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Review on the pharmacological mechanisms and novel drug delivery system of vitexin

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Abstract Vitexin is a natural phytoflavonoid glycoside extracted from the leaves of vitexin, a plant of the Verbenaceae family, which is an active ingredient in many traditional Chinese medicines and is present in a wide range of medicinal plants. In this review, pharmacological effects including anti-inflammatory, diabetes mellitus are described. The novel formulation of vitexin of nano delivery and hybrid micelles are elucidated.

Keywords: vitexin; pharmacological effect; bioavailability

1 Introduction

Vitexin (apigenin-8-C-glucoside) is a biologically active natural flavonoid compound widely distributed in the leaves and stems of dozens of plants in nature [1], the most important sources are the leaves, stems and hawthorns of vitex plants of the Verbenaceae family. The molecular formula of vitexin is $C_{21}H_{20}O_{10}$, and its relative molecular mass is 432.38. At room temperature and pressure, vitexin is a yellow powder.

Vitexin is an active ingredient in many traditional Chinese medicines and is found in a large number of medicinal plants, with a variety of pharmacological and biological activities, such as, attenuating oxidative damage and cerebral ischemia/reperfusion injury [2], promoting angiogenesis and bone formation [3], alleviating inflammation to improve apoptosis [4], and inhibiting insulin receptor [5]. In recent years, vitexin has received increasing attention [6].

Isovitexin (apigenin-6-C-glucoside), an isomer of vitexin that is usually purified with vitexin, also exhibits diverse biological activities. Studies have shown that vitexin and isovitexin are potential alternative medicines for a variety of diseases, as well as adjuvants or nutraceuticals for the treatment of recalcitrant diseases [7]. The structures of vitexin and isovitexin are shown in Fig. 1.

However, poor aqueous solubility of vitexin limits its application [8], resulting in low bioavailability, high drug dosage, many side effects, and low patient compliance, there is a need to find novel drug delivery system to improve the solubility of vitexin [9]. Many promising approaches such as carrier complexes and nanotechnology have been developed and applied to deliver poorly soluble flavonoids. These formulation methods are effective in improving the oral bioavailability of drugs by increasing the solubility, dissolution rate and permeability of flavonoids [10]. The

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present review focuses on the pharmacological effects related to the use of vitexin for anti-inflammatory and treatment of diabetes mellitus, as well as its novel delivery system, with the aim of understanding its therapeutic effects and mechanisms, thus providing a basis for the search for and further development of vitexin-containing drugs with improved bioavailability.

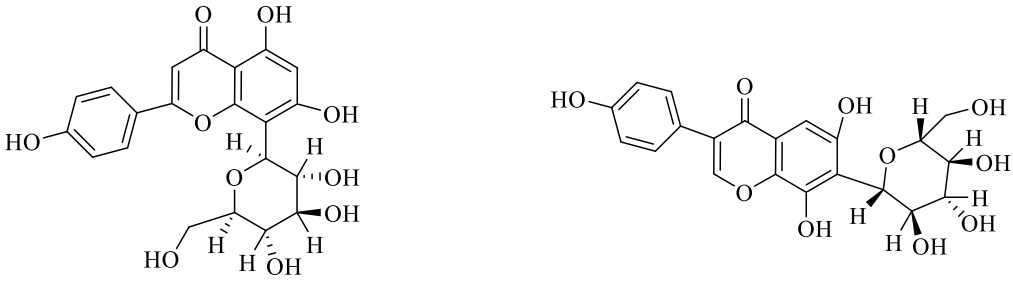

Fig. 1 Molecular structure of vitexin and isovitexin

2 Pharmacological effects and mechanisms of action of vitexin

2.1 Anti-inflammatory

2.1.1 Ulcerative colitis

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon, the incidence of which is on the rise worldwide [11]. Treatment of UC, which includes 5-aminosalicylic acid drugs, steroids, and immunosuppressants, is expanding, and the number of drugs with new targets is rapidly increasing [12]. Functional foods and bioactive compounds are current research hotspots.

Vitexin is a genus of polyphenols, a class of compounds that occur naturally in plants. It can reduce the release of anti-tumor necrosis factor-α (TNF-α), anti-interleukin-1β (IL-1β) and NO in stimulated RAW 264.7 cells [13], to modulate the expression of inflammatory factors, and to improve the clinical symptoms of colitis. Modulation of intestinal flora is a potential therapeutic target for alleviating ulcerative colitis [14], gut flora can interact with the host immune system, participate in various metabolic pathways, and maintain the host immune system [15]. Imbalances in the intestinal flora, including significant changes in intestinal flora, decreased diversity, decreased beneficial bacteria and increased harmful bacteria, have been associated with colitis [16]. An *in vitro* fermentation model [17] was used to study the modulating effect of vitexin on the intestinal flora of patients with inflammatory bowel disease, and 16S rRNA gene sequencing was used to analyze the changes in the microbiota in the feces of patients after 24 h of *in vitro* fermentation with vitexin. The results showed that the structure of bacterial flora in feces changed after vitexin fermentation. By reducing harmful bacteria, increasing beneficial bacteria, and fermenting with the feces of colitis patients *in vitro*, thus changing the structure of intestinal flora, regulating intestinal flora to alleviate colitis.

A mouse model of dextran sulfate sodium (DSS)-induced ulcerative colitis was ameliorated by the study of vitexin [18]. Vitexin treatment reduced body weight loss , and increased bloody and dilute stools of DSS-induced colitis mice [19], increased the length of the colon after DSS-induced colonic atrophy, and reduced colon damage, including adhesions and ulceration [20]. DSS-induced colitis in mice with elevated concentrations of IL-1β, IL-6, and TNF-α and unchanged expression of IL-10 in colonic tissues. Treatment with vitexin significantly reduced the ratios of IL-1β/IL10, IL-6/IL-10 and TNF-α/IL-10 in colon tissues compared with the DSS group, and also significantly down-regulated the phosphorylation of NF-κB p65, IκB and STAT1 in colon tissues of colitis mice. Vitexin had significant therapeutic effects on the DSS-induced colitis mouse model by increasing the expression of ZO-1, occludin and mucin-2 proteins

and inhibiting serum dextran levels in colon tissues, which could inhibit intestinal mucosal inflammation, maintain intestinal barrier homeostasis, and reshape the intestinal flora to counteract colitis.

2.1.2 Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common inflammatory joint disease [21]. The immune defense system is an important part of rheumatoid arthritis [22], and proinflammatory interleukins and tumor necrosis factor-α (TNF-α) are key factors leading to inflammation, bone resorption, and joint destruction [23]. Interleukins-1β, -6, -17 (IL-1β, IL-6, IL-17), TNF-α, and interferon-γ (IFN-γ) are cytokines that trigger arthritis under the control of JAK/STAT [24, 25] and inhibitors of SCOS (cytokine signaling) proteins modulate the Janus kinase (JAK)/transcriptional activator of transcription (STAT) signaling pathway that produces anti-inflammatory effects [26, 27].

The lower toxicity of vitexin reduces some of the life-threatening side effects [28, 29]. Vitexin reduces DSS-induced release of pro-inflammatory cytokines TNF-α, IL-6 and IL-1β. In a rat model of collagen-induced arthritis, vitexin significantly reduced spleen and thymus weights, prevented weight loss and normalized organ weights, and lowered CRP (C-reactive protein) and RF (rheumatoid factor). As a potent anti-inflammatory flavonoid, it inhibits COX-2 and 5-lipoxygenase pathways [30]. Vitexin reduced COX-2 and 5-LOX activities in arthritic rats, prostaglandins are produced by the action of cyclooxygenase, and leukotrienes are synthesized by 5-LOX enzymes. Many inflammatory mediators and neutrophils infiltrate the site of inflammation and produce free radicals [31], and myeloperoxidase (MPO) is a sign of neutrophil infiltration [32].

Overall, vitexin treatment reduced MPO activity and levels of the inflammatory enzyme markers COX-2, 5-LOX, and MPO.JAK/STAT3-mediated signaling plays an important role in RA inflammation and joint destruction. The experimental results suggest that vitexin has anti-inflammatory potential by modulating the JAK/STAT/SOCS signaling pathway to reduce inflammatory factors, enhance apoptosis and exert anti-inflammatory effects. As a natural product, vitexin may prove to be a safe alternative or complementary drug for the treatment of RA [4].

2.2 Diabetes

2.2.1 Diabetes caused by pancreatic β-cell damage

Diabetes mellitus (DM) is a common chronic metabolic disease [33], whose main pathogenesis is damage to pancreatic β-cells leading to inadequate insulin secretion or insulin resistance. The endotoxin lipopolysaccharide (LPS) is present in the outer membrane of Gram-negative bacteria [34], and bacterial infection produces a local or systemic inflammatory response in the host. High mobility group box 1 (HMGB1) [35] is a non-histone nuclear protein that maintains the structure and stability of nucleosomes and regulates gene transcription, alters the normal structure of β-cells, induces insulin resistance [36].

By investigating the effects of vitexin on LPS-induced pancreatic β-cell injury and apoptosis [37], vitexin significantly reduced LPS-induced release of HMGB1, suggesting that vitexin protects pancreatic islet cells from injury, and vitexin inhibits HMGB1 release to reduce LPS-induced pancreatic cell injury and apoptosis. Vitexin treatment attenuated lipopolysaccharide (LPS-)-induced apoptosis and injury of rat pancreatic islet tissues and INS-1 cells by decreasing the levels of pro-inflammatory cytokines, TNF-α, and HMGB1, which protects pancreatic β-cells from LPS-induced pro-inflammatory cytokine production and apoptotic cell death. Vitexin treatment also blocked LPS-mediated initiation of the P38 MAPK signaling pathway in INS-1 cells. In non-alcoholic fatty liver disease (NAFLD) mice, vitexin also improved insulin signaling by upregulating insulin receptor substrate-1 (IRS-1) and its downstream target AKT [38].

2.2.2 Diabetes complications

Diabetes mellitus and its associated complications

are metabolic diseases with high morbidity [39], leading to poor health and quality of life. Vitexin and its analogs have many pharmacological benefits in attenuating diabetic complications, and their antidiabetic mechanisms act primarily through the mitigation of apoptosis, target sites of the hypothalamic-gonadal axis, and other organs affected by persistent hyperglycemia. In addition, oxidative stress due to inflammation is controlled [40].

The destruction of renal blood vessels by hyperglycemia leads to renal insufficiency in diabetic nephropathy (DN) [41], and DN is the most common microvascular complication of diabetes mellitus [42]. Vitexin attenuated HK-2 cell injury in both the HG-induced HK-2 and HFD/STZ-induced models. Vitexin administration alleviated HFD/STZ-induced DN rats presenting significant weight loss due to prolonged hyperglycemia and reduced the levels of blood glucose and renal function markers. Vitexin inhibited the expression of fibrosis-associated proteins Col I and TGF-β1, suggesting that vitexin reduces renal fibrosis, identifying the nephroprotective function of vitexin in HG-attacked HK-2 cells and HFD/STZ-induced DN [43].

In an alpha-glucosidase inhibition assay, vitexin was administered orally to sucrose-loaded normoglycemic mice and induced diabetic rats, and postprandial blood glucose levels were monitored to assess acute toxicity. The results indicate that vitexin inhibits α-glucosidase *in vivo* [44], delays carbohydrate catabolism and reduces postprandial glycemic surge, and that oral administration of vitexin significantly reduces postprandial glycemic levels in rodents, and none of them showed significant signs of toxicity at effective doses.

Assessing histologic and oxidative stress changes in the pancreas of streptozotocin (STZ)-induced diabetic rats following vitexin treatment, atrophic changes in alveolar cells were attenuated, and the border between the exocrine and endocrine fractions became more pronounced. Vitexin decreased serum insulin levels, three indirect indicators predicting insulin sensitivity, HOMA-B, QUICKI and McAuley, were significantly attenuated, and triglyceride levels were significantly reduced after treatment. The results suggest that vitexin increases pancreatic antioxidant enzymes (glutathione reductase (GR) and superoxide dismutase (SOD)), promotes islet regeneration, and attenuates pancreatic oxidative damage [45].

SIRT6 has important roles in physiological and pathological processes, regulating aging, cancer, obesity, insulin resistance, inflammation, and energy metabolism, and is a regulator of glucose homeostasis, as well as a therapeutic target for obesity and insulin-resistant diabetes [46]. Studies have shown that vitexin has a high binding affinity for SIRT6 proteins [47], vitexin acts as a SIRT6 inhibitor [48, 49] preventing pancreatic β-cell damage and inhibiting apoptosis. In contrast to the anti-obesity activity of isovitexin (including isovitexin, isovitexin-7-O-glucoside, and vitexin-2”-O-rhamnoside), vitexin inhibits pancreatic lipase [50], which is therapeutic for both diabetes and its complications.

3 Novel drug delivery system

The poor aqueous solubility of vitexin leads to low bioavailability and absorption, limiting their application [8]. There are many ways to improve solubility such as micronization, solid dispersions, nanosuspensions, nanoemulsions, amorphization, phospholipid complexes, solubilization, co-solvents, pre-drugs, nanoparticles, aqueous solvents, polymeric micelles, solid lipid nanoparticles, and other colloidal drug delivery systems such as microemulsions, self-emulsifying drug delivery systems, self-microemulsifying drug delivery systems and liposomes [51], these formulation methods are effective in improving the oral bioavailability of flavonoids by increasing their solubility, dissolution rate and permeability, preventing their degradation or metabolism in the gastrointestinal tract, and delivering them directly to the target site of action [10]. Novel drug delivery systems for improved bioavailability of vitexin are shown in Table 1.

Table 1 A novel drug delivery system for improved bioavailability of vitexin

Formulation dosage form	Advantage	References
Phospholipid nanocomplexes	Safe phytosome technology combining PC and phytoconstituents to enhance the antioxidant activity and bioavailability of vitexin and increase the drug-carrying capacity for controlled or sustained drug release	[52]
Nanoparticles	Promote the absorption, water solubility and bioavailability of vitexin	[53, 54]
Hybrid micelles	Vi-MMs were developed to improve oral bioavailability and showed promising anti-osteoporotic effects	[55]

3.1 Phospholipid nanocomplexes

Improving the solubility and bioavailability of vitexin while taking into account its safety when applied for use in food products, phytosome technology is an attractive approach to improve the physicochemical properties, solubility and thermal stability of vitexin. Phytosome complex is a technology that combines phosphatidylcholine (PC) and phytoconstituents to improve the limitations of vitexin using soybean phosphatidylcholine (SPC) and egg yolk phosphatidylcholine (EPC) as carrier agents, respectively. The final study showed that the phospholipid complexes prepared with EPC as carrier agent had excellent physicochemical properties, including better encapsulation rate, encapsulation efficiency, solubility and higher TPC, FRAP and DPPH values. The TPC, DPPH and FRAP results of the samples obtained after simulated digestion clearly indicated that the developed phosphatidylcholine-based phospholipid complexes enhanced the bioavailability and antioxidant activity of vitexin during digestion, and increased the drug-carrying capacity for controlled or sustained drug release [52].

3.2 Nanoparticles

Bilayer nanoparticles loaded with vitexin were designed to enhance the bioavailability of vitexin by assembling soy peptide and cuprocyte-targeting peptide CSKSSDYQC (CSK) coupled with N-trimethyl chitosan (TMC). The results showed that the bilayer nanoparticles could protect vitexin from release in the stomach and promote sustained release in the intestine. Nanoparticles embedded in vitexin could not only promote the absorption of vitexin, but also enhance its antioxidant activity *in vivo* [53]. Using a two-step method of oil-in-water emulsion and ionic gelation, vitexin was encapsulated into poly(ethylene glycol) methyl ether grafted chitosan (mPEG-g-CTS)/alginate (ALG) polyelectrolyte composite nanoparticles, and the vitexin-loaded mPEG-g-CTS/ALG nanoparticles were successfully prepared without the use of irritating odorant acids and other cross-linking agents by Fourier transform infrared (FTIR) spectroscopy, UV-visible spectroscopy and X-ray diffraction to characterize the vitexin-loaded mPEG-g-CTS/ALG nanoparticles, which effectively improved their water solubility and oral bioavailability and promoted their absorption in the gastrointestinal tract, and the nanoparticles obtained are suitable for oral-intestinal-specific delivery systems [54]. Nanoparticles may be an effective delivery platform to enhance the bioavailability of vitexin.

3.3 Hybrid micelles

D-α-tocopherol polyethylene glycol succinate, polyvinylpyrrolidone K30 and sodium cholate mixed micelles (Vi-MMs) loaded with vitexin (Vi) were developed, mainly for enhancing oral bioavailability. By transmission electron microscopy, the optimized Vi-MMs were spherical with obvious core-shell nanostructures and well dispersed. The release rates of all Vi-MMs were significantly higher than that of free Vi, and the oral bioavailability of Vi-MMs was increased by a factor of 5.6 compared with that of free Vi. In addition, the alleviation of prednisone-

induced osteoporosis in zebrafish by Vi-MMs further showed a favorable anti-osteoporotic effect. Vi-MMs are expected to be potential nanocarriers for vitexin application in drug development [55].

4 Conclusion

This review discusses the mechanism of pharmacological effects of vitexin concerning anti-inflammatory and diabetes, which suggests that vitexin has a wide range of medical perspectives. However, due to the poor water solubility of vitexin, novel drug delivery systems to improve its bioavailability have also been sought, such as through the preparation of vitexin-phospholipid nanocomplexes, N-trimethyl chitosan-coated targeted nanoparticles, vitexin-loaded mPEG-g-CTS/ALG nanoparticles and hybrid micelles which can improve the solubility, oral bioavailability and antioxidant activity of vitexin. There is also a need to explore more bioactivities of vitexin and formulation methods to enhance its bioavailability and expand the applications of vitexin.

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