



Review Article

Exploring medicinal and edible strategies for plateau hypoxic fatigue: focusing on pathogenesis, material basis, therapeutic mechanisms, and clinical applications

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Abstract: In high-altitude environments, where the low-pressure and hypoxic conditions prevail, the human body undergoes a series of severe metabolic dysfunctions and stress responses. These adverse circumstances are capable of inducing hypoxia-related damage in multiple organs, thereby not only accelerating the fatigue process but also markedly deteriorating health, reducing the quality of life, and diminishing labor productivity. Fatigue represents one of the most common physiological challenges encountered in high-altitude settings. In recent years, dietary supplements and associated natural products of medicinal and edible origin, such as *Phyllanthus emblica*, *Rhodiola rosea*, *Lycium barbarum*, *Cistanche deserticola*, and *Panax ginseng*, have attracted substantial interest. This is attributable to their specific anti-hypoxic fatigue properties, low toxicity, and diverse pharmacological activities. These natural substances, which are characterized by their complex chemical compositions, extensive therapeutic targets, and abundant resources, have a long-standing history and great promise in the prevention and treatment of plateau hypoxic fatigue (PHF), underscoring their substantial potential as medicinal-edible resources. This review commences with an overview of the pathogenesis of PHF and subsequently delves into the mechanisms, bioactive components, and clinical outcomes of medicinal-edible dietary supplements and their related natural products in counteracting PHF. The objective is to furnish a scientific basis and reference for the development and application of drugs, health foods, and functional foods aimed at PHF, thereby facilitating the practice and innovation of medicinal-edible strategies in high-altitude health preservation.

Keywords: plateau hypoxic fatigue; natural medicine; food and medicine homology; pathogenesis; clinical trials

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1 Introduction

High-altitude regions are typified by harsh climatic conditions, among which low atmospheric pressure and hypoxia are the most conspicuous features. For every 100 m increase in altitude, the oxygen content in the air diminishes by 0.67 kPa, rendering hypoxia one of the foremost challenges in high-altitude environments. High-altitude hypoxia ensues when individuals habituated to living at low altitudes abruptly ascend to regions above 3,000 m or reach even higher elevations. This situation gives rise to a substantial reduction in the partial pressure of inhaled oxygen, thereby inducing severe metabolic derangements within

the body. Notably, during physical exertion, the decreased oxygen supply to tissues and the compromised oxygen utilization lead the accumulation of metabolic by-products, upsurge in free radical generation, and heightened inflammatory cell activity. The most immediate consequence is a decline in physical performance and a marked augmentation in fatigue^[1].

Although prolonged exposure to high-altitude environments can trigger acclimatization, enabling a partial restoration of tissue function, it seldom restores the function to its normal state. Residents living at high altitudes display markedly lower physical performance in comparison to those dwelling at low altitudes^[2]. With the rapid progression of society and the burgeoning

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popularity of tourism and economic activities, high-altitude regions have drawn an escalating number of individuals for travel, employment, academic pursuits, and training^[3]. Consequently, an increasing number of people are being subjected to the adverse impacts of low-pressure and hypoxic environments. Acute mountain sickness represents a menace to the health of these newcomers, native inhabitants, and military personnel stationed in high-altitude zones. The resultant fatigue diminishes labor productivity and severely impairs the quality of life. Although certain medications, such as nifedipine, furosemide, and acetazolamide, have been employed to mitigate PHF, their side effects, including allergic responses and liver or kidney impairment, restrict their long-term application^[4].

In the pursuit of safer and more efficacious treatments for PHF, dietary supplements and related natural products sourced from medicinal-edible materials have attracted considerable attention. This is attributed to their long-standing utilization in traditional medicine and the abundance of bioactive components they contain. These compounds possess distinctive pharmacological attributes, presenting novel perspectives and methodologies for the management of PHF. The present review endeavors to investigate the active constituents of medicinal-edible substances and their corresponding natural products in the context of PHF treatment. Particular emphasis will be placed on their pharmacological effects and underlying mechanisms of action. Through an in-depth exploration of these aspects, we aspire to establish a theoretical basis for the development of more effective and safer therapeutic strategies. A more profound comprehension of the potential of medicinal-edible dietary supplements in treating PHF is anticipated to not only enhance the quality of life and labor productivity of high-altitude populations but also pave the way for new research directions in this domain.

2 Pathogenesis of PHF

Hypoxia has long been acknowledged as a principal threat to mammals inhabiting high altitudes. Atmospheric pressure declines exponentially with the ascent in altitude, giving rise to a concomitant decrease in oxygen concentration. This low-pressure and hypoxic milieu leads to inadequate oxygen uptake by tissues and impeded oxygen utilization, inflicting damage to the body and triggering a cascade of alterations in tissue structure and physiological function^[5]. High altitude necessitates a reduction in arterial oxygen partial pressure and oxygen saturation, culminating in tissue hypoxia and compromising normal physiological functions. Acute high-altitude hypoxia can present as mild manifestations, such as acute mountain sickness, or as severe conditions, including high-altitude pulmonary edema and high-altitude cerebral edema. In contrast, chronic high-altitude hypoxia can precipitate conditions like polycythemia and cardiovascular diseases, ultimately culminating in a reduction of labor capacity and exacerbation of fatigue. In comparison with individuals dwelling at low altitudes, those residing at high altitudes display significantly attenuated physical performance^[6]. Individuals who rapidly from low-altitude regions to high-altitude areas frequently encounter physiological and metabolic dysfunction, a decreased in work efficiency, sluggish movement, and a substantial decline in overall physical endurance, rendering them highly vulnerable to exercise-induced fatigue.

2.1 PHF and energy metabolism

Fatigue is a prevalent physiological phenomenon primarily

linked to muscle activity. It is defined as the incapacity of the body to maintain the anticipated muscle strength, thereby resulting in a reduction in physical performance and a degradation of bodily functions^[7]. The occurrence of fatigue is generally accounted for by two mechanisms: oxidative stress and energy depletion. Extended high-altitude hypoxia can initiate oxidative stress, disturbing the redox equilibrium in healthy individuals. Vigorous physical exercise intensifies oxidative stress, and the combined impacts of hypoxia and exercise can significantly disrupt redox balance^[8]. Oxidative stress generates an excess of reactive oxygen species (ROS), upsetting the balance between the oxidative and antioxidant enzyme systems. The over-accumulation of free radicals, in conjunction with the exhaustion of energy reserves and the accumulation of metabolic by-products, causes tissue damage and eventually induces fatigue^[9].

During intense physical exertion in high-altitude hypoxic environments, the combined stimuli of hypoxia and exercise prompt the accumulation of metabolic by-products such as blood urea nitrogen (BUN), creatinine (CRE), prealbumin (PA), lactate dehydrogenase (LDH), nitric oxide (NO), and malondialdehyde (MDA). Concurrently, glycogen, which serves as the primary substrate for energy metabolism, is rapidly exhausted. When the glucose (Glu) supply is inadequate, the body preferentially depletes hepatic glycogen (HG) reserves. In the course of prolonged, low-intensity exercise, muscle glycogen (MG) is decomposed to furnish energy. As a result, physical activity in high-altitude settings leads to a substantial depletion of MG and HG reserves, thereby giving rise to fatigue^[9]. Studies have demonstrated that both sustained hypoxia or short-term normobaric hypoxia (commonly during rest) can also lead to a depletion of cardiac energy reserves. In the hearts of hypoxic rat, fatty acid oxidation and respiratory capacity are diminished. In skeletal muscle, extended exposure to extreme high altitudes reduces mitochondrial density, and even moderate altitudes can inhabit respiratory capacity^[10]. Further research corroborates that, under resting conditions, mitochondria in human muscles are capable of maintain a high resting phosphorylation potential and enhance the oxidation efficiency of long-chain acylcarnitines. This redirection of muscle Glu towards the pentose phosphate and one-carbon metabolism pathways sustains cytosolic redox balance and alleviates the impacts of augmented protein and purine nucleotide catabolism during hypoxia. The accumulation of free amino acids in muscles facilitates these adaptations by coordinating cytosolic and mitochondrial pathways to eliminate excess nitrogen, though this may ultimately impose limitations on muscle oxidative capacity^[10].

Furthermore, the decreased levels of total cholesterol (TC) and triglycerides (TG) in the bloodstream are insufficient to offset the substantial depletion of glycogen and Glu. This is because the fatty acids generated from their degradation are unable to supply adequate energy for muscle contraction. The activities of enzymes such as creatine kinase (CK), pyruvate kinase (PK), LDH, catalase (CAT), glutathione (GSH), nitric oxide synthase (NOS), and total superoxide dismutase (T-SOD), which are responsible for maintaining redox equilibrium, undergo alterations. Such alteration impact the generation of free radicals, thereby disrupting the balance between oxidation and antioxidation within the body.

The low oxygen levels, extreme cold, and high radiation levels at high altitudes profoundly impact the structure and function of the gut microbiota. A stable oxygen content within the intestines is crucial for maintaining the composition and functionality of the gut microbiota. After 12 days of exposure to hypoxia, the ratio of

Firmicutes to Bacteroidetes and the α -diversity index in the gut microbiota of guinea pigs decreased significantly^[11]. Studies further suggest that hypoxia elevates the abundance of pathogenic bacteria while reducing the abundance of beneficial bacteria in the host's gut, resulting in symptoms such as diarrhea, infections, weight loss, and mucosal damage. The decline in the population of gut microbiota attenuates its metabolic activity, consequently reducing the body's energy utilization efficiency^[12].

2.2 Pathophysiology of PHF

When the body is exposed to a high-altitude hypoxic environment, physical activity augments the oxygen demand. In the lungs, incomplete oxygenation of blood and an elevation in cardiac output act as compensatory mechanisms. These mechanisms aim to maintain convective oxygen transport despite reduced arterial oxygen content. The alterations in cardiac output are predominantly attributed to an increase in heart rate. This increase is proportional to the degree of hypoxia and stems from β -adrenergic activation and parasympathetic withdrawal. However, this compensatory mechanism is transient. Within a few days, the increased blood concentration enhances the blood's oxygen-carrying capacity, thus reducing the cardiac output needed to sustain oxygen delivery. In fact, the cardiac output decreases to levels lower than those prior to ascent. The main cause of this reduction is a decrease in blood volume resulting from hemoconcentration, leading to reduced venous return and, consequently, a decrease in stroke volume. Hypoxia at high altitudes exerts a continuous stimulatory effect on the sympathetic nervous system. Initially, this causes an elevation in heart rate. However, over time, the heart's responsiveness wanes, and the initial tachycardia may not be sustained. Another crucial physiological response is the enhancement of blood oxygen-carrying capacity, which aids in maintain oxygen delivery during arterial hypoxemia. Hemoglobin (Hb) concentration initially increases due to a reduction in plasma volume and hemoconcentration. Other consequences of sympathetic stimulation include an increase in resting metabolic rate, a shift from glycogen to free fatty acids as the primary energy source, and an increase in red blood cell production mediated by hypoxia-induced elevation in serum erythropoietin levels. As a result, aerobic exercise capacity is reduced after arriving at high altitudes^[13].

Under conditions of extremely low tissue oxygen partial pressure, multiple changes occur at the tissue level, particularly in skeletal muscle, which affect oxygen transport and utilization. The diffusion distance from capillaries to mitochondria is reduced due to increased capillary density, primarily resulting from a decrease in muscle fiber size rather than angiogenesis. There is no significant change in muscle fiber type (slow-twitch vs. fast-twitch), while mitochondrial volume density decreases with exposure to very high altitudes. Hypoxia may reduce the oxidative capacity of skeletal muscle but has little effect on the glycolytic pathway. There is ongoing debate about whether myoglobin (Mb) expression increases under hypoxia. Mb, a monomeric globulin that facilitates oxygen extraction from blood and intracellular transport, may or may not be upregulated. Similarly, a related protein called cytoglobin may be upregulated during hypoxia and contribute to adaptive responses. Many cellular processes are mediated by hypoxia-inducible factor 1 α (HIF-1 α). Under normoxic conditions, this transcription factor is degraded by prolyl hydroxylases, but under hypoxic conditions, it avoids degradation, enters the nucleus, and forms a complex with

Hypoxia-inducible factor 1 α (HIF-1 β) and other proteins to initiate gene transcription. This affects a wide range of processes, including angiogenesis, chemoreceptor function, energy utilization, erythropoiesis, and NO metabolism. The clinical manifestation of these changes is that exercise at the same absolute intensity becomes increasingly difficult as altitude increases. Studies have shown that research on high-altitude fish reveals that HIF-1 α can enhance cell protection and increase NO production in hypoxic environments^[14]. Moreover, HIF-1 α expression shows an upward trend with the increase in hypoxic altitude and duration^[15]. HIF-1 α is also significantly reduced in all monocyte subsets related to high-altitude pulmonary hypertension^[16]. The increase in HIF-1 α expression during plateau adaptation is also a beneficial factor for improving adipocyte function^[17,18]. Additional evidence suggests that hypoxia affects both the central and peripheral nervous systems, as well as the perception of fatigue, which may also contribute to exercise limitation^[19].

Two critical factors determining muscle oxygen delivery are arterial oxygen content and leg blood flow. During intense exercise, acute high-altitude hypoxia significantly impacts both of these factors. In a high-altitude hypoxic environment, arterial oxygen partial pressure and Hb saturation are markedly reduced. Although the body initiates a hyperventilation response to adapt to hypoxia and mitigate damage, arterial oxygen content ultimately decreases. Under hypoxic conditions, the work of inspiratory muscles during exercise also increases substantially. This elevated inspiratory muscle workload can impair leg blood flow during physical activity. The reduction in both arterial oxygen content and leg blood flow accelerates the onset and progression of exercise-induced muscle fatigue under hypoxia^[20]. As atmospheric pressure decreases with altitude, arterial oxygen partial pressure also declines. When the body is exposed to a low-pressure hypoxic environment, it may lead to maximal or near-maximal recruitment and dilation of pulmonary blood vessels. This limits the body's ability to further expand pulmonary capillaries in response to exercise at high altitudes, as it would under normal conditions. Consequently, during exercise at high altitudes, the restricted recruitment and dilation of pulmonary capillaries prevent an increase in the gas exchange surface area of lung tissue. Simultaneously, the accelerated metabolic demands during exercise cannot be fully met, resulting in excessive increases in pulmonary artery pressure and resistance. Overall, exposure to a hypoxic environment severely impairs exercise capacity^[21].

2.3 Other potential mechanisms and pathways of PHF

There are also multiple potential mechanisms underlying PHF. In terms of the oxidative stress mechanism, as the altitude increases, the partial pressure of oxygen decreases. When the human body is exposed to a hypoxic environment, excessive free radicals such as superoxide anion radicals and hydroxyl radicals are generated. If the endogenous antioxidant system fails to scavenge these free radicals in a timely manner, oxidative stress will be induced, which attacks intracellular lipids, proteins, and DNA, causing cell damage and affecting cell functions, thus leading to fatigue^[4]. Meanwhile, under plateau hypoxic conditions, the activities of antioxidant enzymes in the body, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), change. Prolonged exposure to a hypoxic environment may reduce their activities, weakening the body's ability to scavenge free radicals, disrupting the balance between oxidation and antioxidation, and promoting fatigue^[22].

Regarding the neuroregulatory mechanism, the brain is

extremely sensitive to hypoxia. Plateau hypoxia affects the function of the central nervous system, leading to the inhibition of cerebral cortex function, slowing down of nerve conduction velocity, and impairment of nerve signal transmission. This results in a decline in the body's motor control ability and reaction speed, accompanied by a sense of fatigue. Moreover, hypoxia also affects the synthesis, release, and metabolism of neurotransmitters such as dopamine and acetylcholine, altering the excitability and regulatory function of the nervous system and triggering fatigue. Additionally, plateau hypoxia can cause dysfunction of the autonomic nervous system, with sympathetic nerve excitement predominating, leading to increased heart rate, elevated blood pressure, etc. Prolonged exposure to this state increases the functional burden on various organs in the body, affecting their normal metabolism and function, and thus inducing fatigue^[23,24].

From the perspective of the inflammatory response mechanism, the plateau hypoxic environment activates the body's immune system, releasing a series of inflammatory factors such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α)^[22]. These factors affect the body's physiological functions through multiple pathways, such as causing fever, pain, increasing metabolic burden, and directly or indirectly acting on nerve cells and muscle cells to affect their functions, resulting in fatigue^[25]. Furthermore, the inflammatory response increases vascular permeability, causing the exudation of fluid and proteins in the blood into the tissue space, leading to tissue edema. In muscle tissue, the edema compresses the surrounding nerves and blood vessels, affecting muscle blood supply and nerve conduction, reducing muscle contraction function, and making it prone to fatigue^[26]. Certainly, there are also studies indicating that alterations in the metabolic activity of gut microbiota are closely associated with PHF. The plateau environment can induce

changes in the quantity and composition of gut microbes. Meanwhile, it affects the absorption of drugs and other active ingredients in the intestine, and thus may effectively regulate fatigue^[27,28].

3 Pharmacological effects of medicine-food Supplements & natural products in PHF treatment

The typical pathogenesis of natural products against PHF and the resistance mechanisms are illustrated in Fig. 1.

3.1 Improve hypoxia tolerance and exercise endurance

The enhancement of hypoxia tolerance and exercise endurance is the most direct reflection of the efficacy of natural substances against PHF^[7]. To date, the commonly employed ethological methods for assessing anti-PHF effects involve observing the duration of survival of animals in an airtight, asphyxiating environment, as well as conducting forced weight-bearing or exhaustive swimming tests under simulated high-altitude hypoxic conditions (mimicking low-pressure hypoxia)^[29,30]. The duration of these activities serves as an indicator of the degree of exercise-induced fatigue. Additionally, some studies utilize the rotarod test, forced running test, forelimb grip strength test, or a combination of these models to evaluate fatigue. These methods directly reflect changes in exercise endurance of animals under simulated high-altitude hypoxic conditions and are the most widely applied models^[31].

Many dietary supplements that serve both medicinal and edible purposes demonstrate anti-PHF effects. Rhodiola, a medicinal and edible herb first documented in the *Shennong Ben Cao Jing*, is renowned for its properties of replenishing qi, clearing the lungs,

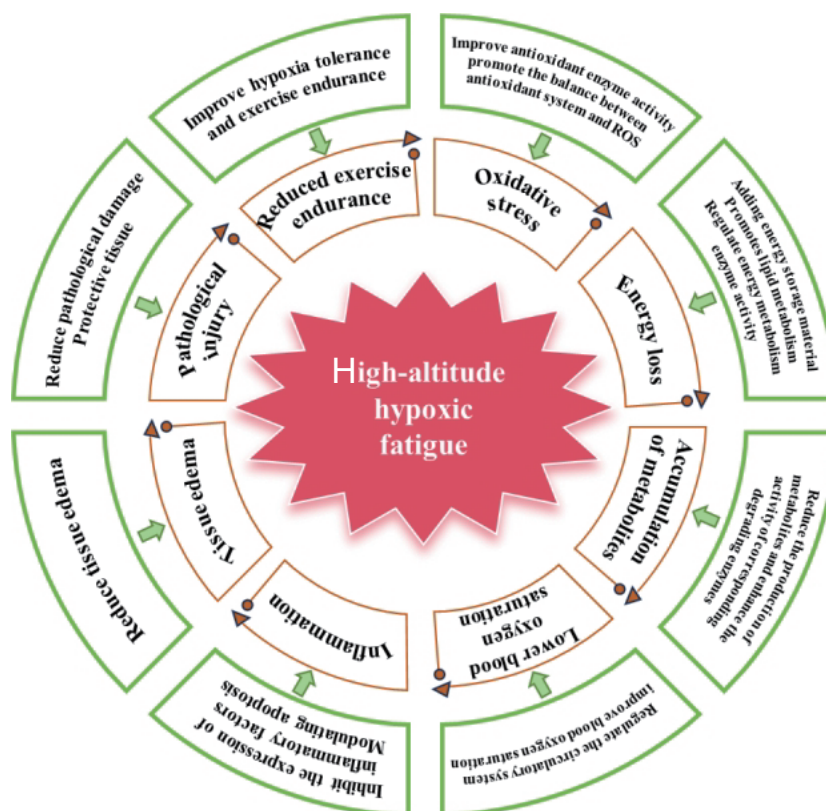


Figure 1 Typical pathogenesis and resistance mechanism of natural products to PHF.

invigorating blood circulation, dispersing stasis, tonifying the spleen, boosting qi, and nourishing the heart, and is classified as a superior medicinal substance. In 1977, *Rhodiola rosea*, as a representative of the *Rhodiola* species, was included in the *Pharmacopoeia of the People's Republic of China*. Modern research has found that *R. rosea*, when administered, exhibits hypoxia tolerance as observed through hypoxic mixed gas and airtight hypoxia models^[32], and demonstrates anti-fatigue effects through weight-bearing swimming tests and rotarod tests. The results indicate that *R. rosea* significantly extends the survival time under hypoxic mixed gas conditions, the duration of weight-bearing swimming, and the time spent on the rod during both the learning and testing phases of the rotarod test in mice. Furthermore, studies on *Hippophae rhamnoides*, *Astragalus membranaceus*, *Phyllanthus emblica*, *Codonopsis pilosula*, *Saussurea involucrata*, *Arenaria kansuensis*, *Scutellaria baicalensis*, *Cordyceps sinensis*, *Crematodinium humile*, *Moringa oleifera* leaves, and yak milk powder have shown that these substances can improve the hypoxia tolerance ability, exhaustive swimming, and weight-bearing swimming times of animals in simulated high-altitude environments, as well as the time spent on the rod, thereby exerting anti-fatigue effects by enhancing hypoxia tolerance and exercise endurance. Research on specific types of active ingredient mixtures extracted from medicinal and edible dietary supplements has also shown significant anti-PHF effects in animal studies, such as *Lycium barbarum* polysaccharides (LBP)^[33], *Cistanche* total glycosides^[34], a mixture of gardenia yellow pigment and *Cistanche* phenylethanoid glycosides (PhGs)^[35], PhGs, *Angelica sinensis* volatile oil, ginsenosides, *Gynostemma pentaphyllum* saponins, *Petasites japonicus* total lactones, *Aster tataricus* total flavonoids, gardenia yellow pigment, and *Panax notoginseng* saponins. Moreover, many studies have been conducted at the level of monomeric active ingredients, such as ginsenoside Rg3, curcumin (CUR), pyrroloquinoline quinone (PQQ), salidroside, verbascoside, echinacoside, resveratrol, theophylline, baicalin, puerarin, cilostazol, and gastrodin, all of which can significantly extend the hypoxia tolerance and exhaustive swimming time of animals in simulated high-altitude environments, markedly improving work capacity.

3.2 Antioxidant activity and amelioration of hypoxia-induced oxidative stress

In the hypobaric hypoxic environment of high altitudes, even moderate exercise can significantly exacerbate the fatigue process, leading to the excessive production of free radicals such as hydroxyl radicals and superoxide anion radicals, collectively known as ROS. These ROS can easily cause lipid peroxidation damage to skeletal muscle and liver mitochondria. Interestingly, the body's enzymatic antioxidant system has corresponding defense mechanisms, such as SOD, GSH-Px, and CAT, which can scavenge ROS in muscle cells^[36]. SOD catalyzes the conversion of ROS into hydrogen peroxide (H_2O_2) and O_2 , which are then decomposed into water and O_2 by CAT and GSH-Px. When the balance between ROS and the antioxidant system is disrupted, the accumulation of ROS can trigger oxidative stress, causing damage to the body by attacking macromolecules (such as lipids, proteins, and DNA) and organelles, leading to the formation of lipid peroxidation products like MDA^[37]. In response, every cell in the body can produce GSH, a potent antioxidant that helps mitigate oxidative stress-induced cellular damage, thereby alleviating fatigue^[38]. The detailed mechanism is illustrated in Fig. 2.

Numerous studies have demonstrated that dietary supplements with both medicinal and edible properties, active ingredient mixtures, and monomeric active components with antioxidant activity can alleviate fatigue induced by high-altitude hypoxia by enhancing the activity of the antioxidant defense system, promoting the balance between the antioxidant system and ROS, scavenging ROS, reducing MDA levels, inhibiting lipid peroxidation, and protecting cell membranes from oxidative stress damage. For example, *A. membranaceus*^[39], *S. involucrata*^[40], *Cordyceps* polysaccharides, and *Cistanche* total glycosides can increase SOD levels and decrease MDA levels in mice under simulated high-altitude conditions; *C. humile*^[41] can also enhance the activity of CAT and GSH-Px in the heart and brain tissues of mice under high-altitude hypoxia. Additionally, *P. notoginseng*, *Ginkgo biloba* leaves, and *Rhodiola*^[42] can reduce MDA levels and increase SOD activity in the serum of rats under simulated high-altitude conditions, thereby improving the body's antioxidant capacity; *Gentiana macrophylla*^[43] can also elevate CAT activity in the serum and myocardial tissues of rats; *A. membranaceus*^[44] can

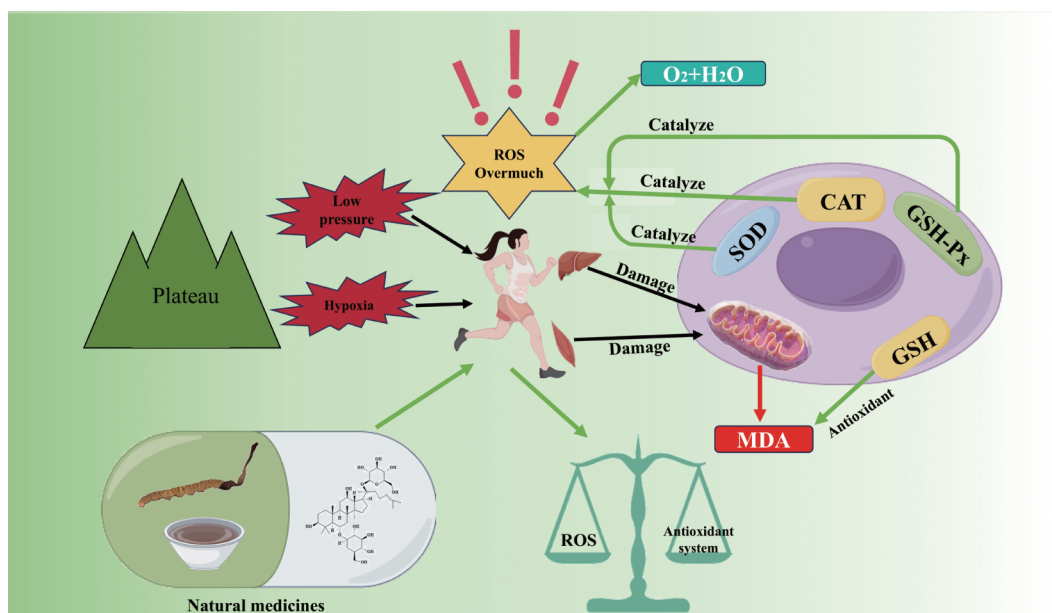


Figure 2 Natural medicines improve PHF by anti-oxidation and ameliorating oxidative stress caused by hypoxia.

significantly increase GSH levels in rats under simulated high-altitude conditions. *C. sinensis*^[45] can upregulate uncoupling protein 1 and maintain metabolic homeostasis to regulate thermogenic responses in rats under simulated high-altitude stress models. It can also improve the condition of animals exposed to hypobaric hypoxia, potentially related to changes in GSH and 2,3-diphosphoglycerate levels.

Specific types of mixtures also exhibit excellent antioxidant effects, enhancing anti-PHF capabilities. Under simulated high-altitude hypobaric hypoxia conditions, Cordyceps peptides can effectively counteract lipid peroxidation reactions in animals and inhibit the production of GSH-Px; a mixture of gardenia yellow pigment and *Cistanche* PhGs can significantly increase the levels of CAT, GSH-Px, and T-SOD in the muscles and liver of mice; PhGs can also reduce MDA levels, and areca nut polyphenols have a similar effect on the liver and lungs of rats; the total polysaccharides of *Brassica rapa* can not only achieve the above effects but also increase the activity of T-AOC; the total flavonoids of *A. tataricus* can effectively reduce MDA and H₂O₂ levels in the brain tissues of mice and increase the activity of SOD, CAT, GSH, and GSH-Px; the total flavonoids of *Epimedium* can elevate SOD levels in the serum, brain, and heart tissues of rats and significantly reduce MDA levels; gardenia yellow pigment can significantly increase GSH content and enhance SOD activity in the liver, muscles, and serum of mice.

Furthermore, many studies have shown that monomeric active components also possess significant antioxidant activity to combat PHF. For example, kaempferol (KA) and ginsenoside Rg1 (GRg1) isolated and purified from ginseng significantly improve the concentrations of SOD and CAT in the lung tissues of rats under high-altitude hypoxia models; ginsenoside Rg2 can increase SOD activity in cell supernatants and reduce MDA levels in a dose-dependent manner; ginsenoside Rg3 can upregulate the activity of manganese-superoxide dismutase (Mn-SOD) in skeletal muscle mitochondria in the serum of rats under simulated high-altitude conditions and reduce MDA levels. Tetrahydrocurcumin (THC) can increase SOD activity in mice under acute hypobaric hypoxia; PQQ can enhance SOD activity and reduce MDA levels in mice; salidroside can also decrease H₂O₂ levels in the liver and muscle tissues of mice and increase GSH levels. Verbascoside can reduce the activity of oxidative stress-related enzymes in the plasma, brain, and hippocampus of rats. Resveratrol (RSV) can restore ROS levels in the myocardial tissues of rats under high-altitude hypobaric hypoxia, alleviate myocardial hypertrophy and cardiac function, and is closely related to reducing ROS and improving myocardial oxidative stress levels. Other studies have found that RSV intervention can reduce ROS levels and increase the content of antioxidant enzymes SOD and GSH-Px in the serum of rats. Additionally, notoginsenoside R1 has a similar effect. Catechin can reduce MDA levels and increase GSH and SOD levels in rat tissues; cilostazol demonstrates analogous effects in the myocardial, brain, lung, liver, and kidney tissues of rats; tanshinone II-A shows similar effects in the hippocampal tissues of animals; and *M. oleifera* leaves exhibit comparable effects in the skeletal muscles of mice.

3.3 Effects on energy metabolism

3.3.1 Increasing the levels of energy-storing substances in the body

Energy sustains various life activities of the organism and is mainly stored in the body in the forms of ATP, Glu, glycogen, etc. Glu, referring to the Glu content in the blood, is the primary

energy source for the human body, ensuring the normal operation of various tissues and organs. Glycogen is an important source of exercise energy, and its storage amount can directly affect the body's exercise ability. Increasing glycogen reserves helps improve endurance and exercise ability and resist the occurrence of PHF^[46]. Therefore, during long-term low-pressure and hypoxic exercise, physical exhaustion is always accompanied by the depletion of MG. To maintain the Glu level, the reserve of HG will decrease. If a drug can increase glycogen reserves, it can provide more energy. Thus, the content of glycogen can indicate the speed of fatigue onset. When the HG reserve in the body is low and the body is in a state of physical exercise, the Glu level drops rapidly, leading to premature depletion of HG^[47]. Even if there is a large amount of HG stored, it is impossible to maintain a constant blood Glu level, which is one of the reasons for fatigue, reduced exercise performance, and the inability to sustain exercise. When the exercise intensity is relatively low and the exercise duration is relatively long, MG will be decomposed to provide energy for exercise. However, the storage of MG is limited (the storage amount in the muscles of an average person is 300–400 g). If MG is largely decomposed and consumed, muscle fatigue will occur. At the same time, long-term contraction of muscle cells leads to fatigue. When muscle cells contract, a large amount of adenosine triphosphate (ATP) is consumed, resulting in a decrease in ATP concentration. The generation of ATP can mainly come from the oxidative decomposition of MG or from the transfer of energy in creatine phosphate^[25].

Researchers have found that medicine-food homologous substances such as *P. emblica*^[48,49], *C. sinensis*^[50], PQQ^[30] can increase the HG content in mice in a simulated hypobaric and hypoxic environment of high altitude. *A. membranaceus* can increase the HG and MG contents in rats, as well as the HG and Glu contents in mice. Yak milk powder can promote gluconeogenesis and fat oxidation in mice and increase the storage level of HG. The mixture of gardenia yellow pigment and *Cistanche* PhGs can increase the levels of ATP, HG, and MG in the liver and muscle tissues of mice, and salidroside can also increase the levels of ATP, HG, and MG in the liver and muscle tissues of mice. The total lactones in *P. japonicus* can reduce the Glu content in rats and increase the glycogen and ATP contents in the liver, skeletal muscle, and myocardium. *P. notoginseng* saponins can increase the HG content and Glu concentration in mice. Ginsenoside Rg3 can up-regulate the Glu level in rats. Verbascoside, echinacoside, and polydatin^[51] can increase the levels of energy-storing substances in rats and reduce protein decomposition. *M. oleifera* leaves can increase the Glu, MG, and LG contents in mice, etc., thus achieving the anti-PHF effect.

3.3.2 Promoting lipid metabolism

Some dietary supplements with homology of medicine and food can also indirectly resist PHF by promoting another form of energy storage, namely fat/lipid metabolism. Through lipid decomposition, the amount of direct energy-supplying substances increases compensatorily. The concentrations of TC and TG in the blood can be used as indicators to measure fatigue. Rational utilization of TC and TG can reduce the consumption of glycogen and Glu, and the fatty acids decomposed from TG can provide energy for muscle contraction, thus achieving the effect of delaying fatigue. *S. involucrata* and octacosane can regulate the increase of TG and TC levels in the plasma of mice in a hypoxic environment at high altitude, indicating that they can optimize the basal metabolic level and ensure the efficient supply of energy

required for the organism's survival under acute hypoxic conditions^[52]. Ginsenoside Rg3^[53] can up-regulate the TC and TG in the serum of rats in a simulated high-altitude environment, indirectly increasing the amount of direct energy-supplying substances, and thus achieving resistance to hypobaric-hypoxic fatigue. Other studies have found that *L*-carnitine combined with trimetazidine regulates and improves the abnormal changes in energy substances caused by high-altitude hypoxia. *L*-Carnitine mainly promotes fatty acid metabolism, and trimetazidine enhances the glycolysis process. *L*-Carnitine combined with trimetazidine also helps to reduce the increase of some tricarboxylic acid (TCA) cycle intermediates, reduce the production of 3-hydroxybutyric acid, and relieve the abnormal energy metabolism process in organisms and cardiac tissues.

3.3.3 Regulating energy metabolism related substances and enzyme activities

ATP, as a high-energy phosphate compound, is the energy currency in living organisms. It can provide direct energy for life activities and also serve as raw materials or catalytic agents for the synthesis of other substances. ATPase is an enzyme that can hydrolyze ATP into adenosine diphosphate (ADP) and phosphate ions, a reaction that releases energy. In most cases, energy can be transferred and used to drive another chemical reaction that requires energy. This process is widely utilized by all known life forms. Specifically, Na⁺, K⁺-ATPase and Ca²⁺, Mg²⁺-ATPase are bio-membrane enzyme systems widely distributed in the body, playing an extremely important role in maintaining the normal physiological functions of cells. Na⁺, K⁺-ATPase is a protein embedded in the lipid bilayer of the cytoplasmic membrane, with the activities of both a carrier and an enzyme. It can catalyze the hydrolysis of ATP to supply energy, drive the counter-transport of Na⁺ and K⁺ across the cell membrane, maintain the membrane potential on both sides of the cell membrane, regulate cell osmotic pressure, provide power for the absorption of nutrients, and play an important role in the impulse conduction of nerve and muscle cells. Ca²⁺, Mg²⁺-ATPase is another important enzyme on the cell membrane. It has a significant impact on maintaining the stable concentrations of Ca²⁺ and Mg²⁺ within the cell, the contraction of the myocardium and other muscles, the conduction of action potentials in nerve cells, and cell secretion and reproduction. Some research indicates that *Gentiana straminea*^[43] can increase the content of ATPase and the activities of Na⁺, K⁺-ATPase and Ca²⁺, Mg²⁺-ATPase in the myocardial tissue of rats in a hypobaric and hypoxic environment. *A. sinensis* volatile oil^[54] and total polysaccharides from *Turnip*^[55] respectively play the same role in the brain tissue of mice. Salidroside^[56] exerts its effect in the liver and muscle tissues of mice.

PK is a key enzyme in the glycolysis pathway. It can catalyze the conversion of phosphoenolpyruvate to enolpyruvate and generate ATP, having important physiological functions. Succinate dehydrogenase (SDH) is part of the mitochondrial respiratory chain, participating in the TCA cycle. It has functions such as oxidative phosphorylation, the TCA cycle, and regulation of cell respiration, promoting electron transfer, helping to decompose substrates to generate energy, and maintaining the energy balance within the cell. Malate dehydrogenase (MDH), mainly involved in the TCA cycle, generates NADH and maintains energy balance, ensuring the efficient utilization and conversion of energy within the cell. CK is mainly present in skeletal muscle and myocardium, participating in the creatine phosphate energy system, energy transfer, and regulation of energy supply, providing energy for

muscle contraction. The increase in LDH activity, mainly involved in the cell respiration process, promotes the conversion and utilization of lactate, helps regulate energy level within the cell, and thus generates sufficient energy for exercise under anaerobic conditions. It is and helps regulate the energy level within. Research shows that PhGs^[57] can enhance the activities of energy-metabolism enzymes (MDH, SDH, PK, CK, LDH) in mice, thus enhancing their resistance to fatigue caused by high-altitude hypoxia. Gardenia yellow pigment^[58] can significantly increase the PK activity in the liver, muscle, and serum of animals, promoting the glycolysis process.

Mitochondrial respiratory chain complex III, also known as CoQ-cytochrome C reductase, is widely present in the mitochondria of animals, plants, and microorganisms. It is a common component of the main and branch paths of the mitochondrial respiratory electron-transport chain, responsible for transferring the hydrogen of reduced CoQ to cytochrome C to generate reduced cytochrome C. Mitochondrial respiratory chain complex IV, also known as CoQ-cytochrome C oxidase, has a corresponding function. Studies have found that ginsenoside Rg3 can up-regulate the activities of skeletal muscle mitochondrial respiratory chain complexes III and IV in the serum of rats in a simulated high-altitude environment, accelerate the reaction of the respiratory chain, and promote energy utilization^[53]. Corticosterone is a hormone secreted by the adrenal cortex, which can regulate energy metabolism (carbohydrates, proteins, fats). When the body is faced with stress, disease, or other stress factors, the adrenal cortex may increase the secretion of corticosterone to cope. Total flavonoids of *Epimedium*^[59] can increase the content of corticosterone in the plasma of hypobaric and hypoxic rats, indicating that it can enhance the function of the adrenal cortex under hypoxic conditions by increasing corticosterone secretion. *L*-Carnitine combined with trimetazidine regulates and improves the abnormal changes in energy substances caused by high-altitude hypoxia. It also helps to reduce the increase of some TCA cycle intermediates, decrease the production of 3-hydroxybutyric acid, and relieve the abnormal energy-metabolism process in organisms and cardiac tissues^[60]. Therefore, the above-mentioned substances and enzymes all play important roles in the regulation of energy metabolism.

3.4 Reducing the accumulation of free radicals and metabolites

The unique hypobaric and low-oxygen partial pressure environment in the plateau is the main factor affecting the work ability of people stationed in the plateau. Prolonged intense exercise in the plateau can exacerbate hypoxia, thus limiting the body's ability to utilize oxygen. A large amount of various metabolites accumulate in the body, such as lactic acid (LA), blood ammonia (BA), and BUN. This state of body hypoxia and metabolite retention leads to a decline in physiological functions and makes it easier to induce exercise fatigue. BUN is the final product of the decomposition of nitrogen-containing nutrients such as body proteins and amino acids in the body. Under normal circumstances, the production and excretion of BUN are in a balanced state. Its content is negatively correlated with the body's exercise endurance and is a sensitive indicator for evaluating the body's exercise endurance. In the fatigue caused by hypoxia in the plateau, a high BUN level indicates an accumulation of urea nitrogen, which can damage kidney function and prevent it from effectively filtering waste and toxins in the blood, ultimately leading to physical fatigue. Because BUN has an inhibitory effect

on the nervous system, affecting energy metabolism and nerve conduction, people feel tired and weak. Therefore, BUN is also an important indicator for measuring physical fatigue. In addition, an increase in the activity of LDH helps to generate sufficient energy for exercise under anaerobic conditions and accelerates the removal of LA. Therefore, LDH activity is an indirect indicator of physical fatigue. At the same time, it is related to the area under the blood lactate curve (AUC-BLA). Its level can reflect some situations in the body during exercise or metabolism. A high AUC-BLA represents that the body produces more LA during exercise or metabolism. An increase in CK in the blood can lead to fatigue because an increase in CK can increase energy metabolism and produce more LA, thereby affecting muscle endurance and exercise ability. At the same time, it also indicates that muscle damage has occurred or is occurring. NO is also a free radical. When its concentration reaches a certain level, it is toxic to cells. Therefore, reducing the content of NO in tissues can protect cells from damage. In a simulated plateau environment, *P. emblica* can reduce the AUC-BLA of mice, increase the LDH activity, and reduce the contents of LA and BUN in the blood. *C. sinensis* has the same effect^[49,50]. *A. membranaceus* shows the same effect in rat experiments and also reduces the AUC-BLA of mice. *S. involucrata* can increase the LDH activity in the plasma of mice and at the same time reduce the LA level.

Troponin T (cTnT) is an important regulatory protein for muscle contraction. Cardiac cTnT exists only in cardiomyocytes. When cardiomyocytes are damaged, cTnT will be degraded from muscle fibers into the blood. Therefore, the level of cTnT in the serum can reflect the degree of myocardial damage. Mb is mainly present in the myocardium and skeletal muscle. It can be rapidly released into the blood during acute myocardial injury and most of it is free in the blood. Therefore, Mb is also a good early diagnostic indicator of myocardial injury. Research shows that *G. straminea* can reduce the levels of cTnT, Mb, LDH in the serum of rats, as well as the content of CK, the levels of LA and NO, in the LDH activity in the myocardial tissue, indicating that it has a protective effect on myocardial injury in rats with plateau hypoxia and thus indirectly reflects the anti-PHF effect^[43]. Yak milk powder and LBP can both reduce the accumulation of metabolites such as LA and BUN in the blood of animals during exercise, thus alleviating the animal fatigue. The mixture of gardenia yellow pigment and *Cistanche* PhGs can significantly reduce the levels of BUN, uric acid (UA), PA, LA, NO, and MDA in the serum, brain, liver, and muscle tissues of mice, inhibit the production of excessive free radicals, protect cells from damage, and delay the occurrence of exercise fatigue. Gardenia yellow pigment can significantly enhance the LDH activity in the liver, muscle, and serum of animals and reduce the accumulation of LA. PhGs show effective scavenging ability for 1,1-diphenyl-2-picrylhydrazyl radical, 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt, BUN, and LA. In addition, research on the monomer ginsenoside Rg2 has found that it can reduce the content of NO in the cell supernatant, thus protecting cells from hypoxic damage^[61]. Catechin can reduce the content of NO in the main tissues of rats^[62]. Eleutheroside B^[63-65] can regulate the two-way balance of the central nervous system and has anti-fatigue, anti-radiation, and anti-hypoxia activities. It mainly achieves the anti-PHF effect by increasing the scavenging ability of free radicals.

3.5 Effects on the circulatory system

NO is not only a free radical but also an important biological

signaling molecule, playing a crucial role in many physiological processes of the body. Research indicates that NO is involved in the contraction and relaxation of muscles. It is also known as the vascular endothelial relaxing factor. During exercise, muscles produce NO, which in turn promotes vasodilation, increases blood flow, provides more oxygen and nutrients to the muscles, helps maintain normal muscle function, and alleviates the feeling of fatigue. Meanwhile, nitrogen oxides (NOx) generated from NO can resist the damage caused by hypoxia. Total flavonoids of *Epimedium* can increase the contents of total NO synthase and NO in the serum, brain, and heart tissues of hypobaric and hypoxic rats, dilate skeletal muscle blood vessels, ensure an increase in skeletal muscle blood flow, reduce oxygen consumption, maintain a high oxygen uptake rate, and be conducive to delaying the onset of exercise fatigue^[59].

When the concentration of red blood cells (RBC) in the blood reaches a specific value, the blood's ability to transport oxygen and carbon dioxide is optimal, and the body's exercise capacity can reach its best. If the concentration of RBC is too low, the oxygen-carrying capacity of a unit volume of blood is insufficient. If the concentration of RBC is too high, it will increase blood viscosity, reduce the efficiency of blood circulation, increase the heart load, and indirectly lead to a decrease in the oxygen-carrying capacity of the blood. Hb is a key protein responsible for oxygen-carrying and oxygen-releasing functions in the body. Its oxygen-supply efficiency is a key index for evaluating its oxygen-carrying and oxygen-releasing functions. It is jointly affected by factors such as the oxygen affinity of Hb, the Bohr effect, and the theoretical oxygen-releasing capacity. Enhancing the oxygen-supply efficiency of Hb is an effective means to alleviate PHF and related injuries. In a simulated plateau environment, *P. emblica* can increase the Hb content in the blood of mice. The water-soluble alcohol extract of *A. kansuensis* also shows the ability to increase the RBC content and Hb concentration in mice, strengthening the oxygen-transport capacity. When CUR^[66] was intraperitoneally injected into mice for 7 consecutive days, it was found that it could effectively enhance the oxygen-supply efficiency of Hb in rats with acute high-altitude hypoxia and significantly improve their work ability. Cilostazol (celastrol) can also increase the Hb oxygen saturation of rats, and decrease the Hb content and hematocrit (HCT)^[22]. Blood oxygen saturation is the percentage of the capacity of oxygen-bound oxyhemoglobin (HbO₂) in the blood to the total bindable Hb capacity. It is an important physiological parameter of the respiratory cycle. For example, areca nut polyphenols have been shown to significantly increase the blood oxygen saturation level of rats with acute high-altitude hypoxia^[26].

3.6 Effects on the immune system

PHF can concurrently trigger a series of inflammatory responses. Experiments have shown that TNF- α can induce central fatigue through mechanisms such as anemia and cachexia. Administration of *P. notoginseng*, *G. biloba*, and *Rhodiola* can reduce the activity of TNF- α in the serum of rats in a hypobaric and hypoxic environment, indicating the inhibition of the expression of inflammatory factors in rats experiencing de-acclimatization to the plateau. IL-6 belongs to the cytokine group that regulates the body's inflammatory response. Prolonged endurance exercise can lead to the release of some cellular inflammatory factors, among which the release of IL-6 is the most significant, suggesting a positive correlation between the occurrence of fatigue and the increase in IL-6 concentration^[67]. Some research indicates that KA and GRg1 isolated and purified

from ginseng can significantly improve the concentrations of IL-6 and TNF- α in rats with a high-altitude hypoxia model. After KA administration, the protein and mRNA levels of *PI3K* and *AKT1* are significantly inhibited^[68]. Catechin^[62] and celastrol^[22] also show the ability to reduce the levels of IL-6 and TNF- α in the main tissues of rats.

Microtubule-associated protein 1A/1B-light chain 3 (LC3) is a marker of autophagy. When autophagy occurs in cells, cytosolic LC3 is enzymatically cleaved to remove a small polypeptide segment and is transformed into the (autophagosome) membrane-bound form. The ratio of the latter to the former can be used to estimate the level of autophagy. RSV can reduce the levels of IL-6 and TNF- α in the serum of rats in a high-altitude environment, decrease the expression of LC3, and increase the expression of translocase of outer mitochondrial membrane 20 (TOMM20), thereby reducing the levels of autophagy and mitophagy^[67]. Complement C3 plays an important role in immune responses and inflammatory processes. Some research has found that the level of complement C3 in the serum increases in a fatigued state. Therefore, fatigue is also considered to be related to the activation of the immune system and inflammatory responses. Cordyceps polypeptide^[69] can effectively reduce the content of C3 in the serum of mice, exerting an anti-inflammatory effect and thus combating PHF.

The PI3K/Akt signaling pathway is involved in various physiological processes and is an important signaling pathway in the development of many diseases, especially tumors. It can regulate cell survival, metastasis, and metabolism, and plays a role in angiogenesis and the recruitment of inflammatory factors. Nuclear factor kappa-B (NF- κ B) proteins can selectively bind to the κ -light-chain enhancer of B cells to regulate the expression of many genes. NF- κ B can be found in almost all animal cells. It is involved in the cell's response to external stimuli and plays a crucial role in processes such as cell inflammatory responses and immune responses. *C. sinensis* can weaken the expression of NF- κ B in rats and enhance the expression of hypoxia-inducible factor and nuclear factor erythroid 2-related factor 2^[45]. Pan *et al.*^[70] found that prophylactic administration of THC for 3 days can significantly reduce the increase in IL-1 β and TNF- α levels caused by acute hypobaric hypoxia. In addition, after THC administration, the expressions of vascular endothelial growth factor (VEGF), matrix metalloproteinase-9, and the NF- κ B are significantly down-regulated both *in vivo* and *in vitro*. Pretreatment with notoginsenoside R1 can reduce the levels of inflammatory indicators in rats and down-regulate the expressions of hypoxia-related proteins HIF-1 α and VEGF^[71]. Nuclear factor erythroid 2-related factor 2 (Nrf2) and its main negative regulator, the E3 ligase adaptor Kelch-like ECH-associated protein 1 (Keap1), play a central role in maintaining intracellular redox homeostasis and regulating inflammation. Interestingly, Nrf2 has been shown to help regulate the heme oxygenase-1 axis, which is an effective anti-inflammatory target. Total flavonoids from *Aster himalaicus* can increase the protein expressions of Nrf2 and SOD and the Bcl-2/Bax ratio in the brain tissue of mice^[72]. Similarly, epigallocatechin-3-gallate has a therapeutic effect on the hearts of rats with chronic hypobaric hypoxia, significantly reducing oxidative stress in the left ventricle and inflammatory responses in the blood, and up-regulating the expressions of Nrf2 and HO-1^[73].

Apoptosis is of extremely important biological significance for the survival, development, and self-stability maintenance of multicellular organisms. With the deepening of research on apoptosis, people have gradually realized that exercise-induced

fatigue is closely related to apoptosis, and apoptosis may also be an important cause of exercise-induced fatigue. Ginsenoside Rg2 can significantly enhance the activity of hippocampal neurons, reduce their apoptosis rate and cell mortality^[61]. Ginsenoside Rb1 can alleviate the hypoxic (apoptotic) damage to hippocampal neurons in SD rats mediated by activated microglia by inhibiting the hypoxia-induced activation reaction of microglia^[74]. Crocin-I can significantly reduce the apoptosis of mitochondria and nerve cells in the CA1 region of the mouse hippocampus and improve the memory impairment of mice in a high-altitude hypoxic environment. After RSV^[67] intervention, the cardiac index of rats decreased significantly, the ventricular wall thickening phenomenon improved, the cardiac cavity volume expanded significantly, the ejection fraction and left ventricular shortening fraction rebounded significantly, and apoptosis was reduced. *M. oleifera* leaves can also reduce the apoptosis rate of mice in a hypobaric and hypoxic environment, and decrease the expressions of GRP78/Bip, C/EBP homologous protein (CHOP), and Caspase-3^[46]. Pretreatment with notoginsenoside R1 can improve abnormal cardiac electrical conduction in rats, relieve plateau-induced tachycardia, alleviate pathological damage, reduce the levels of cardiac injury biomarkers, and reduce cardiomyocyte apoptosis by down-regulating the expressions of apoptotic proteins Bax, cleaved caspase 3, cleaved caspase 9, and cleaved PARP1, and also inhibit the cardiomyocyte apoptosis pathway by activating ERK1/up-regulating the expression of the anti-apoptotic protein Bcl-2. The mixture of gardenia yellow pigment and *Cistanche* PhGs can significantly reduce the expression of apoptotic proteins in hypoxic swimming rats and decrease the expressions of AMPK and Nox2 proteins under hypoxic conditions, thus delaying apoptosis. *A. sinensis* polysaccharide can block apoptosis and autophagy by maintaining cell viability, down-regulating BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), and activating the mTOR signaling pathway, thereby reducing the damage to neural stem cells caused by hypoxia. Ginsenosides^[75] mainly protect against damage caused by hypoxia by reducing the sensitivity of the heart and brain tissues of rats to hypoxia and reducing apoptosis. The mechanism may be related to influencing the expressions of *HIF-1 α* , *EPO*, and *Caspase-3* mRNA, regulating the internal oxygen balance of rat tissues, promoting erythropoiesis, and inhibiting apoptosis, thus combating PHF and damage in turn.

Neuronal damage may also lead to central fatigue, which is the gradual weakening of the active activation of neurons during exercise. One type of central fatigue in brain fatigue, which is manifested as insufficient excitation of the motor cortex. Verbascoside^[76] can significantly reduce the working memory errors, reference memory errors, total errors, and total time of rats, and alleviate the neuronal damage in the CA1 region of the hippocampus. Eleutheroside B can also regulate the two-way balance of the central nervous system and has anti-fatigue, anti-radiation, and anti-hypoxia activities. It mainly protects against and alleviates neuronal damage caused by hypoxia^[63]. In addition, after treating vascular smooth muscle cells under hypoxic conditions with LBP, the content of silent mating-type information regulation 2 homolog 1 (SIRT1) increases with the increase in the dose of LBP, while the contents of matrix metalloproteinase (MMP-9) and HIF-1 α decrease. This indicates that LBP can increase the SIRT1 level in hypoxic pulmonary vascular smooth muscle cells to reduce apoptosis caused by oxidative stress-related factors, decrease MMP-9 to reduce the inflammatory response, and lower the level of HIF-1 α , because

over-activation of HIF-1 α will exacerbate tissue cell damage^[77]. Areca nut polyphenols can significantly reduce the levels of serum inflammatory cytokines (monocyte chemoattractant protein-1 (MCP-1), tissue inhibitor of metalloproteinase-1 (TIMP-1), intercellular adhesion molecule-1 (ICAM-1), *L*-selectin) in rats with acute high-altitude hypoxia. The mechanisms involved in the anti-inflammatory effects of dietary supplements and natural products with homology of medicine and food mentioned above are shown in Fig. 3.

3.7 Other mechanisms against PHF

Most of the research on anti-PHF and related injuries shows intuitive results at the pathological level. For example, the effects are achieved through ways such as reducing organ damage, increasing arterial pressure, improving cardiac function, and alleviating organ edema. Literature review results show that the plateau environment can cause pathological damage and tissue edema, which severely impact exercise ability. Many medicine-food homologous substances can mitigate these issues to exert anti-fatigue effects. *S. involucrata*, THC, octacosane^[31], verbascoside, echinacoside, and polydatin^[51] can all reduce the water content in the organs (heart, brain, lungs, liver, skeletal muscle) of mice and rats under simulated high-altitude hypoxia, alleviate tissue edema caused by hypoxia, and thus achieve the ability to resist PHF. Gypenosides can reduce the damage caused by hypoxia in PC12 cells. After treatment, the contents of Ca²⁺ and ROS are significantly decreased, and the decrease in NO content and mitochondrial membrane potential caused by hypoxia is blocked, demonstrating a neuroprotective effect. Total flavonoids from *A. himalaicus*, total polysaccharides from *Turnip*, areca nut polyphenols^[26], CUR^[66], catechin, cilostazol, tanshinol^[78], and epigallocatechin-3-gallate can respectively reduce the pathological damage of tissues in various parts of the body of hypoxic mice and rats. KA and GRg1 can significantly improve the histopathological changes of rats with lung injury caused by acute hypobaric hypoxia and alleviate pulmonary edema^[68].

P. notoginseng, *G. biloba*, and *Rhodiola* can effectively enhance the ventricular function of rats during the process of

de-acclimatization to the plateau^[42]. After intragastric administration of *A. sinensis* volatile oil to mice, it can reduce the content of excitatory amino acids (EAA) in the brain tissue to protect the brain. Brain ischemia-injury can cause an increase in the content of EAA in the brain tissue. This is because during brain ischemia-injury, the neurons in the brain tissue are depolarized, and the ability of nerve cells to uptake EAA is impaired, resulting in a significant increase in the extracellular EAA content. The reduced EAA includes the contents of Glu, γ -aminobutyric acid (GABA), and aspartic acid (Gly). In addition, some research has found that RSV has a protective effect on the cardiac function of rats. Compared with the hypobaric hypoxia group, the levels of RBC and Hb in the RSV group are significantly decreased, the platelet concentration is significantly increased, the heart coefficient and myocardial fiber thickness are decreased, the ventricular wall thickness is decreased, cardiac function is improved, and the blood-pumping and endurance capacity of the body are enhanced^[79]. The combined treatment of theophylline and an endothelin blocker significantly increase muscle blood flow under hypoxic conditions^[80]. Eleutheroside B can regulate the two-way balance of the central nervous system and has anti-fatigue, anti-radiation, and anti-hypoxia activities. It mainly achieves these effects by increasing the tolerance of tissues to ischemia and hypoxia.

4 Dietary supplements and natural products with homology of medicine and food for combating PHF

4.1 Dietary supplements with homology of medicine and food for combating PHF

The unique low-pressure and low-oxygen environment in plateau areas brings many hazards and troubles to people entering the plateau, seriously affecting the body's physical strength and work ability. After engaging in certain physical or mental labor in the hypoxic environment of the plateau, fatigue is likely to occur,

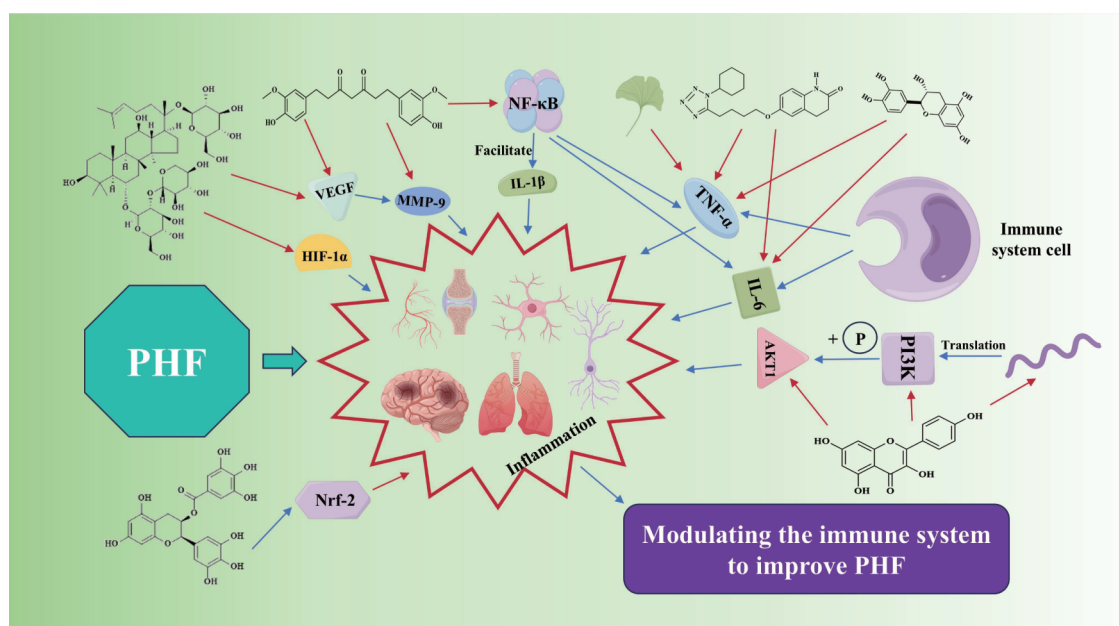


Figure 3 Natural drugs improve PHF through anti-inflammatory effects (involving multiple pathways such as NF- κ B/MMP-9/VEGF/Nrf-2/TNF- α /PI3K/AKT1). The blue arrow indicates the production or promotion effect; the red arrow indicates inhibition.

ultimately manifested as a general decline in work ability. In severe cases, the work ability may even be lost. As the altitude increases, the work ability decreases significantly. Through long-term life experience in adapting to the plateau environment and clinical trials, people have gradually discovered many dietary supplements with homology of medicine and food that can combat fatigue. For example, some research has found that *P. emblica* can achieve the effect of combating hypobaric-hypoxic fatigue by prolonging the exhaustive swimming time of mice in the plateau environment, reducing the AUC-BLA, raising the HG content^[48], significantly prolonging the anti-hypoxia time of mice, increasing the Hb content and LDH activity in the blood, and decreasing the contents of LA and BUN in the blood^[49]. The water extract of *A. membranaceus* can also significantly improve the hypoxic exhaustive swimming time of rats, reduce the contents of BUN and L-lactate, increase the reserve contents of GSH, HG, and MG, counteract the inhibition of the mTOR signaling pathway caused by hypoxia^[44], reduce the AUC-BLA of mice, increase the glycogen and SOD contents in the blood, and reduce the MDA content, thus alleviating the fatigue of mice in a simulated plateau environment^[39]. In experiments using plateau hypoxia models of rats or mice in environments like the multi-factor compound environment simulation medical science experimental cabin, large-

strain *Rhodiola* capsules (mainly containing the extract of large-strain *Rhodiola*), *C. pilosula*, *S. involucreta*, *H. rhamnoides*, *A. kansuensis*, *S. baicalensis*, *C. sinensis*, *P. notoginseng*, *G. biloba*, *R. rosea*, *G. straminea*, and *C. humile* all show significant anti-PHF effects. In addition, in the plateau environment, yak milk powder, which people have consumed for a long time, has also caught the attention of researchers. It has been found that it can prolong the survival time of hypoxic mice, effectively promote gluconeogenesis and fat oxidation in mice, reduce the accumulation of metabolites such as LA and BUN in the blood during exercise, and thus alleviate the body's fatigue. It can also prolong the forced swimming time of mice after exercise and increase the HG content, thereby reflecting the anti-PHF function^[81]. Furthermore, numerous natural drugs and other substances are effective in combating PHF, and their respective mechanisms of action are elaborated in Table 1.

4.2 Crude extracts for combating PHF

Domestic and foreign researchers have found in their studies that mixtures such as polysaccharides, total saponins, total flavonoids, volatile oils, polyphenols, polypeptides, and lactones extracted from some natural products also show significant anti-PHF effects in pharmacological experimental research. For

Table 1 Medicinal and edible homologous substances and dietary supplements against PHF

Name	Medicinal part	Extraction solvent	Mechanisms	The species investigated	References
<i>P. emblica</i> L.	Dry and ripe fruits	Water	Improved hypoxia tolerance and exercise endurance; increased the level of energy storage substances in the body; reduced the accumulation of free radicals and metabolites; improved the function of the circulatory system	Kunming mice ((20 ± 2) g; 100 males and 100 females)	[49]
<i>A. membranaceus</i> (Fisch.) Bge. var. <i>mongholicus</i> (Bge.) Hsiao, <i>A. membranaceus</i> (Fisch.) Bge.	Dry roots	Water	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improved oxidative stress caused by hypoxia; increased the level of energy storage substances in the body and reduced the accumulation of free radicals and metabolites	Male Wistar rats (160–200 g)	[39, 44]
<i>Rhodiola wallichiana</i> var. <i>cholaensis</i>	Dry roots	Water	Improved hypoxia tolerance and exercise endurance; increased the level of energy storage substances in the body and reduced the accumulation of free radicals and metabolites	Male BALB/c mice, aged 6–8 weeks	[4]
<i>Rhodiola crenulata</i> (Hook. f. et Thoms.) H. Ohba	Dry roots and rhizomes	Water	Antioxidant activity and improved oxidative stress caused by hypoxia; regulated immune system; enhanced ventricular function during plateau weaning	Male SD rats (200–220 g)	[42]
<i>C. pilosula</i> (Franch.) Nannf.	Dry roots	Water extraction and alcohol precipitation	Improved hypoxia tolerance and exercise endurance	Kunming mice ((22 ± 2) g; 80 males and 80 females)	[82]
<i>S. involucreta</i> (Kar. et Kir.) Sch.-Bip.	Whole herb	70% ethanol	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improved oxidative stress caused by hypoxia; increased the level of energy storage substances in the body; promoted lipid metabolism; reduced the accumulation of free radicals and metabolites; reduced heart, brain and lung tissue edema	BABL/c mice, ((20 ± 2) g, 40 males and 40 females); Male BALB/c mice (aged 8 weeks, (20 ± 2) g)	[40, 52]
<i>H. Rhamnoides</i> L.	Fruit	70% ethanol; water	Improved hypoxia tolerance and exercise endurance	Kunming mice	[83]
<i>A. kansuensis</i> Maxim.	Whole plants	60% ethanol	Improved hypoxia tolerance and exercise endurance; improved circulatory system function	C57BL mice	[84]
<i>S. baicalensis</i> Georgi	Dry roots	Water	Improved hypoxia tolerance and exercise endurance	Kunming mice ((24 ± 2) g; 80 males and 80 females)	[85]
<i>C. sinensis</i> (BerK.) Sacc.	Dry complexes of fungi and larvae	Water	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improved oxidative stress caused by hypoxia; increased the level of energy storage substances in the body to reduce the accumulation of free radicals and metabolites; regulated the immune system	Rats; Male ICR mice ((20 ± 2) g)	[45, 50]
<i>G. straminea</i> Maxim.	Dry roots	95% ethanol	Antioxidant activity and improved oxidative stress caused by hypoxia; regulated energy metabolism-related substances and enzyme activities to reduce the accumulation of free radicals and metabolites	Male SD rats, (aged 6 weeks, (200 ± 20) g)	[43]

(Continued)

Name	Medicinal part	Extraction solvent	Mechanisms	The species investigated	References
<i>C. humile</i> Maxim	Dried flower	70% ethanol	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improved oxidative stress caused by hypoxia	Male BABL/c mice ((20 ± 2) g)	[41]
<i>M. oleifera</i> Lam.	Dry leaves	Water	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improved oxidative stress caused by hypoxia; regulated energy metabolism-related substances and enzyme activities to reduce the accumulation of free radicals and metabolites; regulated the immune system	Male Kunming mice (18–20 g)	[46]
<i>G. biloba</i> L.	Dry leaves	Water	Antioxidant activity and improved oxidative stress caused by hypoxia; regulated immune system; enhanced ventricular function during plateau weaning	Male SD rats (200–220 g)	[42]
<i>P. notoginseng</i> (Burk.) F. H. Chen	Dry roots and rhizomes	Water	Antioxidant activity and improved oxidative stress caused by hypoxia; regulated immune system; enhanced ventricular function during plateau weaning	Male SD rats (200–220 g)	[42]
Yak milk			Improved hypoxia tolerance and exercise endurance; increased the level of energy storage substances in the body and reduced the accumulation of free radicals and metabolites	Male Kunming mice	[81]

example, *Cordyceps* polypeptide can effectively reduce the content of C3 in the serum complement of experimental animals, effectively counteract the lipid peroxidation reaction in the body, and play a positive regulatory role on GSH-Px. It can reduce the content of MDA in the serum of mice and increase the content of SOD^[86]. After treating vascular smooth muscle cells under hypoxic conditions with LBP, researchers found that it can increase the SIRT1 level and reduce the levels of MMP-9 and HIF-1 α ^[77]. It can also significantly improve the hypoxia tolerance of mice, prolong

the hypoxia-survival time and the time of weight-bearing swimming, and down-regulate the levels of LA and BUN in the blood^[33]. The polysaccharides extracted from *A. sinensis* and Yuanroot also have the same effect, and the details are shown in Table 2.

Wu *et al.*^[34] found that the total glycosides of *Cistanche deserticola* can prolong the hypoxic survival time of mice with acute cerebral hypoxia, increase the SOD activity, and reduce the content of MDA in the brain tissue. The mixture of gardenia

Table 2 Natural herbal crude extracts for anti-PHF

Origins	Extraction	Composition	Mechanisms	The species investigated	References
<i>C. sinensis</i> (BerK.) Sacc.	Dry complexes of fungi and larvae	Polysaccharides	Antioxidant activity and improvement of oxidative stress caused by hypoxia	150 female BALB/c mice weighing 18–22 g (6 weeks old)	[86]
<i>L. barbarum</i> L.	Dry ripe fruit	Polysaccharides	Improved hypoxia tolerance and exercise endurance; regulated the immune system	Vascular smooth muscle cells	[77]
<i>L. barbarum</i> L.	Dry ripe fruit	Polysaccharides	Improved hypoxia tolerance and exercise endurance; reduced the accumulation of free radicals and metabolites	Kunming mice ((20 ± 2) g; 120 males and 120 females)	[33]
<i>A. sinensis</i> (Oliv.) Diels	Dried root	Polysaccharides	Regulated the immune system	H9c2 cardiomyocytes	[87, 88]
<i>B. rapa</i> L.	Dried roots and leaves	Total polysaccharides	Antioxidant activity and improvement of oxidative stress caused by hypoxia; regulated energy metabolism related substances and enzyme activity; reduced the accumulation of free radicals and metabolites; reduced lung and brain tissue damage	Male Kunming mice (6 weeks old, (30 ± 2) g)	[55]
<i>C. deserticola</i> Y.C.Ma	Dried fleshy stems with scaly leaves	Total glycosides (phenylethanol glycosides)	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improvement of oxidative stress caused by hypoxia	Mice (24 males and 24 females)	[34]
<i>C. deserticola</i> Y.C.Ma <i>G. jasminoides</i> Ellis	Dried fleshy stems with scaly leaves; dry and mature fruit	Phenylethanol glycosides and gardenia yellow pigment	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improvement of oxidative stress caused by hypoxia; increased the level of energy storage substances in the body; reduced the accumulation of free radicals and metabolites; regulated the immune system	BALB/c mice ((20 ± 2) g) and Wister rats ((200 ± 20) g)	[35]
<i>Pedicularis kansuensis</i> Maxim.	Dried whole plant	Phenylethanol glycosides	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improvement of oxidative stress caused by hypoxia; increased the level of energy storage substances in the body to regulate energy metabolism related substances and enzyme activity; reduced the accumulation of free radicals and metabolites	BALB/c mice, weighing (20 ± 2) g	[57]
<i>G. jasminoides</i> Ellis	Dried ripe fruits	Gardenia yellow pigment	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improvement of oxidative stress caused by hypoxia; regulated energy metabolism related substances and enzyme activity; reduced the accumulation of free radicals and metabolites; increased the level of energy storage substances in the body	BALE/C mice	[58]

(Continued)

Origins	Extraction	Composition	Mechanisms	The species investigated	References
<i>P. ginseng</i> C. A. Mey.	Dried roots and rhizomes	Saponin	Improved hypoxia tolerance and exercise endurance; regulated the immune system; reduced pathological damage to the brain and heart	Male Wistar rats (170–180 g)	[75]
<i>G. pentaphyllum</i> (Thunb.) Makino	Dried whole plant	Saponin	Improved hypoxia tolerance and exercise endurance; reduced PC12 cell damage	PC12 cell; C57BL/6 mice	[89]
<i>P. notoginseng</i> (Burk.) F. H. Chen	Dried roots and rhizomes	Total saponins	Improved hypoxia tolerance and exercise endurance; increased the level of energy storage substances in the body; reduced the accumulation of free radicals and metabolites	Male Kunming mice (weighing (20 ± 2) g)	[90]
<i>Aster souliei</i> Franch.	Dry inflorescences	Total flavonoids	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improvement of oxidative stress caused by hypoxia; reduced the accumulation of free radicals and metabolites; regulated the immune system; reduce pathological damage to brain tissue	Male BALB/c mice (18–20 g); Male BALB/c mice ((20 ± 2) g)	[72, 91]
<i>Epimedium sagittatum</i> (Sieb. et Zucc.) Maxim.	Dried leaves	Total flavonoids	Antioxidant activity and improvement of oxidative stress caused by hypoxia; regulated energy metabolism related substances and enzyme activity to improve circulatory system function	Male Wistar rats (220–300 g)	[59]
<i>Petasites tricholobus</i> Fanch	Dried rhizomes	Total lactones	Improved hypoxia tolerance and exercise endurance; increased the level of energy storage substances in the body; reduced the accumulation of free radicals and metabolites	ICR mice ((20 ± 2) g, 100 males and 100 females, 6 weeks old); Wistar rats, ((200 ± 20) g, 24 males and 24 females, 6 weeks old)	[92]
<i>P. japonicus</i> (Seib. et Zucc) Maxim					
<i>A. sinensis</i> (Oliv.) Diels	Dried root	Volatile oil	Improved hypoxia tolerance and exercise endurance; regulated energy metabolism related substances and enzyme activity; reduced the accumulation of free radicals and metabolites; reduced the content of EAA in brain tissue	Kunming mice (18–20 g; 20 males and 20 females)	[54]
<i>C. sinensis</i> (BerK.) Sacc.	Dry complexes of fungi and larvae	Polypeptide	Antioxidant activity and improvement of oxidative stress caused by hypoxia; regulated the immune system	Mice	[69]
<i>Areca catechu</i> L.	Dried mature seeds	Polyphenol	Antioxidant activity and improvement of oxidative stress caused by hypoxia; improved the function of the circulatory system; regulated the immune system; reduced liver, lung, brain, and myocardial tissue damage	Male Wistar rats ((200 ± 20) g)	[26]

yellow pigment and *Cistanche* PhGs, as well as the PhGs extracted from *Artemisia kansuensis*, can also significantly prolong the anti-hypoxia and exhaustive swimming time of mice under hypoxic conditions, reduce the levels of BUN, CRE, UA, PA, and LA in the serum, brain, liver, and muscle tissues, and delay the occurrence of exercise fatigue. All kinds of mixtures show anti-PHF effects. In addition, the volatile oil of *A. sinensis* can prolong the survival time of mice with acute hemorrhagic hypoxia, reduce the content of EAA in the brain tissue, protect the brain, significantly prolong the survival time of mice, enhance the activities of Na^+/K^+ -ATPase and $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase in the brain tissue, and reduce the contents of LA, Glu, GABA, and Gly. Ginsenosides can significantly prolong the survival time of rats in a normal-pressure airtight environment. They may also protect against damage caused by hypoxia by reducing the sensitivity of the heart and brain tissues to hypoxia and reducing apoptosis. Its mechanism is related to influencing the expressions of HIF-1 α , EPO, and Caspase-3 mRNA, regulating the internal oxygen balance of rat tissues, promoting erythropoiesis, and inhibiting apoptosis. Other types of saponin-like substances that take effect, such as gypenosides, *P. notoginseng* saponins, areca nut polyphenols, total lactones of *P. japonicus*, total flavonoids of *A. himalaicus*, total flavonoids of *Epimedium*, and gardenia yellow pigment, all exhibit good anti-PHF effects.

4.3 Monomers of natural products for combating PHF

Among the dietary supplements with homology of medicine and food, there are various types of monomeric active ingredients,

many of which exhibit good anti-PHF properties. These include flavonoids (KA, baicalin, puerarin)^[68], terpenoids and their derivatives (Rg1, Rg2, Rg3, Rb1, eleutheroside B, notoginsenoside R1, celastrol, tanshinone IIA)^[53, 68, 71, 93], PhGs (verbascoside, echinacoside, polydatin), ester glycosides (Crocen-I)^[94], phenolic glycosides (salidroside), phenols (RSV, catechin, epigallocatechin-3-gallate, danshensu, gastrodin)^[62, 67, 73, 79], diketones (CUR, THC), quinone compounds (pyrroloquinolinequinone)^[30], alkaloids (theophylline, *L*-carnitine)^[60], and others (octacosane). These substances can exert their effects through alleviating organ edema and damage caused by the plateau environment, enhancing anti-hypoxia ability, scavenging free radicals, and reducing oxidative stress.

Detailed research indicates that the monomeric substances KA and GRg1 can significantly improve the histopathological changes of rats with lung injury caused by acute hypobaric hypoxia under plateau conditions, that is, alleviate pulmonary edema, and improve the concentrations of IL-6, TNF- α , MDA, SOD, and CAT in the body, thus exerting an anti-PHF effect^[68]. Ginsenosides Rg2 and Rg3 take effect by inhibiting apoptosis, increasing the activity of antioxidant enzymes, and scavenging free radicals^[61]. Ginsenoside Rb1 alleviates the hypoxic (apoptotic) damage to hippocampal neurons in SD rats mediated by activated microglia by inhibiting the hypoxia-induced activation reaction of microglia^[74]. Crocen-I extracted from *Gardenia jasminoides* can improve the memory impairment of mice in a high-altitude hypoxic environment, indirectly achieving the anti-PHF effect. CUR can significantly enhance the work ability of mice and effectively relieve acute high-altitude hypoxic injury. THC

regulates inflammatory factors, plays a role in regulating the immune system, and indirectly resists PHF. Octacosane can relieve energy deficiency and metabolic disorders caused by hypoxia, thereby improving the hypoxia tolerance of the animal body. PQQ can prolong the survival and exhaustive swimming time of mice, reduce the content of free radicals in the body, up-regulate the energy storage level, and enhance the activity of SOD. There are also many other active ingredients that show good anti-PHF effects, such as salidroside, verbascoside, echinacoside, polydatin, verbascoside, RSV, theophylline, catechin, epigallocatechin-3-gallate, baicalin, puerarin, eleutheroside B, L-carnitine, notoginsenoside R1, etc. Moreover, we evaluated 27 monomeric compounds against Lipinski's rule of five using

SwissADME (<http://www.swissadme.ch/>). This allowed for a rapid preliminary screening and classification of the drug-making potential of these compounds. Compounds that adhered to the rule are considered to have certain advantages in terms of ADME properties and may be more promising in clinical feasibility. The details are shown in Table 3 and Fig. 4.

4.4 Limitations of existing animal model methods

Despite the widespread use of animal models in studying PHF, current methods have several notable limitations. Firstly, laboratory animals such as Wistar rats, BALB/c mice, C57BL/6 mice, and Kunming mice are commonly utilized. However, they inherently possess different physiological characteristics compared

Table 3 Anti-PHF chemical components in natural medicines

Natural medicine	Bioactive components	Categorization	Lipinski rule	Mechanisms	The species investigated	References
<i>P. ginseng</i> C. A. Mey.	KA (1)	Flavonoid	Yes	Antioxidant activity and ameliorates oxidative stress due to hypoxia; modulates the immune system; attenuated lung injury and pulmonary edema	Male SD rats	[68]
<i>S. baicalensis</i> Georgi	Baicalin (2)	Flavonoid	No	Improved hypoxia tolerance levels and exercise endurance	Female Kunming mice	[95]
<i>Pueraria lobata</i> (Willd.) Ohwi	Puerarin (3)	Flavonoid	Yes	Improved hypoxia tolerance levels and exercise endurance	ICR mice (20 male and 20 female, (20 ± 1) g)	[96]
<i>P. ginseng</i> C. A. Mey.	GRg1 (4)	Terpenes and their derivatives	No	Antioxidant activity and ameliorates oxidative stress due to hypoxia; modulated the immune system; attenuated lung injury and pulmonary edema	Male SD rats	[68]
<i>P. ginseng</i> C. A. Mey.	Ginsenoside Rg2 (5)	Terpenes and their derivatives	No	Antioxidant activity and amelioration of oxidative stress due to hypoxia; reduction of free radicals and metabolite accumulation; modulation of the immune system	Wistar rats hippocampal neurons	[61]
<i>P. ginseng</i> C. A. Mey.	Ginsenoside Rg3 (6)	Terpenes and their derivatives	No	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improvement of oxidative stress caused by hypoxia; increased the level of energy storage substances in the body; promoted lipid metabolism, regulated energy metabolism related substances and enzyme activity; reduced the accumulation of free radicals and metabolites	Male SD rats (age 18 months)	[53]
<i>P. ginseng</i> C. A. Mey.	Ginsenoside Rb1 (7)	Terpenes and their derivatives	No	Regulated the immune system; reduced the accumulation of free radicals and metabolites	Microglia N9	[74]
<i>Acanthopanax senticosus</i> (Rupr.etMaxim.) Harms	Eleutheroside B (8)	Terpenes and their derivatives	Yes	Reduced the accumulation of free radicals and metabolites; regulated the immune system; increase tissue tolerance to ischemia and hypoxia	Mice	[65]
<i>P. notoginseng</i> (Burk.) F. H. Chen	Notoginsenoside R1 (9)	Terpenes and their derivatives	No	Antioxidant activity and improvement of oxidative stress caused by hypoxia; regulated the immune system; improve pathological damage to the heart	Male SD rats (aged 4–5 weeks, 110–120 g)	[71]
<i>Tripterygium wilfordii</i> Hook. f.	Cilostazol (10)	Terpenes and their derivatives	Yes	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improvement of oxidative stress caused by hypoxia; improve the function of the circulatory system; regulated the immune system; improved myocardial, lung, and kidney tissue damage	Male BALB/c mice ((20 ± 2) g)	[22]
<i>Salvia miltiorrhiza</i> Bge.	Tanshinone IIA (11)	Terpenes and their derivatives	Yes	Antioxidant activity and improvement of oxidative stress caused by hypoxia	Rats	[93]
<i>C. deserticola</i> Y.C.Ma	Verbascoside (12)	Phenylethanolic glycosides	No	Improved hypoxia tolerance and exercise endurance; increased the level of energy storage substances in the body; improved liver and skeletal muscle edema and inflammatory infiltration; antioxidant activity and improvement of oxidative stress caused by hypoxia; regulated the immune system	Male Wistar rats (aged 6–8 weeks ((200 ± 20) g); male adult Wistar rats (aged 6–8 weeks)	[51, 76]
<i>C. deserticola</i> Y.C.Ma	Echinacoside (13)	Phenylethanolic glycosides	No	Improved hypoxia tolerance and exercise endurance; increased the level of energy storage substances in the body; improved liver and skeletal muscle edema and inflammatory infiltration	Male Wistar rats (aged 6–8 weeks, (200 ± 20) g)	[51]

(Continued)

Natural medicine	Bioactive components	Categorization	Lipinski rule	Mechanisms	The species investigated	References
<i>C. deserticola</i> Y.C.Ma	Crenatoside (14)	Phenylethanol glycosides	No	Improved hypoxia tolerance and exercise endurance; increased the level of energy storage substances in the body; improved liver and skeletal muscle edema and inflammatory infiltration	Male Wistar rats (aged 6–8 weeks, (200 ± 20) g)	[51]
Extracted from plants such as <i>Polygonum cuspidatum</i> Sieb. et Zucc	RSV (15)	Phenols	Yes	Antioxidant activity and improvement of oxidative stress caused by hypoxia; reduced heart coefficient, myocardial fiber thickness, ventricular wall thickness, and improved heart function; regulating the immune system	Male Wistar rats (aged 9 weeks, 320–330 g); male Wistar rats (aged 8 weeks (220 ± 20) g)	[79]
Green tea, etc.	Catechin (16)	Phenols	Yes	Antioxidant activity and improvement of oxidative stress caused by hypoxia; reduced the accumulation of free radicals and metabolites; relieved myocardial, brain, and lung tissue damage; improve the circulatory system; regulated the immune system	Male Wistar rats ((200 ± 20) g)	[62]
Green tea	Epigallocatechin-3-gallate (17)	Phenols	No	Regulating the immune system; reduced the elevation of myocardial enzymes and alleviated left ventricular mitochondrial damage	Male SD rats (130–150 g)	[73]
<i>S. miltiorrhiza</i> Bge.	Salvianic (18)	Phenols	Yes	Protected myocardial cell damage induced by hypoxia/reoxygenation	H9C2 cardiomyocytes	[78]
<i>Gastrodia elata</i> Bl.	Gastrodin (19)	Phenols	Yes	Improved hypoxia tolerance and exercise endurance	Male BALB/c mice ((20 ± 2) g)	[97]
Tea	Theophylline (20)	Alkaloid	Yes	Improved hypoxia tolerance and exercise endurance; increase muscle blood flow	Sprague-Dawley rats, aged at 9–12 weeks (200–250 g)	[80]
<i>Actinidia chinensis</i> Planch, etc	L-carnitine (21)	Alkaloid	Yes	Promoted lipid metabolism; regulating energy metabolism related substances and enzyme activity	Rats	[60]
<i>Curcuma longa</i> L.	CUR (22)	Diketone	Yes	Improved hypoxia tolerance and exercise endurance; improved the function of the circulatory system; reduced abnormal brain, heart, and lung function and damage	Male BALB/c mice (20.0–20.6 g); Male Wistar rats (220–260 g)	[66]
<i>C. longa</i> L.	THC (23)	Diketone	Yes	Antioxidant activity and improvement of oxidative stress caused by hypoxia; regulated the immune system; reduce brain edema	Male C57BL/6 mice ((20 ± 2) g)	[70]
<i>R. crenulata</i> (Hook. f. et Thoms.) H. Ohba	Salidroside (24) Salidroside	Phenolic glycoside	Yes	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improvement of oxidative stress caused by hypoxia; increased the level of energy storage substances in the body; regulated energy metabolism related substances and enzyme activity; reduced the accumulation of free radicals and metabolites	Male C57BL/6J mice (6–8 weeks old, (20 ± 2) g)	[56]
In plants such as papaya	PQQ (25)	Quinones	Yes	Improved hypoxia tolerance and exercise endurance; antioxidant activity and improvement of oxidative stress caused by hypoxia; increased the level of energy storage substances in the body; reduced the accumulation of free radicals and metabolites	Male adults Wistar rats (aged 6–8 weeks); Male Kunming mice ((39 ± 3) g)	[30]
	Octacosane (26)	Other categories	Yes	Increased the level of energy storage substances in the body; promoted lipid metabolism; reduced edema in heart, brain, and lung tissues	BALB/c mice ((20 ± 2) g)	[31]
<i>G. jasminoides</i> Ellis	Crocin-I (27)	Other categories	No	Regulated the immune system	Wistar rats ((200 ± 20) g)	[94]

to humans. For example, the respiratory and circulatory systems of these rodents may respond to hypoxia in ways that do not precisely mimic human responses^[98]. Their metabolic rates and oxygen-carrying capacities vary, which can lead to discrepancies in the manifestation and progression of hypoxic-induced fatigue. This species-specific variation may limit the direct translation of experimental findings to the human context. Secondly, creating a low-pressure, low-oxygen environment in the laboratory attempts to simulate the high-altitude condition. Nevertheless, it is challenging to fully replicate the complex and dynamic nature of the actual plateau environment. Natural plateaus have additional factors like ultraviolet radiation, temperature fluctuations, and unique geographical features that are absent in laboratory-induced

hypoxia. These missing elements may influence the overall stress response and the development of fatigue in animals, rendering the model less representative of real-world scenarios. Thirdly, While PC12 cell experiments provide valuable insights at the cellular level, they also have limitations. PC12 cells are a transformed cell line, and their behavior may not fully recapitulate that of native cells in the body. The in vitro environment lacks the intricate network of cell-cell interactions, tissue microenvironments, and systemic regulation present in a whole-organism model. As a result, the findings from PC12 cell studies may not comprehensively reflect the complex physiological and pathological processes occurring during PHF in living organisms. Lastly, there is a lack of consistent standardization in the

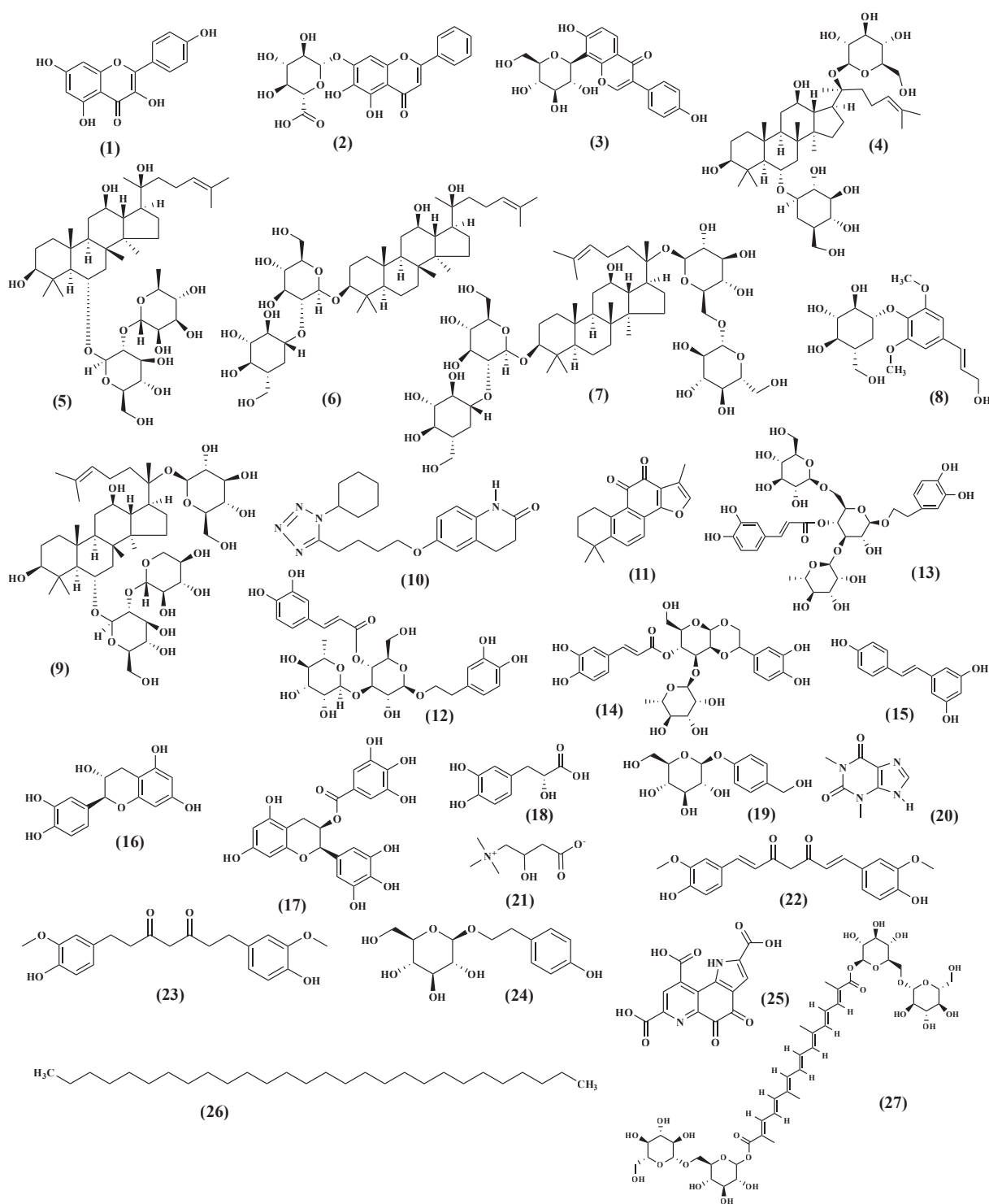


Figure 4 Anti-PHF effects of the monomer active ingredients.

establishment of these animal models across different laboratories. Variables such as the duration and intensity of hypoxia exposure, the age and gender of animals, and the methods of assessing fatigue can vary significantly. This non-standardization makes it difficult to compare and pool data from different studies, hindering the progress of a unified understanding of PHF mechanisms and the development of effective countermeasures.

5 Clinical trials

In addition, there are fundamental differences in clinical

treatment methods for different types of PHF-related diseases. Currently, there are very few clinical trials on the anti-PHF effects of natural medicines. From the perspective of modern medicine, since the oxygen partial pressure is low in plateau areas, any treatment method that can increase the supply of external oxygen or reduce the oxygen consumption in the body can be regarded as an effective therapeutic means. Looking at traditional medicine with modern technology has indeed led to more discoveries. In traditional Chinese medicine clinical practice, the combination of Danshen injection and Gualou Xiebai Banxia Decoction has been

studied. The focus of this research is on the combined treatment of traditional Chinese and Western medicine for plateau hypoxic myocardial injury. This treatment can improve the levels of myocardial enzymes, normalize the electrocardiogram, thereby enhancing the heart's blood-pumping function and achieving the anti-fatigue effect.

Clinical research has also found that for subjects, inhaling oxygen 2–4 times a day (1.5 h each time, 1–2 L/min) and taking soy isoflavones orally (20 mg, twice a day) can significantly reduce the chronic mountain sickness (CMS) score and significantly decrease the Hb value. The results indicate that early prevention of high-altitude polycythemia (HAPC) in high-altitude plateau areas is necessary, and the combination of oxygen inhalation and oral soy isoflavones is an effective preventive method to enhance the body's anti-fatigue ability^[99]. In addition, Feng *et al.*^[100] conducted a clinical trial on plateau hypoxic myocardial injury. In the observation group, based on conventional treatment, patients took Banxia Decoction orally twice a day, and then compared the changes in clinical symptoms, myocardial enzymes, and electrocardiograms between the two groups. The results showed that the combined treatment of traditional Chinese and Western medicine, with Banxia Decoction playing a role, had a good therapeutic effect on plateau hypoxic myocardial injury. Li *et al.*^[101] divided 184 patients with HAPC into an experimental group and a control group. The experimental group received low-molecular-weight dextran plus Danshen treatment, and the control group received low-molecular-weight dextran treatment. One course of treatment was 15 days, and two courses were carried out. The

results showed that the experimental group could more significantly reduce the levels of Hb and RBC. Thus, it was concluded that the treatment of HAPC with low-molecular-weight dextran plus Danshen injection has a significant effect. Xue *et al.*^[102] used naloxone combined with compound Danshen to treat acute high-altitude cerebral edema, and 68 patients with acute high-altitude cerebral edema were randomly divided into two groups, 36 in the treatment group and 32 in the control group. The treatment group received naloxone in addition to comprehensive treatment and was compared with the conventional treatment group. The results showed that the total effective rate of the naloxone combined with compound Danshen treatment group (86.1%) was significantly higher than that of the control group (65.6%), and there were no adverse reactions. This indicates that the treatment of acute high-altitude cerebral edema with naloxone combined with compound Danshen is reliable, rapid-acting, and convenient to use. It has an obvious resuscitating effect, can significantly improve the rescue success rate, and reduce the mortality rate. The details are shown in **Table 4**.

At present, the clinical experimental research on anti-PHF is still in its infancy. With the increasing attention paid to the development of plateau areas, it is believed that the government and researchers should be more concerned about conducting further clinical trials on the prevention of PHF with natural medicines. The following suggestions are put forward. First, expand the scale of the experimental population. Undoubtedly, expanding the sample size is the best solution to ensure the universality and statistical power of the research. Second, design

Table 4 Clinical trials for the treatment of PHF related diseases

Medicine	Subject	Study design	Intervention	Length	Primary endpoint	Outcome	Reference
Danshen Injection + Gualou Xiebai Banxia Tang	60 male patients with high-altitude hypoxic myocardial injury	Randomly double-blind divided into intervention group and control group, with 30 cases in each group	Conventional group: conventional treatment; Intervention group: Danshen injection combined with Gualou Xiebai Banxia Decoction	1 week	Observe the clinical manifestations, electrocardiogram improvement, and changes in myocardial enzymes of two groups of patients	The intervention group can restore normal levels of myocardial enzymes, and 1–2 items on the electrocardiogram are normal	[103]
Soy isoflavon	80 young males who migrated to high-altitude areas (3,500–5,300 m) for more than 10 months and were confirmed to have a Hb value of 190 g/L ≤ Hb < 210 g/L after three tests	Randomly double-blind divided into an oxygen inhalation group and a medication group, with 40 people in each group	Low flow oxygen inhalation (1–2 L/min), 1.5 h/time (2–4 times/day) in the oxygen inhalation group; Drug group oxygen therapy (same method as oxygen therapy group) + oral soy isoflavone (20 mg, twice per day) treatment	12 weeks	Check blood routine and follow up on chronic high altitudes disease (CMS) score, observe changes in RBC, Hb, HCT values, and CMS re scoring	The drug group significantly reduced Hb levels and CMS scores	[99]
Banxia Tang	64 male patients with high-altitude hypoxic myocardial injury	Randomly divide patients into an observation group of 32 cases and a control group of 32 cases based on their visit time	Both groups were routinely treated with hyperbaric oxygen and drugs that promote myocardial metabolism. Observation group: add Banxia Tang twice a day orally	8 days	Observe the clinical symptoms, changes in myocardial enzymes, and electrocardiogram fluctuations of two groups of patients	The observation group significantly improved myocardial enzyme and electrocardiogram abnormalities, with significant clinical efficacy	[100]
Danshen Injection	184 patients with HAPC (148 males and 36 females)	184 patients with HAPC (148 males and 36 females)	The experimental group was given low flow oxygen (flow rate 2 L/min, 2 times/day, 4 h/time) + 250 mL of low molecular weight dextran injection + 20 mL of Danshen Injection; The control group received 250 mL of low molecular weight Dextran Injection alone	15 days	A decrease in Hb below 18 g/L is considered therapeutic, and a decrease of 40 g/L or more but not reaching the normal range is considered effective	The experimental group significantly downregulated the levels of Hb and RBC	[101]

(Continued)

Medicine	Subject	Study design	Intervention	Length	Primary endpoint	Outcome	Reference
Compound Danshen Dropping Pills	68 patients with acute high-altitude cerebral edema	Randomly divided into a treatment group of 36 cases and a control group of 32 cases	Both groups of patients were first given continuous oxygen inhalation and treated with hypertonic Glu, mannitol, adrenocortical hormone, energy mixture, etc. The treatment group was simultaneously given	3 days	During medication, closely monitor heart rate, blood pressure, and recovery of consciousness	In the treatment group, 15 cases showed significant improvement, 16 cases were effective, and 5 cases were ineffective (including 1 death), with a total effective rate of 86.1%. In the control group, 11 cases showed significant improvement, 10 cases were effective, and 11 cases were ineffective (including 1 death), with a total effective rate of 65.6%. The treatment group was significantly higher than the control group	[102]
			naloxone (0.4–0.8 mg) and 0.9% sodium chloride (5–10 mL) intravenously, followed by (1.6–2.0 mg) with 5% Glu and 250 mL intravenous drip, and compound Danshen Injection (16–20 mL) once a day for 3 consecutive days. During the medication period, heart rate, blood pressure, and consciousness recovery were closely observed				

experiments specifically according to the specific causes of fatigue caused by plateau hypoxia. For example, experiments should be designed separately for symptoms such as pathological damage, tissue edema, and polycythemia. Finally, research on toxicity and research on expanding the effective drug concentration range should be carried out. In addition, researchers should consider individual conditions, clinical practice, and research objectives as guidelines for choosing the most reasonable fatigue measurement.

6 Summary and prospect

In summary, dietary supplements and natural products from the homology of medicine and food likely exert anti-PHF effects *via* multiple mechanisms. These include enhancing tolerance and exercise endurance, anti-oxidation to counteract oxidative stress induced by hypobaric hypoxia, promoting energy metabolism, reducing the accumulation of free radicals and metabolites (such as MDA, LA and NO), regulating the circulatory system and immune system, and alleviating pathological damage.

Currently, research on the anti-PHF activity of natural products is scarce. Most existing studies primarily focus on behavioral observations, behavioral epigenetics data, and fatigue-related biochemical indicators, with a rather shallow research foundation. Only a handful of studies have explored gene, protein and pathway expression levels. For instance, prior reports indicate that genes like *EPAS1*, *EGLN1* and *PPARA* enable the Tibetan population to adapt to the harsh hypoxic environment by increasing vital capacity, arterial oxygen level, and folic acid level, thus adapting to the high-altitude hypobaric, hypoxic and high-intensity ultraviolet radiation^[104]. Therefore, future research should delve deeper into the anti-fatigue mechanism at the molecular and cellular levels, intensify the study on the high-quality genomic characteristics of high-altitude populations, particularly focus on genes adaptable to the plateau environment, and design targeted experiments for anti-PHF drugs.

Although there are currently few studies comparing whether the combined treatment of homologous resources of medicine and food through different routes can produce a synergistic effect, based on the current research on combination therapies such as

L-carnitine and Trimetazidine^[60], gardenia yellow pigment and *Cistanche* phenylethanol glycosides^[35], theophylline and endothelin receptor antagonism^[80], and essentially, mixtures like total flavonoids and total polysaccharides are also combinations of multiple small molecule drugs. Based on the favorable anti-PHF results of the above-mentioned studies, combination medications and dietary supplements must be viable approaches for the prevention of PHF in the future. It is recommended that multiple research topics related to combination drugs be carried out hereafter. Simultaneously, the gut microbiota, regarded as the body's second genome, represents a crucial future research area. Strengthening research on gut microbiota populations adaptable to the plateau environment is essential, as they can transform and regulate the energy in exogenous substances, optimize their functional exertion, and thereby achieve anti-PHF activity through brain-heart-gut axis linkage. This may be a significant anti-PHF pathway to reduce central fatigue, increase arterial blood oxygen levels, and enhance energy regulation and utilization. In-depth research is required to clarify the exact molecular and cellular pathways through which natural products and dietary supplements exert their anti-PHF effects. Although some potential mechanisms have been proposed, there is a lack of conclusive evidence. For example, the role of gut microbiota in the anti-PHF process needs further exploration, especially in terms of how it interacts with the host's metabolism and immune system in a hypoxic environment. Additionally, the synergistic effects of combination therapies need to be systematically studied to optimize treatment strategies.

Notably, most experimental results are derived from animal models and lack full validation. The quality of existing limited clinical trials is suboptimal and lacks substantial reference value. These trials often involve compound preparations administered in single doses with small sample sizes and lack in-depth exploration of the anti-fatigue mechanism. Hence, more scientific and representative clinical trials are urgently needed and high-quality clinical trials are essential. There is a lack of large-scale, multi-center, double-blind, and placebo-controlled trials. Such trials should focus on evaluating the efficacy and safety of different treatment modalities, including natural products, dietary supplements, and combination therapies. Standardized treatment

protocols need to be developed, taking into account factors such as the severity of PHF, individual differences in patients, and the optimal dosage and administration routes of treatments.

Polypeptides, polysaccharides, flavonoids, polyphenols, terpenoids and other components isolated from natural substances, especially polysaccharides, are all potential anti-high-altitude hypoxia fatigue agents. Natural products such as cordyceps polypeptide, ginsenosides, KA, RSV and puerarin have demonstrated significant anti-high-altitude hypobaric hypoxia fatigue activity. However, only a small fraction of monomer components with anti-fatigue effects have been identified among natural medicines, necessitating further exploration. Additionally, natural medicines against PHF are found in families such as Euphorbiaceae, Leguminosae, Crassulaceae, Campanulaceae, Compositae, Elaeagnaceae, Caryophyllaceae, Labiatae, Clavicipitaceae, Ginkgoaceae, Araliaceae, and Moringaceae. It is recommended to further investigate whether natural medicines within the same family or even genus share similar functions and whether substances with similar chemical structures possess anti-fatigue properties.

Anti-fatigue nutritional products, mainly composed of dietary supplements and natural medicines or natural products of the homology of medicine and food, are potential treatment strategies for PHF. We anticipate that this review will provide a scientific basis for understanding existing products and prescriptions, clarify the market positioning, facilitate the development of specific products and prescriptions for the fatigue-prone population in the high-altitude hypobaric hypoxia environment, and guide the development of new products with anti-PHF potential.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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