



Review Article

Chinese herbs and acupuncture to improve cognitive function in Alzheimer's disease

Wei WuLi^{a,b}, Horng-Jyh Harn^{a,c}, Tzyy-Wen Chiou^b, Shinn-Zong Lin^{a,d,*}

^aBioinnovation Center, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, ^bDepartment of Life Science, National Dong Hwa University, Hualien, Taiwan, ^cDepartment of Pathology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, ^dDepartment of Neurosurgery, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease with a variety of causes. Traditional Chinese medicine (TCM), which includes the two main approaches of acupuncture and herbal medication, views the human body as a self-controlled system network. Fundamental theories, including "qi," the five elements, and the theory of viscera, form the basis for classification. Diseases in humans are considered to be caused by an imbalance of "yang qi" and "yin qi" that lead to the nonhomeostasis of organs. Acupuncture is derived from 12 main meridians and 365 acupuncture points characterized by "blood and qi." Needling of different positions corresponds to specific disease treatments to increase qi. Treatment with Chinese herbal medicines is based on syndrome differentiation characterized as "Zheng" which differs from the cause orientation approach of Western medicine. In this article, we review basic and clinical research studies that describe TCM herbs and acupuncture for the treatment of AD. Moreover, we propose that these two approaches be integrated to improve the outcomes for AD patients.

KEYWORDS: *Acupuncture, Alzheimer's disease, Qi, Traditional Chinese medicine, Zheng*

INTRODUCTION

Alzheimer's disease (AD) features complex pathogenesis involving multiple pathophysiological processes and has become a serious public health problem worldwide [1]. The complex mechanisms of disease and the continued failure of drug development have created an urgent need for additional treatment options for AD [2].

Traditional Chinese medicine (TCM) using herbal products have been proven to prevent and treat dementia [3,4], and many small molecules that effectively inhibit AD have been extracted from Chinese herbs [5]. Chinese herbal medicines show potential for the treatment of AD. Acupuncture is another standard therapeutic approach of TCM. Using the scientific method, there has been continued exploration of Chinese herbal medicines combined with acupuncture to increase the practical benefits of AD treatment.

Beta-amyloid accumulation

The major hypotheses of AD include the amyloid hypothesis and the tau hypothesis. The genes associated with beta-amyloid deposits include amyloid-beta precursor protein (*APP*) [6] and β -secretase-1 (*BACE-1*) [7], while the genes that primarily regulate γ -secretase are presenilin-1 (*PSEN-1*) and presenilin-2 (*PSEN-2*) [8]. Under normal conditions, the *APP* is cleaved by α -secretase to produce a peptide of 83 amino acid residues that

is then further processed by γ -secretase to form the P3 peptide fragment (24 or 26 residues). Peptides of this length are easily metabolized. Deregulation of these genes can lead to enhanced abnormal cleavage and the formation of amyloid peptides that are not easily metabolized (40 or 42 residues) [9].

Tau protein phosphorylation

Tau is a microtubule-associated protein that is abundant in the central nervous system. In neurodegenerative disease such as AD and Parkinson's disease, Tau aggregates are commonly found, forming neurofibrillary tangles in the brain [10].

Other hypotheses

Among patients diagnosed with AD, only 25% develop dementia caused by limbic predominant age-related TDP-43 encephalopathy (LATE) [11]. Early-onset AD is usually attributed to genetic mutation. These genetic mutations include *APP*, *BACE-1*, *PSEN-1*, and *PSEN-2*. However, 95% of AD patients have late-onset AD, which is not necessarily caused by genetic mutation [12]. The complex natures of this disorder and the continued failure to develop effective drugs for AD have created an urgent need for more treatment options.

*Address for correspondence:

Dr. Shinn-Zong Lin,
 Department of Neurosurgery, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.
 E-mail: shinnzong@yahoo.com.tw

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TRADITIONAL CHINESE MEDICINE HYPOTHESIS: ZHENG

In TCM, the syndrome known as “Zheng” is a major concept in the diagnosis of disease. Zheng can be understood through the following basic features: (1) Visual observation of the appearance of the tongue and detection of the pulse condition reflect disturbances of the “Zang-Fu” organs, channels and collaterals, and qi and blood in the body. (2) Different illnesses may have the same Zheng. Through the visual, auditory, and tactile senses the physician observes the patient’s appearance and asks questions regarding the patient’s feelings, life habits, and physiological changes. The major identification methods of Zheng comprise eight theoretical perspectives: Qi, blood, body fluids, zang-fu, channel collateral, six-channel, Wei-Qi-Ying-blood, sanjiao, and disease causes [13-16].

Qi

Chinese medicine combines Chinese philosophy with rules of thumb and treats diseases by natural methods. In the formation and development of Chinese medicine, the concept of “qi,” often translated as vital energy, is the backbone of the entire system. This includes two main points. The first is the dynamic balance between people and the outside environment; for example, the different seasons and changes in the weather produce wind, cold, heat, moisture, dryness, and fire. When the immune system is weakened, people are unable to bear the natural changes and become sick. The second regards to health protection. Qi flows through the circulatory system, with a strengthening effect on the corresponding organs that are active at different time points. The time period from 1 AM to 3 AM, for example, is considered the most vigorous time for liver metabolism; if one does not rest during this time, the burden on the liver will increase. There are many methods to regulate the circulation of qi in the body, with the major methods being Chinese herbs and acupuncture. Indeed, the National Institutes of Health has acknowledged that acupuncture therapy is an effective treatment for several common diseases, such as back pain, knee pain, headaches, and osteoarthritis [17,18].

Traditional Chinese medicine hypothesis for dementia

TCM explained as a cybernetic approach regards the human body as a self-controlled system network. TCM use qi, five elements, and the theory of viscera as a basis for classification. Chinese herbal medicine also features the same classification system. The theory of Chinese medicine views dementia as a result of the shrinking of the brain. TCM has put forward a theory that “kidneys give rise to the marrow, and the brain is the sea of marrow” [Figure 1]; thus, deficiency in kidney functions will lead to dementia [19-21]. Chinese herbs and acupuncture may increase the chances of treating AD. Continued exploration of Chinese herbal medicine and acupuncture treatment will help provide novel directions for the development of AD drugs and offering practical treatment benefits.

EFFECTS AND MECHANISMS OF ACTION OF SMALL-MOLECULE DRUGS EXTRACTED FROM CHINESE HERBS IN AD TREATMENT

The earliest pharmacopoeia from China is the Shen Nong Ben Cao Jing (“Divine Farmer’s Pharmacopoeia”) [22]. In CA 1596, Li Shi-Zhen compiled the Ben Cao Gang Mu (“Pharmacopoeia

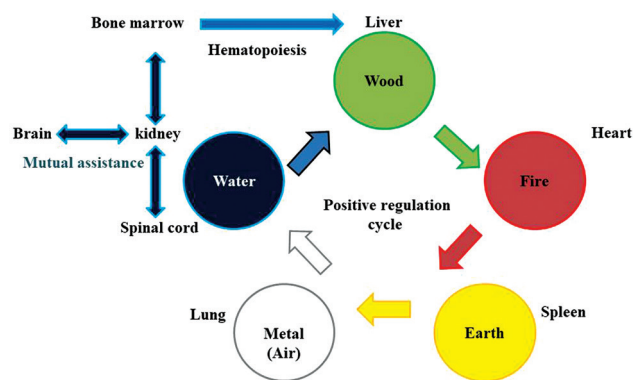


Figure 1: Five elements corresponding to different body organs. Chinese medicine classifies the five internal organs by five elements. Chinese herbal medicines are also classified using the same system. The brain is considered to be closely related to the function of the kidneys. Chinese medicine teaches that the bone marrow, kidneys, and brain function closely together. Kidney deficiency will lead to less bone marrow, which leads to insufficient blood and cerebral dysfunction and ultimately dementia

Classified by Section and Sub-section”). Li’s consolidation of the previous pharmacopoeia together with his own views and observations, created a more thorough pharmacopoeia [23]. TCM classifies Chinese herbs according to qi and five elements theory. The brain and kidneys are categorized in the water element. We summarize the effects and possible mechanisms of small-molecule drugs extracted from 10 commonly used TCMs and the effects of these molecules on meridians and organs in the AD setting.

Epimedii folium (淫羊藿)

Epimedii Folium (Yin yang huo; 淫羊藿) is a major therapy for kidney yang deficiency syndrome, and it can improve androgen hormone levels as well as combat wind qi, damp qi, and cold qi blocking circulation [24,25].

Radix polygalae (遠志)

Radix polygalae (“Yuan Zhi,” 遠志) is a medicinal plant mainly used for the treatment of “insomnia with syndrome of incoordination between heart and kidney” and to improve memory [26-28].

Morinda officinalis (巴戟天)

Morinda officinalis (“Ba Ji Tian,” 巴戟天) is a TCM used to tonify the kidney and strengthen yang. Morinda officinalis has hypoglycemic and antioxidant activities [29].

Acorus tatarinowii schott (石菖蒲)

Acorus tatarinowii Schott (“Shi Chang Pu,” 石菖蒲) has mainly been used for the treatment of neuron-associated and digestive diseases in the clinical practice of TCM [30]. It can also improve the viability of cardiac myocytes and contribute to therapeutic effects on dementia [31,32].

Rehmannia glutinosa (地黃)

Rehmannia glutinosa (“Dihuang,” 地黃) can invigorate the kidney, “nourishing yin clearing heat,” and also ameliorates learning and memory impairment [33-35].

Glycyrrhiza uralensis (甘草)

Glycyrrhiza uralensis (“Gan Cao,” 甘草), is an herbal medicine used for the treatment of sore throat, cough, bronchitis, peptic ulcers, arthritis, and allergic diseases [36].

Table 1. The system of meridians and collaterals

Meridians			
□. Twelve meridians (十二經脈)			
1.Three yin meridians of hand(手三陰經)	2.Three yang meridians of hand (手三陽經)	3.Three yin meridians of foot (足三陰經)	4.Three yang meridians of foot (足三陽經)
1.1. Tai-yin lung Meridian of hand (手太陰肺經)	2.1. Yang-ming large intestine meridian of hand (手陽明大腸經)	3.1. Tai-yin spleen meridian of foot (足太陰脾經)	4.1. Yang-ming stomach meridian of foot (足陽明胃經)
1.2. Shao-yin heart meridian of hand (手少陰心經)	2.2. Tai-yang small intestine meridian of hand (手太陽小腸經)	3.2. Shao-yin kidney meridian of foot (足少陰腎經)	4.2. Tai-yang bladder meridian of foot (足太陽膀胱經)
Jue-yin pericardium 1.3 meridian of hand (手厥陰心包經)	2.3. Shao-yang Sanjiao meridian of Hand (手少陽三焦經)	3.3. Jue-yin liver meridian of foot (足厥陰肝經)	4.3. Shao-yang gallbladder meridian of foot (足少陽膽經)
□. Eight extra meridians (奇經八脈)			
1.Conception vessel (任脈)	2.Governor vessel (督脈)	3.Chong Vessel (沖脈)	4.Belt vessel (帶脈)
5.Yin Link Vessel (陰維脈)	6.Yang Link Vessel (陽維脈)	7.Yin Heel Vessel (陰蹻脈)	8.Yang Heel vessel (陽蹻脈)
□. Twelve divergent channels (十二經別). □. Twelve sinew channels (十二經筋). □. Twelve cutaneous regions (十二皮部). Collaterals. □. Fifteen collaterals (十五絡). □. Superficial collaterals (浮絡). □. Tertiary collaterals (孫絡)			

Salviae miltiorrhizae (丹蔘)

The major function of *Salviae miltiorrhizae* (“Danshen;” 丹蔘) is the activation of blood circulation to dissipate blood stasis. It also offers beneficial effects in the prevention and treatment of cardiovascular diseases [37,38].

Panax ginseng (人蔘)

Panax ginseng (“Renshen;” 人蔘) has anti-inflammatory, anti-oxidant, and anticancer effects. It also improves psychological and immune function as well as conditions associated with diabetes and is used in the treatment of frailty and aging-related symptoms, such as fatigue and hypertension [39,40].

Astragalus membranaceus (黃耆)

Astragalus membranaceus (“Huang Qi;” 黃耆) can be used to treat “qi deficiency constitution” [41]. It can also enhance the natural defense mechanisms in the heart, brain, kidney, intestine, liver, and lung [42-44].

Angelica sinensis (當歸)

Angelica sinensis (“Danggui;” 當歸) used to treat invigorating blood and treating female irregular menstruation and amenorrhea. The *Angelica sinensis* can effectively inhibit inflammation and upregulated growth factor [45].

12 MAIN MERIDIANS

In addition to Chinese herbal treatment, acupuncture is another method used to treat AD. The principle of acupuncture is derived from the study of the 12 main meridians and 365 acupuncture points. The 12 main meridians comprise the path of blood and qi that flow through various organs [46]. The meridian system can be further divided into the meridian–collateral system and the tendon–skin system. The meridian–collateral system relates to nutrition and blood (nutrient qi), whereas the tendon–skin system involves the regulation of motor function and body protection (defensive

qi). The meridian–collateral system is composed of 12 principal meridians, eight extra meridians and 15 collaterals. The tendon–skin system includes 12 sinew meridians and 12 cutaneous meridians [47]. The 12 main meridians are distinguished by their yang or yin qi, three levels of energy flow ranging from strong to weak, and direction of flow to either hand or foot [Table 1]. In addition to the 12 meridians, there is the governor vessel (GV) and conception vessel (CV). GV is located on the back, runs from head to hip and has 28 acupuncture points. CV located on the front of the body and has 24 acupuncture points. The six yang meridians have acupuncture points with confluence (i.e., pairing) in CV, and the six yin meridians have acupuncture points with confluence in GV.

ACUPUNCTURE TREATMENT FOR DEMENTIA

The bladder (BL) and gallbladder (GB) meridians are very important for the treatment of the brain. The BL meridian has a close relationship with the kidneys and can improve blood supply [Figure 2a and b] [48]. There is a major focus of GB acupuncture points on the head, directing impacting the brain [Figure 2c] [49]. These points are effective in treating dementia [50]. Acupuncture points mark the places where needles can be placed in the body without causing serious harm. Different positions correspond to different disease treatments. The local area comprising an acupuncture point contains a combination of mast cells and blood vessel and nerve networks [Table 2] [51]. Acupuncture points, including Dazhui (GV14), Baihui (GV20), and Shenshu (BL23) are considered to have beneficial effects on dementia. Dazhui is the convergence of all positive meridian points, and Baihui is the convergence of the Tai yang, Shao yang, and Jue yin meridian points. These two acupuncture points are common choices for the treatment of dementia [52]. The term Shenshu means that the kidneys transport cold and moisture to the foot Tai Yang meridian. Dazhui, Baihui, and Shenshu, these three points are related to the kidneys and foot

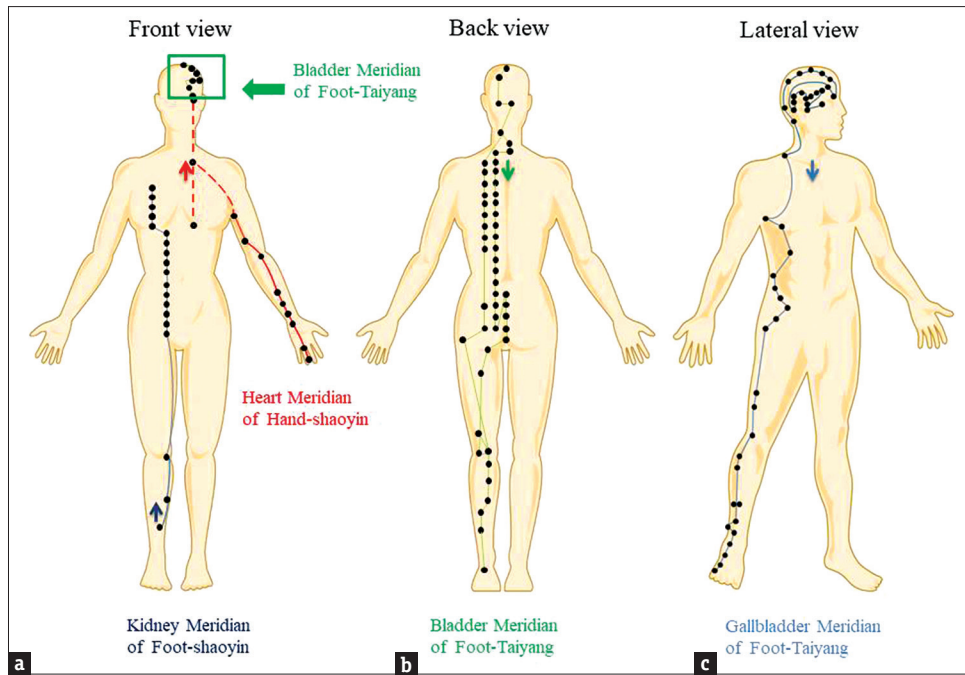


Figure 2: Mapping of the four major meridians directly related to Alzheimer’s disease: bladder, heart, gallbladder, and kidney. The dots indicate acupuncture points along the lines of qi circulation for each meridian. The direction of qi flow is indicated by the arrows. The bladder meridian flows from the head to the back (green line) (a) Kidney, heart, (b) bladder, (c) gallbladder.

Table 2: Twelve main meridians that connect and regulate the flow of qi through different organs in the body

Property	Mean	Hand and Foot	Time	Major influence organ	Abbreviation
Tai yin	Yin qi strong	Hand	3-5 o'clock	Lung	LU
		Foot	9-11 o'clock	Spleen	SP
Shao yin	Yin qi weak	Hand	11-13 o'clock	Heart	HT
		Foot	17-19 o'clock	Kidney	KI
Jue yin	Yin qi final step trans to yang qi	Hand	19-21 o'clock	Pericardium	PC
		Foot	1-3 o'clock	Liver	LR
Tai yang	Yang qi strong	Hand	13-15 o'clock	Small intestine	SI
		Foot	15-17 o'clock	Bladder	BL
Shao yang	Yang qi weak	Hand	21-23 o'clock	Triple energizer	TE
		Foot	23-1 o'clock	Gallbladder	GB
Yang ming	Yang qi final step	Hand	5-7 o'clock	Large intestine	LI
		Foot	7-9 o'clock	Stomach	ST

Tai yang meridian [53]. Zusanli (stomach meridian [ST]36) can effectively regulate the physiological functions of the spleen, stomach, and kidney [54]. Baihui and Zusanli were the first choice acupuncture points used treatment dementia [55-57]. Xuehai (spleen meridian [SP]10) and Sishencong (EX-HN 1) are also often used to treat dementia [58].

Alternative acupuncture points to treat dementia include Taixi (Kidney meridian [KI]3) [59], Danzhong (CV17) [60], Zhongwan (CV12) [60], Qihai (CV6), Waiguan (Triple Burner meridian [TE]5), Xuanzhong (GB39), Neiguan (Pericardium meridian [PC]6), Yintang (GV29), Sanyinjiao (SP6), and Dazhong (KI4). The effects of acupuncture on meridians require scientific verification, but analysis of the main meridians is challenging. Fourier analysis can detect the complete quantitative expression of the pressure wave. Wang *et al.* proposed that the detection of harmonic components could

facilitate an understanding of the circulatory system in terms of the different meridians [61,62]. This is a potential method for demonstrating the effects of acupuncture.

MOXIBUSTION

Methods of treating diseases through acupuncture points include Acupuncture (“zhen,” 針) and moxibustion (“jiu,” 灸). Acupuncture is to insert a needle into acupuncture points to treat diseases, which is an invasive treatment; moxibustion ignites *Artemisia argyi* (“Ai Cao,” 艾草) and through heat generated by cauterization to stimulate the acupuncture points. The function includes adopted to resolve the stagnation, promote circulation in meridian, regulate qi and blood circulation [63]. The moxibustion combine with Typhonium Rhizome (“Bai Fu Zi,” 白附子) was applied to Baihui (BL 20) and the suspended moxibustion was used on Shenting (BL 24) and Dazhui (GV 14). There has a function of improving vascular

dementia and the activity of daily living [64]. In the animal model of AD, moxibustion proved to be helpful for learning and short-term memory capacity [52]. The mechanism of moxibustion treatment of AD is to reduce the content of APP in the frontal cortex and hippocampus [65]. The moxibustion combined with acupuncture is better than the single treatment method to improve the cognitive function and daily activity ability of patients with dementia [66].

CONCLUSIONS

Given the growing research on the identification of active ingredients from Chinese herbs and their use in the treatment of dementia and cognitive impairment, there are also clinical trials using Chinese herbal medicine and acupuncture to treat AD. If these treatments in effect may be possible to reduce the cost of new drug development and help patients avoid unwanted side effects. This will facilitate the development of future treatments for AD. Furthermore, the combination of herbal medicines with acupuncture may provide additional benefit and could form the basis of a new, synergistic treatment approach for AD.

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Conflicts of interest

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