

Review

New Frontiers in the Prevention, Diagnosis, and Treatment of Alzheimer's Disease

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Abstract. One of the major puzzles in medical research and public health systems worldwide is Alzheimer's disease (AD), reaching nowadays a prevalence near 50 million people. This is a multifactorial brain disorder characterized by progressive cognitive impairment, apathy, and mood and neuropsychiatric disorders. The main risk of AD is aging; a normal biological process associated with a continuum dynamic involving a gradual loss of people's physical capacities, but with a sound experienced view of life. Studies suggest that AD is a break from normal aging with changes in the powerful functional capacities of neurons as well as in the mechanisms of neuronal protection. In this context, an important path has been opened toward AD prevention considering that there are elements of nutrition, daily exercise, avoidance of toxic substances and drugs, an active social life, meditation, and control of stress, to achieve healthy aging. Here, we analyze the involvement of such factors and how to control environmental risk factors for a better quality of life. Prevention as well as innovative screening programs for early detection of the disease using reliable biomarkers are becoming critical to control the disease. In addition, the failure of traditional pharmacological treatments and search for new drugs has stimulated the emergence of nutraceutical compounds in the context of a "multitarget" therapy, as well as mindfulness approaches shown to be effective in the aging, and applied to the control of AD. An integrated approach involving all these preventive factors combined with novel pharmacological approaches should pave the way for the future control of the disease.

Keywords: Alzheimer's disease, biomarkers, early detection, meditation, non-pharmacological treatment, nutraceutical compounds, prevention, Traditional Chinese Medicine, Qigong and Taijiquan

INTRODUCTION

Prevention approaches oriented to wellness are becoming more essential toward a high quality of

life and healthy longevity. In this context, research on disease prevention through a holistic pathway is providing useful conceptual schemes to support medicine based on clinical evidence. Alzheimer's disease (AD) is a powerful example on how emerging views based on nutraceuticals, physical exercise, and lifestyles are paving the road to control this disease as well as several other disorders associated with aging.

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In addition, the failure of traditional pharmacological approaches to treat AD, where several hundred clinical trials on new compounds have been discontinued after negative results, has stimulated intensive research based on functional medicine [1, 2]. AD, as well as other neurodegenerative diseases, are a great concern because of the dramatic increase in life expectancy of the population worldwide. After substantial effort to understand the pathogenesis of the neurodegenerative processes, recent concepts are now shedding light to the main causes of these brain disorders [3]. Strong experimental evidence has been cumulated to support the role of neuroinflammation in the pathogenesis of AD and possibly other neurodegenerative diseases [4]. The neuroimmunomodulation theory postulated in the early 2000s has found good correlation with the clinics, thus providing a real framework to this complex disease process, and the search for therapeutic solutions for AD [5, 6].

Psychological stress has been implicated among the potential mechanisms implicated in neurodegenerative pathology. Given the increase in chronic stress in modern society and nowadays potentiated by confinement due to the COVID-19 pandemic, the links between stress and neurodegeneration is a real concern [7]. Stress plays a major role in various pathological processes associated with neurodegenerative diseases [8]. Symptoms of neurodegenerative disorders such as AD, Parkinson's and Huntington's diseases showed a worsening under stress. This is linked with symptoms of anxiety, depressive behaviors, and even mental disorders [9]. AD is a sporadic disease in which a genetic susceptibility seems to be involved but the major culprits are the unhealthy lifestyles of people. In this context, a series of elements appear to play a major role in preventing this disease. These include diet, daily exercise, social life, mental activity, meditation, the practice of disciplines such as Qigong and Taijiquan originated in Eastern medicine, and other approaches. In this review, we will explore the involvement of these lifestyle components in preventing or mitigating the effects of AD and other neurodegenerative disorders. We will discuss how nutraceuticals and meditation or Qigong practices focused on reducing stress could be involved in therapeutic strategies for neurodegenerative diseases (Fig. 1). These studies are finding an increasing set of evidence to favor the importance of nutraceuticals and daily lifestyle in preventing AD and avoiding the burden of comorbidity associated with different neurodegenerative disorders.

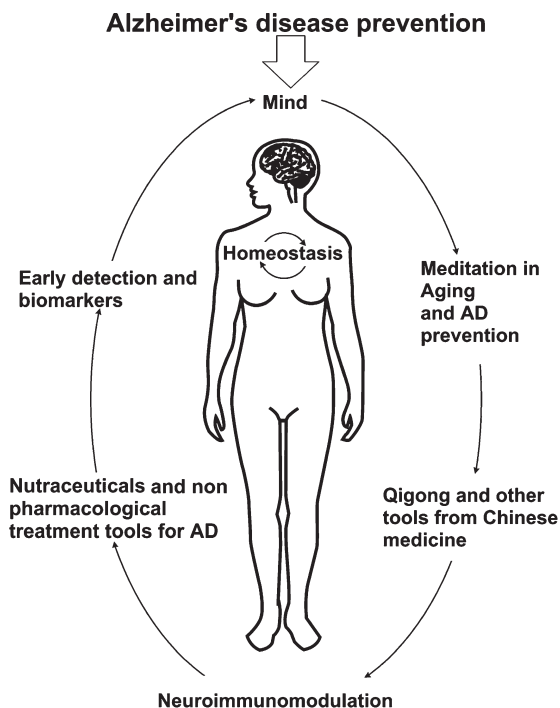


Fig. 1. Representative scheme integrating major elements involved in the prevention of Alzheimer's disease. Within the framework of the theory of neuroimmunomodulation [5, 6], the protective influence of the use of nutraceuticals and therapies typical of Chinese medicine have been evidenced, along with the regular practice of meditation. The elements indicate above, associated with an early detection through evidence-based reliable blood biomarkers, provide us with solid applicable tools for the prevention of Alzheimer's disease.

THE NEED FOR EARLY DIAGNOSIS AND THE ROLE OF BIOMARKERS

An early detection of people with neurodegenerative processes, i.e., at pre-dementia stages, provides highly valuable information in order to proceed with early interventions based on the available therapeutic approaches, but with a significantly larger chance to prevent cognitive impairment and brain deterioration if the patient is diagnosed at the symptomatic stage. In this context, it is an essential tool for AD and related dementias prevention, and therefore biomarkers tests that detect early onset of AD have an enormous preventive role during this disease. Despite the multiple advances in diagnostic technologies for various pathologies, the diagnosis of AD has been largely based on the clinical and neuropsychological study of the patient's cognitive impairment. However, when the process of mental deterioration is already clinically visible, AD is at advanced stages and has already

caused severe damage to the brain. For this reason, the search for reliable, non-invasive, and inexpensive biomarkers for the diagnosis of AD is one of the great edges, with which biomedical research is trying to provide a solution to this disease that affects more than 48 million people around the world, according to official figures from the World Health Organization. Several potential biomarkers for the diagnosis of AD are currently being studied for their ability to indicate the early stages of this disease. Unfortunately, to this day very few biomarkers are at advanced stages of validation for the diagnosis of AD, before the devastating symptoms begin [10]. Some of them are validated and used in AD research [11], while several novel and promising technologies are in the process of validation [12, 13]. It should be noted that no single biomarker can accurately diagnose AD. Although positron emission tomography (PET) imaging of amyloid, as well as the cerebrospinal fluid levels of amyloid- β and tau proteins are used more frequently in clinical studies of AD, thereby increasing diagnostic confidence in AD subjects included, its routine use in the clinic is still premature due to the risk of over diagnosis, increased cost, and/or invasiveness of the evaluation method.

In this context, the search for biomarkers for the diagnosis of AD using less invasive methods is essential. Studies by Maccioni and coworkers have succeeded in developing an innovative detection method for this disease, based on the identification of platelet's tau protein [14–16]. To do this, platelets from AD patients were analyzed, evaluating the presence of tau protein in this cell type. Initial studies with antibodies that recognize total tau protein (tau5) showed the presence of this protein in immunoblots of platelet extracts obtained from peripheral blood in both AD patients and cognitively healthy subjects. In these studies, the presence of tau immunoreactive bands that migrate at much higher molecular weights than expected under denaturing conditions (SDS-PAGE) was striking. These high molecular weight forms of tau, named HMWtau, appear to be oligomeric forms of tau protein, which are found to be increased in AD patients as compared to healthy elderly subjects. Low molecular weight tau species are considered those whose molecular weight is ≤ 70 kDa. On the other hand, HMWtau species are considered to be oligomers of tau between 75 to 240 kDa. These findings indicate that the algorithm derived from the quotient between platelet HMWtau and LMWtau can be used as a biomarker of AD, in addition to being able to track the progress of the disease

[14, 16]. In turn, it has implications for the potential development of biomarkers for other neurodegenerative diseases based on tau [14, 16, 17]. An exploratory study, carried out by Slachevsky et al. (2017), through neuropsychology, imaging, and quantitation of the HMW/LMWtau ratio, confirmed that this ratio is significantly higher in AD patients as compared to the control group of subjects, and that it is associated with specific atrophy of brain regions, such as decreased brain volume in right and middle anterior cingulate gyri, right cerebellum, right thalamus (pulvinar), left frontal cortex and right parahippocampal in patients with AD, and correlation with global measures of cognitive and functional performance in all subjects [15]. In turn, they found an association between the HMW/LMWtau relationship and brain volume in the region of the mesial temporal lobe, cingulate cortex, pulvinar nucleus, frontal cortex, and cerebellum. Our data suggest that peripheral changes in platelet proteins (HMW/LMWtau) are associated with the distribution of neurofibrillary tangles in the cerebral cortex [15]. In turn, recent studies have shown that the presence of tau protein in plasma samples is related to the events that occur at the cerebral level in subjects with AD [18, 19]. In studies conducted by Barthelemy et al. (2020), they demonstrated that measurement of attomolar concentrations (10^{-18} M) of tau isoforms in plasma is feasible, using an enrichment protocol and mass spectrometry, studies that require further clinical validation. Their findings indicate that changes in plasma phosphorylated tau, especially ptau-217, reflect highly specific modifications in the CSF to detect phosphorylation changes in soluble tau protein and amyloidosis [19]. On the other hand, in a recent study, by using our recently generated monoclonal antibody tau-51 [18], it has been established that the electrophoretic pattern of plasma tau protein resembles that obtained with tau protein isolated from platelets. For this reason, this marker evaluates, as in platelets, the proportion of HMWtau and LMWtau. Thus, the HMW/LMWtau ratio was statistically higher in AD patients as compared to cognitively healthy subjects, within the same age group [18].

In the search for new sources of biomarkers for AD, several researchers have focused on the investigation of molecules involved in this constant inflammatory process, which leads to the chronic activation of astrocytes and microglial cells, contributing to the progression of the disease [12, 20]. Studies carried out in the CSF material were focused on the levels of the protein s100B, which is secreted by astrocytes, in the CSF of patients with AD at various stages of the

disease and healthy subjects, finding significantly elevated levels of s100B in patients with mild disease or moderate, but decreases to normal levels in patients in more advanced stages of the disease [21]. On the other hand, elevated serum levels of TNF α and IL-6 have been shown to be associated with an approximately 2-fold increase in Neuropsychiatric Inventory scores and an increased frequency of adverse neuropsychiatric symptoms, regardless of delirium [22]. These studies suggested that acute and chronic systemic inflammation, which is linked to increased serum levels of TNF α , are associated with increased cognitive loss in AD patients [23].

Another major area in the search for biomarkers for AD is neuroimaging. Within this context, these can be divided into three large groups: 1) structural neuroimaging, 2) functional, and 3) molecular imaging [10]. Structural neuroimaging provides information about brain anatomy and volume. Both medial temporal atrophy and hippocampal atrophy have been the most common and reliable structural markers on magnetic resonance imaging (MRI) of progression to AD. The three-dimensional patterns of progression of cerebral atrophy in serial MRI were revealed consistent with the stages of neurofibrillary pathology, evidencing that changes in the antero-medial region of the temporal lobe and the fusiform gyrus occur at least three years before conversion to clinically AD [24]. On the other hand, functional images reveal how well cells are working in various brain regions. In order to measure cerebral glucose metabolism rates as an indicator of neuronal activity, the PET technique has been used to verify that metabolic reductions occur in early preclinical stages, prior to the onset of symptoms by AD [12]. Specifically, regional patterns of hypometabolism have been found in the parietotemporal cortex and in the posterior cingulate with a clinicopathological correlation greater than 85% [25]. Neuroimaging with PET and radiotracers for amyloid provide information on the extent of the load of amyloid plaques and, in turn, the radiotracers for the tau protein provide information on the burden of neurofibrillary tangles at the brain level [26]. This finding is of great importance since tau measurements are more closely linked to the cognitive deterioration of patients [10].

DIETARY APPROACHES TO DEMENTIA PREVENTION

The concepts about the prevention and treatment of AD and related dementias have changed

substantially in recent years. Faced with the failures of the pharmaceutical industry in the search for effective therapies to prevent and eventually stop the progression of dementias and neurodegenerative phenomena, which have focused mainly on the development of immunotherapies that prevent the aggregation and deposit of pathogenic proteins such as tau and amyloid- β ; progress has been made in the study of multimodal therapies based on the management and prevention of cardiovascular risk factors, a healthy lifestyle, and cognitive stimulation. The role of psychosocial and lifestyle factors is related to increased resilience against dementia and these factors are important at early, mid, and late life not only as determinants of brain health but also to general health and wellbeing [27, 28]. In their 2020 report, the Lancet Commission on dementia prevention, intervention, and care concluded that early life education was responsible for a 7% of population attributable factor risk of dementia, i.e., the earliest modifiable risk factor for dementia and the second most important after hearing loss [28].

The importance of the multimodal approach for dementia prevention was demonstrated in the FINGER study [6, 29], which showed how the older adult population at cardiovascular risk could have cognitive benefits with available interventions. In the study, an intervention based on diet, physical exercise, and cognitive training was carried out, recruiting 2,654 subjects who were randomized to control or multimodal therapy and followed up between 2009 and 2011, showing benefits in neuropsychological batteries and serving as a model for similar studies replicated in multiple countries, including the US, South America, and Australia (<http://alz.org/wwfingers>) [30]. In the FINGER study, dietary intervention was based in consumption of whole grains, fruits, vegetables, and oils, while low-fat options were recommended over milk and meat products. Benefits of the Mediterranean diet were suggested by the PREDIMED-NAVARRA randomized trial that followed 522 subjects at high cardiovascular risk and showed better global cognitive performance, measured with Mini-Mental State Examination and Clock Drawing Test, in a mean 6.5 years follow up [31]. Other dietary approaches to prevent dementia include the Dietary Approach to Systolic Hypertension (DASH) diet, which aims to reduce blood pressure, but has also been reported have positive cognitive effects with increased psychomotor speed in sedentary, overweight subjects.

Subjects with a combination of DASH diet and a behavioral weight management program showed greater improvements in executive function, memory, and learning [32], although there has also been reports of no association between dietary patterns and risk of cognitive decline [33]. The combination of Mediterranean diet and DASH diet is known as Mediterranean and DASH Intervention for Neurodegenerative Delay (MIND) diet. This diet was proposed by the Rush Memory and Aging project. The MIND diet increases consumption of berries and green leafy vegetables with 10 brain healthy components and with limited intakes of animal-based and high saturated fat foods in 5 unhealthy components [34]. MIND diet has been reported to reduce incidence of AD [35]. In a 12-year longitudinal cohort study of Australian population DASH but not Mediterranean diet was found to be associated with reduced odds of cognitive impairment [36]. Dietary supplementation has been proposed as a preventive strategy and even as a treatment for AD and related dementias but there is still lack of good quality evidence for food supplements. Omega 3 supplementation may be useful as a therapy for AD only in mild very early cases [37]. Vitamin and mineral supplementation have been reviewed by Cochrane library. In cognitive healthy mid and late life subjects, the only positive evidence is related to long-term use of antioxidant vitamins, i.e., β -carotene, vitamin C, or vitamin E [38], while there was no evidence to support vitamin or mineral supplementation to prevent dementia in people with mild cognitive impairment without nutritional deficiency [39]. Lack of evidence to support use of over the counter supplements has also been described by other authors [40]. Anyhow, the lack of methodologically adequate studies that experimentally evaluate the response to nutritional supplements may largely explain the paucity of positive results; however, new laboratory evidence and controlled studies following the methodologies of the pharmacological industry may contribute to objectively evaluate the effectiveness of these therapies for the prevention and treatment of AD and related dementias.

The mechanisms by which a healthy diet can help prevent cognitive decline are multifaceted and not only related to "classic" mechanisms like cardiovascular health or antioxidant mechanisms. In murine models, a diet rich in salt can increase tau phosphorylation and is associated with cognitive dysfunction [41].

THE EMERGENCE OF NUTRACEUTICALS IN THE PREVENTION OF ALZHEIMER'S DISEASE

As mentioned earlier, the type of diet and particularly nutraceutical compounds and specific formulae are essential elements for AD prevention. One important strategy to prevent AD impairment is based on dietary changes and nutritional supplements, functional foods, and nutraceuticals [42, 43]. Nutraceuticals are chemical constituents of diet that display protective properties against some diseases [2, 44]. These compounds are obtained through rigorous processes of extraction from natural resources and Good Manufacturing Practices (GMP) regulations, and many of them exhibit sound preclinical studies published in high impact medical journals, and double-blind placebo-controlled clinical trials [1].

Nutraceuticals compounds differ structurally, act on different biochemical and metabolic levels, and have shown different types of neuroprotective properties [2, 44]. In the case of AD, they can modify physiopathological processes responsible for neurodegeneration and/or to have pro-cognitive properties [45]. Considering that AD is a multifactorial disease, nutraceuticals offer the advantage of a multitarget approach with different pharmacological actions in the human brain [2]. These targets include, among others, inhibition of specific targets such as acetylcholinesterase, tau protein aggregates, amyloid- β senile plaques, mitochondrial dysfunction, oxidative stress, inflammatory pathways, specific brain receptors (e.g., NMDA), etc. A complete evaluation and metanalysis of most of the nutraceutical compounds already reported to play a possible role in AD prevention is published in the study of Calfo et al., 2020 [2].

Bioactive compounds and nutraceutical formulae include **polyphenols** (curcumin, resveratrol, rosmarinic acid, oleocanthal), **flavonoids** (delphinidin, quercetin, EGCG, luteolin, cyanidin), **carotenoids** (astaxanthin, lutein, crocin), **vitamins** (B6, B9, B12), **Perceptiv®** (N-acetyl cysteine), **AXONA AC-1200®** (caprylic acid), **BrainUp-10®** (*Andean shilajit*, fulvic acid), plant **extracts** (Meganatural-az, aged garlic, *Ginkgo biloba*), and **other natural molecules** (azaphilones, limonoids, huperzine A, S-allyl-L-cysteine, melatonin). These have shown activity at different molecular sites related with the neuropathological changes of AD [1, 2, 42–46]. These nutraceutical family of compounds are

characterized by their properties: antioxidant, anti-inflammatory, anti-depressant, nootropic effect, anti-amyloid activity, anti-cholinesterase, anti-neurotoxic effect, neuritogenesis enhancer, and tau anti-aggregative (prevents tau hyperphosphorylation and promotes tau stabilization) [1, 2, 44, 46]. Properties might be beneficial for the maintenance of a good cognitive performance and represents a great therapeutic action to treat AD and other neurodegenerative diseases.

In recent times, many scientists have given great attention to nutraceuticals for the treatment of AD. These constituents can be obtained directly from diet or found in other natural source such as berries, peppermint, rosemary, olive, garlic, turmeric, apples, grapes, red wine, saffron, onion, celery, green tea, moss (*Huperzia serrata*), fungus (*Aspergillus nidulans*), and medicinal plants (Lemon Balm, Jatamansi, Maca, Ginseng, Moringa) [2, 44]. The above would aid common people to choose better nutraceutical source as prophylactic treatment to combat AD, as they certainly open a solid pathway to benefit a healthy lifestyle.

INTEGRATIVE APPROACHES: MEDITATION FOR HEALTHY AGING AND AD PREVENTION AND THE CONTRIBUTION OF ELIZABETH BLACKBURN

Beyond nutritional aspects described above, and the use of early biomarkers for detection of cognitive decline events, it is worth to look at the support from the mental processing. Thought can modify matter. With work on telomeres, Dr. Elizabeth Blackburn scientifically proved this claim. We, the humans, are the result of the expression of our genes, which are an essential organized matter for life. Thus, under certain environmental conditions, we can modify our genes, and therefore some of their forms of expression. Scientific thoughts, paying a modest tribute to the first Greek philosophers and their successors, is one of the greatest achievements of mankind; it is the most powerful and the safest tool, but at the same time it could turn into a dangerous tool, as the atomic explosions in Hiroshima and Nagasaki of August 6 and 9, 1945. At the other extreme, to wonders that border on the miraculous such as the rescue of premature newborns to the limit, when the same tool is used by members of the same species in such opposite tasks and that leads us to constantly brood on ourselves as

a so extreme and paradoxically ambivalent specie, as pointed out by the Chilean investigator Darío Salas [47]. Perhaps it may serve as an excuse what in the words of Max Scheler in his work "The Place of Man in the Cosmos", he asserts: "We have, then, a scientific anthropology, another philosophical and another theological one, which do not concern themselves with each other" [48]. But we do not have a unitary idea of man.

We mention that in order to understand the constant search for a healthy longevity, mediation provides a powerful tool. Thought, in all its manifestations: artistic, sports, cultural, scientific uses, the nervous system and all its beautiful macro and microscopic structural complexity and delicate functionality. It reaches the no less wonderful anatomy in its double sensitive function and motor, both voluntary and automatic, for its multiple and combined expressions. The genetic information transmitted in a continuous evolutionary process since the appearance of organic compounds on our planet and more recently stored in the nucleus of more complex individuals begins to shed light on its connections with thought and how it can influence it, in its expression. Concrete, at the molecular level, allowing us to approach the profound mystery of the spirit and how this can influence it, in its concrete expression.

One of the most remarkable approaches to the mystery of "spirit" and "life" was made by Dr. Blackburn in the more than great correlation between telomere length and biological age that led her to generate a new research horizon, where she alludes to the influence that factors as subjective as the practice of meditation, exposure to stress, depression, healthy coexistence and others have on them, making them a milestone, not yet fully dimensioned and in the gold standard of biological age measurement. In addition, the ability to voluntarily intervene telomeres can be achieved to shape health through the best use of our mind and thus influence the way of aging to achieve healthy longevity. The use of our mind is a terrain of Western culture in which we differ markedly from the East, in which the practice of meditation is common. Dr. Blackburn participated in an investigation in which she demonstrated a marked and favorable difference in telomere length, in a group of people who underwent the investigation that included a period of meditation, as compared to subjects who did not meditate [49].

This work is transcendent because it could, if we understand its underlying message, prompt us to begin the practice of meditation alongside the already

widespread practice of physical activity, especially in the Baduanjin form of Qigong [50] as a voluntary, self-directed activity. The lifestyle of the elderly changes abruptly when their working life ends and if the person is carried away by the surreptitious social pressures exerted at all levels, they run the risk of falling into a kind of vital involution that will very quickly lead to the term of their lives.

We now know that telomere shortening together with the cumulative expression of aging morbidities, such as Parkinson's disease, AD, some cancerous diseases, cardiovascular diseases, and others, could be postponed by preventive management to achieve life extension by shortening the period of illness or even without illness involving higher quality of life, before dying. Among the preventive activities, the researcher stands out, physical activity, management of toxic or cumulative stress, replacing the attitude of resignation with an attitude of challenge, food, restful sleep, and positive mentality, healthy interpersonal relationships together with an environment reliable and friendly, in addition to the continuous practice of mindfulness. Dr. Blackburn's findings have installed these new players on the science scene: telomeres. These concrete physical structures that can be literally modified by an activity as intangible as meditation, and as a result of its modification, achieve beneficial changes for people and a healthy aging.

Our life has a couple of ingredients that differentiate us from other species: one is culture, widely studied by anthropologists, paleontologists, and sociologists, and the other is a special interrelation with that which transforms us. The human being can, in a promise to himself and by his own decision, putting this knowledge into practice, agree to modify his destiny, assuming in turn the responsibility that this implies. The meditation technique mindfulness [51] has been the subject of countless studies based on modern techniques, which allow visualizing the reflection of the images that the brain projects from the depths of his bone sanctuary. Mindfulness seeks to recover the subject's "full attention" in the present moment through the best use of the will, to direct attention to external and internal stimuli, physical or psychic with serenity, with kindness, excluding prejudices, expectations, or beliefs, allowing the attention to be occupied by the novelty and fresh that in this condition is present, thus remaining in the here and now. Second to second; carefree-to the passage of time. Persistent, volitional practice, no matter how scrawny it may be, will feed back the intention and strengthen the will, entering a virtuous circle through

which it will achieve different states that will make the unique ingredient that differentiates us from other species more evident in them. Physiological sleep, usually nocturnal, is easily recognizable by an external observer, and the sleeper does not realize its dreamlike condition or its various levels of depth. When he opens his eyelids, every morning, he enters another state that we call waking, in which we all believe that we are at the maximum limit, a limit that, apparently, we do not know.

"Mindfulness" demonstrated by EEG and MRI studies in which they share neurophysiological, cerebral loci of the prefrontal cortex as well as metacognition, producing between them some form of mutual feedback. Lucid dreaming is a state in which the subject realizes that he is dreaming while doing so. Similarly, in wakefulness, it is expected that the subject "falls" into sleep while he is with his eyes open, apparently awake. According to Hobson (2009) [52] referring to the concept of consciousness, which he classifies, without defining it, into primary and secondary, he says: "ordinary dreams have characteristics of primary consciousness, where the main components are perception and emotion, unlike secondary consciousness, where self-reflection and metacognition predominate. This distinction between primary and secondary consciousness also occurs in wakefulness, as for example in mental wandering or in automatic behaviors, in which the attention is not in the present experience. In this regard, it is necessary to alert ourselves to the effect that the varied hustle and bustle of the daily routine has on our alleged waking state, captivating our attention to leave it in a state of "automatic pilot" which is counteracted by the practice of mindfulness with all the additional benefits already mentioned. There is increasing evidence that mindfulness can slow down the progress of AD. The modification in the form of presentation of this pathology was also highlighted, which is currently being present in the elderly, but it was reported an increasing number of cases were observed in young people, who should be advised and led toward changes in their way of life to prevent this painful condition.

EVIDENCE-BASED RESEARCH ON CONTRIBUTIONS OF TRADITIONAL CHINESE MEDICINE, ACUPUNCTURE, QIGONG, AND TAIJIQUAN TO HEALTHY AGING, AND PREVENTION OF AD

Traditional Chinese Medicine (TCM) is a complete health system originating from oriental philosophy

and culture, based on ancient theories and methods that has evolved over thousands of years (dating back 5000 years.). The therapeutic approaches utilized by TCM include acupuncture, moxibustion, Chinese Herbal Medicine, Tuina massage, Cupping, Scraping, Dietary therapy, Qigong, and Taijiquan also known as Tai chi.

During the second half of the 20th century, this therapy was introduced in Western countries where it gained great acceptance among users. This TCM was found to be a different medicine, not aggressive, highly preventive, effective and quick, resulting in curative effects, comparative lower costs and reportedly fewer side effects. TCM is considered a holistic medicine since it understands that there are no diseases, but sick people; it takes into consideration not only what happens in the affected organ, but also what happens in the whole organisms; how it manifests itself and how it responds to external influences and environmental stimuli.

The role of TCM in health has started to be widely recognized around the world; with the advancement in medicine and technology, and the quest to better understand the science behind natural medicine, the interests in and acceptance of TCM continues to grow. With the exponential grow of the aging population worldwide, the quality of life and the psychosocial well-being of older adults, especially those with chronic disease, has become of increasing importance. In that context, we are presenting in this review some of the preliminary evidence on the potential correlation of health and TCM. The authors are aware of the limitations of the current evidence-based research on this traditional approach. On the one hand, evidence for TCM remains undefined, and more rigorous evaluation of TCM is still needed [53]. On the other hand, most of the research analyzed has been focused on a single type of treatment such as acupuncture and herbs, and some on Qigong and tuina, and very little has been done to date focused on the whole system of TCM. Many TCM practitioners claim that focusing on one treatment does not recognize the integrity of the whole Chinese medicine paradigm. To date, there are more than 1,200 trials related to TCM, but still some challenges in evidence to support decisions in TCM clinical practice [54]. Nevertheless, since the World Health Organization officially promoted traditional medicine, there has been increasing interest among several countries in integrating traditional medicine into a national health care system. Currently, the WHO Collaborating Centre for traditional medicine,

is working with WHO on the collection and analysis of data, education, and workforce to provide support and technical guidance on the implementation of this complementary approach (<https://www.who.int/western-pacific/news/feature-stories/detail/developing-evidence-based-traditional-medicine-classical-and-modern>). Additionally, federal funders such as the National Center of Complementary and Alternative Medicine at the NIH, The Cochrane Collaboration, and other organizations are supporting more quality-based TCM studies, and we expect evidence-based TCM to grow and become a reality.

Chinese Herbal Medicine (CHM)

CHM are mainly plant based, but some formulations may include minerals or animal products. They can be formulated as powders, pastes, lotions, or tablets, depending on the herb and its intended use. Different herbs have different properties and can help balance specific parts of the body. One of the most emblematic contributions in herbal medicine is the discovery made by Youyou Tu, a female scientist of the China Academy of Traditional Chinese Medicine in Beijing, who was awarded the 2015 Nobel Prize for Physiology or Medicine for the discovery of artemisinin. The main contribution, which led to the award for Youyou Tu, was the 'discovery of artemisinin, a drug which can significantly reduce the mortality rate of patients suffering from malaria, in addition to its unprecedented therapeutic effect in severe malaria treatment.' A speech, "Discovery of artemisinin – a gift from Traditional Chinese Medicine to the world" was delivered by Tu at the Karolinska Institute on December 7, 2015, in which she introduced the discovery process of artemisinin and how it was inspired by TCM. The discovery process was a result of the combination of TCM and modern Western medicine in matching scientific analysis with historical treatises containing TCM treatments and observations on therapeutic uses. Tu Youyou's award provides us, especially researchers of TCM, an opportune time to further rethink the value of TCM and the societal, cultural, and ethical issues for TCM, to make the best use of it for continuing improvements in human health care [55]

Alzheimer's disease

CHM has been a valuable source of medicines for centuries and research has burgeoned in recent years to understand the scientific basis for their use. Modern

pharmacological studies have confirmed the therapeutic effects of many active components derived from CHM, due to the advantages of multi-target effects and fewer side effects. CHM is more appropriate for long-term use in AD [56]. Some CHMs (e.g., Ginkgo biloba extract and huperzine A from *Huperzia serrata*) show pharmacological activities relevant to AD, and promising effects on cognitive functions in clinical trials. Other CHMs show effects relevant to psychological symptoms of dementia (e.g., *Crocus sativus*) [57].

Acupuncture

Acupuncture is a technique of insertion and manipulation of fine needles in specific points on the body to achieve therapeutic purposes. There have been extensive studies conducted on acupuncture, especially for back and neck pain, osteoarthritis/knee pain, and headache. However, researchers are only beginning to understand whether acupuncture can be helpful for various health conditions. In recent decades, its practice has gained popularity around the world. With increasing evidence of its clinical efficacy, acupuncture is now a widely practiced treatment modality in complementary and integrative medicine [58]. Acupuncture has been practiced in China for more than 3,000 years to treat a wide variety of conditions including cardiovascular and psychiatric diseases, acute and chronic pain and reported to be beneficial in treating cognitive impairment of AD. A meta-analysis study showed better effectiveness of acupuncture alone compared to conventional Western medicines for the treatment of AD [59]. Also, in a randomized controlled trial in patients with mild to moderate AD, acupuncture was proven to be safe, well tolerated, and effective in improving cognitive function and global clinical status [60]. Several other reviews evaluated the efficacy and safety of acupuncture in the aspect of anti-dementia, suggesting that acupuncture intervention could be an efficient and feasible approach to the treatment of AD patients [61].

Qigong and Taijiquan

Qigong and Taijiquan (Tai Chi) are centuries-old, related mind and body practices. They involve certain postures and gentle movements with mental focus, breathing, and relaxation. The movements can be adapted or practiced while walking, standing, or sitting. In contrast to Qigong, Taijiquan movements, if

practiced quickly, can be a form of combat or self-defense.

Qigong is one essential elements of traditional Chinese culture and is an important branch of TCM, with a history dating back thousands of years. It is still used today to prevent diseases and known to treat illness and is drawing increasing attention from scientists and practitioners of modern medicine. Qigong could be considered the first therapy or first treatment to be indicated to patients in TCM. It can be safety undertaken by all age groups and levels of ability and it has remarkable effects on general health and stamina, if practiced regularly, to reduce signs of aging. An appropriate definition for Qigong would be: "Qigong is the skill of body-mind exercise that integrates three adjustments of body, breath and mind into one" [62].

Health qigong

Health Qigong is a standardized Qigong modality, where traditional routines were improved, without losing their therapeutic effect, to make them easier to learn in order to reach a greater number of people. In 2003, the Chinese Health Qigong Association began to perform evidence-based studies for validating Qigong routines. Later in 2012, the International Health Qigong Federation was created to promote Health Qigong in the world. Based on extensive investigation, they compiled and standardized nine routines, these are called: Ba Duan Jin (8 Pieces of Brocade), Wu Qin Xi (5 Animal Play), Yi Jin Jing (Muscle/Tendon Classics), Liu Zi Jue (6 Syllable Formula), Ma Wang Dui Dao Yin Shu (Mawangdui Daoyin Exercises), Shi Er Duan Jin (12 Routine Sitting), Taiji Yangsheng Zhang (Taiji Stick Qigong), Daoyin Yangsheng Gong Shi Er Fa (12 Movement Preserve Health), and Da Wu (The Great Dance).

Taijiquan

Taijiquan is part of Wushu (Chinese Martial Arts) and is definitively less ancient in origin than Qigong. It consists of various techniques established on the basis of the rudimentary premise of yin-yang (as represented by Tai Ji) that gives rise to mind-driven interactive combative actions or exercise movements). Taijiquan has traditionally been practiced for multiple purposes, including self-defense, improving health, well-being and fitness enhancement. As traditional physical activities, it is one of the most popular activities practiced by older Chinese adults and people around the world [63].

Several clinical trials have evaluated the effects of Taijiquan and Qigong in people with various health conditions. Research findings suggest that practicing Taijiquan may improve balance and stability in older people and those with Parkinson's disease, reduce pain from knee osteoarthritis, help people cope with fibromyalgia and back pain, and promote quality of life and mood in people with heart failure and cancer. There's been less research on the effects of Qigong, but some studies suggest it may reduce chronic neck pain (although results are mixed) and pain from fibromyalgia. Qigong also may help to improve general quality of life. Both techniques may offer psychological benefits, such as reducing anxiety. However, differences in how the research on anxiety was conducted make it difficult to draw firm conclusions about this.

Qigong and Taijiquan in AD and aging

A range of research suggests that exercise helps reduce depression and anxiety; however, the role of Taijiquan and Qigong for these and other mental health problems is less clear. Some evidence has started to grow in the last years on the effect of these traditional techniques on boosting brain function and reasoning in older adults, and the implications for AD and aging. In a review of health benefits of Qigong and Taijiquan, which analyzed more than 70 articles from randomized controlled trials, research has demonstrated consistent significant results for a number of health benefits, among which the following stand out: bone density, cardiopulmonary effects, quality of life, physical function, physiological symptoms, immune functions, falls, and self-efficacy [64]. Although the wide variation in population and inconsistency in measurement tools point out the need to improve theoretical frameworks for study design and more standardized tools and protocols, the mounting evidence for health benefits and progress in research methodology will give Taijiquan and Qigong a priority role in the emerging integrative medicine systems and prevention-based interventions. Farhang et al. [65] showed that mind body interventions such as Taijiquan improve cognitive functions and functioning in older adults with mild cognitive impairment; however, they also mentioned that small samples, lack of active control groups, heterogeneity of outcome measures, and absence of long term follow up, requires further high quality evidence to determine cost effectiveness of this approach [65]. In other two studies, Breath Qigong demonstrated to improve

recognition in seniors with vascular cognitive impairment [64] and increase grey matter volume in older adults [66]. This finding, although still preliminary, demonstrates the potential of Taijiquan and Baduanjin in preventing cognitive decline. Another review of clinical trials of Taijiquan and Qigong in older adults, including 36 research reports with a total of 3,799 participants, showed that these techniques may help older adults improve physical function and reduce blood pressure, fall risk, depression, and anxiety [67]. Randomized controlled trials examining effects of mind-body exercise on cognitive performance in older adults proved those interventions to be safe and effective, although authors made clear that further research is still needed for conclusive statements [68]. Another work performed a systematic review on four literature databases (Pubmed, Cochrane library, Embase, and Sinomed) up to 2019; the authors found that compared with no specific exercise, mind-body interventions enhances memory in older adults [69]. Supporting additional evidence, a meta-analysis (23 studies, 2,533 participants) evaluating the effect of Taijiquan on cognitive function in older adults, showed promising results [70].

Challenges claimed by most researchers on meta-analysis, include the need for larger, more robust trials with longer follow up period and standardized neuropsychological outcome measures before drawing definite conclusions [71]. The improvement on the current methodological problems will not only help to assess potential application of these techniques in AD but also in general preventive and rehabilitation medicine [71].

The recent pandemic has the potential to cause significant physical and mental damage in older adults. In this context, Qigong could play a role in the prevention, treatment, and rehabilitation of respiratory infections, such as COVID-19. Potential mechanisms of action include stress reduction, emotion regulation, strengthening of respiratory muscles, reduction of inflammation, and enhanced immune function. Three forms of Qigong (abdominal breathing, Ba Duan Jin, and Liu Zi Jue), all of which are gentle, smooth, and simple to practice for the elderly, are recommended in this context [72]. The Biochemist Elizabeth Blackburn won the Nobel Prize in Medicine for her discovery of telomerase, an enzyme that helps cells stay alive and that is related to the biological age of the person. Several studies have suggested that mind-body practices such as Qigong and Taijiquan can help improve telomerase activity [73, 74].

CONCLUSIONS

There are genetic factors that are determinants of functional losses during aging, and an important part is played by epigenetic factors. Thus, the action of genes that confer susceptibility to AD can be mitigated with healthy lifestyle, physical exercise, balanced nutrition, avoiding molecules harmful to health and drugs, as well social life and practicing active aging during the life cycle. Prolonged confinement may increase the risk of increasing cognitive decline in the elderly.

Prevention is crucial considering that there is still no cure for dementia. Approaches are: 1) Molecules that control tau oligomerization, and in particular the use of nutraceuticals. Nutraceuticals are “multi-target” therapies, as they target different targets in the brain, important because AD is a multifactorial disease. 2) Meditation, a highly recommended tool for older adults, slowed telomeric shortening, demonstrating an effective, non-invasive, and non-toxic technique in controlling aging, contributing to reducing the risks of AD. 3) Studies show that Taijiquan (Tai chi) and Chi Kung or Qigong slows down aging and promotes healthy longevity, thereby reducing the probability of dementia (Fig. 1). They produce specific functional and structural changes in the brain demonstrated by nuclear magnetic resonance; modifications that are accompanied by ontological changes. 4) It is critical to reverse the sedentary lifestyle close to 90% among the elderly, where, as mentioned above, moderate aerobic exercise and its practice becomes a true obligation, given its proven action at the telomeres. Our own data suggest that AD is a clear break with normal aging. Understanding this process requires a systems biology-based approach.

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