.
- \*\*This review summarizes patents on natural extracts as potential therapeutics for the prevention and treatment of AD

133. Yusufov M, Weyandt LL, Piryatinsky I. Alzheimer's disease and diet: a systematic review. *Int J Neurosci*. 2017;127(2):161-175.
134. Mielech A, Puścion-Jakubik A, Markiewicz-Żukowska R, et al. Vitamins in Alzheimer's Disease-Review of the Latest Reports. *Nutrients*. 2020;12(11):3458.\*\*This article reviews recent studies on importance of balanced nutrition and vitamins in AD
135. Uddin MS, Kabir MT, Tewari D, et al. Emerging Therapeutic Promise of Ketogenic Diet to Attenuate Neuropathological Alterations in Alzheimer's Disease. *Mol Neurobiol*. 2020;57(12):4961-4977.
136. Wołoszynowska-Fraser MU, Kouchmeshky A, McCaffery P. Vitamin A and Retinoic Acid in Cognition and Cognitive Disease. *Annu Rev Nutr*. 2020;40:247–272.
137. Zeng J, Chen L, Wang Z, et al. Marginal vitamin A deficiency facilitates Alzheimer's pathogenesis. *Acta Neuropathol*. 2017;133(6):967-982.
138. Yuan C, Fondell E, Ascherio A, et al. Long-Term intake of dietary carotenoids is positively associated with late-life subjective cognitive function in a prospective study in us women. *J Nutr*. 2020;150(7):1871–1879.
139. Ulusu NN, Yilmaz G, Erbayraktar Z, et al. A Turkish 3-center study evaluation of serum folic acid and vitamin B12 levels in Alzheimer disease. *Turk J Med Sci*. 2015;45(5):1159–1166.
140. Chen H, Liu S, Ji L, et al. Folic acid supplementation mitigates Alzheimer's Disease by reducing inflammation: A randomized controlled trial. *Mediat Inflamm*. 2016;2016:1–10.
141. Meng H, Li Y, Zhang W, et al. The relationship between cognitive impairment and homocysteine in a B12 and folate deficient population in China. *Medicine*. 2019;98(47):e17970.
142. Kwok T, Wu Y, Lee J, et al. A randomized placebo-controlled trial of using B vitamins to prevent cognitive decline in older mild cognitive impairment patients. *Clin Nutr*. 2020;39(8):2399–2405.
143. Monacelli F, Acquarone FME, Giannotti C, et al. Vitamin C, aging and Alzheimer's disease. *Nutrients* 2017;9(7):670.

144. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and Memantine on functional decline in Alzheimer Disease. *JAMA*. 2014;311(1):33–44.
145. Agarwal P, Holland TM, Wang Y, et al. Association of strawberries and anthocyanidin intake with Alzheimer's dementia risk. *Nutrients*. 2019;11(12):3060.
146. Ashley S, Bradburn S, Murgatroyd C. A meta-analysis of peripheral tocopherol levels in age-related cognitive decline and Alzheimer's disease. *Nutr Neurosci*. 2019. doi:10.1080/1028415X.2019.1681066
147. Dursun E, Gezen-Ak D. Vitamin D basis of Alzheimer's disease: From genetics to biomarkers. *Hormones*. 2018;18(1):7–15.
148. Chai B, Gao F, Wu R, et al. Vitamin D deficiency as a risk factor for dementia and Alzheimer's disease: An updated meta-analysis. *BMC Neurol*. 2019;19(1):284.
149. Aguilar-Navarro SG, Mimenza-Alvarado AJ, Jiménez-Castillo GA, et al. Association of vitamin D with mild cognitive impairment and Alzheimer's dementia in older Mexican adults. *Rev Investig Clin*. 2019;71(6):381–386.
150. Duchaine CS, Talbot D, Nafti M, et al. Vitamin D status, cognitive decline and incident dementia: The Canadian Study of Health and Aging. *Can J Public Health*. 2020;111(3):312–321.
151. Tang M, Taghibiglou C. The mechanisms of action of curcumin in Alzheimer's Disease. *J Alzheimers Dis*. 2017;58(4):1003-1016.
152. Tellone E, Galtieri A, Russo A, et al. Resveratrol: A focus on several neurodegenerative diseases. *Oxid Med Cell Longev*. 2015;2015:392169.
153. Uddin MS, Hossain MF, Mamun AA, et al. Exploring the multimodal role of phytochemicals in the modulation of cellular signaling pathways to combat age-related neurodegeneration. *Sci Total Environ*. 2020;725:138313.\*\*This article describes neuroprotective properties and molecular mechanisms of phytochemicals in neurodegenerative diseases
154. Kou X, Chen N. Resveratrol as a natural autophagy regulator for prevention and treatment of Alzheimer's Disease. *Nutrients*. 2017;9(9):927.



155. Turner RS, Thomas RG, Craft S, et al. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. *Neurology*. 2015;85(16):1383–1391.
156. Famenini S, Rigali EA, Olivera-Perez HM, et al. Increased intermediate M1-M2 macrophage polarization and improved cognition in mild cognitive impairment patients on omega-3 supplementation. *FASEB J*. 2017;31(1):148–160.
157. Román GC, Jackson RE, Reis J, et al. Extra-virgin olive oil for potential prevention of Alzheimer disease. *Rev Neurol (Paris)*. 2019;175(10):705-723.
158. Sharma A, Kumar Y. Nature's derivative(s) as alternative Anti-Alzheimer's disease treatments. *J Alzheimers Dis Rep*. 2019;3(1):279-297. \*\*This review summarizes therapeutic potential of natural products in prevention and treatment of AD
159. Yang X, Zheng T, Hong H, et al. Neuroprotective effects of Ginkgo biloba extract and Ginkgolide B against oxygen-glucose deprivation/reoxygenation and glucose injury in a new in vitro multicellular network model. *Front Med*. 2018;12(3):307-318.
160. Zhou X, Qi Y, Chen T. Long-term pre-treatment of antioxidant Ginkgo biloba extract EGb-761 attenuates cerebral-ischemia-induced neuronal damage in aged mice. *Biomed Pharmacother*. 2017;85:256-263.
161. Yang G, Wang Y, Sun J, Zhang K, Liu J. Ginkgo Biloba for Mild Cognitive Impairment and Alzheimer's Disease: A systematic review and meta-analysis of randomized controlled trials. *Curr Top Med Chem*. 2016;16(5):520-528.
162. Liu H, Ye M, Guo H. An updated review of randomized clinical trials testing the improvement of cognitive function of Ginkgo biloba extract in healthy people and Alzheimer's patients. *Front Pharmacol*. 2020;10:1688.
163. Yuan QJ, Wang CW, Shi J, et al. Effects of Ginkgo biloba on dementia: An overview of systematic reviews. *J Ethnopharmacol*. 2017;195:1-9.
164. Cassano T, Villani R, Pace L, et al. From cannabis sativa to cannabidiol: Promising therapeutic candidate for the treatment of neurodegenerative Diseases. *Front Pharmacol*. 2020;11:124.

165. Uddin MS, Mamun AA, Sumsuzzman DM, et al. Emerging promise of cannabinoids for the management of pain and associated neuropathological alterations in Alzheimer's disease. *Front Pharmacol.* 2020;11:1097.
166. Choi JG, Kim N, Huh E, et al. White Ginseng protects mouse hippocampal cells against amyloid-beta oligomer toxicity. *Phytother Res.* 2017;31(3):497-506.
167. Chang Y, Huang WJ, Tien LT, et al. Ginsenosides Rg1 and Rb1 enhance glutamate release through activation of protein kinase A in rat cerebrocortical nerve terminals (synaptosomes). *Eur J Pharmacol.* 2008;578(1):28-36.
168. Qian ZM, Ke Y. Huperzine A: Is it an effective disease-modifying drug for Alzheimer's disease? *Front Aging Neurosci.* 2014;19:6:216.
169. Oboh G, Ademiluyi AO, Akinyemi AJ. Inhibition of acetylcholinesterase activities and some pro-oxidant induced lipid peroxidation in rat brain by two varieties of ginger (*Zingiber officinale*). *Exp Toxicol Pathol.* 2012;64(4):315-9.
170. Khan H, Ullah H, Aschner M, et al. Neuroprotective effects of quercetin in Alzheimer's disease. *Biomolecules.* 2019;10(1):59.
171. Shi YC, Pan TM, Liao VH. Monascin from *Monascus*-fermented products reduces oxidative stress and Amyloid- $\beta$  toxicity via DAF-16/FOXO in *Caenorhabditis elegans*. *J Agric Food Chem.* 2016;64(38):7114-7120.
172. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochem Pharmacol.* 2008;75(4):787-809.
173. Yanagisawa D, Taguchi H, Yamamoto A, et al. Curcuminoid binds to amyloid- $\beta$ 1-42 oligomer and fibril. *J Alzheimers Dis.* 2011;24 Suppl 2:33-42.
174. Naoi M, Maruyama W, Shamoto-Nagai M. Type A and B monoamine oxidases distinctly modulate signal transduction pathway and gene expression to regulate brain function and survival of neurons. *J Neural Transm (Vienna).* 2018;125(11):1635-1650.
175. Zhang L, Fang Y, Xu Y, et al. Curcumin improves Amyloid  $\beta$ -Peptide (1-42) induced spatial memory deficits through BDNF-ERK signaling pathway. *PLoS One.* 2015;10(6):e0131525.

176. Ng TP, Chiam PC, Lee T, et al. Curry consumption and cognitive function in the elderly. *Am J Epidemiol.* 2006;164(9):898-906.
177. Ihl R, Tribanek M, Bachinskaya N; GOTADAY Study Group. Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761® in Alzheimer's disease and vascular dementia: results from a randomised controlled trial. *Pharmacopsychiatry.* 2012;45(2):41-6.
178. Savaskan E, Mueller H, Hoerr R, et al. Treatment effects of Ginkgo biloba extract EGb 761® on the spectrum of behavioral and psychological symptoms of dementia: meta-analysis of randomized controlled trials. *Int Psychogeriatr.* 2018;30(3):285-293.
179. Cordero JG, García-Escudero R, Avila J, et al. Benefit of Oleuropein Aglycone for Alzheimer's disease by promoting autophagy. *Oxid Med Cell Longev.* 2018;2018:5010741.
180. De Nicoló S, Tarani L, Ceccanti M, et al. Effects of olive polyphenols administration on nerve growth factor and brain-derived neurotrophic factor in the mouse brain. *Nutrition.* 2013;29(4):681-7.
181. Heo JH, Lee ST, Oh MJ, et al. Improvement of cognitive deficit in Alzheimer's disease patients by long term treatment with Korean red ginseng. *J Ginseng Res.* 2011;35(4):457-61.
182. Qian ZM, Ke Y. Huperzine A: Is it an effective disease-modifying drug for Alzheimer's disease? *Front Aging Neurosci.* 2014;6:216.
183. Naoi M, Wu Y, Shamoto-Nagai M, et al. Mitochondria in neuroprotection by phytochemicals: Bioactive polyphenols modulate mitochondrial apoptosis system, function and structure. *Int J Mol Sci.* 2019;20(10):2451.
184. Lee CL, Kuo TF, Wang JJ, et al. Red mold rice ameliorates impairment of memory and learning ability in intracerebroventricular amyloid beta-infused rat by repressing amyloid beta accumulation. *J Neurosci Res.* 2007;85(14):3171-82.

**Abbreviations:** A $\beta$ , amyloid beta; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; ApoE, apolipoprotein e; ABCA1, ATP-binding cassette transporter G-1; BACE-1,  $\beta$ -site amyloid precursor protein cleaving enzyme-1; BDNF, brain derived neurotrophic factor; CBD, Cannabidiol; COX-2, cyclooxygenase 2; CSF, cerebrospinal fluid; GABA, gamma aminobutyric acid; GDNF, glial cell-derived neurotrophic factor; GSK-3b, glycogen synthase kinase-3b; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LRP1, lipoprotein receptor-related protein 1; MAO, monoamine oxidase; MCI, mild cognitive impairment; NF $\kappa$ B, nuclear factor kappa B; NGF, neural growth factor; NMDA, N-methyl-D-aspartate; NFT, neurofibrillary tangles; PI3K, phosphoinositide 3-kinase; RAGE, receptor for advanced glycation end products; RNS reactive nitrogen species; ROS, reactive oxygen species; Sirt-1, sirtuin 1; THC,  $\Delta$ 9-tetrahydrocannabinol; TNF1 $\alpha$ , tumor necrosis factor alpha; Trk, tropomyosin-related kinase A