

Study On the Improvement of Amyotrophic Lateral Sclerosis in Mice by Traditional Chinese Medicine Yiqi Shengji Decoction with Combined Acupuncture

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ABSTRACT

Objective: To describe the composition, efficacy, production process and advantages of Yiqishengji decoction, a new product developed by our team. Clinical experiments prove that acupuncture can improve the intestinal flora of amyotrophic lateral sclerosis patients and slow down amyotrophic lateral sclerosis. Experimental method. On March 2024, 107 patients with ALS were recruited in this study and the generation of Yiqishengji decoction was made for them. Forty ALS-SOD1G93A mice were also given Yiqishengji decoction compared with control group. Results. After 7 days' treatment of Yiqishengji decoction with combined acupuncture, the behavior of both patients and mice was improved. 99% of the patients felt comfortable after drinking. A small part of the taste may be slightly sweet, salty and milky. Conclusion. Yiqishengji decoction with combined acupuncture might improve the symptoms of amyotrophic lateral sclerosis in ALS-SOD1G93A mice and its taste deserves to be more widely promoted.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a chronic, progressive neurodegenerative disease. According to the clinical signs and symptoms, it can be divided into three types. Primary amyotrophic lateral sclerosis, the main manifestations were weakness of upper and lower limbs, muscle atrophy, and finally respiratory failure. Patients with medulla amyotrophic lateral sclerosis have no obvious symptoms of peripheral spinal cord damage in the first six months of morbidity. After that, there will be obvious symptoms such as unclear speech, vague pronunciation, inability to speak, dysphagia, fasciculation, tongue atrophy and so on. Pyramidal amyotrophy and lateral sclerosis, characterized by severe muscle spasticity, paraplegia, or quadriplegia.

Amyotrophic lateral sclerosis is a rare disease, with an incidence of about 3 to 7 per 100000. Most of them are 30-60 years old, and the majority of patients are over 45 years old. Men are always more than women. Although that mechanism of morbidity in amyotrophic lateral sclerosis remains unclear, however, it is generally believed to be related to genetic and environmental factors, oxidative stress, mitochondrial dysfunction, toxic effects of excitatory amino acids, calcium homeostasis, Imbalance, abnormal aggregation of proteins, etc Zhou et al. (2024). Familial amyotrophic lateral sclerosis (fALS) is present in 10% of patients and sporadic amyotrophic

lateral sclerosis. Edaravone and riluzole are the only two drugs approved by the FDA to delay the progression of ALS, and they are not only expensive but also have a poor prognosis. The quality of life of patients is worrying, and more research and investment are urgently needed.

The modern medical science divides the pathogenesis of the flaccidity syndrome morbidity into approximately eleven types according to the theories left by the ancient physicians, They are lung heat, deficiency of spleen and stomach, deficiency of liver and kidney, excessive stomach heat, hyperactivity of fire due to yin deficiency, deficiency of essence and blood, deficiency of primordial qi, deficiency of extra meridians, retention of damp-heat, invasion of wind-cold-dampness, deficiency and excess wang et al. (2012). Clinically, the survival time of patients with amyotrophic lateral sclerosis is 3 to 5 years. Most of them died because of extreme difficulty in breathing and severe muscle atrophy.

Different from common neurological diseases such as AD, PD, and senile cerebrovascular disease, amyotrophic lateral sclerosis receives relatively low social attention, less investment, less output, and relatively slow development. However, there are more than 23000 new patients with amyotrophic lateral sclerosis in mainland China every year, excluding those misdiagnosed as other diseases. Therefore, what we think of as "rare diseases" is not rare.

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In recent years, with the implementation of the "14th Five-Year" National Health Plan and the promotion of research on traditional Chinese medicine by various policies, Cai Lei's "Ice Breaking Post" The "live broadcast room" has aroused widespread concern in the society and the desire of ALS patients to thaw. At present, modified Sijunzi Decoction, Guiluerxianjiao Prescription and Fuyuan Prescription are mentioned in the published papers on traditional Chinese medicine compound prescription for the treatment of ALS. Although Fuyuanshengji Decoction and Yiqiqiangji Decoction have certain curative effect on the alleviation of ALS, they cannot play the role of meal substitution. ALS patients are in urgent need of a nutritional meal replacement that uses the homology of medicine and food to slow down the course of amyotrophic lateral sclerosis to meet their daily nutritional needs. At the same time, improve the quality of life.

It is estimated that there are about 60,000 patients in China, and with the aging of the population, the population of ALS patients will continue to expand. Only about 1/3 of Chinese ALS patients can afford the price of riluzole, and no drug can cure them completely, and there are few drugs to improve symptoms. With the aging of the population, the prevalence of amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease is increasing in China. The demand of patients is increasing and the market scale is expanding. With the increase in the number of ALS patients, the demand for special nutritional meal replacement foods may rise. Therefore, the quality and safety of food is essential to meet the specific nutritional needs of patients. In terms of functional characteristics, food should be easy to swallow and provide enough energy and nutrition. The price also needs to be balanced between affordability and quality.

We have learnt from the viewpoint left by ancient physicians that "Yangming meridian is important taken for the treatment of flaccidity syndrome". Improving Muscle Mass by Regulating Intestinal Microflora Status of Muscular Atrophy Patients Based on "Gut-Muscle Axis" Theory Wang et al. (2022), Our team wants to combine Chinese medicine Yang et al. (2022) with acupuncture He et al. (2021), LI et al. (2023) regulates the intestinal microflora of patients with amyotrophic lateral sclerosis, an enteral nutrient was developed to regulate intestinal flora for the treatment of amyotrophic lateral sclerosis and to play the role of nutritional meal replacement Nutrient.

Ingredients and efficacy of Yiqishengji decoction

According to the published research Yang et al. (2022), Wu et al. (2024), Monomers, active ingredients or components of many traditional Chinese medicines can regulate intestinal microecology and improve intestinal flora disorders. Therefore, the team selected five kinds of Chinese medicinal materials from the homology of medicine and food to improve intestinal flora. And can be

use for improving that characteristic of liver, spleen and kidney deficiency, lung heat and the like of ALS patients.

Yiqishengji decoction is a dietary substitute designed to maintain and promote the physical health of ALS patients, which is the first meal replacement drink in China specifically developed for amyotrophic lateral sclerosis patients, the one can alleviate the disease by improving the intestinal flora Gong et al. (2021), the one uses homologous ingredients of medicine and food.

Yiqishengji decoction not only adopts six traditional Chinese medicines with homology of medicine and food as main materials. At the same time, ten kinds of food with high nutritional value are selected as auxiliary materials. The product comprises the following components:

The effects of each component of the Yiqishengji decoction are as follows:

Six medicinal and edible homologous main ingredients:

Radix Astragali: Sweet and warm. Belonging spleen and lung meridians. Its effects include tonifying qi and assisting yang, promoting fluid and nourishing blood, removing stagnation and dredging arthralgia, removing toxin and promoting granulation. It is primarily therapeutic syndrome of spleen-qi deficiency, syndrome of lung-qi deficiency, syndrome of spontaneous perspiration due to qi deficiency, deficiency of qi and blood, difficult ulceration and decay of sores and ulcers, and difficult healing of ulcer for a long time.

Herba epimedii: Sweet and neutral. Belonging liver and spleen meridians. Invigorating the spleen and lung, nourishing the blood and promoting the production of body fluid. Treating qi deficiency of spleen and lung, anorexia, lassitude, cough, asthenia and asthma, deficiency of qi and blood, sallow complexion, palpitation, shortness of breath, thirst due to body fluid deficiency, and diabetes due to internal heat. It can also promote the production of gastrointestinal bifidobacteria Li et al. (2011).

Poria: Sweet and neutral. Belonging heart, lung, spleen and kidney meridians. Promoting diuresis and eliminating dampness, invigorating spleen, calming heart and tranquilizing mind. Also, can be used for treating edema, oliguria, phlegm retention, dizziness, palpitation, spleen deficiency, anorexia, loose stool, diarrhea, restlessness, palpitation, insomnia.

Rhizama Dioscoreae: Sweet and neutral. Belonging spleen, lung and kidney meridians. Invigorating qi and nourishing yin, tonifying spleen, lung and kidney, and arresting seminal emission and leucorrhea. It also can be used for treating anorexia due to spleen deficiency, chronic diarrhea, asthma and cough due to lung

Table 1: Nutritional components of Yiqishengji decoction

Ingredient/100g	Energy/kcal	Protein/g	Fat/g	Carbohydrate/g	Dosage/g
Fructus Chaenomelis	29	0.4	0.1	7	2.5
Rhizama Dioscoreae	327	9.4	1	70.8	2.5
Poria	16	1.2	0.5	1.7	2.5
Herba epimedii	312	10.4	1.8	53.7	2.5
Radix Astragali	287	14.9	1	33.4	5
Solomon's seal	50	1.15	1	17.5	5
Oat	367	15	0.15	61.6	20
Gorgon euryale seed	353	8.3	6.7	79.6	20
Chinese Date	122	1.1	0.3	28.6	20
Highland barley	339	8.1	1.5	73.2	20
Low-lactose milk powder	478	26.5	22	43.4	200
Fried rice	403	10.2	2.1	84.5	50
Peanut	589	26.5	44.8	20	50
Almond	597	25.7	51	9	40
Apple	60	0.2	0.6	15	40
Coconut	241	3.3	33.5	15	20
	2033.15	90.2075	96.6975	206.125	500
		22.95%	24.60%	52.45%	

deficiency, spermatorrhea due to kidney deficiency, leukorrhagia, frequent micturition, and diabetes due to deficiency heat.

Fructus Chaenomelis: Sour and warm. Belonging liver and spleen meridians. Relaxing muscles and tendons, activating collaterals, eliminating dampness and regulating the middle warmer. It also can be used for treating arthralgia and spasm due to dampness, soreness and pain of waist and knee joint, vomiting and diarrhea due to summer-heat and dampness, spasm and pain of tendons, and edema due to beriberi.

Solomon's seal: Sweet and neutral. Belonging spleen, lung and kidney meridians. Invigorating qi, nourishing yin, invigorating spleen, moistening lung, and tonifying kidney. It also can be used for treating qi deficiency of spleen and stomach, fatigue, fatigue, stomach yin deficiency, xerostomia, anorexia, dry cough due to lung deficiency, hemoptysis, deficiency of essence and blood, soreness of waist and knee, and symptoms such as early white hair, internal heat and thirst.

Ten major accessories:

Oat: Sweet and neutral. Belonging spleen and stomach meridians. It can smooth intestines and inducing labor, arresting sweating and stopping bleeding. It is rich in vitamins and minerals and has strong antioxidant effect.

Gorgon euryale seed: Sweet and astringent in taste,

neutral in nature. Belonging spleen and kidney meridians. Stimulate the appetite, invigorate the spleen and strengthen the kidney.

Chinese Date: It is the fruit of jujube of Rhamnaceae. Sweet and warm. Belonging heart, spleen and stomach meridians. Tonifying the middle-jiao and qi, strengthening the spleen and stomach.

Highland barley: It is the kernel of highland barley of Gramineae. Salty in taste, neutral in nature. Belonging liver, spleen and lung meridians. Removing dampness and inducing perspiration, lowering qi, widening the middle, and strengthening the essence.

Low-lactose milk powder: It is made by dehydration of skim milk made from milk of cattle or Buffalo. Sweet and neutral. Belonging heart, lung and stomach meridians. Invigorating qi and nourishing blood, tonifying lung and stomach, promoting the production of body fluid and moistening intestines. It is rich in protein and amino acids and is suitable for patients with lactose intolerance.

Fried rice: An annual herbaceous cereal crop belonging to the genus *Panicum* of the family Gramineae. It can nourish the stomach, tonifying the middle-jiao and qi, strengthening the spleen and benefiting the lung.

Coconut: The fruit of a plant of the genus *Cocos* in

the palm family. Sweet and neutral. Belonging heart and spleen meridians. Tonifying deficiency and strengthening, benefiting qi and expelling wind.

Peanut: The seed of the leguminous plant *Arachis hypogaea*. Sweet and neutral. Belonging spleen and lung meridians. Nourishing spleen and stomach, moistening lung and resolving phlegm, nourishing and regulating qi, clearing throat and stopping malaria.

Apple: The fruit of the Rosaceae family. Sweet and cool. Belonging spleen, stomach and heart meridians. Promoting healthy intestinal microflora, reducing inflammation, promoting the production of body fluid and moisten the lung, strengthening the spleen and stomach.

Almond: Bitter and acrid. Belonging lung and large intestine meridians. Moisten the lung and relax the stomach, eliminate phlegm and relieve cough.

The six natural plant raw materials with homology of medicine and food and the ten auxiliary materials have synergistic effect, can relieve the symptoms of amyotrophic lateral sclerosis while supplementing the daily required nutrition.

Advantages of Yiqishengji decoction

At present, the existing Chinese herbal compounds Bao et al. (2016) have a certain effect on the alleviation of amyotrophic lateral sclerosis Jin et al. (2013), wang et al. (2009), Su et al. (2006), but cannot play a role in meal replacement.

Nutritional meal replacements for amyotrophic lateral sclerosis (ALS) include Propulac, Nengquanli Nutrition Suspension (Nuditia Pharmaceutical (Wuxi) Co., LTD.), Ruidai, Ruineng (Huarui Pharmaceutical Co., LTD.), Ruisen (Fresenius Ka Biarui Pharmaceutical Co., LTD.), and Ansu (ABBOTT LABORATORIES B.V.). Production). The shortcomings of these nutritional meal replacement include high price, inconvenient to take drugs, poor taste, low dietary content, inconvenient storage, and non-application of the same origin of medicine and food. The main reason is that most of the existing enteral nutrients are directly composed of small molecules such as proteins and carbohydrates, but those products ignoring the taste problem.

Compare with that prior art, Yiqishengji decoction has the following advantage:

As the first enteral nutrient with the homology of medicine and food, the ratio of ingredients meets the recommended energy intake of patients with amyotrophic lateral sclerosis. It is specially designed for patients with amyotrophic lateral sclerosis. It is consistent with the problem of high basal energy consumption in patients with amyotrophic lateral

sclerosis (energy value of the product: 1,261.87 kcal/510g). It is rich in dietary fiber, which meets the requirements of Chinese dietary residents (protein 15% -20%, fat 25% -30%, Carbohydrate 50% -60%). Besides, that auxiliary material has high nutritional value, has the function of synergistically protecting multiple system of a human body (containing vitamin, crude fiber and the like, regulate immunity, protect cardiovascular and nervous system, etc.).

Except being suitable for amyotrophic lateral sclerosis patients, Yiqishengji decoction can also be suitable for other patients who need supplement nutrition. It can improve the content of beneficial bacteria and inhibit the content of harmful bacteria by acting on intestinal flora while supplementing daily required nutrients, achieve the effects of invigorating spleen, protecting liver, strengthening kidney and tonifying lung Teng et al. (2021), slow the progression of amyotrophic lateral sclerosis. After the successful production of the first product, the team members have personally tasted it, and the product taste design is balanced in nutrition and moderate in sweetness.

In addition, the raw materials used in Yiqishengji decoction are easy to obtain, and the price is lower than all enteral nutrients in the market. While ensuring the taste, it provides the basic nutrition for the human body every day. The prepared powdery product is taken by being brewed, which is convenient for patients with dysphagia to use and overcomes the problem of short preservation time.

The preparation and application method of Yiqishengji decoction

The Yiqishengji decoction can be prepared into proper oral preparations according to needs, including powder and granules. The powder is prepared by grinding and mixing the raw materials of the components. The granule is prepared by mixing the powder prepared from the components with hot water or warm water.

In the product packaging design, we use vacuum packaging, so the appearance is durable, distinctive, easy to save. The packaging material is high temperature resistant and recyclable polypropylene, which is easy to brew with hot water. The product has a paper filter screen, which can filter the residue and bring better taste to patients. The design of the bottle mouth is generally suitable for all kinds of patients, which can be convenient for patients with normal diet to take, and can also be suitable for patients with nasal feeding through the stomach tube to eat. Product packaging reserved crease, easy to squeeze, ready to throw away. At the same time, we strive to facilitate the preparation of daily diet for patients' families and reduce the pressure of life.

The eating method comprises the following steps:

Table 2: Competitive product analysis

Name	Day rate	suitable for a low-slag diet or not	There is indication restriction or not	Whether it contains dietary fiber	Whether easy to store	
Clinical commonly used enteral nutrition preparation products	Yiqishengji decoction	lowest	√	×	√	Store at room temperature and refrigerate for 24h after opening
		75yuan/day				
	Baipuli	It's too expensive for normal gastrointestinal patients	√	×	×	
	Nengquanli	moderation	×	√	√	
	Ruixian	lower	×	√	√	
	Ruineng	Commonly used in severe cases. Expensive.	×	√	√	
	Ruidai	higher	×	√	√	
	Weiwo	highest	√	√	×	
Ansu	Low	√	×	×	√	
	90yua/day					

The raw materials of the components are subjected to impurity removal, purification, air drying and pulverization by a pulverizer, the peanuts and the almonds are sieved by a 40-mesh sieve. The rest of the materials are sieved by 60 meshes. Weighing the powder according to the composition proportion and uniformly mixing the powder to prepare the required dosage form.

Animal experiment verification of Yiqishengji decoction

In order to verify that Yiqishengji decoction has the effect of improving muscle atrophy, the team first conducted animal experiments after the first generation of products were made. The specific experimental process is as follows:

SOD1G93A mouse, which is recognized as an animal model of ALS in the world, was used as the research object. Study whether this product can slow down the course of ALS, supplement nutrients needed by life, and has no toxic effect on life.

According to the product composition, the formula was used to calculate: human (60 kg) dose ÷ 7.7 = mouse dose/kg, the number of grams of Yiqishengji decoction needed by the mice in the experimental group for one meal was calculated. According to the calculated dosage and the actual experimental condition, the dosage of Yiqishengji decoction was adjusted to 5g per mouse per meal.

In This experiment, 8-week-old male ALS-SOD1^{G93A}

mice were divided into model group (n = 10) and Yiqishengji decoction group (n = 10). All of them were reared in a Specific pathogen free (SPF) environment with constant temperature (25-27 °C) and humidity. The mice in Yiqishengji decoction group were treated with 5g of Yiqishengji decoction, and the rats in the model group were fed with the same amount of sterilized SPF granular rodent feed three times a day, and ensure the same amount of water supply. According to the growth characteristics of ALS-SOD1G93A mice, the mice in the Yiqishengji decoction group were given intragastric administration for 7 days. Observe the state of mice during the experimental period of 0 day and 7 days after intragastric administration, and weigh the muscle strength once a day. After 7 days of intragastric administration, the body weight and muscle strength of the model mice and the mice in the Yiqishengji decoction group were detected before and after intragastric administration, and the results are shown in Table 3.

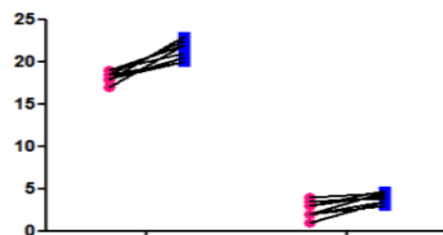


Table 3: Results of mice after intragastric administration for 7 days

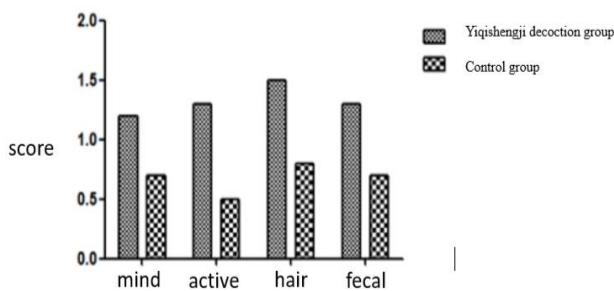
Evaluation index: The general condition of mice was evaluated according to the principle of clinical research index of traditional Chinese medicine in the treatment of spleen deficiency syndrome. The mice were separated into observation cages every day, and the

general state of the mice was observed and scored. Including mental status, activity status, hair status and stool status, each index accounts for 25% of the weight, and the scoring criteria are shown in Table 4. The results are shown in Table 5.

Table 4: Scoring criteria for general status of mice.

Observation index	Score		
	0	1	2
State of mind	Sleepiness and lack of strength	The spirit is tired and weak	Normal
Active status	Sleepiness and moveless	Moveless and be lazy	Lively and active
Hair status	Unkempt and unclean	Less light and slightly disorderly	Bright and clean
Fecal status	Loose stools	Soft	Normal

Table 5: Evaluation of general Status of mice.



It can be concluded from the above experiments that the clinical signs and symptoms scheme of Yiqishengji decoction for improving amyotrophic lateral sclerosis by changing intestinal flora is feasible. Yiqishengji decoction can increase the content of beneficial bacteria in the intestinal tract and inhibit the growth of harmful bacteria in the intestinal tract, to alleviate the progress of muscle atrophy, dysphagia, fasciculation and other symptoms in ALS patients. The traditional Chinese medicine can tonify the spleen, protect the liver, strengthen the kidney and benefit the lung, improve the quality of life of ALS patients and support healthy qi. The auxiliary material are used for supplement that daily required nutrition and realizing the function of replacing meal.

Clinical feedback of Yiqishengji decoction

As of March 2024, 107 patients with ALS were recruited in this study, and the second generation of Yiqishengji decoction was made for them. Patient perceptions and opinions were collected and a questionnaire was developed. After tasting by 107 patients, the overall taste was evaluated as good.90% of the patients felt satiety immediately, and 77% of the

patients still felt satiety after 30 minutes.99% of the patients felt comfortable after drinking.

A small part of the taste may be slightly sweet, salty and milky, resulting in weak taste, and we will further improve it according to the evaluation.

Table 6: Investigation results of ALS patients' taste of Yiqishengji decoction.

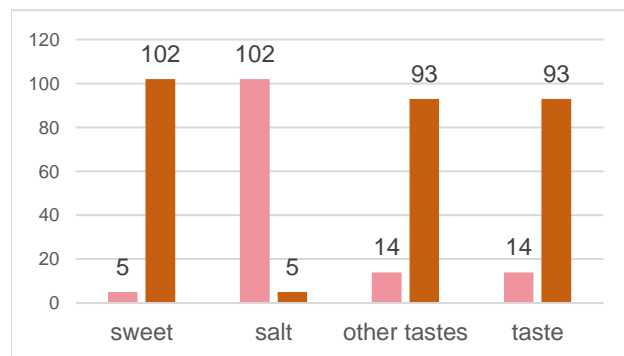
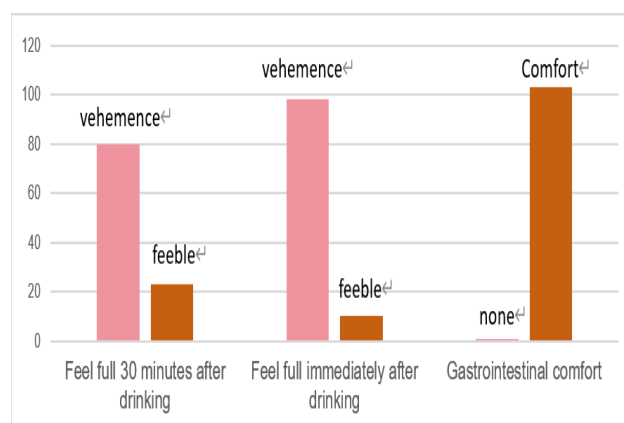


Table 7: Patient Satiety and Gastrointestinal Comfort Survey Results



DISCUSSION

At present, there is no effective cure for ALS, and the treatment is mainly to delay the disease process and improve the quality of life of patients. The main symptoms of ALS are deficiency of qi and blood, phlegm blocking collaterals, blood not dissolving tendons, qi deficiency of heart and spleen, and yin dryness of liver and kidney. In traditional Chinese medicine, ancient and modern physicians generally focus on the causes of lung heat and withered leaves, weakness of spleen and stomach, hyperactivity of fire due to yin deficiency, and deficiency of both qi and blood. The damaged organs are mostly lung, spleen and kidney, and there are deficiency and excess syndromes such as dampness, phlegm and blood stasis. The proposed treatment methods include taking Yangming alone, nourishing yin and clearing fire, clearing lung and moistening dryness, tonifying spleen and stomach, clearing blood and eliminating dampness, regulating liver and kidney, and promoting blood circulation, remove blood stasis Zhou et al. (2014). The team aims to meet the daily nutritional needs of ALS patients, improve their quality of life and slow down the process of disease aggravation. Yiqishengji decoction is the first substitute liquid food product specially designed for ALS patients in China, and the Chinese herbal ingredients in the product include Radix Astragali, Herba epimedii, Poria, which have been used repeatedly in existing Chinese herbal compounds to treat ALS.

The six medicinal and edible homologous medicinal materials are matched with acupuncture points to effectively regulate the intestinal flora of ALS patients. It also can relieve complication such as anorexia and abnormal emotion (such as depression and irritability). Yiqishengji decoction has moderate sweetness, and the mouthfeel is not too thick and greasy. For patient in critical condition, it is expected to slow down the progress of the disease and prolong the life span of patients.

The nutrient content of the Yiqishengji decoction reaches the standard and meets the dietary requirements of the patients with amyotrophic lateral sclerosis: the protein is 23%, the fat is 25%, Carbohydrates 52%. Every 500g can provide 2000kcal energy, which can meet the daily energy intake of 60 kg healthy people. In addition, the product is also rich in crude fiber, vitamin B1, vitamin B2 and a plurality of essential amino acids for human bodies. It has the functions of regulating immunity, protecting cardiovascular and nervous system, etc. Not only that, the packaging design of drinks is conducive to the connection of gastric tubes or nasal feeding tubes, and it is easier to supplement nutrition through gastrostomy or nasal feeding.

However, the product still has the problem of lack of

sufficient clinical experimental evidence to prove the curative effect. At present, the viewpoint of "taking Yangming alone to treat flaccidity syndrome" and the theory of "intestine-muscle axis" have been put forward.

Our experiment is based on the following ideas: Starting with the intestinal flora, to investigate the effect of Chinese medicine and acupuncture on the development of amyotrophic lateral sclerosis. It is consistent with the results of our experimental study on the intestinal flora of ALS patients, which shows that our idea is based on scientific evidence and has research prospects.

DECLARATIONS

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Authors' contributions

Conceptualization, Wang TQ and Zhang YW; Statistics, Zhao H and Zhou RQ; Supervision, Wang TQ. All the authors read and approved the final manuscript for submission.

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