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Buzhong Yiqi decoction attenuates acquired myasthenia by regulating the JAK2/STAT3/AKT signaling pathway, inhibiting inflammation, and improving mitochondrial function

Yuanfeng Zeng[a], Haihua Zeng[b]*, Xinghua Liu[c], Tingting Fan[d]

[a]Department of Emergency, The Third Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China
[b]Department of Ultrasound, Foshan Traditional Chinese Medicine Hospital Chancheng High tech Zone Hospital, Foshan, China
[c]Department of Neurology, The Third Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China
[d]Department of Hematology and Oncology, The Third Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China

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Abstract
Acquired myasthenia (AM), a debilitating autoimmune disease, is typically characterized by skeletal muscle fatigue and weakness. Despite advances in myasthenia gravis treatment, current approaches remain unsatisfactory and many result in unexpected side effects. Traditional Chinese medicine has shown great potential in the treatment of myasthenia gravis, including relieving myasthenic symptoms, improving patients' quality of life, and reducing Western medicine side effects. This study investigates the protective effects and mechanism of BZYQD in mice with acquired myasthenia. BZYQD alleviates the reduced grip strength and increased expression of MAFbx and MuRF-1 in mice with acquired myasthenia. It also reduces levels of pro-inflammatory factors IL-1ß, IL-6, and TNF-α in the mouse serum. In addition, BZYQD reduces ROS accumulation and the mitochondrial ROS production rate, while increasing ATP levels and mitochondrial membrane potential in mice with acquired myasthenia. Moreover, BZYQD decreases the expression of p-JAK2, p-STAT3, and p-AKT in the skeletal muscle of mice with acquired myasthenia. In summary, BZYQD reduces inflammation, enhances mitochondrial function, and regulates the JAK2/STAT3/AKT signaling pathway to treat acquired myasthenia.

***Corresponding author:** Hailong Zeng, Department of Ultrasound, Foshan Traditional Chinese Medicine Hospital Chancheng High tech Zone Hospital, No. 10 Chunyang Road, Chancheng District, Foshan City, Guangdong Province, China. *Email address*: hh_zeng6@163.com

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Introduction

Acquired myasthenia (AM) is a debilitating autoimmune condition characterized by skeletal muscle fatigue and weariness.[1] Between 60% and 100% of sepsis patients subsequently develop acquired myasthenia, a condition that leads to persistent physical impairment due to muscle strength loss.[2] Several intricate and poorly understood pathophysiological processes contribute to this condition, including impaired autophagy, mitochondrial dysfunction, inflammasome activation, cell death, and necroptosis.[3] Recent research indicates that the accumulation of damaged mitochondria and reduced mitochondrial activity are significant initiators of acquired myasthenia.[4]

Traditional Chinese medicine has gained prominence in disease treatment in recent years. Research suggests that integrating Western and traditional Chinese medicine has produced significant outcomes in managing acquired myasthenia. There are distinct benefits to combining traditional Chinese and Western medicine rather than relying solely on Western medicine.[5] In traditional Chinese medicine, acquired myasthenia falls under the category "impotence syndrome". Its primary pathophysiology consists of the following: the loss of blood and bodily fluids; the loss of essence and qi in the five internal organs; the loss of muscles and bones; and the incapacity to create bones and joints.[6] Traditional Chinese medicine prescribes herbs with diverse functions, containing multiple bioactive compounds that act synergistically on specific targets 7). Buzhong Yiqi decoction contains traditional Chinese medicines such as astragalus, Atractylodes, and Codonopsis pilosula, which strengthen the spleen, nourish it, and benefit lung function. Angelica sinensis, cohosh, bupleurum, tangerine peel, and licorice nourish blood, replenish qi, strengthen the spleen, and increase yang qi.[5] Current studies demonstrate that Buzhong Yiqi Decoction can alleviate myasthenia symptoms by reducing muscle junction damage, inhibiting the development of anti-acetylcholine receptor antibodies (AchR-Ab), and regulating humoral immune function through medication interactions.[8] Studies have elucidated BZYQD's mechanisms and effects in preventing cerebral ischemic damage and have highlighted its potential in modulating gut microbiota for ischemic stroke treatment.[9] Buzhong Yiqi Decoction has also been shown to prevent and treat loperamide-induced constipation in rats by regulating the arachidonic acid pathway.[10] However, the specific role and mechanism of Buzhong Yiqi Decoction (BZYQD) in acquired myasthenia are not yet fully understood.

In our study, we demonstrated that BZYQD reduces inflammation, enhances mitochondrial function, and regulates the JAK2/STAT3/AKT signaling pathway to treat acquired myasthenia.

Methods

Animal feeding

Male C57BL/6 mice were purchased from Beijing Huafukang Biotechnology Company at 6–8 weeks of age. Each animal was housed at temperatures between 21°C and 25°C under a 12-h light/dark cycle, with ad libitum access to clean water and standard laboratory feed.

Mice in the control group underwent no surgical procedures, while those on the model group received intraperitoneal injections of LPS (2.5 mg/kg, once daily for 3 consecutive days) and had their left hind limbs immobilized for 7 days. After 1 week, 18 randomly selected mice from the model group were intraperitoneally administered low, medium, and high doses of BZYQD. Mice were sacrificed after 14 days, and biological samples were collected for analysis.

BZYQT was prepared by decocting 18g astragalus, 9g licorice, 6g ginseng, 6g angelica, 6g orange peel, 6g cimicifuga, 6g bupleurum, and 9g atractylodes to 100% concentration. The concentrations of low, medium, and high doses were 1.78g/kg, 3.55g/kg, and 7.1g/kg, respectively.

Grip strength measurement

Gently pull the back of the mouse's tail after allowing its paw to grasp a horizontal metal rod attached to a force sensor. The force sensor automatically records the peak tension when the mouse's limbs are removed from the horizontal bar.

ELISA

After removing the mouse eyeballs to collect blood, the supernatant was obtained by centrifuging the mixture at 3000 rpm for 10 min to detect interleukins (IL-1ß and IL-6) and TNF-α levels. Rat tibialis anterior muscle tissue was cut into pieces. PBS was added to the minced skeletal muscle tissue at a ratio of 1:9 and ground. The homogenate was then centrifuged at 5000 g for 10 min, and the supernatant was taken to detect the ATP concentration. Interleukin (IL-1ß and IL-6), TNF-α, and ATP levels were assessed by ELISA (Beyotime, Beijing) according to the instructions in the kit.

Immunofluorescence

Fresh mouse skeletal organ tissue was embedded in embedding agent at −20°C. Section to a thickness of 10 μm, and adhered the specimens to an adsorption-type glass slide. DHE (Invitrogen, Carlsbad, CA, USA) was added dropwise to the sections and incubated at 37°C for 30 min in the dark. After washing with PBS, add anti-fluorescence quencher mixed with DAPI (Invitrogen, Carlsbad, CA, USA) was added and the sections were sealed. Finally, the sections were observed under a fluorescence microscope.

Mitochondrial reactive oxygen species production rate (ROS) detection kit

Mouse tibialis anterior muscle was cut into pieces, ground with PBS, and centrifuge to obtain the supernatant. Trypsin digestion solution and mitochondria isolation reagent were added to resuspend the tissue, and then centrifuged to obtain the supernatant for mitochondrial reactive oxygen species (ROS) production rate using the Mitochondrial reactive oxygen species production rate (ROS) detection kit (Beyotime, Beijing, China) according. to the instructions in the kit.

Mitochondrial membrane potential (JC-1) measurement

Sections were analyzed using fluorescent dye JC-1 (Nanjing Kaiji Biotechnology Co., Ltd., Nanjing, China) using CytoFLEX (Beckman Coulter, Brea, CA, USA). Cells were treated with 1 μl of JC-1 solution at 37°C for 20 min. Fluorescence was measured on a flow cytometer using excitation and emission spectra of 488 nm and 530 nm, respectively.

Western blot

Mouse tibialis anterior muscle was lysed with RIPA buffer (Solarbio, Beijing, China). Protein concentration was determined by the BCA method (Beyotime, Beijing, China). Denatured sample was loaded to a 12% polyacrylamide gel lane, performed SDS-PAGE electrophoresis, and transferred to a PVDF membrane via wet transfer. The membrane was blocked with blocking solution at room temperature for 2 h. Primary antibody was added to the blocked PVDF membrane and incubated overnight with shaking at 4°C. After washing the membrane with TBST, a secondary antibody (horseradishase-conjugated goat anti-rabbit IgG; 1:3 000, ZSGB-BIO, China) was added and incubated at room temperature for 60 min. The membrane was washed again with TBST, developed color with ECL reagent, exposed in a dark room, and the image was scanned and processed. GAPDH was used as the internal reference During the experiment to calculate the relative expression of proteins in each group. Band grayscale was analyzed using Image J software.

The primary and secondary antibodies used were as follows: JAK2 (1:1000, ab 108596, Abcam, UK), p-JAK2 (1:1000, ab195055, Abcam, UK), Akt (1:1000, ab 8805, Abcam, UK), p-Akt (1:1000, ab38449, Abcam, UK), STAT3 (1:1000, ab68153, Abcam, UK), p-STAT3 (1:1000, ab267373, Abcam, UK), MuRF-1 (1:1000, ab172479, Abcam, UK), MAFbx (1:1000, ab168372, Abcam, UK) and GAPDH (1:1000, ab8245, Abcam, UK).

Statistical analysis

Statistical analyzes were performed using GraphPad Prism version 8.0 (La Jolla, CA, USA). Data are expressed as mean±SD. The unpaired Student's t-test was used to determine differences between two independent groups, while one-way or two-way ANOVA was used to compare the means of multiple groups. Data with $P < 0.05$ were considered statistically significant.

Results

BZYQD attenuates muscle damage in mice with acquired myasthenia

Western blotting assessed the expression levels of the ubiquitin ligases MAFbx and MuRF-1, associated with muscle atrophy, to investigate the impact of BZYQD on muscular atrophy in mice with acquired asthenia. MAFbx and MuRF-1 are major factors causing skeletal muscle atrophy under various stress conditions.[11] Compared with the control group, mice in the AM group exhibited a significant decrease in grip strength and a significant increase in the expression of MAFbx and MuRF-1. Administration of BZYQD counteracted these effects in a dose-dependent manner (Figure 1A–D), demonstrating that BZYQD attenuates muscle damage in mice with acquired myasthenia.

BZYQD inhibits inflammatory response in mice with acquired myasthenia

The inflammatory response in mice with acquired myasthenia was detected using ELISA technology. Compared to the control group, levels of IL-1β, IL-6, and TNF-α were significantly increased in the AM group. Administration of BZYQD counteracted this increase in a dose-dependent manner (Figure 2), demonstrating that BZYQD inhibits systemic inflammation in mice with acquired myasthenia.

BZYQD attenuates mitochondrial function in mice with acquired myasthenia

Mitochondria play a crucial role in regulating the metabolic state of skeletal muscle. Therefore, we conducted immunofluorescence and other experiments to determine whether BZYQD can attenuate mitochondrial dysfunction in mice with acquired myasthenia. Compared to the control group, AM group showed significantly increased ROS accumulation and mitochondrial ROS production rate along with decreased mitochondrial membrane potential and ATP levels. Administration of BZYQD could offset this increase in a dose-dependent manner (Figure 3A–D), indicating that BZYQD attenuates mitochondrial dysfunction in mice with acquired myasthenia.

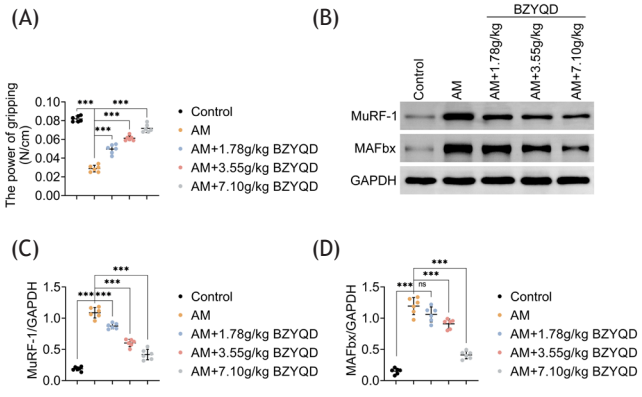

Figure 1 BZYQD attenuates muscle damage in mice with acquired myasthenia. (A) Grip strength test on mice. (B) Expression of MAFbx and MuRF-1. (C) Ratio of MuRF-1 to GAPDH gray value. (D) Ratio of MAFbx to GAPDH gray value. Values are represented as mean ± SD. ***$P < 0.001$ versus control group. n=6.

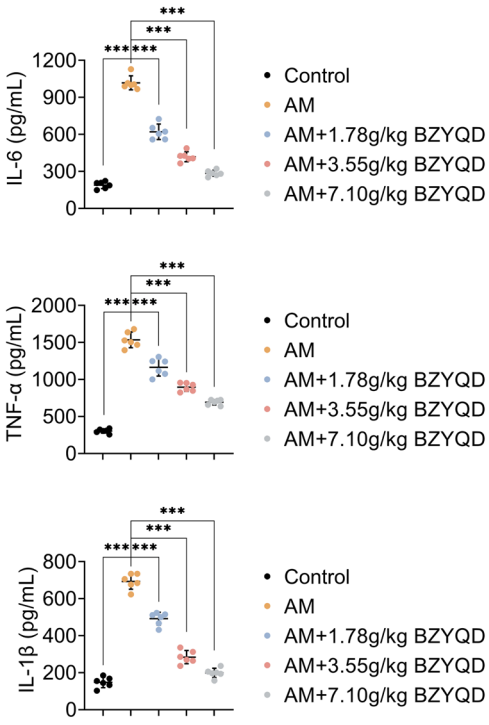

Figure 2 BZYQD inhibits inflammatory response in mice with acquired myasthenia. ELISA detects the levels of IL-1β, IL-6, and TNF-α in serum. Values are represented as mean±SD. ***$P < 0.001$ versus control group. n=6.

BZYQD inhibits JAK2/STAT3/AKT pathway

Finally, we investigated the effect of BZYQD on the JAK2/STAT3/AKT signaling pathway in mice with acquired myasthenia. Our results indicated a significant increase in p-JAK2, p-STAT3, and p-AKT levels in the AM group compared to the control group. Administration of BZYQD counteracted this activation in a dose-dependent manner (Figure 4), indicating that BZYQD inhibits the JAK2/STAT3/AKT pathway.

Discussion

Our data demonstrate that intraperitoneal injection of LPS as well as immobilization can successfully induce the AM model. BZYQD attenuates the reduced grip strength of AM model mice through the JAK2/STAT3/AKT pathway, increases the expression of MAFbx and MuRF-1 in skeletal muscle tissue, increases the expression of inflammatory factors (IL-1β, IL-6, and TNF-α) in serum, and increases mitochondrial dysfunction.

In recent years acquired myasthenia has been successfully treated by combining Western and traditional Chinese medicine.[12] Research has demonstrated the analgesic, hepatoprotective, and blood microcirculatory benefits of astragalus and atractylodes. Atractylodes is a crucial immunomodulator that can attenuate immunity and control gastrointestinal processes. Wolfberries, rich

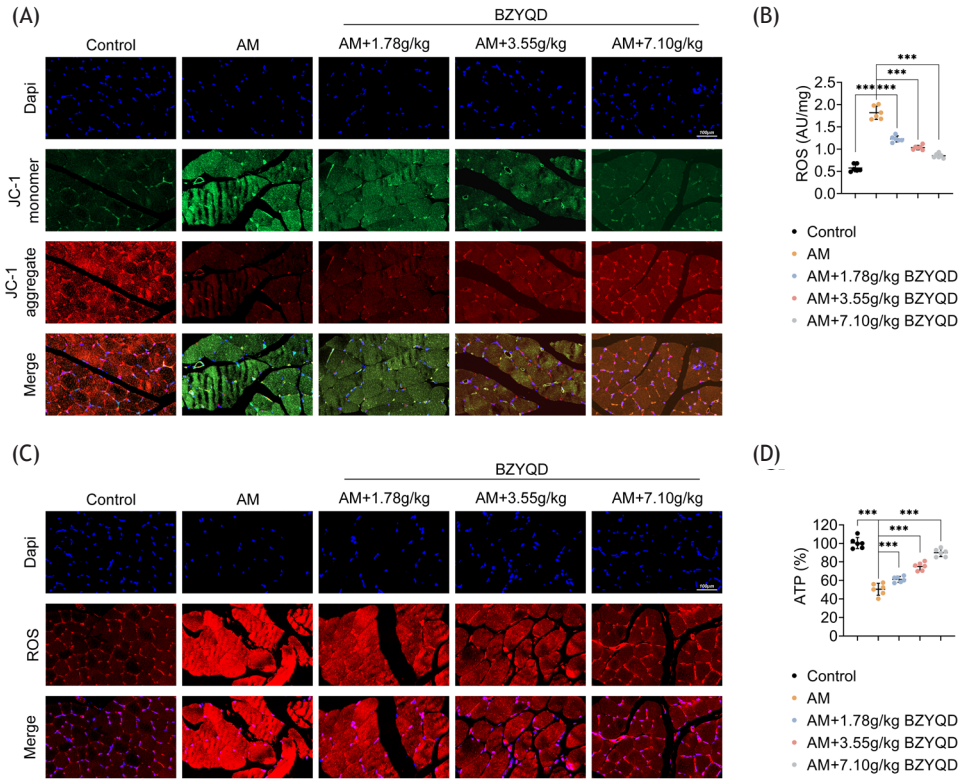

Figure 3 BZYQD inhibits inflammatory response in mice with acquired myasthenia. (A) Mitochondrial membrane potential detection. (B) Immunofluorescence image of ROS. (C) Mitochondrial ROS production rate. (D) ATP level. Values are represented as mean±SD. ***P<0.001 versus control group. n=6.

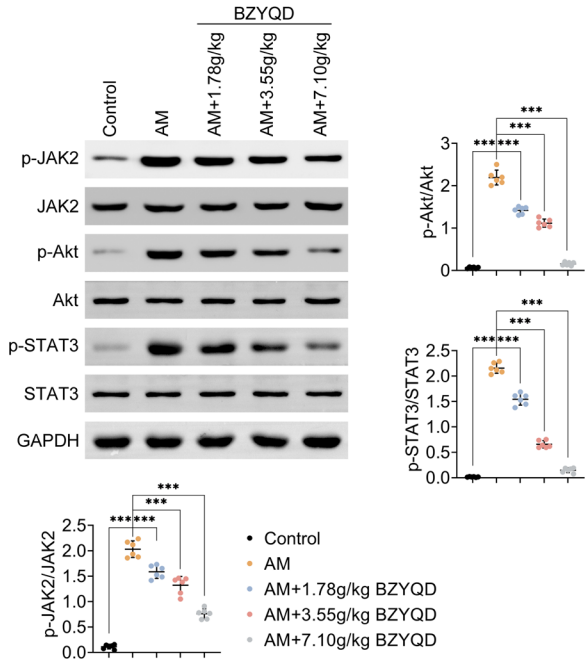

Figure 4 BZYQD inhibits JAK2/STAT3/AKT pathway. Expression of JAK2, p-JAK2, STAT3, p-STAT3, AKT, p-AKT. Values are represented as mean±SD. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus control group. n=6.

in vitamins and trace minerals, can boost non-specific immune function and enhance macrophage phagocytosis capacity. Angelica sinensis, abundant in vitamins and amino acids, enhances blood flow, stimulates circulation, and reduce inflammation. This comprehensive formula successfully boosts the patient's immune function and clinical efficacy by promoting antibody production.[5,13] For instance, by controlling the symbiotic balance between intestinal flora and the host, BZYQD can ameliorate myasthenia gravis and clinically benefit teenage ocular myasthenia gravis anti-acetylcholine receptor antibodies.[14,15] Our experimental results confirmed that BZYQD can improve reduced grip strength and increased expression of MAFbx and MuRF-1 in mice with acquired myasthenia, demonstrating its ability to attenuate muscle damage.

LPS is one of the main mediators of sepsis, affecting skeletal muscle, which is a primary target tissue for sepsis, which affects the respiratory and limbs muscles and eventually leads to atrophy paralysis of the muscles.[16,17] Thus, a potentially effective treatment for sepsis-induced acquired myasthenia is to block LPS-induced inflammation. Previous studies have demonstrated that BZYQD can reduce serum levels of pro-inflammatory cytokines in osteoporosis models.[18] Our experimental results confirmed that BZYQD reduces levels of pro-inflammatory factors IL-1ß, IL-6, and TNF-α in mouse serum, demonstrating its ability to inhibit the inflammatory response in mice with acquired myasthenia.

As one of the greatest reserves of calcium in skeletal muscle and a major factor in skeletal muscle contractility, mitochondria play an important role in various functions.[19] Mitochondrial damage is a possible major contributing factor to acquired myasthenia. Previous research has shown that by controlling mitochondrial biogenesis, BZYQD can correct aberrant lipid and glucose metabolism in obesity.[20] Experimental results confirm that BZYQD can reduce ROS accumulation, mitochondrial ROS production rate, increase ATP levels, and mitochondrial membrane potential in mice with acquired myasthenia, indicating its ability to attenuate mitochondrial dysfunction.

In mice with LPS-induced acquired myasthenia, pro-inflammatory factors are significantly elevated. It is well known that activating IL-6 can activate the JAK family and STAT, leading to muscle atrophy.[21] Decreased Atrogin-1 expression due to STAT3 inhibition has been observed to attenuate cancer-associated muscle atrophy in mice with colon 26 carcinoma. In vitro and in vivo, sepsis-induced muscle atrophy is reduced by the JAK2 inhibitor AG490. Trim63/MuRF1 and Fbxo32/Atrogin-1 expression levels were shown to be lowered in correlation with this.[22,23] Therefore, a potentially effective treatment for sepsis-induced acquired myasthenia is to block the JAK2/STAT3/AKT signaling pathway. Experimental results confirm that BZYQD can reduce the expression of p-JAK2, p-STAT3, and p-AKT in the skeletal muscle of mice with acquired myasthenia.

Finally, some limitations of this study need to be pointed out. In this study, the effect of BZYQD was only studied through some in vivo experiments, and further clinical research is needed in the future. Traditional Chinese medicine has shown great potential in the treatment of myasthenia gravis. If the effect of BZYQD is confirmed, it can relieve myasthenia symptoms, improve patients' quality of life, and reduce the side effects of Western medicine in the future.

Conclusion

In summary, we studied the effect of BZYQD on acquired myasthenia for the first time, and confirmed that BZYQD can inhibit muscle atrophy, inflammatory response, and mitochondrial dysfunction in mice with acquired myasthenia. In addition, the anti-muscle atrophy effect of BZYQD is likely mediated by inhibiting the JAK2/STAT3/AKT signaling pathway. Although the article has limitations, it lays a foundation for relieving myasthenic symptoms, improving patients' quality of life, and reducing the side effects of Western medicine in the future.

Conflict of Interest

The authors declare no conflict of interest.

Ethics Approval

Ethical approval was obtained from the Ethics Committee of Foshan Traditional Chinese Medicine Hospital Chancheng High tech Zone Hospital.

Data Availability

The authors declare that all data supporting the findings of this study are available within the paper and any raw

data can be obtained from the corresponding author upon request.

Author Contributions

YZ, HZ designed the study and carried them out, YZ, HZ, XL, TF supervised the data collection, YZ, HZ, XL analyzed and interpreted the data, YZ, HZ prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

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