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Research Article

Treatment of diabetic muscular hyperplasia with natural and nutritional supplements

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Abstract

Skeletal muscle is an important part of the human body. Most glucose metabolism is accomplished by skeletal muscle through insulin mediation. Skeletal muscle metabolism disorder can affect glucose metabolic homeostasis and insulin sensitivity of the body, and diabetic muscular Hypoplasia is a secondary lesion of muscle tissue caused by diabetes. In recent years, it has been found that in addition to mainstream western medicine and traditional Chinese and Western medicine combined treatment programs, natural products, and nutritional supplements also play an important role in the prevention and treatment of diabetic muscular Hypoplasia. Therefore, this paper will discuss the definition and pathogenesis of diabetic muscular Hypoplasia, as well as the prevention and treatment mechanism of some natural products and nutritional supplements, to provide more theoretical reference for non-drug targeted therapy of diabetic muscular Hypoplasia.

Introduction

It is estimated that by 2045, the number of patients with type 2 diabetes worldwide will reach 693 million [1] and the accompanying diabetic muscular Hypoplasia has gradually become one of its complications that cannot be ignored. In 1995, Professor GALRAND [2] formally named the muscle Hypoplasia caused by diabetes diabetic muscular Hypoplasia. Diabetic muscular Hypoplasia occurs in peripheral neuropathy caused by diabetes. Peripheral neuropathy can lead to increased loss of motor units in patients, resulting in insufficient innerve of muscle fibers and compensatory nerve redistribution, further inducing muscle fiber Hypoplasia, and ultimately resulting in loss of skeletal muscle mass, strength, and endurance [3]. As an important metabolic tissue of the human body, skeletal muscle wilting will affect glucose absorption and further aggravate insulin resistance, which further aggravates skeletal muscle Hypoplasia, thus forming a vicious cycle that has a serious negative impact on the life of type 2 diabetes patients. Therefore, glycosuria muscle Hypoplasia has been paid more attention to. In recent years, studies have found that in addition to the mainstream western medicine and Chinese and western medicine combined treatment program, diet therapy means can play a role in the pathogenesis of diabetes to relieve and prevent muscular Hypoplasia. Among them, natural products such as berberine (BBR), tea polysaccharides (TPS), and salidroside (SALidroside, Sal can inhibit inflammation, reduce the activity of reactive oxygen species (ROS) and reduce the degree of peripheral nerve injury. However, nutritional supplements such as Leucine (Leu), creatine (Cr) and omega-3 fatty acids (fatty acids) can promote protein synthesis in skeletal muscle and relieve the symptoms of skeletal muscle Hypoplasia caused by diabetes. Therefore, this paper mainly discusses the alleviating or prevention of diabetes-induced muscular Hypoplasia from the perspectives of supplementing natural products or regulating protein metabolic balance, and explores the role and targeted molecular mechanism of nutritional intervention in diabetic muscular Hypoplasia, so as to provide theoretical reference for the diversified selection of prevention or intervention strategies.

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Inducible factors and mechanism of diabetic muscular hypoplasia

Diabetes muscle Hypoplasia, as a kind of multiple factors of chronic disease, its pathogenesis is mainly of skeletal muscle protein synthesis and degradation of signal tong road damage [4], peripheral neuropathy, oxidative stress, mitochondrial dysfunction, cell dysfunction autophagy, and apoptosis, etc., in its essence is the protein metabolism disorder, low synthesis, and decomposition, This results in a negative balance of skeletal muscle metabolism, resulting in skeletal muscle Hypoplasia and mass loss [5]. Among them, protein decomposition is mainly regulated by the ubiquitin protein system (UPS) and autophagolysosome system. Meanwhile, UPS is mainly composed of ubiquitin activase E1, ubiquitin-binding enzyme E2, and ubiquitin-protein ligase E3 [6]. On the one hand, E3 contains muscle Hypoplasia F-box protein (MUSCLE Hypoplasia F-box, Atrogin-1 (MAFbx/ Atrogin-1), and Muscle Ring Finger protein 1(MuRF1). Protein synthesis, on the other hand, is mediated by phosphatidylinositol 3 kinase (PI3K)/ protein kinase B, AKT)/ mammalian target of Rapamycin complex 1(mTORC1) pathway [7]. However, insulin resistance will break the balance of protein synthesis above, leading to intensified protein decomposition [8].

Insulin receptor substrate 1/2(IRS1/2), In addition, downstream PI3K, Phosphoinositide dependent kinase 1(PDK1), and AKT are activated, and the activated AKT further activates downstream mTORC1, thereby increasing protein synthesis. Among them, mTORC1 not only regulates protein synthesis and acts as a negative regulator in autophagy, but also affects skeletal muscle homeostasis and quality control [9]. At the same time, activated AKT promotes the expression of glucose transporter 4(GLUT4), which speeds up glucose uptake in the blood, thereby lowering blood glucose levels.

Insulin resistance refers to the decline in the efficiency of insulin in promoting glucose uptake and utilization due to various reasons. The body compensates for excessive secretion of insulin to produce hyperinsulinemia to maintain the stability of blood glucose [10]. Among them, IRS1 gene mutation and GLUT4 expression reduction will lead to abnormal glucose uptake in tissues, thus accelerating the occurrence and development of insulin resistance [11]. Lack of energy intake leads to hunger, which increases AMP/ATP value and activates AMPactivated protein kinase (AMPK) to promote Beclin1 expression, which can induce autophagy and protein degradation. At the same time, the downstream histone deacetylase (sirtuin1, SIRT1)/ peroxisome proliferator-activated receptor-1 α(peroxisome proliferator-activated receptor-γ coactivator-1 α) pathway, Enhance mitochondrial function and antioxidant capacity [12].

As a common chronic metabolic inflammation in diabetes, obesity also affects the occurrence of diabetic muscular Hypoplasia. Among them, IκB inhibitor Kappa B kinase β(IKK1β)/ Nuclear factor kappa-B (NF-κB) is a common pathway of insulin resistance and inflammation. It can affect the progression of diabetic muscular Hypoplasia [13]. The expression of IKK1β and C-Jun N-terminal kinase (JNK) was activated by lipopolysaccharide (LPS). Activation of NF-κB and downstream activator protein-1 (AP-1) can increase inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (INTERleukin-6). Il-6) and IL-1β promote the binding of cell signaling molecule SOC-3 with IRS and inhibit the activation of AKT, thereby aggravating insulin resistance [14]. At the same time, insulin is also a kind of angiotensin, which can slow down blood flow and skeletal muscle metabolism when resistance occurs, which accelerates protein decomposition of skeletal muscle [15]. Lipase can induce vascular angiogenesis, endothelin-1 (END1) secretion, an increase in nitric oxide levels, and induce vascular systolic and diastolic dysfunction [16]. In addition, peripheral neuropathy complicated by diabetes, such as peripheral nerve axonal degeneration and demyelination, can affect the function and structure of peripheral nerves, reduce the survival rate of Schwann cells and the regeneration capacity of peripheral nerves, and thus affect the microcirculation of bone iliac muscle [17].

In summary, due to the blocked IRS function in diabetes, the sensitivity of pancreatic insulin is reduced, which then leads to the accumulation of oxidative stress, resulting in autophagy dysfunction, weakened microcirculation, impaired vascular endothelial function, and peripheral neuropathy, which further accelerates the decomposition of protein and leads to diabetic muscle Hypoplasia.

The mechanism of natural products on diabetic muscular hypoplasia

Berberine: Berberine, also known as berberine, berberine, the chemical formula for the C2OH18NO4 Chinese name (S)-5,8,13,13 A-tetrahydro-6H-dibenzo [A,G] quinazine; It belongs to isoquinoline quaternary ammonium alkaloid and is the main part of the efficacy of traditional Chinese medicine, such as Coptis Chinensis, Sanzicao and Phellodendron chinense [18]. The medicinal part is mainly extracted from the bark, root, and stem of berberis [19]. Preocular studies have found that BBR has certain efficacy in anti-inflammatory, antioxidant, hypoglycemic, improvement of insulin resistance, and lipid metabolism disorders. As a common anti-inflammatory drug in clinical practice, BBR can play an anti-inflammatory role by inhibiting inflammation [20]. In a randomized controlled trial of 182 diabetic patients, TNF-α, IL-6, and C-reactive protein (C-REACTIVE protein) in 3T3-L1 adipocytes were found in the control group after taking compound berberine tablets and berberine. CRP, IL-1β, and other inflammatory factors were significantly reduced [21]. Inhibition of the above inflammatory factors can reduce the activity of NF- κB, and AP-1 and thus alleviate the inhibition of IRS, promote the activation of the PI3K/AKT pathway to accelerate the translocation of GLUT4 membrane and increase the uptake of glucose by muscle cells, thereby reducing insulin resistance and lowering blood glucose [14]. In addition, BBR can increase AMP/ATP value and activate the AMPK/ PGC-1α pathway to enhance mitochondrial function in skeletal muscle and achieve the antioxidant effect. In addition,

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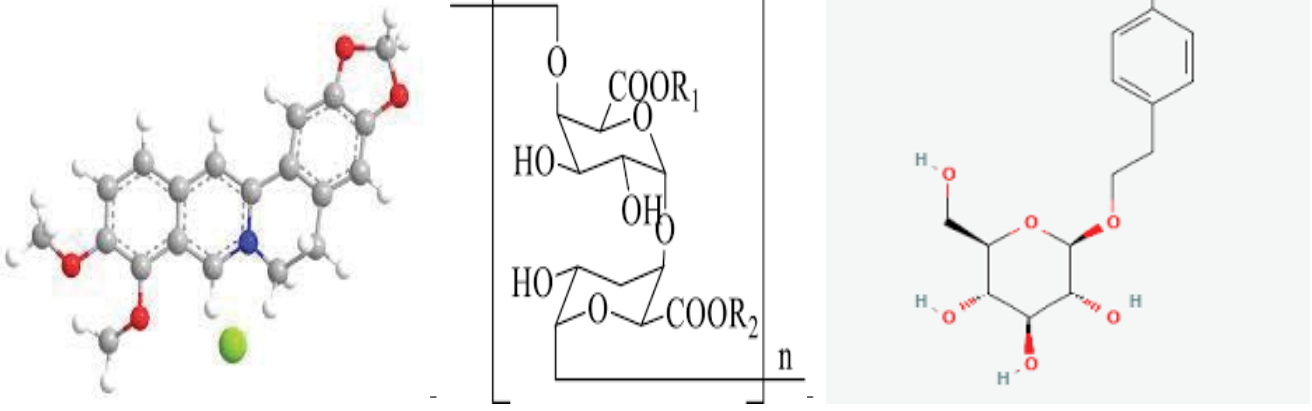
activation of AMPK may increase the transcription-promoting hypoglycemic effect of GLUT4 [22]. At the same time, Berberis (Berberis) fruit also has a similar effect, such as distribution in Iran, the whole Berberis, with anti-inflammatory, lipid-lowering effect; However, domestic Barberis Barberis, Barberis Barberis, berberis Barberis, and berberis Barberis are edible and have the effect of relieving hypertension and dispelling wind and fire [19]. In summary, BBR can inhibit the expression of inflammatory factors, weaken the inhibitory effect on IRS, increase insulin sensitivity, and promote protein synthesis in diabetic muscular Hypoplasia (Figure 1).

Chemical structures of Berberine, Tea polysaccharide, and Salidroside.

Tea polysaccharide

Tea is a traditional Chinese drink, which is rich in tea polysaccharides and tea polyphenols, etc. TPS is a heteropoly sugar combined with protein and has extensive biological activities in anti-inflammatory, antioxidant, anti-tumor, immune modification, and other aspects [23]. Polysaccharides are widely distributed in plants and are polymers of high molecular weight linked by at least 10 monosaccharides [24]. TPS is mainly extracted from leaves, flowers, and bark [25]. It has been found that it has certain biological activities in antioxidant and INSULIN resistance [26]. Experimental studies have shown that TPS can reduce blood glucose and increase body weight in diabetic mice by activating the PI3K/AKT/GLUT4 pathway. In addition, studies have found that oral TPS



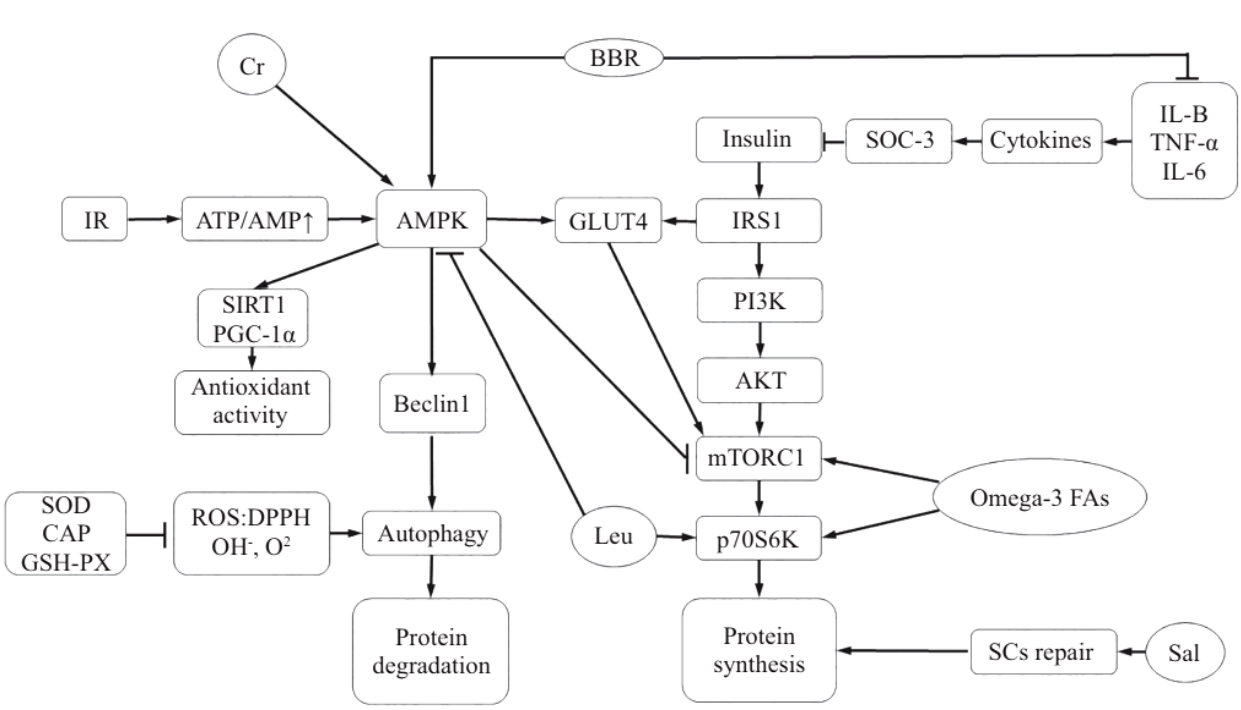


Figure 1: Diabetic muscular Hypoplasia and underlying mechanisms upon interventions with natural products and nutritional supplements. BBR: berberine; TBS: tea polysaccharides; Sal: salidroside; Leu: leucine; Cr: creatine; omega-3 FAs: omega-3 fatty acids.

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can enhance superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GCE) in mice. Gsh-px has the ability to remove free radicals such as 1,1-diphenyl-2-picrylhydrazyl (DPPH), OH-, and O2-, thus showing a good antioxidant effect [27]. Due to the different antioxidant effects of TPS with different quality, TPS with medium molecular weight was found to have the strongest antioxidant activity in damaged cells simulated by HK-2 cells, and has antioxidant activity and repair effect on mitochondria, lysosome, and intracellular DNA [28], and also has therapeutic effect on ROS induced vascular endothelial injury [23]. TPS can significantly reduce the expression of TNF-α and other pro-inflammatory factors, and also increase the levels of immunoglobulin A(IgA), IL-4, IL-2, IgG, IgM, IL-10, and other anti-inflammatory factors [29]. At the same time, TPS is widely distributed in green tea, black tea, and other tea drinks. Moderate consumption of tea drinks, especially coarse tea and aged tea, can increase the intake of TPS, thus removing ROS in the body and reducing cell tissue damage.

Salidroside

Salidroside also known as salidroside; Rhodiola is a phenylpropanoside extracted from plants. Named by Soviet scholars after the main component of Rhodiola, salidroside is found in plants such as ligustrine, bilberry, and salix, and has functions of nerve repair and regeneration, anti-oxidation, and anti-muscle Hypoplasia [30]. One of the causes of diabetic muscular Hypoplasia is peripheral nerve injury caused by poor peripheral microcirculation, hypoxia of nerve cells, insufficient nutrient supply, ROS accumulation, etc., thus aggravating skeletal muscular Hypoplasia [31]. Sal plays a significant protective role against ROS and hypoxic nerves [32]. In hypoxia-induced models, Sal can activate the SIRT1/FoxO3α pathway to improve hypoxia-induced vascular smooth muscle injury and nerve injury to reduce apoptosis. Moreover, intervention on SIRT1-related pathways can effectively improve type 2 diabetes [33]. In terms of neural repair, Sal regulates the proliferation and growth of RSC96 Schwann cells in vitro and regulates neurotrophic factors such as brain-derived neurotrophic factor, BDNF, Glial cell line-derived neurotrophic factor, GDNF and cerebral dopamine neurotrophic factor (CDNF) were also up-regulated [34]. Immunohistochemistry and HE staining showed that bone marrow mesenchymal stem cells pretreated with Sal had a significant inhibitory effect on LPS-induced neuroinflammation [35], indicating that Sal can delay nerve injury and neurodegenerative diseases caused by inflammation [36]. At the same time, relevant reviews on the effects of Sal on nerves show that Sal also has positive effects on neurotransmission and regeneration, choline system, anti-apoptosis, anti-oxidative stress, and improvement of AD, PD, and epilepsy [37]. Thus, Sal can directly and interconnect to ameliorate peripheral nerve injury, increase nerve action on the muscle, and achieve the purpose of slowing down the occurrence of skeletal muscle Hypoplasia (Figure 1).

Skeletal muscle protein synthesis related nutritional supplements.

Leucine

Leu is a kind of essential branched-chain amino acid of the human body, which can produce ATP similar to the carbon skeleton of other amino acids. Leu can regulate some cellular processes, such as tissue regeneration, metabolism, and protein synthesis [38]. It has the most significant effect on promoting protein synthesis among all branched-chain amino acids [39]. It can activate the mTOR signaling pathway, an important regulator of mammalian protein synthesis, and reduce the inhibition of mTOR by phosphorylation of AMPK, thereby increasing protein synthesis [40]. However, there was no significant difference in promoting protein synthesis between oral and injection in terms of uptake [41]. Experiments showed that the protein synthesis rate approached the maximum value when Leu reached 0.14 g/kg in rats [42]. Oral essential Leu supplements need at least 15~20 g per day in young and old people to cause an increase in muscle protein synthesis [43], and an increase in the proportion of Leu intake can restore inactivated muscle protein synthesis and increase insulin synthesis and metabolism [44]. Studies have found that in the 2-week Leu supplement experiment, on the assumption that catabolism did not change, venous blood and muscle biopsy found that muscle egg white synthesis increased by about 4% after Leu intake [45]. Therefore, supplementation on the day after exercise, which is the peak of protein synthesis, is more likely to increase muscle protein synthesis [46], possibly through the activation of the AMPK/mTORC1 pathway by Leu. This caused an increase in the downstream P70 ribosomal protein S6 kinase (p70S6K) [47]. Therefore, appropriate supplementation of Leu can effectively reverse muscle protein loss in the treatment and prevention of diabetic muscular Hypoplasia.

Creatine

Cr is a nitrogen-containing organic acid composed of glycine, arginine, and methionine, which can promote protein synthesis and increase muscle strength in skeletal muscle [48]. Cr is a natural non-protein amino acid complex with a high content in red meat and seafood [49]. Cr supplementation prevents movement injury, promotes post-exercise recovery, and regulates body temperature; In addition, for neurodegenerative diseases, diabetes, fibromyalgia, aging, and other aspects, the daily supplementation of 3 g has significant health benefits [50]. Half of Cr in the human body is absorbed through diet, and the rest is synthesized by the liver and kidney [51]. Studies have shown that Cr supplementation can increase the storage of intramuscular phosphocreatine, promote the faster recovery of ATP level after exercise, reduce the expression level of pro-inflammatory factors, enhance the stimulation of satellite cell proliferation, and promote the up-regulation of protein synthesis and cell repair genes, to improve exercise time and intensity [52]. One mechanism may be activation of AMPK, alteration of glucose metabolism and oxidation, reduction of Lactoacid production, and mitochondrial ROS production [53]. On the other hand, it may be that Cr supplementation can activate metabolic pathways such as AMPK/IGF-1/mTOR, regulate GLUT4 and increase protein synthesis of muscle fibers [54]. In addition, in the 16-week Cr combined resistance exercise experiment, it was found that the number of muscle satellites and muscle nuclei induced by training increased, the response of muscle fibers to force training was enhanced,

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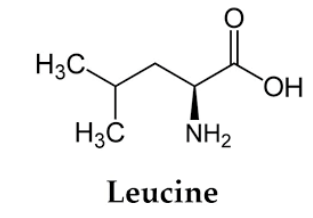
and the performance of sub-maximum strength functional tasks was improved, thereby enhancing the maximum muscle strength [55]. Therefore, Cr combined with exercise training can effectively promote and improve skeletal muscle mass and motor function.

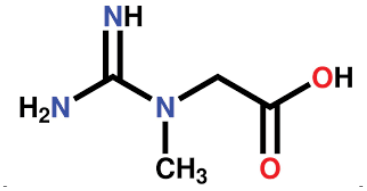
Omega-3 fatty acids

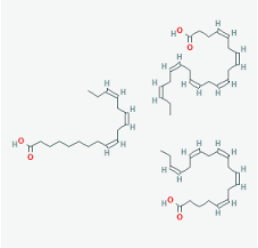
Omega-3 fatty acids, also known as N-3 fatty acids, are a kind of polyunsaturated fatty acids essential to the human body, composed of eicosapentaenoic acid and docosahexaenoic acid. Fish, fish oil, and some vegetable oils are their rich sources and play an increasingly important role in disease prevention and health. Lack of intake of essential fatty acids can lead to a series of diseases such as diabetes, hypertension, infant development, cancer, and so on [56]. In addition, omega-3 fatty acids can also reduce skeletal muscle Hypoplasia, anti-inflammatory and improve blood lipids, etc. [57]. Studies on obese mice induced by a high-fat diet have found that 20-week conjugated linoleic acid /ω-3 combined exercise intervention can inhibit protein degradation, improve muscle strength and mass, and enhance muscle protein synthesis rate [58-59]. It was found that ω-3 fatty acids can increase the expression of muscle protein through the mTOR/p70S6K signaling pathway, increase the value of modulator muscle satellite cells, and improve the protein synthesis of skeletal muscle [60-63]. Similarly, increasing fish intake in the diet has been shown to promote protein synthesis by activating the mTORC1/p70S6 K-related pathway [64]. At the same time, increased omega-3 intake in adolescents improved glucose tolerance and insulin sensitivity [65-68]. In addition, muscle strength and neuromuscular function were significantly improved during 90 days of progressive resistance exercise combined with 2 g of omega-3 fatty acids per day. It is suggested that resistance exercise combined with omega-3 fatty acids has a significant additive effect on muscle gain [69-72]. At the same time, it has also been found that ω-3 fatty acids can not only increase protein synthesis in muscle but also regulate blood lipids and reduce glucose uptake, thus reducing the formation of obesity [73-75].

Chemical structures of Leucine, Creatine, and Omega-3 fatty acids



Leucine





Conclusion

With the rapid increase of the diabetic population, diabetic muscular Hypoplasia has gradually become a factor affecting the health and quality of life of diabetic patients, so the control of diabetic complications and inducing factors attracts special attention. In this paper, the mechanism of tea polysaccharides, creatine, ω-3 fatty acids, and other natural products and nutritional supplements were discussed. Among them, the natural product BBR reduces protein degradation and increases protein synthesis by inhibiting inflammatory factors, increasing insulin secretion, and activating AMPK, TPS reduces ROS in vivo by enhancing antioxidant factors, and Sal reduces peripheral nerve injury by promoting the repair of Schwann cells. Leu, Cr, and ω-3 fatty acids in nutritional supplements can increase protein synthesis by acting on the mTOR/p70S6K pathway, and can also promote glucose uptake by activating the AMPK/GLUT4 pathway to regulate protein homeostasis. Both natural products and nutritional supplements have potential therapeutic value in dealing with the sub mechanism of diabetic muscular Hypoplasia. Therefore, food or drink containing a high amount of effective natural products can be purposefully selected in the food regimen, or the combination of natural products and nutritional supplements can be considered in dealing with diabetes-induced muscular Hypoplasia. In addition, the effect of nutritional supplements combined with exercise intervention may be better, which can be used as a further research point for the prevention and intervention strategies of diabetic muscular Hypoplasia.

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