EVALUATION OF THE ANTI-FATIGUE EFFECTS OF NSDVT EXTRACT IN EXPERIMENTAL ANIMALS

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Chronic fatigue syndrome (CFS) is characterized by persistent or recurrent fatigue, cognitive dysfunction, impaired physical performance, and a reduced ability to perform daily activities, with symptoms that do not improve after rest. NSDVT extract is a traditional herbal formulation composed of Radix Ginseng, Radix Paeoniae Lactiflorae, Radix Angelicae Sinensis, Radix Rehmanniae Praeparata, Radix Astragali Membranacei, Rhizoma Atractylodis Macrocephalae, Poria cocos, Radix Glycyrrhizae, Cortex Cinnamomi, Pericarpium Citri Reticulatae, Radix Polygalae, Fructus Schisandrae, Rhizoma Zingiberis, and Fructus Ziziphi Jujubae. This formulation has long been used in traditional medicine to tonify Qi and blood, nourish the heart, and calm the mind. In this study, we evaluated the anti-fatigue effects of NSDVT extract in Swiss albino mice. NSDVT extract administered orally at 2.5 and 5 g/kg significantly increased forelimb grip strength and prolonged swimming endurance in a time- and dose-dependent manner, with superior persistence of effect compared to sulbutiamine. In addition, NSDVT extract showed a tendency to increase blood glucose levels, total serum protein concentration, and red blood cell count after two weeks of administration. These findings suggest that NSDVT extract possesses significant anti-fatigue properties and may serve as a promising natural therapeutic option for the management of chronic fatigue syndrome.

Keywords: Chronic fatigue syndrome, traditional medicine, herbal formulation, anti-fatigue activity, mice.

I. INTRODUCTION

Chronic fatigue syndrome (CFS) is characterized by severe, persistent fatigue accompanied by multi-system dysfunction, resulting in a substantial reduction in patients' ability to perform daily activities.[1] Fatigue in CFS is typically exacerbated after physical or mental exertion, is not alleviated by rest, and lacks an identifiable organic cause. The condition is often associated with neurological, cardiovascular, respiratory, and gastrointestinal symptoms.[2,3] CFS is diagnosed when symptoms persist for at least six months and affects approximately two million individuals in the United States, with a reported prevalence ranging from 0.007% to 2.8% of the adult population. The syndrome predominantly affects women, individuals of Caucasian ethnicity, and those aged 40-70 years old.[4] Despite extensive research, the etiology of CFS remains unclear. Proposed mechanisms include genetic predisposition, infectious agents, immune dysfunction, and abnormalities of the reticular activating system.[1] Current treatment strategies primarily focus on non-pharmacological interventions, such as cognitive behavioral therapy, graded exercise therapy, and dietary modification, as well as symptomatic pharmacological management. However, these approaches often provide

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Received: 23/12/2025
Accepted: 05/02/2026

limited and inconsistent benefits.[1]

Traditional medicine has long documented remedies aimed at alleviating fatigue and enhancing physical strength. “Nhan Sam Duong Vinh thang” (NSDVT), a classical herbal formulation originating from the Southern Song Dynasty, comprises fourteen medicinal herbs and has been reported to improve immune function, enhance protein and amino acid synthesis, and reduce oxidative stress.[5-8] Nevertheless, the anti-fatigue effects of this multi-herbal formulation have not been systematically investigated. Therefore, the present study aimed to evaluate the effects of NSDVT on physical endurance and muscle strength in experimental animal models, with the goal of identifying a safe and effective natural therapeutic option for CFS.

II. MATERIALS AND METHODS

1. Research materials

NSDVT liquid extract containing fourteen herbal components was prepared at a concentration ratio of 2:1, such that 1 mL of extract corresponded to 2 g of raw herbal materials.

2. Chemicals and equipment

The control drug Sulbutiamine (Arcalion) 200mg from Les Laboratoires Servier, France. NaCl 0.9% solution; distilled water. Traction meter, model 47105-001 from Ugo Basile, Italy. ADVIA 60 hematology analyzer from Bayer, USA. Artohumalyzer 900Splus automated biochemical analyzer from Human (Germany). On-Call Plus venous blood glucose meter from Acon Laboratory, USA. Total protein kit from Erba, Germany.

3. Animals

Swiss mice, both sexes, healthy, weight 20 ± 2 g, provided by the National Institute of Hygiene and Epidemiology (NIHE). Animals were housed in individual cages of 10 each and maintained under standard room conditions (temperature 25 ± 1°C; humidity 80 ± 10%; 12-h light/dark cycle). After randomization and before the initiation of the experiment, animals were allowed to feed on the standard diet and water ad libitum, and were acclimatized to the laboratory conditions for 7 days in the Department of Pharmacology, Hanoi Medical University.

4. Animal study conduct

Swiss albino mice of both sexes (20 ± 2 g) were randomly assigned to four groups:

- Group 1 (normal control group): distilled NaCl 0,9% at 0.2 mL/10g b.w.

- Group 2 (Sulbutiamine): sulbutiamine at 15 mg/kg b.w.

- Group 3 (NSDVT-2,5): NSDVT at 2,5 g/kg b.w.

- Group 4 (NSDVT-5): NSDVT at 5 g/kg b.w.

The dose of NSDVT used in studies on *Swiss* mice was based on the literature-referenced dose used in humans, multiplied by a conversion factor of 12 for mice. The liquid extract of NSDVT was dissolved in warm water before being given to mice at 8:00 a.m daily.

Effect of NSDVT on traction (Grip strength test)

Swiss mice were given the medication continuously for 5 days, and their muscle strength was measured before and after the 5-day treatment. On the 5th day after medication, muscle strength was measured at 1 and 3 hours using the following procedure: the mice were placed on a wire mesh (9*15cm) with their heads facing an isotonic force transducer. When the mouse’s tail was pulled in the opposite direction, the mouse reflexively clung to the mesh to resist the pulling force. The device recorded the maximum pulling force when the mouse’s forelimbs left the mesh.[9]

Effect of NSDVT on swimming time (Weight-Loaded Forced Swimming Test)

Swiss mice were given the medication continuously for 2 weeks. Weighted swimming time (wearing a weight equal to 8% of body weight at the base of the mice's tail) was assessed before medication, and 1 and 2 weeks after medication, provided the mice were fasted for at least 3 hours before assessment. At each assessment time, the mice were placed in a cylindrical tank (15 cm in diameter, approximately 15 cm deep to prevent the mice's feet from touching the bottom) filled with water at a temperature of 37 ± 2°C. Swimming time h_1 was measured from the moment the mouse was placed in the water until it was completely submerged, at 8 seconds (the point of complete exhaustion).[10,11] Retrieve the mice from the water, wipe them dry, keep them warm, and give them medication. The swimming time h_2 is reassessed one hour after taking the medication.

At two weeks post-medication, the venous blood glucose levels in the mice's tails were measured before the mice were allowed to swim (G1). After the final swim, all mice were euthanized by cervical spine dislocation, and blood was collected to determine glucose content (G2), total protein concentration, and red blood cell count.

Statistical analysis

The data were expressed as the mean ± standard deviation (SD), and statistical analysis was carried out employing Student's T-test. Both analyses were performed using SPSS 25.0. The p-value < 0.05 was statistically significant.

III. RESULTS

Table 1. Changes in the traction strength of mice after drug administration (n = 10)

Group	Traction (gam) (% increase)		
	Before	After taking the medicine (day 5)	
		1 hour	3 hours
Normal control group	131,23 ± 22,31	136,77 ± 20,36 (4,22)	136,46 ± 26,69 (3,99)
Sulbutiamine	131,55 ± 22,17	190,36 ± 28,09$^{**\$\$\$}$ (44,71)	172,82 ± 25,38$^{**\$\$}$ (31,37)
NSDVT-2,5	132,08 ± 29,37	164,54 ± 27,60$^{*\$\$}$ (24,58)	179,23 ± 22,55$^{**\$\$}$ (35,69)

Group	Traction (gam) (% increase)		
	Before	After taking the medicine (day 5)	
		1 hour	3 hours
NSDVT-5	131,85 ± 19,07	180,31 ± 25,96**$$$ (36,75)	196,37 ± 22,48**$$$# (48,93)

*, **: p < 0,05; p < 0,01 compared to before

$, $$, $$$: p <0,05; p < 0,01; p < 0,001 compared to normal control group

#: p < 0,05 compared to the sulbutiamine group

The muscle-pulling strength of mice was investigated at time points before and 5 days after drug administration (1 and 3 hours after the last dose), yielding the results shown in **Table 1**. Both NSDVT and sulbutiamine groups increased the pulling strength of mice at post-administration time points (p < 0.05). NSDVT groups showed a greater sustained pulling strength in mice than sulbutiamine 15 mg/kg (pulling strength after 3 hours was higher than after 1 hour). A difference was observed in the NSDVT-5 group (p < 0.05).

Table 2. Changes in swimming time of mice before and after drug administration (n = 10)

Group	Swimming time (s) (% increase)		
	Before	After taking the medicine 1 week	After taking the medicine 2 weeks
Normal control group	224,62 ± 21,31	235,1 ± 20,2 (4,60)	239,4 ± 26,90 (6,59)
Sulbutiamine	225,39 ± 18,98	291,9 ± 20,1*$$ (29,45)	334,7 ± 28,1**#$$$ (48,49)
NSDVT-2,5	230,75 ± 22,56	279,6 ± 25,4*$ (21,16)	312,4 ± 23,8**#$$$ (35,39)
NSDVT-5	228,12 ± 18,43	296,8 ± 20,1*$$ (30,14)	341,2 ± 23,4**#$$$ (49,59)

**, **: p < 0,05; p < 0,01 compared to before; #: p < 0,05 compared to after taking the medicine 1 week*

$, $$, $$$: p < 0,05; p < 0,01; p< 0,001 compared to normal control group

Table 2 shows the swimming time of mice before and after 1 and 2 weeks of drug administration. It indicates that NSDVT and Sulbutiamine groups significantly increased the swimming time of mice after 1 and 2 weeks of treatment, compared to before treatment and compared to the normal control group. The longer the treatment duration, the greater the swimming time. In the NSDVT groups, swimming time increased by 21.16% and 30.14% after 1 week, and by 35.39% and 49.59% after 2 weeks of treatment. The increase in swimming time was significantly greater in the NSDVT-5 group than in the NSDVT-2.5 group.

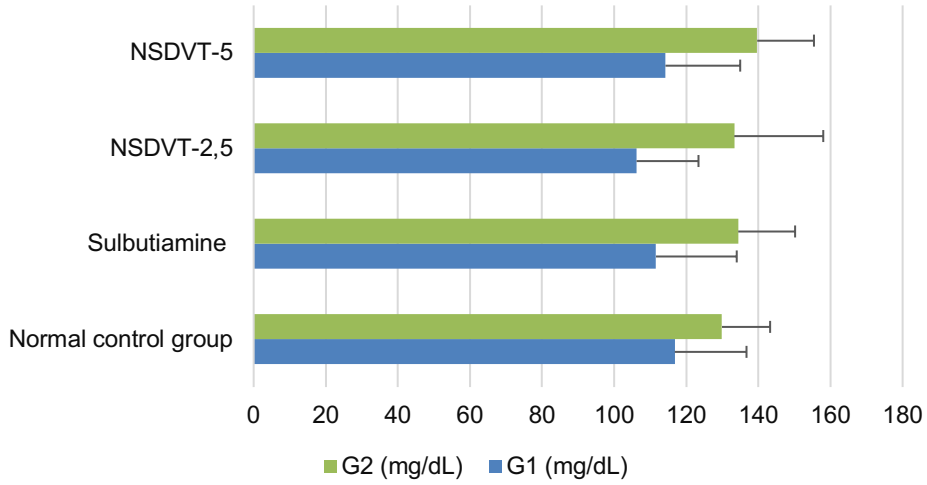

Figure 1. Blood glucose levels 2 weeks after taking the medication (n = 10)

After two weeks of medication, glucose levels in mice were measured before and after the last swim. Before the last swim, there were no significant differences in glucose levels between the groups ($p > 0.05$). After the last swim, blood glucose levels increased in all groups; the NSDVT and sulbutiamine groups had higher levels than the normal control group, but the difference was not statistically significant ($p > 0.05$).

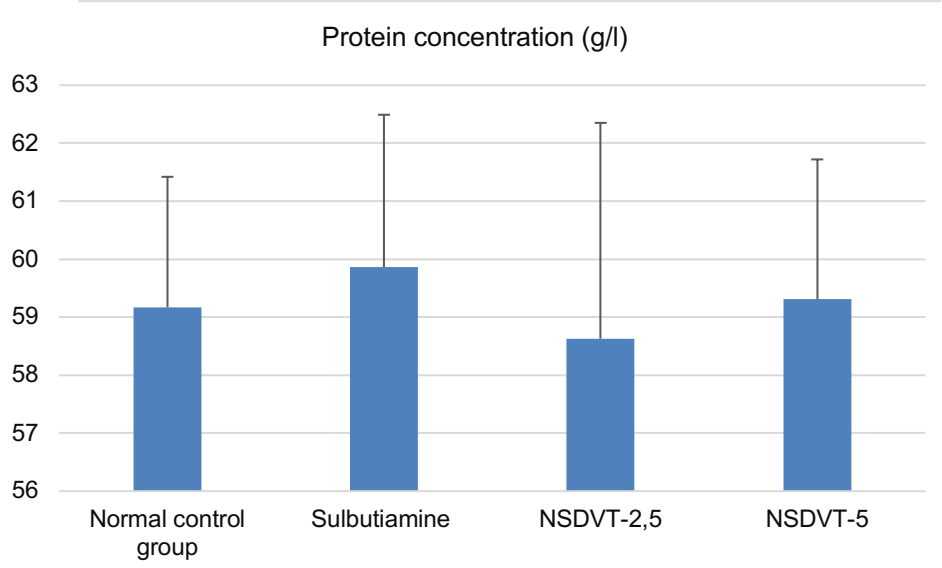

Figure 2. Total protein concentrations 2 weeks after drug administration (n = 10)

The total protein concentration of mice after 2 weeks of drug administration did not differ significantly between the groups ($p > 0.05$). The NSDVT and sulbutiamine groups had higher total blood protein concentrations compared to the normal control group, especially the NSDVT-5 group, which had the highest total protein concentration.

Table 3. Red blood cells in mice after 2 weeks of drug administration (n = 10)

Group	Red blood cells (T/L)
Normal control group	4,11 ± 0,65
Sulbutiamine	4,37 ± 1,12
NSDVT-2,5	4,55 ± 0,79
NSDVT-5	4,72 ± 0,83

The number of red blood cells in the mice's blood after 2 weeks of drug administration did not differ between the groups. The number of red blood cells tended to increase in the NSDVT groups; however, the difference was not statistically significant ($p > 0.05$).

IV. DISCUSSION

Chronic fatigue syndrome (CFS) is common among patients with various medical conditions in Vietnam and worldwide. This syndrome has a relatively high prevalence in the community, is chronic, frequently recurs, leading to decreased quality of life and increased anxiety in patients. CFS is characterized by prominent symptoms such as sleep disturbances, appetite loss, and muscle aches. Therefore, one of the fundamental requirements of medical treatment for this syndrome is to increase energy levels and reduce fatigue.[1] Therefore, traditional medicine remedies that are effective in treating these symptoms are of particular interest to researchers both domestically and internationally. Furthermore, the use of modern medical scientific methods to clarify the effects of traditional medicine remedies is even more practically significant, especially in Vietnam, a country with a long tradition of using traditional medicine to treat many diseases. For these reasons, NSDVT has been studied experimentally and clinically to demonstrate its safety and effectiveness in treating chronic fatigue syndrome. In this study, sulbutiamine - a lipophilic derivative of thiamine - was used as the control drug. This substance can cross the blood-brain barrier and has a selective effect on specific brain structures directly involved in chronic fatigue syndrome.[12]

NSDVT comprises 14 ingredients: *Radix ginseng*, *Radix Paeonia Lactiflora*, *Radix Angelicae sinensis*, *Radix Rehmanniae glutinosiae praeparata*, *Radix Astragali membranacei*, *Rhizoma Atratici macrocephalae*, *Poria cocos*, *Radix Glycyrrhizae*, *Cortex Cinnamomi*, *Pericarpium Citri reticulatae perenne*, *Radix Polygalae*, *Fructus Schisandrae*, *Rhizoma Zingiberis*, and *Fructus Ziziphi jujubae*. Its safety has been proven in animal studies. This formula has also been used in capsule form at the Pharmacy Department of the Central Traditional Medicine Hospital.

In this study, we evaluate the muscle endurance-enhancing effects of NSDVT using a forced swimming model and measured forelimb muscle traction in mice before and after drug administration. These are widely used animal models to assess the anti-fatigue efficacy of drugs or natural compounds.[11] Testing forelimb strength during a grip-strength test helps assess changes in neuromuscular coordination and forelimb muscle strength.[9] The results in Table 1 show that the use of NSDVT increased forelimb traction compared to the biological control group at the time points after drug administration. NSDVT also showed better sustained muscle traction over

time than sulfoniamine, suggesting its potential to increase muscle strength without training. Another parameter for assessing endurance is the duration of the training session/exercise, a key indicator of the anti-fatigue effect of the drug or natural compounds.[13] The weight-loaded swimming test is the most widely used method to evaluate the anti-fatigue properties of compounds by assessing the reduction in muscular force or the exhaustion of contractile function.[9] According to Table 2, NSDVT showed a significant improvement in swimming time in a dose- and duration-dependent manner compared to the biological control group. This result demonstrates the effectiveness of NSDVT in reducing fatigue during high-intensity exercise.

In addition to assessing the endurance of animals in forced swimming tests, several biochemical and hematological indicators were also used to examine the fatigue status of mice (Figures 1, 2, and Table 3). Glucose is broken down from glycogen in the liver and released into the blood, becoming the source of ATP - the body's main energy molecule. High-intensity exercise requires a large amount of energy, leading to increased glucose utilization in tissues and increased blood glucose levels, which then decrease upon cessation of exercise.[11] This situation was reflected in the quantification of blood glucose levels in mice before and after swimming. NSDVT tended to increase blood glucose levels more than the biological control group and the sulbutiamine-administered group, with the highest increase observed in the NSDVT-5 group. Thus, NSDVT may enhance exercise performance by providing/maintaining high blood glucose levels without causing diabetes.

Protein is a crucial component in muscle function, acting as a "second energy source" during high-intensity and prolonged exercise, which can lead to decreased muscle strength and fatigue.[14] Quantifying blood protein levels helps determine nutritional status, liver disease, kidney disease, and many other underlying medical conditions. The results showed that NSDVT tended to increase total blood protein levels compared to the biological control group, with the greatest increase observed in the NSDVT-5 group. Positive changes in total blood protein levels indicate that NSDVT has a beneficial effect in maintaining nutritional balance and enhancing energy retention for exercise. Meanwhile, red blood cells function to transport O_2 from the lungs to the tissues and carry CO_2 from the tissues back to the lungs for elimination. Hemoglobin also contributes to the blood's buffering capacity, and ATP and NO release from red blood cells contribute to vasodilation and improved blood flow to working muscle.[15] Similarly, the number of red blood cells also tended to increase in the NSDVT groups, suggesting the potential for improved muscle metabolism.

The above results all demonstrate the benefits of NSDVT in enhancing muscle strength and endurance during training. These positive effects are mainly due to the synergistic actions of the component herbs, including *Radix Ginseng*, *Radix Polygalae*, *Fructus Schisandrae*, and *Fructus Ziziphi jujubae*, which have been shown in numerous studies to enhance strength and combat fatigue through various mechanisms.[9,16-18] In addition, other components such as *Rhizoma Atrarilodis macrocephalae*, *Radix Glycyrrhizae*, *Radix Angelicae sinensis*, *Radix Rehmanniase glutinosiae praeparata*, *Pericarpium Citri reticulatae perenne*, and *Rhizoma Zingiberis* also have systemic effects that positively influence chronic fatigue syndrome.[6,19-23] These components may reduce fatigue through various pathways, including antioxidant

activity, reduction of metabolite accumulation, anti-inflammatory effects, regulation of the hypothalamic-pituitary (HPA) axis, energy metabolism, and the immune system. However, further research is needed to evaluate the targeted effects of each component in NSDVT.

V. CONCLUSION

NSDVT at 2.5 and 5 g/kg showed a dose-dependent anti-fatigue effect, as evidenced by increased endurance in forced swimming tests, and increased muscle strength in traction tests. NSDVT was associated with increased blood glucose levels, total protein concentration, and red blood cell count. Of these, the 5 g/kg dose of NSDVT showed better effects across all indicators.

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