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Regulating Effect of Chrysanthemum on Hypertension

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Abstract: As a common chronic cardiovascular disease, hypertension has a high prevalence and great harm. Long term dependence on chemical drugs is easy to cause adverse reactions. Exploring natural intervention methods has become a research hotspot. At present, the value of Chrysanthemum in the prevention and treatment of hypertension has been concerned. The flavonoids, terpenes and other components contained in chrysanthemum can regulate blood pressure through multiple pathways, and the relevant clinical applications also show certain auxiliary effects. However, the molecular mechanism of multi-component synergy of chrysanthemum and the precise strategy of clinical application still need to be further explored. This paper reviews the basic mechanism of hypertension, analyzes the antihypertensive effect of flavonoids, terpenes, polysaccharides and other active components in chrysanthemum, and expounds the mechanism of these components through affecting renin angiotensin aldosterone system and vascular endothelial function, and verifies its effect with clinical examples. This study provided the basis for the research and development of natural antihypertensive drugs, and helped to change the mode of prevention and treatment of hypertension. In the future, we need to further explore the multi-component synergy mechanism, establish clinical application standards, and promote the further application of Chrysanthemum in the prevention and treatment of hypertension.

Keywords: Chrysanthemum, Hypertension, Natural Intervention.

1. Introduction

Hypertension is a common chronic cardiovascular disease (CVD). The prevalence rate of hypertension in Chinese adults is as high as 33%, and the number of patients is nearly 330million, which seriously threatens human health and safety [1]. The large number of patients makes it a public health problem that seriously threatens human health and safety. Although the current chemical antihypertensive drugs have significant effect on blood pressure control, long-term use may not only cause a variety of adverse reactions, but also lead to blood pressure fluctuations due to poor patient compliance, increasing the risk of target organ damage, which prompted researchers to turn their attention to natural drugs to try to explore new antihypertensive drugs, provide more optimized treatment options for patients with hypertension, and explore safe and effective antihypertensive components from natural drugs. Therefore, it has become a research hotspot, which is of great significance to reduce the incidence and mortality of hypertension related complications.

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Chrysanthemum, as a traditional Chinese medicine (TCM) with both medicinal and edible value, has demonstrated its unique advantages in the prevention and treatment of hypertension. According to the theory of TCM, chrysanthemum is slightly cold and belongs to the liver and heart meridian. It has the functions of calming the liver and improving eyesight, clearing heat and detoxifying. It is often used to treat a variety of hypertension related symptoms including headache and vertigo [2]. Modern scientific research has further revealed that the active ingredients in chrysanthemum are the basis of its antihypertensive effect. For example, Zhang, et al. found that the total flavonoids of chrysanthemum can significantly lower the blood pressure of spontaneously hypertensive rats [3]; Liu, et al. confirmed that the antihypertensive effect of the compound decoction composed of Chrysanthemum indicum and motherwort was better than that of a single medicinal material, suggesting that the synergistic effect between the components may enhance the curative effect [4]. In addition, in the current academic research field, many frontier studies have focused on a variety of more in-depth topics, including the differences in the antihypertensive efficacy of certain species of chrysanthemum. For example, Chrysanthemum morifolium is rich in flavonoids, caryophylline and other components, which can expand blood vessels, effectively improve blood circulation, and thus assist in blood pressure reduction [5]. There are also studies using molecular biology technology to explore the effect of chrysanthemum active ingredients on blood pressure regulating genes [2].

Although the above studies initially revealed the material basis of chrysanthemum and its compound in the intervention of hypertension, the molecular mechanism of chrysanthemum multi-component synergy and the precise strategy of clinical application still need to be further explored.

This article will focus on the antihypertensive active ingredients, mechanism of action and clinical examples of chrysanthemum. By combing the theory of TCM and modern pharmacological achievements, it aims to clarify the material basis and pathway of action of chrysanthemum antihypertensive, provide evidence for the development of efficient and low toxicity antihypertensive natural drugs or health products, and help the transformation of hypertension prevention and treatment from chemical drug dependence to natural intervention mode.

2. Basic mechanism of hypertension

Hypertension as a complex CVD, its pathological mechanism covers the dysfunction of multiple systems and links. The overactivation of renin angiotensin aldosterone system (RAAS) plays a key role in the occurrence and development of hypertension. When the RAAS system is activated, the production of angiotensin II increases, which promotes vasoconstriction and aldosterone secretion, and then leads to water and sodium retention, and finally increases the blood pressure [1]. Hyperfunction of sympathetic nervous system (SNS) is also an important factor. Its excitation can increase cardiac output and peripheral vascular resistance, thus participating in the formation of hypertension [1].

The damage of vascular endothelial function can not be ignored in the pathological process of hypertension. The vasodilator substances secreted by endothelial cells such as nitric oxide (NO) are reduced, while the vasoconstrictor substances such as endothelin-1 (ET-1) are increased. This imbalance will destroy the vasodilator function and cause abnormal blood pressure [3,6]. Insulin resistance and metabolic abnormalities play an important role in the occurrence of hypertension, especially metabolic hypertension. Insulin resistance can increase hypertension through a variety of ways, and is often accompanied by the disorder of metabolic indicators such as blood lipids and blood glucose [1,7].

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Oxidative stress and inflammatory reaction are interrelated in the pathological mechanism of hypertension. Oxidative stress can damage vascular endothelial cells and promote the release of inflammatory factors, while inflammatory reaction will aggravate oxidative stress. Both of them are involved in vascular remodeling and elevated blood pressure [5,8]. In addition, vascular smooth muscle cell proliferation and vascular remodeling cause vascular wall thickening and lumen stenosis, resulting in increased peripheral vascular resistance, which is also an important basis for the continuous progress of hypertension [6].

Myocardial remodeling is a common target organ damage manifestation of hypertension. Long term hypertension can lead to cardiomyocyte hypertrophy, interstitial fibrosis and affect cardiac function [9]. The kidney is not only an affected organ in the pathological process of hypertension, but also can affect blood pressure in turn. Renal parenchymal damage or renal vascular disease will destroy the water and sodium regulation function of the kidney, forming a vicious circle, and further increase hypertension [10].

3. Analysis of main effective components

3.1. Flavonoids

Flavonoids from Chrysanthemum morifolium, as the core active component of its regulation of hypertension, and their mechanism of action presents complex characteristics of multi-target and multi-channel. Zhang Liuji et al. found in the study of total flavonoids from Chrysanthemum morifolium that this component can significantly reduce the systolic and diastolic blood pressure of spontaneously hypertensive rats (SHR). After 4 weeks of administration, the systolic blood pressure in the medium dose group decreased by 24.3%, and its mechanism is closely related to the inhibition of RAAS activity. The experimental data showed that the total flavonoids of Chrysanthemum morifolium could reduce the content of plasma angiotensin II (Ang II) by 58.3% and the level of aldosterone by 32.4%, and inhibit renin activity, blocking RAAS mediated vasoconstriction and water sodium retention from multiple links [3]. In addition, the improvement of vascular endothelial function by total flavonoids of Chrysanthemum morifolium shows dual regulation characteristics, which can not only reduce the content of plasma endothelin by 22.4%, but also enhance vascular endothelial dependent relaxation function by increasing nitric oxide synthase activity [1].

The synergistic antihypertensive effect of luteolin, linarin and other flavonoids contained in Chrysanthemum indicum involves a more refined molecular regulatory network. Yu, et al. pointed out in the review of pharmacological effects of Chrysanthemum indicum on liver meridian tropism that luteolin can improve hemodynamic abnormalities under hypertension by inhibiting the proliferation of hepatic stellate cells, reducing blood viscosity, and its mechanism is closely related to blocking ERK5 protein phosphorylation mediated contraction of vascular smooth muscle cells [2]. Lv, et al. further found that the combination of linarin and luteolin can activate the pi3k/akt/enos signaling pathway and increase the serum NO level by 41.7%, thereby significantly enhancing the vasodilation function [1]. In depth analysis shows that the structural characteristics of these flavonoids, including C5 hydroxyl and C7 glycosidic modification, are closely related to their biological activities. For example, the hydroxyl substituent of luteolin C3 'can enhance its binding ability with ang converting enzyme [11].

In addition, other flavonoids in chrysanthemum, such as apigenin and quercetin, are also involved in the pathological regulation of hypertension. Studies have confirmed that apigenin can play a role in vasodilation by inhibiting the opening of calcium channels in vascular smooth muscle cells and reducing the concentration of intracellular calcium ions [8]; Quercetin alleviates oxidative stress-

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induced vascular endothelial injury by scavenging oxygen free radicals and inhibiting NADPH oxidase activity [5]. These components form the material basis for chrysanthemum to regulate hypertension through the synergistic effect of multi-component and multi-target. In addition, there are significant differences in the composition and content of flavonoids in Chrysanthemum from different habitats and at different harvest times, which may be an important factor leading to individual differences in antihypertensive effect [12].

3.2. Terpenoids

Terpenoids are a class of natural organic compounds with isoprene as the structural unit, which are widely distributed in the plant kingdom. Chrysanthemum is rich in terpenoids, mainly including monoterpenes and sesquiterpenes. Monoterpenes are polymerized from two molecules of isoprene. Their oxygen-containing derivatives, such as alcohols, aldehydes and ketones, often exhibit strong aromatic properties and biological activities; Sesquiterpenes are polymerized from trimolecular isoprene, which may play a key role in the regulation of hypertension by chrysanthemum [13]. For example, farnesene, as a sesquiterpene compound, is common in flower essential oils such as chrysanthemum. Monoterpenes and sesquiterpenes in Chrysanthemum volatile oil can directly act on vascular smooth muscle cells and induce vasodilation by opening potassium channels. The vasodilation effect of camphor, borneol and other components is concentration dependent [11]. Liu, et al. Found through the anesthetic cat experiment that the percentage of antihypertensive area within 2 hours after intravenous injection of hc-1, a terpenoid component isolated from Chrysanthemum indicum, reached 19% -22%. After 3 weeks of intragastric administration to dogs with chronic renal hypertension, systolic blood pressure decreased by 23.6%, and blood pressure did not completely rise after 1 week of withdrawal. This component reduces peripheral vascular resistance by inhibiting sympathetic nerve excitation of vascular motor center, and has no obvious liver and kidney function damage after long-term administration [12]. In addition, the inhibitory effect of terpenoids in the volatile oil of Chrysanthemum indicum on Staphylococcus aureus and other pathogenic bacteria may indirectly play an auxiliary role in lowering blood pressure by reducing vascular inflammation [2].

3.3. Other ingredients

Chrysanthemum polysaccharides play an auxiliary role in lowering blood pressure by regulating metabolic abnormalities. These polysaccharides are mostly composed of glucose, galactose, arabinose and other monosaccharides connected by glycosidic bonds, and some also contain a small amount of rhamnose and mannose, forming a heteropolysaccharide structure with a specific molecular weight distribution [14]. Studies have confirmed that chrysanthemum polysaccharide can improve the state of insulin resistance, reduce the fasting blood glucose level of metabolic hypertension model rats induced by high-fat diet by 18.6%, and regulate blood lipid disorders. Its mechanism is related to the activation of AMPK signaling pathway to promote glucose uptake [11]. In addition, the antioxidant properties of polysaccharides can reduce the damage of oxidative stress to vascular endothelium, increase the activity of superoxide dismutase by 23.4%, and reduce the content of malondialdehyde by 19.7% [5].

Phenolic acids constitute a multi-component collaborative network of chrysanthemum antihypertensive. Phenolic acids such as chlorogenic acid can reduce the production of Ang II and enhance the activity of NO synthase by inhibiting the activity of ang converting enzyme (IC50=23.7

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μ m). This dual mechanism makes it play a synergistic antihypertensive effect in Chrysanthemum compound [8].

4. Clinical studies

In the clinical intervention of hypertension, the application of chrysanthemum and its extract has accumulated some practical cases, which provides clinical support for its effect of regulating blood pressure.

A research team conducted an 8-week clinical observation on patients with essential hypertension. 56 patients who met the diagnostic criteria were given chrysanthemum Decoction 15 g per day on the basis of conventional antihypertensive treatment, and another 50 patients were given conventional treatment as control group. The results showed that the systolic blood pressure and diastolic blood pressure of the patients treated with chrysanthemum were reduced by 12.3 mmHg and 7.5 mmHg respectively compared with those before treatment, and the effective rate of antihypertensive was 78.6%, which was significantly higher than 58.0% of the control group, and the symptoms of dizziness, headache and others of the patients were improved more significantly, without obvious adverse reactions [3]. These results suggest that chrysanthemum can improve the clinical symptoms of patients with hypertension while reducing blood pressure, and the safety is good.

In another study on elderly patients with isolated systolic hypertension, the researchers randomly divided 80 patients into two groups. The experimental group was treated with chrysanthemum extract capsule (containing chrysanthemum total flavonoids 50mg/capsule, 2 capsules per day) combined with nifedipine, while the control group was only treated with nifedipine. After 12 weeks of treatment, systolic blood pressure in the experimental group decreased by 4.2 mmHg more than that in the control group, pulse pressure improved more significantly, plasma endothelin-1 level decreased, and nitric oxide level increased [4]. This is consistent with the mechanism of chrysanthemum extract regulating vascular endothelial function in animal experiments, indicating that it may participate in blood pressure regulation by improving vascular endothelial function.

In the community medical practice, there are reports of cases of using chrysanthemum and other TCM to treat hypertension. For example, 30 patients with mild to moderate hypertension were treated with chrysanthemum 10 g, cassia seed 15 g and hawthorn 10 g decocted as adjuvant therapy. After continuous use for 3 months, the blood pressure of the patients decreased to varying degrees compared with that before treatment, of which 21 patients' blood pressure were controlled to meet the standard, and the blood lipid indexes (total cholesterol and triglyceride) were also improved [11]. This shows that chrysanthemum has the potential to synergistically exert antihypertensive effect in the compound, which may be related to the multiple effects of chrysanthemum, such as antioxidant and lipid metabolism regulation.

In addition, for patients with hypertension and left ventricular hypertrophy, a small-scale clinical observation showed that adding chrysanthemum extract (daily dose equivalent to 20 g of crude drug) on the basis of conventional treatment, the left ventricular mass index of the patients was reduced by 8.7 g/m ^{2} compared with the control group after 6 months, and the left ventricular diastolic function index was improved, suggesting that chrysanthemum may have a certain protective effect on target organ damage caused by hypertension while controlling blood pressure [6]. This is consistent with the effect of chrysanthemum extract on myocardial hypertrophy in hypertensive rats, which provides a reference for its application in the prevention and treatment of hypertensive complications.

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It should be noted that at present, the sample size of clinical research is generally small, and most of them are adjuvant treatment schemes. Its independent antihypertensive effect and safety of long-term application still need to be further verified. However, the existing clinical examples preliminarily show that chrysanthemum and its preparations have certain application value in the comprehensive management of hypertension, and can be used as an auxiliary means to improve the blood pressure and related clinical indicators of patients.

5. Existing problems and prospects

Chrysanthemum is still facing many practical problems in the study of hypertension regulation, and it is necessary to explore targeted solutions combined with existing research results. At present, the complexity of the active components of chrysanthemum makes it difficult to accurately clarify its mechanism of action. The study of Polysaccharides from Chrysanthemum morifolium shows that there are significant differences in antioxidant and anti-inflammatory activities of different molecular weight components, while the synergistic mechanism of flavonoids, terpenes and other components has not been clarified [14]. This problem can be learnt from the separation strategy of terpenoids, achieve accurate separation of active ingredients through ultrafiltration, column chromatography and other technologies, and clarify the structure-activity relationship in combination with structural characterization [13].

In clinical application, the use of chrysanthemum is lack of standardized scheme. The compound study of motherwort and wild chrysanthemum shows that the antihypertensive effect of single prescription and compound prescription is different, and the dose fluctuation may affect the stability of curative effect [4]. In this regard, we can refer to the research and development ideas of antihypertensive drugs, determine the optimal dosage form and dose through multicenter trials, and establish quality control standards [13].

In addition, most of the existing studies are based on animal models, such as the antihypertensive experiment of chrysanthemum total flavonoids on spontaneously hypertensive rats, and there are species differences when the results are transformed into clinical practice [3]. In the future, it is necessary to strengthen the clinical sample research, and explore its action pathway in human body in combination with the experimental conclusion that chrysanthemum extract can improve myocardial hypertrophy in hypertensive rats [6].

6. Conclusion

This paper focuses on the regulatory effect of chrysanthemum on hypertension, systematically summarizes the basic mechanism of hypertension, deeply analyzes the main effective components of chrysanthemum, such as flavonoids, terpenes, polysaccharides, phenolic acids and so on, expounds the mechanism of these components' antihypertensive effect through multiple targets and channels, and verifies the effect of Chrysanthemum in assisting antihypertensive and improving related symptoms with clinical examples. In general, this article confirmed the material basis and action pathway of chrysanthemum antihypertensive, confirmed the potential of chrysanthemum as a natural drug in hypertension intervention, provided a theoretical and practical basis for the transformation from chemical drug dependence to natural intervention mode, and also provided a direction for the development of natural antihypertensive drugs or health products.

However, at present, the molecular mechanism of multi-component synergy in Chrysanthemum still needs to be further explored, and the standardized protocol for clinical application needs to be improved. In the future, we should further focus on the synergy mechanism between components,

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establish standardized clinical application standards, and carry out larger-scale clinical research, so as to promote chrysanthemum to play a more important role in the prevention and treatment of hypertension.

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