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Research Progress on Modern Pharmacological Action of Rhubarb

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Abstract: Rhubarb is the dry root and rhizome of Rhubarb palmatum (Rheum palmatum, L.) Rheum tanguticum (Rheum tanguticum Maxim. ex Regel) or Medicinal rhubarb (Rheum officinale Baill.)It is widely distributed in Shaanxi, southeastern Gansu, Qinghai, western Sichuan, Yunnan and eastern Tibet. Before the stem and leaves wither in late autumn or sprout in the next spring, dig them, remove the fine roots and skins, cut the petals or segments, and dry them. Rhubarb is one of the oldest, most commonly used and most important Chinese medicinal materials in China, with unique efficacy, rich resources and high medicinal value. Modern pharmacological research shows that rhubarb has pharmacological effects such as anti-tumor, antiviral, antibacterial and anti-inflammatory, hemostasis, and improvement of microcirculation. In this paper, the modern pharmacological effects of rhubarb in recent years are reviewed in order to provide some references for future research, development and use of rhubarb resources.

1. Introduction

Rhei Radix et Rhizoma, also known as General, Huoshen, Huangliang, Niutong, etc.is a traditional Chinese medicine with a long history, rich resources and extensive clinical application. It is one of the drugs exported to foreign countries in the early stage. Rhubarb was first recorded in the Shennong Herbal Classic [1]: "Rhubarb has a bitter and cold taste. It is mainly used for blood stasis, blood stasis, cold and heat, breaking the mass accumulation, drinking, sleeping, cleaning the intestines and stomach, introducing the old to the new, promoting diuresis and killing, regulating the middle and the food, and calming the five internal organs." The rhubarb included in the 2020 edition of the Pharmacopoeia of the People's Republic of China [2] is the dried roots and rhizomes of Rheum palmatum, Rheum tanguticum or medicinal rhubarb, and is described as "bitter, cold. It can be used to regulate the spleen, stomach, large intestine, liver, and pericardium meridians, and has the effects of purging and attacking, clearing heat and fire, cooling blood and detoxicating, removing blood stasis and clearing meridians, and removing dampness and yellow." Modern pharmacology shows that rhubarb mainly contains anthraquinones, anthrones, tannins, stilbenes, and benzophenones a variety of chemical components such as chromogenic ketones, anthraquinone compounds and their derivatives such as emodin, aloe emodin, rhein, chrysophanol, etc.are

important components of rhubarb activity, with anti-tumor, antiviral, antibacterial and anti-inflammatory, treatment of blood diseases, regulation of gastrointestinal function, diuresis, kidney protection, liver protection and other pharmacological effects [3-6].This paper systematically collates the research reports on rhubarb at home and abroad in recent years, and summarizes them from the aspects of modern pharmacological effects, so as to provide some reference for the future research, development and application of rhubarb.

2. Pharmacological action

2.1 Antitumor

Emoin significantly reduced the activity of thyroid papillary cancer cells (B-CPAP), and induced apoptosis through the release of apoptosis factors such as CytC and activation of Cleaved caspase-3 and Bax in the outer membrane. Scratch test showed that the migration and invasion ability of B-CPAP decreased with the increase of emodin dose. The relative expressions of p-AKT,p-GSK3β and p-β-catenin in B-CPAP were significantly decreased by Western blot analysis. This suggests that emodin may negatively regulate the AKT/GSK3β/β-catenin pathway to inhibit the activity of B-CPAP cells [7].Li Zhonghui et al. [8] found through experiments that emodin inhibited the proliferation of colon cancer CACO-2 cells in a dose-time dependent manner.20μmol/L-24hr emodin inhibited the proliferation of CACO-2 cells in the G0/G1 phase, decreased the mitochondrial membrane potential, promoted the apoptosis of the cells, and decreased the protein expression of ILK, p-PI3K and CyclunD1.Ma Liang et al. [9] found that rhein not only increased the drug resistance of TRAIL by up-regulating the mRNA expression of DR5 receptor, but also promoted the TRAIL-mediated apoptosis of bladder cancer cells. Treatment with a non-toxic concentration of 10 μ g/mL rhein combined with 20 ng/ mL TRAIL significantly inhibited the growth of bladder cancer cells, especially T24 cells and BIU87 cells, indicating that the combination of rhein and TRAIL could enhance the cleavage level of caspase-3 and caspase-8 and promote the apoptosis of cancer cells. Rhein has an inhibitory effect on the proliferation of laryngeal cancer Hep-2 cell. The higher the concentration of rhein, the stronger the inhibitory effect, and has an effect on the expression of related proteins in Hep-2 cells, which can significantly reduce Dvl2 and p-GSK-3β and β-Catenin protein expression, increases GSK-3β Protein expression, in which the expression of β-catenin protein is related to the invasion and malignancy of tumor. It is concluded that rhein can reduce the expression of β-catenin and Dvl2, increases GSK-3β can reduce the risk of cell metastasis and inhibit Wnt/ β-catenin signal pathway, and then the proliferation, invasion and migration of Hep-2 cells [10].

2.2 Antiviral

It was found that [11] emodin has the ability of anti-herpes simplex virus (HSV) activity. Compared with the control group, emodin group can significantly improve the survival rate of mice infected with HSV. The effect of emotin on HSV increases with the increase of dose. When the concentration is 50g/ml,the replication of HSV-1 and HSV-2 can be effectively inhibited, and the antiviral index of HSV-2 is 2.07 and 3.53, respectively.When the concentration is 300g/ml,the antiviral index of HSV-2 is 3,4 times that of HSV-1.The mechanism may be that emodin inhibits casein kinase 2 in HSV, affects the phosphorylation of related proteins, and inhibits HSV biosynthesis. The analysis of traditional Chinese medicine components showed that the accumulation of emodin and other anthraquinones could inhibit the replication of RNA polymerase of novel coronavirus (Omicron strain) after reaching a certain dose. A series of software was used to analyze the structure of emodin and the protein structure and energy of the novel coronavirus

RNA polymerase, and it was found that emodin 3 could better bind to the active site of the protein ALA688,form hydrogen bonds, play a role in inhibiting the protein, and prevent nucleotide substrates from entering this site. The results showed that the mean value of CT in the control group was 32.968±0.772 and that in the virus model group was 32.968±0.772, 14.935±0.594, the mean CT value of emodin low-dose group was 19.703±0.522, the mean CT value of emodin medium-dose group was 24.343±1.442,and the mean CT value of emodin high-dose group was 22.883±0.840, indicating that emodin could significantly inhibit RNA replication of Omicron strain. It has pharmacological effects of anti-novel coronavirus activity [12].

2.3 Antibacterial and anti-inflammatory

It was found that [13] rhein could significantly inhibit bacteremia induced by methicillin-resistant Staphylococcus aureus (MRSA), with the lowest inhibitory concentration of 8μg/mL and the lowest bactericidal concentration of 16μg/mL. Moreover, rhein with the increase of concentration can effectively promote the rupture of MRSA, increase the content of alkaline phosphatase, reduce the level of soluble protein, affect the total amount and type of bacterial protein, and then reduce the number of bacteria in the blood. Zhang Liheng et al. [14] measured the antibacterial activity of emodin against Escherichia coli in vitro. The results showed that emodin could improve the conductivity of bacterial fluid, calcium ion concentration, macromolecular concentration, alkaline phospholipase activity and total leakage rate compared with the control group, indicating that emodin could be used as the cell membrane and cell wall of Escherichia coli, so that a large amount of contents in the bacteria could be leaked, and then play an antibacterial role. Vitamin C, resveratrol and emodin have inhibitory effects on Helicobacter pylori (Hp).Resveratrol can inhibit the growth of cagA+ strain in Hp and the expression of vac A protein. The inhibitory effect of emodin on the growth of Hp increases with the increase of dose and can damage Hp deoxyribonucleic acid. The bacteriostatic rate of the combination of resveratrol and metronidazole, emodin and clindamycin is higher than that of the single drug [15].Dai Shanshan et al. [16] found in vivo experiments that emodin of 10mg/kg and 20mg/kg could significantly reverse the increase of LDH and CKMB, markers of myocardial injury induced by LPS, alleviate pathological changes such as myocardial cell arrangement disorder and myofilm destruction, and improve survival rate. Emodin can reduce the levels of LPS-induced inflammatory cytokines IL-1β, IL-18 and TNF-α,reduce the cardiac inflammatory response, down-regulate the expression levels of NLRP3,GSDMD and GSDMD-NT and the ratio of GSDMD-NT/GSDMD-FL in the heart tissue of mice in vivo. These results suggest that emodin has an effect on the expression of NLRP3 and the activation of GSDMD, which may have a protective effect on the heart. In addition, emodin decreased the cleavage of caspase-1,IL-1β and GSDMD-NT and the ratio of GSDMD-NT/GSDMD-FL, effectively blocking the LPS-induced cell damage. Emodin can significantly raise the mechanical pain threshold in mouse inflammatory pain models induced by complete Freund's adjuvant (CFA),and effectively relieve CFA induced thermal hyperpain in a dose-dependent manner. Emotional intervention can significantly reduce the contents of inflammatory factors IL-1β,IL-6 and TNF-α in serum and dorsal root ganglion induced by CFA, and down-regulate the levels of TRPV1 and TRPV4 induced by CFA in dorsal root ganglion, thus relieving inflammatory pain [17].Rhein alleviated histopathological changes in male C57BL/6 colitis mice induced by anti-dextran sulfate sodium,such as inflammatory cell infiltration and epithelial tissue destruction,increased colon length, and decreased colon pathological score and fecal LCN-2 level.The weight of spleen and the content of Cxell and IL-17A in serum were decreased,and the number of Th17 cells in mesenteric lymph nodes was significantly decreased.This experiment has proved the efficacy of rhein in treating colonic inflammation at the animal level [18].

2.4 Treat blood diseases

2.4.1 Hemostatic effect

Wang Lanfang et al. [19] found that chrysophanol could significantly shorten bleeding time by intragaenically and intraperitoneally injecting three components of water suspension into experimental mice, while chrysophanic acid could prolong bleeding time, while chrysophanic acid was ineffective. Guo Dongyan et al. [20] compared the chemical composition of rhubarb before and after char-frying with thin layer fingerprint, and determined the contents of rhein, emodin, chrysophanol and emodin methyl ether with liquid chromatograph before and after char-frying. The contents of the four chemical components all decreased, of which chrysophanol was the most significant. The changes of blood coagulation and hemostasis time before and after char were compared in animal experiments. Compared with the blank control group, char group can significantly shorten the coagulation and bleeding time. These experimental results suggest that rhubarb can be used in clinical bleeding treatment. Wang Riquan [21] found through clinical observation that micron rhubarb charcoal could reduce the hemostasis time of patients under gastroscopy, shorten the conversion time of fecal occulted blood, increase TXA2 in plasma, and decrease PGI2. It was found that medium and high dose micron rhubarb charcoal could shorten the blood clotting time and bleeding time of mice, and increase the platelet count. Different doses of rhubarb charcoal can increase TXB2,decrease the level of 6-keto-PGF1α,and increase the content of platelet granular membrane protein, especially in high doses. In summary, micron rhubarb charcoal can increase platelet content by regulating the relative balance between TXB2 and 6-keto-PGF1α, promote the release of coagulant in platelets, enhance platelet aggregation, enhance platelet activation, enhance adhesion and aggregation, and further promote coagulation

2.4.2 Blood activating effect

Studies [22] found that Chrysophanol-8-O-glucoside (CP8-O-GLC) had the strongest inhibitory effect on platelet aggregation induced by collagen and thrombin. These results indicate that CP-8-O-glc has significant antiplatelet and anticoagulant activities, suggesting that the compound may have a certain therapeutic effect on the prevention of platelet aggregation. Zhao Ling et al. [23] used heat Chinese medicine and subcutaneous injection of loperamine hydrochloride to induce heat and blood stasis in rat models, and treated raw rhubarb and cooked rhubarb respectively. The levels of NO-1, ET-1,VWF and PGI2 in both raw and cooked rhubarb groups tended to be normal, especially in cooked rhubarb group. The effect of rhubarb in promoting blood circulation and removing blood stasis may be through maintaining the level of NO and ET-1, which dilates blood vessels and constricts blood vessels, so that the two are in dynamic balance and jointly maintain blood vessel morphology and blood flow in blood vessels. And by regulating PGI2 and VWF, it can reduce platelet aggregation, inhibit blood coagulation and thrombosis, and improve blood microcirculation.Sui Feng et al. [24] compared the differences of four kinds of rhubarb products from raw rhubarb, cooked rhubarb, wine rhubarb and rhubarb charcoal in promoting blood circulation and removing blood stasis, and found that these four kinds of rhubarb products had varying degrees of influence on indexes such as whole blood viscosity, plasma viscosity, fibrinogen, hematocetus, prothrombin time and partial thromboplastin time. The anticoagulant effect of wine rhubarb was very strong, the anticoagulant effect of carbon rhubarb was significantly weakened, and the blood-activating effect of cooked rhubarb was slightly weaker than that of raw Rhubarb.

2.5 Regulate gastrointestinal function

2.5.1 Diarrhea and antidiarrheal effect

Research shows that [25] perfusion of 10μg/ml rhubarb free anthraquinone in vivo can significantly increase the protein concentration, $Na^+$and Cl^- concentrations in intestinal effluents of rats, increase the amount of effluents, and reduce glucose absorption, which is related to the activity of NOS, especially iNOS. iNOS can be expressed in a variety of intestinal cells, and the secretion of NO can lead to the accumulation of fluid in the intestinal cavity. The free anthraquinone of rhubarb directly acts on the iNOS in the small intestine, producing a large amount of NO, producing a large amount of protein into the intestinal lumen, inhibiting the absorption of $Na^+$and Cl^-,and then making the intestinal lumen into a hypertonic state. In this state, the intestinal contents enter the large intestine, and the intestinal reabsorption of water is significantly weakened under the osmotic pressure, and the liquid is discharged together with the contents. Emodin (1,3, 8-trihydroxy-6-methylanthraquinone) can significantly increase the expression of AQP3 in mouse colon and human intestinal epithelial cells (HT-29),and increase the water content of colon stool in mice, and the evaluation index of defecation is dose-dependent. Emodin upregates the expression of Cyclic Adenosine monophosphate (cAMP) -dependent protein kinase A and phosphorylated cAMP element-binding protein (p-CREB Ser133) in HT-29 cells. This suggests that the laxative effect of emodin may be related to the up-regulation of AQP3 expression in PKA/p-CREB signaling pathway [26].The tannin component of rhubarb has an antidiarrheal effect, and it is easy to cause constipation symptoms when used in small doses or for a long time [27].Studies have found that the synergistic effect of combined anthraquinone and condensed tannin in rhubarb can lead to uni-diarrheal effect. Long-term use of anthraquinone components in rhubarb can damage intestinal mucosa and nerve plexus and reduce intestinal peristalsis, and condensed tannin is hydrolyzed into monomone tannin through gastrointestinal digestion, and gallic acid is accumulated in the body, resulting in uni-intestinal astringent effect, which can lead to constipation [28].

2.5.2 Protect gastrointestinal mucosal barrier

Zhang Qian et al. [29] found that emodin can inhibit the expression of trigger receptor-1 (sTREM-1),TNF-αand NF-κB in soluble myeloid cells in peripheral blood, reduce inflammation in the gastrointestinal tract and the whole body, and block the occurrence and development of intestinal ischemia-reperfusion injury. Studies have shown that [30] emodin can reduce the damage of intestinal mucosal structure in mice, inhibit the activation of intestinal mast cells and release of degranulation, and play a role in preventing and treating intestinal ischemia-reperfusion injury. Qi Lei [31] found that emodin can inhibit intestinal inflammatory response by blocking NF-κB/HIF-1a-COX-2 signaling pathway, and protect the function of intestinal epithelial cells and intestinal barrier. Studies have shown that [32] emodin at 5μmol/mL is the optimal concentration to promote the growth of IEC-6 cells in rat small intestinal crypt epithelial cells in hypoxia environment, and emodin can up-regulate the expression of autophagy related genes of Beclin-1 and LC3,especially within 6 hour. These results indicate that emodin can protect gastrointestinal mucosal barrier by enhancing autophagy in low temperature environment. Wang Yu et al. [33] found that emodin can significantly improve the activity of diamine oxidase in intestinal mucosa of rats with acute radiation colitis. This enzyme exists in the upper villus cells of intestinal mucosa of humans and mammals, and has the function of protecting intestinal mucosa and promoting the repair and healing of damaged intestinal mucosal cells.

2.6 Diuretic action

Lu Yin et al. [34] found that both ethanol extract and water extract of Rhubarb could improve the urine excretion rate of rats, especially ethanol extract, which could not only increase the excretion of Na^+, $K^+$and Cl^-,but also significantly increase pH value. The results indicated that ethanol extract of Rhubarb had obvious diuretic effect compared with water extract. Bao Junqiang [35] found through experiments that the total anthraquinone of rhubarb in medium and high dose groups could effectively increase the urine volume of rats at 24h, and the urine Na^+ concentration and urine osmotic pressure decreased with the increase of urine volume, while the low dose group only increased the urine volume at 24h, and had no effect on the urine ion volume. The total anthraquinone of rhubarb can down-regulate the expression of Aquaporin 2(AQP2) and Aquaporin 2(AQP2) in the kidney of rats, but does not affect the content of Na^+,K^+,Cl^- in blood and Na^+in urine, which is different from other commonly used diuretics. Studies have shown that [36] emodin and rhein both have strong inhibitory effects on Na^+-K^+ -ATPase activity in rabbit kidney medulla, and the inhibitory effects between them are competitive. This enzyme is a regulatory enzyme, and its decreased activity inhibits the reabsorption of Na^+ by renal tubules, reduces the exchange of H^+-Na^+, promotes the exchange of K^+-Na^+, increases the excretion of Na^+ and K^+ in urine, and plays a diuretic role.

2.7 Nephroprotective effect

Chen Yakun et al. [37] established a streptozotocin induced diabetic kidney fiber rat model and found that compared with the model group, Low, medium and high doses of rhein (62.5μg/ml, 125μg/ml, 250μg/ml) could reduce 24h urinary protein, blood creatinine, blood urea nitrogen, toll-like receptor 4, rat transformational growth factor-βand connective tissue growth factor of diabetic model rats, and the most significant reduction was found in rhein high dose group. Moreover, the proliferation of renal interstitial fibrosis and the degree of glomerular atrophy were improved in the low, medium and high dose groups, indicating that rhein can effectively improve the level of renal function indicators in diabetic rats, inhibit the expression of inflammatory secretion-induced protein, protect endothelial cells, and then improve renal fibrosis. Gu Mingjia et al. [38] used unilateral ureteral ligation to induce Chronic kidney disease mouse model and TGF-β1stimulated human renal tubular epithelial cell (HK-2) model. It was found that chrysophanol can significantly improve renal dysfunction, alleviate renal pathological changes, and reverse the elevation of renal fibrosis markers, Effectively inhibit the production of TNF-α,IL-6 and IL-1β,inhibit the activation of NF-κB and the expression of NKD2 protein. The results of in vitro study are consistent with those of animal experiment. The use of HK-2 cells overexpressing NKD2 also demonstrated that overexpression of NKD2 significantly weakened the antifibrotic effect of chrysophanol. In conclusion, chrysophanol can effectively ameliorate renal fibrosis by inhibiting the NKD2/NF-κB pathway. Chrysophanol may prevent Chronic kidney disease by directly inhibiting the expression of NKD2 in the kidney. Gao Bingpeng et al. [39] found that emodin could reduce the damage of renal tubular epithelial cells caused by calcium oxalate crystals by regulating ROS and NLRP3 inflammatory pathway. Emodin at 10μmol/L can significantly reduce the rise of reactive oxygen species (ROS) caused by calcium oxalate crystals,and can also significantly inhibit the expression of NLRP3,IL-18,IL-1β,Pro-caspase-1 and other related inflammatory factors.

2.8 Hepatoprotective effect

Li Jifeng et al. [40] found through experiments that emodin methyl ether could significantly improve liver tissue necrosis and cell inflammatory infiltration in mice with drug-induced liver

injury induced by acetaminophen. Compared with the model group, the expressions of serum aspartate transferase, alanine transferase, liver malondialdehyde, high mobility group protein B1,NLRP3,Caspase-1 protein and mRNA in emodin methyl ether low and high dose groups were significantly decreased, while the expressions of IL-1βand IL-18mRNA were significantly decreased. Hepatic glutathione activity was significantly increased. Pan Guangtao et al. [41] found that emodin can improve liver function and liver pathological changes, regulate liver oxidative stress, alleviate liver cell apoptosis, reduce the secretion of pro-apoptotic factors, and increase the expression of anti-apoptotic factors. The mechanism may be related to regulating oxidative stress and reducing hepatocyte apoptosis. Qin Lushan et al. [42] prepared a rat model of acute liver injury using carbon tetrachloride. Except the blank group and the model group, rats in all groups were given total anthraquinone and total tannin of rhubarb by intragastrically (5.40g/kg and 14.69g/kg).Results: Compared with blank group, AST, ALT and HA levels were significantly increased in blank + high dose total tannin group. Compared with the model group, AST, ALT,ALP, HA, and TGF-β1 in the model+low-dose total anthraquinone group, model+high-dose total anthraquinone group, and model+low-concentration total tannin group were significantly reduced. The pathological results were as follows: slight swelling of hepatocytes in model+high-dose total anthraquinone group. Steatosis and fragment necrosis occurred around the central vein in the blank+high-dose total anthraquinone group. The pathological damage of model+low dose total anthraquinone group was improved. These results indicate that total anthraquinone and total tannin of rhubarb have protective and harmful effects on liver. High dose of total tannin can affect liver injury to some extent. At the same dose, total anthraquinone of rhubarb had better liver protection than total tannin.

2.9 Other

Rhubarb also has the functions of regulating immunity, lowering blood lipids, antioxidation and anti-aging. Emodin can induce cell apoptosis, reduce cell proliferation activity, increase the percentage of $CD3^+$, $CD4^+$and $CD4^+/CD8^+$in T lymphocytes in peripheral blood, improve the index of immune organs, and improve its immune function [43].Total anthraquinone of rhubarb reduces blood lipids and biochemical indicators in a dose-dependent manner, delays liver damage caused by excessive fat intake, and improves lipid metabolism disorder in the body to prevent atherosclerosis [44]. Emodin inhibits the expression of inflammatory cytokines by regulating Nrf-2/HO-1 and MAPK signaling pathways, and down-regulates ROS to play an antioxidant role [45]. The anti-aging effect of rhubarb is mainly related to the effective elimination of free radicals and other ROS, and the inhibition of the synthesis of lipid peroxide [46].

3. Conclusion

Rhubarb is a pure natural Chinese medicine with a long history of medicinal use. It is one of the commonly used traditional Chinese medicine in clinical practice. It has the effects of purging the lower part of the body, clearing heat and fire, cooling blood and detoxicating, removing blood stasis and dredging the meridians. At present, scientific research on rhubarb is increasing. Relevant research shows that rhubarb contains a variety of chemical components, including but not limited to: anthraquinones, polysaccharides and tannins. To sum up, we found that rhubarb has a variety of pharmacological effects, and is suitable for clinical treatment of tumor, antiviral, anti-inflammatory, blood disease, gastrointestinal disease, kidney disease, liver disease, and other diseases, and the curative effect is satisfactory. In recent years, with the continuous in-depth study of modern medicine, the pharmacological effects of rhubarb have achieved remarkable results. Its various components can be obtained by refining and other methods, which can effectively improve the

clinical efficacy, and is worthy of promotion and application.

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