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## Beneficial effects of psyllium on the prevention and treatment of cardiometabolic diseases

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Cardiometabolic diseases are reaching epidemic proportions worldwide. Dietary fiber intake can improve the risk factors associated with CMD. Psyllium, especially its husk, is one of the most widely used dietary fiber supplements, which is often used to enrich cereals and other food products. Numerous pharmacological studies have investigated the active ingredients and therapeutic effects of psyllium and its extracts, including antioxidant, anti-tumor, antidiabetic, hypotensive, anti-inflammation, neuroprotection, antidiarrheal, and antiviral activities. In this review, we will summarize the available studies on the therapeutic potential and possible mechanisms of psyllium in treating CMDs, such as hyperlipidemia, diabetes mellitus, and its complications, hypertension, hyperuricemia and obesity, and its applications in food systems.

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### Introduction

Cardiometabolic diseases (CMDs) are reaching epidemic proportions worldwide and are the leading cause of death in both developed and developing countries.<sup>1</sup> In addition to genetic factors, dyslipidemia, poor glycemic control, abdominal obesity, smoking, lack of exercise, and dietary factors are associated with CMD.<sup>2</sup> Dyslipidemia is one of the major risk factors contributing to cardiovascular diseases (CVD) through atherosclerosis development and progression.<sup>3</sup> Sustained exposure to high glucose levels significantly increases the risk of CVD complications.<sup>4</sup> Obesity, particularly severe obesity, is capable of producing hemodynamic alterations that result in alterations in cardiac structure and function which may contribute to the development of CVD.<sup>5</sup> Individuals with CMDs face a higher risk of developing myocardial infarction, stroke, and heart failure. Current evidence indicates that interventions to control modifiable risk factors can reduce the occurrence of CVD or slow down its progression. A growing amount of evidence suggests that dietary fiber intake can improve the risk factors associated with CMD,<sup>6</sup> and major organizations support increasing fiber intake as part of a healthy lifestyle

promotion. Among the most popular, supplemental, soluble dietary fibers globally are the seed husks of psyllium,<sup>7</sup> which is often used to enrich cereals and other food products.

Psyllium, also known as isabgol, is the seed of an annual plant of the *Plantago* genus, which is widely cultivated in tropical regions of the world, such as India, Iran, Egypt, China, *etc.*<sup>8</sup> In China, psyllium is commonly called “Che Qian Zi”, and is used as folk medicine with a long history for antipyretic, diuretic, and expectorant purposes. It was recommended for “disorders of vital energy, pain, diuresis and rheumatism” in the Shen Nong Ben Cao Jing (Herbal of the Divine Plowman).<sup>9</sup> Furthermore, psyllium is also commonly used in traditional Indian medicine for the treatment of skin irritations, constipation, and diarrhea.<sup>10</sup> Recently, psyllium, especially its husk, has been widely used both as a pharmacological supplement and a food product.<sup>11</sup> Pharmacological studies have shown that psyllium exhibits several biopharmacological activities, including against constipation,<sup>12–15</sup> diarrhea,<sup>15,16</sup> obesity,<sup>17,18</sup> diabetes,<sup>19–23</sup> nonalcoholic fatty liver disease (NAFLD),<sup>24</sup> hypercholesterolemia,<sup>20,25–30</sup> irritable bowel syndrome,<sup>31,32</sup> and colon cancer,<sup>33</sup> some of which are closely related to the development of CMDs. Psyllium husk can be used in food product development, such as in ice cream, bakery goods, dairy and gluten-free products, beverages, chocolates, noodles, and breakfast cereals.<sup>11,34–41</sup> Most health-beneficial effects and food applications of psyllium are attributed to its high water-holding capacity and gel-forming nature.<sup>42–45</sup> The purpose of this review is to summarize the available studies on the beneficial health effects of psyllium on CMDs and its applications in functional foods.

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## Chemical constituents

Psyllium is the common name related to the seeds of an annual herb of the *Plantago* genus.<sup>46</sup> The genus *Plantago* is one of the largest of the three genera of the Plantaginaceae family, comprising about 270 species, such as *Plantago ovata* Forssk., *Plantago asiatica* L., *Plantago major* L., and *Plantago depressa* Willd., among others.<sup>46</sup>

The genus *Plantago* is widely distributed in temperate and high-elevation tropical regions.<sup>47</sup> The seed and the whole plant are shown in Fig. 1. Once harvested, the husk is mechanically separated from the seed by milling.<sup>8</sup> The husk is the white membranous structure covering the seed, and it constitutes about 30% of the dried seed's weight.

The whole psyllium consists of soluble (mostly arabinoxylans) and insoluble polysaccharides (hemicellulose, cellulose,

and lignin), as well as tannins, phenols, and flavonoids<sup>48–51</sup> (Fig. 2). The husk of psyllium is a mixture of neutral and acid polysaccharides containing galacturonic acid with a ratio of soluble/insoluble fiber of 70/30.<sup>52</sup> Most of the health-beneficial effects and food applications of psyllium and its husk are attributed to their high content of arabinoxylans (polysaccharides mainly composed of xylose and arabinose), with the husk containing more.<sup>53,53</sup> Polysaccharide extracted from psyllium seeds is a very important biological active ingredient that has been widely reported in recent years.<sup>9,50,54,55</sup> Psyllium polysaccharides are composed of xylose, arabinose, galactose, rhamnose, glucose, and mannose in different molar ratios. According to these reports, psyllium polysaccharide possesses various human health-promoting effects, such as antioxidant, antitumor, immunomodulatory, anti-proliferative,<sup>56</sup> hypoglycemic, hypotensive, and antiviral activities,<sup>57</sup> among others.<sup>55</sup> It is worth mentioning that the raw materials, extraction temperature, and time will affect the composition, structure, and function of psyllium polysaccharides.<sup>55</sup> Moreover, both psyllium seeds and husks are rich in bioactive compounds and different primary and secondary metabolites.<sup>51,58</sup> Among these, the most abundant compounds are fatty acids, amino acids, polyphenols, and flavonoids.<sup>58,59</sup> Metabolites such as polyphenols and flavonoids that possess antioxidant activity thus have the potential for the treatment of excessive reactive oxygen species (ROS)-triggered diseases.



Fig. 1 The *Plantago* genus plant (left), and traditional Chinese herb Che Qian Zi/psyllium (right).

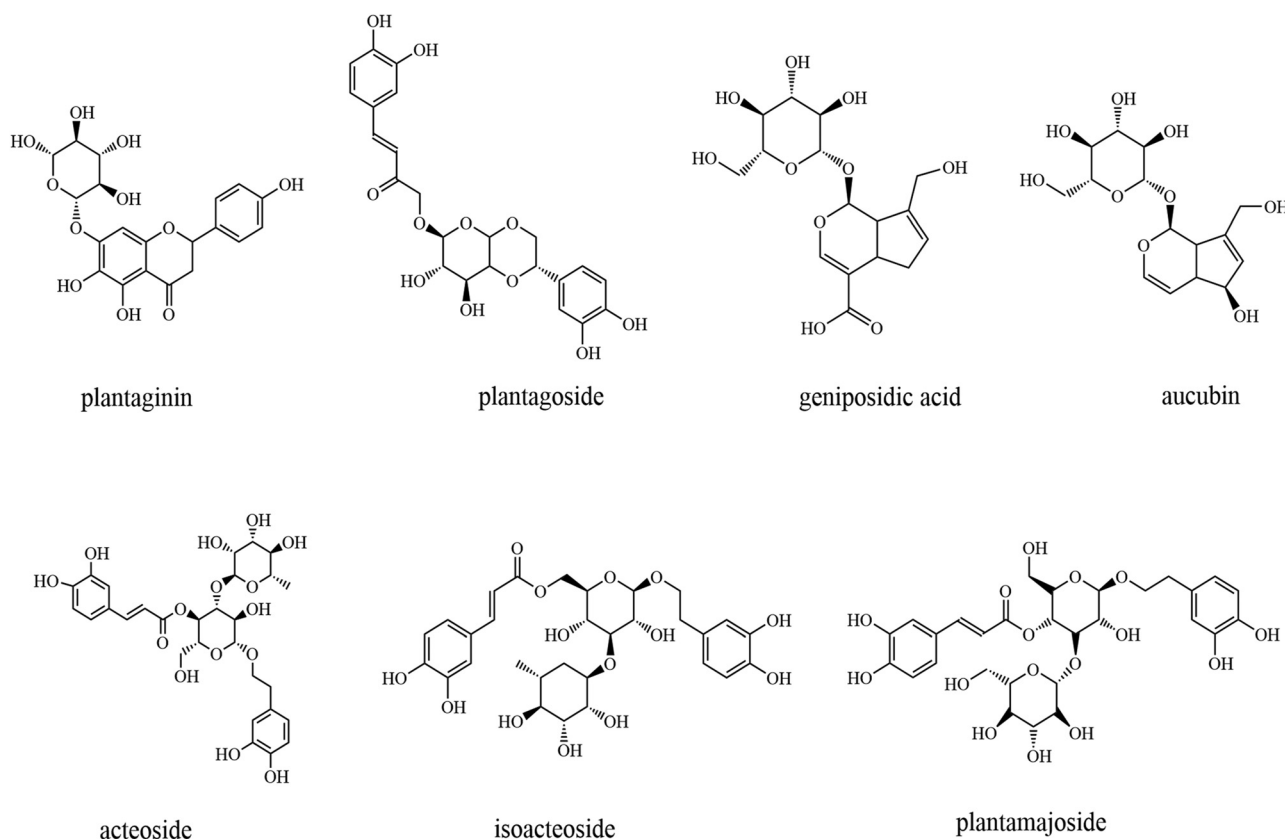


Fig. 2 Chemical structures of the representative components of psyllium.



## Psyllium applications in food systems

The growing awareness of a healthy diet has led to an increasing demand for functional food, which has induced the food industry to search for new functional products with health benefits.<sup>60</sup> Meanwhile, the sensory properties, such as color, flavor, texture, and overall acceptability, will affect consumers' acceptance.<sup>61</sup> According to previous studies, some researchers have added psyllium husk into food products (such as ice cream, biscuits, gluten-free bread, noodles, pizza, pasta, and cakes), and reported health benefits such as cholesterol control, glycemic control, and satiety, among others (Fig. 3).<sup>11,41,61</sup> In addition, the addition of psyllium has been shown to obtain a softer crumb in high-fiber wheat bread and improve dough mechanical properties and gluten-free bread shelf-life.<sup>35,37,38,40,62</sup> However, the incorporation of psyllium husk in different foods is limited, as high levels of fiber may cause disagreeable changes in the texture and color of foods.<sup>46</sup> Particularly in baked products, it was observed that cookies with psyllium husk were darker than those without it.<sup>61,63</sup> Thus, further research may focus on minimizing the undesired effects of a great incorporation of psyllium husk in food to improve its quality and consumer acceptability.

## Adverse effects

Psyllium is safe to use as a functional ingredient in food systems.<sup>11</sup> A clinical trial<sup>64</sup> involving 93 healthy subjects showed that psyllium husk (10.5 g, 52 weeks) was well tolerated and the majority of adverse events recorded were minor, of short duration, and either unrelated or only possibly related to the study treatment. Similarly, a clinical trial involving 12 type 2 diabetic patients showed that psyllium administration did not adversely affect either mineral or vitamin A and E concentrations.<sup>65</sup> Despite this, several studies have reported possible adverse effects of psyllium intake, such as altering nutrient absorption and eliciting allergic reactions. One study reported that psyllium intake reduced calcium bioavailability and induced negative changes in bone composition in weanling Wistar rats, although there was virtually no binding of exogenous calcium by psyllium *in vitro*.<sup>66,67</sup> Lantner briefly

reviewed and discussed the allergic reactions to psyllium and suggested physicians and consumers should be aware of potentially serious reactions to it.<sup>68</sup> Moreover, based on *in vitro* studies, psyllium has once been characterized as “fermentable”, which could cause symptoms related to excessive gas production. However, McRorie *et al.* reviewed six clinical studies and emphasized that gel-forming psyllium is not fermented in the human gastrointestinal tract and does not produce excess gas.<sup>69–71</sup> Moreover, some researchers are concerned about whether long-term exposure to psyllium may adversely affect health or increase the risk of colon tumorigenesis.<sup>72</sup> Psyllium has been shown to reduce colon cancer risk, both in humans and in animals.<sup>73,74</sup> Citronberg *et al.* used a large clinical study (75 214 participants) which examined the association between colorectal cancer incidence and constipation, non-fiber laxative use, and fiber laxative use (*e.g.*, psyllium).<sup>75</sup> The authors concluded that the risk for colorectal cancer increases with non-fiber laxative use and decreases with fiber laxative use (*e.g.*, psyllium). McRorie *et al.* reported that psyllium husk should be taken at higher doses with sufficient water to maximize its efficacy response.<sup>76</sup> In summary, psyllium can be safely used in the run for numerous health benefits.

## Therapeutic potential psyllium in CMDs

### Hyperlipidemia

Hyperlipidemia, referring to a metabolism disorder, is characterized by increased total cholesterol, triglyceride, and low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) in serum. Epidemiologic data suggest that dyslipidemia is the major causal factor for ischaemic heart disease and stroke worldwide, accounting for 84.9% of CVD deaths.<sup>3,77</sup> Research has shown that dyslipidemia leads to the deposition of cholesterol and lipids in blood vessel walls, chronic inflammation, and the formation of atherosclerotic plaques that block blood flow and (when they rupture) lead to acute ischemic attacks.<sup>78</sup> Measures to adjust abnormal lipid metabolism are commonly agreed to prevent the outbreak of CVD. However, many lipid-lowering drugs, such as statins, carry various side effects or contraindications.<sup>79</sup>

Plenty of randomized clinical studies and meta-analyses have evaluated the effect of psyllium on lipid levels (Table 1). McRorie *et al.*<sup>69</sup> analyzed 21 randomized, well-controlled clinical studies (>1500 subjects) using doses of 6 to 15 g d<sup>-1</sup> (most studies at 10 g d<sup>-1</sup>) and assessed the effectiveness of psyllium for lowering elevated serum cholesterol concentrations. In all studies, there were significant cholesterol-lowering effects of psyllium, ranging from a -6% to -24% change for LDL cholesterol and -2% to -20% for total cholesterol, *versus* placebo. The authors concluded that the cholesterol-lowering efficacy of psyllium was greatest in studies with unrestricted diets and patients with high baseline cholesterol concentrations.<sup>80</sup> A meta-analysis of 28 studies (*n* = 1924) found that supplement-



Fig. 3 Psyllium applications in food systems.



**Table 1** Table of meta-analyses investigating the hypolipidemic, hypoglycemic, antihypertensive, and anti-obesity effects of psyllium

Outcomes	Evidence type and population	Dose	Duration	Findings	Ref.
Hypolipidemic effect	Meta-analysis (21 studies, $n = 1030$ )	3.0–20.4 g d <sup>-1</sup>	2 weeks	↓Total cholesterol (−0.375 mmol L <sup>-1</sup> ) ↓LDL cholesterol (−0.278 mmol L <sup>-1</sup> )	30
Hypolipidemic effect	Meta-analysis (28 studies, $n = 1924$ )	10.2 g d <sup>-1</sup>	8 weeks	↓LDL-cholesterol (−0.33 mmol L <sup>-1</sup> ) ↓Non-HDL cholesterol (−0.39 mmol L <sup>-1</sup> ) ↓apoB (−0.05 g L <sup>-1</sup> ) Psyllium could produce dose- and time-dependent serum cholesterol-lowering effects in mildly and moderately hypercholesterolemic patients	27
Hypolipidemic effect	Meta-analysis (3 studies, $n = 204$ )	10.8 g d <sup>-1</sup>	4–12 weeks	Adding psyllium fiber resulted in reductions in low-density lipoprotein-cholesterol equivalent to doubling the statin dose	25
Hypoglycemic effect	Meta-analysis (35 studies, $n = 535$ )	10 g d <sup>-1</sup>	1 meal to 6 months	↓Fasting blood glucose (−37.0 mg dL <sup>-1</sup> ) ↓Glycated hemoglobin (−0.97%) The glycemic control effects of psyllium were proportional to baseline FBG	90
Antihypertensive effect	Meta-analysis (11 studies, $n = 592$ )	3.7–15 g d <sup>-1</sup>	4 weeks to 6 months	↓SBP (−2.04 mmHg) Psyllium supplementation revealed significant reductions in blood pressure in subjects with higher baseline blood pressure	7
Anti-obesity effect	Meta-analysis (8 studies, $n = 395$ )	9 g d <sup>-1</sup> (3.4 to 15 g d <sup>-1</sup> )	8–20 weeks	↓Triglycerides (−19.18 mg dl <sup>-1</sup> ) ↓LDL (−8.96 mg dl <sup>-1</sup> ) ↓Fasting blood sugar (−31.71 ml dl <sup>-1</sup> ) ↓Hemoglobin A <sub>1c</sub> (−0.91%) No significant change in high-density lipoprotein, body mass index, cholesterol, and weight	131
Anti-obesity effect	Meta-analysis (22 studies, $n = 1458$ )	1.7–15 g d <sup>-1</sup>	2–48 weeks	Psyllium supplementation does not reduce body weight (−0.28 kg), body mass index (−0.19 kg m <sup>-2</sup> ), and waist circumference (−1.2 cm) significantly	132

tation with a median dose of 10.2 g d<sup>-1</sup> psyllium for 8 weeks significantly lowered LDL cholesterol by −0.33 mmol L<sup>-1</sup>, non-HDL cholesterol by −0.39 mmol L<sup>-1</sup>, and apolipoprotein B by −0.05 g L<sup>-1</sup>. The authors concluded that psyllium fiber potentially delayed atherosclerosis-associated CVD risk in individuals with or without hypercholesterolemia.<sup>27</sup> According to the FDA, the consumption of 7 g or more of psyllium per day, associated with a diet with low amounts of saturated fat and cholesterol, can reduce the risk of CVD by lowering serum cholesterol levels.<sup>81</sup> In addition, Wei *et al.*<sup>30</sup> analyzed 21 studies ( $n = 1030$ ) using doses of 3.0 to 20.4 g d<sup>-1</sup> and reported a dose–response relationship between psyllium and serum cholesterol level and a time-dependent effect of psyllium in mildly to moderately hypercholesterolemic subjects. The cholesterol-lowering benefit of psyllium has also been shown to be an effective co-therapy for statin drugs. Moreover, a recent meta-analysis reported that the addition of psyllium (mean, 10.8 g d<sup>-1</sup> in divided doses before meals) would add to the efficacy of statins and result in reductions in LDL cholesterol equivalent to doubling the statin dose.<sup>25</sup> The authors concluded that combining statin therapy with psyllium supplementation may provide an option for patients who cannot tolerate the higher-dose statins. Furthermore, an economic analysis<sup>82</sup> found that if adults aged 45 years and older with elevated LDL-cholesterol levels (*e.g.*,  $\geq 130$  mg dL<sup>-1</sup>) consumed psyllium 10.2 g d<sup>-1</sup>, there could be an average saving of \$870 million in healthcare costs and quality of life productivity gains (estimates from 2013–2020). Psyllium has a notable role in lowering elevated serum cholesterol concentrations, which

is mainly due to its viscosity. Cholesterol is one of the main components of bile, and therefore, an increase in bile salt excretion causes increased cholesterol use for hepatic bile synthesis.<sup>83</sup> Psyllium is rich in soluble fiber, which forms a viscous gel that binds to bile salts in the gut and increases their excretion with stools, leading to the reduction of the bile acid pool. This reduction causes hepatocytes to compensate by stimulating LDL receptor expression,<sup>84</sup> which promotes the conversion of cholesterol to bile acids. When the conversion is increased in the body, it promotes the reduction of blood cholesterol concentrations, contributing to a reduction of the risk of CVD. Note that the cholesterol-lowering efficacy of psyllium is a viscosity-dependent phenomenon: the higher the fiber viscosity, the greater its cholesterol-lowering effect.<sup>85</sup>

In summary, psyllium possesses a favorable effect on lowering cholesterol levels, which is highly related to the ability to form a viscous gel to augment bile acid-binding and its fecal excretion, promoting the conversion of cholesterol to bile acids, and thus leading to a reduction of blood cholesterol concentrations. Furthermore, psyllium as adjuvant anti-lipid therapy could help achieve the target lipid plasma levels with lower drug dosages and fewer adverse effects.

### Diabetes mellitus and its complications

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia due to deficient insulin production (type 1 diabetes mellitus) or peripheral insulin resistance of the cells (type 2 diabetes mellitus).<sup>86</sup> Both of them could lead to a variety of cardiovascular complications. Sustained



exposure to high glucose levels is associated with the development of macrovascular complications, such as coronary artery disease, peripheral vascular disease, cerebrovascular disease, and microvascular complications, including retinopathy, nephropathy, and neuropathy.<sup>86</sup>

Currently, numerous studies suggest that psyllium can improve glycemic indicators, such as fasting blood glucose (FBG), glycated hemoglobin (HbA<sub>1c</sub>), and insulin resistance (HOMA-IR), and exert protective actions against these cardiovascular complications of diabetes, suggesting that psyllium administration is a promising therapy for diabetes (Table 1).<sup>19,20,65,87–89</sup> A meta-analysis of 35 randomized, controlled, clinical studies showed that psyllium (mean, 10 g d<sup>-1</sup> in divided doses before meals) showed a significant decrease in both FBG level and HbA<sub>1c</sub>.<sup>90</sup> Similar to cholesterol-lowering, the glycemic effects of viscous/gel-forming fiber are also proportional to baseline FBG. There was no significant effect on FBG in euglycemic subjects, a modest effect in subjects with pre-T2DM (up to -4.7 mg dL<sup>-1</sup>), and the greatest effect in subjects who were being treated for T2DM (-37.0 mg dL<sup>-1</sup>).

McRorie *et al.* reported that the primary mechanism for improving glycemic control with a soluble, viscous fiber supplement is by significantly increasing the viscosity of chyme in a dose-dependent manner.<sup>69</sup> Psyllium forms a viscous gel that increases chyme viscosity, which leads to a decrease in the interactions between the digestive enzymes and nutrients, slowing down the degradation and absorption of glucose and other nutrients. Nutrients are normally absorbed early in the small bowel, but this delay leads to an increased delivery of nutrients to the distal ileum. With more nutrients delivered to the distal ileum, mucosal L-cells are stimulated to release more glucagon-like peptide-1 (GLP-1) into the bloodstream,<sup>91</sup> which plays a central role in the coordination of postprandial glucose homeostasis.

Sustained exposure to high glucose levels contributes to oxidative stress. Oxidative stress is thought to be a major factor contributing to the pathogenesis and progression of diabetes-induced CVD.<sup>92</sup> Recent experiments showed that psyllium could enhance the antioxidative defense system as illustrated by the increase in superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) levels and decreased endogenous ROS production, and malondialdehyde (MDA) content, thereby protecting the body from oxidative stress.<sup>93,94</sup> Plantamajoside, a major compound of psyllium, effectively elevated the activities of SOD, CAT, and GSH-Px to inhibit hypoxia/reoxygenation-induced ROS production, and significantly enhanced the activation of the Akt/Nrf2/HO-1 signaling pathway.<sup>95</sup> Studies have demonstrated that nuclear factor erythroid 2-related factor 2 (Nrf2)<sup>96</sup> can upregulate the transcription of antioxidant enzymes involved in cellular antioxidant defenses, which protects cells from oxidative stress damage. One study indicated that psyllium can enhance the expression of Nrf2, thereby increasing the levels of antioxidant enzymes such as glutathione S-transferase mu 2 (GSTM2) and superoxide dismutase 2 (SOD2), and enhancing the expression of SIRT5, SIRT6, and SIRT7, which contributes to protecting

against myocardial ischemia/reperfusion injury through the elimination of ROS.<sup>97</sup>

Diabetic retinopathy is envisioned as a biomarker of generalized hyperglycemic damage in the microvasculature.<sup>98</sup> The mechanisms of hyperglycemia leading to diabetic retinopathy mainly include increased free radical production, AGEs, inflammatory factors, and vascular endothelial growth factor.<sup>99</sup> Administration of psyllium (100, 200, or 300 mg kg<sup>-1</sup> for 8 weeks) alleviated the blood glucose level, the diameter of the retinal vessels, and retinal vascular permeability in streptozotocin-induced diabetic rats.<sup>93</sup> Moreover, it increased the activities of SOD and CAT, and GSH levels, and down-regulated the expression of TNF- $\alpha$ , interleukin-1beta (IL-1 $\beta$ ), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in diabetic retiniae, which demonstrated that psyllium may be a potential therapeutic agent for the prevention of retinal microvascular complications of diabetes. In addition, plantagoside and its aglycone, isolated from *Plantago major* seeds, inhibited the formation of advanced glycation end products, which suggested that psyllium has potential therapeutic effects in the prevention of diabetic complications.<sup>100</sup>

According to these studies, psyllium, through its viscous property, forms gel-like substances in our gastrointestinal tract, which can lead to a decrease in the interactions between the digestive enzymes and nutrients, slowing down the degradation and absorption of glucose and other nutrients, thereby helping to manage blood sugar. Meanwhile, psyllium has great potential therapeutic effects in the prevention and treatment of diabetic complications for the antioxidant activity.

## Hypertension

Hypertension is a multifactorial cardiovascular disorder that has a variety of genetic and environmental factors. Globally, the prevalence of hypertension is expected to reach approximately 1.6 billion by 2025.<sup>101</sup> Long-term elevated or unstable blood pressure can lead to cardiac hypertrophy, and irreversible changes in the left ventricular wall, making it harder, thinner, and weaker, resulting in a larger left ventricular volume, and ultimately leading to cardiac insufficiency.<sup>102</sup>

A clinical trial showed that the psyllium group (10.5 g d<sup>-1</sup>, 6 months) showed a significant improvement in plasma TG concentration, SBP, and diastolic blood pressure (DBP), suggesting that psyllium was effective in lowering blood pressure.<sup>103</sup> Another clinical trial yielded similar results; subjects with hyperlipidemia were instructed to take psyllium (10.5 g d<sup>-1</sup>, 3 months), and it was observed that their weight, SBP, and DBP reduced by 1.34%, 2.57%, and 4.57% respectively.<sup>104</sup> A recent meta-analysis of 11 trials ( $n = 592$ ) showed that supplementation with psyllium revealed a reduction of 2.04 mmHg in SBP, and its anti-hypertensive effect was stronger in subjects with a higher baseline blood pressure (Table 1).<sup>7</sup> Similarly, another meta-analysis found that of the five viscous fiber supplementations, only psyllium revealed a reduction of 2.39 mmHg in SBP.<sup>105</sup> Furthermore, as excess weight is associated with an increased risk of inhibited blood



pressure control, Khan *et al.*<sup>105</sup> suggested that the reduction of blood pressure is presumably secondary to weight loss.

The renin–angiotensin–aldosterone system (RAAS) is a major mechanism for blood pressure regulation. Previous animal studies reported that psyllium has an anti-hypertensive effect through the inhibition of angiotensin-converting enzyme (ACE) activity. In spontaneous phase-1 hypertension rats, psyllium extract (0.36 g kg<sup>-1</sup>) could play acute antihypertensive effects, with systolic pressure decreased by 31.5 mmHg and diastolic pressure decreased by 18.5 mmHg within an hour.<sup>106</sup> In spontaneously hypertensive rats, psyllium extract (400 mg kg<sup>-1</sup>) reduced systolic, diastolic, and mean blood pressures, and the levels of serum angiotensin I (Ang I) and angiotensin II (Ang II), the ratio of Ang II to Ang I, and aldosterone (ALD) were lowered.<sup>107</sup> Meanwhile, *in vitro*, it was observed that psyllium extracts and their major constituents have ACE inhibitory activity.<sup>108</sup>

In addition, previous studies found that psyllium was applied to treat hypertension clinically due to its traditional diuretic effect. High salt intake increases the burden on the kidneys, which has long been associated with high blood pressure. In the salt-accelerated hypertensive rat, psyllium increased fecal excretion of sodium and attenuated hypertension.<sup>109</sup> Aquaporin 2 (AQP2) is associated with water reabsorption in the renal collecting ducts, which is the key process of body water homeostasis. In another saline-loaded rat, crude and salt-processed psyllium increased urine volume excretion and urine electrolyte excretion and decreased ALD and AQP2 levels.<sup>110</sup>

Endothelial dysfunction may contribute to increased systemic vascular resistance, thus leading to the development of hypertension. In obese Zucker rats, psyllium treatment improved endothelial dysfunction and hypertension.<sup>111</sup> In human umbilical vein endothelial cells, it was observed that plantamajoside from psyllium treatment could improve advanced glycation end product-induced endothelial cell dysfunction.<sup>112</sup> Oxidative stress and inflammation can cause endothelial cell dysfunction. In phase-1 hypertension rats, psyllium extract could play anti-inflammatory and antioxidant effects by inhibiting the activity of NF- $\kappa$ B, TNF- $\alpha$ , cyclooxygenase-1 (COX-1), COX-2, and NO production.<sup>58,93,94,113,114</sup> Fu *et al.* suggested that the sustained administration of psyllium extract may improve chronic high blood pressure.<sup>106</sup>

Additionally, long-term hypertension usually causes cardiac hypertrophy. In isoproterenol-induced cardiac hypertrophy mice, psyllium extract treatment (20, 40, and 80 mg kg<sup>-1</sup> day<sup>-1</sup>) improved cardiac function indexes, including ejection fraction, fractional shortening, stroke volume, and cardiac output, decreased the heart weight/body weight ratio and cardiomyocyte size, and downregulated the mRNA and protein expressions of the hypertrophic markers ANP, BNP, and  $\beta$ -MHC.<sup>115</sup> In addition, isoproterenol-induced the alteration in autophagic markers, such as the increase of Beclin1 and LC3II, and decrease of p62, which were rescued by the treatment of psyllium extract. In terms of the proteins involved in the apoptosis, isoproterenol-induced the decrease of Bcl-2 but

the increase of Bax and Cleaved-caspase3, which was reversed by psyllium extract treatment. These results implied that psyllium extract treatment might prevent cardiomyocyte injury through anti-autophagy and anti-apoptosis. Uniformly, plantamajoside, an active component that can be extracted from psyllium, inhibited the mRNA and protein expression of ANP, BNP, Myh7, COL1, and COL3, as well as suppressing the activity of histone deacetylase 2 and its downstream proteins, protein kinase B and glycogen synthase kinase-3 $\beta$ , both *in vitro* and *in vivo*.<sup>116</sup> These results suggested that psyllium may play a therapeutic role in CVDs caused by long-term hypertension.

In short, the antihypertensive effect of psyllium can be directly attributed to the regulation of the RAAS, the diuretic effects, and the improvement of endothelial function. Indirectly, psyllium can improve the control of body weight, exerting a hypotensive effect. Moreover, psyllium can also improve cardiac hypertrophy caused by long-term hypertension.

### Hyperuricemia

Uric acid (UA) is the final product of purine metabolism, which is a well-known risk factor for gout.<sup>117</sup> Recent epidemiological studies show that high levels of serum UA are important biomarkers for CVDs morbidity and mortality. Moreover, asymptomatic hyperuricemia has been reported to lead to a significantly increased risk for cardiometabolic conditions.<sup>118</sup> Despite extensive research, the underlying molecular mechanisms remain unclear. Experimental studies show that hyperuricemia mainly promotes the occurrence and development of CVDs by regulating molecular signals, such as inflammatory responses, insulin resistance/diabetes, oxidative stress, endoplasmic reticulum stress, and endothelial dysfunction.<sup>119,120</sup> It was reported that the mean level of uric acid was 10% lower after psyllium administration.<sup>65</sup>

Currently, several studies have shown that psyllium exerts a UA-lowering effect through two mechanisms: inhibiting UA synthesis (xanthine oxidase (XOD) inhibitors) and increasing UA excretion. Firstly, xanthine oxidase is a key enzyme that catalyzes xanthine to uric acid. Zeng *et al.* have demonstrated the XOD inhibitory effects of the psyllium extract acteoside, and 1*H*-indolo-3-carbaldehyde, by the electron transfer signal blocking activities (ETSBA) method, suggesting that psyllium was effective in inhibiting XOD activities to reduce hyperuricemia.<sup>121</sup> Another *in vitro* research study has yielded similar results. Secondly, urate anion transporter 1 (URAT1) is the main transporter for UA reabsorption.<sup>122</sup> URAT1 inhibition can reduce the reabsorption of UA in the renal tubules, accelerate the renal excretion of UA, reduce blood uric acid, and ultimately play a therapeutic role in hyperuricemia. In the potassium oxonate-induced hyperuricemia rat, psyllium treatment may achieve the effect of treating hyperuricemia by downregulating the mRNA expression of URAT1.<sup>123</sup> Additionally, a high dose of psyllium possesses inhibitory activity over the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway,



which plays a role in anti-inflammatory and renal protection, and ultimately indirectly improves hyperuricemia.

These studies demonstrated that psyllium is a potential therapeutic agent for the treatment of hyperuricemia *via* inhibiting XOD activities and URAT1 expression.<sup>123</sup>

### Obesity

Obesity, a worldwide epidemic, originates from an imbalance between food intake and energy expenditure, which leads to an excessive accumulation of adipose tissue, and is often associated with chronic inflammation.<sup>124</sup> One epidemiological study estimated that the global obesity prevalence will reach 18% in men and surpass 21% in women by 2025.<sup>125</sup> Recent clinical and epidemiological evidence has shown a strong association between obesity and CVDs including coronary heart disease, atrial fibrillation, ventricular arrhythmias, cerebrovascular disease, heart failure, and sudden cardiac death.<sup>126</sup> Data from both humans and animals have suggested that psyllium can significantly suppress appetite and energy intake that can contribute to weight loss, body mass index (BMI), and waist circumference (WC).

As previously mentioned, the rate of digestion and absorption is delayed because of the formation of the psyllium gel within the small intestine, which prolongs satiety/delays hunger, thus leading to decreased energy intake and weight loss. Furthermore, as a kind of fiber-rich food, the act of chewing it needs a longer time, which may increase sensory satiety and diminish meal size. One publication comprises two clinical trials that investigated the satiety effects of psyllium in healthy adults.<sup>127</sup> The first study determined the effects of 3 different doses of psyllium (3.4 g, 6.8 g, and 10.2 g;  $n = 30$ ) before breakfast, lunch, and dinner for 3 consecutive days. The authors reported that all 3 psyllium doses resulted in directional or statistically significant mean reductions in hunger and desire to eat, and increased fullness between meals compared with placebo, with both higher doses better than placebo or 3.4 g. As the 6.8 g dose provided more consistent satiety benefits *versus* placebo in the first study, the second study selected the 6.8 g dose (taken before breakfast and lunch on days 1 and 2 and before breakfast on day 3) to verify whether the satiety effect of psyllium following the consumption of a less satiating breakfast in a similar population of healthy individuals ( $n = 44$ ) was reproducible. The results showed a significant decrease in the 3-day mean hunger and desire to eat, as well as an increase in fullness for psyllium compared with placebo. Other studies have also confirmed the efficacy of psyllium for increasing satiety/decreasing hunger.<sup>128–130</sup> A study assessed the efficacy of psyllium on gastric emptying, hunger feeling, and food intake in 14 normal volunteers. Results showed that psyllium (7.4 g d<sup>-1</sup>) reduced hunger feelings and energy intake.<sup>128</sup> Meanwhile, the postprandial increase in serum glucose, triglyceride and insulin levels was less with psyllium than with placebo. Overweight and obesity are two important risk factors for NAFLD, and a clinical study reported that calorie intake, carbohydrate intake, liver enzyme alanine aminotransferase, waist

circumference, BMI, weight and body fat percentage were reduced in the psyllium supplement group (10 g d<sup>-1</sup>,  $n = 80$ ) as compared with the placebo group. The authors concluded that the weight loss diet program which was supplemented with psyllium in parallel with increasing physical activity can be useful in reducing NAFLD outcomes.<sup>24</sup>

The effectiveness of psyllium in weight loss was also reported in some clinical studies. A 12-week study in 51 patients with type 2 diabetes and chronic constipation compared the effects of psyllium (10 g d<sup>-1</sup>, divided doses before meals) on weight.<sup>22</sup> The authors reported that psyllium significantly reduced body weight by 2.0 kg *versus* placebo. Two recent meta-analyses reviewed the effects of psyllium consumption on weight loss (Table 1). Xiao *et al.*<sup>131</sup> analyzed 8 studies containing nine arms with 395 participants and found a relationship between the consumption of psyllium and weight, body mass index, lipid profile, and glucose metabolism in diabetic patients. The results showed no significant change in HDL, body mass index, cholesterol, and weight. Another meta-analysis included 23 randomized clinical trials and concluded that psyllium did not reduce body weight, BMI, and WC significantly.<sup>132</sup> Due to the fact that the dosages, forms, and intervention periods of psyllium, as well as the physiological statuses of the participants, were varied among those studies, this cannot negate the beneficial effects of psyllium in obesity or overweight patients.

In addition, it has been reported that CVD is the collateral damage of obesity-driven adipose tissue dysfunction that promotes a chronic inflammatory state within the organism. This chronic inflammatory state could trigger or even worsen CVD by upregulating pro-inflammatory adipokines and downregulating anti-inflammatory adipokines.<sup>133</sup> A recent piece of clinical evidence has demonstrated that psyllium is effective in reducing IL-6 in obese adolescents.<sup>17</sup> Despite this, there was a study that demonstrated that psyllium supplements had no ameliorating effect on CRP levels or other inflammatory markers in overweight or obese individuals.<sup>134</sup> It was the length of the study that may affect the psyllium supplementation intervention. Moreover, the activation of nuclear factor-kappa B (NF- $\kappa$ B) plays a central role in inflammation, which positively regulates the gene transcription of many pro-inflammatory cytokines, inflammatory cytokines, and adhesion molecules such as interleukin-6 (IL-6), TNF- $\alpha$ , monocyte chemoattractant protein-1 (MCP-1), ICAM-1, VCAM-1, inducible nitric oxide synthase (iNOS), and matrix metalloproteinase-9 (MMP-9). What is more, the intake of psyllium husk supplements not only decreased the TNF- $\alpha$  concentration but also prevented endothelial dysfunction in obese rats.<sup>111</sup> In advanced glycation end products-induced human umbilical vein endothelial cells, plantamajoside has been shown to suppress inflammatory cytokines and adhesion molecule expression, due to inhibition of the MAPK/NF- $\kappa$ B pathways.<sup>112</sup> Another *in vitro* study on RAW 264.7 mouse macrophage cells showed that the extracts of psyllium suppressed the expression of inflammatory cytokines, such as IL-1 $\beta$ , IL-6, and cyclooxygenase-2 (COX-2).<sup>135</sup>



In a word, psyllium can suppress appetite and energy intake, and reduce body weight. Furthermore, psyllium can also upregulate pro-inflammatory adipokines and downregulate anti-inflammatory adipokines to improve the obesity-driven chronic inflammatory state of CVDs.

## Conclusions

Due to its high medicinal and economic values, psyllium, especially its husk, has attracted significant attention from researchers. Psyllium husks encompass rich dietary fiber that is highly viscous, highly soluble in water, and higher in gel-forming capacity with a long history of multiple health beneficial effects, preventing or withstanding a series of common diseases, including hyperlipemia, diabetes, obesity, CVD, constipation, irritable bowel syndrome symptoms, diarrhea, and cancer, some of which are closely related to the development of CMDs.

Observational and experimental studies have indicated that most of the health-beneficial effects and applications of psyllium are mainly due to its viscosity (Fig. 4): psyllium forms a viscous gel in the water, which binds to bile acids in the gut and eliminates bile acids *via* the stools, and promotes the conversion of cholesterol to bile acids, thus leading to a reduction of blood cholesterol concentrations; the gel increases chyme viscosity, which can lead to a decrease in the interactions between the digestive enzymes and nutrients within the gastrointestinal system, slowing down the degradation and absorption of glucose and other nutrients, thereby helping to manage blood sugar; the delay in nutrient digestion and absorption prolongs satiety/delays hunger, leading to

decreased energy intake and weight loss in overweight/obese patients. Notably, the high water-holding capacity and gel-forming nature of psyllium fiber are viscosity-dependent phenomena. Moreover, previous studies have revealed that psyllium and its extracts can directly or indirectly exert a hypotensive effect, and improve the cardiac hypertrophy caused by long-term hypertension. In addition, hyperuricemia has become the fourth major risk factor after hypertension, hyperlipidemia, and hyperglycemia, and is often associated with all three, causing damage to the cardiovascular system. Our previous study showed that psyllium and its extracts are a potential therapeutic agent for the treatment of hyperuricemia. Questions remain to be answered and fully explored about the uric acid-lowering effects of psyllium and its mechanisms. Such answers may pave the way to developing more effective pharmaceutical strategies using psyllium for the treatment of patients with CMDs.

The growing awareness of a healthy diet has led to an increasing demand for functional food; some researchers have added psyllium husk into food products, which has been proved to exert positive effects on health. Further research should focus on minimizing the undesired effects of the great incorporation of psyllium in food to improve its quality and consumer acceptability.

Collectively, the activities against CMDs and clinical implications of psyllium have been extensively studied (Fig. 5). Based on the pleiotropic health benefits and fewer adverse effects, other high-quality trials with long-term follow-up are required to provide more compelling evidence of its safety and efficacy. In addition, with the growing awareness of a healthy diet, psyllium has been added to food products, and further research should focus on minimizing the undesired effects of

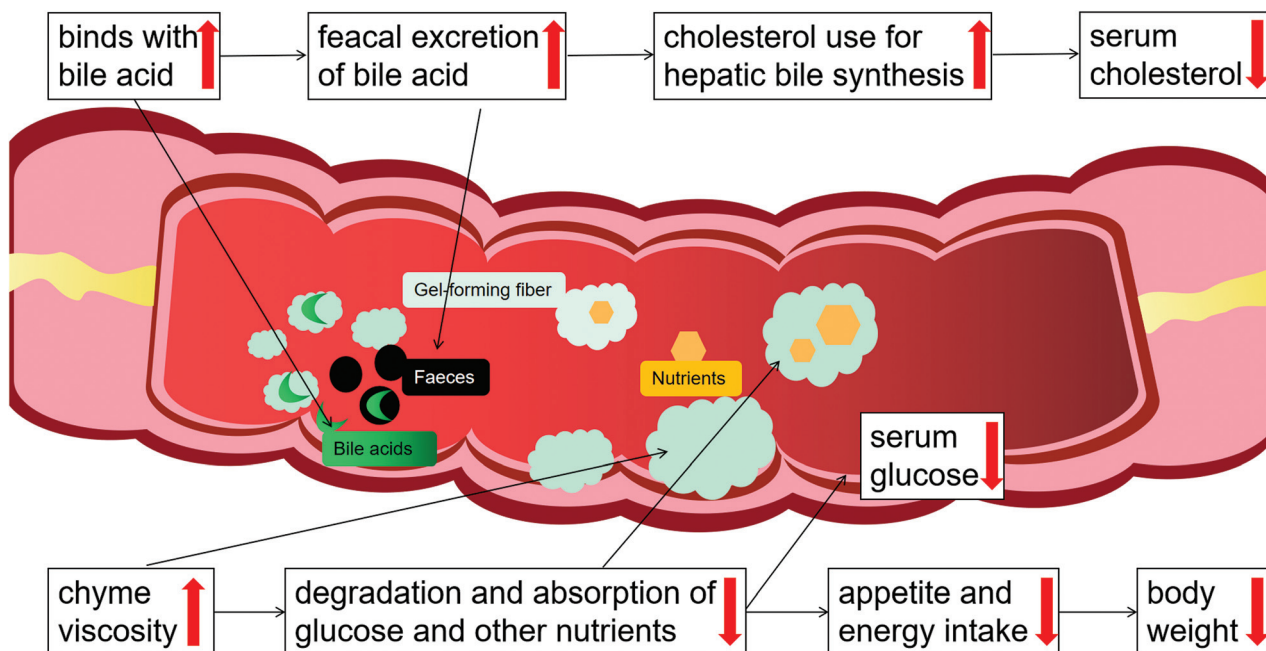


Fig. 4 The health benefits derived from the physical effects of psyllium gel in the intestine.



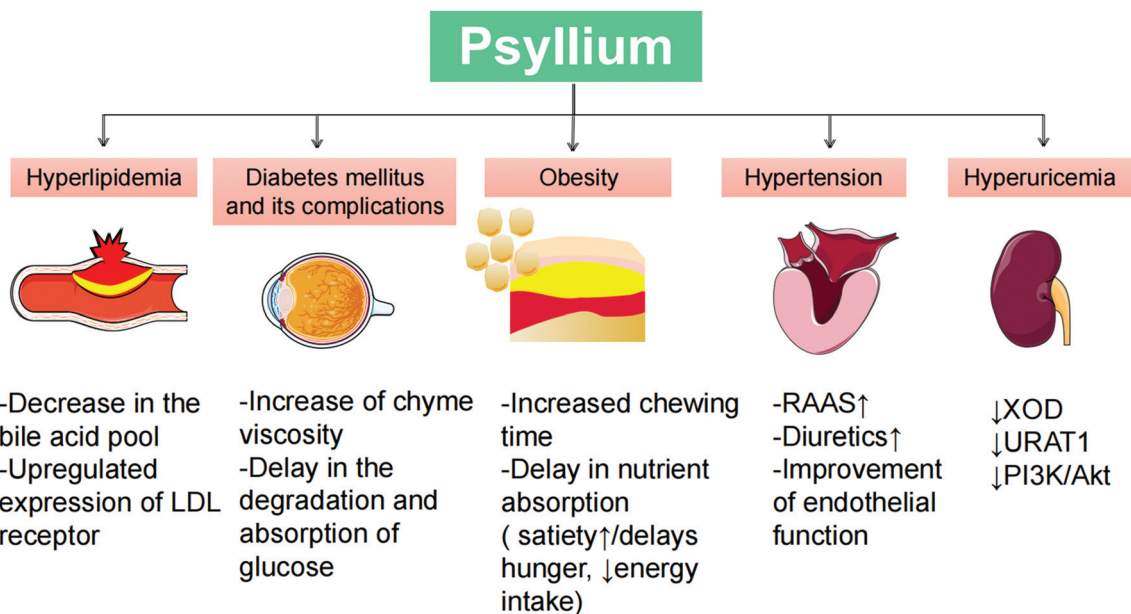


Fig. 5 An overview of the major beneficial effects of psyllium on CMDs and their underlying mechanisms.

a great incorporation of psyllium in food to improve its quality and consumer acceptability.

## Author contributions

CC and CS wrote the main text. LY-X, MX, YL-W, ZH-S, LK-J and FD participated in the conception of the review. XN-C revised the manuscript.

## Conflicts of interest

The authors declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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