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Research progress of konjac dietary fibre in the prevention and treatment of diabetes

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Abstract

In today's society, the incidence of diabetes is getting higher. It can cause a variety of complications and endanger human health. How to safely and effectively reduce blood sugar has become a hotspot of concern. Konjac dietary fibre is one of the most excellent soluble dietary fibres found so far. Its health benefits include weight loss, lowering blood fat and blood sugar, and it has a laxative effect. This article mainly reviews the clinical observations, related mechanisms of action, appropriate dosages and toxic side effects, providing a basis for the clinical application of konjac dietary fibre and proposing a new mechanism for its hypoglycaemic effect. It provides new ideas for the research and development of konjac in the prevention and treatment of diabetes.

Keywords: konjac; diabetes; clinic; mechanism.

Practical Application: This article providing a basis for the clinical application of konjac dietary fibre and proposing a new mechanism for its hypoglycaemic effect. It provides new ideas for the research and development of konjac in the prevention and treatment of diabetes.

1 Introduction

The World Health Organization (WHO) predicts that by 2025, the number of patients with diabetes will exceed 300 million globally while showing a gradual growth trend (Guariguata et al., 2014). The vast patient population has brought a heavy burden to society, and the United Nations Health Organization has listed it as a serious threat to human health. Among the 'five carriages' for the treatment of patients with diabetes, the most challenging and attracting the most attention is none other than 'diet'. Diet therapy is the most basic and effective treatment for all types of diabetes. The combination of diet and medication, through dietary regulation, can reduce the amount of medication, promote the stability of the disease and prevent or reduce the occurrence of complications. Soluble dietary fibre currently plays an essential role in the adjuvant treatment of diabetes (Sood et al., 2008; Chiu & Stewart, 2012). Several studies have confirmed that soluble dietary fibre has better effects on improving blood sugar (Landin et al., 1992), lowering serum low-density lipoprotein and improving blood lipids (Keithley & Swanson, 2005). Konjac is a kind of perennial herbaceous plant in the Araceae family (Chua et al., 2010). It is a food with low heat energy and high dietary fibre. It is called a 'precious natural health food' by WHO. As the earliest country to grow konjac, China has a record of using konjac as a 'famine-relief' food and medicinal material to treat diseases as early as 2,000 years ago. It provides references and ideas for the current diabetes diet intervention. Modern research has proven that konjac not only has multiple functions, such as lowering blood sugar and blood lipids, regulating the gastrointestinal tract (Zhou et al., 2019), preventing and treating tumours (Chen et al., 2017) and enhancing immunity (Chen et al., 2016), it can also reduce the potential harm of high blood pressure (Khan et al., 2018), cardiovascular diseases (Vuksan et al., 2020) and diabetes (Gao et al., 2019). This article describes the research progress of konjac dietary fibre in diabetes from the aspects of active ingredients, clinical reports and mechanism research.

2 Active ingredients

The main active ingredient in konjac is konjac glucomannan (KGM), which has been extracted from its tuber. KGM is a kind of compound polysaccharide. The content of KGM in the grown konjac can reach 60% (Gómez et al., 2017). KGM also contains alkaloids, pectin, amino acids and trace elements, including potassium, phosphorus and selenium (Devaraj et al., 2019). KGM is a non-ionic polymer polysaccharide composed of D-glucose and D-mannose through a β -1,4-pyranoside bond in a molar ratio of 1 : 1.6 to 1 : 1.4. The average relative molecular mass varies between 200,000 and 2 million depending on the origin, variety, processing method and storage time of raw materials (Jian et al., 2015). There is a β -1,3 glycosidic bond branched-chain structure at the C3 position of the main mannose chain. See Figure 1.

As a food with low caloric energy and high dietary fibre, domestic experts discovered that konjac is rich in soluble hemicellulose KGM as early as the 1990s (Li et al., 1996). Since then, it has gradually become a research hotspot at home and abroad

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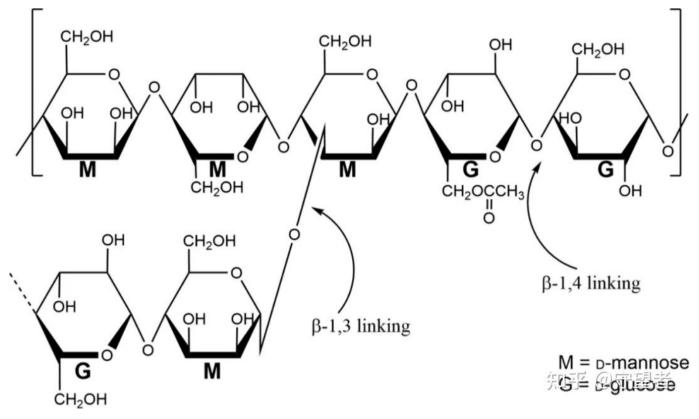


Figure 1. β-1,3 glycosidic bond branched-chain structure at the C3 position of the main mannose chain.

because of its wide application value and unique physiological activity. KGM has a variety of excellent characteristics, strong water-holding performance and can reach 80-100 times its own dry weight after swelling with water. After entering the human body through diet, it can hardly produce energy and its viscosity is relatively large. It can be mixed with other foods to delay digestion and absorption, forming a benign stimulus to the surface of the digestive tract and regulating metabolism. This is currently considered to be the primary mechanism of konjac hypoglycaemia. Diabetes diet treatment requires maintaining a good sense of satiety while also controlling total calories. KGM is a fermentable water-soluble dietary fibre. It is an excellent dietary fibre product. It can absorb glucose, thereby affecting the absorption rate and amount of nutrients such as glucose and fat. Its superior water absorption and swelling properties promote the secretion of saliva and digestive juice, and it is not easily digested or absorbed. Compared with easily digestible monosaccharides and polysaccharides, dietary fibre has a more obvious effect on increasing satiety (Rebello et al., 2016) and reducing high-calorie diet intake, which is conducive to effective weight control and can prevent hunger for patients with diabetic diet control, playing an active role in the prevention and treatment of diabetes and metabolic syndrome. In addition, due to its unique structure, KGM is widely used as an emulsifier, gelling agent, thickener, filler and stabilizer in medicine, environmental protection, food production and other fields (Anderson et al., 2009). It can be said that KGM is one of the better dietary fibres developed so far (Wang et al., 2015).

3 Clinical research

The formation and development of diabetes have a great relationship with diet (Dong et al., 2019). Encouraging people with diabetes to develop a diet of eating more foods with strong satiety and low glycaemic index (GI) is essential for controlling blood sugar. As a high-quality soluble dietary fibre, konjac dietary fibre has attracted scholars from all over the world. As early as the 1990s, researchers found that patients with T2DM with the same caloric intake, compared with the rich KGM, the normal diet control group had a significant increase in blood glucose and C-peptide levels after eating (P < 0.01) (Melga et al., 1992). Vuksan et al. (2001) compared KGM with other soluble substances (such as xanthan gum) at a concentration of 1% (v/v). Konjac showed the greatest viscosity. Therefore, it is concluded that the use of KGM as an alternative therapy for type 2 diabetes has strong feasibility. A previous randomized crossover trial study by their team also found that a high concentration of KGM added to the diet (0.5 g per 100 kcal [8-13 g/d]) can reduce the hidden dangers of three high-risk factors (hyperglycaemia, hyperlipidaemia and hypertension) in patients with high-risk T2DM (Vuksan et al., 1999). The insulin resistance (IR) syndrome can also improve the symptoms of hyperglycaemia (Vuksan et al., 2000). Doi et al. (1983) took blood samples from 11 patients with diabetes and found that the absorption rate of vitamin E into the intestines of subjects who added 3.9 g of glucomannan was reduced. Adding dietary fibre such as KGM to bread can effectively improve the postprandial blood glucose (PBG) of patients with T2DM in developed countries such as Southeast Asia, where carbohydrates

are the primary food source (P < 0.01); the PBG decline is greater than 30% (Boers et al., 2017). The statistical model of the four in vitro parameters (digestibility, % RDS, AUC, carbohydrate level) is highly predictive of PBG results (adjusted R2 = 0.89).

In clinical observations, another mechanism of konjac dietary fibre for reducing blood sugar is to inhibit the absorption of cholesterol and bile acids in the intestine. The research team led by Chen et al. (2003) conducted a randomised, doubleblind crossover clinical experimental study on diabetes with hyperlipidaemia. Patients in the experimental group were supplemented with 3.6 g KGM daily. The results showed that the patients' total cholesterol (TC), low-density lipoprotein (LDL) to high-density lipoprotein (HDL) ratio, apolipoprotein B and apolipoprotein A significantly decreased. The concentration of neutral sterol and bile acid in the patients' stool increased (18%, P = 0.004; 75.4%, P < 0.001, respectively), proving that KGM inhibited cholesterol and bile acid absorption. The studies by Kraemer et al. (2007) on overweight patients also showed that adding anaerobic and physical training to the KGM diet can significantly improve the body's HDL content and the TC/ HDL ratio. Another randomized controlled study showed that (Chearskul et al., 2007). However, long-term dietary glucomannan cannot improve IR in patients with diabetes. It can reduce the area under the curve of the patient's 2-hour oral glucose tolerance test (OGTT) and lower LDL and TC levels. The results of McCarty (2005) and his research team showed that KGM has no difference with acarbose in reducing FBG, 2h PBG, TC, LDL, etc. The two effects are equivalent, similar to the protective effect of acarbose.

Numerous clinical data show that konjac dietary fibre has a positive effect on the adjuvant treatment of diabetes, and it has a broad prospect for development. From the perspective of health economics, its safe and cheap advantages are more suitable for the majority of people with diabetes. However, we have also seen that clinical research is mostly simple preliminary research, which only involves the observation of simple blood sugar and blood lipids. Its internal mechanism is less involved, which leaves a lot of space for developing konjac health food.

4 Mechanism research

4.1 Inhibit the α -glycosidase activity

As a soluble dietary fibre with high viscosity, high swelling and strong satiety, KGM's hypoglycaemic mechanism mainly lies in its flow characteristics. After KGM absorbs water, it can quickly swell in the stomach to form a highly viscous konjac gum solution, which cannot be digested by the stomach in a short time. This feature delays the emptying of the stomach, prolongs the time for food to enter the small intestine from the stomach and forms an immobile water layer on the surface of the intestinal mucosa (Devaraj et al., 2019). This blocks the digestion and absorption of most carbohydrates and monosaccharides and reduces the rate of glucose absorption by the intestines, thereby lowering blood sugar levels. Research has shown that a KGM soluble fibre diet can limit the absorption of carbohydrates and improve blood glucose parameters (McCarty, 2005). Research has also shown that some natural foods, including KGM, can mimic the protective effects of acarbose, slow down the absorption of fat, protein and carbohydrates, and increase the glycaemic index (Jenkins et al., 2018). Chinese scholars, through experiments, have also shown that KGM can significantly inhibit the activity of α -glycosidase and inhibit the absorption of sucrose (Wang et al., 2005), but its inhibitory strength is not as good as that of voglibose. This suggests that glucomannan may have the properties and pharmacodynamic mechanism of inhibiting α -glycosidase. However, the above experiments have limitations. They have not been verified in vitro and in vivo. The effect of konjac dietary fibre in inhibiting α -glycosidase activity needs further verification.

4.2 Inhibition of inflammation

In 1993, an article in Science magazine first introduced the relationship between tumour necrosis factor (TNF) and obesity, as well as the relationship between inflammation and IR (Hotamisligil et al., 1993). At present, the concept that diabetes is a chronic low-concentration inflammatory disease has gained more recognition in the industry. Inflammation is closely related to IR in T2DM, and T2DM is even regarded as an inflammatory, metabolic disease (Donath & Shoelson, 2011). Studies have found that inflammatory factors such as interleukin-6 (IL-6), interleukin-1 β (IL-1 β) and tumour necrosis factor- α (TNF- α) inhibit the insulin signalling pathway and lead to IR and induce T2DM (Jager et al., 2007; Stienstra et al., 2010). It can be seen that long-term infiltration of inflammatory factors can lead to impaired β -cell function (Cerf, 2013), and inflammation plays a vital role in the occurrence and development of IR in T2DM. Supplementing the KGM diet can significantly inhibit the overproduction of IL-10, IL-4 and TNF- α (Dai et al., 2021). Zhao et al. (2020) demonstrated in in vitro experiments that low and high concentrations of KGM can promote the proliferation of lymphocytes in immunosuppressed mice induced by cyclophosphamide (CTX) and also significantly increase the levels of TNF-a, IgG and IL-2 in mouse serum, compared with the model group, which was significant (P < 0.01). It reflects the mutual restriction between KGM regulation of anti-inflammatory and pro-inflammatory cytokines and shows a certain concentration and time dependence. Researchers in China have studied T2DM rats induced by a high-fat diet combined with STZ and found that after a medium dose of KGM (80 mg/kg b.w.) treatment, the pathway of nuclear factor- κB (NF- κB) was improved and positively regulated (Rehman & Akash, 2017). This indirectly indicates that the hypoglycaemic mechanism of KGM is related to the inhibition of the expression of inflammatory factors.

4.3 Antioxidant stress response

By detecting oxidative stress markers in patients with diabetes and experimental animals, much experimental evidence shows a direct link between oxidative stress and diabetes. Eriksson (2007) studied the levels of 8-hydroxydeoxyribonucleic acid-modified protein in GK rats and showed that hyperglycaemia is the main potential factor of oxidative stress in pancreatic β -cells. Oxidative stress caused by glucose explains the mechanism behind sugar toxicity. IR caused by chronic hyperglycaemia is also believed to be related to the induction of oxidative stress (Chen et al., 2019). The polysaccharides in konjac are a scavenger of ROS, which can effectively remove hydroxyl, superoxide and metalinducing genes, thereby preventing lipid peroxidation damage to cells caused by oxidative stress.

Research has found that the fasting blood glucose concentration and blood lipids of rats in the KGM intervention group were significantly reduced (P < 0.05, P < 0.01, respectively) (Wang et al., 2002). The total antioxidant capacity and insulin secretion levels were significantly increased (P < 0.05), and the oxidative stressrelated genes Hmox1 and epidermal growth factor receptor genes were significantly upregulated (P < 0.05). It has been proven that KGM can inhibit the body's oxidative stress damage caused by diabetes and enhance its antioxidant capacity. High-fat-fed obese SD rats given six weeks of quantified konjac powder can significantly increase SOD activity and reduce lipid peroxide (LPO) content. This effect can last for one week after drug withdrawal (Aydin et al., 2018). Continuous research on konjac dietary fibre foods undoubtedly provides a broad research and development space for clinical adjuvant replacement therapy to delay the chronic damage and complications of diabetic pancreatic islet β -cells.

4.4 Improve intestinal prebiotic activity

The balance of intestinal flora and T2DM have also been current research hotspots. There have been many domestic and foreign studies focusing on the correlation between intestinal flora and the pathogenesis of diabetes (He et al., 2015; Mejía-León & Barca, 2015). Researchers have found that compared with healthy people, the structure of the intestinal flora in patients with diabetes that are obese changes significantly, and the species richness is also reduced (Liu et al., 2016). KGM can selectively stimulate the growth of lactobacillus and bifidobacteria in the intestine after hydrolysis (Al-Ghazzewi et al., 2007) and, at the same time, inhibit the growth of pathogenic bacteria such as Bacteroides and Escherichia coli in the intestine (Behera & Ray, 2016). Through the observation and analysis of the flora in people who added KGM and undigested plant fibre to their diet, the beneficial bacteria such as lactobacillus and bifidobacteria also increased significantly (Tan et al., 2016). An animal experiment on sows with gestational diabetes showed that feeding sows a konjac flour diet increased the insulin sensitivity index (P < 0.05) and significantly increased the abundance of Firmicutes and Bacteroides (P < 0.01), reducing the abundance of protein bacteria (P < 0.01) (Al-Ghazzewi & Tester, 2012). Ghazzewi et al. added hydrolysed KGM to MRS agar medium. Higher colony growth was observed in the agar, and the growth rate was accelerated under a high-temperature environment, which directly proved the development potential of KGM as a prebiotic (Bindels et al., 2015). One of the latest strategies for the clinical treatment of diabetes is probiotics, which usually refers to 'selectively fermented indigestible food ingredients or substances that specialize in the gastrointestinal tract to support the growth and/or activity of health-promoting bacteria' (Gómez et al., 2017). Konjac extract, konjac glucomannan and konjac oligosaccharides are also believed to act as prebiotics by inducing beneficial physiological effects (Gibson et al., 1995). Konjac glucomannan and oligosaccharides have a highly selective effect on the human intestinal microbiota.

The main reason is to increase the number of bifidobacteria and lactobacillus while reducing Bacteroides, Clostridium and Fusobacterium (Holscher et al., 2015). In contrast, most dietary fibres cannot induce selective changes in the gut microbiota (Akın & Bölük, 2020). Therefore, konjac dietary fibre can be used as a new type of prebiotic that can be added to food. This provides the experimental basis for further developing konjac dietary fibre composition as a food supplement for people at high risk of diabetes or diabetes.

4.5 Inhibit intestinal absorption

Diabetes combined with hyperlipidaemia and obesity accounts for 20 to 90% of patients with diabetes (McGarry, 2002). Most of the root causes of type 2 diabetes and its complications are lipid metabolism disorders (Gallaher et al., 2000). The hypoglycaemic and lipid-lowering effects of konjac dietary fibre are almost synchronized. Animal experiments speculate that the dual effects of konjac in reducing blood sugar and lipids are achieved by increasing sterols or bile acids in excretion (Jenkins et al., 1993). The other mechanism may be to reduce the Na⁺/K⁺-ATPase activity of the small intestinal mucosa and inhibit the absorption of cholesterol and bile acids (Pencek et al., 2002). Na⁺/K⁺-ATP is also called the 'sodiumpotassium pump', which provides conditions for the secondary active and transmembrane transports of glucose and amino acids. The level of its activity indicates the ability of the small intestine to absorb nutrients. When the enzyme activity decreases, the intestinal absorption of glucose, amino acids and other nutrients will decrease. The excessive storage of Na+ in the cells will also cause the intestinal osmotic pressure to increase, increasing the water content, stimulating intestinal peristalsis and promoting excretion (Han et al., 2016).

4.6 Suppress gluconeogenesis

Gluconeogenesis is the process by which mammals convert nutrients (lactic acid, amino acids, glycerol, etc.) into glucose or glycogen in the body and is one of the source channels of blood sugar (Guasch-Ferré et al., 2020). Gluconeogenesis is closely related to diabetes. The more obvious the effect of gluconeogenesis, the higher the fasting blood sugar. One of the functions of insulin is to synthesize liver glycogen, promote the conversion of glucose into fat, transport it to adipose tissue for storage and inhibit gluconeogenesis (Hatting et al., 2018). It has been established that insulin acts by activating the PI3K/Akt signalling pathway, and the loss of PI3K and Akt may be involved in the occurrence of IR and T2 (Garofalo et al., 2003). FOXO1 is a sensor for the liver to regulate blood insulin levels and glucose and lipid metabolism (Guo, 2014). Overexpression of FOXO1 can damage the ability of insulin to regulate liver glucose and lipid metabolism (Qu et al., 2006). Blocking FOXO1 can improve liver glucose and lipid metabolism in patients with IR (Cheng et al., 2009). The 8-week ladder training combined with the low-fat konjac diet can activate the high-fat diet to induce the PI3K/Akt pathway in IR rats. The FOXO1 content is significantly reduced (P < 0.05), showing that aerobic exercise combined with KGM supplementation can improve the liver PI3K/FOXO1 signalling pathways to inhibit the liver's gluconeogenesis, reduce the production of glycogen,

effectively prevent the occurrence of liver IR and maintain the stability of fasting blood glucose (Tang et al., 2014). Therefore, the decrease of blood glucose concentration in rats may also be related to the regulation of Konjac's promotion of glycogen synthesis and inhibition of gluconeogenesis.

4.7 Improve immune function

Under normal circumstances, the body, with the removal of risk factors disappear, the immune response is temporary. However, if obesity, IR or persistent hyperglycaemia and other damaging factors exist for a long time, a pathological chronic inflammatory process will occur, which is involved in the occurrence of many diseases (Hotamisligil, 2006). Studies have shown that T2DM is an autoimmune disease (Stadhouders et al., 2018). The accumulation of a large number of metabolites may trigger the body's immune dysfunction, and abnormal immune responses can aggravate the progression of the patient's condition. It has been reported that KGM can reduce the symptoms of diabetes by enhancing the body's immune regulatory function and antioxidant capacity (Jiang et al., 2018). The results of in vitro experiments also confirmed that konjac oligosaccharides could directly act on monocytes derived from human dendritic cells to regulate immune function (Lehmann et al., 2015). The active ingredients of konjac, glucomannan and oligosaccharides are also beneficial intestinal probiotics, regulating glucose and lipid metabolism and improving the body's immune function (Tester & Al-Ghazzewi, 2016). Chinese scholars used microbial enzymatic hydrolysis to degrade KGM molecules and found that the decomposition products have a good hypoglycaemic effect (Li et al., 2004). The study found that mouse macrophage phagocytic red blood cell percentage and phagocytic index increased significantly after administration (P < 0.01), which can enhance the phagocytic function of mouse peritoneal macrophages and the delayed allergic reaction caused by 2,4-dinitrofluorobenzene (DNFB). It is speculated that the goal of reducing blood sugar is achieved through autoimmunity. However, there are still few related studies, and further discussion is needed.

5 Adverse reactions and effective doses

As a soluble dietary fibre with high viscosity and high swelling properties, konjac will form a highly viscous sol after being dissolved in water, which can also cause some adverse reactions to the gastrointestinal tract while reducing blood sugar and fat, such as bloating, anorexia and diarrhoea. It is generally believed that excessive intake of konjac may cause flatulence and even lead to an imbalance of essential nutrients, which is counterproductive (Liu et al., 2016). At present, there are still some controversies about the dosage of KGM causing gastrointestinal adverse reactions in clinical practice, and the safety of konjac is still worth studying. Research has shown that KGM up to 2.5 g/kg has neither maternal toxicity nor teratogenicity in pregnant rats (Jiang et al., 2016). There is also the view that a small dose of 3.6 g of glucomannan per day does not change intestinal function (Arvill & Bodin, 1995). With the gradual increase of research, the safe dose of konjac reported in the literature is between 3.6 and 13.0 g per day, and it has a clear hypoglycaemic and lipid-lowering effect (Arvill & Bodin, 1995). However, various studies have different sample sizes, different races, dietary habits and inclusion criteria. Therefore, there is currently no consensus on the side effects and safe doses of konjac dietary fibre.

6 Konjac and food

KGM is a neutral plant polysaccharide. As a thickening and gelling agent, KGM is more and more widely used in the food industry (Ye et al., 2022). KGM hydrogel has good gel forming ability, but its poor swelling ability and poor controlled release performance limit its application. Oxidized hyaluronic acid (OHA) can effectively improve the performance of KGM hydrogels (Wu et al., 2022a). KGM and κ-carrageenan (CAR) showed a synergistic effect, thus forming a composite hydrophilic gel (if frozen) with great prospects in the field of food. It was found that appropriate addition of MD (0.4%) and deacetylated KGM could change the tensile properties of KGM/CAR blend gels, which might meet the needs of consumers and further design innovative tensile gel products in the soft gel industry (Wu et al., 2021). KGM can be used as additive to improve the properties of wheat products. KGM with high viscosity can improve the quality of steamed bread (Guo et al., 2022). KGM hydrolysate can be used as a low heat health gel enhancer in surimi processing (Wu et al., 2022b).

7 Discussion and outlook

China's konjac production is abundant, and the price is low. With the enhancement of people's health awareness and recognition of the benefits of dietary fibre in the 21st century, konjac products have a huge market development potential. At present, the development of various konjac dietary fibre foods on the market is also gradually prospering.

In summary, konjac dietary fibre is beneficial to patients with diabetes and has attracted the attention of researchers. It can achieve the effect of reducing blood sugar from many aspects. Its strong water absorption, swelling and viscosity can delay the absorption of food, which is considered the main mechanism for lowering blood sugar. More studies have shown that konjac dietary fibre can act in the gastrointestinal tract, so whether the secretion and release of related hormones and enzymes, such as GLP-1, DDP-4, etc. can be regulated by the endocrine system in the intestine, the research contents will be significant. However, in recent years, there has been little research on the mechanism of konjac in reducing blood sugar and lipids. Some studies have only shown that the administration of konjac glucomannan significantly decreased the levels of type 2 diabetic rats' fasting blood glucose, serum insulin, glucagon-like peptide 1 and glycated serum protein (Gamboa-Gómez et al., 2020). Whether there is an undiscovered mechanism of action will be the direction we need to study next.

At the same time, safe and effective health foods have brought good news to patients with diabetes and obesity. However, through our observations, there is still room for improvement in clinical research and food development. 1. Unify the production process and evaluation standards to ensure the uniformity and comparability of the edible effect of health foods in the market. 2. As far as possible, the processing of konjac is refined and nano-sized, which is more conducive to absorption and metabolism and reduces adverse reactions, such as abdominal distension and diarrhoea after consumption of traditional konjac foods. Consumers should be fully informed in the manual and in promotion to alleviate their panic. 3. Konjac is difficult to promote clinically because of its poor taste. It should be mixed with other foods to improve the taste as much as possible to ensure the synergistic effect and enhance patient compliance. 4. Because konjac has a strong hypoglycaemic effect, and different patients have different tolerance levels, further research should be done on the dosage and rheological biological effects of dietary fibre and, at the same time, prevent the occurrence of hypoglycaemia after use.

We believe that there are safer and more reliable methods to prevent and treat diabetes, and the treatment of diabetes based on the regulation of konjac dietary fibre could provide an innovative and critical idea for its prevention and treatment.

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