

Review

Exploring the Efficacy of Acupuncture in Alzheimer's Disease: A Narrative Review.

Explorando a Eficácia da Acupuntura na Doença de Alzheimer: Uma Revisão Narrativa.

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Abstract: Alzheimer's disease is a progressive neurodegenerative disorder with limited treatment options. Acupuncture, a traditional Chinese medicine technique, has emerged as a potential complementary therapy for Alzheimer's disease. By searching major databases, this narrative review analyses the current state of evidence of acupuncture for Alzheimer's disease management. Preclinical studies suggest that acupuncture may improve cognitive function by promoting neurogenesis and reducing neuroinflammation, while human studies provide some evidence for acupuncture's benefits in cognitive function. Acupuncture may also address Alzheimer's disease-related comorbidities like depression, anxiety, and pain. However, high-quality clinical trials are limited. While preliminary evidence suggests acupuncture's potential for Alzheimer's disease, further research, including larger, well-designed randomized controlled trials, is necessary to definitively establish its efficacy, optimize treatment protocols, and elucidate its mechanisms of action. Acupuncture may offer a valuable complementary therapy for Alzheimer's disease, improving patients' quality of life.

Keywords: Acupuncture; Traditional Chinese Medicine; Alzheimer's disease; Dementia; Neurodegenerative Diseases.

Resumo: A doença de Alzheimer é uma doença neurodegenerativa progressiva com opções de tratamento limitadas. A acupuntura, uma técnica da medicina tradicional chinesa, surgiu como uma potencial terapia complementar para a doença de Alzheimer. Ao pesquisar as principais bases de dados, esta revisão narrativa analisa o estado atual da evidência da acupuntura para o tratamento da doença de Alzheimer.

Estudos pré-clínicos sugerem que a acupuntura pode melhorar a função cognitiva, promovendo a neurogênese e reduzindo a neuroinflamação, enquanto estudos em humanos fornecem algumas evidências dos benefícios da acupuntura na função cognitiva. A acupuntura também pode tratar comorbidades relacionadas à doença de Alzheimer, como depressão, ansiedade e dor. No entanto, os ensaios clínicos de alta qualidade são limitados. Embora evidências preliminares sugiram o potencial da acupuntura para a doença de Alzheimer, mais investigação, incluindo ensaios clínicos randomizados maiores e bem desenhados, é necessária para estabelecer definitivamente a sua eficácia, otimizar protocolos de tratamento e elucidar os seus mecanismos de ação. A acupuntura pode oferecer uma valiosa opção complementar para o tratamento da doença de Alzheimer, melhorando a qualidade de vida dos pacientes.

Palavras-chave: Acupuntura; Medicina Tradicional Chinesa; doença de Alzheimer; Demência; Doenças Neurodegenerativas.

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1. Introduction

The population ageing has been advancing over the past decades globally. The United Nations ¹ estimates that the world population will consist of approximately 2.1 billion elderly individuals by 2050. The aging transition is accompanied by an increase in the prevalence of neurodegenerative diseases, with dementia being the most observed, and among them, Alzheimer's disease being the most prevalent, representing between 60 to 70% of cases ². This has been corroborated by post-mortem studies, where it was observed that between 50 and 70% of dementia cases were of this type ^{3,4}.

Alzheimer's disease is a chronic degenerative disorder of the central nervous system marked by progressive cognitive decline. It represents a high cost to public health ⁵, in addition to the familial and social cost, due to its slow progression and high impact on quality of life ^{6,7}. Traditional pharmacological therapy includes various drugs that lack effectiveness to a certain degree ^{5,8,9}. Therefore, the search for other treatment modalities is an important part of caring for these patients, aiming to provide a better quality of life ¹⁰⁻¹³.

Based on philosophical principles and careful observations of both nature and the human body, traditional Chinese medicine has its roots deeply embedded in a rich history that spans millennia ¹⁴⁻¹⁸. Acupuncture is a traditional Chinese medicine therapeutic technique based on the stimulation with needles on specific catalogued points, validated by a long history of use among Eastern societies ¹⁹⁻²². In traditional Chinese medicine, neurodegenerative diseases are considered brain diseases. From this perspective, acupuncture has been used as a therapy for various neurodegenerative diseases, including Alzheimer's disease ^{23,24}.

Therefore, by searching major databases, this article aims to analyse the efficiency and effectiveness of acupuncture application in different aspects of Alzheimer's disease through a literature review.

2. Acupuncture for Alzheimer's disease

According to Traditional Chinese Medicine, a deficiency in the "sea of marrow" (which corresponds to the brain) and apraxia are the primary causes of Alzheimer's disease ²⁵. Throughout history, acupuncture has been utilized for both the prevention and treatment of Alzheimer's disease. It works by unblocking meridians, enhancing the heart and *Yang Qi* (which corresponds to the functional capacity of the body's systems), nourishing the liver and kidneys, calming the mind, and replenishing the marrow. These effects collectively contribute to improved cognitive function and a better quality of daily life ^{26,27}.

Modern medical treatment for Alzheimer's disease primarily focuses on symptomatic relief using cholinesterase inhibitors like galantamine, rivastigmine, and donepezil for mild to moderate severity and memantine, an N-methyl-D-aspartate (NMDA) antagonist, for moderate to high severity ²⁸.

While these medications can enhance cognitive function and temporarily slow disease progression, Alzheimer's disease has a prolonged course, and long-term use of these drugs often leads to significant adverse effects ^{28,29}.

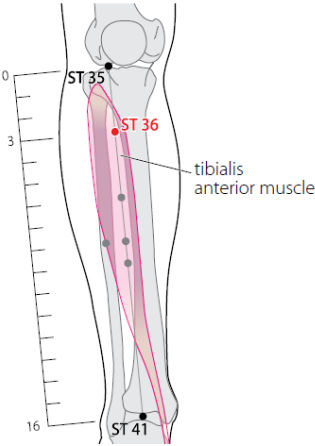
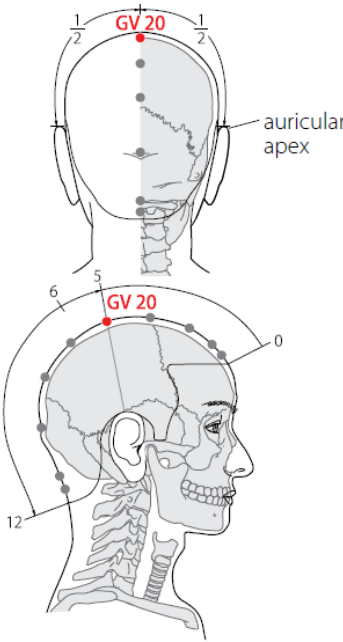
2.1. Animal studies

One of the most plausible theories about the mechanism of action of acupuncture is that it induces neurogenesis in the adult brain ³⁰. Studies show that acupuncture has proven to be effective in the birth of new stem cells, stem cells, and neural/glial differentiation ^{30,31}. In other studies, ^{32,33} aiming to explain the mechanism of action of acupuncture, it was noted that it reduces the activity of acetylcholinesterase and acetylcholine transferase in the neocortex and hippocampus of rats. It is then suggested that acupuncture can mitigate memory and cognition impairments, restoring cholinergic neurochemical abnormalities.

Furthermore, the study by Jiang, Ding ³⁴ demonstrated that electroacupuncture treatment effectively inhibited the inflammatory response in the hippocampus of an animal model of Alzheimer's disease. According to the study, the possible mechanism behind this effect involves the reduction of IL- β and NLRP3 inflammasome-related protein expression.

The main stimulation points, according to Nam, Ahn ³⁵, whether through electroacupuncture or manual acupuncture, are ST36, GV20, PC6, HT7, GV26, CV17, CV12, CV6, SP10, LI11, TE5, GB30, GV16, GV8, CV4, CV6, and CV24. Among these points, the most studied are ST36 and GV20 (Table 1).

Table 1. ST36 and GV20 localization according to the World Health Organization ³⁶.

Point	Localization
<div>ST36 Zusanli</div> <div>足三里</div>	<div>On the anterior aspect of the leg, on the line connecting ST35 with ST41, 3 B-cun inferior to ST35.</div> <div>Note: ST36 is located on the tibialis anterior muscle.</div> <div></div>
<div>GV20</div> <div>Baihui</div> <div>百會</div> <div>(会)</div>	<div>On the head, 5 B-cun superior to the anterior hairline, on the anterior median line.</div> <div>Note 1: GV20 is located in the depression 1 B-cun anterior to the midpoint of the line from the anterior hairline to the posterior hairline.</div> <div>Note 2: When the ears are folded, GV20 is located at the midpoint of the connecting line between the auricular apices.</div> <div></div>

The ST36 and GV20 points have been shown to induce adult neurogenesis in the sub-ventricular zone and the dentate gyrus of the brain in experimental animals (rats) ³⁰. Specifically, electroacupuncture can be applied using a continuous wave, at a low frequency of 2 Hz for ST36 and 4 Hz for GV20, with low pulse width. However, some studies suggest

using electroacupuncture in a dense-disperse wave of 1-20 Hz or 5-20 Hz, which also yields good results ^{37,38}.

Also, according to the study of Dong Lin, Wu ³⁹, stimulation of the ST36 point can activate Brain-Derived Neurotrophic Factor (BDNF) in rats with telomerase deficiency (a pattern shown in Alzheimer’s and Parkinson’s), thereby improving signalling pathways. The study suggests that electroacupuncture on ST36 provides neuroprotective and neuroregenerative effects.

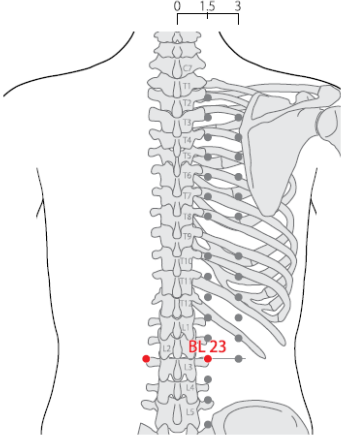
In another study ⁴⁰, manual acupuncture stimulation on ST36 measured by positron emission tomography revealed elevated glucose metabolism in the left olfactory cortex and bilateral amygdaloid bodies in the acupuncture group compared to that in a sham group in a rat model of Alzheimer’s disease. Accordingly, manual acupuncture at ST36 may have specific effects on regional brain activation. The regions activated were centred in the limbic system, which is involved in emotion, sensation, and memory; therefore, acupuncture at ST36 may improve emotional processing and help patients get over fear or pain.

According to Du, Liu ²⁵ the GV20 point is related to the brain and spinal cord. Electroacupuncture at GV20 has been shown to significantly enhance the expression levels of mature BDNF and proBDNF in mice. Additionally, an upregulation of phosphorylated tropomyosin receptor kinase B expression levels and a decrease in p75 neurotrophin receptor expression were observed. This study highlights the possible effects of electroacupuncture at GV20 in addressing cognitive impairment ⁴¹. In another study ⁴², electroacupuncture at the GV20 acupuncture point significantly enhanced learning and memory in behavioural tests, upregulated N-Acetylaspartate (NAA), glutamate (Glu) and myoinositol (mI) metabolism, increased the number of surviving neurons in the hippocampus, and promoted the expression of BDNF and its receptor TrkB in mice.

However, Du, Liu ²⁵ suggest using another acupuncture point not considered by Nam, Ahn ³⁵.

The BL23 point (Table 2) is related to the Kidney essence and marrow, the origin of the congenital constitution. It strengthens the Kidney, drains the *Du Mai* (Governing Vessel - GV) meridian, and regulates the mind and state of consciousness ²⁵.

Table 2. BL23 localization according to the World Health Organization ³⁶.

Point	Localization
BL23 Shenshu 腎俞 (俞)	In the lumbar region, at the same level as the inferior border of the spinous process of the second lumbar vertebra (L2), 1.5 B-cun lateral to the posterior median line. <div></div>

The combination of *Baihui* and B23 strengthens the Kidney essence and restores intelligence according to traditional Chinese medicine. In the study conducted by these authors, the simulation of these points was made by moxibustion rather than acupuncture. The experiment was conducted on rats divided into four groups: control, model, moxibustion, and pre-moxibustion. The results indicated that early moxibustion at *Baihui* and

Shenshu (BL23) can reduce cell apoptosis in the hippocampus and improve learning and memory abilities in Alzheimer's disease.

2.2. Human studies

According to Leung, Yip ⁴³, studies conducted on animals have proven to have more consistent results than those conducted on humans.

Acupuncture has been used to treat cognitive impairment in humans. However, high-quality evidence is lacking, as stated by the authors. The limited number of published human studies and the inconsistent results of the three human studies included in their review highlight this gap.

However, a more recent study ⁴⁴, reported that acupuncture-related treatments effectively improve cognitive function with a treatment duration of at least 6 weeks, while improvements in self-care ability begin to appear after 12 weeks of treatment. Additionally, an increase in muscle strength was confirmed. Therefore, acupuncture-related treatments, particularly non-invasive ones such as moxibustion, have few complications and high safety, potentially offering patients and caregivers a variety of options and valuable clinical care guidelines for reference.

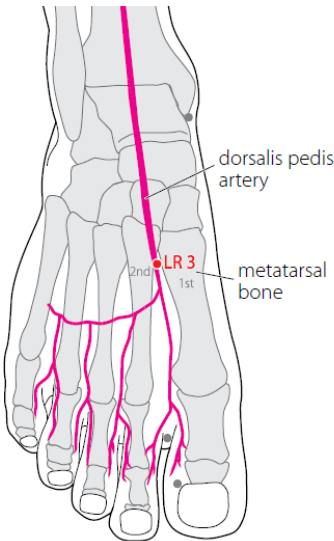
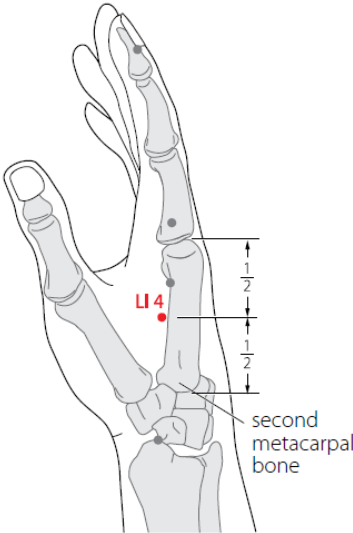
In fact, the study of Zheng, Su ⁴⁵ aimed to examine the effect of acupuncture on functional connectivity in Alzheimer's disease by using resting-state functional magnetic resonance imaging. Compared to the pre-acupuncture phase, various regions exhibited altered ALFF (Amplitude of Low-Frequency Fluctuations) in Alzheimer's disease patients following acupuncture. Furthermore, acupuncture led to enhanced functional connectivity between the hippocampus and the precentral gyrus. As well, strong correlations were observed between functional activity, connectivity, and clinical performance in these patients. This study provided confirmation that acupuncture, specifically targeting *Tai Chong* (LR3) and *He Gu* (LI4), can effectively modulate the functional activity and connectivity of specific regions associated with cognition in Alzheimer's disease patients.

In Traditional Chinese Medicine, acupuncture at LR3 and LI4 (Table 3) is believed to enhance the circulation of *Qi* and blood throughout the body, thereby improving the nourishment and blood supply to the brain ⁴⁶. These effects are initially observed in the Default Mode Network (DMN) regions, which serve as central hubs in the brain's overall network ⁴⁷.

However other acupuncture methodologies were also used to activate brain areas related to memory and learning.

In a study by Guo, Shi ⁴⁸, it was found that electroacupuncture stimulation at the acupuncture point *Jingming* (BL1) activated the hippocampus and hypothalamus in individuals with senile dementia, mostly focusing on Alzheimer's disease. Similarly, Zhou and Jin ⁴⁹ employed electroacupuncture at acupuncture points *Shenmen* (HT7), *Zusanli* (ST36), *Fenglong* (ST40), and *Taixi* (KI3). Their findings revealed numerous activations in response to electroacupuncture, including the hippocampus, insula, and cerebellum, as well as various regions in the temporal and parietal lobes.

Table 3. Liv3 and LI4 localization according to the World Health Organization ³⁶.

Point	Localization
<div><div>LR3</div><div>Taichong</div><div>太衝</div><div>(冲)</div></div>	<div><div><div>On the dorsum of the foot, between the first and second metatarsal bones, in the depression distal to the junction of the bases of the two bones, over the dorsalis pedis artery.</div><div>Note: LR3 can be felt in the depression when moving proximally from Lr2 in the gap between the first and second metatarsal bones towards the base of two metatarsal bones.</div></div><div></div></div>
<div><div>LI4</div><div>He Gu</div><div>合谷</div></div>	<div><div><div>On the dorsum of the hand, radial to the midpoint of the second metacarpal bone.</div><div></div></div></div>

Employing an association rule analysis data mining technique, Wang, Wu 50 found that the core combination of acupuncture points for the treatment of Alzheimer's disease in literature is SP6, BL10 and (Table 4). The authors suggest that this combination of acupuncture points could potentially serve as the main acupuncture treatment strategy for Alzheimer's disease patients in the future.

Acupuncture treatment at HT7 (*Shenmen*) has been clinically applied to address cognitive impairment and sleep disturbances ^{51,52}. In a rat model of Alzheimer's disease, HT7 stimulation led to enhancements in cognitive function and increased cortical and hippocampal glucose metabolism compared to untreated Alzheimer's disease rats ⁵³. Moreover, the HT7-treated Alzheimer's disease rats exhibited a reduced total reaction time in the Y maze test compared to untreated counterparts. Therefore, manual acupuncture at HT7 seems to exert specific effects on cerebral glucose metabolism and regional brain activation in rodent models of Alzheimer's disease.

As for SP6, stimulation of this acupuncture point resulted in dense labelling in brain areas such as the CA1-3 regions of the hippocampus, suprachiasmatic nucleus, dorsal endopiriform cortex, piriform cortex, and bed nucleus of the stria terminalis ⁵⁴, which has implications in Alzheimer's disease.

Table 4. SP6, HT7 and BL10 localization according to the World Health Organization ³⁶.

Point	Localization	
<div>SP6</div> <div>Sanyinjiao</div> <div>三陰(阴)交</div>	<div>On the tibial aspect of the leg, posterior to the medial border of the tibia, 3 B-cun superior to the prominence of the medial malleolus.</div> <div>Note: 1 B-cun superior to KI8.</div>	
<div>HT7</div> <div>Shenmen</div> <div>神(神)門</div> <div>(門)</div>	<div>On the anteromedial aspect of the wrist, radial to the flexor carpi ulnaris tendon, on the palmar wrist crease.</div> <div>Note: In the depression radial to the proximal border of the pisiform bone, on the palmar wrist crease.</div>	
<div>BL10</div> <div>Tianzhu</div> <div>天柱</div>	<div>In the posterior region of the neck, at the same level as the superior border of the spinous process of the second cervical vertebra (C2), in the depression lateral to the trapezius muscle.</div>	

These brain regions are involved in various cognitive functions, memory processing, and regulation of circadian rhythms, all of which are affected in Alzheimer's disease. BL10 is an acupuncture point with several clinical uses often involved in the treatment regimen for spastic cerebral palsy⁵⁵, vertebrobasilar insufficiency⁵⁶, headache⁵⁷, and stroke patient recovery⁵⁸.

2.3. Comparison of acupuncture with other approaches

According to Lai, Wen⁵⁹, who evaluated nine different treatments for Alzheimer's disease, including pharmacology (two different types of drugs), Ginkgo, acupuncture, music therapy, physical exercise, and nutritional therapy, found that music therapy and acupuncture appear to be the most effective treatment for mild cognitive impairment in Alzheimer's disease.

Individuals with Alzheimer's disease and other forms of dementia appear to have a good response to music therapy⁶⁰. This discovery could unlock a multitude of possibilities by incorporating the patient's preferred music into Traditional Chinese Medicine sessions as an adjunctive approach.

On the other hand, the study of Lai, Wen⁵⁹ aimed to compare and rank non-pharmacologic treatment modalities for mild cognitive impairment in Alzheimer's disease, with the aim of identifying an optimal intervention for mild cognitive impairment and strategies to prevent or delay the onset of Alzheimer's disease.

The results of the study suggest that acupuncture therapy and exercise interventions have the potential to enhance Activities of Daily Living (ADL) and Mini-Mental State Examination (MMSE) scores. Also, acupuncture and Repetitive Transcranial Magnetic Stimulation (rTMS) seem to exhibit benefits in reducing Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog) scores.

2.4. Acupuncture as an adjunct treatment

In the face of the challenges posed by Alzheimer's disease, the exploration of adjunctive treatment approaches, such as acupuncture, holds promise in complementing conventional therapies to enhance cognitive function and quality of life in affected individuals.

In the RCT of Pang, Yin⁶¹, acupuncture plus donepezil was superior to donepezil alone in regulating the latency and amplitude of event-related potential P300, increasing cerebral blood flow, and improving the learning and memory abilities of Alzheimer's disease patients.

As well, the experimental study of Wang, Qin⁶² showed that both treatment groups, those receiving cranial suture acupuncture combined with and those receiving donepezil alone, showed improvements after treatment. However, the combined acupuncture and medication group showed greater statistically significant improvement compared to the medication-only group.

The Systematic review of Zhou, Peng⁶³, concluded that acupuncture plus donepezil was superior to donepezil alone in improving the Mini Mental State Examination (MMSE) scores. According to the authors and Alzheimer's clinical research criteria⁶⁴, the treatment of Alzheimer's disease with acupuncture can be considered clinically meaningful regarding improving cognitive function.

A recent systematic review⁶⁵, also suggests that acupuncture plus medication may have a superior effect for Alzheimer's disease patients than medication alone on general cognitive function in the short and medium term and on Activities of Daily Living (ADL) in the medium term.

Overall, these findings support the potential of acupuncture as an adjunctive therapy in the management of Alzheimer's disease, offering additional benefits beyond standard

medication alone. However, further research, including larger randomized controlled trials, is suggested by the authors to validate these findings and determine the long-term efficacy and safety of acupuncture in the treatment of Alzheimer's disease.

2.4.1. Acupuncture to address Alzheimer's comorbidities

While acupuncture shows promise in improving the quality of life for Alzheimer's patients, further research is needed to understand how it affects specific comorbidities, potentially revealing a broader range of benefits.

Alzheimer's disease is associated with neurodegeneration in brain regions and circuits critical for emotional processing⁶⁶. This neurodegeneration is hypothesized to contribute to the development of anxiety and depression, particularly in the early stages. These early-stage mood disorders may also arise as a psychological response to the disease and the associated challenges of coping. In contrast, the later stages of Alzheimer's disease, characterized by a significant cognitive decline, may lead to a dampening of emotional responses and outward expression⁶⁶. In the pilot study of Lombardo, Dresser⁶⁷, statistically significant improvements were found in three of the four scales used to assess the effect of acupuncture on mood in Alzheimer's disease and vascular dementia patients. Therefore, acupuncture has the potential to be a feasible and effective treatment for depression and anxiety in patients with dementia.

As much as 66% of Alzheimer's disease patients are affected by sleep disturbances^{68,69}.

Kwok, Leung⁷⁰ observed that acupuncture can be useful in improving several domains of sleep quality of Alzheimer's disease patients, with good intervention acceptance. Sleep is fundamental in this population, especially considering that sleep disturbances negatively affect cognitive function and functional impairment in patients with Alzheimer's disease^{68,71-73}.

However, several other comorbidities are associated with Alzheimer's disease. The most common are osteoporosis⁷⁴, cardiovascular diseases⁷⁵, diabetes^{76,77}, and pain^{78,79}. Overall, Acupuncture offers a promising approach to pain management, supported by scientific studies⁸⁰⁻⁸². Acupuncture analgesia likely operates through a multi-modal mechanism involving the activation of various endogenous pain-modulatory systems. These include the release of opioids, which act peripherally to desensitize nociceptors and centrally to reduce pro-inflammatory cytokine production in the spinal cord. Additionally, acupuncture stimulates the release of serotonin and norepinephrine, which contribute to analgesia by decreasing spinal N-methyl-D-aspartate (NMDA) receptor subunit GluN1 phosphorylation⁸³.

As well, preclinical and clinical studies provide mounting evidence for acupuncture's role in promoting bone health and alleviating clinical symptoms associated with bone loss⁸⁴. The underlying mechanisms for these benefits are hypothesized to involve the modulation of the hypothalamic-pituitary-gonadal (HPG) axis, potentially influencing sex hormone levels. Additionally, acupuncture may activate the Wnt/ β -catenin and OPG/RANKL/RANK signalling pathways, known to be crucial for osteogenesis (bone formation) and osteoclastogenesis (bone breakdown)⁸⁴.

Regarding cardiovascular diseases, although more research is needed in several areas, hypertension seems to be the most frequently investigated cardiovascular disease positively addressed by acupuncture⁸⁵⁻⁸⁷. The findings of the review by de Lima Pimentel, Duque⁸⁸ suggest that acupuncture and electroacupuncture may hold promise for improving cardiovascular responses in patients with cardiovascular diseases.

Finally, evidence suggests that acupuncture has some advantages in addressing obesity combined with type 2 diabetes mellitus⁸⁹ and diabetic complications such as neuropathy, nephropathy, and hepatopathy^{90,91}. The proposed mechanisms underlying acupuncture's effects encompass the modulation of nerve conduction, signalling pathways, hormonal balance, protein expression patterns, oxidative stress levels, and potential tissue structure restoration⁹¹.

3. Final remarks

This research provides some insights into the potential of acupuncture as a complementary therapy for Alzheimer's disease. Meanwhile, further research is warranted to definitively establish its efficacy and optimize treatment protocols. Future studies should focus on larger, well-designed randomized controlled trials since those will provide stronger evidence of acupuncture's effectiveness compared to the current findings. As well, investigating the long-term safety and efficacy of acupuncture for Alzheimer's disease management is fundamental.

This review suggests that acupuncture may address not only cognitive decline in Alzheimer's disease but also its associated comorbidities. However, more studies on specific Alzheimer's comorbidities are warranted to comprehend and strengthen acupuncture's role as a complementary therapy to conventional approaches.

As well, future efforts should focus on improving communication and collaboration between traditional Chinese medicine practitioners and Western medical professionals for integrative management of Alzheimer's disease patients. This could involve developing evidence-based guidelines for incorporating acupuncture into standard Alzheimer's disease treatment plans.

Given the growing prevalence of Alzheimer's disease and the limitations of current treatment options, acupuncture, with its low side effect profile and potential benefits, may offer a valuable public health intervention. Further research with robust clinical trials can pave the way for the wider adoption of acupuncture as a complementary therapy for Alzheimer's disease, empowering patients with a broader range of management options.

4. Conclusions

Acupuncture holds promise as a complementary therapy for Alzheimer's disease. Studies show potential benefits for cognitive function, mood, sleep, pain management, and quality of life in Alzheimer's disease patients. However, further research is necessary to definitively establish its efficacy and deeply elucidate its mechanisms of action.

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