Pharmaceutical composition and drug effect of synthetic *Bacopa monnieri* L. health promoting agent from the perspective of resistance fatigue

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Abstract: *Bacopa monnie*ri has effect on the nervous system, digestive system and blood circulation systems. In this paper, the authors conducted pharmacological analysis on *Bacopa monniera* and its innovative pharmaceutical preparation of promote motor function. The extract of the drug has some effect on relieving the fatigue and providing the movement function. By analyzing the composition and efficacy of Chinese herbal extracts, it can be seen that these drugs have obvious effect on improving immunity. Experimental results show that the agent can increase the liver glycogen energy reserves, reduce Bla and BUN levels, balance and energy metabolism of muscle cells in the environment, it plays a positive role to improve the exercise capacity and exercise fatigue.

Keywords: Pharmaceutical effect, bacopa monniera, traditional Chinese medicine, sports fatigue.

INTRODUCTION

Recent studies showed that *Bacopa monnieri* had good tonic effect on the nervous system, digestive system, blood circulatory system, can protect the brain mitochondrial enzyme and improve the concentration of thyroid hormone, anti tumor, liver protection, smooth muscle relaxation and so on. Although herbal medicines are good for health, they are either less effective or have a lot of side effects when using herbs to treat complex diseases such as cancer, osteoporosis, and AD. *Bacopa monnieri* has the effect of clearing heat and detoxifying, clearing liver and improving eyesight. At present, the world has more than 35000 kinds of plants containing more than 4000 kinds of flavonoids (polyphenols), terpenoids and alkaloids used in medicine related purposes(Cahill *et al*., 2015). However, Chinese herbal medicine preparation such as there is a huge difference between the different batches of the many problems, because of the impact of biological activity of herbal medicine largely by its growth the shadow of the ring. These limitations have prompted pharmaceutical companies to synthesize single molecules as therapeutic agents (Hu *et al*., 2013). Modern research has proved that the total saponin of BM is the effective part of *Bacopa monnieri*, and *Bacopa monnieri* saponin I is the main active component. In view of the *Bacopa monnieri* has a variety of biological activity, it is the domestic and foreign research on the chemical composition and pharmacological effects of the monnieri to provide a reference for the comprehensive development and utilization of Bacopa. *Bacopa monnieri (L.)* has been used for centuries in medicine, as a memory and learning enhancer. It grows in wet tropical environments and under its common English name of water hyssop, is a popular aquarium plant. A survey showed it to be one of the most popular aid for memory among 60–64-year-old consumers. Animal studies of *B. monnieri* whole plant have reported cognition-enhancing effects including improved motor learning and acquisition, consolidation, and retention of memory in rats. Memory-enhancing effects have been attributed to saponins.

A health promoter of this experiment contains five kinds of natural extracts: fake purslane, milk thistle, India ginseng, turmeric and green tea (Zhu *et al*., 2015). In recent years, the chemical constituents and pharmacological effects of these extracts have been studied extensively. Especially turmeric and green tea, these two components in enhancing the ability of sports, has combat free radical damage was confirmed; milk thistle in the sports scientific research is mainly reflected in its antioxidant effects and promote glycogen synthesis ability; India ginseng not only has antioxidant effect, but also can improve the immune capacity; fake purslane extract on anti fatigue and improve exercise capacity on research is not much, mainly concentrated in the central nervous system, which can enhance the three rat frontal cortex, striatum and hippocampus, parts of the oxygen free radical scavenging enzyme antioxidant activity, and can protect brain mitochondria enzymes (Li, 2014; Mellotte *et al*., 2015). Internationally, these components are widely used in the study of antitumor and anti-inflammatory drugs. At present, the research of health promotion is mainly focused on anti oxidative stress, protecting myocardial cells and preventing apoptosis (Shi, 2010; Xuan, 2015; Liu *et al*., 2016; Tsiaras *et al*., 2016). This study through the exhaustive swimming mice model,

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to explore the health promoters are delaying sports fatigue, improve athletic ability and through the sport performance ability, antioxidant system and biochemical indexes, sugar metabolism, inflammation factor in determination of the composition mechanism.

Sports nutrition supplements on exercise physiology state integral regulation has its outstanding advantages and enhance the role, it has also been studied and recognized widely in anti fatigue, enhance immunity, anti-oxidation function, but its type there is a lack of in-depth research, extensive (Jarvinen *et al*., 2007; Hu *et al*., 2013). Exercise induced fatigue has been a research focus in the field of sports physiology and its mechanism and recovery methods are related to the improvement of exercise ability (Bergström *et al*., 1967; Cahill *et al*., 2015). Fatigue timely recovery can improve the body movement function level, so as to improve exercise capacity, but decreased excessive exercise fatigue accumulation will lead to changes in metabolism and exercise performance, and even cause sports injury. Fatigue recovery means a lot, the study of sports nutrition has been playing an important role (Dindo *et al*., 2004; Chen *et al*., 2009; Gao, 2015). The focus of the study is to supplement mechanism clear, including the formulation of chemical composition of supplements of inquiry, the molecular mechanism of the clear and standard dosage, and analyze the composition of drugs and drug effects.

Overview of pharmaceutical composition

Health promoter contains five kinds of natural extracts: fake purslane, milk thistle, India ginseng, turmeric and Green Tea. *Bacopa monniera* L. for the India subcontinent common spread plants, the present study, more than and 20 compounds have been isolated from the fake purslane, of which three triterpenoid saponins compounds. In the past thirty years, more and more research on the separation of compounds and pharmacological effects of different compounds from the fake purslane. Study on the pharmacological effects of the involved nerve, digestion, circulation and other systems. The role of fake purslane on the nervous system including the important embodiment in anti depression and cognitive function and improve the compression treatment of dementia, and relief of pain and morphine withdrawal symptoms.

According to modern pharmacological studies, silybin can scavenge free radicals, inhibiting lipid per oxidation and inhibition of 5- lipoxygenase, anti glutathione emptying, anti-tumor, reducing blood lipid and protecting liver cells, promote liver cell repair and anti hepatic fibrosis pharmacology effect, currently silymarin is mainly used as a hepatoprotective plant, the main the preparation has been widely used in the treatment of acute and chronic hepatitis and cirrhosis and other liver disease.

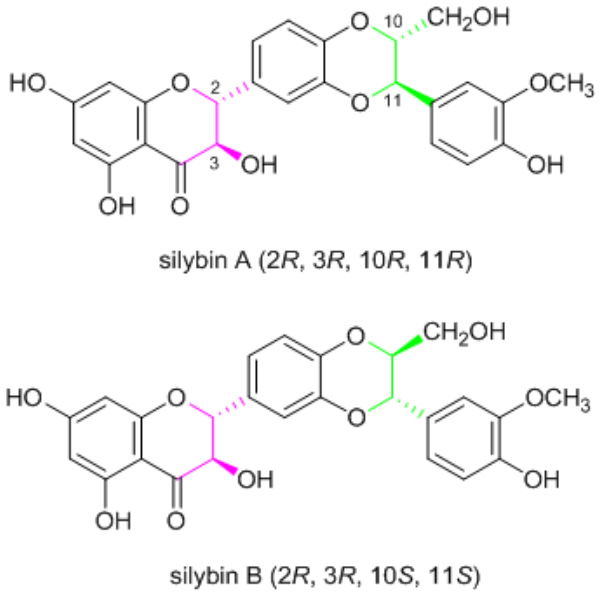

Fig. 1: Silybin type structure

Withania sonmnifera is the main active ingredient of Withanolide Withanolide compounds, such compounds can be transformed into physiological hormone the body needs, its biological activities including antibacterial, anti-inflammatory, cytotoxicity, cell immunity and anti-tumor aspects. In the present study, the ability to exercise the ability to improve the body's ability to fight and improve the body's immune function. Turmeric is a traditional Chinese medicine, pharmacological effects of curcumin in many aspects, including reducing blood lipid, anti platelet aggregation, antioxidation, disease of respiratory tract, and by improving the phagocytic capacity of immunity function change. On this basis, domestic and foreign scholars have conducted in-depth research on its anti-tumor effect. Curcumin in skin cancer, gastric cancer, breast cancer, colon cancer and twelve finger cancer in animal experiments, have a significant performance, can reduce the number and size of the tumor and reduce the probability of metastasis. The research on the mechanism of curcumin anticancer found that curcumin can suppress malignant tumor cell proliferation, and induce its differentiation; curcumin has certain effect on apoptosis of tumor cells; antioxidant and anti-inflammatory properties of curcumin could indirectly inhibit tumor cell.

Studies on tea extracts have found 600 kinds of compounds, organic compounds including proteins, lipids, carbohydrates, cellulose, sterols such as tea polyphenols, caffeine, organic acid, vitamin etc. Tea also contains a variety of inorganic mineral elements, which is the most important component of tea polyphenols. As a natural antioxidant, tea polyphenol, 20 kinds of polyphenols, mainly by catechins, flavonoids, anthocyanins and phenolic acids and other 4 categories of material composition. The catechin dominant, epigallocatechin

gallate Epigallocatechin gallate table in the main components of catechin in the majority (EGCG). EGCG is the main functional component of green tea extract, and its antioxidant activity and the ability to scavenge free radicals are the strongest of all components. The ingredients can only be extracted from tea, but also can not be artificially synthesized.

MATERIALS AND METHODS

Instruments and reagents

Paraformaldehyde (Shanghai Chinese medicine group), 0.05% (Beijing Ximeijie dye Thioflavin Technology Co., Ltd.), super oxide dismutase (SOD), catalase (CAT), glutathione S-transferase (GSH-Px), malondialdehyde (MDA) and kit assay kit from Nanjing Jiancheng Biological Engineering Institute

2D electrophoresis (2 -DE) and image analysis

Tg2576 blank control group and BS-I treatment (15 mg/kg) of the Tg2576 group of mice with frozen brain tissue, each group of 3, each taking a mixture of 0.1g of health promoter synthetic drugs. Thaw at room temperature and in 9M urea, containing 9 times the volume of 4%CHAPS, 65m M DTT 0.5% (Bio-Lyte 3-10) carrier ampholytes (Bio-Rad) tissue lysis buffer and protease inhibitors were homogenized, 12000 RPM (4 DEG C) centrifugal 0.5 hours to remove DNA, RNA and other granular materials (Dindo *et al*., 2004). Determination of protein concentration in supernatant by Bradford assay kit (Bio - Rad). Protein samples were stored at -80 DEG C for subsequent use. According to the program provided by the manufacturer (Bio-Rad) 2 - DE experiment. The first dimension, when the 1mg protein is fixed at a length of 17cm, P H 3-10 of the nonlinear IPG adhesive strip (Bio-Rad). The hydration condition was 50 V, for 12 hours. Isoelectric focusing (IEF) was performed on the I12 IEF system (Bio-Rad), with an initial voltage of 250 V, and gradually increased to a maximum of 10000 V and remained unchanged until 80000. The second dimensional separation was performed on a standard gel device (Bio-Rad). Using 10%SDS -PAGE gel (200mm x 200mm x 1mm), current fixed at 30m A / gel. After electrophoresis, two-dimensional gel with Coomassie brilliant blue G-250staining 13 hours, using UMAX 2100XL gel scanning image scanner. Using PDQuest 8 software (Bio-Rad company) for point detection, matching and quantitative strength analysis. In simple terms, the protein spots are automatically detected and then manually selected, and the gels need to be standardized and matched. Tg2576 - control group and BS-I - treated Tg2576 mice (15 mg/kg) were compared between groups to carry out the three paired gel experiment. The same quantitative changes that were detected in the three pairs of repeated experiments were preserved (Chen *et al*., 2009). The variation in the expression of the selected differential point must be more than 2 times to ensure that it reflects the difference in the amount of true protein expression.

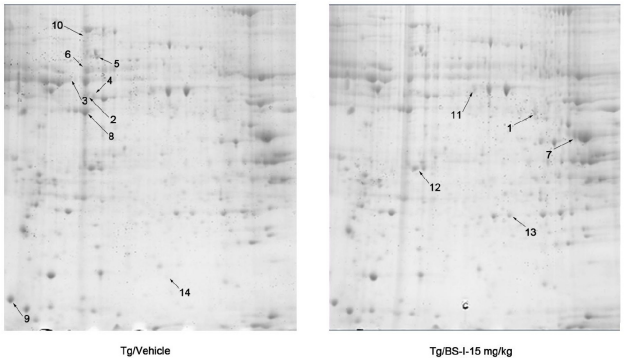

Fig. 2: The gray value of protein spots

Experimental study

Tg2576 transgenic mice expressing human APP Swedish mutation (K595N/M596L) and human premature senescence 1 delta E9 mutation gene to Pr P base as promoter. The transgenic mice were randomly assigned to two kinds of C57BL/6J gene to obtain the transgenic mice. 27 Tg2576 mice and 9 age-matched wild-type C57BL/6J mice (20±2g) were purchased from Beijing Medical & Biotechnology Co., ltd.. All animals were kept in a strictly controlled SPF level environment with free access to food and water (temperature 21-22°C, humidity 50-60%, light / dark cycles, 12 h/12 hours). To adapt to the local environment after 2 weeks of feeding, the mice were randomly divided into treatment groups (n = 9) wild type (WT /Control) control group, blank control group Tg2576 mice (Tg2576/Vehicle) low dose group and BS-I treated Tg2576 mice (Tg2576/BS-I - 15 mg/kg/d) and high dose group (Tg2576/BS-I-50 mg/kg/d). The animal experiment program has been approved by the experimental animal ethics committee, which conforms to the principles of animal protection, animal welfare and ethics, and conforms to the relevant provisions of the national laboratory animal welfare ethics, No.WDKZPF/16SQ.

In the exercise experiment, mice were randomly divided into experimental groups were divided into four groups, control group (C), exercise group (CE), drug group (HP1), drug and exercise group (HP1E), the control group means without any intervention, exercise group means make movement intervention, drug group means feeding this health promoter contains, drug and exercise group means feeding this health promoter contains with movement intervention. Each group, 20 mice, 8 weeks of age. After adaptive feeding, HP1 group and HP1E group every morning the 10 point of administration, and ensure the movement time interval of more than 2h, by gavage at a dose of 2.5mg/d dissolved in 0.6 ml of distilled water (equivalent to one day dose). At the same time, C group and CE group were given distilled water as placebo. Blood lactate levels were measured in 5 mice in each group, and blood lactate was measured in the resting state, immediately after exercise, and after exercise for 60 minutes with the Kyoto portable blood lactate analyzer.

Dry the mouse tail tip, cut the tail blood, the first drop away, with strip draw blood, measured readings (Gao, 2015).

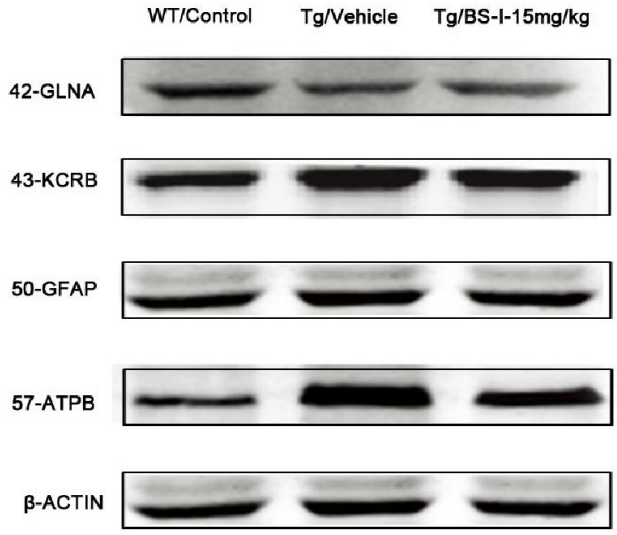

Fig. 3: Differentially expressed protein

RESULTS

Proteomic analysis and Western blot analysis of differential proteins

All the differentially expressed proteins in this study were expressed by measuring the gray values of protein spots. 9 down regulated proteins (labeled on Tg /Vehicle gel) and 5 up-regulated proteins (marked on Tg/BS-I-15 mg/kg) are shown in fig. 2. In order to verify the results of proteomic identification, we identified 4 differentially expressed proteins by Western blotting. We further applied matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF) MS / MS to compare proteomic experiments with BS-I treated and blank treated mice brains. We found that in the BS-I treatment of brain tissue, the expression of 5 proteins were significantly up-regulated ($P<0.05$), including glutamine synthetase (GLNA), the same type of fructose two phosphate aldolase 2 (ALDOA), alpha enolase (ENOA), tubulin beta chain 2A (TBB2A) and phosphorus acid triose isomerase (TPIS), 9 protein expression was significantly reduced ($P<0.05$) by using SPSS, including glial fibrillary acidic protein (GFAP), ATP synthase beta subunit (ATPB), creatine kinase B (KCRB), Internexin (ANIX), alpha tubulin alpha chain (1C TUBA1C) and cytoplasmic beta actin (ACTB), beta synuclein (SYUB), heat shock protein 8 (SHP7C) and ATP synthase subunit alpha (ATPA). We identified 4 differentially expressed proteins: GLNA, ATPB, GFAP and KCRB (fig. 3 and 4) using Wesern blotting.

Enrichment of differentially expressed genes in BS-I therapy

Gene Heatmap and PLSDA spectra showed that the transgenic expression of all the difference (Tg2576) mice and wild-type (WT) mice genotypes are very different, and BS-I treatment had significant effect on AD model mice (figs. 5 and 6). We found that BS-I treatment group (L) and blank treatment Tg2576 control group (M) compared with 568 differentially expressed genes (397 genes down regulated and 171 up-regulated genes); Tg2576 transgenic and wild type controls 823 genes (318 genes, compared to 505 on regulating gene). Pathway enrichment analysis was performed to determine the pathway of BS-I treatment significantly regulated, and the P values were used to indicate the degree of confidence of the genes enriched. The calculation of 15 pathways: the enrichment of the phagocytosis, endocytosis, neuroactive ligand receptor interaction pathway, Alzheimer's disease, calcium signaling pathway, MAPK signaling pathway, NK cell mediated cytotoxicity, phagocytosis of Fc gamma R- mediated, antigen processing and presentation, hematopoiesis cell lineage, chemokine signaling pathway, T cell receptor, Toll like receptor, neurotrophic factor signaling pathway and apoptosis of neural pathways ($P < 0.05$). We used real time fluorescence quantitative PCR method to verify the 10 genes in BS - I treatment group and placebo treated Tg2576 mice, the expression of gene chips and m RNA real-time fluorescence quantitative PCR method to test the 10 selected genes consistent (fig. 7).

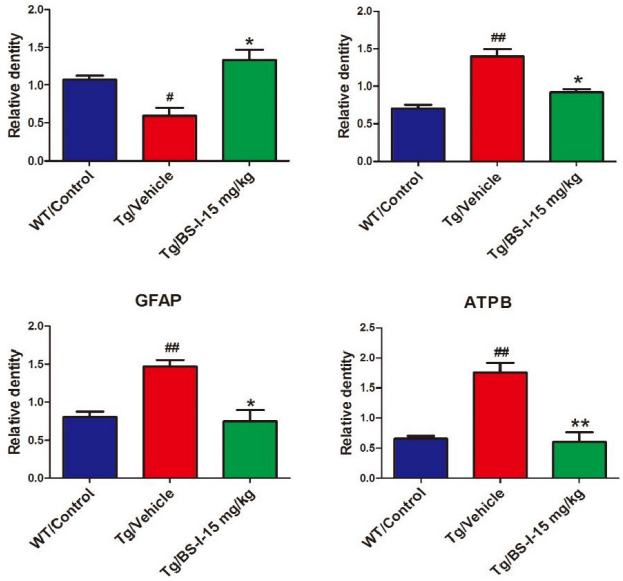

Fig. 4: GLNA ATPB, GFAP and KCRB

Effect on body weight in mice

The effect on body weight can be seen from table 1, after administration of HP-1 for eight weeks, the body weight of mice showed the change as shown above. It can be seen from the table that the weight of the 4 groups of mice showed an increasing trend and the weight of mice in group HP1 and group HP1-E were significantly lower than those in group C and group CE after the experiment for 8 weeks. There was no significant difference between

C group and CE group, HP1 group and HP1-E group.

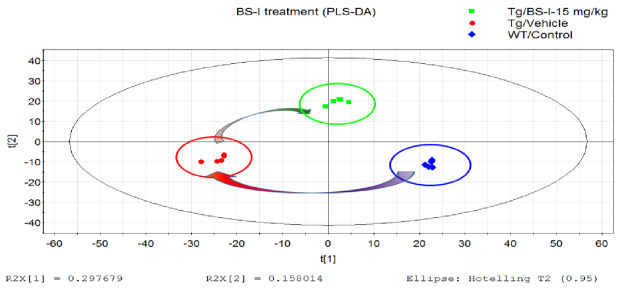

Fig. 5: PLS-DA of all probes in three different treatment groups

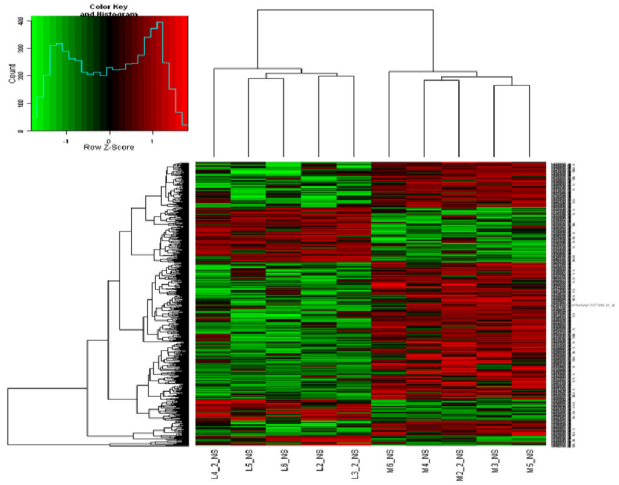

Fig. 6: Thermal differential gene

The influence of exercise time

The movement of mice after exhaustive comparison of mean time above, the results showed that: CE group, HP1 group and HP1-E group mice compared with control group C force exhaust time was prolonged significantly (P<0.01); HP1-E group compared with CE group also increased significantly (P<0.01). The results showed that both HP-1 extract and exercise training had an effect on the increase of exercise time in mice.

Effect of BUN on the content of blood

Fig. 9 shows the change of BUN content in each group of mice, compared with the C group, the serum BUN of group CE showed significant decrease (P<0.05), HP1 group and HP1-E group decreased significantly compared with C group (P<0.01). There was no significant difference between HP1-E group and CE group, HP1-E group and HP1E group.

Effect of MDA on the activity of SOD and the content of serum in mice

The results showed that SOD activity was significantly higher in the HP1-E group compared with the C group and the HP1 group (P<0.05), and the HP1-E group had significant changes compared with the CE group (P< 0.01). No significant difference was observed between the 3 groups. In the detection of MDA content, HP1 group and HP1-E group were significantly lower (P<0.05) compared with the C group, there was no difference between the other groups.

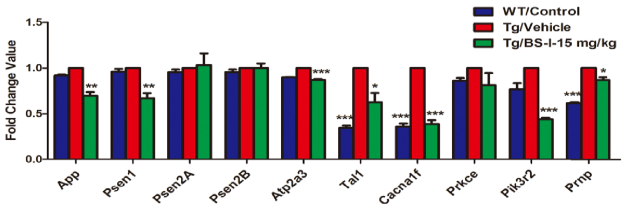

Fig. 7: Fluorescent quantitative PCR test

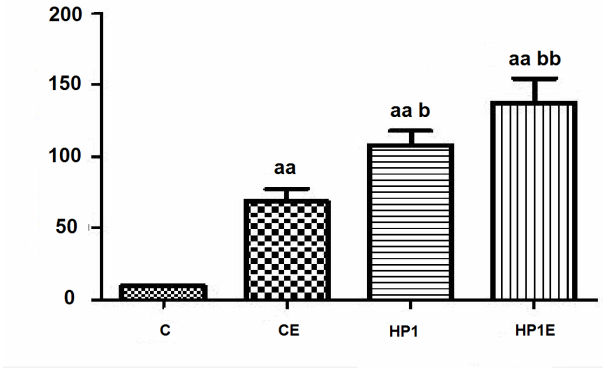

Fig. 8: Effect of swimming time on swimming time

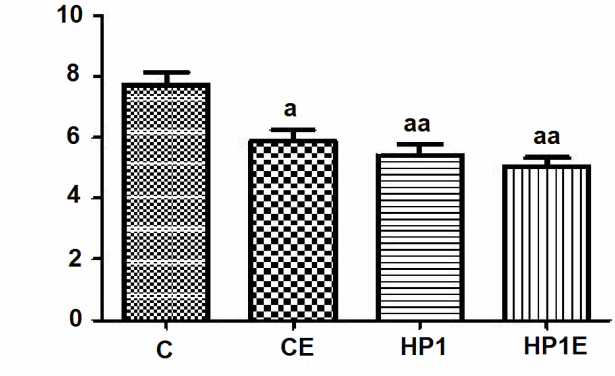

Fig. 9: Effect of HP-1 on the content of BUN

Effect on serum content of mice

After exhaustive exercise, 4 groups of mice serum IL-1 beta index as shown above, CE group, HP1 group and HP1-E group compared with C group, there were significant decrease (P<0.01), HP1-E group and HP1 group decreased with significant difference (P<0.05), HP1 group and CE group significantly change (P<0.05). The detection of serum IL-6 content in mice showed that CE group and HP1 group compared with HP1-E group and C group were significantly decreased (P<0.01), there was significant difference in the HP1-E group compared with CE group (P<0.05), significant differences were observed between the 4 groups.

Table 1: Effect of drug on body weight in mice

Grouping	Before experiment	After experiment
C	29.2±0.4	37.4±2.5
CE	28.7±0.6	37.1±3.2
HP1	29.5±0.7	33.5±3.1
HP1E	28.3±0.5	33.1±2.9

DISCUSSION

Natural small molecules that regulate complex chronic diseases are usually regulated by the production of multiple genes or multiple genes. Therefore, a web-based system approach may help to identify candidate genes associated with the complex regulatory role of BS-I in AD (Li, 2014; Mellotte *et al*., 2015). In this paper, we investigated the effect of BS - I treatment on protein interactions in Tg2576 mice by means of a combination of proteomics and genomics data. We constructed a specific BS-I effect PPI network and identified the potential pathways associated with the BS-I effect. Finally, we proposed the possible mechanism of BS-I in the treatment of AD (fig. 14).

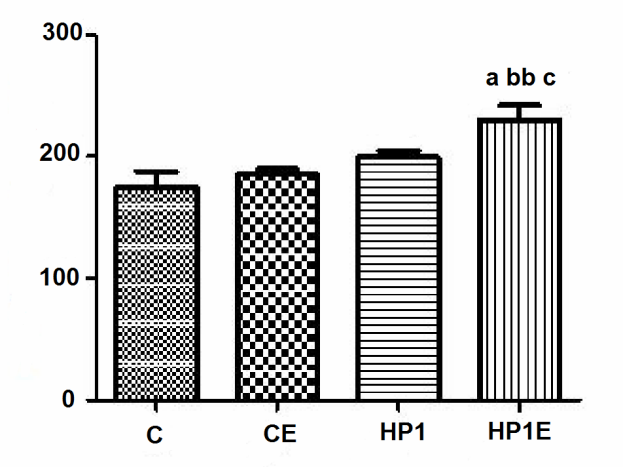

Fig. 10: Effect of SOD on mice

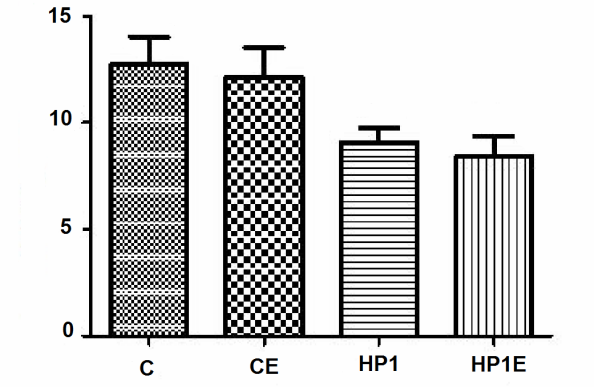

Fig. 11: Effect of MDA on the content of mice

The test of the 4 groups of mice at 8 weeks after the experiment, the treatment group mice weight growth is lower than the drug group, simple exercise group and non exercise group weight no difference, indicating the intensity of experimental design is appropriate, no adverse reactions. It is generally believed that the weight gain of mice is inhibited by high intensity exercise training. In addition, the green tea extract of health promoting agent HP-1 has the effect of reducing weight and reducing fat, so as to achieve the inhibition of weight gain in mice. Obesity is a chronic disease with multiple factors, which is characterized by an imbalance of energy metabolism (Jarvinen *et al*., 2007; Hu *et al*.,2013). On the one hand, EGCG can inhibit the differentiation of fat cells; on the other hand, EGCG can enhance the expression of beta-oxidation activity and liver acyl -Co A oxidase and medium chain acyl -Co dehydrogenase A m RNA make the fat metabolism in the liver increased. In this experiment, health promoter HP-1 reflected in the control of body weight, may be due to the reduction of body fat weight / body weight ratio and mice to improve exercise capacity, but also the need for further studies to be confirmed, the future research should be on food intake, body weight of mice peripheral growth, discusses some related indexes of body fat deep, and through the Real-time PCR technique to detect motion or HP1 intervention for key genes SREBP-1c, SCD1, FAS, ACC1 and GPAT m RNA etc. the further study of body fat synthesis (Abu 2017; Fang and Ruan 2017; Liu *et al.* 2017; Takahashi 2017).

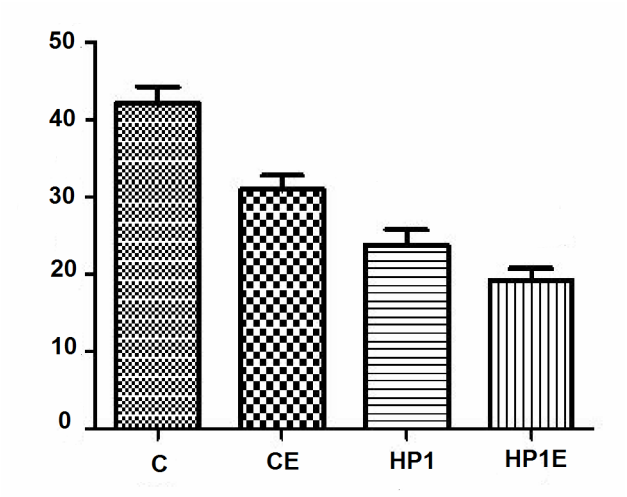

Fig. 12: Effects of IL-1 on serum levels of beta in mice

The exhaustive swimming time of mice can directly reflect the ability of exercise, and is closely related to the

delayed fatigue and fatigue recovery. In this experiment, HP1 mice exhaustive swimming intervention time was significantly longer than non HP1 group, and after a long period of moderate intensity swimming training mice compared to untrained mice showed obvious advantages in the sports ability, that exercise training can improve the motor function in mice; similarly, a significant strengthening effect the HP-1 intervention on mouse movement ability, and HP1 intervention for training mice exercise has obvious synergistic effect (Cahill *et al*., 2015). That combined with other experimental data of this experiment, the HP-1 collaboration to improve exercise capacity, HP1 is the main effect of intervention can reduce the body fat weight / body weight ratio, activation of autophagy related signaling pathways in response to oxidative stress response to the movement process and strengthen the removal of metabolic waste in the body, and realize the activation of NRF2-Keap1 signaling pathway on antioxidant function in order to achieve the elimination of free radical, protect the integrity of the cell membrane, while HP-1 can also increase the liver glycogen reserves, to ensure energy supply during exercise, these factors combined to complete muscle inner environment balance and strong energy metabolism, so as to realize the occurrence and development of delaying sports fatigue and improve exercise capacity.

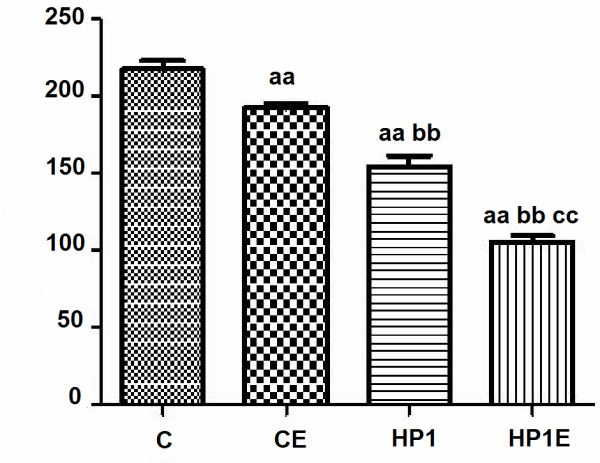

Fig. 13: Effect of IL-6 on serum level of mice.

CONCLUSION

Aerobic training could prolong the swimming time, reduce BUN and IL-1 of serum beta and IL-6 levels, promote autophagy activation, in order to improve the ability to adapt to the mouse muscle exercise can reduce cell damage caused by sports, improve the function of the way. In addition, health promoter HP-1 can prolong the exhaustive swimming time of mice, increase the liver glycogen energy reserves, reduce Bla and BUN levels, balance and energy metabolism of muscle cells in the environment, can promote the optimization of energy supply, accelerate the excretion of metabolic waste, enhancing immunity, improving on exercise capacity of mice and fatigue the delay plays an active role; at the same time for health promoter movement caused by long-term exercise training improved also has synergistic effect.

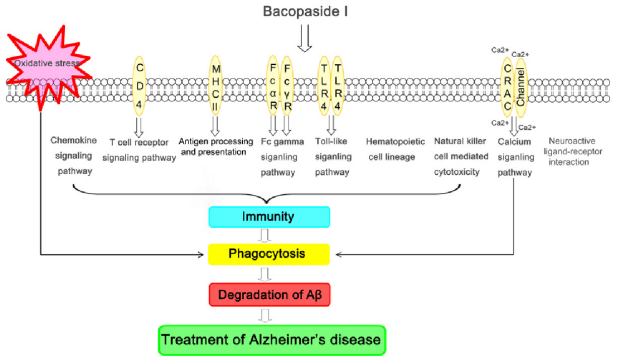

Fig. 14: BS-I mechanism for the treatment of AD network diagram.

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