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

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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 (Aβ) 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 Aβ in mice hippocampus [29] and was associated with fewer cortical Aβ 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 Aβ40 and Aβ42 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 Aβ 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 Aβ1-42 [24]. However, it did not influence the level of Receptor for advanced glycation end products (RAGE) [30], which facilitates the influx of circulating Aβ 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 Aβ42 decrease, p-tau181, and total-tau increase, or the cortical Aβ accumulation [33]. In agreement, among clinically normal older participants, objectively measured physical activity was not associated with Aβ burden, although greater engagement in physical activity was prospectively associated with slower Aβ-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 Aβ 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) Aβ 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 Aβ deposits in humans [39], might still be protective against Aβ-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 β-amyloid characterizing an AD-like condition in rats [27]. Moreover, continuous aerobic training had the greatest effects on soluble Aβ1-42 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 Aβ-induced cognitive decline, reduced inflammation, decreased level of oxidative stress, and consequently grey matter volume loss.

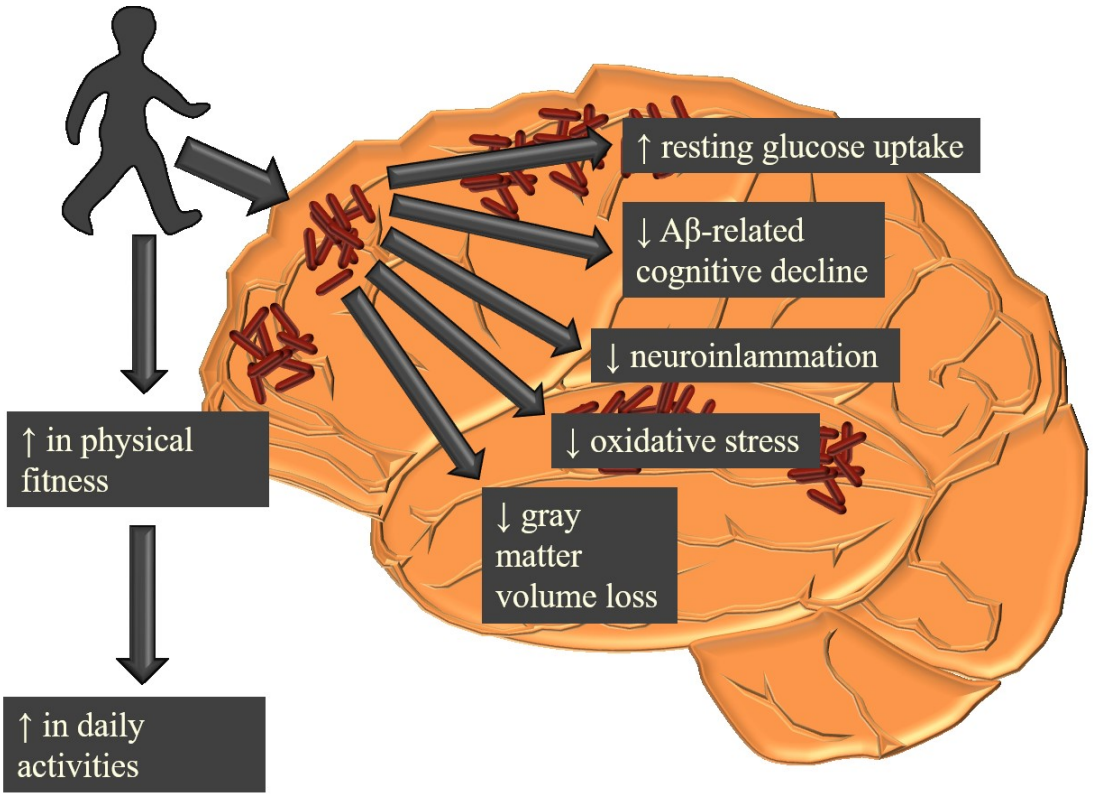

Figure 1. Schematic representation of the effects of increased physical activity and physical fitness on the AD brain.

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 Aβ 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 Aβ-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 Aβ levels [74], and various brain responses related to different acupoints [67]. All of these strategies may alleviate AD symptoms.

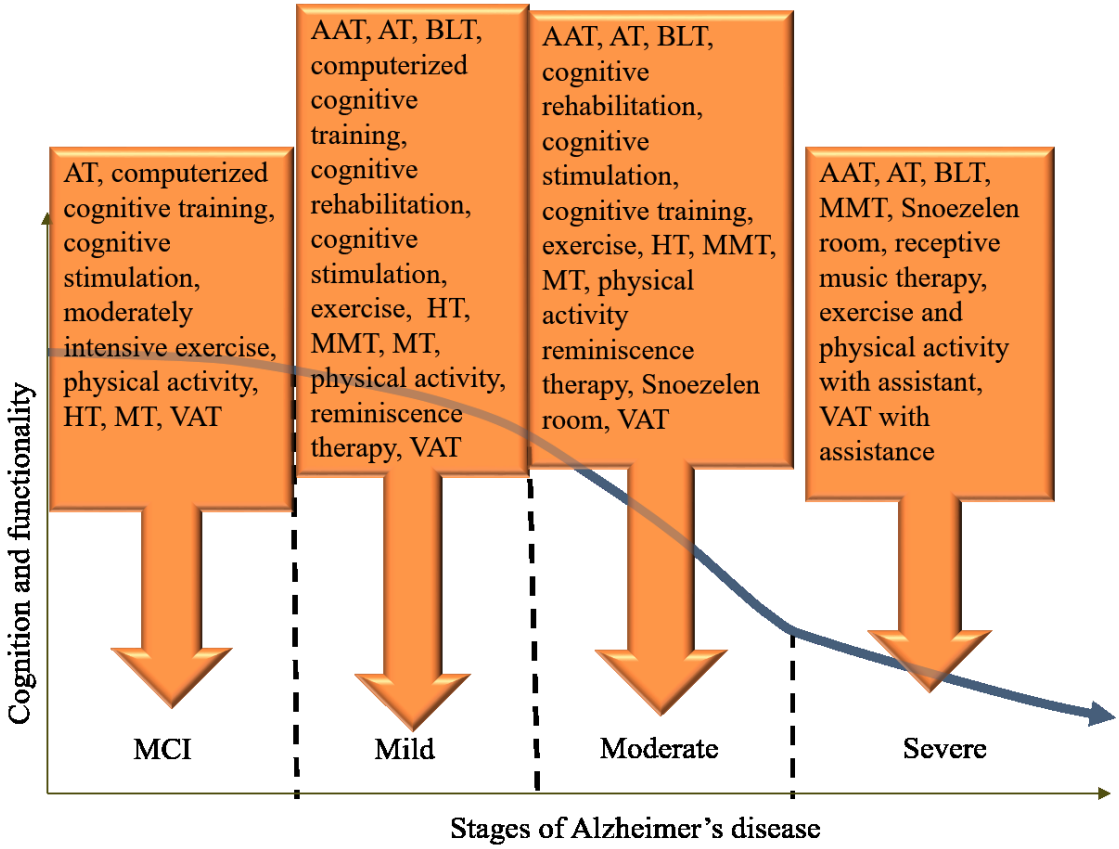

Figure 2. Schematic presentation of the nonpharmacological treatments across stages of Alzheimer's disease. AT= acupuncture therapy; AAT= animal-assisted therapy; BLT= bright light therapy; HT=horticultural therapy; MT=music therapy; VAT= visual art therapy; MCI= mild cognitive impairment; MMT= manual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

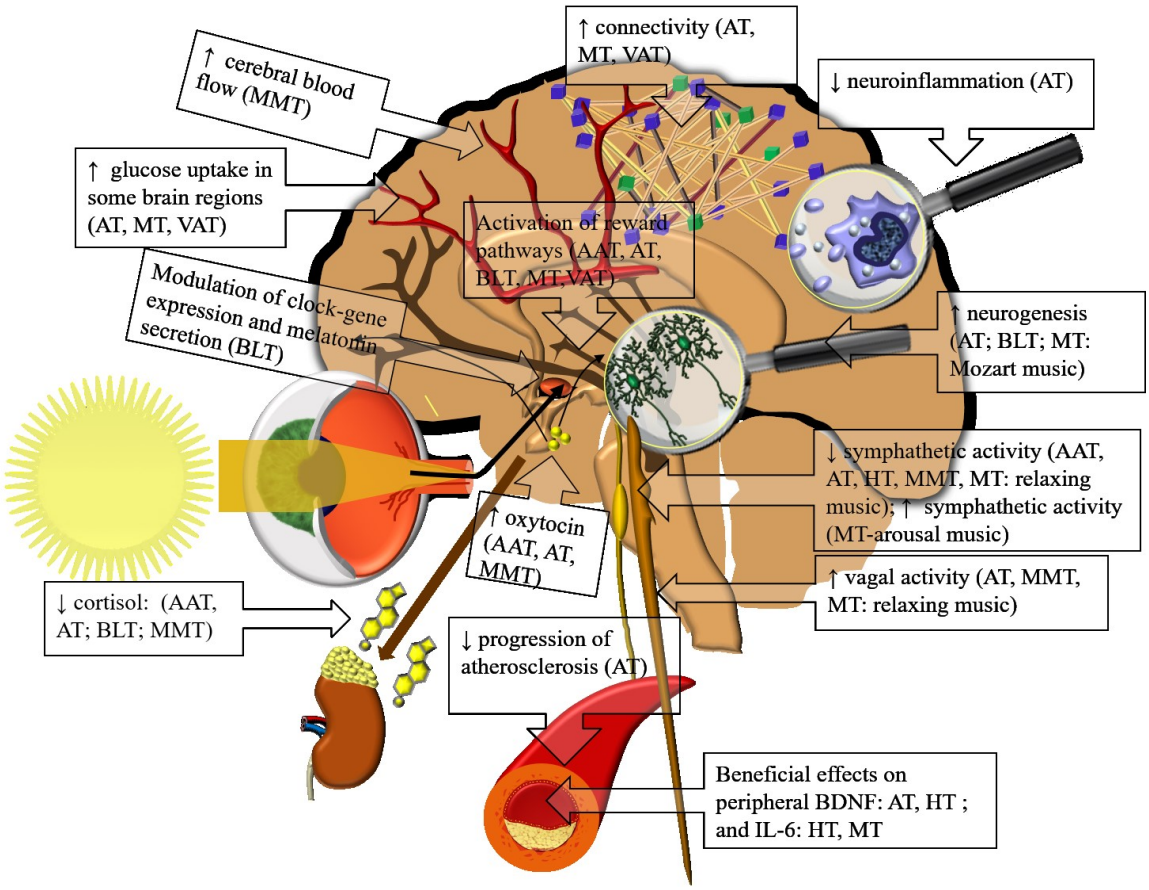

Figure 3. Schematic representation of the distinct physiological effects of different nonpharmacological treatments.

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 Aβ 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^{2+} influx, overexpression of glycogen synthase kinase-3b (GSK-3b) and β- and γ-secretases resulting in generation of protein aggregates such as Aβ and NFT. β-secretase, also known as β-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 Aβ 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 β-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 Aβ 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 Aβ formation and deposition and reduced neuroinflammation, possibly by maintaining homeostasis of Ca^{2+} [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 Aβ 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^{2+} levels, and reducing the over-expression of proinflammatory miRNA [154]. Recent clinical trials reported association of resveratrol supplementation and reduced levels of Aβ-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 (TNF1α), interleukin 6, interleukin

1β (IL-6, IL-1β), nuclear factor kappa B (NFκB) 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 ginkogolic 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 Δ9-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), Aβ 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 Aβ, 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 Aβ 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 Aβ 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 Aβ, 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 Aβ fibril formation and, in that manner, protect neurons from Aβ 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 Aβ 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

Natural therapeutic	**Main active compound(s)**	**Potential mechanism of action (in vitro and in vivo studies)**	**Reported beneficial effect in animals and humans**
Curcuma longa (turmeric)	Curcumin	• 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] • anti-inflammatory properties: suppression of NFκB, IL-6, IL-1B, TNF1A, inhibition of cyclooxygenases (COX-2) and lipoxygenase [151]	• enhanced memory functions and behavioral symptoms in animal models [175] • better cognitive performance (Mini-Mental State Examination, MMSE) in elderly [176]

		• reducing accumulation of toxic aggregations: destabilization of Aβ plaques and NFT [173] • lowering glucose and cholesterol levels [151] • inhibition of AChE and MAO-B activity, increased the expression of glial cell-derived neurotrophic factor (GDNF) [174]	
Mulberries, red wine, tea	Resveratrol	• antioxidant activity: reducing iNOS levels and increasing the expression of antioxidant enzymes [153] • reducing accumulation of toxic Aβ aggregations by activation of sirtuin 1 (Sirt-1), decreasing β-secretase expression, attenuating hyperphosphorylation of tau proteins [153] • antiapoptotic activity: inhibiting B-cell lymphoma xL (Bcl-xL) and Bax, activating Bcl-2, blocking the activation of *c-Jun* N-terminal kinase (JNK), activating phosphoinositide 3-kinase/Akt (PI3K/Akt) and ERK/cyclic AMP-response-binding element [153,175] • anti-inflammatory properties: reducing the over-expression of proinflammatory miRNA, reducing COX-2 levels suppressing the release of NFκB, IL-6, IL-1B, TNF1A [154] • inhibition of mitochondria membrane permeability [153] • increasing Ca^{2+} levels, suppressing MAO-B activity, increasing the expression of GDNF [174]	• reduced levels of Aβ-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).
Ginkgo biloba	Flavonoids (quercetin, kaempferol), terpenoids (ginkgolides), ginkogolic acid	• anti-inflammatory properties: downregulating the expression of proinflammatory molecules (TNF1α, IL-6, IL-1β, prostaglandin E_2) [157,158] • stimulating neuronal autophagy [157,158] • antiapoptotic properties: preventing mitochondrial release of cytochrome c, increasing the expression of Bcl-2-like protein, triggering PI3K/Akt and PKC signaling pathway [153] • suppressing MAO-A activity and triggering expression of BDNF [174]	• lower neuronal damage in multicellular network model [159] and in animals [160], • stronger therapeutic effect memantine when administrated with Ginkgo extracts [161,162] • enhancement in cognitive function and neuropsychiatric symptoms in people with dementia [177,178]
Olea europea	Oleuropein aglycone	• free radical scavengers [157] • downregulating the expression of proinflammatory cytokines TNF1α, IL-6, IL-1β, inhibition of COX-2 [153,157] • stimulating neuronal autophagy via	• improved cognitive performance in transgenic mice [157] • ameliorated depressive symptoms in animal

		5'AMP-activated protein kinase (AMPK)/mTOR pathway [179] • inhibiting toxic protein aggregation [157] • increased expression of BDNF and tropomysin-related kinase A (TrkA) and B (TrkB) [153,180]	models [180]
Cannabis sativa	cannabidiol (CBD), Δ9-tetrahydrocannabinol (THC)	• antioxidant properties: reducing levels of ROS/RNS, iNOS and caspase 3 activity [165] • downregulating the expression of proinflammatory cytokines such as TNF1α, IL-6, IL-1β [158] • stimulating neuronal autophagy and expression of autophagy related genes [158] • reducing levels of Aβ senile plaques and tau hyperphosphorylation through reduction in phosphorylated p-GSK3β [153,165] • inhibiting AChE activity [158]	• improved memory and learning in animal models of AD [164]. • management of chronic pain and associated neuropathology in AD [165]
Panax ginseng	Ginsenosides	• upregulation of choline acetyltransferase, stimulation of GABA-A and glycine receptors, inhibition of NMDA receptors [158,167] • reducing pro-inflammatory mediators such as COX-2, TNF*α*, and inducible nitric oxide synthase (iNOS) [153,167] • degrading the Aβ plaques by activating autophagy [158]	• increased cortex thickness and synaptic density in vivo [167]. • improved thinking and working memory in AD patients [181]
Huperzia serrata	Huperazine A	• scavenging free radicals, activation of antioxidant enzymes [168] • upregulating the NGF [168] • enhanced activity of electron-transport chain, lowering the mitochondrial cytochrome *c* release [182] • antiapoptotic properties: attenuating the increase of caspase-3 activity [153] • inhibiting BACE-1 activity [132]	• attenuated cognitive decline and better neuronal protection against Aβ toxicity in animal models [168]
Zingiber officinale (ginger)	6-gingerol, 6-shogaol	• increasing the NGF levels, inhibiting AChE activity [169] • anti-inflammatory properties: suppressing BACE-1 activity [132] • decreasing the levels of Aβ [169]	• improving learning and memory in rodents [169]
Punica granatum (pomegranate)	Myricetin, quercetin	• antioxidant activity: metal chelation, scavenging free radicals, increasing the activity of antioxidant enzymes [183] • antiapoptotic properties: inhibition of Bax and Bak and induction of Bcl-2 and Bcl-xL [183] • downregulating pro-inflammatory mediators (TNF1α, IL-6, IL-1β, NF-κB, iNOS) [153]	• improved attention, memory and learning in humans [170]

		• inhibiting the formation and destabilizing the structure of Aβ fibrils [153,183] • enhanced activity of electron-transport chain, inhibition of mitochondria membrane permeability, increasing the expression of AMPK [153]	
Red mold rice	Monacolines (ankaflavin, monascin)	• reducing the ROS levels [170] • anti-inflammatory properties: attenuating the activity of BACE-1 [170] • decreasing the levels of ApoE, NFT and accumulated Aβ [171]	• ameliorating the of memory impairment and increasing learning ability in rodents [184]

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, γ-secretase or monoamine oxidase (MAO) activity, metal chelation or prevention of formation and accumulation of Aβ 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.

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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.

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Abbreviations: Aβ, amyloid beta; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; ApoE, apolipoprotein e; ABCA1, ATP-binding cassette transporter G-1; BACE-1, β-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; NFκB, 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, Δ9-tetrahydrocannabinol; TNF1α, tumor necrosis factor alpha; Trk, tropomysin-related kinase A