

Application Of Xiaoke Pill in Treatment of Type 2 Diabetes Mellitus

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Abstract. As a metabolic chronic disease, the number of patients with diabetes and its fatality rate remain high. At present, many drugs have been developed for the prevention and treatment of diabetes, such as glibenclamide, insulin and other drugs in the clinical treatment of diabetes, has achieved very good therapeutic effects. However, there are research on the treatment of diabetes with traditional Chinese medicine (TCM). In this paper, through the dissolving analysis of Xiaoke Pill, the action mechanism and effect of the effective ingredients in Xiaoke pill for the treatment of diabetes were specifically analyzed, and it was found that the main ingredients in Xiaoke pill were effective for the treatment of diabetes, and could minimize the incidence of adverse consequences like hypoglycemia. Through the analysis and research of Xiaoke Pill, this paper hopes to provide theoretical help for TCM treatment of diabetes, and hope to increase the intensity of TCM treatment of diabetes.

Keywords: Type 2 diabetes mellitus, Xiaoke pill, traditional Chinese medicine.

1. Introduction

Nowadays, the populations with diabetes increase rapidly. According to International Diabetes Federation (IDF) projections, the number of people with diabetes will go to 783 million, which means there is one in eight people with diabetes [1]. There are a large number of complications in the later stages in diabetes, especially for Type 2 diabetes mellitus (T2DM). These complications have very bad effects on people's daily life and physical health. With the advancement of western medical technology, insulin, metformin and other drugs have become effective drugs for treating diabetes. Meanwhile, traditional Chinese medicine (TCM) in the clinical treatment of diabetes also has a great effect.

Diabetes belongs to "Xiaoke" in TCM dialectics. The clinical treatment of T2DM by Xiaoke pill (including *Pueraria Lobata Radix*, *Rehmanniae Radix*, *Astragali Radix*, *Radix trichosanthis*, corn silk, *Schisandra chinensis*, Chinese Yam, Glibenclamide) has achieved certain results. The experiment showed that the main active components of Xiaoke Pill had good effect on treating hyperglycemia and protecting islet cells in rats with diabetes mellitus. As one of the medications used to treat diabetes the most commonly, Xiaoke Pill has the hypoglycemic effect similar to glibenclamide and other drugs and can reduce the risk of hypoglycemia caused by glibenclamide. The main components of Xiaoke pill can increase the body's sensitivity to insulin, halt pancreatic β cell death, enhance insulin release, and so on. Meanwhile, the extracts of traditional Chinese medicine components of Xiaoke pill are effective inhibitors of α -glucosidase, which can effectively reduce blood sugar.

This article will conduct TCM dialectics on T2DM, analyze the Xiaoke pill prescription, analyze the efficacy of the ingredients of Xiaoke Pill, and introduce and summarize Xiaoke Pill, intending to synthesize the study on Xiaoke Pill's potential therapeutic benefits for type 2 diabetes and incorporate the unique roles of its elements. It will improve people's understanding of diabetes, help diabetic patients understand the effects of Chinese patent medicines on the treatment of diabetes, and provide help for future research on diabetes Chinese medicine.

2. Dialectical Analysis of Diabetes in TCM

Diabetes is a complicated chronic metabolic disease, it has been divided into Type 1 diabetes and T2DM [2]. Ninety-five percent of people with diabetes have T2DM. The symptom of diabetes in clinic treatment are mainly for “polydipsia, polyphagia, polyuria and lose weight” [3]. Hyperglycemia causes relative insulin deficiency or biological efficacy of insulin on target organs reduce (IR) is the main reason for T2DM [3]. Diabetes is recoded in Huangdi Neijing and Synopsis of Golden Chamber and other classic works. Diabetes is called “Xiaoke” in the dialectical analysis of TCM. According to TCM, the primary causes of diabetes are an overabundance of dry heat and a shortage of "Yin" [4]. The pathogen is a deficiency of "Yin", and the symptom is excessive dryness and heat [4]. Deficiency of “Yin” and excessive dryness-heat can mutually transform and keep balance [4]. Lung, kidney and other “zang fu” will be damaged if the balance break down [4].

Summing up 24748 Chinese herbal prescriptions used to treat T2DM, the prescription number for Xiaoke Pill was found to be 1370, accounting for 5.5% of the total [5]. The use frequency of traditional Chinese medicine from high to low is Astragali Radix, Rehmanniae Radix, Chinese yam, Pueraria Lobata Radix, Radix trichosanthis, etc [5]. The traditional Chinese medicine Xiaoke Pill is a typical prescription for the clinical treatment of T2DM. Its main ingredients are 265g of Pueraria Lobata Radi, 159g of Rehmanniae Radix, 53g of Astragali Radix, 265g of Radix trichosanthis, 265g of Corn silk, 53g of Schisandra chinensis, 26.5g of Chinese Yam, and 0.25g of glibenclamide [6]. It can be seen that the ingredients of Xiaoke Pill are very similar to those of traditional Chinese medicines that are frequently used in clinical practice.

3. Analysis of the Composition and Efficacy of Xiaoke Pill

3.1. Pueraria Lobata Radix

Pueraria Lobata Radix is the dried root of *Pueraria lobata* (Wild.) Ohwi, a plant of the Leguminosae family [7]. It accesses the meridians of the spleen, stomach, and lungs and is sweet, pungent, and chilly in character[7]. Isoflavones, triterpenes, saponins, polysaccharides, etc. are present in *Pueraria Lobata Radix* [8]. In diabetic rats, *Pueraria Lobata Radix* can lower blood sugar and blood lipid levels by enhancing liver function, protecting pancreatic β cells, and activating the Akt pathway downstream of insulin receptors [8]. It can also inhibit IR, enhance the sensitivity of peripheral tissues to insulin, promote insulin secretion, and inhibit the expression of liver acetyl-CoA carboxylase (ACC) mRNA, thereby reducing blood glucose and blood lipids in diabetic rats and further promoting glucose and lipid metabolism [8]. *Pueraria Lobata Radix* ethanol (75% extract) was discovered to have anti-diabetic qualities in a study by Wang Shengguang et al [9]. This was due to the extract's ability to inhibit the activity of diabetes-related proteins, increase glucose absorption, and improve glucose tolerance [9]. Adding up to 0.2% w/w of *Pueraria Lobata Radix* extract to the diet for eight months decreased fasting blood glucose baseline and improved glucose and insulin tolerance in a study on the effect of *Pueraria Lobata Radix* extract on improving impaired glucose and lipid metabolism in male type 2 diabetic (C57BL/6J-ob/ob) obese mice [9].

3.2. Rehmanniae Radix

Rehmanniae Radix is the fresh or dried root of *Rehmannia glutinosa* Libosch, a plant of the Scrophulariaceae family [10]. The root of *Rehmannia glutinosa* is dried to 80% dry to obtain raw *Rehmannia glutinosa* [10]. Raw *Rehmannia glutinosa* is sweet and cold, and enters the heart, liver, and kidney meridians [10]. It functions by dispelling heat, lowering blood pressure, replenishing yin, and encouraging bodily fluid, and is used to treat fever due to yin deficiency, and internal heat and thirst [10]. Catalpol is an iridoid glycoside in *Rehmanniae Radix*, which can reduce blood sugar in diabetic mice, protect pancreatic islet cells, increase insulin secretion, improve serum insulin levels, reduce insulin resistance, lower lipid metabolism, lessen inflammatory damage brought on by diabetes and associated byproducts, and lower cholesterol and triglyceride levels brought on by a

high-fat diet [8]. It can effectively reduce fasting blood sugar and 24-hour urinary albumin excretion rate in type 2 diabetic mice, improve kidney pathology, reduce kidney cell damage, and protect the kidneys [8]. The key to using catalpol to treat diabetes is its diverse biological activity, which includes its ability to scavenge free radicals and act as an antioxidant [11]. According to studies, catalpol can activate AMPK/PGC-1 α /TFAM signaling, thereby increasing glucose absorption and adenosine triphosphate production, and regulating the AMPK pathway to produce a hypoglycemic effect [11].

3.3. Astragali Radix

Astragali Radix is the dried root of *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. of the Leguminosae family [12]. It enters the lung and spleen meridians and has a sweet, somewhat warm flavor. Its primary purposes are to nourish blood, encourage the body to produce fluids, alleviate edema brought on by a lack of qi, and quench thirst brought on by internal heat [12]. Modern research shows that Astragali Radix includes a wide range of active components, such as flavonoids, triterpenes, polysaccharides, and saponins [8]. Astragaloside IV can lower blood sugar, increase insulin sensitivity, and improve IR [8]. Astragalus polysaccharide (APS), as the main active ingredient of Astragali Radix, can successfully prevent pancreatic β -cell death, enhance insulin sensitivity, and lower blood sugar levels, thus having a significant impact on the treatment of diabetic complications [5]. Experiments have shown that APS treatment of HFD-induced IR mice was basically equivalent to metformin, and was able to control body weight and blood sugar at a stable level and restore insulin sensitivity [3]. Quercetin, also an active ingredient of Astragali Radix, has several anti-hyperglycemic actions, including decreasing insulin resistance, increasing glycogen synthesis, raising insulin sensitivity, and blocking α -glucosidase activity [13]. The absorption of glucose by skeletal muscle can be decreased by obesity or a high-fat diet. Because it affects insulin receptor signals and glucose transport, quercetin improves the absorption of glucose by skeletal muscle, leading to better use of glucose [13].

3.4. Radix trichosanthis

Radix Trichosanthes is the dried root of *Trichosanthes kirilowii* Maxim. or *Trichosanthes rosthornii* Harms of the Cucurbitaceae family [14]. It reaches the stomach and lung meridians and has a mildly bitter, sweet, and slightly cool nature [14]. Its main functions include promoting body fluid and quenching thirst, treating fever and polydipsia, and quenching thirst caused by internal heat [14]. Pharmacological effects of Radix Trichosanthis include anti-tumor, anti-virus, enhancing immunity, and decreasing blood sugar [8]. Its main components are trichosanthes protein (TCS), trichosanthes lectin (TKL) and trichosanthes proteoglycan [8]. TCS prevents or treats diabetes by regulating the imbalance of Th1/Th2 cell function. TKL can control the metabolism of fats and sugars and enhance the body's antioxidant defenses [8].

3.5. Schisandra Chinensis

Schisandra chinensis is the dried mature fruit of *Schisandra sphenanthera* Rehd. et Wils of the Magnoliaceae family [15]. It accesses the meridians of the kidney, heart, and lungs and has a warm, sour, and sweet quality [15]. Its primary benefits include restoring qi, encouraging bodily fluids, reducing internal heat, and satiating thirst [15]. An important feature of T2DM is elevated blood sugar levels. Experiments have shown that the water polyphenol extract of *Schisandra chinensis* contains an effective inhibitor of rat intestinal α -glucosidase [16]. After oral administration of sucrose solution, the *Schisandra chinensis* preparation can lower the blood sugar level of rats, and its efficiency is higher than acarbose [16]. Pancreatic β cells, which secrete insulin, are essential for maintaining glucose homeostasis [16]. Because these cells have low quantities of the antioxidant enzymes catalase (CAT), glutathione peroxidase, and superoxide dismutase (SOD), they are particularly vulnerable to oxidative stress brought on by high glucose and free fatty acid levels [16]. Therefore, The protective effect of *Schisandra chinensis* extract against β cell malfunction or death is attributed to its high antioxidant activity and ability to scavenge free radicals [16]. At the same time, the water extract of

Schisandra chinensis also shows an insulinotropic effect and can successfully increase mouse Min6 cells' glucose-stimulated insulin production [16].

3.6. Chinese Yam

Chinese Yam is the dried rhizome of *Dioscorea oppositifolia* Thunb, a plant of the Dioscoreaceae family [17]. It is sweet and neutral in nature and enters the spleen, lung and kidney meridians [17]. Its main functions are to nourish the kidney and astringe the essence, relieve deficiency heat and quench thirst [17]. Yam polysaccharides are composed of tuber compounds, polysaccharides, amino acids and fatty acids. They can lower blood sugar, promote insulin secretion, protect the function of insulin, regulate lipid metabolism disorders in diabetic mice, and improve insulin sensitivity. In the diabetic mouse model, it can reduce blood sugar induced by streptozotocin in a concentration-dependent manner; it can effectively control related blood lipid indicators such as cholesterol and triglycerides; it can also improve the function of injured pancreatic β cells and increase insulin release in diabetic rats, helping to treat diabetes, lowering blood sugar, and increasing C-peptide values [8]. By observing the effects of Chinese yam and Chinese yam extract on blood sugar in rats, it is believed that Chinese yam extract is a potent inhibitor of α -glucosidase [18]. The small intestine's brush border contains the enzyme α -glucosidase, which converts starch to glucose [18]. A multitude of α -glucosidase inhibitors have been created into pharmaceuticals to reduce blood glucose levels [18]. Experiments have shown that consuming different doses of yam or its extracts can improve blood sugar by improving fasting blood sugar levels and insulin sensitivity, thereby achieving the effect of treating T2DM [18]. In addition, diosgenin in yam extract also has anti-diabetic effects due to the fact that diosgenin can prevent α -amylase and α -glucosidase from functioning [19].

3.7. Glibenclamide

The U.S. Food and Drug Administration (FDA) has approved glibenclamide, a second-generation sulfonylurea medication, to treat type 2 diabetes. Glibenclamide exerts its therapeutic effect by increasing insulin secretion from beta cells in the pancreas. This class of drugs binds to the SER1 receptors in the beta cell membrane of the potassium ATP-dependent channel protein and, by blocking these channels, releases insulin following cell depolarization [20]. After the initial secretion of insulin, glibenclamide can also reduce insulin clearance from the liver, thereby increasing plasma insulin levels [20].

This article analyzes the disassembly of Xiaoke Pill and finds that these active ingredients can treat T2DM. Using methods include raising insulin sensitivity and blocking α -glucosidase, it achieves therapeutic effects such as lowering blood sugar and restoring insulin sensitivity, and has good clinical performance. Due to the development and popularization of contemporary Chinese medicine, as well as the lower cost of Xiaoke Pill compared to Western medicine, Xiaoke Pill have become the choice of many diabetic patients.

4. Clinical Therapeutic Effect of Xiaoke Pill

When Xiaoke Pill are used for clinical treatment, they are taken orally, 5 to 10 pill each time depending on the condition, twice or thrice day, along with warm water thirty minutes prior to meals. The therapeutic effect of Xiaoke Pill is observed by observing blood sugar. The treatment effects were markedly effective (fasting blood sugar dropped to 7.2mmol/L and blood sugar dropped to 8.3mmol/L two hours after meal), effective (fasting blood sugar dropped to 8.3mmol/L and blood sugar dropped to 10.0mmol/L two hours after meal), and ineffective (no change in TCM syndrome differentiation signs). After treatment and observation of 40 groups of patients, it was found that the number of patients with marked effect after Xiaoke Pill treatment was 35 (87.5%), the number of patients with effective effect was 3 (7.5%), and the effective rate reached 95.0% [21]. This proves that Xiaoke Pill have a good effect in regulating blood sugar.

Another set of experimental data showed that fasting blood sugar and blood sugar two hours after meal were improved after taking Xiaoke Pill. The fasting blood sugar value before Xiaoke Pill was 11.43 ± 3.26 , and after Xiaoke Pill intervention treatment, the fasting blood sugar value was 6.50 ± 0.38 . For the blood sugar content two hours after meal, the blood sugar before Xiaoke Pill treatment was 15.53 ± 4.92 , and the blood sugar after Xiaoke Pill intervention treatment was 9.33 ± 1.20 . This further proves the important role of Xiaoke Pill in clinical treatment of diabetes and regulation of blood sugar [22].

In China, Xiaoke Pill are widely used to treat diabetes. It is a combination of the ancient prescriptions "Xiaoke Recipe" and "Yuquan Powder", in which ingredients such as Astragalus and Pueraria are important ingredients for treating diabetes. In clinical practice, Xiaoke Pill are compared with Western medicine or other Chinese medicine prescriptions. Studies have found that Xiaoke Pill alone or used with other Chinese medicine prescriptions have better effects in blood sugar control. In addition, patients who use Xiaoke Pill with other drugs have fewer adverse reactions, which shows that Xiaoke Pill are safer [23]. It has been reported that Xiaoke Pill not only increases insulin secretion, which is mostly mediated by glibenclamide, but also increases adiponectin secretion, which increases the sensitivity of insulin receptors in diabetes patients [23].

When glibenclamide is used clinically to control diabetes, hypoglycemia symptoms often occur. Xiaoke Pill have shown good effects in overcoming this adverse reaction of hypoglycemia. The usage of Xiaoke Pill by itself and in conjunction with other antidiabetic medications was examined in a randomized, double-blind, multicenter clinical experiment [23]. The results of the study indicated that Xiaoke Pill had comparable blood sugar management effects to glibenclamide, but a lower risk of hypoglycemia. This suggests that the Chinese herbs in Xiaoke Pill provide protection against hypoglycemia caused by glibenclamide [23]. In terms of cost and effectiveness, metformin is less effective than certain other popular glucose-lowering medications, such as gliclazide and Xiaoke Pill, but it has a lower rate of side effects. Simultaneously, Xiaoke Pill added to metformin can increase its effectiveness and lower its risk of side effects [23].

5. Conclusion

This article analyzes the treatment of T2DM with Xiaoke Pill and finds that Chinese medicine prescriptions have good therapeutic effects in the treatment of T2DM. The research on the compound prescription and component drugs of Xiaoke Pill in T2DM is summarized and it is found that the main monomer components can treat diabetes to a certain extent and have achieved certain clinical efficacy. The main single Chinese medicine ingredients in Xiaoke Pill have active ingredients for treating T2DM and have little toxic and side effects. In addition to efficiently lowering blood sugar and enhancing insulin sensitivity, the combination of Xiaoke Pills and other medications can greatly lessen the negative effects of metformin and other medications. Treating T2DM with traditional Chinese medicine and fundamentally dialectically analyzing T2DM can greatly alleviate a series of symptoms of diabetes. This article mainly analyzes and studies Xiaoke Pill by breaking them down, and the compatibility research of the whole Xiaoke Pill needs to be improved. This article hopes to provide a basis for the future treatment of diabetes with traditional Chinese medicine prescriptions through research and analysis, and to provide assistance for the clinical treatment of diabetes.

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