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Review

Soluble Dietary Fibers as Antihyperlipidemic Agents: A Comprehensive Review to Maximize Their Health Benefits

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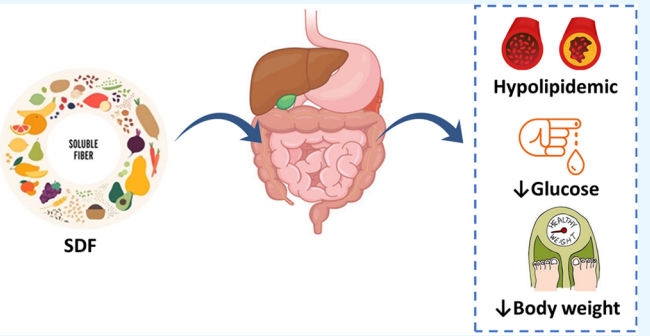
ABSTRACT: The number of hypercholesterolemic people is increasing rapidly worldwide, with elevated lipid profiles representing a major risk factor of coronary heart diseases. Dietary intervention was shown to improve the lipid profile, thus enhancing the quality of life. Dietary fiber is a nondigestible form of carbohydrates, due to the lack of the digestive enzyme in humans required to digest fiber, and is classified according to its water solubility properties as either soluble (SDF) or insoluble dietary fiber (IDF). Consumption of SDF is associated with several health benefits such as reduced lipid levels, lower blood pressure, improved blood glucose control, improved immune function, and reduced inflammation. SDF has been shown to lower blood cholesterol by several action mechanisms including directly due to the gelling, mucilaginous, and viscous fiber nature, and indirectly due to its fermented products and modulation of the gut microbiome. This review aims to provide a holistic overview on how SDF impacts the lipid profile. We start by providing an overview of the chemical structure of the major SDFs including mucilage, gums (gum arabic and guar gum), pectin, and inulin.



INTRODUCTION

Dietary fiber (DF) is described in different ways all over the world. Several definitions are based on analytical approaches for separating fiber, whereas others define fiber according to a physiological basis. Conventionally, DF is defined as plant polysaccharides which cannot be digested by intestinal enzymes, but are adequately fermented entirely or partly by the intestinal microbiome.[1] High fiber foods intake can improve the metabolic profile, decrease blood pressure, assist in weight management, and increase insulin sensitivity.[2] The recommended daily allowances (RDAs) of fiber for men and women aged 19−50 years is 38 g/day for men and 25 g/day for women.[3] RDA recommendations are for healthy people and not for individuals with chronic diseases. High fiber foods are presented in Figure 1.

DF can be categorized according to the composition and solubility. Regarding structure, polysaccharides are classified into linear or branched molecules. On the basis of solubility, DF is classified into soluble fiber, which is made up of noncellulosic polysaccharides (e.g., pectin, gums, mucilage), or insoluble dietary fiber (IDF), which forms cell wall components (e.g., cellulose, lignin, hemicellulose).[4] The solubility of fibers also can be totally changed depending on the temperature and pH value.[5] For example, the chemical modification of insoluble fibers such as cellulose could produce a gelatinous methyl cellulose that is entirely fermented in water rapidly with the viscous structure vanishing.[6] Moreover, the solubility of pectin is enhanced with the increase of the quantity of its terminal chains.[7] The categorization of DF according to solubility is presented in Figure 2.

Hyperlipidemia is defined as an increased level of total cholesterol with or without increased triglycerides. This could be attributed to genetic and/or environmental factors or as a comorbidity of another disease such as obesity, hypothyroidism, and diabetes.[8] Cholesterol is an insoluble molecule transported in the blood via lipoproteins. There are two types of lipoproteins: high density lipoprotein (HDL), which absorbs cholesterol and transports it back to the liver where it is cleared out from the body, and low density lipoprotein (LDL), which is known as the bad cholesterol since it accumulates on the walls of blood vessels, forming plaques that result in narrowing or occlusion of blood vessels and eventually causing cardiovascular disease (CVD) and stroke.[9] According to the World Health

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Figure 1. Quantity of fibers in different dietary sources per 100 g.

Organization (WHO), hypercholesterolemia accounts for 4.5% of total deaths or 2% of total disability-adjusted life years (DALYs).[10]

Despite the presence of lipid-lowering medications, such as statins,[11] some studies showed beneficial effects from the intake of SDFs on the lipid profile. Recent studies state that a 10 g/day increase in intake of SDFs can lower the risk of coronary heart disease by 14% and the risk of coronary death by 27% with lower side effects compared to the use of statins, famous antihyperlipidemic drugs.[12]

Significantly, SDF supplies the gut microbiota with carbon and energy; besides, SDF improves the intestinal environment by augmenting the beneficial bacteria.[13] Moreover, SDF increases mucus production by the intestinal epithelium that retains bacteria insulated from the intestinal lining epithelium.[14] Insufficient consumption of SDFs will diminish the quantity of probiotics and affect the metabolism of the intestinal bacteria to consume amino acids which increases the possibility of intestinal injury by the accumulation of toxic metabolites, involving amines, ammonia, fatty acids, and phenolic compounds.[15] Hence, a dietary pattern with low fiber and high fat, protein, and sugar may induce chronic diseases such as obesity and cardiovascular disease.[16] Therefore, sufficient consumption of SDF is recommended to prevent the degradation of intestinal mucosa by intestinal microbiota and the incidence of these diseases.[17]

Besides increasing mucus production, SDF has other valuable physiological functions. SDF was found to decrease total cholesterol, LDL cholesterol, and serum triglyceride levels.[18,19] The aim of this review is to summarize the clinical trials and *in vivo* research data interrelating the hypolipidemic properties of soluble dietary fibers involving mucilage, gum, pectin, and inulin.

Although SDF is beneficial for human health, the inappropriate consumption of SDF can result in several health hazards and limit its use.[20] Consumption of large amounts of SDF suddenly may lead to several gastrointestinal tract (GIT) complaints including abdominal bloating, flatulence, constipation, and diarrhea.[21] Recently, a study done by Singh et al. revealed that fortification of the diet with SDF such as refined inulin resulted in intestinal dysbiosis in mice.[22] Moreover, the

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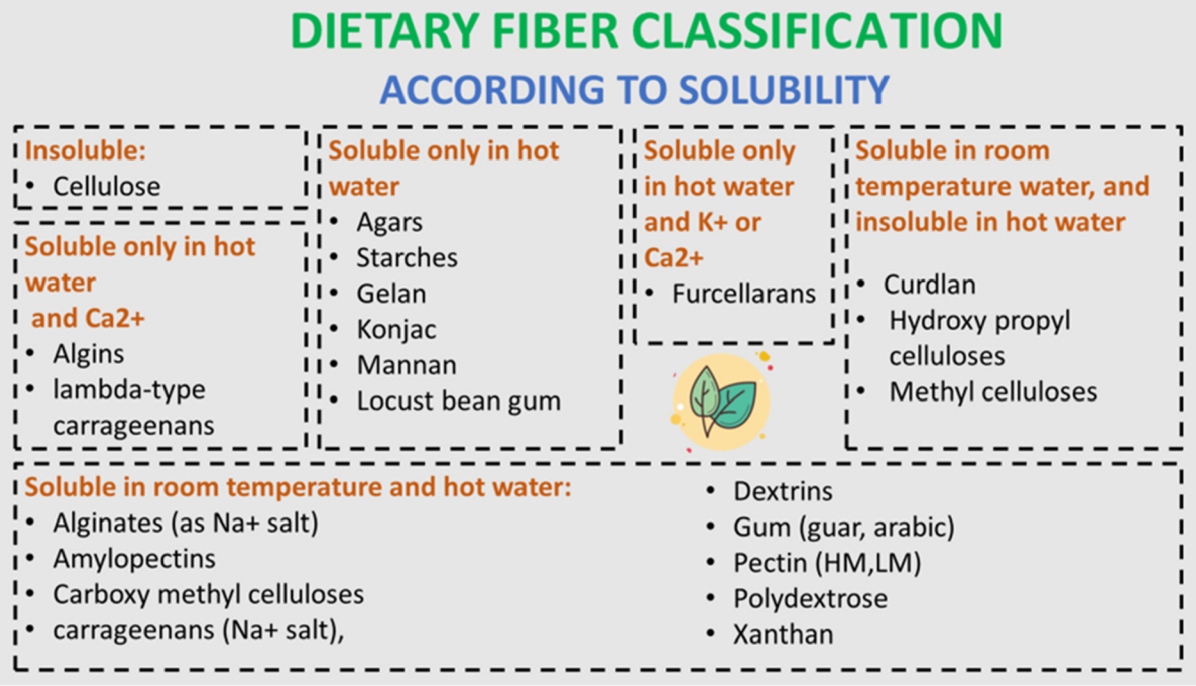

Figure 2. Classification of dietary fibers according to their solubility.

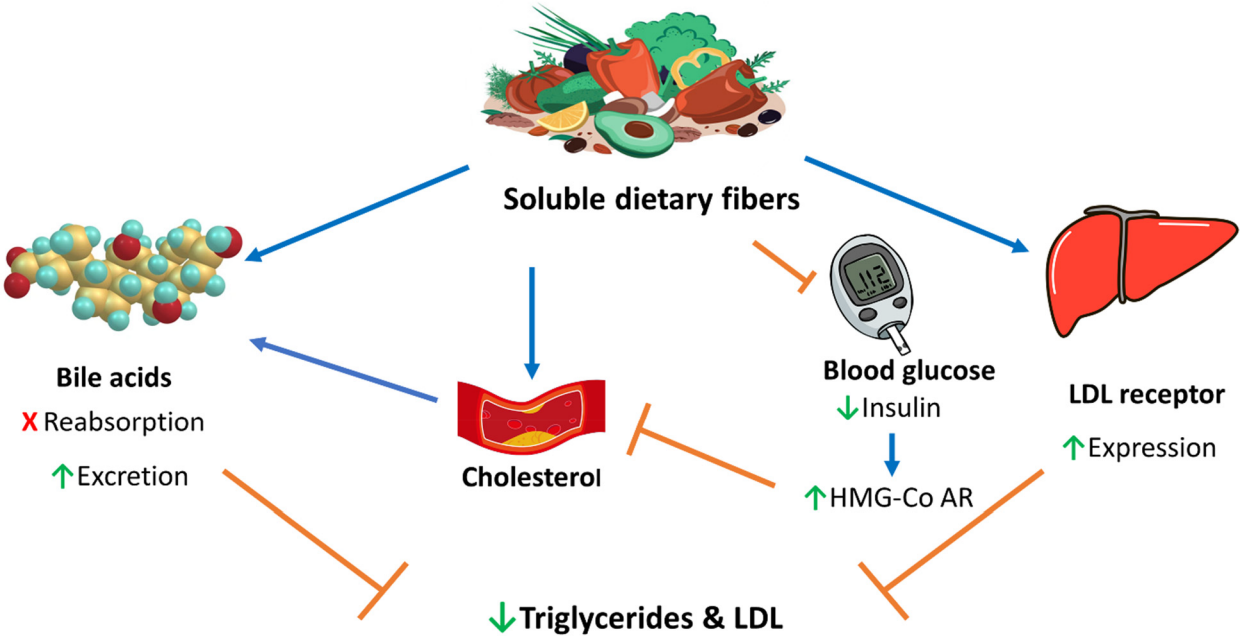

Figure 3. Main lipid lowering action mechanisms of soluble dietary fiber. Brown lines point to blocking actions, and blue arrows point to stimulating actions.

binding affinity of certain SDFs, such as pectin and guar gum, can reduce the bioavailability of certain bioactive compounds such as β-carotene, lycopene, and lutein as well as micronutrients.[20] Hence, despite their physiological actions, a diet fortified with SDFs should be consumed with caution to avoid possible GIT disorders and disruption in gut microbiota.

CHOLESTEROL-LOWERING MECHANISMS OF SDF

The water holding capacity of SDF increases the bulk weight and dilutes the nutrients inside the intestine due to the presence of water inside involving carbohydrates and lipids and their movement via the intestinal wall.[19] These bulking and viscosity features of SDF prolong satiety and decrease food consumption, which was considered as one of the important mechanisms of lipid lowering.[23] Another underlying principle behind the reduction of lipid by SDF is attributed to the ability of fibers to bind to bile acids/salts and prevent their reabsorption into the enterohepatic circulation as well as enhance their excretion into feces. Hence, formation of new bile salts from cholesterol occurs, so dropping blood cholesterol levels and having a lipid-lowering effect.[24]

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Table 1. Clinical Trials and *In Vivo* Studies on the Hypocholesterolemic Effect of Mucilage (MC)[a]

study	subject	dose of MC	results	ref
clinical trial	randomized, double blind, crossover study applied on 15 diabetic patients	pudding containing yellow mustard MC (15.5 g, 3.10 wt %), flaxseed MC (11.4 g, 2.28 wt %), fenugreek gum (5.9 g, 1.18 wt %) three times daily for 2 weeks	↓ BG, insulin, and ↑ intestinal viscosity significantly	48
	double blind, randomized, and placebo controlled study applied on 72 obesity patients	flaxseed MC (2560 mg and 1280 mg twice daily for 12 weeks)	↓ BW ($p < 0.001$), TC ($p = 0.038$), TG ($p = 0.040$), compared to placebo group	49
in vivo	hypercholesterolemic rabbits	fenugreek seeds MC (40 mg/kg for 3 months)	↓ TC, TG, and LDL ($p < 0.05$)	50
	hypercholesterolemic rats	diet containing 10% *Lepidium sativum* MC for 3 weeks	↓ TC, TG, LDL, and VLDL	51
	hyperlipidemic rats	*Cordia dichotoma* MC (0.50 and 1.00 g/kg) for 4 weeks	↓ TC and LDL	52
	diabetic rats	*Aloe vera* MC (1.2 g daily for 6 weeks)	↑ genes involved in lipid metabolism	53
	hyperlipidemic rats	flaxseed or cress seed mucilage (40 mg/kg for 4 weeks)	↓ TC, TG, LDL, and MDA	54
	diabetic rats	*Aloe vera* MC (1 mL daily for 3 weeks)	↓ TC, TG, and BG	34
	rats	HFD plus Nopal MC 500 mg/kg daily for 30 days	↓TC, TG, BG, and abdominal circumference	55
	hyperlipidemic rabbits	*Trigonella foenum-graecum* MC (75 mg/kg for 90 days)	↓TC, TG, LDL, and ↑HDL	56
	diabetic mice	okra MC (150 mg/kg for 21 days)	↓TC, TG, LDL, and BG	57

[a]BW, body weight; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; V-LDL, very low density lipoprotein; BG, blood glucose; HFD, high fructose diet. MDA, malondialdehyde.

Furthermore, hepatic LDL receptors become upregulated to restore hepatic cholesterol stores, which will lead to decreased serum LDL concentrations.[25] Many studies indicate that SDF adsorbs and sequesters cholesterol; it increases the rate of bile acid excretion, leading to a reduction in triglycerides and LDL levels.[26] A third mechanism involves reduction of the postprandial blood glucose which reduces insulin production. This is then reflected by a reduction of cholesterol biosynthesis, since insulin activates 3-hydroxy 3-methylglutaryl coenzyme A reductase (HMG-Co AR), a rate-limiting enzyme in the cholesterol biosynthesis pathway. Finally, through fermentation of SDF by the intestinal microbial flora into short-chain fatty acids (SCFAs), such as acetate, propionate, or butyrate, it may play a role in the inhibition of hepatic cholesterol synthesis.[27] Butyrate is metabolized by colonic mucosal cells, while acetate and propionate are rapidly absorbed. The production of SCFAs and in particular changes in the propionate:acetate ratio may influence lipid metabolism, decreasing hepatic absorption and increasing excretion through bile and fecal lipids.[28] Another hypothesis for the hypocholesterolemic effects of SDF is based on a lower overall energy intake. Since fiber-rich foods contain fewer calories and take a longer time to digest, SDF promotes increases of satiety.[12] During adipogenesis, the MAPK signaling pathway controls the expression of both CCAAT-enhancer binding proteins α (C/EBPα) and peroxisome proliferator-activated receptors γ (PPARγ) mRNA. Guar gum (10% for 12 weeks) was found to regulate the metabolic changes caused by PPARγ suppression in mice fed a high fat diet. Afterward the expression of mitochondrial uncoupling protein 2 (UCP2) was upregulated, inducing the triggering of the AMPK pathway.[29] The underlying hypolipidemic mechanism of SDF discussed in the text is illustrated in (Figure 3).

SOLUBLE DIETARY FIBERS

Mucilage. There were few reports on plant-derived mucilage before 1991; after that, curiosity in plant mucilage emerged.[30] The progress of analytical instruments and better awareness of the chemical composition of mucilage has launched the way for novel applications of this biocompatible and nontoxic compound.

Mucilage (MC) is typically present as a jelly-like substance in different parts of plants including root, stem, or leaf besides being present in seeds following treatment with water. Characterization of MC varied according to their source as well as extraction method affect the ratio of individual constituents. The main sources of soluble mucilaginous dietary fiber are psyllium seed husk (outer coat),[31] *Zizyphus mauritiana* fruits,[32] flaxseeds,[33] chia seeds,[33] and *Aloe vera* leaf.[34]

From a chemical perspective, MC is formed of uronic acids, glycoproteins, and highly branched polysaccharides as D-xylose, L-arabinose, D-galactose, L-rhamnose, D-mannose, D-glucose, or L-fucose linked by glycosidic bonds.[35] The distribution and molecular weights of polysaccharides determine the features of mucilage. High-molecular-weight polysaccharides promote the ability of MC to be used as a thickening and gel-forming agent.[36]

On top of polysaccharides, the main constituents of mucilage are several proteins, lipids, minerals, and water. Moreover, small constituents are detected in mucilage such as tannins, flavonoids, sterols, and alkaloids. The protein concentration in mucilage influences its water-holding capacity.[30] Greater protein concentrations in mucilage are recognized to enrich the quality of products having mucilage.[37]

Several studies revealed the capability of using mucilage in the pharmaceutical industry and in drug-delivery systems due to its binding features.[38] Moreover, the thickening and binding capacities of mucilage also make it useful in the food industry.[39] Since mucilage is principally an abundant source of dietary fiber, it exerts multiple therapeutic effects including a laxative effect, satiety regulation, and reduction of hyperlipidemia, hyperglycemia, and obesity.[40] Mucilage was found to be poorly fermented inside the small intestine and has the ability to absorb water into the gut leading to the formation of gel.[41] This feature provides a desired laxative effect, supplies a poorly fermented substance for microbial multiplication, and produces as a result a greater bacterial bulk and increases the content of colon.[42] Conversely, mucilage has the capacity to hinder gastric and colon emptying time; this is helpful for the treatment of diarrhea,[43] irritable bowel disease, ulcerative colitis, and hemorrhoids.[44]

As mentioned above, the mechanism of the hypocholesteremic action of gel-forming fiber is attributed to accordingly hindering intestinal motility and the gastric emptying rate.[45] Moreover, mucilage could hinder the absorption of carbohydrates inside the small intestine and thus inhibit the cholesterol

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Table 2. List of Gum Arabic (GA) Effects as a Hypolipidemic Agent in Human and Animal Models[a]

study	subject	dose of GA	results	ref
clinical trial	controlled study applied on 55 hyperlipidemic patients	30 mg of GA plus atorvastatin (20 mg) daily for 4 weeks	↓ TC (7.8%), TG (2.9%), and LDL (8.1%) compared to atorvastatin treated group	65
	controlled study applied on 40 diabetic patients	10 g/day for 16 weeks	↓ TC, TG, BG, and HbAc1 significantly	66
	randomized, placebo controlled, double blind trial applied on 100 diabetic patients	30 g/day for 3 months	↓ TC (8.28%), LDL (5.95%), TG (10.95%), and BG; ↑ HDL (19.89%)	67
	randomized, placebo controlled trial applied on 45 diabetic patients	30 g/day for 3 months	↓ body adiposity index (3.9%) and visceral adiposity index (23.7%)	68
	phase II, single-arm trial applied on 47 sickle cell anemia patients	30 g/day for 12 weeks	↓ TC, TG, and LDL significantly	69
	controlled, randomized, single blind, parallel-design study trial applied on 31 participants	20 g/day for 12 weeks	↓ ($p = 0.008$) and diastolic blood pressure (0.009), fat free mass ($p = 0.03$), mass, carbohydrate ($p = 0.008$), and calorie ($p = 0.014$) intake, and fasting plasma glucose ($p = 0.046$)	70
in vivo	male albino rats	diet supplemented with 30% GA for 30 days	↓ TC and LDL	71
	male donkeys	25 g/day for seven successive days	↓ TC, TG, urea, and creatinine	72
	female CD-1 mice	GA (10%) in drinking water for 6 weeks	↓ TC, HDL, and LDL but not TG	63
	diabetic rats	GA (10%) in drinking water for 10 weeks	↓ TC, LDL, TG and ↑ HDL	73
	diabetic rats	GA in drinking water (10% w/v) for 12 weeks	↓TG, TC, TG, LDL, urea, and creatinine	74
	metabolic syndrome (MS) rat model	diet containing GA (5%) mixed with Kishk Sa'eedi (KS, 10%) or pomegranate seed oil (1%)	↓ plasma dyslipidemia, BG, AST, creatinine, and urea; ↑ HDL	75
	mice	high fat diet containing 10% w/w GA for 15 weeks	↓ TC, LDL, BG, and ↑ HDL	76

[a]HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; V-LDL, very low density lipoprotein; BG, blood glucose.

biosynthesis pathway as well as stimulate the secretion of insulin.[46] MC was found to alter the gut microbiota in individuals with obesity. Administration of flaxseed mucilage daily for 6 weeks for obese patients reduced the quantity of *Faecalibacterium prausnitzii* species in intestine. Unexpectedly, decreasing the concentration of *F. prausnitzii* improves insulin sensitivity through producing SCFA butyrate in a large amount which has an anti-inflammatory effect and recovers the metabolic disorder related to obesity such as insulin resistance.[47]

Overall, several studies focused on mucilage over 20 years. Despite this, large numbers of studies presented only basic information regarding the chemical composition and properties of mucilage. Besides, few studies have relatively evaluated mucilage as a hypolipidemic agent in both human and animal models. The hypocholesterolemic effects of mucilage in animal models and in humans are listed in Table 1.

Gums. Major gums used as sources of drugs include gum arabic and guar gum. Gum arabic (GA), African gum belt, is a natural edible gum from various species of the acacia seyal trees. GA is formed of polysaccharide sugars and glycoprotein, attached to carbohydrate (D-galactose and L-arabinose) with a covalent bond. GA includes amino acids and trace elements such as aluminum, phosphorus, magnesium, copper, zinc, and iron.[58] GA exhibits antioxidant,[59] renoprotective, and blood glucose reducing properties.[60] GA is not degraded in the small intestine; thus it is digested with difficulty by animals and humans. It is fermented inside the colon, yielding short-chain fatty acids, mainly propionate, by the enzymatic action of intestinal bacteria.[61]

Several studies have reported on the lipid-lowering effects of GA in both animal and human models (Table 2). GA reduces lipid levels mostly through the downregulation of gene levels included in lipid metabolism such as11β-hydroxysteroid dehydrogenase type I, HMG-CoA reductase, and adipose triglyceride lipase.[62] Likewise, GA was found to downregulate peroxisome proliferator-activated receptor γ and stearoyl-CoA desaturase mRNA expression in mice liver as well as steroid 17-α-monooxygenase (CYP17) in mice muscle.[63] Further, GA hinders intestinal lipid absorption by increasing the viscosity of intestinal content.[64]

The second example of gum is guar gum (GG). Guar gum, *Cyamopsis tetragonoloba* or cluster bean, is a viscous soluble fermentable fiber. Guar seeds were found to be formed of endosperm (42%) in which the main portion is gum.[77] Roughly 80−85% of the gum is made up of a galactomannan polymer that develops a gel in water causing a thickening which makes it suitable for food processing.[78]

Moreover, GG has shown several beneficial therapeutic effects against diabetes, colon cancer, heart, and liver disease.[79,80] Further, partially hydrolyzed guar gum (PHGG) was found to improve abdominal pain and bowel habits when consumed by irritable bowel syndrome patients at a dose of 5 g/day for 4 weeks.[81] A meta-analysis of 34 trials indicated GG showed a nonsignificant difference in the body weight of patients compared to patients receiving placebo with the incidence of side effects such as diarrhea and cramps. Hence, GG cannot be recommended as a medicine for body weight reduction.[82]

Like gum arabic, GG exhibits its hypolipidemic effect by increasing the viscosity of the intestinal content besides altering levels of beneficial bacteria (e.g., bifidobacteria) and pathological microbiota (e.g., *Clostridium* species) resulting in limiting lipid absorption.[83] Guar-containing bread readily incorporated into the diet with minimal alteration in the normal eating pattern and palatability is likely to increase compliance and be of considerable therapeutic use in the future owing to its added value in the management of hyperlipidemia.[84] The use of large doses of high-molecular-weight guar galactomannan gum (~2.4 × 10^6) can, however, lead to problems of palatability upon

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Table 3. Guar Gum (GG) as a Hypolipidemic Agent in Human and Animal Models[a]

study	subject	dose of GG	results	ref
clinical trial	randomized trial applied on 141 hypertensive, overweight patients	3.5 g twice daily before meal for 6 months	↓ HbA1c, LDL, and ApoB without altering TG	86
	controlled study applied on hyperlipidemic patients	guar gum bread for 4 weeks	↓ TC (10%)	84
	randomized trial applied on 9 diabetic patients	7 g three times daily for 3 months	↓ TC and LDL	87
	controlled study applied on 60 diabetic patients	10−20 g daily for 15−30 days	↓ TC, TG, LDL, VLDL, and blood glucose; ↑ HDL	88, 89
	randomized trial applied on 17 diabetic patients	21 g/day for 3 weeks	↓ TC (14%)	90
	controlled trail applied on 20 nonalcoholic steatohepatitis (NASH) with obesity and osteoarthritis patients	GG (5 g) plus metadoxine (0.5 g) twice daily for 90 days	↓ obesity, absorption of carbohydrates, and fermentation products in the intestine	91
in vivo	guinea pigs (male, female, and ovariectomized)	diet mixed with GG (2.5 g/100) for 4 weeks	↓ TC (64%), LDL (44%) cholesterol, and TG (22%)[b]	92
	hyperlipidemic male rats	diet supplemented with 10% GG for 3 weeks	↓ TC, TG, glucose, insulin, glucagon, and corticosterone levels	93
	pigs	diet supplemented with 3.5% GG for 4 weeks	↓ TC, LDL, and TG	94
	hyperlipidemic male rats	flour mixed with GG (3 g/100 g) for 8 weeks	↓ TC (17.2%), LDL (29.7%), and TG (28.4%)	95
	hyperlipidemic rats	diet containing 5% (w/w) GG for 28 days	↓ TC	96
	hyperlipidemic rats	diet containing 5, 10, and 20% (w/w) GG for 28 days	↓ TC, TG, and LDL	97
	diabetic rats	diet containing 5, 10, and 20% (w/w) GG for 28 days	↓ TC, TG, LDL, and blood glucose	79
	hyperlipidemic guinea pigs	high fat diet mixed with partially hydrolyzed GG (12 g/100 g of diet) for 4 weeks	↓ TC; ↑ excretion of fatty acids and neutral sterols[c]	98

[a]HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; V-LDL, very low density lipoprotein. [b]Ovariectomized guinea pigs had higher TC and TG compared to males and females. [c]Excretion of fatty acids and neutral sterols did not alter the fecal fatty acid profile.

inclusion of the polymer into foods. Sensory studies have shown that improvements in the quality of guar wheat bread can be achieved by using low-molecular-weight guar galactomannan ($(0.5-1.0) \times 10^6$), warranting production of different varieties of bread and other foods containing guar gum to provide a wide selection of products and improve long-term compliance for consumers.[85] The hypolipidemic effects of GG in human and animal models are listed in Table 3.

Pectin. Pectin (PC) is the main structure of cell walls of several plants including in citrus peel, apple, and carrot.[99] Pectin is extensively used in the food industry as a thickener and gelling agent.[100] Moreover, pectin is considered a good source of SDF and has a several biological benefits for human health.[100] Pectin is rich in galacturonic acid, where homogalacturonan (HG), formed by the α-1,4 linkage of D-galacturonic acids, represents the smooth region of the pectin backbone and is about 65% of pectin polysaccharides, and the hairy regions are comprised of rhamnogalacturonans I and II (RG-I and RG-II). The degree of methyl esterification (DE), whether it is high (DE > 50%) or low (DE < 50%), defines the solubility and gelling properties of pectin.[101]

Pectin was found to be indigestible by intestinal enzymes; conversely, it could be simply degraded by intestinal bacteria, resulting in the production of SCFAs.[102] Besides, pectin enhances the intestinal integrity and supports the connection of intestinal epithelial cells with probiotic *Lactobacillus* strains to epithelial cells.[103] Moreover, several studies have shown that PC stimulates the growth of bacterial populations such as lactobacilli, bifidobacteria, and *F. prausnitzii*.[104] Pectin was found to be degraded by several bacteria species such as *Bacteroides* and *Prevotella* that secrete carbohydrate-active enzymes including lyases, methylesterases, and acetylesterases.[105]

Several *in vitro* and *in vivo* studies have been carried out to examine the lipid-lowering effects of pectin. A study by Brouns et al.[106] explored the cholesterol-lowering effect of pectin from different sources, with different physicochemical properties. Pectin, extracted from citrus, apple, and orange pulp fiber, processed to achieve different DEs and molecular weights (MWs), were used in a crossover clinical study on individuals with mild hypercholesterolemia. Results showed that the pectin source, along with the DE and MW, accounted for the LDL-C lowering capacity, where high DE and MW pectin showed a better LDL-C lowering effect than low DE pectin. Whether such structural features are also linked to other effects like lowering the blood glucose level should be examined.

To assess the potential of pectin to serve as a prebiotic that confers health benefits, *in vitro* fermentation studies were done using human fecal samples to determine alterations of the microbiota profile and the produced SCFAs. Baobab fruit pulp powder (BP) was examined by Foltz et al.,[163] owing to its high composition of HG pectin polysaccharide with a low DE. The study was done using a 48 h *in vitro* incubation with human microbiota from three different stool sample donors. Despite the observed interindividual differences, acetate and propionate SCFAs were constantly increased and butyrate was increased to some extent. It is worth noting that propionate is proposed to reduce the serum cholesterol level by inhibiting HMG-Co AR. Also, among the five taxonomic gut microbial groups quantified, *Bacteroidetes* was found enriched in the three samples, compared to the control. Another study by Min et al. investigated the effect of different pectin sources on gut microbiota and SCFA production. The bacterial fermentation of high methoxy pectin (HMP) and two low methoxy pectins extracted from sugar beet (SBP) and soy (SOY) was tested through anaerobic incubation with four human fecal samples. Although results showed

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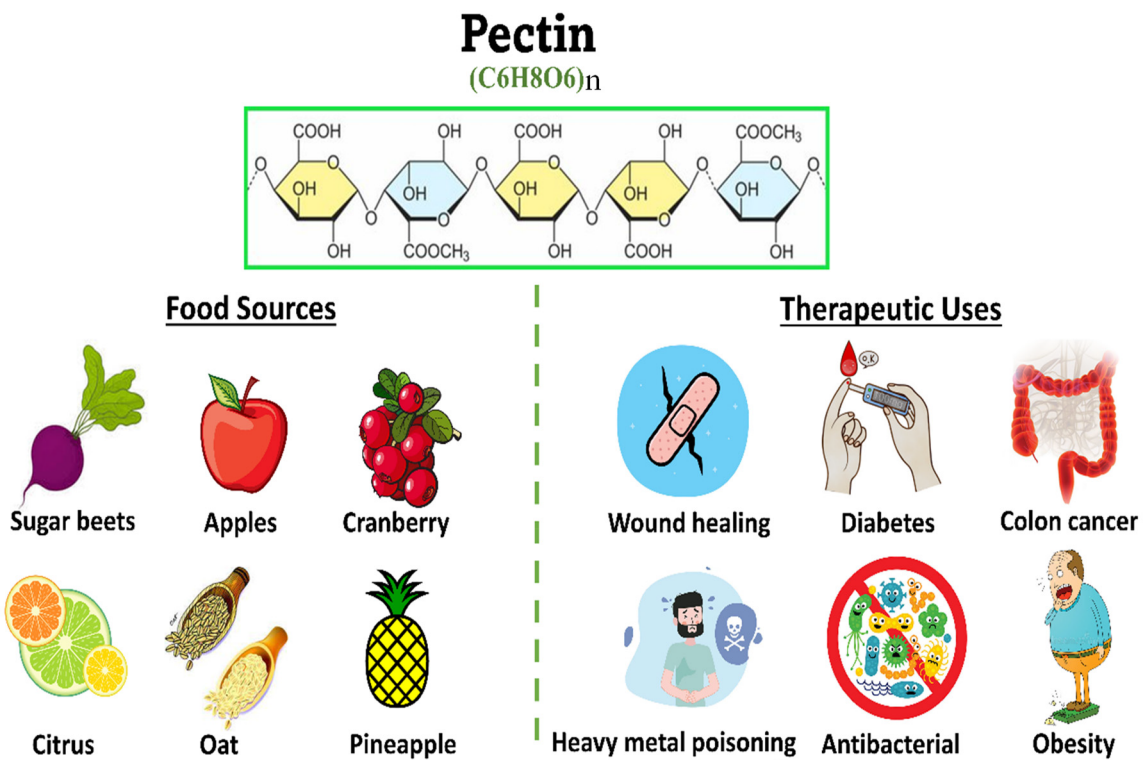

Figure 4. Chemical composition, dietary sources, and therapeutic effects of pectin.

different microbiota profiles, especially that three of the participants were overweight, the composition was altered after the 30 h post fermentation period. SCFA production was higher with citrus and apple pectin compared to SBP and oat. Moreover, propionate and butyrate production were found significantly higher in the case of soy fermentation compared to SBP, likely attributed to differences in structures leading to different fermentation levels acting as a better prebiotic.[107] Moreover, pectin oligosaccharides derived from lemon peel waste (LPOS) and sugar beet pulp (SBPOS) provide better prebiotic potential than their pectin counterparts. Studying the fermentation profile by human fecal microbiota showed the enrichment of bifidobacteria and lactobacilli in all pectin preparations. However, a marked bifidogenic effect was evident by SBPOS fermentation, while LPOS showed a significant increase in lactobacilli count.[104]

Moreover, the hypocholesterolemic effect of pectin was verified in humans and animals. Food sources, the chemical structure, and therapeutic effects of pectin are concluded in Figure 4. The hypocholesterolemic effects of pectin in human and animal models are revealed in Table 4. The clinical trials are considered inadequate and poorly designed. Thus, more trials should be performed on humans in the future to evaluate the therapeutic effects of pectin as a hypolipidemic agent.

Inulin. Inulin is a nondigestible carbohydrate formed of D-fructose units joined by β-(2−1) bonds and an α-(1−2) terminal D-glucose.[129] It is found in a variety of plants such as chicory, artichoke, leek, asparagus, and garlic. The ability of fructans to be selectively fermented by health promoting *Bifidobacterium* bacteria underscores their use as functional food and in nutraceuticals.[130] A recent study has evaluated the effect of gut microbiota in mediating the antihyperlipidemic action of inulin. Briefly, inulin stimulated the production of SCFA-producing bacteria such as Ruminococcaceae and Lachnospiraceae as well as the expression of angiopoietin-like protein 4 that may be enhanced by the greater production of SCFAs. These findings pointed to the mediating effect of bacteria on the effect of inulin.[131]

A study by Van De Wiele et al.[132] compared the prebiotic effects of fructans with a low degree of polymerization (DP), oligofructose (DP 2−20), and with a higher DP, chicory inulin (DP 3−60), under *in vitro* conditions using the Simulator of the Human Intestinal Microbial Ecosystem (SHIME) reactor inoculated with fecal bacteria of a healthy donor. Although inulin required a longer fermentation period, owing to its longer chain length, the prebiotic effectiveness was higher even in the distal region of the colon. Both fructans increased propionate and butyrate production; however, the propionate level was significantly higher with inulin fermentation in all colon vessels.[133] Also, inulin was shown to exert a greater bifidogenic effect along with a significant reduction in the ammonium level than oligofructose; hence it was considered a safer option than oligofructose. Furthermore, increased abundance of *Bifidobacterium* and *Anaerostipes* bacteria together with decreased *Bilophila* bacteria were observed with the intake of 12 g of chicory inulin for a period of 4 weeks by healthy adults with mild constipation.[133] Foods high in inulin and the chemical composition and therapeutic benefits of inulin are demonstrated in Figure 5. Besides, clinical trials and *in vivo* studies over 20 years are revealed in Table 5.

Although inulin has been established to act as a prebiotic, studies regarding the lipid-lowering effect of inulin are somehow controversial. For example, intake of 20 g of chicory inulin per day for 3 weeks was found to significantly reduce serum TG, with a slight reduction in serum TC of 12 males with mild hypercholesterolemia.[110,134] However, no significant effect on the lipid profile was shown in a randomized, double blind, placebo controlled study where healthy individuals consuming

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Table 4. Clinical Trials and *In Vivo* Studies Reported on the Hypolipidemic Effect of Pectin (PC)[a]

study	subject	dose of PC	results	ref
clinical trial	randomized trial applied on 53 healthy humans	diet contains 4.11 g of soluble fiber (PC, gums, and mucilage) and 25.08 g of insoluble fiber for 3 months	↓ LDL (12.8%) and glucose (12.3%)	108
	placebo controlled, randomized, parallel double blind study applied on 66 diabetic patients	sugar beet PC, 12 weeks	fasting plasma glucose concentration did not change; ↑ HbA1c and HDL significantly	109
	crossover studies applied on hypercholesterolemic patients	15 g of apple low MW PC for 4 weeks; 6 g/day citrus and high MW PC for 3 weeks	apple PC reduced LDL by 7−10%, while citrus PC reduced LDL by 6−7%	106
in vivo	male Sprague−Dawley rats	diet containing 15% fat and 6% PC	↓ TC, V-LDL, and LDL; ↑ HDL and CoA reductase activity	110, 111
	hamsters	high cholesterol (0.1% w/w) diets plus 3% lemon PC for 8 weeks	↓ TC	112
	male Wistar rats	diet containing 5 g/100 g apple PC and 10 g/100 g high polyphenol freeze-dried apple for 21 days	↓ TC, TG, and cholesterol absorption (13%)	113
	male rats	high cholesterol diet containing PC (60 g/kg) for 4 weeks	↓ TC (from 2.08 to 1.67 μmol/mL)	114
	female Zucker fatty rats as a model of genetic obesity	diet containing 10% PC for 15 weeks	↓ BW, TC, and TG	115
	laying hens	diet containing 0.5% PC	↓ egg yolk cholesterol	116
	hypercholesterolemic swine	diet containing 30 g of PC daily for 4 weeks	↓ LDL and TG	117
	diabetic rats	0.5−25 mg/kg orally for 5 successive days	↓ TG and blood glucose	118
	hypercholesterolemic rats	diets containing 5% of PC for 6 weeks	↓ TC	119
	hypercholesterolemic New Zealand rabbits	combination of PC, niacin, and apple cider vinegar 3 mL/kg/day for 4 weeks	↓ TC, LDL, and TG; ↑ HDL	120
	hypercholesterolemic rats	diet containing pea proteins (90%) and apple pectin (7.5%)	↑ CYP7A1 and NTCP genes, which were involved in cholesterol turnover	121
	male Wistar rats	High fat diet plus GG with low, medium, or high viscosity degree (1%, w/v) and two different doses of PC (24%, LM or 70%, HM) for 3 weeks	both PC and GG ↓ TC, BG, and liver steatosis but to varying extent depending on degree of methoxylation and viscosity of fibers; only GG with medium and high viscosities ↑ levels of butyric acid in cecum and blood	122
	hypercholesterolemic rats	diet supplemented with PC pectin (5 wt %/wt) for 6 weeks	↓ BW, TC, TG, and development of adipose tissue	123
	diabetic rats	diet containing citrus PC, 4 weeks	↓ TC, LDL, TC, insulin resistance, and BG levels	124
	hypercholesterolemic mice	ϵ-polylysine and PC for 13 weeks	↓ TC and TG	125
	hypercholesterolemic mice	high fat diet containing 4 or 8% of PC for 12 weeks	↓ BW, TC, and LDL in a dose dependent manner	126
	male mice	high cholesterol diet containing 20 wt %/wt PC for 12 weeks	↓ cholesterol absorption	127
	male C57BL/6 mice	high fat diet and 200 mg/kg/day PC orally for 17 weeks	↓ TC, LDL, leptin, and adiponectin	128

[a]HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; V-LDL, very low density lipoprotein; BW, body weight; BG, blood glucose; LM, low methoxylation; HM, high methoxylation.

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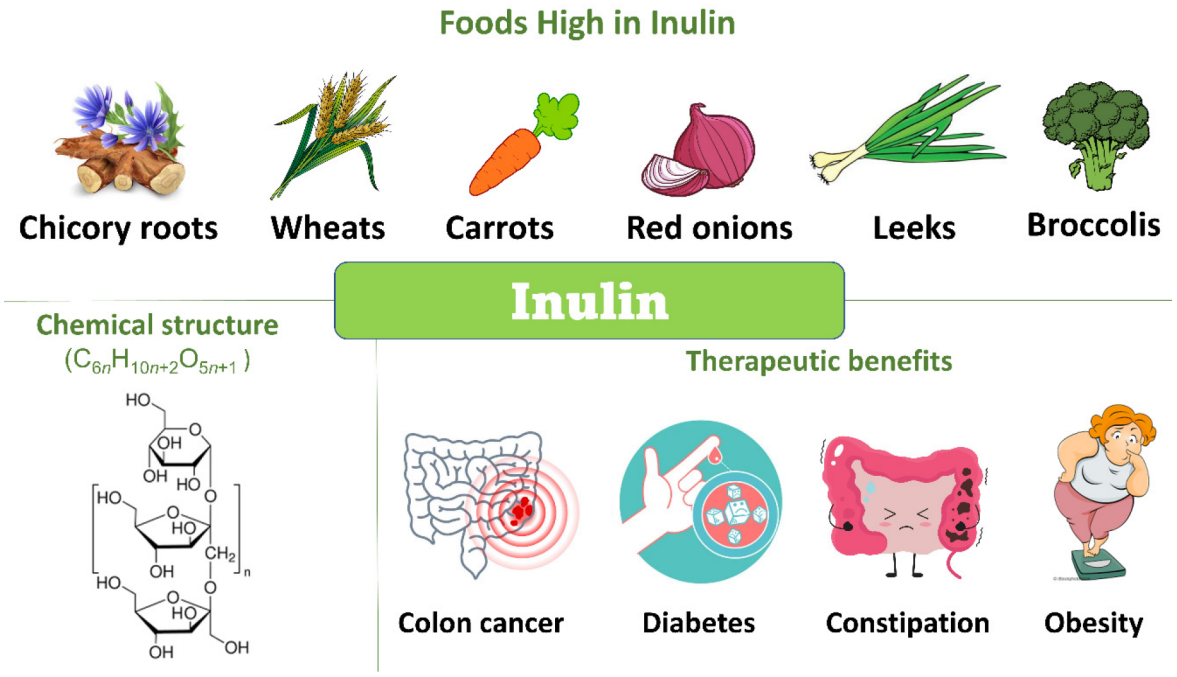

Figure 5. Chemical composition, dietary sources, and therapeutic benefits of inulin.

10 g of fructan preparation (inulin and oligofructose) for a long term (6 months).[135] These results are in line with those demonstrated by Mistry et al., where neither the lipid profile nor cholesterol metabolism changed in mice fed long-chain or short-chain inulin for 2 weeks, despite the significant increase in fecal SCFA level.[136]

SAFETY OF SDF

Although SDF exhibits valuable health benefits, it cannot be disregarded that improper SDF consumption may induce specific health hazards that differ according to the nature and amount of SDF as well as the medical history of the subject.[16] An unexpected increase of SDF ingestion could induce constipation, diarrhea, and other abdominal disorders.[158] Besides, rapid fermentation of SDF (60 g/kg of fructooligosaccharides) by intestinal bacteria revealed a marked injury to intestinal mucosa as well as increased intestinal permeability in rats infected with *Salmonella enterica*.[159] SDF also was found to increase the extent of several elements such as metal ions through its binding capacity. In spite of this, a previous study showed that the bioavailability of β-carotene, lycopene, and lutein were reduced significantly in six healthy young women by different types of SDF including pectin, guar gum, and alginate.[160]

Moreover, intake of a diet rich in purified inulin (7.5%), pectin (2.5%), and fructooligosaccharides (2.5%) for 6 months induced icteric hepatocellular carcinoma (HCC) to mice that were deficient in Toll-like receptor 5, through the promotion of secondary bile acids in the systemic circulation and cholestasis, followed by triggering of several inflammatory pathways that ended with necrosis of hepatocytes. These findings could not be induced by cellulose (7.5%), the insoluble and nonfermentable fiber.[161]

Similarly, it has been reported that daily administration of a high dose of psyllium (20.4 g) that was rich in mucilage for 3 months caused diarrhea in 30 hypocholesterolemic patients.[162] However, the dose and time relationship was established in another study that revealed that administration of psyllium for 8 week at a dose of 3.0−20.4 g daily reduced cholesterol significantly in a dose and time dependent manner.[88] This study was performed on 1039 mild and moderate hypercholesterolemic patients that were included in the meta-analysis studies including randomized placebo controlled trials, double blind or open label. These data suggested that, despite the prominent physiological benefits of a diet rich in SDF, its consumption should be made with caution.

CONCLUSIONS AND FUTURE DIRECTIONS

Hypercholesterolemia is a risk factor for coronary heart disease, and nutrition management is the best therapeutic approach. Soluble dietary fibers have several protective effects against chronic diseases, including cardiovascular disease, diabetes, and metabolic syndrome. The attempt to manage these conditions through dietary intervention could improve the quality of life of many individuals, reducing morbidity and mortality rates while leading to suffering from fewer side effects compared to medical treatment strategies. Despite the differences of the gut microbiota composition due to either dietary habits or health condition, SDFs have shown to positively alter the microbiota profile with the production of beneficial SCFAs. SDFs also have multiple non-nutritive health effects that help improve lipid profiles via multiple action mechanisms. The inclusion of SDF in the diet appears to be the right approach to reduce the risk of hypercholesterolemia, atherosclerosis, and cardiovascular disease based on extensive reports in this review.

These studies will possibly drive scientists to establish novel antihyperlipidemic agents from natural resources and to validate their mechanistic approaches using pharmacological assessments. More clinical studies with a larger cohort group, a chemically well-characterized type of SDF by a specified clinical context, and suitable predictors of metabolic health and SDF pharmacokinetic/pharmacodynamic behaviors are still required to extrapolate the experimental data to human scenarios. The interaction of SDF in combination with specific antihypercho-

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Table 5. Clinical Trials and *In Vivo* Studies Evaluating the Hypocholesterolemic Effect of Inulin (IN)[a]

study	subject	dose of IN	results	ref
clinical trial	double blind, randomized, placebo trial applied on 12 obese patients	7 g/day orally in morning for 4 weeks	↓ TC (p = 0.028), LDL (p = 0.028), VLDL (p = 0.046), TG (p = 0.046)	137
	randomized study applied on 15 obese patients	IN enriched cookies for 1 month	↓ TC and LDL significantly	138
	randomized, controlled study applied on 30 obese Mexican women	5 g/day for 3 months	↓ TC, TC, LDL, and blood glucose level significantly	139
	randomized, placebo controlled trial applied on 24 diabetic women	10 g/day for 8 weeks	↓ FBS (8.5%), HbA1c (10.4%), TC (12.9%), TG (23.6%), LDL (35.3%), LDL/HDL ratio (16.25%), and TC/HDL ratio (25.2%), and ↑ HDL (19.9%)	140
	randomized, controlled trial applied on 25 diabetic women	10 g/day for 4 weeks	↓ TC, insulin, and blood glucose level	141
	randomized, controlled trial applied on 10 diabetic patients	30 g/day for 9−18 weeks	↓ BFI, FBG, and insulin	142
	randomized, controlled trial applied on 25 diabetic women	10 g/day for 8 weeks	↓ FBG (9.4%), HbA1c (8.4%), TC (14.1%), LDL (21.7%), TC/HDL ratio (20.7%), and LDL/HDL ratio (27.5%)	143
	randomized, controlled trial applied on 14 obese men	high fat milkshake containing 24 g of IN one time	↑ fat oxidation, ↓ blood glucose, and insulin; no effects on TG free glycerol and satiety hormones GLP-1	132
	randomized, controlled trial applied on 51 obese patients	16 g/day for 3 months	↓ FBG, insulin, HbA1c, TC, LDL, and TG	144
	randomized, placebo controlled, double blind applied on study 42 obese patients	10 g of IN plus 10 g of resistant maltodextrin daily in 400 mL of milk for 12 weeks	↓ TC, TG, and LDL	145
	randomized, controlled trial applied on 14 obese men	high fat milkshake with 24 g of fermentable IN	↓ fat oxidation and ↑ FFA	.146
in vivo	Balb/c mice	diet containing 5% IN for 3 weeks	↓ TC and TG	147
	rats	FRD supplemented with IN (10 g/100 g) for 4 weeks	↓ blood pressure and TG	148
	albino rats	FRD supplemented with 0.174 g/100 g body weight	↓ TC, TG, LDL, serum glucose, and insulin level	8
	piglets	diet supplemented with 2% IN for 12 days	↓ TC and ↑ IgA and IgG concentrations	149
	hyperlipidemic hamsters	combination of IN and Fibersol-2 orally at 864, 1727, or 2591 mg/kg/day for 9 weeks	↓ TC, TG, LDL, LDL/HDL ratio; hepatic TC and TG levels in a dose dependent manner	150
	rats	diet containing 5% fat with 5% 5% IN for 28 days	↓ TC and TG	151
	diabetic rats	2.5, 5, or 10 g/kg daily for 8 weeks	↓ blood glucose, insulin, TC, TG, and NEFA in a dose dependent manner	152
	C57BL/6J mice	HF/HS diet supplemented with IN (9%) for 4 weeks	↓ TC and fecal cholesterol and bile acid excretion	153
	Syrian hamsters	HFD containing 20% IN for 3 weeks	↓ TC (24%), TG (34%), and LDL (29%); ↑ fecal excretion of total fat, TG, and bile acids	154
	Sprague−Dawley rats	HFD containing IN (8% w/w)	↓ TC, TG, and LDL	155
	C57BL/6 pregnant female mice	HF/HS diet plus 1.67 or 3.33 g/kg/day orally for 4 weeks	↓ TC, TG, LDL, blood glucose level, and insulin level	156
	diabetic female rats	oral administration of 10 mg/kg daily for 2 weeks	↓ TC, TG, LDL, serum glucose, and insulin level	157

[a]FRD, fructose-rich diet; HFD, high fat diet; HF/HS, high fat/high sucrose; NEFA, nonesterified fatty acid; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; V-LDL, very low density lipoprotein; BFI, body fat index; FFA, free fatty acid.

lestorlemic drugs should also be considered in different cohort groups and populations.

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Notes

The authors declare no competing financial interest.

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