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Review Article

Complementary and alternative medicine for treating amyotrophic lateral sclerosis: a narrative review

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ARTICLE INFO

Article history:

Received 3 June 2019

Received in revised form 14 August 2019

Accepted 20 August 2019

Available online 29 August 2019

Keywords:

Amyotrophic lateral sclerosis
Complementary alternative medicine
Acupuncture
Herbal medicine

ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease that is characterized by selective motor neuron cell death in the motor cortex, brainstem, and spinal cord. Two drugs for ALS, riluzole and edaravone, have been approved by FDA for the treatment of ALS patients. However, they have many side effects, and riluzole extends the patient's life by only 2–3 months. Therefore, ALS patients seek an effective therapy for treating the symptoms or delaying the progression of ALS. Based on this, we review the effects of complementary and alternative medicine (CAM) in ALS animals or patients to verify the efficacy of CAM in incurable diseases.

Methods: For this review, we searched published papers focusing on the effect of CAM in pre-clinical and clinical study in ALS. The search keywords included amyotrophic lateral sclerosis, acupuncture, herbal medicine, Traditional Chinese medicine, CAM, animals, and clinical study through electronic databases PubMed and Google Scholar from their inception until March 2019.

Results: In the ALS animal model, CAM modulated the immune system to increase motor function by reducing the expression levels of neuroinflammatory proteins in the spinal cord. Besides this, ALS patients treated with herbal medicine showed improved disease symptoms, but clinical trials with larger sample sizes are needed to develop a treatment with this herbal medicine.

Conclusion: This review shows that CAM may be useful for ALS treatment, but more evidence regarding the efficacy and molecular mechanisms is required to establish CAM as a good therapy for the treatment of ALS patients.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily causes motor neuron death in the cerebral motor cortex, brainstem, and spinal cord, leading to restricted voluntary movement. In addition, ALS patients develop difficulty in swallowing, speaking, and breathing because of muscle paralysis.¹ About 90% of ALS cases are classified as sporadic ALS (sALS). sALS results from a combination of environmental and genetic risk factors that are not well known. The remaining 10% of ALS cases are of the familial type. Around 66% of familial ALS cases have been linked to identified genetic mutations, including in chromosome 9 open reading frame 72 (C9orf72), Cu/Zn superoxide dismutase (SOD1), TAR DNA-binding protein

(TARDBP), and fused in sarcoma (FUS) genes.² The major cellular mechanisms implicated in ALS disease include disturbances in protein quality control, hyperactivation of microglia, diminished energy supply from reduced MCT (monocarboxylate transporter) 1 transporter, excitotoxicity, cytoskeletal defects, and disturbances in RNA metabolism (splicing, miRNA biogenesis, translation).¹ In addition, several neurotoxic mechanisms are well known in mtSOD1-mediated ALS, such as excitotoxicity, ER stress, mitochondrial dysfunction, axon transport disruption, prion-like propagation, and non-cell autonomous toxicity of neuroglia.² Two drugs that have been developed to address the pathological mechanism of ALS, riluzole and edaravone, have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ALS patients. Riluzole (an anti-glutamatergic drug) extends the patient's life by only about 2–3 months.³ The second FDA-approved drug is edaravone, an antioxidant drug which is used in Japan to assist with recovery from stroke. Although these drugs have been used for the treatment of ALS, side effects such as liver problems, serious allergic reaction (swelling of face or throat), depressed

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mood, diarrhea, fever, vomiting, dizziness, fatigue, and nausea have been reported. Therefore, there is currently no effective treatment for ALS that is able to cure or stop the progression of the disease. ALS patients and their families have begun to consider the use of complementary and alternative medicine (CAM) in order to relieve their illness⁴ and find an effective treatment.

Complementary and alternative medicine (CAM) is defined as non-mainstream treatment used together with (complementary) or in the place of (alternative) conventional medicine. The use of CAM therapy, including acupuncture, herbal medicine, and massage, yoga, relaxation therapy, and homeopathy has been popular for thousands of years in East Asia. Recently, more and more patients with chronic and incurable diseases have decided to use herbal medicine or acupuncture as part of their healthcare in the United States and in European countries.^{5,6} In the 2012 National Health Interview Survey ($n = 33,557$), more than 25% of American adults reported having two or more chronic conditions, and they often used CAM, despite limited evidence.⁵ Moreover, 54% of ALS patients reported using CAM therapy in a survey by the German Association for Neuromuscular Diseases (DGM); the most widely used methods were acupuncture, homeopathy, and naturopathy.⁶ However, there has not been any reviews covering research focused on the effects and mechanisms of CAM in ALS. Therefore, we summarized, herein, the effects of CAM and its mechanism based on published papers involving ALS animal models and patients using CAM (Table 1).

2. Methods

For this review, we searched published papers focusing on the effect of CAM in pre-clinical and clinical study in ALS. The search keywords included amyotrophic lateral sclerosis (or ALS), acupuncture, herbal medicine, Traditional Chinese medicine (or TCM), CAM, animals, clinical study through Pubmed, Google Scholar electronic databases from their inception until March, 2019.

3. Use of CAM for amyotrophic lateral sclerosis

The summarized information of CAM for ALS is shown in Table 1.

3.1. Acupuncture for ALS

Acupuncture is one of type of CAM and has also been widely used in Korea, China, and Japan for centuries. Acupuncture needles (thin needles) are inserted into certain locations (called acupoints) of the body. Electroacupuncture (EA) is a form of acupuncture in which a weak electric current is passed through the acupuncture needles into acupoints in the skin. Acupuncture is widely used for musculoskeletal problems, particularly chronic pain⁷ or neurodegenerative diseases including Alzheimer's disease (AD)⁸ and Parkinson's disease (PD).⁹ Generally, acupuncture is protective, or improves the phenotypes (cognitive function in AD, tremor in PD) through brain functional activity in neurodegenerative disease.^{8,9} In the case of ALS, some papers have demonstrated the effects of EA treatment in the spinal cord and lung of a symptomatic ALS animal model.^{10,11} Yang et al. showed that EA at Zusanli (ST36) improved motor function and reduced neuronal cell loss through the reduction of microglial cells and the expression of TNF- α in the brainstem and spinal cord of hSOD1^{G93A} animals.¹¹ In addition, EA treatment also reduced the levels of pro-inflammatory cytokines (TNF- α and IL-6) and increased cell survival-related protein (pAKT and pERK) expression in the lung of hSOD1^{G93A} animals.¹⁰ These studies suggest that EA treatment could be helpful in increasing anti-inflammation activity in the central nervous system (CNS) and respiratory system of ALS animals.

Saam acupuncture is one of type of acupuncture based on the traditional concepts of yin–yang, five elements (Wood, Fire, Earth, Metal, and Water), ZangFu (viscera and bowels), qi, and meridians, and is representative of traditional Korean medicine.¹² Korean saam acupuncture has lung tonification effects, which were investigated in this study through the analysis of Korean traditional literature. Lee et al. showed that saam acupuncture treatment at Taibai (SP3), Taiyuan (LU9), Shaofu (HT8), and Yuji (LU10) acupoints regulated respiratory physiology parameters in ALS patients.¹³ Patients who had high Korean Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised (K-ALSFRS-R) scores had greater changes in pulse rate after acupuncture stimulation. In addition, saam acupuncture decreased end-tidal carbon dioxide (EtCO₂), respiratory rate (RR), and pulse rate, and increased the peripheral oxygen saturation (SpO₂) in ALS patients. Therefore, the authors suggested that saam acupuncture would be more effective in early stages of the disease to increase the effects of treatment using saam acupuncture.

3.2. Herbal medicine for ALS

Herbal medicine is a part of CAM therapy defined as the utilization of herbs, animals, and minerals commonly used in East Asia. Herbal medicine contains hundreds of components and targets multiple pathways. Based on holistic concepts and dialectical theory, herbal medicine has been used for over two thousand years.

3.2.1. Bee venom

Bee venom (BV), also called apitoxin, is extracted from honeybees and contains enzymes, lipids, amino acids, carbohydrates, and peptides such as melittin, apamin, phospholipase A2 (PLA2), and hyaluronidase.¹⁴ BV has been mainly used for rheumatic disease for anti-inflammatory effects in human and mice models.^{15,16} In addition, phospholipase of BV enhanced the cognitive function, increased glucose metabolism, and decreased A β deposit by microglial deactivation and reduction of CD4 (+) T cell infiltration in an AD mice model,¹⁷ and for its protective effect on dopaminergic neurons in a PD mice model.¹⁸ In the case of ALS, Kim et al. demonstrated that BV treatment recovered proteasome activity and attenuated the accumulation of misfolded SOD1 in mtSOD1-overexpressing NSC34 motor neuronal cells.¹⁹ In an ALS animal model, Yang et al. demonstrated that BV treatment improved motor activity and increased survival by reducing neuroinflammation in the spinal cord and brainstem of hSOD1^{G93A} mice.²⁰ In addition, BV treatment suppressed the expression of active caspase-3 protein and inhibited mitochondrial structure impairment in the lumbar of the spinal cord of hSOD1^{G93A} at the symptomatic stage. Furthermore, Cai et al. and Lee et al. reported anti-inflammatory effects of BV at acupoints. In this study, the authors considered BV treatment via two ways (the ST36 acupoint or intraperitoneal (i.p.) injection) and investigated BV's effects on the CNS and peripheral organs, such as the liver, kidney, and spleen of symptomatic hSOD1^{G93A} animals. BV treatment at the ST36 acupoint increased the anti-neuroinflammation effect compared to BV treatment by i.p. injection via a decrease in the level of TLR4-inflammatory signaling-pathway-related proteins (TLR4, CD14, and TNF- α) in the spinal cord of hSOD1^{G93A} mice.²¹ In addition, Lee et al. showed that inflammation-related proteins (Iba-1, COX2, and TNF- α) were significantly reduced by BV treatment at the ST36 acupoint compared to i.p. injection of BV in the peripheral organs such as the liver, spleen, and kidney of ALS mice.²² Taken together, this indicates that BV treatment would be useful for improvement of the immune system in the CNS and peripheral nervous system (PNS), at least in hSOD1^{G93A} ALS animals.

Melittin (MT) is a major component of BV. Yang et al. investigated the effect of MT in BV to characterize the bioactive component

Table 1
Summary of the effects of complementary and alternative medicine (CAM) used in ALS.

CAM modality	Type of study	Method	Effectiveness	Author (year)
Electroacupuncture (EA)	Animal	Zusanli (ST36) acupoint, (1 mA, 2 Hz, 30 min), 6 times	(Spinal cord) Increased motor activity, neuronal protection, and anti-neuroinflammation	Yang (2010) ¹¹
Electroacupuncture (EA)	Animal	Zusanli (ST36) acupoint, (1 mA, 2 Hz, 30 min), 6 times	(Lung) Reduced pro-inflammatory cytokines, and increased cell survival-related protein	Jiang (2010) ¹⁰
Saam acupuncture	Clinical	Taibai (SP3), Taiyuan (LU9), Shaofu (HT8), and Yuji (LU10) twice a day for 5 days	Regulated respiratory physiology	Lee (2013) ¹³
Bee venom (BV)	Animal	0.1 µg/g, Zusanli (ST36), 14 times	(Brainstem and spinal cord) Increased motor activity, survival, anti-inflammation, and neuronal protection	Yang (2010) ²⁰
Melittin (MT)	Animal	0.1 µg/g, Zusanli (ST36), 14 times	(Brainstem and spinal cord) Increased motor activity, anti-neuroinflammation, and proteasome activity	Yang (2011) ²³
Melittin (MT)	Animal	0.1 µg/g, Zusanli (ST36), 14 times	(Lung) Increased anti-inflammation (Spleen) Increased anti-inflammation and cell survival	Lee (2014) ²⁴
<i>Scolopendra subspinipes mutilans</i> (SSM)	Animal	2.5 µg/g, Zusanli (ST36), 6 times	(Brainstem and spinal cord) Increased neuronal protection, anti-inflammation, and anti-oxidation	Cai (2013) ²⁹
Ginsenoside Re (G-Re)	Animal	2.5 µg/g, Zusanli (ST36), 6 times	(Spinal cord) Increased neuronal protection, anti-inflammation, and anti-oxidation	Cai (2016) ³⁴
<i>Withania somnifera</i>	Animal	5 mg/per animal, p.o., 8 or 16 weeks	(Gastrocnemius muscle and spinal cord) Increased motor activity, cognitive function, muscle innervation. Anti-inflammation, anti-NF-kb activation	Dutta (2017) ³⁷
Bojungkigi-tang (BJGT)	Animal	1 mg/g, p.o., 6 weeks	Decreased mislocalization and aggregation of TAR DNA-binding protein 43 (TDP43) (Spinal cord and gastrocnemius muscle) Increased motor activity, survival, anti-inflammation, and anti-oxidation	Cai (2018) ⁴⁰
Gamisoyo-San (GSS)	Animal	1 mg/g, p.o., 6 weeks	Decreased autophagy dysfunction, muscle atrophy, and denervation of neuromuscular junctions (Spinal cord) Increased neuronal protection, anti-inflammation, and anti-oxidation	Cai (2018) ⁴³
Gamisoyo-San (GSS)	Animal	1 mg/g, p.o., 6 weeks	Decreased metabolism dysfunction (Gastrocnemius muscle) Increased anti-inflammation and anti-oxidation	Park (2018) ⁴⁴
Jaeumganghwa-Tang (JGT)	Animal	1 mg/g, p.o., 6 weeks	(Spinal cord) Increased motor function, anti-inflammation, and anti-oxidation	Lee (2019) ⁴⁷
Huolingshengji Formula (HLSJ)	Animal	4.5 g/kg-d, p.o., 100 days	(Spinal cord, Gastrocnemius muscle) Increased motor activity and survival, anti-apoptosis and anti-inflammation, Decreased muscle atrophy	Zhou(2018) ⁴⁸
Huolingshengji Formula (HLSJ)	Clinical	200 ml, p.o., 12 weeks	Decreased Advanced Norris scale score (ANSS)	Sui (2016) ⁴⁹
Dihuang Yinzi (DHYZ)	Clinical	Decoction, p.o., twice daily, 12 years	Improved TCM syndrome Increased survival, muscle fibrillation, and muscle strength	Qiu (2016) ⁵⁰
Jiawei Sijunzi (JWSJZ)	Clinical	Decoctions, p.o., 50 ml, twice daily	Delayed use of ventilator support Fewer adverse effects Improved neurological evaluation according to the ALS functional rating scale (ALSFERS)	Pan (2013) ⁵¹
Creatine	Animal	2% creatine-fed, 4 weeks	Improved motor performance, weight maintenance, and survival	Andreassen (2001) ⁵²
Creatine	Animal	2% creatine-fed, 60 days	No effect on muscle metabolic parameters, muscle weight, muscle contractile parameters, and fatigability	Derave (2003) ⁵³
Creatine	Clinical	doses ranging from 5 – 10 g per day	No effect on survival and ALS functional rating revised scores (ALSFERS-R) progression or percent predicted forced vital capacity (FVC) progression	Pastula (2012) ⁵⁴
Vitamin D	Clinical	2000 IU/day, 9 months, daily	Decreased revised ALS functional rating scale (ALSFERS-R) score	Karam (2013) ⁵⁶
Vitamin E	Animal	200 IU/kg of mouse chow, Treatment continued until end-stage disease	Delayed disease onset and slow progression	Gurney (1996) ⁵⁷

ALS, Amyotrophic lateral sclerosis; ALSFRS, ALS functional rating scale; ALSFRS-R, revised ALS functional rating scores; ANSS, Advanced Norris scale score; FVC, forced vital capacity; IU, international unit; p.o., Per os; TCM: Traditional Chinese Medicine.

providing anti-neuroinflammation effects in ALS animals.²³ They demonstrated that MT treatment restored proteasome function and modulated the levels of inflammation-related proteins (Iba-1 and TNF- α) in the spinal cord and brainstem of hSOD1^{G93A} animals.²³ In addition, MT treatment showed anti-inflammation

effects in the lung and spleen through the reduction of Iba-1, CD14, TNF- α , and COX2 proteins in hSOD1^{G93A} ALS animals.²⁴ These data suggest that MT in BV plays a critical role in the improvement of motor function, and delays the disease progress of ALS.

3.2.2. *Scolopendra subspinipes mutilans*

Scolopendra subspinipes mutilans (SSM) is utilized in traditional Chinese medicine, and the compounds contained in SSM have many biological effects, including anticancer,²⁵ immunomodulatory,²⁶ antimicrobial,²⁷ and antifungal activities.²⁸ Based on a previous study, Cai et al. investigated the effects of SSM in SOD1^{G93A} mice, and showed anti-inflammation effects due to the reduction of microglial cells and astrocytes, and antioxidation effects due to decreases in CD14, HO-1, and NQO1 protein levels in the brainstems and spinal cords of hSOD1^{G93A}.²⁹

3.2.3. *Ginseng*

Ginseng is well known as a traditional herbal medicine and has various effects, including antifatigue and antiaging effects, and can induce improved immunity.³⁰ Ginseng is composed of various substances, including proteins, carbohydrates, ginsenosides (ginseng saponins), amino acids, vitamins, and fatty acids. In particular, ginsenosides are classified as protopanaxadiols (PPD; e.g., Ra, Rb, Rc, Rd, Rg3, Rh2) and protopanaxatriols (PPT; e.g., Re, Rf, Rg1, Rg2, Rh1).^{31,32} Lee et al. demonstrated that pretreatment with Ginsenoside Re (G-Re) has a neuroprotective effect against lipopolysaccharides (LPS)-induced microglial cell lines through inhibition of the expression of pp38, iNOS, and COX2 proteins.³³ Furthermore, G-Re treatment attenuated motor neuron loss through the reduction of neuroinflammation-related proteins (Iba-1, GFAP, TLR4, CD14, and TNF- α) and oxidative stress-related proteins (pp38 and HO-1) in the lumbar spinal cord of hSOD1^{G93A} animals.³⁴

Withania somnifera, also called Indian ginseng, has been utilized in the traditional Indian medical system. *Withania somnifera* has demonstrated antimicrobial, anti-inflammatory, antineoplastic, antistress, cardioprotective, antidiabetic, and neuroprotective properties in multiple disease models, including of AD, PD, Huntington's disease (HD), and spinal cord injuries.^{35,36} Dutta et al. demonstrated that treatment with a *Withania somnifera* root extract led to improved motor function, cognitive function, and neuromuscular junction (NMJ) innervation, and reduced neuroinflammation and NF- κ B activation. Moreover, this treatment was found to reverse human TAR DNA-binding protein 43 (hTDP43) cytoplasmic mislocalization and reduce hTDP43 aggregation in the spinal cord motor neuron and cortical neurons of hTDP43^{A315T} ALS mice.³⁷

3.2.4. Traditional herbal prescription

Traditional herbal prescription is a common form of CAM therapy and has been used for various diseases according to traditional Chinese medicine (TCM) theory or Korean medicine (KM) theory.

Bojungikgi-tang (BJJGT), known as Bu-Zhong-Yi-Qi-Tang in Chinese medicine and Hochuekkito in Japan, is used for the improvement of immune function in allergic rhinitis.^{38,39} In an ALS animal model, BJJGT enhanced motor activity and extended survival rate through the induction of anti-neuroinflammation and antioxidant effects in the spinal cord and gastrocnemius of hSOD1^{G93A} animals.⁴⁰ Furthermore, this study showed that BJJGT treatment prevented muscle atrophy and the denervation of neuromuscular junctions in the gastrocnemius of ALS hSOD1^{G93A} mice.

Gamisoyo-San (GSS) has often been used as an herbal prescription to improve stress-related neuropsychological disorders, anorexia, insomnia, functional dyspepsia dysmenorrhea, and infertility.^{41,42} Cai et al. observed that GSS decreased the expression of microglial cells and astrocytes, and prevented neuronal loss in the spinal cord of ALS mice.⁴³ Furthermore, GSS attenuated the expression levels of oxidative stress-related proteins (transferrin, HO-1, and BAX) and metabolism dysfunction in the spinal cord of ALS animals.⁴³ Park S et al. demonstrated that GSS

ameliorated inflammation through the inhibition of inflammatory proteins (TLR4 and CD11b) in the gastrocnemius in hSOD1^{G93A}.⁴⁴

Jaeumganghwa-Tang (JGT) is useful for the treatment of bronchitis and tuberculosis⁴⁵ and anti-allergic inflammatory responses.⁴⁶ In ALS animals, Lee et al. shown that JGT treatment improved motor function using a footprint behavior test. They found that JGT treatment decreased the levels of inflammatory proteins (Iba-1, TLR4, and TNF- α) and oxidative stress-related proteins (transferrin, ferritin, HO1, and NQO1) in the spinal cord of ALS mice.⁴⁷ From these data, we can see that herbal prescriptions such as BJJGT, GSS, and JGT would be helpful in improving the immune response and delaying disease progress in ALS.

Huolingshengji (HLSJ) improves vital energy (Qi) and the function of spleen and kidney, and invigorate yang in order to relieve the TCM pathogenesis of flaccid syndrome.⁴⁸ Zhou et al. demonstrated that HLSJ increased the lifespan and prevented motor neuron loss through ameliorating muscle atrophy and inflammatory effects in SOD1^{G93A} ALS mice.⁴⁸ In addition, Sui et al. showed that HLSJ treatment for 12 weeks decreased the Advanced Norris scale score in ALS patients. Moreover, the total effective rate in the HLSJ-treated ALS patients (15.15%) was similar to that in the riluzole-treated group (16.13%). In addition, TCM syndrome was significantly improved in HLSJ-treated ALS patients (33.33%) compared to in the riluzole-treated group (6.45%). These data suggest that HLSJ may be an effective therapy for ALS.⁴⁹

Dihuang Yinzi (DHYZ) is a classical traditional Chinese medicine (TCM) prescription. DHYZ is used for treating neurological disorders, like speech and language impairment and motor paralysis. In a case report, Qiu et al. showed that DHYZ extended the survival and improved symptoms of muscle fibrillation and low muscle strength in a female ALS patient. This result suggested that DHYZ could be helpful for the treatment of ALS patients, and further rigorous randomized controlled trials are needed.⁵⁰

Jiawei Sijunzi (JWSJZ) is a famous traditional decoction which nourishes the spleen and enriches body vitality.⁵¹ JWSJZ treatment for 3 or 6 months resulted in improved neurologist evaluation of ALS patients through the ALS functional rating scale (ALSFRS), compared with prior to the treatment.⁵¹ These data suggest that the JWSJZ decoction may be safely used to treat ALS and delay the disease progression.

3.3. Other types CAMs for ALS

Nutritional supplements, massage, and relaxation techniques are also included in the most commonly considered CAM therapies. Most of the currently used nutritional supplements, including vitamins, minerals, proteins, and amino acids, have antioxidant properties. Nutritional supplements provide nutrients and remedy deficiencies in the body. The beneficial effects of using nutritional supplements in treating ALS have been demonstrated in both pre-clinical and clinical studies.

Creatine was synthesized in the kidney and liver, and then transported to the muscles and brain via blood for energy production. In an ALS animal model, creatine treatment improved motor function, maintained body weight, and extended survival.⁵² However, another study showed that creatine treatment was not effective for improvement of muscle function in ALS animals.⁵³ In the clinical study, creatine intake at doses 5–10 g per day did not extend survival, ALSFRS-R progression, or the percentage of predicted forced vital capacity (FVC) progression.⁵⁴

Vitamin D is a fat-soluble secosteroids and helps in increasing intestinal absorption of calcium, magnesium, and phosphate. In ALS patients, Camu et al. reported that the risk of death was 4 times increase in those with severe vitamin D deficiency group compared to the group with normal vitamin D group.⁵⁵ In addition, another clinical study showed that patients with ALS were detected low

level of vitamin D. Patients taking 2000 international units (IU) of vitamin D daily declined ALSFRS-R score in the 9 months but was not significant at 3 or 6 months.⁵⁶

Vitamin E as a fat-soluble antioxidant includes four tocopherols and four tocotrienols. In ALS transgenic mice, treatment with vitamin E delayed disease onset and slowed progression, but did not prolong survival.⁵⁷ Graf et al. could not demonstrate the efficacy of vitamin E therapy in ALS patients.⁵⁸ However, Wang et al. interestingly showed that vitamin E intake may reduce the risk of developing ALS.⁵⁹ Therefore, the effect of vitamin E in ALS patients is controversial, but it should be used with caution since hypervitaminosis E could increase the risk of bleeding.⁶⁰

To investigate the use of CAM therapy in the treatment of ALS in China, Pan et al. surveyed 12 hospitals in Shanghai. This study reported that 229 (99% of the total) of 231 (qualified people) used at least one CAM therapy for the treatment of ALS. Vitamins and Chinese herb decoctions, Chinese herb compounds, massage therapy, and acupuncture were the five most commonly used therapies.⁶¹ In addition, Pan et al. showed that CAM therapy alleviated weakness and fatigue, muscle atrophy to inhibit ALS progression and side effects associated with riluzole.⁶¹

4. Summary of the effects of CAM therapy in ALS

This review summarized the effects of CAM therapy in ALS human and animal models (Table 1). Several types of CAM are used for treating ALS including acupuncture and herbal medicines. In ALS patients and animal models, acupuncture or electroacupuncture (EA) improved motor activity and the pulmonary system. This suggests that acupuncture could be helpful for increasing the body's vital energy, which is connected to bodily organs and functions, and circulates throughout the body via the meridian system, because ALS patients are deficient in qi, according to the theory of oriental medicine.⁶²

In ALS animal models, herbal medicine modulates the immune system to protect motor neurons and motor activity. Herbal medicine may regulate immune function in the spinal cord, brainstem, lung, spleen, and muscle through inhibiting proinflammatory cytokines and glial cell activation. In a clinical study, an herbal medicine formula improved disease symptoms according to a neurological evaluation, but the sample size was too small to evaluate the effects of CAM therapy.

ALS has multiple pathological mechanisms, such as neuroinflammation, oxidative stress, glutamate excitotoxicity, protein misfolding, cytoskeletal abnormalities, defective axonal transport, and inadequate growth factor signaling, leading to motor neuron death and muscle paralysis. Since herbal medicine contains various components which display multiple effects, it would be helpful in alleviating the pathological phenomena affecting patients with ALS, and in this way, increase the quality of life for the families of patients. However, more researches must be performed regarding the efficacy and safety of CAM therapy, and clinical studies will be required to demonstrate the effects of CAM therapy in ALS.

Author contributions

MC searched the papers and drafted the manuscript; EJY conceptualized the review; searched for additional information and revised critically; MC & EJY read the final manuscript and agreed to the submission.

Conflict of interest

The authors declare no conflict of interest.

Funding

This study was supported by the Korea Institute of Oriental Medicine (KIOM) under Grant C18040.

Ethical statement

Not applicable.

Data availability

Data will be made available upon request. All data used for this study are from previous studies which are included in References.

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