Recent progress in the study of chemical constituents and pharmacological effects of Cassia Semen

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Abstract:

Cassia Semen is the mature seed of the leguminous plant Cassia obtusifolia L. or Cassia tora L. They are known for clearing heat, improving vision, and promoting bowel movements. Modern chemical research has shown that Cassia Semen is rich in anthraquinones, naphthopyranones, and fatty acids, among other chemical components. Pharmacological studies have demonstrated various effects of Cassia Semen, including lowering blood lipid levels, reducing blood pressure, regulating blood glucose, promoting bowel movements, protecting the liver, improving vision, exhibiting antioxidant and anti-aging properties, inhibiting bacteria, and exerting anti-cancer effects. By reviewing recent domestic and international modern research on Cassia Semen, this article provides a literature review on its chemical constituents, pharmacological effects, and recent progress in clinical studies. The aim is to offer references for the rational clinical application of Cassia Semen, the mechanisms of its pharmacological and toxicological effects, as well as the modern development of traditional Chinese medicine.

Keywords: Cassia Semen, Chemical composition, Pharmacological effects

1. Introduction

According to the 2020 edition of the Chinese Pharmacopoeia, Cassia Semen is the mature seed of the leguminous plant Cassia obtusifolia L. or Cassia tora L. It tastes sweet, bitter, and slightly salty, with a slightly cold property. It belongs to the liver and large intestinal meridians. Cassia Semen is known for its effects in clearing heat, improving vision, and moistening the intestines for relieving constipation. It is commonly used to treat red and painful eyes, excessive tearing, headaches, dizziness, blurred vision, and constipation [1]. Cassia Semen is distributed in most regions of China, such as Zhongning in Ningxia, Bengbu, Wuhu, Heqing, and Hefei in Anhui, Wenjiang, Jintang, and Shiqi in Sichuan, Qingyuan, Gaoyao, and Deqing in Guangdong, and Jianqiao in Zhejiang.

Studies have shown that Cassia Semen mainly contains anthraquinones, ketones, amino acids, and fatty acids, among other chemical components. It exhibits various biological activities, including lowering blood pressure, reducing blood lipid levels, protecting the liver, inhibiting platelet aggregation, and antimicrobial effects. The "Shennong Bencao Jing" (Divine Farmer's Materia Medica) states, "It treats green blindness, excessive tearing, red and white membranes of the eyes, redness, pain, and excessive tearing. Long-term use benefits the essence and brightness." The "Rihua Zi Bencao" (Materia Medica of Rihua Zi) records, "It assists the liver qi and benefits the essence. When mixed with water, it can be applied to reduce swelling and pain. Applied to the temples, it treats headaches. It can also be applied to the brain and heart to stop nasal congestion. It is used as a pillow to treat wind-induced headaches and improves vision, surpassing black beans." These historical records highlight the medicinal value of Cassia Semen since ancient times. In recent years, scholars from various countries have made continuous progress in studying the active components and medicinal value of Cassia Semen. Therefore, this article will provide an overview of the research literature on Cassia Semen in the past eight years, as a reference for further in-depth studies.

2. Chemical Composition of Cassia Semen

The chemical composition of Cassia Semen includes various components, primarily anthraquinone compounds such as rhein, emodin, aloe-emodin, rhein-8-glucoside, and emodin-8-methyl ether, which make up approximately 1% of the total content. Additionally, Cassia Semen contains components such as naphthopyrone, glycosides, fatty acids, polysaccharides, amino acids, and inorganic elements. Additionally, Cassia Semen is also a substance rich in active ingredients and is considered a homologous material for food-medicine. Furthermore, Cassia Semen is a substance rich in active ingredients, with abundant nutrients such as proteins, vitamins, polysaccharides, and minerals.

2.1 Anthraquinones

Cassia Semen contains a large amount of anthraquinone compounds. The total content of anthraquinones in raw Cassia seeds is about 1.2%, while in small Cassia seeds, it is about 1.1%, with an average range of 0.85% to 1.25%[2]. The anthraquinone compounds found in Cassia Semen mainly include chrysophanol, physcion, obtusifolin, chryso-obtusin, obtusin, aruantio-obtusin, emodin, aloe-emodin, alatenin-1-O-β-D-glucopyranoside, 1-desmethylchryso-obtusin, chryso-obtusin 2-O-β-D-glucoside, glucosyl obtusifolin, glucosyl chryso-obtusin, glucosyl aruantio-obtusin, physcion-8-O-β-D-glucoside, 1-desmethyl obtusin, chrysophanol-10,10'-anthraquinone, emodin-8-methyl ether, chrysophanol-9-anthraquinone, chrysophanol-1-O-triglucoside,chrysophanol-1-O-tetraglucoside, and obtusifolin-2-O-β-D-glucoside[3].

2.2 Naphthopyrone Compounds

Cassia Semen contains various naphthopyrone compounds, including rubrofusarin, cassiaside, toralactone, torosachrysone, isotoralactone, rubrofusarin-6-O-gentiobioside, cassialactone, and 2,5-dimethoxybenzoquinone[4].

2.3 Fatty Acid Compounds

Cassia Semen contains approximately 4.65% to 5.79% oil, with the main components being linoleic acid[5], oleic acid, palmitic acid, linolenic acid, dihomo-gamma-linolenic acid, (Z)-9-octadecenoic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, and lignoceric acid. It also contains methyl hexadecanoate (palmitic acid methyl ester), methyl linoleate, methyl oleate, methyl stearate (stearic acid methyl ester), ethyl oleate, methyl arachidate (peanut acid methyl ester), and methyl behenate (montanic acid methyl ester)[6].

2.4 Polysaccharide Compounds

The polysaccharide compounds in Cassia Semen are mostly water-soluble polysaccharides composed of galactose and mannose. The structure of the polysaccharides consists of a main chain of mannose linked through 1-4 connections, with a galactose molecule attached to the sixth carbon atom of every sixth mannose, forming a galactomannan[7].

2.5 Amino Acids and Inorganic Elements

Cassia Semen contains amino acids such as cysteine, gamma-hydroxy arginine, histidine, and galactomannan with glucose, galactose, mannose, xylose, and rhamnose. It also contains amino acids like cysteine, aspartic acid, gamma-hydroxy arginine, and eight inorganic elements, including zinc, copper, manganese, iron, magnesium, calcium, sodium, and potassium.

2.6 Unsaponifiable Compounds

Cassia Semen contains hexadecane to triacontane, cholesterol, stigmasterol, beta-sitosterol, and 1,3-dihydroxy-3-methylanthraquinone. Small amounts of malvalic acid, sterculic acid, and campesterol are also present in the oil of Cassia Semen.

3. Pharmacological Effects

Cassia Semen, also known as cassia seeds, has various pharmacological effects and is widely used in drug development. According to statistics, more than 80 Chinese patent medicines containing Cassia Semen are included in the "Chinese Pharmacopoeia" and "Drug Standards of the Ministry of Health"[8]. Modern pharmacological studies have shown that the active ingredients in Cassia Semen have effects such as lowering blood pressure, reducing blood sugar, protecting the liver, lowering blood lipids, and having antioxidant, antibacterial, and anti-cancer effects.

3.1 Hepatoprotective Effect

Cassia Semen has a significant hepatoprotective effect. Zhang Bo et al. [9]conducted experiments on mice using total anthraquinone extract from Cassia Semen to investigate its protective effect on immune-mediated liver injury. The results showed that compared to the model group, the low and high-dose groups of total anthraquinone extract from Cassia Semen significantly reduced ALT, AST, IL-6, TNF-α, and CD4+/CD8+ ratio levels. Furthermore, compared to the model group, the low and high-dose groups of total anthraquinone extract from Cassia Semen significantly increased the levels of CD4+ and CD8+ lymphocytes. The severity of liver cell damage in mice treated with total anthraquinone extract from Cassia Semen was significantly reduced, indicating a protective effect on immune-mediated liver injury in mice. Pu et al.[10]used lipopolysaccharide to induce acute liver injury in rats and found that total anthraquinone extract from Cassia Semen could inhibit the activation of high mobility group protein B1 (HMGB1), Toll-like receptor 4 (TLR4), and nuclear factor kappa-B (NF-κB) signaling pathways, alleviate inflammation, and exert hepatoprotective effects. Through research, Wan Min [11] demonstrated that both raw and stir-fried Cassia Semen have significant protective effects against ConA-induced immune-mediated liver injury in mice. They can both alleviate drug-induced liver injury in mice by reducing the activity of ALT and AST while increasing the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in liver tissue, thus reducing liver damage in mice. Shijinggan et al. conducted a study using total

anthraquinone extract from Cassia Semen as the main drug and preparing Cassia Semen dispersible tablets with suitable excipients. They established an HPLC fingerprint of Cassia Semen dispersible tablets and determined their AST and ALT efficacy indicators. The grey relational analysis method was used to study the spectral efficacy relationship of Cassia Semen dispersible tablets in protecting against acute liver injury in rats. The results showed that the hepatoprotective effect of Cassia Semen dispersible tablets on acute liver injury in rats is related to the synergistic or antagonistic effects of multiple active ingredients depending on the dosage, thus confirming the hepatoprotective effect of total anthraquinone extract from Cassia Semen.

3.2 Hypolipidemic Effect

Cassia Semen has a significant hypolipidemic effect. Zhu Zhouliang et al. [12] used solvent extraction to prepare ethyl acetate extract (JMZ-EA) and residue extract (JMZ-Residue) from Cassia Semen. They established fingerprint profiles and a high-fat diet-induced hyperlipidemia rat model to study the effects of Cassia Semen extracts on blood lipid and liver and kidney function in hyperlipidemic rats. The study found that JMZ-EA and JMZ-Residue significantly reduced serum triglyceride (TG) levels, indicating a lipid-regulating effect. Additionally, JMZ-EA also reduced LDL-cholesterol (LDL-C) levels. Li Yujing et al. [13] investigated the therapeutic effect and mechanism of action of anthraquinone glycosides from Cassia Semen on nonalcoholic fatty liver disease (NAFLD) by studying the core enzyme peroxisomal acyl-coenzyme A oxidase 1 (ACOX1) and carnitine palmitoyltransferase 1A (CPT1A). Through rat experiments, they concluded that anthraquinone glycosides from Cassia Semen can promote the excretion of liver fat droplets by increasing the mRNA and protein expression levels of key enzymes ACOX1 and CPT1A in the beta-oxidation pathway of fatty acids, ultimately improving liver function. Guo Huan et al. [14] established a nutritional hyperlipidemia rat model by feeding a high-fat diet. They measured the levels of triglycerides (TC), total cholesterol (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and atherosclerosis index (AI) in the serum, as well as TC, TG, malondialdehyde (MDA), and total superoxide dismutase (T-SOD) in liver tissue. Using GraphPad Prism5.0 software to fit dose-response curves, they evaluated the dose-response relationship of Cassia Semen decoction in reducing blood lipids in hyperlipidemic rats and the lipid content in liver tissue. The study concluded that Cassia Semen decoction showed a good sigmoidal dose-response relationship, as it reduced TC, TG, LDL-C, and AI while increasing HDL-C in the serum of hyperlipidemic rats. It also reduced TC and TG in liver tissue, demonstrating a good hypolipidemic effect.

3.3 Antihypertensive Effect

Cassia Semen extract also has therapeutic effects in reducing blood pressure. Li Yanwen et al. [15] studied the effects of Cassia Semen water extract on blood pressure and the renin-angiotensin-aldosterone system (RAAS) related indicators in a hypertension rat model. In the hypertensive state, the RAAS system is activated, and Cassia Semen water extract inhibits the RAAS system by reducing AngII, renin, and aldosterone levels. The ability to reduce these three active components is comparable to captopril. Ye Quanying et al. [16] constructed a hypertension rat model by administering N-nitro-L-arginine methyl ester orally and treating the rats with Cassia Semen water extract. They analyzed the protein and gene expression of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) in renal tissue using immunohistochemistry and real-time quantitative PCR. The results showed that the Cassia Semen water extract effectively reduced the mean arterial, diastolic, and systolic pressure of the hypertensive rats after four weeks of treatment ($P < 0.05$). It also improved the liver and kidney markers, lipid distribution, and oxidative status.

Additionally, the Cassia Semen water extract significantly reduced the activity of angiotensin-converting enzyme in the liver and kidney of hypertensive rats ($P < 0.05$). In the kidneys of rats treated with Cassia Semen water extract, both the gene and protein expression of eNOS were significantly higher than in the hypertensive model group. These results indicate that Cassia Semen water extract has significant antihypertensive potential, and its mechanism includes upregulating the expression of eNOS, antioxidant effects, and inhibition of angiotensin-converting enzyme.

3.4 Eye-protective Effect

According to ancient texts, Cassia Semen has the effect of clearing heat and improving vision. Tang Zihan [17] used network pharmacology and molecular docking techniques to explore the mechanism of Cassia Semen in treating dry eye. They obtained the effective ingredients and targets of Cassia Semen through TCMSP and UniProt. They obtained the target genes of the dry eye through disease databases such as DrugBank, OMIM, GeneCards, and Disgenet. The intersection of Cassia Semen and dry eye targets was analyzed using Venny 2.1.0, and a Venn diagram was plotted. Protein-protein interaction networks and “drug-ingredient-disease-target” topological maps were constructed using String and Cytoscape. Metascape, the KEGG database, and Pathview were used for GO functional analysis, KEGG pathway analysis, signal pathway annotation, and visualization of the targets. Molecular docking was used to verify the possibility of binding between the core components of the herbal medicine and key target proteins. The results showed that Cassia Semen exerted therapeutic effects on 17 dry eye targets, including TNF, TP53, ESR1, and IL1B,

through 14 effective ingredients. It exerted anti-inflammatory, anti-apoptotic, antioxidant, and hormone-regulating effects through multiple signaling pathways such as MAPK and p53, thereby treating dry eye. He Yu [18] et al. used the HLE-B3 cell line, a human lens epithelial cell line, for in vitro culture. They used different concentrations of Cassia Semen total alkaloids (CSTA) on HLE-B3 cells to screen for the most suitable treatment concentration. They observed the protective effect of CSTA on cell oxidative damage, providing new ideas for developing drugs for cataract treatment.

3.5 Antioxidant Effect

Li Lei et al. [19] analyzed the antioxidant mechanism of Cassia Semen using network pharmacology. They found that Cassia Semen exerted antioxidant effects through 11 components such as emodin, aloe emodin, and stigmasterol, acting on 34 targets including TP53, MYC, CASP3, ESR1, and JUN through multiple pathways. Lin Shuihua et al. [20] studied the content and antioxidant activity of free anthraquinones and total anthraquinones in different processed products of Cassia Semen using spectrophotometry and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method. The results showed that different processed products of Cassia Semen exhibited antioxidant activity, and among different processing methods, stir-frying with martial fire for 3 minutes could achieve the highest content of free anthraquinones and the strongest antioxidant activity. Cai Juntai et al. [21] found that the peptide component UF2h (2h hydrolysis product) and its active peptides isolated from the hydrolysis of Cassia Semen could serve as antioxidants when studying the oxidative activity and stability of Cassia Semen hydrolysates. Long Yuanchun et al. [22] determined the in vitro antioxidant activity of total anthraquinones from Cassia Semen from different origins. They found that the antioxidant activity of Cassia Semen from India was the lowest, while the Cassia Semen from Hebei had the strongest antioxidant activity. Li Xiaofang [23] studied the antioxidant activity of the complex of Cassia Semen and tangerine by selecting five ratios of the samples to study the scavenging effect on ·OH, O2 - ·, and the reducing power. The results showed that the complex of Cassia Semen and tangeretin exhibited antioxidant activity. The antioxidant activity increased with the concentration of the complex, and the scavenging capacity was stronger than that of a single flavonoid.

3.6 Antibacterial Effect

Cassia Semen has antibacterial effects against various bacteria. Green silver nanoparticles synthesized using Cassia Semen extracts have been shown to have strong antibacterial activity [24]. Secondary metabolites from other parts of the plant, such as seeds, flowers, and bark, have been reported to possess antibacterial and antifungal activities [25].

3.7 Laxative Effect

Li Fengqing et al. [26] found through their research that Cassia Semen contains various anthraquinone components. Cassia Semen has pharmacological effects such as liver-clearing and vision-improving, as well as intestinal moisturizing and laxative effects. The differences in the substances that cause non-laxative effects in Cassia Semen from different sources are due to variations in the content of emodin, chrysophanol, aloe-emodin, and rhein. Wu Suhui et al. [27] found in their study that Cassia Semen significantly reduced the duration of starvation tolerance in silkworms. The anthraquinone substances present in Cassia Semen can inhibit the absorption of colon luminal water, increase the water content in the intestinal lumen, and cause diarrhea. Gao Wa et al. [28] found through their research that Cassia Semen decoction contains various compounds, among which a moderate dose of emodin can significantly enhance the propulsive effect of charcoal powder in the small intestine, promote intestinal peristalsis and have a regular laxative and intestinal moisturizing effect.

3.8 Renal Protective Effect

Song Yunmei [29] conducted a controlled experiment on diabetic rats and found that Cassia Semen anthraquinone glycosides have a protective effect on renal damage in diabetic rats. This effect is related to its inhibition of renin and AngII expression and the reduction of KIM-1 and β2-MG levels in urine. Wang Xue [30] studied the protective effect of Cassia Semen crude extract on acute renal injury induced by mercuric chloride in rats. Their research found that Cassia Semen extract can almost completely improve the histological changes caused by mercuric chloride in rat kidneys, confirming the protective effect of Cassia Semen against mercury toxicity. Chen Jianshuang [31] observed the effects of Cassia Semen anthraquinone glycosides on a two-kidney, one-clip hypertensive rat model and found that Cassia Semen anthraquinone glycosides significantly reduced the expression of renin, AngII, and aldosterone in the renal tissue of two-kidney, one-clip hypertensive rats, demonstrating significant antihypertensive and renal protective effects.

3.9 Anti-Diabetic Effect

Wang Qiuyan [32] explored the mechanism of action of Cassia Semen extract on diabetic nephropathy. Through experimental studies, they found that Cassia Semen extract has weaker hypoglycemic and anti-inflammatory effects than positive drugs. Still, it has advantages in lowering lipid levels and improving oxidative stress levels in the body. This suggests that Cassia Semen can be used as an adjuvant drug or health product for the treatment and health maintenance of type 2 diabetes, such as in combination with other drugs to enhance the effects of lipid-lowering and improvement of oxidative stress levels and to enhance renal protection. Additionally, Cassia Semen can improve mitochondrial function and play a key role in insulin

resistance and insulin secretion in type 2 diabetes (T2D) [33].

4. Summary and Prospect

The medicinal use of Cassia Semen has a long history. The pharmacological action and clinical application of Cassia Semen are recorded in detail in ancient Chinese traditional medicine books. Therefore, many scholars at home and abroad have conducted a lot of studies on the chemical composition and pharmacological effects of Cassia Semen. In recent years, the pharmacological effects of the drug components of Cassia Semen in protecting the liver and kidney and lowering blood pressure and lipids have been supported and expanded by more and more experimental results. Theoretical support for existing effects and exploration of new effects are also ongoing. However, most of the research is still focused on the anthraquinone components of Cassia Semen. In the aspects of traditional Chinese medicine preparations and health products, most of the research is focused on the effects of lowering blood pressure, lowering blood lipids and eye care, so continue to broaden the research ideas. It is necessary to study the polysaccharides, phenylpropyrrolidone, and glycosides, which are less involved in previous studies, to broaden the clinical application of other pharmacological effects, and it is also an important idea to continue in-depth research on Chinese medicine Cassia Semen.

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