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A comprehensive review of recent advances in the extraction and therapeutic potential of berberine

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The extraction methods of berberine hydrochloride include water, acidified water, lime milk, and ethanol extraction. The water extraction method is mainly a decoction method, whereas the alcohol extraction method mainly includes microwave, ultrasonic and cable reflux extraction. In the alcohol extraction method, the solvent has low restriction and can be used repeatedly, making the operation simple and increasing the extraction rate; however, the equipment investment for ultrasonic extraction and other methods is substantial. This method can shorten the extraction time and achieve a higher extraction rate; however, it has disadvantages such as high solvent cost, large solvent amount, difficult recovery, hidden danger of safety in operation, the extraction process involving heating steps, and high energy consumption. Thus, it is not suitable for industrial mass production. The extraction processes of sour water and lime milk are relatively simple and inexpensive, which are commonly used in industry at present; however, the lime milk method consumes a considerable amount of lime milk. Therefore, considering production maneuverability and cost, the acid–water impregnation method is easier for industrial implementation. Berberine has many functions, including antibacterial effects, anti-inflammatory effects, detoxification, and lowering of blood sugar and blood fat levels. To clarify the hypoglycemic mechanism of berberine, a better understanding of its pharmacological effects is helpful, providing a basis for the rational application of berberine in the treatment of type 2 diabetes.

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1. Introduction

As a compound with broad application prospects, berberine has made significant progress in extraction technology in recent years, with several available extraction methods. Besides the commonly used extraction methods employing acidic water and alkaline water, there are new extraction methods with low pollution and high extraction efficiency, such as supercritical fluid extraction, enzymatic extraction and aqueous two-phase extraction. Berberine has been used in clinics owing to its functions of removing heat and toxic materials and resisting bacteria. It exhibits various pharmacological activities, such as anti-dysentery, anti-infectious protozoa and anti-tumor effects, and is involved in lowering blood sugar, regulating blood lipids, lowering blood pressure and mediating anti-arrhythmia effects. Here, the preparation, structure, and function of berberines are discussed and analyzed.

2. Natural sources of berberine

Berberine, as an active ingredient, is found in the roots, leaves, bark, branches and stems of many plants.[1] Natural berberine is found in plants such as *Coptidis chinensis* Franch, *Phellodendron chinense* Schneid, *Mahonia bealei*, *Argemone mexicana*, *Berberis aristata*, *Berberis aquifolium*, *Berberis heterophylla*, *Berberis beaniana*, *Coscinium fenestratum*, *Coscinium chinensis*, *Coscinium japonica*, *Coscinium rhizome*, *Hydratis canadensis*, *Phellodendron amurense*, *Phellodendron chinense*, *Tinospora cordifolia* and *Xanthorhiza simplicissima*.

Among them, *Coptis chinensis*, *Berberis vulgaris* L. and *Scutellaria baicalensis* are the most abundant in berberine. It was reported that the content of berberine in the bark and roots was more abundant than that in other parts. The content of berberine in different parts was investigated, and its highest content was found in *Berberis* roots (1.6–4.3%). The altitude at which plants grow may also affect the berberine content in plants. In one study, it was found that plants grown at low altitudes contained more berberine than those grown at high altitudes. In addition, through phytochemical analysis, it was found that berberine was rich in alkaloids, with a content as high as 1.43%. The difference in berberine content among different varieties of the same genus was also investigated: the content of *Berberis asiatica* was higher, 4.3%, followed by *Berberis lycium* (4.0%). The quantification of *Tinospora cordifolia* and *Tinospora sinensis* contents yielded 0.3192% and 0.0967% (w/w), respectively.[1] Seasonal changes will also affect the content of berberine. The yield of berberine was the highest in summer, 2.8% in root, 1.8% in stem bark and 1.9% in winter.

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Although there are several types of compounds produced by plants, most of them are considered to be secondary metabolites, and the physiological and developmental factors of plants significantly influence their production. Callus culture has become the focus of research on the *in vitro* production of metabolites. Different kinds and concentrations of auxin, 3% sucrose and 0.7% Agar corn, and different concentrations of Skoog (MS) Agar were used as explants to establish an excellent plant callus culture system with high contents of small leaf tin fruit and berberine. The content of berberine was higher in the medium containing 5 μM α-naphthylacetic acid. After 40 μM tyrosine was added to the MS medium, the yield of berberine was increased by 3.19-fold. Therefore, this method can be used for the mass harvest of berberine. Such callus cultures could also be used to initiate suspension cultures of *T. cordifolia* for studies on berberine.[2]

The main plant sources of berberine include *Coptidis rhizoma* and *Cortex phellodendri*. Effects of environmental factors on berberine content: (1) different soil types can affect the absorption and accumulation of nutrients by plants, thus affecting the berberine content. For example, soil rich in organic matter contributes to the synthesis and accumulation of berberine. (2) Climate factors such as temperature, humidity and light will also affect the content of berberine. Appropriate temperature and light conditions can promote its synthesis, while extreme weather conditions may inhibit its synthesis. (3) Planting methods and fertilization will also affect its content. Reasonable fertilization and planting management can improve the berberine content. Effects of biological factors on berberine content: (1) there are genetic differences between different varieties of *Coptis chinensis* and *Phellodendron amurense*, which will affect the berberine content. Selecting high-content varieties for planting can increase the yield. (2) Pests and diseases can affect the growth and development of plants, which in turn affect the synthesis and accumulation of berberine. Effective pest control measures can reduce this negative impact.

3. Ultrasonic-assisted extraction of berberine

The extraction process of berberine involves a saline–alkali conversion reaction caused by two different pK_a values (2.47 and 15.7) of berberine, in which the salt is soluble in water, stable in acidic and neutral media, and alkali-soluble in organic solvents. Therefore, berberine is usually converted to berberine hydrochloride in the presence of a specific alkali and then extracted with organic solvents.[3]

Ultrasonic-assisted solvent extraction (USE) is considered a green, simple, efficient and cost-effective technology. Compared with the distillation method and Soxhlet extraction method to extract berberine from fresh *Phellodendron* bark, an efficient method was established. The yield of berberine extracted by USE was the highest, which was about 100 mg g^{-1}. The yield of berberine by distillation and Soxhlet extraction was 50 mg g^{-1} and 40 mg g^{-1}, respectively. In addition, the effective matrix recovery of berberine was shown when using methanol acidified with hydrochloric acid. Another study also obtained a relatively high yield of berberine in *Rhizome coptidis*, and the optimal extraction conditions were 59% ethanol, 66 °C and 45 min. Meanwhile, USE, with a green solvent, ionic liquid solutions, reduced the extraction time (40 min) for berberine in *Coptis chinensis*. A non-toxic, environmentally-friendly mixed solvent of water and glycerol was used to extract berberine from *B. vulgaris* root bark using the USE technique. Berberine concentration and DPPH radical scavenging activity of the extracts (RSA IC_{50}) varied with temperature, glycerol concentration, and ultrasound power. A high berberine yield of 145.5 μg mL^{-1} (80 °C, 50%, 144 W) and RSA IC_{50} of 58.88 μg mL^{-1} (80 °C, 30%, 720 W) were obtained under different optimum conditions.[4]

A single-factor experimental method is used to explore the range of optimal extraction conditions for ultrasonic and microwave collaborative extraction of berberine, and then optimize the conditions by the response surface method. The results show that the best extraction conditions are as follows: extraction solvent, 0.05 mol per L H_2SO_4; material-to-liquid ratio of 15 g mL^{-1}; ultrasonic time of 10 min; microwave time of 3 min; microwave power of 600 W, and the xanthin extraction rate of 11.43%. Compared with traditional ethanol immersion extraction and sulfuric acid immersion extraction, ultrasonic-microwave collaborative extraction saves a significant amount of time, and the extracted flavinin is no different from that extracted by traditional methods.

With the assistance of an ultraviolet-visible spectrophotometer, a single-factor test analysis is carried out by the ultrasonic-assisted extraction process. The maximum influence level of each factor is as follows: 70% ethanol concentration, material–liquid ratio of 1 : 25 (g : mL), 180 W ultrasonic power, and ultrasonic treatment for 30 minutes at 50 °C ultrasonic temperature. At the same time, in order to further investigate the reliability and stability of the best process, the orthogonal experiment is used, which shows that the process has good stability and high reliability. This provides experimental support for the extraction of berberine hydrochloride. Through the study of ultrasonic-assisted and enzymatic-assisted extraction processes, the optimum process conditions for the combined enzymatic hydrolysis-ultrasound extraction of berberine hydrochloride were investigated. HPLC was used to determine the content of berberine hydrochloride in the lower foot of Huanglian. Through this method, the reliability of this test and the stability of instrument operation are effectively verified, and the purity of ultrasonic-assisted extraction, enzymatic paralysis-assisted extraction and enzymatic hydrolysis-ultrasound combined extraction of berberine hydrochloride products is further analyzed and evaluated simultaneously. At the same time, as a quality control of the extraction process, specific components can be analyzed more accurately.

The extraction method of berberine was explored, and the difference between Soxhlet and ultrasonic extraction was mainly compared. The results showed that the optimal conditions for Soxhlet extraction are 100 mL of ethanol solvent and extraction for 3 hours. The optimal conditions for ultrasound extraction are 100 mL of ethanol solvent and ultrasound

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extraction for 1 hour, which is divided into three 20-minute intervals. The extraction efficiency of the ultrasound method is 9.6% higher than that of the traditional Soxhlet extraction method, with higher repeatability. The method is simpler and easier to operate than the Soxhlet extraction method. The effect of ultrasonic extraction is better than that of traditional Soxhlet extraction methods.

The ultrasonic method is better than the immersion method for extracting berberine from huanglian. Within 30 minutes, the extraction rate of berberine increases with the increase in ultrasound treatment time, and there is a peak. When the ultrasound treatment time is 30 minutes, the extraction rate is 8.12%. Huanglian powder is soaked in a sulfuric acid solution with a concentration of 0.094 mol L^{-1}, and then treated with ultrasonic waves. The extraction rate of berberine is high. For berberine in huanglian, ultrasonic extraction at a frequency of 20 kHz is appropriate. Huanglian powder is soaked for 24 hours, and then treated with ultrasound, resulting in a relatively high extraction rate of berberine.

4. Comparison of the ultrasonic extraction method with other methods

In traditional extraction methods, the selection of solvents plays a critical role in extracting berberine. Water, methanol, ethanol, dilute sulfuric acid and lime solution are the most commonly used extraction solvents. According to the different solvents selected, the traditional extraction methods for berberine can be divided into decoction, alcohol, acid and alkali methods (Fig. 1).

4.1 Decoction method

The decoction method involves the steps of adding an appropriate amount of water to a traditional Chinese medicine, boiling it, determining the boiling time according to the specified situation, and then removing the residue to obtain the filtrate. The extraction process of *Coptis chinensis* in Yiqing granule is a water extraction method; the first extraction time is 1.5 h, the second time is 1 h. The filtrate is filtered, decompressed and concentrated, and the dry extract powder is obtained by spray drying. Most of the prescriptions in the Chinese Pharmacopoeia are decocted. Although the solvent in this method is inexpensive and readily available, it has some disadvantages, such as low extraction rates, low utilization rates of traditional Chinese medicine materials, easy mildew and so on.

4.2 Alcohol extraction

Impregnation is the main extraction method in alcohol extraction, followed by percolation. With the progress of modern technology research, the method of ethanol extraction also has important applications. Using 60% ethanol as solvent, reflux extraction was carried out 3 times, with a 1 h soaking period before the first extraction, followed by extraction for 1 h, and 50 min for the last two extractions. After three extractions, all the extracts were combined and set aside. Although the ethanol extraction solvent is clean and easy to obtain, it has some shortcomings, such as a complex recovery operation, flammability and safety concerns. In 1972, berberine was extracted from *Coptis japonica* with methanol. Due to the diversity of the solubility of berberine, it was successfully separated, which is an ecologically friendly separation method with moderate yield.[5]

4.3 Acid–base extraction method

In 1985, berberine was isolated using sulfuric acid in northeastern Thailand. This discovery provides us with a method of extracting berberine. The acid–alkali method is one of the most commonly used methods for extracting berberine, because berberine sulfate has high solubility in water, but hydrochloric

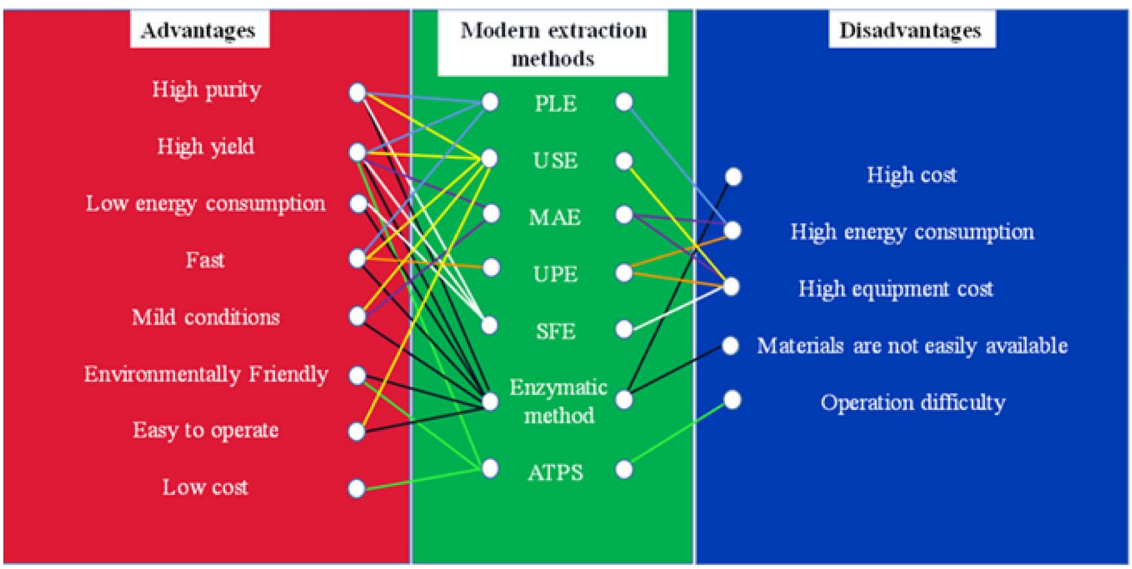

Fig. 1 Traditional extraction methods of berberine and their advantages and disadvantages.

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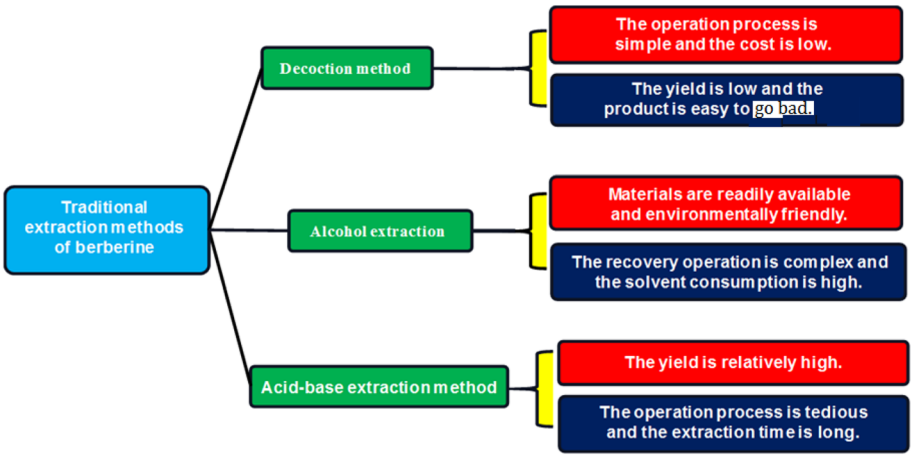

Fig. 2 Advantages and disadvantages of major modern extraction methods.

acid is almost insoluble in water. The technology of extracting berberine from *Coptis chinensis* by the dilute sulfuric acid method was comprehensively studied, and the optimum extraction conditions were obtained as follows: soaking for 24 hours, dilute sulfuric acid concentration 0.4%, solid–liquid ratio 1 : 16, lime milk adjusting pH = 12, hydrochloric acid adjusting pH = 5, sodium chloride addition 25%, berberine extraction rate 8.4%, purity 7.27%. The method has the advantages of simple and rapid operation, easy availability of experimental raw materials, mature process and stable extraction rate. It systematically improved the extraction process of berberine and laid a foundation for further industrialization. Later studies have shown that deep eutectic solvents (DESs), obtained by mixing two or more inexpensive, environmentally friendly and biodegradable solvents, are an efficient and selective green solvent for the extraction of berberine.

High temperatures and light can lead to the automatic degradation of berberine, and the matrix recovery of these extraction methods varies significantly due to its sensitivity to temperature and light. The influence of temperature for extracting berberine in *Coscinium fenestratum* stem tissue samples was investigated and a 4.6% weight/weight (w/w) yield was observed in the case of samples dried under the constant shade, which was higher than from samples dried in an oven at 65 °C (1.32% w/w) or sun drying (3.21% w/w). Hot and cold methanol or ethanol were also applied to compare the matrix recovery yield of berberine. The yield in the shade-dried samples was 4.6% (w/w) for the methanolic cold extraction and 1.29% (w/w) for the methanolic hot extraction.

It is worth noting that the extractant affects not only the extraction rate but also the activity of microorganisms. The bark extracted from the root bark of Chinese cabbage yields better medicinal food value. Among different solvents, ethanol has the highest extraction rate (173.36 mg g^{-1}), followed by water (24.54 mg g^{-1}), *n*-hexane (11.88 mg g^{-1}) and acetone (6.56 mg g^{-1}). Bacteriostatic experiments revealed that ethanol and water extracts exhibited strong antibacterial activity against *Staphylococcus aureus* (*S. aureus*), even at concentrations as low as 12.5 mg mL^{-1}, even after several dilutions, while *n*-hexane and acetone extracts did not show such strong activity. The difference in inhibition rate and yield may be attributed to the higher content of polyphenols and/or alkaloids in water and ethanol extracts than in acetone and *n*-hexane extracts. It must be noted that acetone and *n*-hexane are non-polar solvents and therefore have low solubility in polyphenols and/or alkaloids.[6] Another study also found that the ethanol extract of *Berberis* root collected from Meduvrhi and Kiza (Croatia) had significant inhibitory activity against *S. aureus* ATCC6538 (minimum inhibitory concentration (MIC) was 25 mg mL^{-1}). Later studies found that the minimum inhibitory concentration of alkaloids extracted from the roots against *S. aureus* ATCC25923 was 5–10 mg mL^{-1}.

Despite this, the method also has disadvantages, including the need for a large amount of solvent, long extraction time and increasing extraction costs. For instance, berberine was extracted from 800 g of the powder and stem bark by a 2.5 L methanol thermal extraction (50 °C, 3 h).[7] It was also extracted from 100 g of *C. fenestratum* plant material by soaking in 3.2 L of ethanol (80%) for 16 h.

In order to improve the selectivity and effectiveness of the extraction process, some green, simple and efficient technologies such as microwave-assisted solvent extraction (MAE), ultrasound-assisted solvent extraction (USE), ultra-high pressure extraction (UPE), supercritical fluid extraction (SFE), pressurized liquid extraction, enzymatic extraction, aqueous two-phase extraction have been successfully developed (Fig. 2).

Microwave-assisted solvent extraction (MAE) is a green and economical traditional extraction method that can increase intracellular temperature, release berberine from broken cells, and reduce the use of organic solvents and extraction time. The relatively high yield of berberine content at 1.66% from *Tinospora cardifolia* was achieved using MAE under optimized conditions (60% irradiation power, 80% ethanol concentration, and an extraction time of 3 minutes), while only 1.04% and 0.28% were obtained from Soxhlet and maceration, respectively. Compared with Soxhlet extraction (3 h) and impregnation (7 d), MAE significantly shortened the extraction time (3 min) and reduced solvent and energy consumption.

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Table 1 Advantages and disadvantages of other modern extraction methods

Extraction methods	Advantages	Disadvantages
Maceration; Soxhlet; percolation; reflux	Mature methods with inexpensive equipment and large-scale extraction	Large solvent volumes, long extraction time, low extraction recovery and purity
Molecularly imprinted polymer extraction	Environmentally friendly technique with high selectivity, affinity, specificity, extraction yield and purity	High-cost and rigorous condition limit its use for large-scale extraction
Nano strategies	Novel method with high selectivity, affinity, specificity, extraction yield and purity	High costs and rigorous conditions limit its use for large-scale extraction

Ultra-high pressure extraction (UPE) is another environment-friendly extraction technology. Its principle is to use different pressure levels inside and outside the cell (high value) and extracellular (low value) at room temperature to promote the transfer of bioactive substances through the plant matrix in the extraction solvent, thereby improving the extraction rate and quality, shorten the extraction time and reduce the solvent consumption. One study compared UPE, MAE, USE, and heat reflux extraction to extract berberine from *C. phellodendri*, and UPE exhibited the highest extraction yield (7.7 mg g^{-1}) and the shortest extraction time (2 min), followed by MAE (6 mg g^{-1} and 15 min), USE (5.61 mg g^{-1} and 1 h) and reflux (5.35 mg g^{-1} and 2 h).

Supercritical fluid extraction (SFE) is an environmentally friendly and efficient technology that can reduce the degradation of bioactive substances in the absence light and oxygen. Furthermore, inert and non-toxic carbon dioxide is used as the main extraction solvent of SFE, and various modifiers (such as methanol) and surfactants (such as Tween 80) are combined at a low temperature and relatively low pressure to effectively extract bioactive compounds. The recovery rate of berberine in the rhizome of *Coptis chinensis* was the highest when 1,2-propanediol was used as the modifier of supercritical CO_2.

Pressurized liquid extraction is considered a green technology for extracting sensitive compounds from various plants, offering advantages such as improving the extraction rate, shortening the time, reducing solvent consumption and so on. The extraction of berberine from Canadian narcissus by four extraction methods, including PLE, multiple use, single use and Soxhlet extraction, was studied. The extraction time of PLE was shorter (30 min), while the extraction times of multiple extraction (2 h) and Soxhlet extraction (6 h) were longer.

The principle of enzymatic extraction of berberine is to use cellulase to convert cellulose into soluble glucose, destroy the cell wall and release berberine. This method has the advantages of being time-efficient, low consumption and convenient post-processing, and is beneficial to the environment. Nevertheless, the activity conditions of the corresponding enzymes are complex, and the high selectivity of the enzyme limits its application in the treatment of different plants containing berberine.[8]

A magnetic ionic liquid (MILs) aqueous two-phase system (MILATPs), consisting of five choline ionic liquids (MILS) containing piperidinyl anions, was synthesized by mixing with a series of inorganic salts. The MIL-ATPs coupled with HPLC-UV analysis were used to quantify berberine hydrochloride in *Rhizoma coptidis*, and a high partition coefficient of berberine (127.68) was observed with precision values (RSD%) of 1.40% and 2.83% for intra-day ($n = 6$) and inter-day ($n = 3$), respectively. The limits of detection (LOD) and quantification (LOQ) for berberine were 0.023 mg L^{-1} and 0.077 mg L^{-1}, respectively. This method also yielded a high content of berberine (123.95 mg g^{-1}) from the raw material of *Rhizoma coptidis*. After removing berberine hydrochloride with D101 resin, the recovery rate is 99.8%, which can be recycled.

Rosin-based polymer microspheres (RBPM) with a clean surface, narrow particle size distribution, mesopic structure and excellent thermal stability were prepared using ethylene glycol maleate as a cross-linker and methacrylic acid as a functional monomer. The results exhibited that the dynamic adsorption capacity of RBPM on total alkaloids was 612.4 mg g^{-1}, and the separation capacity of total alkaloids increased from 34.2% to more than 91.0%.

Functional magnetic adsorbents have good biocompatibility and unique physical and chemical properties. An aptamer is an oligonucleotide or peptide molecule that can be bound to a specific target molecule with high selectivity, affinity, and specificity, comparable to or better than antibodies, enabling biosensors based on fluorescence intensity detection, electrochemical changes, or color changes. Aptamer-functionalized Fe_3O_4 magnetic nanoparticles were prepared and used as a SPE adsorbent to extract berberine from the *C. phellodendri.* Under the optimal conditions (pH = 7.5, Mg^{2+} concentration of 5 mmol mL^{-1}, incubation temperature of 30 °C, desorption time of 5 min and elution solvent of acetonitrile (2.5 mL)), the purity of berberine extracted from *C. phellodendri* was as high as 98.7% compared with that of 4.85% in the extract, indicating that aptamer-functionalized Fe_3O_4 MNPs-based SPE method was very effective for berberine enrichment and separation from a complex herb extract. Furthermore, berberine was separated from nine different concentrations of a single *C. phellodendri* extract to demonstrate the applicability and reliability of this technique, and the relative recoveries of the spiked solutions in all samples were between 95.4 and 111.3%, with relative standard deviations ranging between 0.57 and 1.85% (Table 1).

5. Advantages of the ultrasonic extraction method

To sum up, the extraction methods of berberine hydrochloride include water, acid water, lime milk, ethanol extraction and so on. Decocting method is the main water extraction method, and

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microwave extraction, ultrasonic extraction and cable reflux extraction are the main alcohol extraction methods. The solvent has low restriction, reusability, simple operation and high extraction rate, but ultrasonic extraction and other methods and equipment have large investment. It can shorten the extraction time and achieve a higher extraction rate, but the solvent price is high, the solvent consumption is large, the recovery is difficult, the operation safety is hidden, and the extraction process is heated and the energy consumption is high, which is not suitable for industrial production. The extraction process of acid water and lime milk is relatively simple and low cost, which is commonly used in industry at present, but lime milk method consumes a lot of lime milk. Therefore, considering the operability and cost of production, acid–water impregnation method is easier to realize industrial extraction.

With the development of modern science and technology, new modern separation methods, each with its own advantages and disadvantages have emerged, including PLE, USE, MAE, UPE, and SFE. These methods improve the extraction rates of berberine, shorten the extraction time, and are more suitable for industrial production. Enzymatic extraction has almost no effect on the extraction of original plant contents; however, the cost of biological enzymes is very high; hence, it is only suitable for low-dose research in the laboratory. However, the whole process of supercritical CO_2 extraction does not require organic solvents, and there is no residual solvent; however, it increases the equipment investment and operation difficulty of the process.

6. Antidiabetic mechanism of berberine

Decreased insulin sensitivity and insulin target resistance are the central links in the pathogenesis of type 2 diabetes. The main manifestation is the translocation dysfunction of the glucose transporter GLUT4. In general, when insulin is stimulated, the GLUT4 transporter translocates from the cell to the membrane to perform the transport function, thereby enabling blood glucose levels to tend towards the normal level. Berberine can treat type 2 diabetes by improving insulin resistance (IR), exhibiting an anti-inflammatory effect, reducing oxidative stress, increasing glucose consumption in HepG2 cells, repairing islet β cells and activating the AMPK pathway.

However, the GLUT4 transport function of patients with type 2 diabetes is low, which leads to an increase in blood glucose. The experimental results of Yan *et al.* showed that berberine could improve the state of insulin resistance (IR), enhance the expression of PI3-K and GLUT4 in target tissues, increase the circulation speed of GLUT4 in cells, and improve the affinity and binding capacity of the insulin receptor in hepatocyte membranes.[1]

Some studies have shown that the anti-inflammatory effect of berberine can inhibit the development of diabetes. It was found that the levels of inflammatory factors (CPR, IL-6, TNF-α and IL-1) in the serum of diabetic rats treated with berberine decreased significantly, while the level of adiponectin increased significantly.[2]

Oxidative stress occurs when the body is subjected to various harmful stimuli, and the excessive production of highly reactive molecules leads to an imbalance between the oxidative and antioxidant systems, which induces and mediates the apoptosis of pancreatic cells and destruction of islets, resulting in an increase in blood sugar levels.[3] It has been found that berberine has a beneficial therapeutic effect on oxidative stress. It can not only significantly reduce the level of malonic acid in the serum and liver tissue of diabetic rats and increase the activities of superoxide dismutase, glutathione peroxidase, catalase and glutathione, but also up-regulates the gene expression of positive transcription elongation factor B and regulates blood glucose through antioxidation.[4]

Studies have shown that small doses of berberine can significantly increase glucose uptake in HepG2 cells without insulin dependence, showing a good hypoglycemic effect.[5]

The experimental study found that berberine can promote the repair of islet β cells in diabetic rats, increase the content of insulin in blood glucose, facilitate the transport of glucose, and thus reduce blood glucose levels.[6]

The results of an experimental study have shown that berberine has a beneficial hypoglycemic effect, which can increase glucose metabolism by stimulating glycolysis or inhibit glucose heterogeneity by inhibiting glucose oxidation in mitochondria, thereby assisting in the regulation of blood sugar levels.[7] Another study showed that berberine can increase the level of fasting blood glucose in diabetic rats by inhibiting hepatocyte gluconeogenesis.

Insufficient insulin secretion in diabetic patients will lead to an increase in plasma FFAs and TG concentrations, which will affect glucose metabolism, and high FFAs can also cause triglyceride accumulation in β-cells and β-cell apoptosis, resulting in further deterioration of blood glucose. It has been found that berberine can improve insulin resistance induced by free fatty acids, reduce the expression of PCSK9 in HepG2 cells and affect the level of blood cholesterol. Berberine can help statins play a lipid-lowering role.[8,9]

AMPK is one of the key molecules in the regulation of biological energy metabolism, and it is essential for the body to maintain blood glucose balance by activating the AMPK protein pathway to improve energy metabolism and regulate blood glucose.[10] Berberine is a natural monomer in medicinal food, which has a good affinity for AMPK. Berberine may have a synergistic effect on blood glucose regulation by acting with AMPK. Berberine may improve insulin resistance by activating the AMPK pathway and coordinating blood glucose regulation by combining with other pathways.[11]

7. The antioxidant potential of berberine in T2DM treatment

Several studies, both *in vitro* and *in vivo*, have confirmed that the antioxidant properties of berberine are beneficial in the treatment of diabetes and insulin resistance (IR).[12] Some of these

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studies were conducted in alloxan or streptozotocin-induced hyperglycemic rats, revealing the relationship between the hypoglycemic effect of berberine and its antioxidant properties. After berberine treatment, the levels of SOD, CAT, GPx, GSH, GSHPx, vitamin E and vitamin C increased significantly, while the level of MDA decreased significantly.[13] Other studies on diabetic mice have shown that berberine treatment can inhibit the levels of GSH and GSHPx in the serum, liver, kidney, pancreas, heart, cortex and hippocampus, and up-regulate the mRNA content of SOD.[14]

Berberine promotes the expression of SIRT1 by increasing the expression level of SOD. SIRT1 is a deacetylase that triggers the deacetylation of forkbox O (FOXO) factor in oxidative stress and stimulates the transcription of FOXO target genes including SOD.[15] Berberine can also inhibit oxidative stress by up-regulating the mRNA content of SOD in diabetic mice.[16] The MIR-106b/SIRT1 pathway is involved in the role of berberine in reducing oxidative stress in diabetic mice.[17]

NADPH oxidase is another source of increased ROS by up-regulating the contents of various glycosylation products, fatty acids and glucose. Berberine inhibits its expression, thus reducing oxidative stress.[18] In addition, berberine reduced the production of ROS by inhibiting the expression of NADPH oxidase 2max 4 (NADPH oxidase 2max 4).[19]

AMPK is also considered one of the anti-diabetic mechanisms of berberine, as its activation has a negative effect on the regulation of NADPH oxidase and a positive effect on the up-regulation of CD36 expression.[20] The correlation between berberine down-regulation of NADPH oxidase and activation of AMPK was studied. The results showed that the activation of AMPK was not only related to the down-regulation of NADPH oxidase but also to the up-regulation of SOD expression.[21] The correlation between berberine down-regulation of NADPH oxidase and activation of AMPK was studied. It showed that the activation of AMPK was not only related to the down-regulation of NADPH oxidase, but also related to the up-regulation of SOD expression.[22]

Uncoupling protein 2 (UCP2) plays a negative role in the regulation of reactive oxygen species (ROS) production and oxidative stress. The increased expression of UCP2 induced by berberine inhibited the production of ROS in the kidney or adipose tissues, but the up-regulated UCP2 also inhibited the insulin secretion of islet β-cells. Berberine can increase the expression of UCP2 in the artery, but the expression of berberine in hepatocytes is opposite to that of berberine. Therefore, it is necessary to further explore the relationship between berberine regulation of UCP2 and specific tissues.[23]

The Nrf2 pathway is also involved in berberine inhibiting oxidative stress and improving the condition of diabetes. Berberine can stimulate the expression of Nrf2, activate the expression of antioxidant enzymes, increase the levels of GSH and SOD, and inhibit the production of ROS by activating P38, AMPK and PI3K/Akt signal pathways.

Berberine has been shown to strongly affect carbohydrate metabolism. The compound also protects pancreatic β cells and increases the sensitivity of peripheral tissue to insulin by inducing the activities of GLUT-1, GLUT-4 and insulin type 1 (Ins-1) receptors. It also stimulates glycolysis and reduces insulin resistance by polarizing macrophages, inducing lipolysis and increasing energy consumption (by losing weight and limiting insulin resistance caused by obesity). In the liver, berberine inhibits the FOX01, SREBP1 and ChREBP pathways, as well as HNF-4 α (hepatocyte nuclear factor 4 α) mRNA, which hinders the process of gluconeogenesis. In the gut, it blocks glucosidase, which reduces glucose absorption. Its interference with intestinal flora reduces the level of monosaccharides and inhibits the development of diabetic complications.[24]

The introduction of a glycosylation group at the berberine 9-*O* position can improve the antidiabetic activity of the compound; however, the compound is unstable. A glycosylated berberine derivative (**1**) was designed and synthesized to provide stable physicochemical properties by introducing a triazole spacer into the berberine structure. The antidiabetic and cytotoxic effects of these compounds on HepG2 cells were tested. The results showed that the cytotoxicity of berberine derivative modified by glucose, galactose and mannose (**2a–c**) was lower, and the hypoglycemic activity of compounds **2c** and **2d** was higher than that of berberine.[25]

A series of disaccharide-modified berberine derivatives with potential for the treatment of type 2 diabetes (**2**) were designed and synthesized by Wang and colleagues. An anti-diabetic investigation of the synthesized compounds was performed in a zebrafish model using a fluorescently labelled glucose analog 2-deoxy-2-[(7-nitro-2,1,3-benzoxadiazol-4-yl) amino]-D-glucose (2-NBDG) as a glucose tracker. The results showed that compound **2e** modified with berberine 9-*O* disaccharide had the highest antidiabetic activity. In addition, the dose-dependent study of compound **2e** confirmed that the derivative could significantly promote 2-NBDG uptake by zebrafish larvae and eyes, achieving a hypoglycemic effect.[26] It was found that the introduction of disaccharides at the 9-*O* position resulted in a higher hypoglycemic activity than monosaccharides.

Khvostov and his colleagues synthesized a new berberine derivative **3** and analyzed its hypoglycemic effect. Biological tests show that the compound exhibits a highly significant hypoglycemic activity, which is attributed to an increase in insulin sensitivity after single and multiple uses. Obese type 2 diabetic (T2DM) mice exhibited improved glucose tolerance, decreased fasting insulin level and sensitivity, decreased total body weight and interscapular fat, and increased interscapular brown fat activity. All these effects were also histologically confirmed, with reduced steatosis in the liver and smaller fat droplets in brown adipose tissues.[27]

8. The anti-inflammatory potential of berberine in DM treatment

The strong anti-inflammatory effect of berberine is also attributed to the improvement in diabetes and its complications. Therefore, several studies have been carried out *in vivo* and *in vitro* to investigate the special relationship between the hypoglycemic effect of berberine and its anti-inflammatory effect. One of these studies conducted on STZ-induced diabetic rats

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reported there was a significant decline of pro-inflammatory mediators (TNF-a, NF-kB, phospho-NF-kB-p65, COX-2 and iNOS) and pro-apoptotic proteins (caspase-8, t-Bid, Bax, cytochrome-c and cleaved caspase-3), as well as the elevation of anti-apoptotic protein Bcl-2, anti-inflammatory mediator IL-10 and GLUT-2 after administrating berberine.[28] In berberine-fed DM or IR animals, the levels of pro-inflammatory cytokines and acute phase proteins in the kidney, liver, fat and other tissues decreased.[29] Other studies have revealed the relationship between the insulin-sensitizing effect of berberine and its anti-inflammatory effect. In HepG2 cells treated with palmitic acid, the production of cytokines and the level of serine phosphorylation decreased significantly, while the level of insulin-mediated tyrosine phosphorylation of the insulin receptor increased significantly.[30] Some of these studies have also demonstrated that berberine treatment ameliorated type I diabetic conditions in NOD mice through the inhibition of various pro-inflammatory cytokines, such as IL-6, IL-17, TNF-a, and interferon-g (IFN-g).[31] In addition, patients with diabetes were given berberine 1 g per day for 3 months to explore the relationship between berberine and inflammation. The results showed that berberine could reduce the serum IL-6 levels.[32]

The hypoglycemic effect of berberine is also related to the activation of AMPK. The increase in glucose levels led to the inhibition of AMPK activity, and berberine could activate AMPK activity.[33] When AMPK is inactivated, it can also inhibit the production of pro-inflammatory cytokines, such as COX2 and iNOS. On the other hand, berberine-activated P38 plays an important role in anti-inflammation. After treatment with berberine (400 mg kg^{-1}) in female SD rats, GLUT4 was up-regulated and IR was decreased by activating the PI3K/AKT pathway and inhibiting MAPK pathway.[34] Therefore, these effects of berberine are partly due to the bi-directional regulation of the AMPK signal pathway. The hypoglycemic effect of berberine is attributed to the inhibition of inflammatory polarization by interacting with TLR4 and interfering with the TLR4/MyD88/NF κ B signal pathway.[35] The effect of berberine-inhibited pro-inflammatory cytokines on improving diabetes is also mediated by Nrf2, and Nrf2 promotes the expression of anti-inflammatory enzyme HO-1.[36]

The role of berberine in diabetes mellitus and insulin resistance by targeting the NF-κB pathway has also been reported.[37] The nuclear transfer of NF-κB transcription factor is limited by berberine's stable IκB-α, which can induce the expression of pro-inflammatory cytokines such as IL-6, iNOS, COX-2 and TNF-α. In addition, it has been reported that berberine can protect HIT-T15 pancreatic γ cells from palmitic acid-induced apoptosis by up-regulating PPAR-β expression.[38]

9. Clinical application

The safety and efficacy of berberine in the treatment of type 2 diabetes mellitus were studied.[39] After berberine 0.2–10 g per day was used for treatment, the blood glucose value decreased by 20–40%, similar to rosiglitazone and metformin. In addition, berberine has been shown to significantly reduce the fasting blood glucose, postprandial blood glucose and fructosamine levels in patients with T2DM over a one-month period.[40] In addition, the synergistic effect of berberine in combination with sulfonylureas or metformin in the treatment of Italian T2DM patients was also observed.[41] Berberine is safer and more effective than synthetic medicinal food in improving liver function and blood sugar.[42] However, further large-scale, high-quality and long-term randomized clinical trials are needed to verify the efficacy of berberine in the treatment of diabetes and its complications. It is recommended for routine clinical application as an effective medicinal food for the treatment of diabetes.

Currently, studies indicate that berberine has certain potential in improving blood sugar control and liver function; however, its safety, adverse reactions and contraindications need to be scientifically evaluated. Pre-diabetes intervention: large-scale clinical trials (involving more than 2800 people) have shown that taking berberine for 18 consecutive months can reduce the risk of pre-diabetes progressing to diabetes by 41%, and the mechanism is related to activating AMP kinase, promoting glucose utilization and inhibiting intestinal glucose absorption. Synergistic hypoglycemic effect: some studies have found that berberine combined with metformin can significantly reduce glycosylated hemoglobin, but the improvement effect of berberine alone on glycosylated hemoglobin is not clear. Gastrointestinal adverse reactions: common gastrointestinal discomfort, such as nausea, vomiting and constipation, can be relieved after meals. Alternative drugs should be used cautiously: their hypoglycemic effect is weaker than that of mainstream drugs (such as metformin), and thus cannot be used as an alternative alone; long-term use may cause intestinal flora imbalance. Risk of hypoglycemia: the combination with hypoglycemic agents may increase the probability of hypoglycemia, which needs close monitoring. Improve the mechanism of liver fibrosis: by repairing the intestinal barrier (increasing the expression of tight junction proteins Occludin and ZO-1 by 83–89%), inhibiting the inflammatory pathway of TLR4/NF-κB and regulating the intestinal flora (increasing the abundance of short-chain fatty acid-producing bacteria), liver injury and fibrosis can be alleviated. In animal experiments, berberine reduced the deposition of liver collagen by 42.3%, and the safety window was wide (IC_{50} = 128.7 μM).

10. Potential therapeutic effects of berberine on diabetic complications

Diabetic complications are divided into acute complications and chronic complications: the common acute complications of diabetes are diabetic ketoacidosis, hyperosmotic non-ketotic diabetic coma (also known as diabetic hyperosmotic state), and diabetic lactic acidosis. If diabetes is not treated, there will be chronic complications. Chronic complications usually occur years or more after the diagnosis of diabetes, some of which already exist at the time of diagnosis. The common chronic complications are vascular disease, liver disease, kidney disease, cerebrovascular disease, neuropathy, ophthalmopathy, diabetic foot disease and so on.[43] Numerous researches have shown that berberine not only has a strong biological activity

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against diabetes, but also has a good therapeutic effect on diabetic complications such as diabetic neuropathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic cystic disease and diabetic osteopathy.

10.1. Diabetic neuropathy

Diabetic neuropathy is one of the most common chronic complications, which can involve the peripheral nerve, autonomic nerve, cranial nerve, brain and spinal cord. Generally, the probability of complicated neuropathy is related to the course of the disease and the control of hyperglycemia. In general, about 50% of patients with a long course of disease are complicated by neuropathy.[44]

The effects of berberine on cognitive function in patients with diabetes include the inhibition of anti-inflammatory activity and improvement of insulin resistance. Berberine not only activated the PI3K/AKT/mTOR and MAPK signal pathways but also down-regulated the translocation of new PKC subtypes and NF-κB in neurons. In addition, berberine also inhibited the expression of amyloid precursor protein and BACE-1, and reduced the production of oligomer AB42.[45]

The relieving effect of berberine on diabetic and diabetic neuropathic pain is related to its inhibitory effect on oxidative stress and neuroinflammation, which may be mediated by the μ-opioid receptor (MOR). Berberine significantly inhibited lipid peroxidation, activity of reactive oxygen species (ROS) and catalase (CAT), and the tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) protein levels; however, it significantly increased the μ-opioid receptor (MOR) protein and mRNA levels.[46]

AMPK is beneficial to metabolism and mitochondria in many chronic diseases. It has been reported that AMPK has a therapeutic effect on mitochondrial dysfunction in cultured dorsal root ganglion (DRG) neurons. Berberine increased the expression of p-AMPK in STZ-induced diabetic rats, which prevented mitochondrial dysfunction and autophagy damage. In addition, berberine enhanced the endogenous antioxidant defense system mediated by Nrf2, thereby inhibiting neuronal injury and neuroinflammation.[47]

In addition, berberine can promote Nrf2-dependent NGF protein expression and neurite growth at a specific concentration, thereby treating diabetic neuropathy.[48] In addition, berberine activates the PI3K-Akt signal transduction pathway in type 2 diabetic rats, which has the effect of anti-apoptosis and reducing cerebral ischemia/reperfusion injuries.[49]

Another study evaluated the protective effect of berberine on diabetic encephalopathy through the SIRT1/ER stress pathway. The endoplasmic reticulum stress-related proteins (PERK, IRE-1A, EIF-2A, PDI and CHOP) were significantly reduced, and the SIRT1 protein expression was increased.[50]

One study also showed that berberine improves the irS-1 levels in the brain and restores the expressions of Glut-1 and Glut-3, which changes glucose homeostasis in the brain.[51]

10.2. Diabetic nephropathy

Diabetic nephropathy (DN) is not only a common complication of diabetes, but also one of the manifestations of diabetic systemic microangiopathy. The late stage is characterized by proteinuria, progressive renal damage, hypertension, water inhibition and severe renal failure. It is one of the leading causes of death in patients with diabetes.[52] It has been reported that berberine can reduce renal damage and prevent renal tubular epithelial cell apoptosis by modulating the EPs and MMPs/TIMPs systems in diabetic nephropathy rats induced by low-dose streptozotocin (STZ).[53–55]

In addition, the renal protective effect of berberine in DN progression may be due to its ability to inactivate the TLR4/NF-κB pathway, thereby relieving stZ-induced renal injury, inflammatory response and HG-induced apoptosis of podocytes.[56] On the other hand, berberine can inhibit palmitic acid (PA)-induced activation of dynamic related protein 1 (Drp1) and help stabilize podocyte mitochondrial morphology, suggesting that berberine has a therapeutic effect on diabetic nephropathy.[57] Another study showed that berberine reduced the protein and mRNA expression levels of TGF-β1, vimentin and α-SMA in DN rats.[58] In addition, berberine inhibits the transfer of TGF-β1 from glomerular Mesangial cells to podocytes, thus protecting the function of podocytes, which may be one of the potential mechanisms of berberine's protective effect on diabetic nephropathy.[59]

Renal tubular epithelial to mesenchymal transition (EMT) and renal tubulointerstitial fibrosis are the main pathological changes of DN. The anti-fibrosis effect of berberine in the kidney can reduce podocyte apoptosis and inhibit EMT in DN. In the study of DN model KKAy mice and high glucose-induced renal tubular epithelial cell EMT,[60] it was found that berberine could inhibit renal tubular epithelial cell EMT and renal interstitial fibrosis, and berberine-mediated EMT inhibition was achieved through the Notch/Snail pathway.[61]

The relationship between the protective effect of berberine on diabetic nephropathy and the podocyte injury induced by high glucose levels was discussed. Berberine can significantly enhance the activation of AMPK and protect AMPK-silenced podocytes from apoptosis induced by high glucose levels. Furthermore, berberine significantly increased the high glucose-elevated Unc-51-like autophagy-activating kinase 1 (ULK1) S317/S555 phosphorylation, Beclin-1 expression, the ratio of LC3II to LC3I expression and the number of autophagosome; however, it reduced ULK1 S757 phosphorylation in podocytes. In addition, berberine significantly reduced the inhibitory effect of compound C on podocyte autophagy. The protective effect of berberine on podocyte apoptosis induced by high glucose levels could be significantly alleviated by pretreatment with 3-methyladenine or baffinomycin A1. Therefore, berberine can promote the activation of AMPK, promote autophagy in podocytes and protect podocytes from glucose-induced injury. This may help to design new interventions for the treatment of diabetic nephropathy.[62]

10.3. Diabetic cardiomyopathy

Diabetic heart disease refers to the heart disease that is complicated or accompanied by diabetes in patients. It involves cardiac macrovascular, microvascular and neuropathy

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complications on the basis of metabolic disorders such as high glucose and fat levels. Diabetic heart disease covers a wide range, including coronary atherosclerotic heart disease based on diabetes, visceral microvascular disease and visceral autonomic neuropathy.[63]

Diabetic cardiomyopathy is a kind of diabetic heart disease, which refers to myocardial dysfunction without hypertension and coronary artery disease. Unless diabetic patients have hypertension and myocardial ischemia, there are few obvious clinical symptoms, which include mainly the left ventricular diastolic dysfunction. Berberine can stimulate glucose uptake and consumption in H9c2 cardiomyocytes, and has anti-apoptotic activity by increasing AMPK activity, thereby promoting the recovery of cardiac function. In addition, the hypoglycemic effect of berberine on differentiated cardiomyocytes may be related to changes in neutral lipid metabolism.[64–66] Another study also reported that activation of the AMPK signaling pathway by berberine treatment could improve myocardial cell damage induced by high glucose, stimulate mitochondrial biogenesis, and restore autophagy flux in H9C2 cells.[67] In addition, berberine can prevent diabetic cardiomyopathy by interfering with the metabolism of phosphatidylcholine (PCs), phosphatidylethanolamine (PEs) and sphingolipids (SMs).[68] A study to investigate combination therapy to control hyperglycemia and hypertension simultaneously with diabetes was conducted. After 8 weeks of continuous administration of berberine at 100 mg per kg per day, blood glucose levels and blood pressure were decreased, and the function and expression of the BKCaβ1 subunit in cerebrovascular smooth muscle cells were increased.[69]

10.4. Diabetic cystopathy

Diabetic cystitis is a common diabetic bladder dysfunction, characterized by the loss of bladder filling sensation, weakening of bladder contraction function and the increase of bladder volume, which is mainly caused by diabetes-related neuropathy. Studies have shown that berberine may have a preventive and therapeutic effect on diabetic cytopathies by promoting neuroregulation.[70]

10.5. Diabetic osteopathy

Osteoporosis is one of the chronic complications of diabetes, with a current incidence rate of 24% to 52%. Osteoporosis can cause fractures and lead to high disability; it is challenging to treat patients with diabetic fractures and facilitate recovery.[71] At present, there are several prevalent causes of osteoporosis caused by diabetes: the first is the decrease of insulin-like growth factor (IGF), the second is the abnormality of active vitamin D, the third is the abnormality of glucose metabolism, and the fourth is the block of calcium absorption in renal tubules.[72] It is the result of decreased osteoblast production and increased osteoclast production. Literature has shown that berberine increases osteoblast differentiation and reduces osteoclast activity through the AMPK and MAPK pathways.[73] Another study was conducted on bone characteristics in streptozotocin plus HFD-induced diabetic rats and the results showed that higher concentrations of berberine (100 mg kg^{-1}) had an apparent control effect on bone loss in diabetic osteoporosis, which may be the result of reducing the damage of DNA oxidation level and up-regulating the activity of serum antioxidants.[74] Pioglitazone is a PPAR-g agonist associated with bone loss and fracture risk in patients with T2DM. A study of diabetic rats *in vitro* showed that berberine, either alone or in combination with pioglitazone could significantly improve urinary calcium abnormalities, AMPK mRNA expression, bone turnover index, femoral epiphyseal microstructure, histological changes, and increase bone mineral density. Berberine has a protective effect on bone loss induced by pioglitazone in diabetic rats, and its mechanism may be realized through the AMPK activation pathway.[75]

The effects of berberine on anti-diabetes and anti-osteoporosis have been documented. The purpose of this study was to observe the effect of berberine on bone disorders induced by experimental type 1 diabetes in rats. Londzin and his team conducted experiments on 3-month-old female rats dividing them into three groups: I-healthy control group, II-diabetic control group, and III-diabetic rats treated with berberine. Diabetes was induced by a single injection of streptozotocin. After a period of administration of berberine (50 mg per kg per day p. o.), biochemical indexes, such as serum bone turnover markers, bone mass and mineralization, histomorphometric parameters and mechanical properties, were studied. It was found that berberine could antagonize the effects of bone formation markers (osteocalcin) concentration, growth plate and cancellous bone microstructure parameters in diabetic rats; however, it could not improve bone mineralization and bone mechanical properties in diabetic rats.[76]

10.6. Diabetic retinopathy

Diabetes damages very tiny blood vessels behind the eyes. The medical name for this damage is diabetic retinopathy, which is one of the most common complications of diabetes and a major cause of visual impairment in older patients. This disease can lead to poor eyesight and even blindness. Diabetes can cause a variety of eye diseases, such as retinopathy, corneal ulcers, glaucoma, vitreous hemorrhage, optic neuropathy, *etc.*, among which diabetic retinopathy has the greatest impact on vision. According to statistics, the probability of diabetic retinopathy ranges from 21% to 36%.[77] A study on Müller cells cultured with high glucose showed that berberine treatment enhanced autophagy, activated the AMPK/mTOR signal pathway, and played a protective role in apoptosis induced by high glucose.[78]

Wang *et al.* investigated the role of berberine in slowing the progression of diabetic retinopathy in diabetic patients treated with insulin. The results showed that insulin intervention could specifically stimulate the activities of hypoxia inducible factor-1 α and vascular endothelial growth factor in different types of retinal cells. Berberine can inhibit its activity in a dose-and time-dependent manner. Berberine inhibits the activity of AKT/mTOR and resumes the AKT/mTOR signalling pathway, thereby weakening the inhibitory effect of berberine on the expression of hypoxia inducible factor-1 α and vascular

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endothelial growth factor. Berberine inhibits the progression of diabetic retinopathy in experimental type I and type II diabetic mice treated with insulin. It is proven that berberine inhibits insulin-induced activation of retinal endothelial cells through the Akt/mTor/HIF-1α/VEGF pathways, thus improving insulin-induced diabetic retinopathy.[79]

The formation of advanced glycation end products (AGEs) and the activation of AGEs-related signal pathways in the retina of diabetic patients lead to diabetic retinopathy. Wang *et al.* found that berberine (BBR), a natural compound, is an effective AGEs inhibitor, which can significantly inhibit the formation of AGEs and its related TLR4/STAT3/VEGF signal pathway in retinal endothelial cells, thus contributing to the treatment of diabetic retinopathy (DR).[80]

10.7. Diabetic hyperglycemia

Glucose homeostasis is regulated by the hypoglycemic hormone insulin and the hyperglycemic hormone glucagon. Insufficient insulin secretion or decreased sensitivity to insulin are the main causes of type 1 and type 2 diabetes, respectively. The lack of sufficient insulin in the human body will cause metabolic disorders, elevated blood sugar and dehydration. This complication is characterized by an acute onset and serious illness, posing a significant threat to the health and safety of elderly patients with diabetes.[81] Fortunately, recent studies have shown that berberine can reduce blood sugar by regulating glucose metabolism, thereby achieving the purpose of treating diabetes, which broadens its application direction. Its mechanism involves inhibiting hepatocyte mitochondria, thereby increasing the ratio of AMP/ATP and significantly reducing fasting blood glucose levels in diabetic rats.[82] In addition, the hypoglycemic effect of berberine increases the expression of glucose transporter 1 (GLUT1), activates its activity and promotes glucose uptake by activating the AMPK pathway. It was found that berberine could inhibit the oxidation of mitochondrial glucose, increase the ratio of AMP/ATP, and activate AMPK to promote glycolysis.[83]

Berberine can also reduce intestinal glucose absorption, inhibit α-glucosidase and lower postprandial blood glucose levels, which is similar to the hypoglycemic effect of α-glucosidase inhibitors.[84] In addition, berberine can also reduce the intestinal disaccharidase activity of diabetic mice and Caco-2 cells.[85]

10.8. Treatment of polycystic ovary

Insulin resistance (IR) refers to the state in which the insulin effect decreases, that is, the insulin receptor is less sensitive to insulin. Increasing evidence suggests that IR is the pathophysiological basis of PCOS.[86] Recent studies have shown that at least half of women with polycystic ovary syndrome have insulin resistance. This evidence proves that insulin resistance is the pathophysiological basis of polycystic ovary syndrome.[87,88] The study found that despite the increase in glucose uptake and utilization in diabetic mice treated with BBR, insulin release and synthesis did not increase, indicating an improvement in insulin sensitivity in diabetic mice.[89] A recent study also confirmed that BBR can treat impaired glucose tolerance in PCOS patients by regulating the IRS1 signal pathway and improve ovarian polycystic and adenomyosis-like manifestations.[90] Studies have shown that patients with polycystic ovary syndrome produce 20 times more androgens than normal people, including testosterone, androstenedione (A4) and androgen precursor DHEAS.[91] However, too much androgen can increase the secretion of luteinizing hormone and hinder follicular maturation. BBR treats PCOS by reducing the level of serum androgen, which is mainly reflected in three aspects. Firstly, BBR can inhibit androgen receptor signal transduction. Several assays have proved that BBR can increase the level of SHBG in endometrial stroma, while SHBG can inhibit the bioavailability of androgen.[92–94] It has been found that BBR suppresses the AR signal, and it is suggested that the anti-androgen effect of BBR may be achieved by directly acting on the ovary. For example, Li *et al.* found that BBR can induce the degradation of AR protein.[95] Finally, BBR inhibits androgen synthesis. Another study showed that BBR can reduce serum T by reducing the density of steroid-producing acute regulatory protein (STAR) on the theca. Limiting the production of STAR will inhibit the speed and quantity of androgen production.[96]

A rat model of polycystic ovary syndrome by intraperitoneal injection of testosterone propionate was established. The experiments were divided into the model group, low-dose berberine group (BL), high-dose berberine group (BH), metformin (Met) group, and control group (CON). The morphology of the ovary, hormone level and glucose and lipid metabolism were measured. The UID-mRNA-SEQ of ovarian tissue was detected to explore the mechanism of berberine in promoting ovulation. Three biomarkers of endometrial receptivity were detected by the immunohistochemical method. The results showed that the number of vesicles increased and the number of corpus luteum decreased in the model group. A high-dose berberine intervention can reverse these changes. Berberine could also reduce the levels of serum luteinizing hormone (LH) and total cholesterol (TC) in PCOS rats. At the same time, berberine improved the impairment of abnormal oral glucose tolerance without affecting fasting insulin levels and homeostasis model assessment-insulin resistance (HOMA-IR). The ovarian protein expression of LHCGR and CYP19A1 and the mRNA expression in granulosa cells decreased in the model group, and the expression could be restored to a certain extent by the intervention of berberine. In the model group, the thickness of the endometrium decreased and the expression of integrin αvβ3 and lysophosphatidic acid receptor 3 (LPAR3) increased, which could be reversed by berberine. This suggests that berberine can promote ovulation in patients with PCOS, and its mechanism may be related to the up-regulation of LHCGR and CYP19A1. Berberine can also improve endometrial receptivity by down-regulating the expression of αvβ3 and LPAR3.[97]

11. Conclusion

Traditional extraction methods for berberine mainly include acid–water extraction, alkali–water extraction and ethanol

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extraction, among others. With the deepening of research on the effective components of natural products in the industry, various improved methods utilizing the latest technology, such as the liquid membrane method, two-phase extraction method and supercritical fluid extraction method, have opened up new ways and ideas for the extraction and industrial production of berberine. The extraction method involving acidified water and alkaline water is a simple and low cost process; however, it presents some problems, such as a low extraction rate, easy corrosion of equipment, and concerns regarding safety and environmental protection.

Alcohol extraction methods include microwave extraction, (Soxhlet's) reflux extraction, ultrasonic extraction, flash extraction, *etc.*, which have the advantages of low solvent restriction, repeated use, energy saving, environmental protection, high safety, simple operation and high extraction efficiency. However, ultrasonic extraction involves a large investment in equipment.[98,99] With the improvement of methods and the exploration of conditions, new methods such as aqueous two-phase extraction, enzymatic extraction, supercritical CO_2 extraction, liquid membrane extraction and ultra-high pressure water jet extraction have emerged, which have improved the berberine extraction rate, shortened the extraction time and are more suitable for industrial production.

Each extraction method has its own unique advantages. For example, the enzymatic extraction method has negligible effect on extracting the components of the original plant contents.[100] The entire process of supercritical CO_2 extraction does not utilize organic solvents and the extract has no residual solvent. Liquid membrane has a strong enrichment effect. It can be predicted that more advanced extraction technologies will emerge in the future, providing a reference for the extraction, production and clinical application of berberine.

Berberine has been used in clinics for its functions of clearing away heat and toxic materials, as well as resisting bacteria. It exhibits many pharmacological activities, including as anti-dysentery, anti-infectious protozoa and anti-tumor, along with lowering blood sugar, regulating blood lipids, lowering blood pressure and anti-arrhythmia.

One of the main functions of berberine is to activate the enzyme AMP-activated protein kinase (AMPK) *in vivo*. AMPK is a very powerful enzyme in the body, which is often called the "metabolic master switch". AMPK is responsible for regulating the metabolism of the body at the cellular level. The currently used hypoglycemic medicinal food are officially approved in seven categories, namely, biguanidine α-glucosidase inhibitors, insulin sensitizers, secretagogues, as well as new DPP-4 inhibitors and SGLT-2 inhibitors, are oral medicinal food, including injectable hypoglycemic medicinal food, while berberine hydrochloride is not included in the regular hypoglycemic medicinal food. Berberine has unique advantages in multi-target regulation (hypoglycemic, lipid-regulating and anti-inflammatory) and diabetes prevention, but its clinical orientation is still mainly adjuvant therapy. Compared with traditional secretagogues, the risk of hypoglycemia is lower; compared with the DPP-4 inhibitor, it has a wider effect but less convenience. Compared with SGLT-2 inhibitors, the evidence of cardiac and renal hard endpoints is weak. It is necessary to strengthen dosage form improvement and long-term benefit verification in the future.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Conflicts of interest

There are no conflicts of interest to declare.

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