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Review Article

Research Progress on the Hypoglycemic Effects and Mechanisms of Action of *Momordica charantia polysaccharide*

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With the improvement of living standards, the number of people diagnosed with diabetes is increasing, leading to diabetes-related expenditures reaching billions of dollars. Finding a simple, convenient, effective, and long-lasting drug for the treatment of diabetes is urgent. Bitter melon has a history of thousands of years of consumption and medicinal use in China, with numerous health benefits, including the prevention and treatment of diabetes, promotion of appetite, improvement of eyesight, aid in digestion, detoxification, and diuretic effects, earning it the title of "medicinal vegetable." *Momordica charantia polysaccharide* (MCP) is a type of heteropolysaccharide extracted from bitter melon fruit, which is an important component of bitter melon and has multiple biological functions, particularly in the treatment of type 1 and type 2 diabetes. This article summarizes the research results on the use of MCP in the treatment of diabetes over the past 20 years, using data from various databases, including PubMed, Web of Science, Science Direct, Springer, Wiley, ACS, and CNKI, as well as doctoral and master's theses. The article discusses the most commonly used methods and techniques for extracting, isolating, and purifying MCP. It also explores the extraction methods, molecular weight, monosaccharide composition, and structural characteristics of MCP and provides a detailed account of the hypoglycemic effects of MCP in cell models, animal models, and human experiments. This review lays the foundation for the further development and application of MCP.

1. Introduction

Bitter melon has a long history as a medicinal herb in China, with its medicinal value recorded in ancient Chinese texts such as "Compendium of Materia Medica" and "Dian Nan Ben Cao." In ancient China, bitter melon was used by folk medicine to treat diabetes mellitus (DM), and its hypoglycemic and anti-DM effects have now been scientifically proven. Bitter melon is a traditional Chinese medicine with both medicinal and food values, and many traditional Chinese medical books have recorded its use in treating thirst and polydipsia. Its medicinal and food values have been widely used in nutritional formulations for assisting in blood sugar reduction. In many countries' traditional medicine, bitter melon is used to prevent and treat DM. Modern pharmacological experiments have also shown that bitter melon and its extracts have strong hypoglycemic activity, and various mechanism experiments and clinical trials have confirmed the efficacy of bitter melon in treating DM [1]. *Momordica charantia polysaccharide* (MCP) (bitter melon polysaccharide, bitter gourd polysaccharide, and balsam pear polysaccharide) is a heteropolysaccharide obtained from bitter melon fruit. As a biological macromolecule, it is an essential component of bitter melon and the primary bioactive substance with antihyperglycemic activity. MCP, extracted from bitter melon, has many functions and effects, such as hypoglycemic activity [2–4], antibacterial activity [5], antitumor effect [6], immune regulation [7, 8], and antioxidant activity [9–13]. It is a safe, effective, and potentially valuable natural product with strong pharmacological activity, making it a natural product with potential medicinal values.

2. Extraction Methods of MCP

With the development of science and technology, scientists have not only studied the hypoglycemic effects of bitter melon but also delved into the hypoglycemic effects of MCP. The hypoglycemic effects of MCP have been widely applied, including in cell models, animal models, and even in the treatment of diabetic patients. To better apply MCP, scientists have developed various extraction methods [14], including water-alcohol precipitation extraction (traditional extraction method) [15–20], microwave-assisted extraction [21, 22], ultrasound-assisted extraction [23–25], enzyme-assisted extraction [26–28], ultrasound and enzyme-assisted extraction [29, 30], and microwave and enzyme-assisted extraction [31]. Among them, water-alcohol precipitation extraction is the most commonly used method for extracting polysaccharides. The preliminary extraction of MCP can be divided into two types: acid extraction and alkaline extraction. Currently, acid extraction is widely used, such as the anthrone-sulfuric acid method and the phenol-sulfuric acid method, which can measure the content of polysaccharides. To further analyze the composition, relative molecular weight, and other properties of MCP, purification and identification are needed. The methods of purification and separation include gradient precipitation, membrane separation, and column chromatography. Nowadays, two or more methods are often combined organically to achieve efficient separation. Column chromatography is currently the most commonly used method for polysaccharide purification, which is divided into cellulose column chromatography, ion exchange column chromatography, gel column chromatography, affinity chromatography, and high-pressure liquid chromatography. Ion exchange chromatography and gel chromatography are the most commonly used methods in research, and these two methods are often used in combination in practical operations. The commonly used ion exchange agents are DEAE-cellulose or DEAE-sepharose, and the commonly used gels are Sephadex and Sephacryl. There are also many methods for determining the composition of MCP [14], mainly including gas chromatography (GC) [32], high-performance liquid chromatography (HPLC) [33], and high-performance gel permeation chromatography (HPGPC) [34]. In the dried bitter melon powder, the polysaccharide content of bitter melon is only about 6%, which is a heteropolysaccharide of a biological macromolecule. Although the molecular structure and molecular weight of MCP are very complex [35], the monosaccharide composition has been basically identified as a heteropolysaccharide composed of Gal, Glu, Ara, Rha, Man, and Xyl, which are water-soluble [15–17]. MCP has both α-D-pyranosidic and β-D-pyranosidic bonds, which are both bioactive polysaccharides [36]. Table 1 summarizes the extraction methods, monosaccharide composition, percentage and molar ratio, and molecular weight relationship. Panda et al. [8] isolated and identified pectic polysaccharides (PS) from bitter melon, which is composed of a repeat unit of one main chain and one side chain. According to the results of monosaccharide composition, methylation studies, and nuclear magnetic resonance experiments, the repeat unit of MCP is shown in Figure 1, and the schematic diagram of MCP is shown in Figure 2.

According to Table 1 and Figures 1 and 2, it can be seen that different extraction methods of MCP have their own advantages and limitations. Hot water extraction: this method is simple to operate, low in cost, and applicable to a variety of plant materials, but it is limited by the thermal stability of polysaccharides, and the extraction rate is relatively low, and the extracted polysaccharides contain impurities. Acid-base method: this method has a high extraction rate and a high content of extracted polysaccharides and is suitable for a variety of plant materials, but acid-base treatment will destroy the structure of polysaccharides and is susceptible to the concentration of acid and alkali and the processing time, and the processing liquid has corrosivity. Enzymatic method: this method can extract high-purity polysaccharides, and the operation is simple and applicable to a variety of plant materials, but the selection of enzymatic solution and the enzymatic time will affect the extraction efficiency, and the cost is relatively high. Ultrasonic method: this method has a fast extraction rate, is applicable to a variety of plant materials, and can extract high-quality polysaccharides, but the intensity and time of ultrasonic waves will affect the extraction efficiency, and the cost is relatively high. Therefore, when selecting a polysaccharide extraction method, factors such as experimental requirements, material characteristics, and equipment conditions need to be comprehensively considered in order to choose the most suitable extraction method. Different extraction methods have significant effects on the extraction rate, chemical composition, average molecular weight, monosaccharide composition, molar ratio, preliminary structural characterization, and microstructure of MCP. Overall, current research on MCP is limited to the basic primary structure characteristics of individual-level fractions, and further in-depth research is needed to clarify its fine primary structure, higher-order structure, and structure-function relationships.

3. Relationship between Diabetes Mellitus and MCP

The definition of diabetes mellitus (DM) varies, but it is essentially a group of metabolic disorders characterized by high blood sugar, mainly manifested as chronic hyperglycemia. The main cause is insufficient insulin secretion, impaired insulin action, or both. With the increase in the number of DM types and the advancement of scientific technology, the classification or classification of DM has also varied. Currently, the World Health Organization (WHO) [41, 42], the Chinese Diabetes Expert Consensus (CDEC) [43], and the American Diabetes Association (ADA) [44, 45] have classified DM, as shown in Table 2.

Once diagnosed with DM, all types of DM patients are at risk of developing the same chronic complications although the progression rate may differ. According to the latest global health organization statistics, there are over 100 known complications associated with DM, making it the

Table 1: Extraction methods, monosaccharide composition, percentage and molar ratio, and molecular weight relationship of MCP.

Extraction types	Extraction method	Monosaccharide composition and ratio	Molecular weight size	References
1	Water extraction and alcohol precipitation extraction method	MCP isolation yielded MCP 1 and MCP 2, which yielded 48.74% and 15.16% of MCP yields, respectively. The polysaccharide content of MCP, MCP 1, and MCP 2 was 62.76%, 84.03%, and 72.57%, respectively, and the protein content was 4.62%, 2.08%, and 6.87%, respectively. MCP 1 and MCP 2 consist of Rib, Rha, Ara, Xyl, Man, Glc, and Gal. The molar ratio of MCP 1 is 1.00 : 6.33 : 9.07 : 3.78 : 4.71 : 27.28 : 19.58, and the molar ratio of MCP 2 is 1.86 : 1.00 : 8.92 : 9.62 : 34.18 : 44.20 : 23.61	MCP 1 and MCP 2 were 85.5 kDa and 441 kDa	[7]
		Water-soluble pectin polysaccharide (PS) consists of D-Gal and D-Gal A with a molar ratio of nearly 1 : 4	200 kDa	[8]
		MCP 1, MCP 2, MCP 3, MCP 4, and MCP 5. MCP 2 is composed of Gal. The MCP 4 is composed of Ara, Gal, Rha, and Xyl	—	[19]
		MCP 1, MCP 2, and MCP 3 were analyzed. MCP 1 was composed of Man, Rha, GlcA, GalA, Glc, Gal, Xyl, and Ara with a molar ratio of Rha, GalA, Gal, Xyl, and Ara at 1.63 : 21.88:4.66 : 1.00 : 1.29.	MCP 1 and MCP 2 were 1.16×10^6 Da and 7.45×10^5 Da	[20]
		MCBP extraction was 36%, MCBP total carbohydrate content was 45.4%, glucuronic acid was 22.1%, and protein was 0.71%. MCBP consists of Man, GalA, Rha, Glc, Gal, Xyl, and Ara with a molar ratio of 0.01 : 0.15 : 0.02 : 0.38 : 0.31 : 0.05 : 0.09	92 kDa	[17]
		The glycosaminoglycan (GAG) isolated from balsam pear consists of hexosamine (D-glucosamine or D-galactosamine) and another neutral sugar (D-Gal, keratin sulfate) or glucuronic acid (D-GlcA or L-aduronic acid)	—	[16]
		The MCP contains 2 main components	The first is 1832.80 kDa and the second is 41.52 kDa	[18]
		MCP I purification yields MCP Ia and MCP Ib, MCP Ia consists of L-Rha, D-Xyl, D-Fru, and D-Gal at a molar ratio of 4.4 : 2.3 : 1.0 : 5.7, and MCP Ia may also contain Glc	—	[37]
		MCP-A, MCP-B, MCP-C, and MCP-D. MCP-A purification yielded MCP-A1. MCP-A1 without protein, nucleic acid, and glyonic acid and was a nonstarch polysaccharide	MCP-A1 is 93577 Da	[34]
		The MCP is composed of Man, Rha, Glc, Gal, and Ara. Percentage was 6.77%: 3.59%: 35.58%: 38.82%: 14.55%. Mar ratio: 1.00 : 0.51 : 5.22 : 5.67 : 2.54	—	[33]
		The MCP consists of Gal, Rha, Man, Ara, Glc, and Xyl. Percentage was 48.14%: 9.84%: 2.32%: 15.93%: 21.64%: 2.12%. The molar ratio is 2.22 : 0.50 : 0.11 : 0.88 : 1.00 : 0.12	—	[32]
		The MCP consists of Rha, Ara, Man, Glc, and Gal with a percentage of 24.03%: 16.47%: 6.7%: 24.84%: 27.94%	8000 Da	[36]
		MCP separated insoluble MCP 1, MCP 3, MCP 4, MCP 5, and MCP 6, percentage of 3.93%: 25.00%: 10.32%: 7.90%: 28.80%: 24.05%. The MCP 2 is used for Gal. MCP 4 consists of L-Rha, D-Ara, D-Glc, D-Gal, and D-Xyl with a percentage of 24.30%: 16.47%: 6.72%: 41.55%: 11.23% and molar ratio of 1 : 0.75 : 0.25 : 1.83 : 0.85	MCP 2 and MCP 4 were 5.37×10^4 Da and 9.65×10^4 Da	[38]
		The MCP consisted of GalA, Rha, Xyl, Man, Glc, and Gal with percentages of 93.7%: 0.06%: 0.18%: 0.03%: 0.8%: 0.28%, respectively	—	[15]
		The MCP was 2.3% extracted, with a total content of 72.6 ± 1.2% carbohydrate, 8.9 ± 0.2% protein, and 20.1 ± 0.4% glyonic acid. The MCP consists of Ara, Xyl, Gal, and Rha with a molar ratio of 1.00 : 1.12 : 4.07 : 1.79	85–100 kDa	[39]

Table 1: Continued.

Extraction types	Extraction method	Monosaccharide composition and ratio	Molecular weight size	References
2	Microwave-assisted extraction method	MCP, the extraction rate is 1 times higher than the traditional extraction method. However, the purity of the MCP was roughly the same as the traditional extraction method, or about 50%	—	[22]
		The average extraction rate of MCP was 4.798%	—	[21]
		The MCP extraction rate was 16.84%. The MCP content was 83.76%	—	[24]
		The average extraction rate of the MCP was 4.43%	—	[23]
		The MCP extraction rate was 13.94%	—	[25]
3	Ultrasonic-assisted extraction method	The extraction rates of BPS-J, BPS-W, BPS-C, and BPS-A were 14.36%, 3.09%, 3.82%, and 4.18%, respectively, and the polysaccharide content was 76.57%, 79.85%, 85.49%, and 80.74%, respectively. The BPS consists of Ara, Xyl, Gal, Glc, Man, and GalA. The molar ratio is BPS-J = 9.6 : 17.8 : 19.1 : 17.4 : 8.2 : 1.0, BPS-W = 2.0 : 2.2 : 13.0 : 2.2 : 1.0 : 1.7, BPS-C = 8.2 : 32.3 : 20.2 : 20.4 : 4.0 : 1.0, BPS-A = 3.1 : 6.1 : 20.2 : 1.4 : 0 : 1.0	BPS-J, BPS-W, BPS-C, and BPS-A are 384.63 kDa, 400.25 kDa, 373.50 kDa, and 70.00 kDa, respectively	[40]
4	Enzyme-assisted extraction method	MCP was 3.48% extracted and 94.6% polysaccharide content. 10% of the enzyme dosage. Compared with the conventional method, the extraction rate of polysaccharide was more than doubled, the polysaccharide content was increased by 11.5%, and the protein content was decreased by 75.2%	—	[26]
		From MCP, isolated D1, D2, and D3 represent 40.3%, 35.5%, and 21.3%, respectively	—	[28]
		The MCP consisted of Rib, Rha, Ara Xyl, Man, Glc) and Gal with percentages of 1.18%, 8.36%, 12.08%, 5.11%, 6.30%, 37.54%, and 29.43%	—	[27]
5	Ultrasonic and enzyme-assisted extraction method	The extraction rate of MCP was 29.75 ± 0.48%	—	[29]
		The extraction rate of MCP was 21.1%, which increased 7.8%, 13.5% and 7.77% over thermal immersion, ultrasound, and cellulase, respectively	—	[30]
6	Microwave and enzyme-assisted extraction	The extraction rate of crude MCP was 23.33%	—	[31]

Note: Glc: glucose; Man: mannose; Gal: galactose; Rha: rhamnose; Ara: arabinose; Xyl: xylose; Rib: ribose; Fru: fructose; GalA: galacturonic acid; GlcA: glucuronic acid.

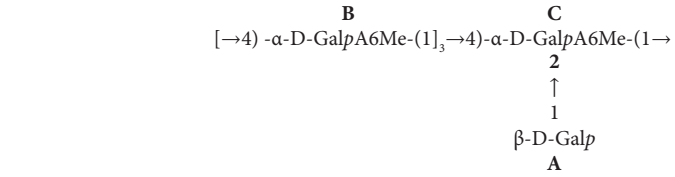

Figure 1: Repeat unit of MCP primary structure.

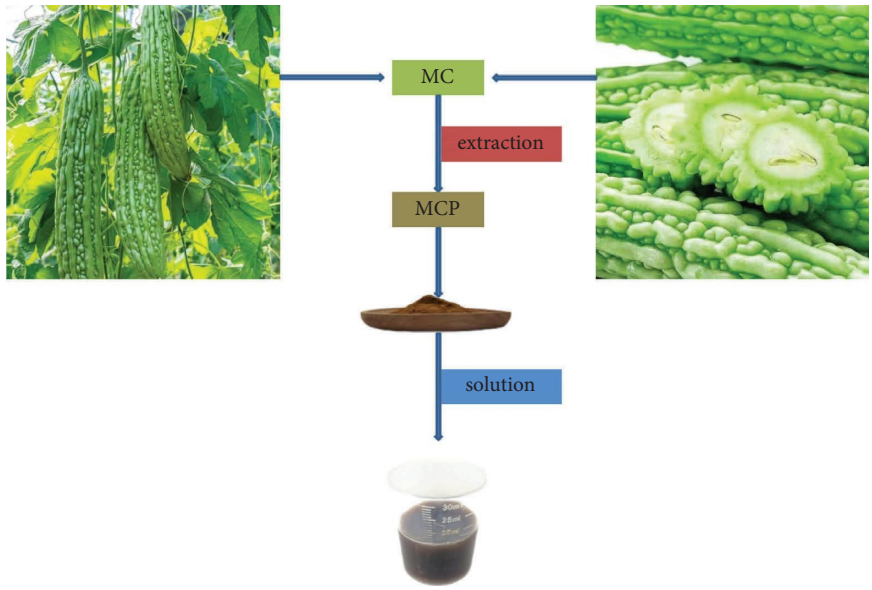

Figure 2: MCP schematic diagram.

Table 2: Classification of DM by the WHO, the CDEC, and the ADA.

Different classification	Somatotype					
WHO	Type 1 DM	Type 2 DM	Encyesis DM	Special-type DM	Mixed-type DM	Unclassified DM
CDEC	Type 1 DM	Type 2 DM	Encyesis DM	Single-gene DM	Secondary DM	Unfinalized DM
ADA	Type 1 DM	Type 2 DM	Encyesis DM	Specific type DM		

disease with the highest number of complications [46]. DM has acute complications, including diabetic ketoacidosis, hyperosmolar hyperglycemic state, and lactic acidosis. DM also has chronic complications, including diabetic nephropathy [47] (kidney failure), diabetic retinopathy [48], diabetic foot [49], DM cardiovascular disease [50], DM cerebrovascular disease [51], and DM neuropathy [52]. Patients with type 2 DM are most common, both in China and around the world, accounting for 90%–95% of all DM cases [53]. According to the latest report by the IDF, in 2017, approximately 425 million people worldwide had DM, and by 2021, the number of DM patients globally reached 537 million. It is estimated that by 2045, the number of DM patients could reach 783 million, with China already having become the country with the highest number of DM patients worldwide [53]. According to domestic estimates, there are currently over 140 million DM patients in China [54]. According to the WHO's estimation [55], in 2019, global direct health expenditures for DM were $760 billion, with an expected increase to $825 billion by 2030 and $845 billion by 2045. The top three expenditures globally were the United States at $294.6 billion, China at $109 billion, and Brazil at $52.3 billion. There are two main types of drugs used to treat DM: oral and injectable. Currently, there are eight oral medications available, such as metformin, sulfonylureas, and alpha-glucosidase inhibitors. These three drugs are the most commonly used oral medications for treating DM, but they have many adverse reactions and side effects [56]. Bitter melon is often used as a treatment for DM in China, India, and other European countries [57–59]. Although bitter melon has been used to treat DM for a long time, its evaluation by people varies due to its bitter taste, different varieties, and methods of use. However, MCP has become the subject of scientific research due to its excellent hypoglycemic activity and almost nonexistent toxic side effects. The hypoglycemic function of MCP has been extensively studied, but current research on the hypoglycemic activity of crude MCP is mostly conducted through cell and

animal experiments, with very few human research experiments. The efficacy and mechanism of action of MCP in treating DM are very complex. A summary of the effects and related mechanisms of MCP in the treatment of DM is discussed below. Research content on the hypoglycemic effect of MCP is given in Figure 3.

4. Hypoglycemic Effect and Mechanism of MCP

4.1. In Vitro Hypoglycemic Effect of MCP. Currently, there are not many in vitro cell studies on the use of MCP for the treatment of DM and its complications. These studies involve pancreatic cells, skeletal muscle cells, tumor cells, adipocytes, and spleen cells. Various methods are used to establish type 1 or type 2 DM cell models, followed by the use of MCP extracts at different purities to prevent and treat DM cell models and their complications. Modern scientific research has confirmed that MCP has a significant in vitro hypoglycemic effect.

In a pancreatic cell model, Cui [60] found in their cell experiments that MCP can protect pancreatic β-cells by regulating the mutual relationship between Th1 and Th2 cell subgroups, thereby promoting the repair of the diseased pancreatic tissue and normal secretion of insulin substances, ultimately leading to its hypoglycemic function. In a skeletal muscle cell model, Zhou [61] used water extraction and alcohol precipitation to prepare fresh bitter melon crude polysaccharides (FMP) and dried bitter melon crude polysaccharides (DMP), respectively. The physical and chemical characteristics, antioxidant activity, inhibition of α-glucosidase activity, and stimulation of glucose uptake in L6 mouse skeletal muscle cells were analyzed before and after drying MCP. The results showed that the IC50 values of α-glucosidase inhibition for FMP and DMP were 148.8 μg/ml and 166.1 μg/ml, respectively, and DMP effectively stimulated glucose uptake by L6 mouse skeletal muscle cells. Drying significantly affected the physical and chemical characteristics of MCP, reduced its antioxidant activity, and had a significant effect on its hypoglycemic activity. Evaluation of the hypoglycemic activity of DMP: a cell toxicity experiment on L6 skeletal muscle cells showed that MCP1-3 did not produce cell toxicity at doses below 1 mg/ml. The stimulatory effect of MCP1-3 on glucose uptake by L6 skeletal muscle cells was analyzed using a glucose oxidase method at doses ranging from 100 to 1000 μg/ml. The results showed that only MCP2 and MCP3 were able to effectively stimulate glucose uptake by the cells, with MCP2 showing a dose-dependent effect and being equivalent to insulin at a dose of 1000 μg/ml. MCP3 showed the highest activity at a dose of 800 μg/ml. In addition, the IC50 values of MCP1-3 for inhibiting α-glucosidase activity were 560.2 μg/ml, 720.3 μg/ml, and 748.7 μg/ml, respectively. The hypoglycemic mechanisms of MCP1 may differ from those of MCP2 and MCP3. In a tumor cell model, He et al. [62] conducted research on the separation and purification techniques of MCP using DEAE-52 cellulose column chromatography and Sephadex G-100 gel column chromatography. The experiment used SMMC-7721 liver cancer cells as a template and set the appropriate concentration of MCP samples to 50 μg/ml and tested their activation ability on γ and δ receptors at this concentration. The results showed that MCP2 and MCP4 had activation effects on PPARγ receptors, with activation factors of 1.726 and 1.602, respectively. MCP2-1 and MCP2-2 could activate PPARγ receptors with activation factors of 1.593 and 1.678, respectively. MCP2, MCP2-1, and MCP2-2 were identified as the hypoglycemic active components of MCP. He and Liu [63] also conducted PPAR in vitro stimulation experiments on MCP, using a high-throughput screening model with PPAR subtypes α, γ, and β/δ as targets to test MCP activity. The results showed that MCP had a strong activation effect on PPARδ and PPARγ, with activation factors of 1.995 and 1.689, respectively. MCP was also found to be an inhibitor of PPARγ and PPARβ/6 and may be a potential antihyperglycemic drug and an active component for hypoglycemic and lipid-lowering effects. He [64] studied a high-throughput screening (HTS) model for PPAR agonists at the cellular level based on the transactivation mechanism. MC3 and MC2-3 were identified as the main active factors for the lipid-lowering, hypoglycemic, and weight-loss effects of bitter melon. Using high-throughput detection technology for PPAR agonists, the researchers confirmed that bitter melon has physiological functions for lowering blood glucose and reducing fat. MCP and bitter melon saponins were identified as the main active components for hypoglycemic and lipid-lowering effects of bitter melon. The hypoglycemic and lipid-lowering activities of MCP may be closely related to the composition of monosaccharides, the connection method of glycosidic bonds, and the size of the molecule. MCP with a lower molecular weight has stronger hypoglycemic and lipid-lowering activities, and there is also a synergistic effect between different MCP components. In a fat cell model, Liu [65] used a bead mill to obtain MCP by ultrafine grinding of bitter melon and explored the regulatory function of MCP on blood glucose levels at the molecular level. After DEAE-52 ion exchange chromatography, three polysaccharide components, MCPI, MCPII, and MCPIII, were obtained. Hypoglycemic active components in MCP were screened using a 3T3-L1 fat cell model for insulin resistance: MTT assays showed that MCPI, MCPII, and MCPIII had no toxic effects on 3T3-L1 fat cells, and MCPI could promote cell growth. Glucose oxidase assays showed that MCPII had higher hypoglycemic activity than MCPIII. In a spleen cell model, Cui [66] cultured normal and DM model mouse spleen cells in vitro and examined the cytokines in the culture supernatant by ELISA. The results showed that MCP and ABP could control the production of IFN-γ by Th1 cells in DM model mouse spleen cells to varying degrees and promote the production of Th2 cytokine IL-4.

In summary, the hypoglycemic mechanisms of MCP in vitro cell experiments are mainly as follows: (1) repair and regenerate damaged pancreatic islet cells, restore and activate normal pancreatic islet cells, control islet cell apoptosis, protect islet cell function, increase islet β-cell ability, increase the number of islet β-cells, and promote the re-production of insulin by normal islet cells. This leads to an increase in plasma insulin concentration, control of glucagon release, and a decrease in glucagon ability (JNK signaling can act on

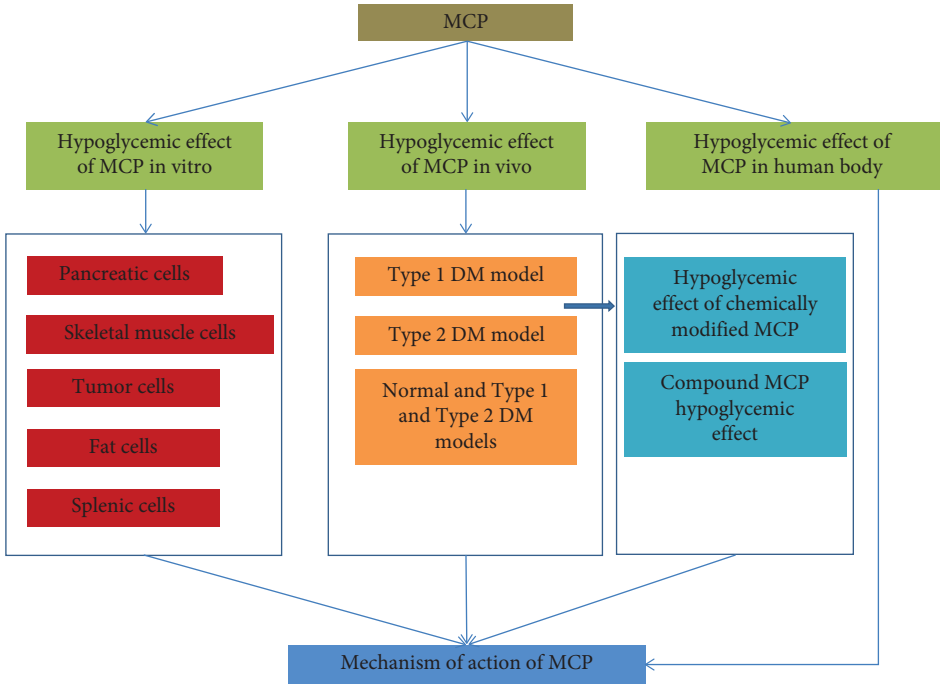

Figure 3: Research content on the hypoglycemic effect of MCP.

different receptors to induce cell apoptosis). (2) Regulate the activity of glucose metabolism enzymes in cells (control the activity of α-glucosidase, α-amylase, and key enzymes in gluconeogenesis and increase the activity of key enzymes in glycolysis and the pentose phosphate pathway), control intracellular α-glucosidase, affect the dissolution and absorption of carbohydrates, and delay the absorption of glucose in cells. (3) Enhance the glucose circulation in peripheral tissues by promoting effective utilization of glucose in other parts of the body. This process includes accelerating the breakdown and metabolism of glucose in the body, promoting the synthesis of muscle glycogen, and regulating the reabsorption of glucose (enhancing the expression of GLUT 4 through pathways such as PI3K, AMPK, mTOR, and Sirt 1).

4.2. In Vivo Hypoglycemic Effects of MCP. Currently, most of the experiments on MCP are animal experiments, mostly using rats and mice. A 1st type DM model is formed in rats or mice by intraperitoneal or intravenous injection of streptozotocin (STZ) or aloxan (ALX), or a 2nd type DM model is formed in rats or mice by first feeding them a high-sugar and high-fat diet for a period of time, followed by intraperitoneal or intravenous injection of a lower dose of STZ or ALX. Various methods are then used to extract MCP at different purities for the prevention and treatment of DM and its complications.

4.2.1. Type 1 DM Model. Zhang et al. [67] conducted a comparative study of the hypoglycemic effects of MCP on STZ-induced DM model mice and made preliminary analyses of the hypoglycemic mechanisms. The results showed that the dosage of MCP at 400 mg/kg could significantly reduce the average blood glucose level of type 1 hyperglycemic mice and the concentration of fructosamine. Meanwhile, MCP could also increase the glucose tolerance and liver glycogen concentration of DM model mice. The hypoglycemic mechanism of MCP may be due to the reduction of pancreatic β-cell damage caused by STZ or an improvement in the regulatory function on damaged β-cells, thus achieving the effect of regulating blood glucose. Shi and Yao [68] used a hot water extraction method to study the hypoglycemic activity of water-soluble MCP on bitter melon's water-soluble crude polysaccharides. The results showed that the water-soluble polysaccharides of bitter melon could significantly reduce the blood glucose level in diabetic mice, and the therapeutic effect was very significant. In addition, the hypoglycemic activity of MCP was positively correlated with the speed of blood glucose reduction and dosage. When the dosage exceeded 500 mg/kg, the hypoglycemic activity of MCP was significantly higher than that of the conventional hypoglycemic drug metformin. Chen et al. [69] demonstrated through scientific research that MCP with high antioxidant activity in vitro, i.e., the medium-dose group (100 mg/kg) and high-dose group (250 mg/kg), could significantly reduce the glucose levels of mice and increase the superoxide dismutase activity of mice. The high-dose group could also increase the liver glycogen concentration of mice, but the group without antioxidant activity had no significant inhibitory effect on ALX-induced hyperglycemia. Xu et al. [4] found through experiments that water-soluble polysaccharides obtained from bitter melon could effectively reduce the blood glucose levels of mice with ALX-induced hyperglycemia, thereby improving glucose tolerance. Both water-soluble polysaccharides (MCW) and

alkaline-soluble polysaccharides (MCB) showed significant hypoglycemic effects, and more MCW and MCB could repair the damaged pancreatic tissue and enhance insulin secretion in STZ-induced DM mice. Dong and Zhang [70] obtained bitter melon alkaline polysaccharides (AEMP) from bitter melon. AEMP at 200 and 400 mg/kg bw could significantly reduce the blood glucose, glucose tolerance, and liver glycogen concentration of STZ-induced hyperglycemic mice, as well as significantly reduce the fructosamine concentration of hyperglycemic mice. The MCP with a large number of macromolecules obtained from alkaline polysaccharides has a good hypoglycemic effect, and its mechanism may be to promote the production of insulin by pancreatic β-cells or to reduce the damage to pancreatic β-cells caused by STZ or to improve the function of damaged β-cells to achieve the hypoglycemic effect.

Cui [60] extracted MCP from fresh bitter melon using a hot water extraction method. DM experimental mice models were created by intraperitoneal injection of STZ at 200 mg/kg, and then the model mice were treated with MCP solution at doses of 200 mg/kg and 300 mg/kg by gavage. After 2 weeks, the blood glucose levels decreased by 50.23% and 53.68% compared with before treatment, and the serum insulin levels also increased to varying degrees, thus confirming the hypoglycemic activity of MCP. Histological observations showed that the pancreatic tissue of DM model mice was severely damaged, and inflammatory cell infiltration and necrosis occurred, but after MCP treatment, although inflammatory cell infiltration occurred, tissue necrosis did not occur. Xu et al. [4] dissected the pancreas of STZ-DM mice after continuous gavage of MCP for 10 days to observe the morphology of the pancreatic tissue in the mice. The results of pancreatic tissue slices of normal mice showed that the islets were round to oval cell clusters with a complete cell structure and regular arrangement, and the boundary with the surrounding pancreatic tissue was clear and distinguishable, with a lighter color after HE staining than the surrounding pancreatic tissue. In contrast, the number of islets in the STZ blood glucose control group mice was reduced, and the nuclei of the islet β-cells showed varying degrees of condensation, cell destruction occurred, and local tissue necrosis occurred. Compared with the STZ blood glucose control group mice, after MCP treatment, although inflammatory infiltration was observed in some pancreatic tissue, no obvious tissue necrosis was observed. This indicates that the hypoglycemic effect of MCP is due to the restoration of the damaged pancreatic tissue, which promotes the proliferation of pancreatic β-cells and insulin production, and then uses the insulin effect to affect the central and peripheral metabolism, thereby improving synthetic metabolism, controlling catabolic metabolism, and achieving the goal of lowering blood glucose levels. Song [71] studied the effects of MCP on the hypoglycemic function and insulin abilities of DM mice. The study used STZ-induced DM models in Kunming mice, and MCP extract was used as a treatment method. The results showed that the blood glucose levels of mice in the high-dose MCP group (2 g/kg/d) continuously administered for 15 days decreased significantly compared with DM mice, and insulin ability increased significantly, while the insulin resistance index (HOMA-IR) increased to a certain extent, and the insulin sensitivity evaluation index (ISI) decreased significantly. This also indicates that MCP has a significant hypoglycemic effect on DM mice and can also increase insulin production. Yang [27] randomly divided experimental mice into the blank group, DM model group, and low, medium, and high-dose groups of MCP and measured blood glucose levels, insulin concentrations, and resistance indices. The results showed that after MCP treatment, MCP could significantly lower blood glucose levels, thereby increasing insulin concentrations and resistance indices significantly, while the insulin sensitivity index decreased significantly.

In summary, the hypoglycemic mechanism of MCP for type 1 DM mainly includes the following aspects: (1) repair and regenerate damaged islet cells, restore and activate normal islet cells, control islet cell apoptosis, protect islet cell function, improve the ability and number of pancreatic β-cells, and promote the re-production of insulin by normal islet cells; increase plasma insulin concentration, control glucagon release, and decrease glucagon ability (JNK signaling can act on different receptors to induce cell apoptosis); (2) enhance insulin sensitivity, improve glucose tolerance, increase insulin affinity or receptor number, increase insulin resistance index, and decrease insulin sensitivity index; (3) the PI3K/AKT signaling pathway plays a role in normal cell metabolism, generally involving insulin receptor (InsR), insulin receptor substrate-2 (IRS-2), phosphatidylinositol-3-kinase (PI3K), and multiple upstream and downstream information factor proteins; and (4) inhibit glycogenolysis, increase liver glycogen synthesis, regulate gluconeogenesis, inhibit the absorption rate of glucose in the small intestine, and regulate sugar metabolism.

4.2.2. Type 2 DM Model. Xu et al. [3] isolated a water-soluble polysaccharide (MCP) from bitter melon fruit and studied its hypoglycemic effect in both normal healthy mice and ALX-induced DM mice. After 3 days of ALX induction, MCP was orally administered at doses of 100, 200, and 300 mg/kg body weight once a day for 28 days. The data showed that compared with the DM control group, the fasting blood glucose concentration (BGL) decreased significantly, and the glucose tolerance of ALX-induced DM mice increased significantly, and the weight loss of DM mice was also prevented. The dose of 300 mg/kg body weight had the best effect. The results showed that MCP had a significant dose-dependent anti-DM activity in ALX-induced DM mice. It can significantly reduce the blood glucose level of ALX-induced DM mice and improve glucose tolerance. The study showed that MCP's antihyperglycemic activity may be exerted by improving glucose tolerance, intestinal absorption of glucose, and glucose metabolism to increase insulin secretion and protect β-cells, thereby improving the condition of type 2 DM. Zhang et al. [72] isolated a polysaccharide with a molecular weight of 13,029 Da from bitter melon (MCP). The hypoglycemic function of MCPIIa was detected in STZ-induced DM mice. After STZ induction, MCPIIa (100, 200, or 300 mg/kg body weight) was orally

administered once a day for 28 days. The blood glucose of STZ-induced DM mice was significantly reduced, and the serum insulin concentration increased significantly after MCPIIa administration compared with DM mice. Transmission electron microscopy showed that the STZ lesions in the pancreatic tissue of mice treated with MCPIIa were alleviated. MCPIIa has excellent hypoglycemic activity in STZ-induced DM mice and has a certain protective and restorative effect on the damaged pancreas of DM mice. In addition, using MCP can regulate the body weight of type 2 DM rats, reduce FBG, regulate blood lipids and oxidative stress levels, and alleviate kidney tissue damage.

Wang et al. [73] compared the anti-DM effects and potential mechanisms of bitter melon saponins (SMC) and polysaccharides from bitter melon (PMC) in STZ-induced high-fat diet type 2 DM mice. All mice were orally administered once a day for five weeks (from day 63 to day 98). The results showed that M-SMC (40 mg/kg) and PMC (500 mg/kg) were the best doses for preventing and treating DM, which significantly restored body weight, reduced fasting blood glucose levels, improved insulin resistance, and increased the ratio of liver phosphorylated adenosine monophosphate-activated protein kinase (p-AMPK) to total protein. The results demonstrated that the hypoglycemic mechanism of SMC may be involved in the AMPK/NF-κB signaling pathway by activating AMPK phosphorylation and regulating energy metabolism. However, oral administration of PMC can significantly increase antioxidant capacity by increasing SOD levels and reducing MDA levels and alleviate STZ-induced organ tissue damage (kidney and pancreas), which indicates that the hypoglycemic mechanism of PMC may involve the repair of STZ-damaged pancreatic β-cells. Liu [65] obtained MCP by superfine grinding of bitter melon and obtained three MCP components, MCPI, MCPII, and MCPIII, by DEAE-52 ion exchange chromatography. The hypoglycemic effect of MCPII was tested in a rat model of type 2 DM. The study showed that when the oral dose was 200 mg/kg, MCPII could significantly reduce fasting blood glucose levels and glucose tolerance in rats with type 2 DM and significantly affect the antioxidant defense system in the body by increasing SOD and GSH-Px activities, reducing MDA and TG contents, but could not alleviate the symptom of weight loss in type 2 DM.

Miura et al. [74] found that the water extract of bitter melon had a strong stimulating effect on AMPK cells in skeletal muscles of type 2 DM KK-A^y mice. The results showed that when the water extract of bitter melon was fed to mice at doses of 100 mg/kg and 20 mg/kg (by body weight), a significant hypoglycemic effect was observed between 2 and 4 hours; when mice were fed at a dose of 100 mg/kg, the quantity of AMPK in mice measured at the 4th hour was increased by 1.6 times. Zhang [75] extracted crude polysaccharides of bitter melon using the 50°C water extraction and alcohol precipitation method, and the three obtained components were named MCPI, MCPII, and MCPIII, respectively. A type 2 DM rat model was established, and the experiment found that MCP mainly regulated the level of blood lipids by regulating the utilization and distribution of lipids and improved the symptoms of lipid metabolism disorder in the DM body. By upregulating insulin receptor (INR), glucose transporter (GLUT), inositol phosphate kinase, and NADP to activate the PI3K/AKT signaling pathway and enhance the transport and utilization of glucose, excess glucose storage was reduced. At the same time, upregulating epidermal growth factor, initiating signal cascade reactions, promoting the increase of intracellular Ca^{2+} concentration, and increasing glycolysis were carried out. Improving the body's immune response and reducing oxidative damage to the body jointly controlled the blood glucose of type 2 DM rats. Sajadimajd et al. [76] investigated whether the Notch signaling pathway is involved in the anti-DM and pancreatic regeneration effects of polysaccharides isolated from bitter melon in DM rats. MCP was isolated from bitter melon. Male Wistar rats were intraperitoneally administered STZ to establish a DM model and were divided into control group, DM group, metformin (500 mg/kg, once daily) group, and treatment (10 mg/kg, once daily) group. MCP normalized high blood glucose in DM rats. MCP increased mRNA levels of Ins1, Jagged1, Pdx1, and Hes1, while reducing the ratio of Notch1, Dll4, and Bax/Bcl2 in DM rats. In addition, compared with the DM group, MCP-treated DM rats showed increased immunohistochemical staining levels of hes1, cyclin D1, and VEGF proteins in the pancreas. These findings provide insight into the anti-DM potential of MCP by regulating pancreatic regeneration and suggest that regulating the Notch and angiogenesis pathways may play a key role in mitigating DM. MCP can normalize blood glucose levels in STZ-induced type 2 DM rats by regulating the Notch and angiogenesis pathways. Given that this effect is associated with increased expression of Pdx-1 and insulin in the pancreas. Luo [77] studied how MCP controls glucose levels in high blood glucose DM rats and changes their manifestations such as high blood glucose and high blood lipids. MCP downregulated the gene expression of some enzymes in glycogen protein, while upregulating the gene expression of some important enzymes in glycolysis and the tricarboxylic acid cycle (TCA), thereby increasing glycolysis and promoting the process of the TCA cycle produced during glycolysis, controlling glycogen breakdown, and lowering glucose production. MCP also increased the body's immune response and reduced oxidative stress to control blood glucose levels in type 2 DM. It also strengthened the control of lipid metabolism processes to regulate lipid levels in the body. Bai et al. [2] obtained the whole transcriptome from the liver of type 2 DM rats and type 2 DM rats treated with DMCPIIa using RNA-seq. Gene ontology and pathway analysis showed that 17 differentially expressed genes were enriched in specific biological processes mainly related to glucose and lipid metabolism. The study showed that pdk4, pkl, hsd11β1, msmo1, rbp4, and fads2 may be promising candidates for regulating type 2 DM.

In summary, the hypoglycemic mechanism of MCP in type 2 DM is mainly as follows: (1) repair and regenerate damaged pancreatic cells, restore and activate normal pancreatic cells, control pancreatic cell apoptosis, protect pancreatic cell function, improve the ability of pancreatic beta cells, increase the number of pancreatic beta cells, and

thus promote the re-production of insulin in normal pancreatic cells; increase plasma insulin concentration, control glucagon release, and decrease glucagon ability (JNK signaling can act on different receptors to induce cell apoptosis); (2) enhance insulin sensitivity, improve glucose tolerance, increase insulin affinity or receptor quantity, increase insulin resistance index, and decrease insulin sensitivity index; and (3) regulate the activity of glucose metabolism enzymes in cells (control the activity of key enzymes such as α-glucosidase, α-amylase, and gluconeogenic enzymes and increase the activity of important enzymes in glycolysis and the pentose phosphate pathway), control intestinal α-glucosidase, affect the dissolution and absorption of carbohydrates, and delay the absorption of glucose in the small intestine; (4) increase the circulation and utilization of glucose in peripheral tissues (increase GLUT4 expression through the PI3K, AMPK, mTOR, and Sirt1 pathways), increase the utilization of glucose in peripheral tissues and target organs such as the liver and muscles, accelerate glucose dissolution and metabolism in the body, increase muscle glycogen synthesis, and control the redigestion and absorption of glucose in the body; (5) may participate in the AMPK/NF-κB signaling pathway by activating AMPK phosphorylation and regulating energy metabolism in the body; (6) activate the PI3K/AKT signaling pathway by upregulating insulin receptor (INR), glucose transporter protein (GLUT), inositol kinase, and NADP, thereby enhancing glucose transport and utilization and reducing the storage of excess glucose; (7) simultaneously upregulate epidermal growth factor, initiate signal cascade reactions, promote the increase of intracellular Ca^{2+} concentration, and increase the progress of glycolysis; (8) enhance the body's immune response and reduce oxidative damage; (9) normalize blood glucose levels by regulating the Notch and angiogenesis pathways, which may be associated with increased expression of Pdx-1 and insulin in the pancreas; (10) increase glycolysis and promote the process of the TCA cycle produced during glycolysis by downregulating the gene expression of some enzymes in glycogen protein, while upregulating the gene expression of some important enzymes in glycolysis and the TCA cycle, controlling glycogen breakdown and thus reducing glucose production; (11) enhance the antioxidant capacity of the body and pancreas: eliminate free radicals and lipid peroxidation (enhance SOD and CAT activity, increase GSH levels, and reduce MDA levels), thereby reducing the level of antioxidant reaction caused by high blood glucose in DM and enhancing the antioxidant function; (12) inhibit inflammatory reactions, enhance GLUT expression, and reduce IL-6 and TNF-α expression levels; (13) reduce blood lipid function, increase serum HDL-C concentration, reduce LDL-C, TC, and TG concentrations, and reduce lipid metabolism disorders caused by high blood glucose, thereby alleviating high blood glucose manifestations, reducing blood lipids, reducing body weight, and improving glucose, protein, and fat metabolism disorders and thus comprehensively improving metabolism.

4.2.3. Normal and Type 1 and Type 2 DM Models. Zheng et al. [78] performed oral glucose tolerance tests (OGTTs) on normal mice and administered MCP at a dose of 1 g/kg BW to the experimental group. DM mice (type 1 and type 2 DM models) were randomly divided into two groups. The experimental group was given MCP at a dose of 1 g/kg BW under the conditions of soluble-free diet and fasting, and blood glucose was measured at different time points. The results showed that in normal mice, after glucose stimulation (3 g/kg BW), the blood glucose levels in the experimental group were significantly lower than those in the control group at 0.5 and 1 hour. In DM mice, after taking MCP, the fasting and random blood glucose values at 2 h and 4 h were lower than those in the control group. MCP improved OGTT in normal mice and produced a strong hypoglycemic effect in both types of DM mice. The experimental results also confirmed that MCP crude extract had a certain effect on improving glucose tolerance in normal mice, significantly reducing the random and fasting blood glucose levels in the DM model, and exerting a strong hypoglycemic effect on type 1 DM mice with random feeding, with a prominent hypoglycemic effect 4 hours after administration. MCP significantly reduced the random blood glucose levels of type 2 DM mice and had a significant hypoglycemic effect on the fasting blood glucose concentration of both type 1 and type 2 DM mice. MCP exhibited a significant hypoglycemic effect on normal mice and both DM models, suggesting that MCP can regulate blood glucose metabolism in various ways, possibly due to its antioxidant and immune-modulating functions, which can repair damaged pancreas and reduce oxidative stress caused by DM hyperglycemia.

Figure 4 provides a simple summary of the hypoglycemic effects and related mechanisms of MCP on diabetic animal models, with the hypoglycemic mechanism of type 2 diabetes being the most complex and having varying effects. Therefore, researchers have conducted chemical modifications on MCP and combined it with other drugs to further increase its efficacy and stability.

4.3. Hypoglycemic Effects of Chemically Modified MCP. Currently, the solubility of purified MCP is insufficient, and its poor solubility also affects the full exertion of its biological activity. Chemical modification of polysaccharides has been reported to enhance their biological activity, and the introduction of trace elements related to the treatment of DM combined with polysaccharides can form complexes that produce synergistic hypoglycemic effects. This has significant practical applications for the treatment of DM.

4.3.1. Fermented MCP. Gao [79] used a high-fat diet combined with STZ induction to establish a type 2 DM rat model. Plant lactobacillus NCU116 was used to ferment MCP, and the proportion of glucose in fermented MCP was reduced compared to unfermented MCP. The peak shape of the small molecular weight components in MCP changed significantly after fermentation, while the large molecular weight components did not change significantly. The functional groups of MCP before and after fermentation did

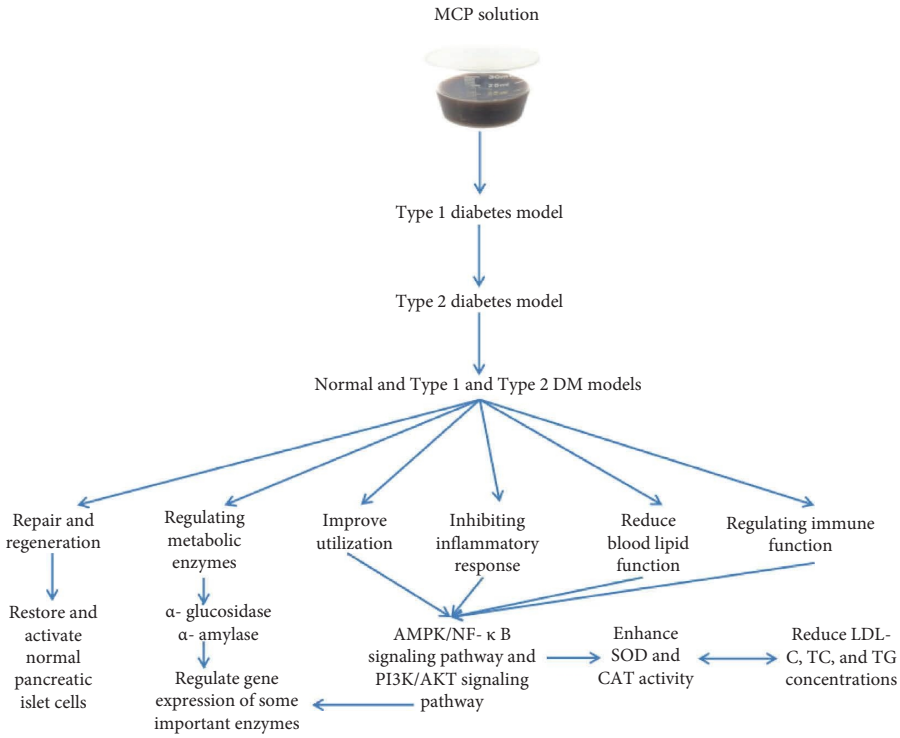

Figure 4: The hypoglycemic effects and mechanisms of MCP on diabetic animal models.

not change significantly. The results showed that compared to unfermented MCP, fermented MCP significantly promoted the synthesis of aminoacyl-tRNA, metabolism of arginine and proline, metabolism of D-arginine and D-asparagine, metabolism of niacin and niacinamide, interconversion of pentose and glucuronic acid, metabolism of starch and sucrose, and biosynthesis and metabolism of steroid hormones in type 2 DM rats. In addition, the metabolism of carbohydrates, amino acids, and lipids in normal rats was also improved by both unfermented and fermented MCP. The study showed that plant lactobacillus fermentation improved the biochemical functions of bitter melon and its polysaccharides to a certain extent, thereby enhancing the hypoglycemic effects of bitter melon and its polysaccharides. Gao et al. [80] studied the effect of plant lactobacillus fermentation on the structural composition and anti-DM function of MCP. Type 2 DM rats induced by a high-fat diet and STZ were treated with fermented and unfermented bitter melon (FP and NFP) polysaccharides for 4 weeks. After intervention with FP and NFP, the richness of the intestinal microbiota in DM rats increased significantly. After oral administration of a dose of 100 mg/kg of FP, the content of acetic acid and total short-chain fatty acids (SCFAs) increased significantly, and the colonic pH decreased significantly. Compared with NFP, FP treatment could significantly change the high blood glucose, high insulinemia, hyperlipidemia, and oxidative stress in DM rats. Plant lactobacillus fermentation can optimize the gut microbiota and increase SCFA production by changing the structure of polysaccharides, thereby enhancing the anti-DM effects of MCP in rats.

4.3.2. Chromium Complex of MCP. Zhang [81] extracted polysaccharides with hypoglycemic activity from bitter melon and combined them with trivalent chromium ions under certain conditions to prepare MCP-chromium complex. The hypoglycemic activity of MCP-chromium complex was studied in DM mice, and its possible hypoglycemic mechanism was explored. The results showed that after treatment with MCP-chromium complex for 4 weeks, the fasting blood glucose level of STZ-induced hyperglycemic mice showed a significant decrease, while the insulin level and antioxidant enzyme activity were significantly higher than those in the high blood glucose model group. The dosage of MCP-chromium complex at a weight of 30 mg/kg showed the best therapeutic effect. In addition, the dosage of MCP-chromium complex was 6.6 times lower than that of previous MCP studies. Histological analysis showed that MCP-chromium complex slowed down the oxidative damage in the liver, kidney, and pancreatic tissues of mice caused by high blood glucose. Zhang et al. [82] synthesized and characterized a novel MCP-chromium (III) complex (MCPIIaC) and studied its anti-DM effect and potential hypoglycemic mechanism in STZ-induced DM mice. After 4 weeks of MCPIIaC treatment, STZ-induced DM mice showed a significant reduction in fasting blood glucose levels and body weight, while insulin levels and antioxidant enzyme activity were higher than those in the DM group. The dosage of MCPIIaC at a weight of 30 mg/kg showed the best effect. Histological analysis showed that MCPIIaC alleviated oxidative tissue damage in STZ-damaged mice.

4.3.3. Selenium Complex of MCP. Bai [83] used selenium as a modifier to prepare selenium-modified MCP (Se-MCP). The low-dose group was orally administered 100 μg/kg Se-MCP per day, the medium-dose group was orally administered 200 μg/kg Se-MCP per day, and the high-dose group was orally administered 300 μg/kg Se-MCP per day (with selenium content as the marker, and MCP content was 6 mg/kg). After 28 days of oral administration, the hypoglycemic effect of Se-MCP was studied in a DM mouse model. The results showed that the medium dose of Se-MCP significantly reduced the blood glucose of DM mice, increased the INS level, liver SOD, GSH-Px, and CAT levels of hyperglycemic mice, reduced the liver MDA concentration of hyperglycemic mice, and effectively controlled the total cholesterol (CHO) content in the serum of DM mice. The high dose of Se-MCP helped to inhibit the concentration of TG in the serum of DM mice. In the histological experiments of the liver and kidneys of experimental mice in the three groups of Se-MCP oral administration, it was found that while Se-MCP effectively lowered blood glucose, it also protected the liver and kidneys, and the medium dose of Se-MCP had a better protective effect on the liver and kidneys of DM mice. Ru et al. [84] obtained an effective anti-DM polysaccharide derivative, selenium-modified bitter melon polysaccharide (Se-MCPIIa-1), with an average molecular weight (MW) of 4.0038×10^4 Da, which was synthesized using ascorbic acid to reduce sodium selenite in the presence of MCPIIa. The oral administration of Se-MCPIIa-1 showed a gradual return to normal levels in the hypoglycemic test of STZ-induced DM mice. Se-MCPIIa-1 has been proven to have a significant effect on preventing and treating hyperglycemia in mice and can significantly reduce fasting blood glucose levels and increase insulin levels and antioxidant enzyme activity in DM mice, with the optimal dose being 20 mg/kg body weight. In addition, it can be observed in histopathology that Se-MCPIIa-1 can prevent damage to the pancreas, liver, and kidney function caused by DM.

4.3.4. Iron Complex of MCP. Du et al. [85] studied the effect of chelation on the biological function of polysaccharides and extracted water-soluble MCP from bitter melon to prepare MCP-iron complex. MCP (250 mg/kg/d) and MCP-iron complex (250 mg/kg/d) were orally administered for 28 days. The hypoglycemic effect of MCP and iron complex on the ALX-induced DM mouse model was compared, and pancreatic cell morphology was studied by paraffin sectioning under a microscope. The results showed that both MCP and iron complex treatment significantly lowered blood glucose levels in hyperglycemic mice, but the hypoglycemic effect of MCP-iron complex was more significant. Furthermore, MCP-iron complex showed a strong protective and restorative effect on β cells, promoting the regeneration of β granules and mitochondria and enhancing the insulin-producing function of β cells.

4.4. Hypoglycemic Effect of Composite MCP. Currently, studies have found that the use of various polysaccharide complexes for the treatment of DM and its complications is more effective than using MCP alone and has greater application value for the treatment of DM.

Kim et al. [86] found that the water extract of β-glucan purified from oat grains (OG) and bitter melon (MC) had a good therapeutic effect on DM and its complications. After 7 days of STZ administration, the extract was orally administered once a day for a total of 28 days. Based on blood glucose and body weight on day 6 after STZ administration, there were a total of 15 groups: intact group, STZ group, OG group, MC group, variable mixed group, and so on. After 28 days of administration, changes in body weight, liver and kidney weight, blood glucose, blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST) and alanine transaminase (ALT), low-density lipoprotein (LDL), and total cholesterol levels were examined. The results showed that the weight of the STZ control group decreased, while the liver and kidney weight, blood glucose, BUN, creatinine, AST, ALT, LDL, and total cholesterol levels all decreased. However, these changes of high blood glucose, diabetic nephropathy, liver disease, and hyperlipidemia were significantly reduced in the OG and MC single-dose groups as well as all mixed groups. In addition, all mixed groups had better therapeutic effects than the OG and MC single-dose groups. Among the variable mixed groups, the 1 : 2 mixture of OG : MC showed the most synergistic effect in this study.

He et al. [87] investigated the joint effects and mechanisms of MCP and bitter melon saponins on the control of hyperglycemia. DM model mice were established by intraperitoneal injection of STZ and treated with MCP and bitter melon saponins separately or in combination for 3 weeks. The results showed that compared with the DM group, the combined group (ratio of 1 : 1) had a decrease in blood glucose levels, an increase in serum insulin concentration, an increase in liver glycogen, a decrease in lactate dehydrogenase (LDH) and lactate (LD) concentrations, and a decrease in malondialdehyde (MDA) concentration. The liver glycogen content in the combined group (12.24 ± 0.57) mg/g was significantly higher than that in the MCP group and saponin group. The combination of MCP and saponins in equal proportions can lower blood glucose levels by increasing liver glycogen storage, improving pancreatic tissue oxygen supply, and enhancing antioxidant capacity. The combined effect of polysaccharides and saponins in increasing liver glycogen storage is significantly better than the single effect, indicating a certain synergistic effect. In another study by He et al. [88], the synergistic preventive and therapeutic effects of MCP and saponins on hyperglycemia were investigated. The mice were divided into a polysaccharide group, an MCP group (400 mg/kg/d), a bitter melon saponin group (400 mg/kg/d), and a combination group, which received a mixture of MCP and saponins (in a ratio of 1 : 1, 800 mg/kg/d) by gavage once a day for 3 weeks. The mice were induced with hyperglycemia by intraperitoneal injection of STZ. The results showed that before STZ injection, the blood glucose levels of all groups of mice were not different. After STZ injection, compared with the control group, the combined group had an increase in the liver coefficient, a decrease in blood glucose levels, an increase in insulin, an increase in liver superoxide dismutase

(SOD) and LDH activity, a decrease in MDA concentration, and an increase in muscle glycogen. The insulin level in the combined group was $(17.74 \pm 1.19)\,\mu$IU/mL, and the SOD level was $(366.43 \pm 28.28)\,\mu$/mg prot, which was significantly higher than that in the polysaccharide group and saponin group, while the serum LDH concentration was $(1039.77 \pm 98.44)\,\mu$/L, which was significantly lower than that in the polysaccharide group and saponin group. These results suggest that MCP and saponins can jointly increase glucose storage, enhance cellular antioxidant capacity and tissue supply capacity, and protect the secretory function of islets, thereby preventing and treating DM.

In summary, chemically modified MCP and composite MCP have better therapeutic effects on DM. The main mechanisms of hypoglycemic effects of chemically modified MCP and composite MCP are as follows: (1) they improve the repair and regeneration of damaged pancreatic cells, restore and activate normal pancreatic cells, regulate pancreatic cell apoptosis, protect pancreatic cell function, increase the capacity and number of pancreatic β cells, and promote the production of insulin by normal pancreatic cells. They increase plasma insulin concentration, control glucagon release, and reduce glucagon ability (JNK signaling can act on different receptors to induce cell apoptosis). (2) They enhance the antioxidant capacity of the body and the pancreas by clearing free radicals and lipid peroxidation (enhancing SOD and CAT activity, increasing GSH level, and reducing MDA level), thereby reducing the oxidative stress caused by high blood glucose in DM and improving antioxidant function. (3) They inhibit glycogen breakdown, increase liver glycogen synthesis, regulate gluconeogenesis, and inhibit intestinal absorption of glucose and glucose metabolism. (4) They lower blood lipid function, increase HDL-C concentration in serum, decrease LDL-C, TC, and TG concentrations, and reduce lipid metabolism disorders caused by high blood glucose, thereby alleviating hyperglycemic symptoms, reducing blood lipids, reducing body weight, improving glucose, protein, and fat metabolism disorders, and comprehensively improving metabolism. (5) They slow down the damage caused by high blood glucose to the liver, kidneys, and pancreatic tissues and provide better protection for pancreatic, liver, and kidney tissues. (6) They increase the peripheral tissue glucose circulation (through PI3K, AMPK, mTOR, and Sirt1 pathways and increasing GLUT4 expression), improve the utilization of glucose by peripheral tissues and target organs such as the liver and muscles, accelerate the dissolution and metabolism of glucose in the body, increase muscle glycogen synthesis, control the reabsorption of glucose in the body, and improve carbohydrate, amino acid, and lipid metabolism. (7) They regulate the intestinal microbiota, optimize the intestinal microbial community, and increase the production of SCFAs.

4.5. Hypoglycemic Effects of MCP in Humans. Currently, there have been more human experiments on using bitter melon to treat DM and its complications, while there have been few studies on using MCP in humans, possibly due to the variety of polysaccharides, insufficient purity of MCP extraction, limited research personnel, and unclear side effects.

Zhang [89] studied the effects of MCP on blood glucose, blood lipids, and blood parameters in patients with type 2 DM. The treated patients were randomly divided into two groups, and both groups stopped using other hypoglycemic drugs for the first 7 days of treatment. The treatment group received 10 ml of MCP extract in combination with metformin hydrochloride, twice a day, while the control group received only 1.5 g/day of metformin hydrochloride. The treatment lasted for 60 days. The study investigated the levels of cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL-C), fasting blood glucose (FBG), and glycated hemoglobin (HbA1C) in patients with type 2 DM before and after treatment with MCP, as well as its effects on glucose tolerance and blood parameters. The results showed that MCP could effectively control various clinical indicators of blood glucose, blood lipids, and blood parameters in patients with type 2 DM. Although there have been few studies on MCP in humans, it has shown promising results in treating type 2 DM and improving blood lipid and blood parameters.

In summary, current research indicates that MCP has hypoglycemic effects in cell experiments, animal experiments, and limited human experiments. Figure 5 describes the related mechanisms of MCP's hypoglycemic action, but the specific mechanisms for lowering blood glucose are still unclear. In addition, MCP's hypoglycemic action mechanisms extend beyond those shown in Figure 5 [73, 90–95]. They may also include improving plasma rheology and platelet aggregation, reducing whole blood viscosity, improving systemic circulation and tissue metabolism, indirectly enhancing pancreatic beta cell function, regulating hormone levels, and closely related to its effects of promoting insulin secretion [96, 97].

4.6. Factors Affecting MCP's Hypoglycemic Effects. Due to the different varieties of bitter melon, different levels of maturity, different extraction methods, different dosages, different target cells, and different animal models used, MCP's various functions can vary. Yan et al. [12], using fresh bitter melon as the raw material, extracted polysaccharides using room temperature extraction techniques in different solvents. The results showed that compared with BPS-C extracted with citric acid, BPS-a extracted with 1.25 mol/L NaOH/0.05% NaBH4, and BPS-J extracted with TPP, the BPS-W sample of bitter melon residue extracted with UAE in distilled water had a higher glucuronic acid content (24.22%), stronger antioxidant activity, and stronger α-amylase and α-glucosidase inhibitory activity. Wu et al. [98] demonstrated in vitro hypoglycemic effects of MCP's various components on pancreatic tissue protection and repair. These functions are closely related to their antioxidant activity and depend not only on their antioxidant function but also on the collective function of other features. Chen et al. [69], by exploring the correlation between MCP's in vitro antioxidant activity and in vivo hypoglycemic activity, found that MCP's hypoglycemic activity increases

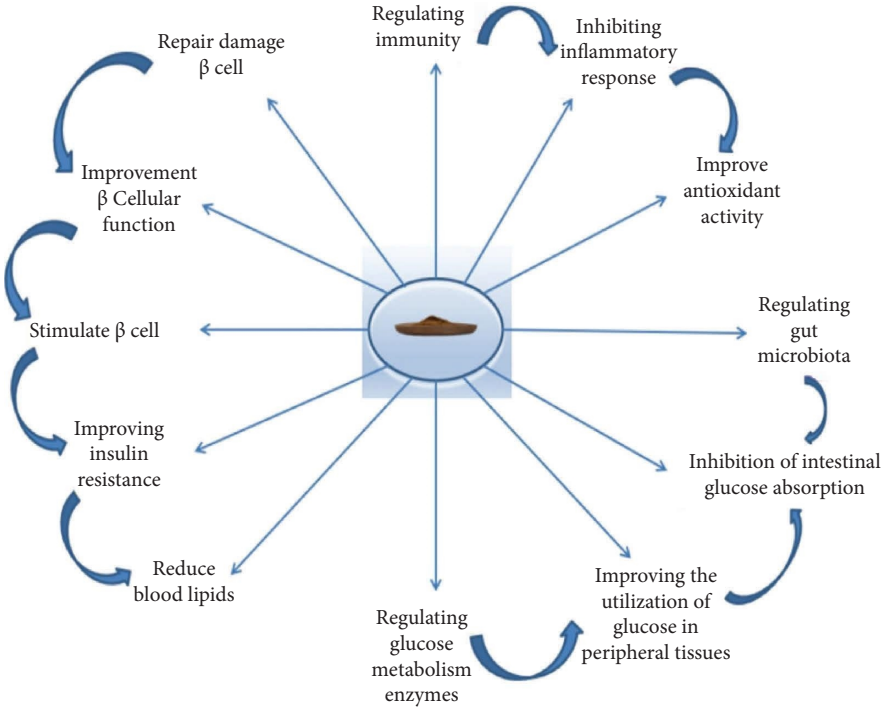

Figure 5: MCP's mechanisms of hypoglycemic action.

with its antioxidant capacity. Water-soluble polysaccharides (MCW) and alkali-soluble polysaccharides (MCB) extracted from bitter melon both showed significant anti-hyperglycemic effects, and further research revealed that MCW and MCB can repair the damaged pancreatic tissue and enhance insulin secretion in STZ-induced diabetic mice [99]. MCP obtained by methanol also demonstrated dose-dependent hypoglycemic activity in ALX-induced diabetic mice [100]. The purification technology and method also affect MCP's hypoglycemic activity. A comparison of the hypoglycemic effects of MCP obtained by water extraction and alkali extraction on STZ-induced diabetic mice demonstrated that the hypoglycemic activity of alkali-extracted polysaccharides was better [70]. Therefore, the dosage, chemical modification, structural complex, extraction method, extraction purity, composition, molecular weight, and the degree of influence of other bioactive molecules can all affect MCP's hypoglycemic effects.

5. Conclusion and Outlook

With the increasing attention to polysaccharide research, MCP has gradually entered people's vision. Currently, there are at least 200 types of polysaccharides, such as *Lycium barbarum polysaccharides*, *Astragalus polysaccharides*, and mulberry leaf polysaccharides, which can be used for the prevention and treatment of DM. However, the specific polysaccharide structures are unclear, and the mechanisms of action are incomplete. MCP is one of them. DM is a metabolic disease, and MCP is considered to have the effect of reducing blood glucose, making it widely used in the treatment of diabetes. In recent years, many studies have confirmed the therapeutic effects of MCP on DM. Current research indicates that MCP can lower blood glucose through various pathways, including increasing insulin sensitivity, promoting glucose utilization, and inhibiting glucose absorption. It also has certain benefits for improving the overall health of MCP patients. In addition, MCP has many biological activities, such as antitumor, lipid-lowering, immune-enhancing, antibacterial, anti-inflammatory, antioxidant, and weight-loss effects. Many studies and technologies have been developed on various important biological activities of MCP. The biological functions of MCP are closely related to its chemical composition, molecular weight, type, and dosage used, but the relationship between specific structure and function is not yet clear. People have conducted extensive research on the extraction methods, purification efficiency, molecular structure, molecular weight, and various biological activities of MCP. However, from the current research, MCP, as one of the biologically active substances with a research value, still has many problems to overcome. For example, the best extraction method, the highest purification efficiency, the composition of the first, second, third, and fourth-level molecular structures, molecular weight, the highest application dosage of different biological activities, the final application effect, the mechanism of action of different biological activities, and the undiscovered biological functions and mechanisms of influence are all worthy of further study. Currently, domestic and foreign research on MCP mainly focuses on its hypoglycemic function, antioxidant activity, antitumor effect, and immune regulation, with less research on other aspects. The current work on bitter melon is mainly preclinical trials, with few clinical cases, and less research on adverse reactions and side effects. There have been reports of side effects from using bitter melon.

However, there have been no reports on the toxic side effects and adverse reactions of using MCP, which require further study. Although MCP has potential advantages in the treatment of DM, some studies have also found that its hypoglycemic effects are not as stable as drugs, and there is a certain difference between dosage and efficacy. In addition, the indications for MCP are mainly diabetes and other metabolic diseases, and its therapeutic effects on other diseases have not been fully confirmed. There may also be some minor side effects, such as gastrointestinal discomfort. MCP has a certain bitterness, which may cause gastrointestinal discomfort, such as nausea and vomiting. Allergic reactions may also occur, and some individuals may be allergic to MCP, which may cause allergic reactions such as rashes and urticaria. Future research should focus on the dosage, efficacy, and safety of MCP in the treatment of DM, as well as exploring the combination of MCP with other treatment methods to better leverage its role in the treatment of diabetes. In addition, although the medicinal value of MCP has been discovered in many ways, its usage value has not been fully developed, especially the impact of MCP's structure composition and molecular weight on its function. In summary, bitter melon has a wide research background, and the study of MCP has become a hot research direction in recent years. Therefore, finding the medicinal value and dietary function of MCP will be a key issue in future scientific research. This article provides new ideas for further research and development of MCP and provides new methods for future treatment of DM.

In summary, the hypoglycemic effect of MCP has been extensively studied, but its mechanism of action is still unclear and requires further investigation. In addition, there are currently six methods for extracting MCP, but the extraction rate and purity are not high enough. Further research into the molecular structure and molecular weight of MCP is also needed, as well as its relationship with its biological activity. Currently, MCP also has many other functions, such as antioxidant, antitumor, antibacterial, anti-inflammatory, antiaging, antiapoptosis, immune regulation, lipid-lowering, and weight-loss effects, which require further study, especially its mechanism of action. The protective effects of MCP on various organs, tissues, and cells in the body also require further research. Currently, there is a lot of research on the pancreas, liver, and kidneys, but research on the heart, spleen, lungs, brain, and eyes is limited, especially regarding diabetes-related complications such as diabetic retinopathy and diabetic nephropathy. As a result, there are many research directions for MCP, and its hypoglycemic effect is just one of them. This hypoglycemic effect is the foundation and core component. Therefore, research on MCP and DM is very important and may become a candidate drug for the prevention and treatment of DM, as well as a food and nutritional supplement.

Data Availability

No data were used for the research described in the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Jinshen Liu contributed to conception and design of the study, generation, collection, assembly, analysis and/or interpretation of data, drafting and revision of the manuscript, and approval of the final version of the manuscript. Yuxin Lei and Mingyi Guo contributed to collection, analysis, and/or interpretation of data, and drafting and revision of the manuscript. Linhong Wang contributed to collection and interpretation of data.

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