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Research on the Pharmacology and Toxicity of Rhubarb Anthraquinones in the Body

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Abstract. Rhubarb, as an important traditional Chinese medicine (TCM) with a long history, has core active ingredients known as anthraquinone compounds (such as aloe-emodin, rhein, chrysophanol, etc.). These have been confirmed to possess broad biological activities, exerting significant regulatory effects in multiple key systems of the human body, including the digestive, hepatic, renal, and cardiovascular systems. However, clinical precision medication strategies and long-term safety assessments under different preparation forms and individual variability backgrounds still require more substantial data support. This paper systematically summarizes the chemical basis, in vivo pharmacokinetic characteristics, and core pharmacological mechanisms of rhubarb anthraquinones in the digestive, hepatic, renal, and cardiovascular systems. It concurrently evaluates their clinical application efficacy in related indications like constipation and hepatobiliary diseases, alongside potential adverse reaction risks. The review results clearly elucidate the intrinsic relationship between the "structure-metabolism-activity/toxicity" of rhubarb anthraquinones, providing crucial theoretical support for precise and rational clinical medication. The integrated pharmacological and toxicological evidence in this study lays a scientific foundation for the subsequent development of highly effective and low-toxicity rhubarb-derived drugs. Future research needs to focus on in-depth analysis of the pharmacodynamic material basis of anthraquinone monomers, deep exploration of structural modifications of anthraquinones, and the construction of long-term toxicity prediction models based on metabolomics, to promote the high-quality development and international application of rhubarb resources within the modern TCM system.

Keywords: Rhubarb, anthraquinones, organ effects, pharmacological mechanism, cathartic effect

1. Introduction

Rhubarb is the dried root or rhizome of Rheum palmatum L., Rheum tanguticum Maxim. ex Balf., or Rheum officinale Baill. (Polygonaceae), primarily produced in Qinghai, Gansu, and Sichuan regions of China. Rheum palmatum and Rheum tanguticum are collectively called "Northern Rhubarb," while Rheum officinale is called "Southern Rhubarb." This herb is cold in nature and bitter in taste, acting on the spleen, stomach, large intestine, liver, and pericardium meridians. It

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possesses effects such as purging accumulation, clearing heat and purging fire, cooling blood to resolve toxins, stopping bleeding, dispelling stasis to unblock menstruation, draining dampness to reduce jaundice, and breaking down phlegm masses. Since ancient times, it has been widely used to treat constipation due to excess heat accumulation, hematemesis and epistaxis due to blood heat, red swollen eyes and sore throat, gum swelling and pain, abscesses and boils, intestinal abscess with abdominal pain, amenorrhea due to blood stasis, postpartum blood stasis, traumatic injuries, dysentery due to damp-heat, jaundice with reddish urine, strangury syndrome, edema, burns and scalds, as well as stubborn phlegm and blood stasis syndromes [1]. The Shennong Bencao Jing (Divine Farmer's Materia Medica Classic) classified it as a lower-grade herb, stating it "masters breaking blood stasis, amenorrhea with alternating chills and fever, breaks concretions and conglomerations, accumulations and gatherings, lingering rheum and undigested food, cleanses the stomach and intestines, eliminating the stale to bring forth the new." Modern pharmacological studies indicate that the active components of rhubarb mainly include anthraquinones, tannins, polysaccharides, organic acids, and volatile oils. Among these, anthraquinone compounds (Anthraquinones) are the core pharmacologically active substances, accounting for 3%-5% of the dry weight, with their content and types varying significantly depending on the species, origin, and processing methods. Anthraquinones possess both therapeutic potential and toxic risk, characteristic particularly prominent in metabolic organs like the liver and kidneys. With the development of modern drug analysis techniques, research has found that anthraquinone components exhibit multi-organ targeted distribution characteristics in the human body, exerting complex effects in the digestive, circulatory, and urinary systems by regulating inflammatory pathways, oxidative stress, apoptosis, and other processes. In recent years, increased reports of adverse reactions such as rhubarb anthraquinone hepatotoxicity, nephrotoxicity, and "cathartic colon" highlight the urgency of in-depth research into their organ-specific mechanisms of action and safety boundaries. This article focuses on the chemical structural characteristics, in vivo pharmacokinetics, and bidirectional regulatory effects of rhubarb anthraquinone components in the liver, intestines, cardiovascular system, and kidneys. It systematically elaborates their multi-target, multi-organ mechanisms of action and proposes safety optimization strategies based on clinical practice, providing a scientific basis for advancing the precise use of rhubarb.

2. Chemistry and metabolism of rhubarb anthraquinones

Rhubarb anthraquinones mainly include two types: free and conjugated. Free anthraquinones primarily include rhein, emodin, aloe-emodin (AE), chrysophanol, isoemodin, physcion, etc. Conjugated anthraquinones are mainly glycosides formed by the combination of free anthraquinones with sugar groups, such as sennosides, which are also the main substances responsible for rhubarb's cathartic effect. After oral administration, conjugated anthraquinones are hydrolyzed into aglycones by intestinal flora (e.g., β-glucosidase), absorbed into the blood, and enter the liver via the portal vein. In the liver, they undergo hydroxylation, methylation, and glucuronidation reactions catalyzed by hepatic microsomal enzymes (CYP450), forming water-soluble metabolites. For instance, emodin is metabolized by UDP-glucuronosyltransferase (UGT) into emodin-3-O-glucuronide, while aloe-emodin readily forms sulfate conjugates. The metabolites are primarily excreted via the kidneys, partially reabsorbed through the enterohepatic circulation, and a small amount is excreted in feces [2]. Notably, the significant hepatic first-pass effect influences their bioavailability, and differences in metabolic rates among different anthraquinone components lead to varying accumulation concentrations in organs, which is closely related to their tissue-selective toxicity.

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Rhubarb anthraquinones exhibit both significant therapeutic effects and potential toxicity in liver regulation, necessitating further optimization of medication strategies for safe application.

3. Mechanisms of action of rhubarb anthraquinones in major human organs

3.1. Liver

The action of rhubarb anthraquinones on the liver is a "double-edged sword," demonstrating significant pharmacological potential alongside potential toxic risks. On one hand, anthraquinones play an effective regulatory role in hepatic lipid metabolism. Liu Yuanyang et al., through studies on NAFLD mice, zebrafish, etc., found that these compounds exert a very obvious therapeutic effect on non-alcoholic fatty liver disease (NAFLD) through multi-target, multi-pathway mechanisms, lowering total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) content while increasing high-density lipoprotein (HDL) content, reducing lipid deposition and steatosis in NAFLD mice. They also improve glucose tolerance and insulin resistance in obese mice via glucose and insulin metabolic pathways [3]. Simultaneously, Feng Liu et al., through research on a carbon tetrachloride (CCl4)-induced liver fibrosis rat model, found that emodin can also block the intracellular Smad signaling pathway of transforming growth factor-β (TGF-β), reducing the expression of fibronectin and type I collagen in the extracellular matrix of hepatic stellate cells, thereby inhibiting their activation and preventing liver fibrosis to some extent [4]. Free anthraquinones like rhein can exert antioxidant effects, scavenging free radicals and enhancing the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) [5]. Emodin can even accumulate reactive oxygen species (ROS) in HepG2 cells, affecting ATP synthesis, thereby inhibiting the growth of hepatocellular carcinoma HepG2 cells. On the other hand, large doses of rhubarb can cause damage to liver cells. Studies show that the -8-O-glucoside in chrysophanol can impair mitochondrial function; long-term, high-dose emodin inhibits glutathione (GSH) synthesis in cells, preventing the timely clearance of harmful substances like free radicals and heavy metals in the liver [4]; the carboxyl group in rhein can induce hepatocyte apoptosis and even cause drug-induced liver injury [6]. Rhubarb anthraquinones exhibit both significant efficacy and potential toxicity in liver regulation, requiring further optimization of medication strategies for safe application.

3.2. Intestines

In the intestines, free rhubarb anthraquinones can effectively enhance intestinal function through multi-layered molecular mechanisms, demonstrating their potential value in constipation treatment. Aloe-emodin, rhein, and chrysophanol among rhubarb anthraquinones are the main substances responsible for softening feces. Through research on rats, Lv found that free rhubarb anthraquinones can upregulate vasoactive intestinal peptide (VIP) expression, activate the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway, and stimulate cystic fibrosis transmembrane conductance regulator (CFTR) expression, leading to hyperosmolarity in the colonic lumen [7]. Due to the osmotic gradient, water shifts into the colonic lumen. To accommodate this water shift, the expression levels of aquaporins AQP3, AQP4, and AQP8 are passively upregulated, improving gastrointestinal motility and promoting fecal excretion [5].

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3.3. Cardiovascular system

Rhubarb anthraquinones also play a very important role in the cardiovascular system. Studies show that rhubarb anthraquinone compounds have significant therapeutic effects on myocarditis, atherosclerosis, hyperlipidemia, hypertension, and thrombosis [8]. Emodin can inhibit the translation of ribosomal L32 by inhibiting the protein kinase B (AKT) and protein signaling pathways, hindering the synthesis of Coxsackievirus group B type 3 (CVB3), a major subtype causing viral myocarditis, thereby improving viral myocarditis. Simultaneously, emodin can downregulate levels of inflammatory factors such as interleukin-23 (IL-23) and IL-17 in cardiomyocytes. Emodin can also downregulate hydroxymethylglutaryl-CoA (HMG-CoA) reductase, reducing cholesterol synthesis to achieve lipid-lowering and anti-atherosclerotic effects. Furthermore, modern research indicates that emodin also has very good therapeutic effects on diabetic cardiomyopathy, myocardial toxic injury, myocardial hypertrophy, and other myocardial diseases [8].

3.4. Kidneys

The effects of rhubarb anthraquinones on the kidneys also present a coexistence of pharmacology and toxicity. Rhubarb can reduce intestinal absorption, promote the synthesis of urea nitrogen into protein, increase the excretion of urea and creatinine, reducing toxic effects on the kidneys. It can also exert antioxidant effects to alleviate the oxidative state of the kidneys. Additionally, rhubarb inhibits the expression of renal transforming growth factor-β1 (TGF-β1), reducing the synthesis of extracellular matrix and delaying renal fibrosis [9]. However, anthraquinones at ultra-high doses can cause a certain degree of renal injury, manifested as renal tubular epithelial cell damage, posing a risk of "aristolochic acid-like nephropathy" [10]. Therefore, although rhubarb anthraquinones show significant potential in renal protection, dosage control is crucial, requiring a balance between efficacy and toxicity risks.

4. Current clinical application status and safety optimization strategies

Research and development of anthraquinone drugs are currently being conducted in multiple clinical fields. Among them, anti-tumor drugs represent the frontier of research in this area and have achieved significant results. The research team of Yuanyuan Liu et al., through studies on the anthraquinone drug doxorubicin (DOX), designed a responsive multifunctional nanosystem that combines immunotherapy and chemotherapy by targeting immune cells and cancer cells to treat breast cancer. The prodrug HA-DOX, formed by doxorubicin and hyaluronic acid (HA), was encapsulated in a carrier composed of the anti-tumor immunomodulator R848 and poly-L-histidine (PHIS) to form nanoparticles. PHIS ionizes around pH 6.5 (close to the pH of the tumor microenvironment), changing the properties of this material from hydrophobic to hydrophilic, thereby triggering the release of R848 to exert immunomodulatory effects. The hydrazone bond in HA-DOX breaks at about pH 5.5 (the pH of endosomes/lysosomes), accelerating the release of DOX to exert cytotoxic effects, thus achieving the goal of cancer treatment [11]. Kai-Wei Lin et al. found through research that the anthraquinone derivative 1-hydroxy-3- [(E)-4-(piperazine-diyl)but-2-enoxy]-9,10-anthraquinone difluoroacetate triggers ROS generation-mediated autophagy and necrotic cell death, providing valuable insights for finding new anti-tumor drugs for cancer treatment [12]. Besides anti-tumor drugs, anthraquinones have also made progress in research on antibacterial drugs. Jiang et al. found in their study that AE significantly inhibited the hemolytic activity of Staphylococcus aureus supernatant in a dose-dependent manner when co-cultured with

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the bacteria. AE can bind to the main toxin α-toxin produced by S. aureus through hydrogen bonding and hydrophobic interactions. By establishing a mouse S. aureus model for comparison, they further confirmed that AE can effectively protect patients infected with S. aureus [13]. Similarly, there are also some problems with the current application of anthraquinone drugs. Ningning Yang et al. found through research that the use of anthraquinone drugs is closely related to the development of melanosis coli. Research shows that the cathartic effect of anthraquinone drugs can cause damage or even death to intestinal epithelial cells. These cells are immediately phagocytosed by nearby macrophages. Macrophages produce tumor necrosis factor (TNF), which has a toxic effect on capillaries, subsequently damaging neurons and inducing cell swelling and breakdown. Then, under the action of heterolysosomes in macrophages, apoptotic bodies are converted into lipofuscin. These lysosomes migrate through the basement membrane into the mucosal layer. As a result, brown or black pigmentation appears on the mucosa, leading to melanosis coli [14]. Furthermore, Niccolò Lombardi, through case-control analyses and observational studies like randomized observational experiments, found that the use of anthraquinone drugs also increases the risk of colon cancer. They observed that the proportion of colon cancer patients was significantly higher among specific populations and high-dose users, further confirming a close link between anthraquinone drug dosage and risk [15]. In summary, the current research and development of anthraquinone drugs still require further clinical trials. How to structurally modify anthraquinones to reduce toxicity, control dosage, monitor toxicity indicators, and strengthen surveillance for contraindications have become essential issues to resolve in the anthraquinone drug R&D process.

5. Conclusion

This paper systematically reviews the core chemical structural characteristics and in vivo metabolic pathways of rhubarb anthraquinone drugs, and deeply analyzes their key pharmacological mechanisms of action in multiple organs, including the digestive system, liver, kidneys, and cardiovascular system. The study also comprehensively evaluates the clinical application efficacy and potential adverse reactions of these substances in indications such as constipation and hepatobiliary diseases, with particular attention to their hepatorenal toxicity risks. It systematically elucidates the material basis and action network behind the seemingly contradictory yet critically important characteristic of rhubarb anthraquinones—"exerting significant multi-organ pharmacological activity" while "harboring hepatorenal organ toxicity"—providing vital theoretical basis and scientific reference for clinically precise control of medication indications, dosage, and treatment duration to achieve safe, effective, and rational application. However, due to the current relative scarcity of detailed data on the refined efficacy differences of rhubarb anthraquinone drugs under different preparation forms (such as decoctions, extracts, monomers) and on the long-term safety in broad populations (especially those with significant individual differences), the existing findings still require refinement. Based on the above analysis, future research should focus on the following directions: The primary task is to deeply conduct research on the structural modification and optimization of anthraquinone compounds, aiming to reduce their toxicity to organs like the liver and kidneys while maximizing the retention or enhancement of their core therapeutic activities (such as efficacy in the digestive, hepatic, and immune systems). This is the core pathway to promote their safe and rational application. Simultaneously, deepening research on the pharmacodynamic material basis of anthraquinone monomers and the synergistic/antagonistic effects of complex components, as well as exploring long-term toxicity prediction models based on new technologies like metabolomics, are also crucial. These efforts will collectively work towards

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fully unlocking the therapeutic potential of rhubarb resources, ultimately serving to more effectively safeguard human life and health security.

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