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Dietary Polysaccharides in the Amelioration of Gut Microbiome Dysbiosis and Metabolic Diseases

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Abstract

The prevalence of metabolic diseases including obesity, diabetes, cardiovascular diseases, hypertension and cancer has evolved into a global epidemic over the last century. The rate of these disorders is continuously rising due to the lack of effective preventative and therapeutic strategies. This warrants for the development of novel strategies that could help in the prevention, treatment and/or better management of such disorders. Although the complex pathophysiology of these metabolic diseases is one of the major hurdles in the development of preventive and/or therapeutic strategies, there are some factors that are or can speculated to be more effective to target than others. Recently, gut microbiome has emerged as one of the major contributing factors in metabolic diseases, and developing positive modulators of gut microbiota is being considered to be of significant interest. Natural non-digestible polysaccharides from plants and food sources are considered potent modulators of gut microbiome that can feed certain beneficial microbes in the gut. This has led to an increased interest in the isolation of novel bioactive polysaccharides from different plants and food sources and their application as functional components to modulate the gut microbiome composition to improve host's health including metabolism. Therefore, polysaccharides, as prebiotics components, are being speculated to confer positive effects in managing metabolic diseases like obesity and diabetes. In this review article, we summarize some of the most common polysaccharides from plants and food that impact metabolic health and discuss why and how these could be helpful in preventing or ameliorating metabolic diseases such as obesity, type 2 diabetes, hypertension and dyslipidemia.

Keywords: Polysaccharides; Prebiotic; Gut; Microbiome; Microbiota; Metabolic syndrome; Diabetes; Obesity; Probiotics; Hypertension; Dyslipidemia

Introduction

Polysaccharides are a major group of organic macromolecules that are formed by the polymerization of simple sugar units. They are produced in plants with the primary purpose of storing energy and forming structural components. Starch, which is found mainly in two forms, amylose and amylopectin, is one such example of an energy storing polysaccharide. Cellulose is another most abundant polysaccharide in nature that acts as a structural component of the plant cell wall [1].

The characteristics and metabolic behavior of polysaccharides through the mammalian digestive process explains their valuable nutritional and health effects [2]. The digestion of plant polysaccharides starts right away in the mouth from mechanical stress and with the release of salivary enzymes such as amylase. Then, through the esophagus, these polysaccharides make it to the stomach where these polysaccharides absorb water, swell and get solubilized either completely or partially in the digestive fluid. The kind and magnitude of the process of acid hydrolysis in the stomach and enzyme digestion in the intestine depend on the constitution of the monosaccharide units, the array of covalent bonds and their position within the polymer, anomeric forms and substitutions on the sugar molecules of the polysaccharide. A major proportion of the sugar subunits originating from these digested polysaccharides are then absorbed in the small intestine. However, some polysaccharides (i.e. dietary fibers) resist hydrolysis in the stomach and the small intestine of humans. These polysaccharides are classified into two groups: fermentable

and non-fermentable. Non-fermentable polysaccharides pass to the large intestine and are eventually excreted out as waste/feces. However, the indigestible but fermentable polysaccharides are consumed (i.e., metabolized) by the microflora of the large intestine and are fermented to produce diverse products or metabolites that act as an additional energy source for the host. Short Chain Fatty Acids (SCFA), the major microbial metabolites found in the human gut, are produced mainly as a result of this microbial fermentation of such polysaccharides [3,4].

Given the well-established importance and beneficial roles of SCFAs in human gut physiology, it is suggested that the host gut microbiota is positively modulated by the fermentable polysaccharides wherein the growth and population of specific beneficial bacterial groups is promoted in the gut; and this phenomenon is called the *prebiotic effect* [5]. Since the prebiotic activity of these complex polysaccharides influences the host metabolism, the polysaccharide consumption is suggested to be able to beneficially enhance the host gut physiology and metabolic health by influencing the metabolic functions [6]. It is well known that perturbations in the gut microbiome composition (gut dysbiosis) and intestinal SCFAs levels can negatively impact the host metabolism and physiology and hence could also play a role in the pathology of metabolic diseases like obesity and diabetes [7-9]. Increasing the production of SCFAs in the gut by manipulating the gut microbiome using probiotics and prebiotics enhances metabolic functions and significantly reduces obesity- and diabetes-related metabolic derangements [7,10-12]. Herein, we review and summarize some of the major and recent evidences about the types of polysaccharides present in various edible plants, and how these polysaccharides could be exploited to improve host metabolic health and ameliorate the pathophysiology of metabolic diseases such as obesity, type 2 diabetes, hypertension and dyslipidemia.

Structural Features of Polysaccharides in Edible Plants

Distribution and structural diversity of polysaccharides in nature is highly complex and wide-ranging. Starch, cellulose, pectin, chitosan, xyloglucan, β-glucan, xanthan, arabinoxylan, carrageenan, inulin, agar and plant gums are common polysaccharides found in our daily food ingredients and around the nature. The molecular structures of food polysaccharides are shown in Table 1 and their molecular structure and chemical bonding and formula are depicted in Figure 1. Classification of polysaccharides is highly diverse; they are classified in different ways eg. on the basis of composition, function and origin. Depending on the single sugar moieties (i.e. glucose, galactose, fructose, mannose, etc.), polysaccharides are classified in two groups: 1) *homo-polysaccharides*, i.e., containing only one kind of polymerized sugar unit like starch, xylan, galactan and froctan, and 2) *hetero-polysaccharides,* i.e., containing two or more kinds of sugar units like pectin. Although, several hetero-polysaccharides are common; however, the abundance of homo-polysaccharides is found to be higher in the food forms [1,13]. These polysaccharides are extensively used in the manufacturing of food products such as confectionery, dairy, desserts, meat products, ready-to-eat foods, food dressings and also as fat replacers to produce low-fat products [14,15]. The digestion, metabolism and end-products produced from diverse polysaccharides depend on the sugar moieties as well as the covalent bonding between these units to form a complex polysaccharide chain. Thereby, as mentioned above, some of the polysaccharides gets digested and absorbed by human digestive enzymes with in the upper intestine; however, many complex polysaccharides are resistant to acidic as well as enzymatic digestion of human gastric and intestinal juices and thus reach to the complex world of microbes constituting the colonic microbiome. Several microbial communities are able to digest these non-digestible complex polysaccharides and produce metabolites that can interact with host cells and impact cellular and whole body metabolism. However, due to highly complex chemical structures, certain polysaccharides are still resistant to be digested by human gastrointestinal enzymes and microbiome and hence are eventually discarded as fecal waste at the end of digestion process.

Table 1: Plant polysaccharides and their chemical composition, covalent linkage, source, abundance and degree of digestion

Polysaccharides	Composition and linkage	Source	Abundance in compartment	Degree of digestion or fermentation
Cellulose	Glucose , Unbranched, β 1→4	Plants	Cell walls	Non-or poorly fermentable
Starch (Amylose)	Glucose , Unbranched, α: 1→4	Plants	Fruits, seeds, tubers	Two types: 1- Non digestible readily fermentable 2- Gelatinization making it more accessible to digestion
Starch (Amypectin)	Glucose , Branched α: 1→4 and 1→6	Plants	Cell walls	Digestible
Inulin	Fructose Unbranched, β2→1	Artichokes	Tuber	Readily fermentable
β- glucan	Glucose , Branched β1→3 , 1→6	Cereal, bacteria, and fungi	Cell walls	Readily fermentable
Pectins	Linear chains of α-(1–4)-linked D-galacturonic acid	Terrestrial plants	Non-woody parts specially fruits	Readily fermentable

Xyloglucans	β1→4- Linked glucose 1-6 xylose followed by galactose or fucose	Vascular plants	Primary cell wall	Readily fermentable
Arabinoxylan	D-xylosyl monomeric units linked β-1,4 and extensively modified with α-L-arabinofuranosyl residues on positions 2 and 3	Rye and wheat	Bran	
Arabic gum	Branched chains of (1–3)-linked D-galactopyranosyl units containing L-arabinofuranosyl, L- rhamnopyranosyl, D - glucuronopyranosyl and 4-O-methyl-D-glucuronopyranosyl units	Acacia senegal	Exudated gum from stems and branches	Readily fermentable

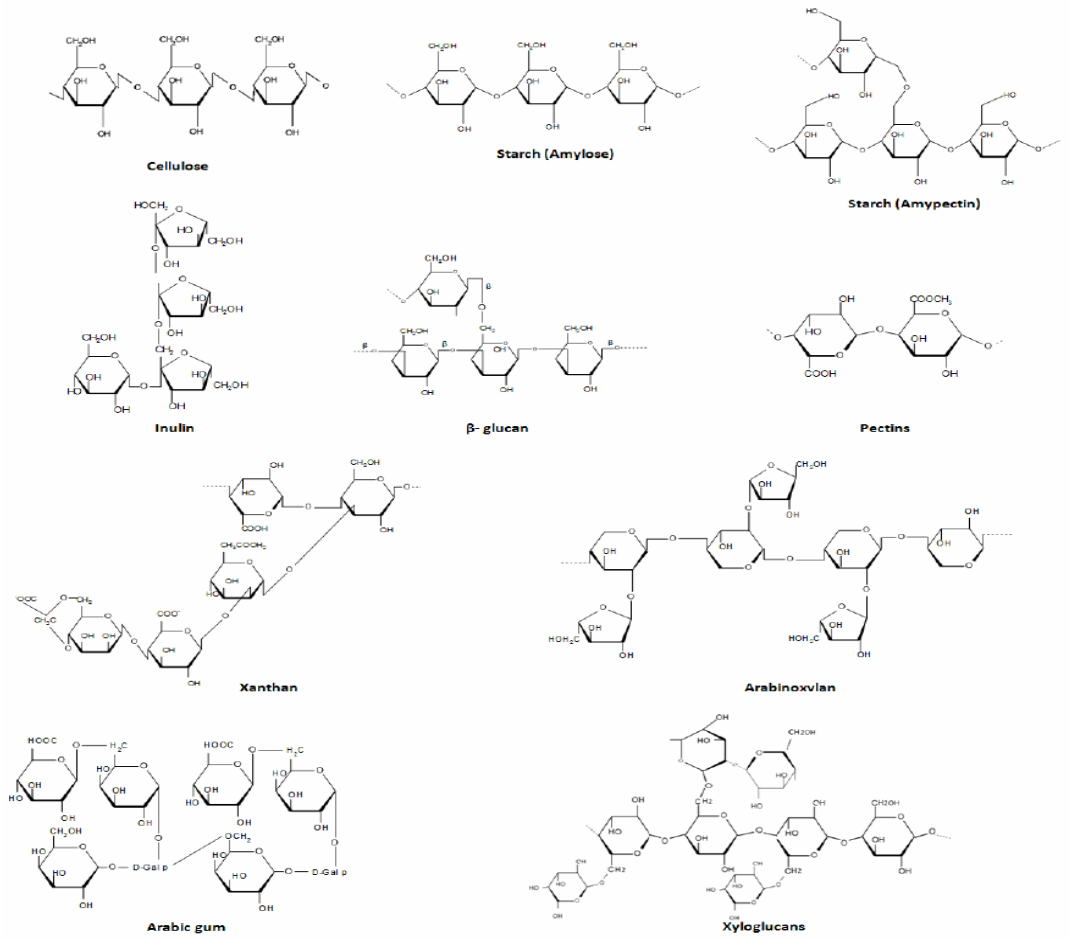

Figure 1: Structure of basic units of sugar moieties and their covalent bonding involved in formation of polysaccharide chains.
Cellulose consists a linear chain of several hundred to many thousands of β(1→4) linked D-glucose units. **Starch** (**Amylose**) has α(1→4) glycosidic bonds connecting α-D-glucose units, while **Starch** (**Amylpectin**) consists glucose units linked in a linear manner with α(1→4) glycosidic bonds and α(1→6) bonds on branches which occur every 24 to 30 glucose units. **Inulin** possess β (2,1) bonds that connects terminating glucosyl moieties and a repetitive fructosyl moieties. **β-Glucan** composes β-D-glucose moieties that form a linear backbone with 1-3 β-glycosidic bonds. **Pectins,** preferentially form linear chains of α-(1–4)-linked D-galacturonic acid, however other saccharide residues i.e. D-xylose, D-apiose, rhamnose, D-galactose, L-arabinose and D-xylose also presents in the branching and linear chains inserted as random sequences. **Xanthan** has the monosaccharides i.e. β-D-glucose, α-D-mannose and α-D-glucoronic acid that are found in a ratio of 2:2:1 and linked with β-(1- > 4) glycosidic linkage. **Arabinoxylan** consist big chains of 1,4-linked xylose units. **Arabic gum** contains a complex chemical structure comprising with contiguous hydroxyprolines that are attached to oligo-α-1,3-L-arabinofurans and non-contiguous hydroxyprolines attached to galactose residues of oligo-arabinogalactans. Structure also consists β-1,3-D-galactopyran core with side chains of β-D-uronic acids, β-D-galactose, α-L-arabinose and α-L-rhamnose that are branched to the main chain by 1,6-linkages and single termini of α-L-rhamnopyranose, α-L-arabinofuranose and β-D-uronic acids via 1,2- and 1-4-linkages. **Xyloglucan** contains a core chain of β1→4-linked glucose moieties, in which of are substituted with 1-6 linked xylose sidechains.

Metabolic Diseases and Diet

The interaction of diet and metabolic health related to metabolic diseases like obesity, diabetes and cardiovascular diseases is well known and reviewed [16-20]. Common metabolic abnormalities are obesity and type 2 diabetes that are associated with hyperglycemia, hyperinsulinemia, dyslipidemia and hypertension. These abnormalities, collectively called as syndrome X or metabolic syndrome, are considered a strong risk factor for cardiovascular diseases. Metabolic syndrome is also associated with several other disorders like non-alcoholic fatty liver disease, reproductive disorders and sleep disorders. Low-grade inflammation and insulin resistance are common pathologies causing the obesity and type 2 diabetes. Growing prevalence of these metabolic diseases is due to over-nutrition and sedentary lifestyles [21-24]. Some of the common pathologies associated with these metabolic diseases that can be impacted by dietary polysaccharides are summarized in Figure 2 and described in brief below:

Insulin Resistance: Insulin resistance leads to a rise in insulin levels during fasting and after meals in order to maintain blood glucose at appropriate levels [25,26]. Increased insulin levels promote fat storage into the adipose tissues and other metabolic organs like liver and skeletal muscles [27,28]. On the other hand, insulin resistance leads to an increase in the amount of fatty acids in the blood circulation due to the loss of insulin's ability to suppress lipolysis via Lipoprotein Lipase (LPL) activity in the adipose tissue [29]. Increased fatty acids from the adipose tissue disturb the lipid production function in the liver and result in more free fatty acids released into the bloodstream that cause high VLDL (very low-density lipoproteins) and low HDL (high-density lipoprotein) levels and dense LDL particles [30-32].

Some studies have also hinted at mechanisms explaining how insulin resistance is associated with blood pressure (hypertension) [33,34]. Insulin also acts as a vasodilator, and hence, in insulin resistant state, although insulin sodium re-absorption function remains normal but insulin vasodilatory actions become non-functional that causes blood pressure increase [35,36]. In addition, fatty acids also act as vasoconstrictor, and hence accompanied by the increased activity of the sympathetic system by insulin, these are collectively affected during the insulin resistance state [37,38].

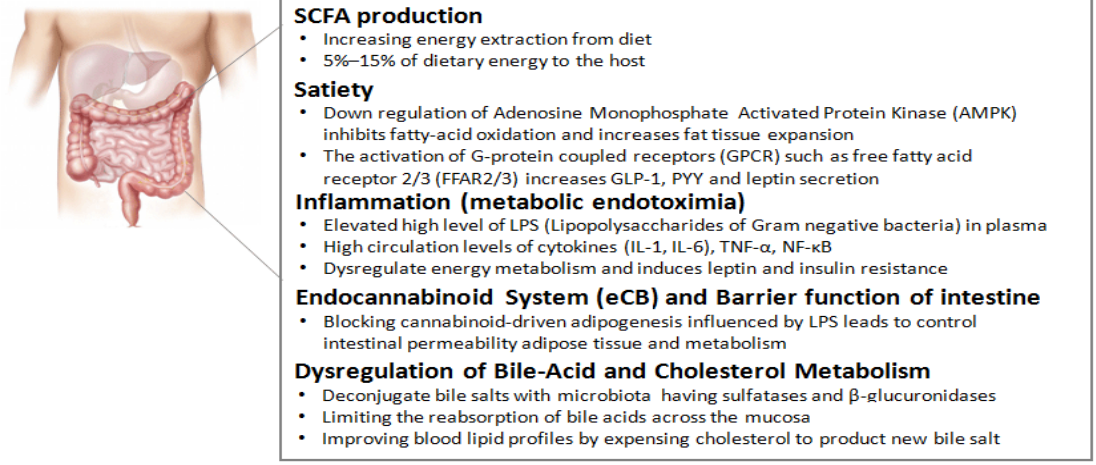

Figure 2: Pathological mechanisms/pathways involved in pathology of metabolic diseases like obesity and diabetes.
In obesity and type 2 diabetes, **Adipose Tissue** pathology is known to be mediated Suppression of angiopoietin-like protein 4/fasting-induced adipose factor (Angptl4/Fiaf) and increased LPL (lipoprotein lipase) activity that ultimately promote fat storage. **SCFA production** is contributing in increasing energy extraction from diet that may contribute in extra supply to the host to promote obesity, however, the biological function of SCFA is highly important as they contribute in 5%–15% of dietary energy to the host. Hunger versus **Satiety** remains one of the important mechanism to regulate energy homeostasis. Down regulation of Adenosine Monophosphate Activated Protein Kinase (AMPK) inhibits fatty-acid oxidation and increases fat tissue expansion. In addition, activation of certain G-protein coupled receptors (GPCRs) i.e. free fatty acid receptor 2/3 (FFAR2/3) increases GLP-1, PYY and leptin secretions. **Inflammation (metabolic endotoximia)** characterized with elevated high level of LPS (Lipopolysaccharides of Gram negative bacteria) in plasma, high circulation levels of cytokines (IL-1, IL-6), TNF-α and NF-κB, is another critical factor contribute in pathology of obesity/diabetes that contribute in dysregulation of energy metabolism and induces leptin and insulin resistance. **Endocannabinoid system (eCB) and gut barrier function** is crucial as blocking of cannabinoid-driven adipogenesis influenced by LPS leads to control intestinal permeability adipose tissue and metabolism. **Dysregulation in bile-acid and cholesterol metabolism** ie. deconjugation of bile salts with microbiota having sulfatases and β-glucuronidases, limiting the reabsorption of bile acids across the mucosa and improving blood lipid profiles by expensing cholesterol to product new bile salt are also prominent mechanism to contribute in obesity and diabetes pathologies.

Low-Grade Inflammation: The relationship of metabolic diseases i.e., obesity and diabetes with low-grade inflammation has been previously documented and reviewed [39,40]. In brief, the levels of pro-inflammatory cytokines such as IL-6, tumor necrosis factor α (TNFα), resistin and C-Reactive Protein (CRP), all known to be released from the adipose tissues, are found to be significantly higher in obese and diabetic individuals [39,41]. In addition, mucosal immune system and the macrophages stimulated by dietary and microbial ingredients across the intestinal epithelial layer plays a crucial role in the regulation of metabolic function. However, the precise role of inflammation in the progression of obesity and diabetes still remains unclear. The presence of inflammatory cytokines remains higher in the blood circulation as well as in the local tissues i.e. adipose tissues and the vascular tissues of metabolic organs, thereby increasing the risk of cardiovascular diseases [42,43]. The level of endotoxin, called Lipopolysaccharides (LPS), is also commonly found to be increased in the circulation of obese and diabetic individuals and this condition is termed as Endotoxemia [44,45]. Increase LPS levels are another indicator of inflammatory state in obese and diabetic conditions, and provide evidence that dysbiotic gut microbiome may be the source of LPS [46]. Increased low-grade inflammation is further known to induce insulin resistance in different animal models and human studies [39,47].

Satiety Dysregulation: Increased energy/food intake with reduced energy expenditure remains one of the biggest factors in inducing obesity and diabetes rate [48,49]. Food intake is tightly regulated by gut-brain axis, where gut hormones influence the hypothalamic area of brain to regulate hunger and satiety signals [50-52]. Ghrelin, a gut hormone, is released from an empty state of stomach, while others like Cholecystokinin (CCK), Glucagon-Like Protein-1 (GLP-1), Peptide YY (PYY), and Gastric Inhibitory Polypeptide (GIP) are decreased during hungry stage [53]. Ghrelin activates neuronal activity of hunger related neurons i.e. Agouti-related peptide (AgRP) and Neuropeptide Y (NPY) expressing cells and suppresses activity of satiety related neurons i.e. proopiomelanocortin (POMC) expressing cells in the hypothalamus [54]. This results to induce a response to search and seek the food. However, in full stomach, ghrelin levels reduces significantly and CCK, GLP-1, PYY and GIP levels increases that cause to reverse the hypothalamic signals to stop food search and seeking behavior [55]. Obese individuals show abnormalities in gut-hormones-hypothalamic axis to regulate energy sensing that results to increased food intake and fat accumulation. Dietary fibers in combination of microbiome may influence the gut-brain axis to regulate pathophysiology of metabolic diseases [56,57].

Endocannabinoids System and Tight Junctions in the Intestine: The endocannabinoid system (ECS) is widely available in different metabolically active tissues and cells, that exert regulatory control on diverse aspects of metabolic functions including storage and burning of calories [58,59]. Therefore, this system represents a potential pharmaco-therapeutic target for obesity, diabetes and other eating disorders. Cannabinoid type 1 (CB-1) receptor blockers have been known for beneficial effects against obesity, diabetes and cardiovascular diseases; however, their clinical use has been paused due to the occasionally occurring psychiatric side effects upon their use [60,61]. Although, recent research in animals and humans has provided new knowledge on the mechanisms of actions of the ECS in the regulation of metabolism, detailed mechanisms underlying the pathology of metabolic diseases still remains to be illustrated completely. Wide spectrum studies have shown that the ECS is widely distributed throughout the gut. Impact of ECS in the regulation of food intake, nausea and emesis, gastric secretion and gastro-protection, GI motility, ion transport, visceral sensation, intestinal inflammation and cell proliferation in the gut is well known [62-64]. Molecular and cellular targets for ECS that include cannabinoid receptors, transient receptor potential vanilloid 1 receptors, peroxisome proliferator-activated receptor alpha receptors and the orphan G-protein coupled receptors, GPR55 and GPR119, which are widely expressed in the enteric nervous system, epithelial and immune cells, are also becoming clear [65]. ECS is also known to control the tight junctions of the intestinal tissues that regulate the integrity of the intestinal epithelial barrier and also prevent the abnormal permeability (leaky gut) conditions which is otherwise often found to occur in obesity and diabetic conditions [66].

Bile Acids and Cholesterol Metabolism: Dietary fat is solubilized by the emulsification process mediated by bile acids that allows dietary fat to intestinal absorption. In liver tissues, cholesterol is converted into bile acids, thus the synthesis of bile acids regulate the whole body cholesterol metabolism [67]. Chenodeoxycholic acid and cholic acid that are the primary bile acids conjugate with taurine or glycine in human liver, and this conjugated form of bile acids enable the solubilization of fat that results in their intestinal absorption[68,69]. During digestion process, the absorption of primary bile acids happen actively in the distal ileum and results in their recycling; however, non-absorbed bile acids encounter colonic bacteria – mostly the bacteroides species – and are de-conjugated to deoxycholic acid and lithocholic acid that are further reabsorbed through the portal system [70]. Treatment of bile acids and their derivatives are strongly correlated with the improvement in glucose and lipid metabolism in rodent and human studies. Bile acids are known to activate intestinal L-cells and increase the release of GLP-1, that exhibit several beneficial effects in obese and diabetic individuals [71-74].

Microbiome Dysbiosis and SCFA Production: Although the pathophysiology of metabolic diseases remains complex; the contribution of environmental and dietary factors, however, remain significant in the progression and management of these disorders. Weight loss, exercise and physical activity contribute in controlling the blood glucose, insulin sensitivity, lipid levels, and blood pressure in obese and diabetic individuals [75]. However, recent research has shown that gut microbiome is an important factor in the pathophysiology of glucose hemostasis and incidence of obesity and diabetes [76]. Consequently, the gut microbiome has recently been viewed as a potential target for the development of preventive and therapeutic strategies against metabolic diseases like obesity, diabetes and cardiovascular diseases [77].

There are numerous convincing evidences about the involvement of gut microbiota in glucose homeostasis and hence in obesity and diabetes [78,79]. Dietary changes can cause diversion in both quantitative and qualitative microbial population of the gut, where Gram-negative bacteria are significantly increased [80]. In the study on germ-free or gnotobiotic mice models, high-fat and high-sugar diets changed the intestinal microbial ecosystem, metabolic pathways, and gene expression only after two days and doubled the host body weight after two weeks, as compared to healthy diet. This indicates that changes in the gut microbiota appear earlier than expected in response to obesogenic diets that cause progression of obesity. In addition, fecal microbiome transplantation studies further evidence that the germ-free mice receiving microflora from obese mice gain twice fat as compared to the mice receiving microflora from lean mice, while eating the same diet, clearly suggesting that the gut microflora contribute in the progression of obesity and diabetes regardless the type of diets [81-83].

Role of Polysaccharides in Metabolic Health: Biological activities of polysaccharides such as antibacterial, anti-cancer, antithrombotic, antioxidant, antiangiogenic and antiviral are known and reviewed in several independent articles [84,85]. Complex polysaccharides also help in regulating and lowering blood glucose levels, cholesterol levels, lipid levels, inhibition of fat accumulation, enhancing the absorption of minerals, regulating gastric emptying and bowel movement, increasing satiety and modulating the gut microbiota [15,85]. A number of in-vivo studies using different model systems (e.g. mice, rats, rabbits and humans) have reported that complex polysaccharides show positive effects in decreasing the risk of metabolic diseases like diabetes, obesity, cardiovascular disease, hypertension, hyperlipidemia and hypercholesterolemia as well as help in better management of these disorders [86,87]. Diverse metabolic effects of polysaccharides and their derived metabolites i.e., SCFAs on host health are summarized in Figure 3.

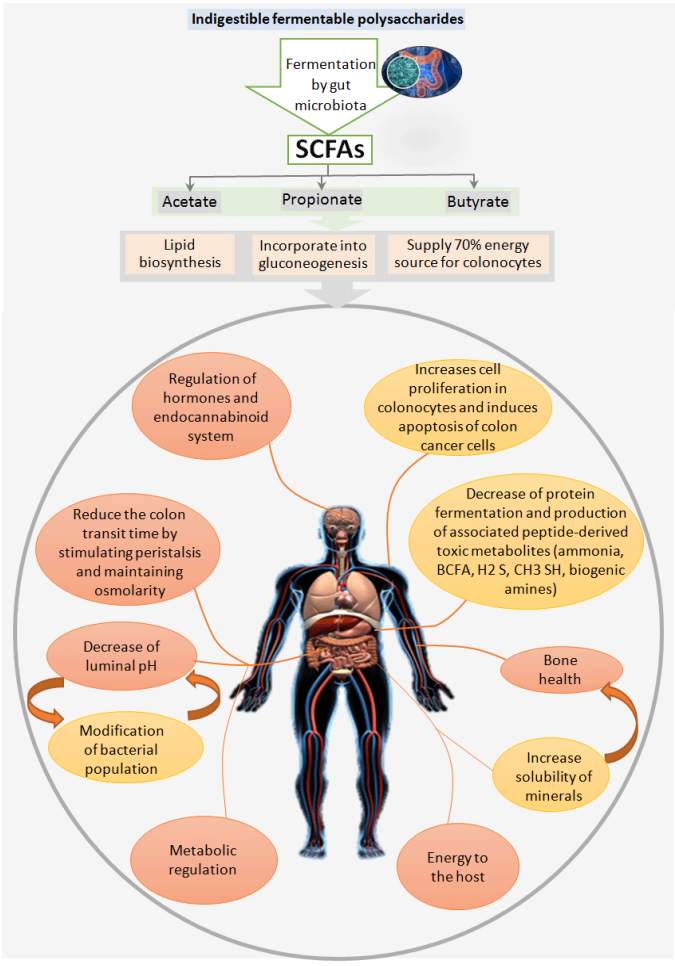

Figure 3: Fermentation of indigestible polysaccharides in colon and production of SCFA, that can further impact diverse mechanisms to maintain human health.
SCFA i.e. acetate, propionate and butyrate as fermented end products of oligosaccharides contributes in lipid biosynthesis, gluconeogenesis and energy source for colonocytes. In addition, SCFA are also known impact several biological pathways in the host i.e. hormones, eCB system, cell proliferation, cell death, bone health, mineral absorption, gut motility, intestinal pH and back to impact gut microbiome composition and its metabolic function, all these system manipulations contribute in changing metabolic health and energy homeostasis of the host.

Studies reporting the effect of polysaccharides from different plant sources on metabolic diseases are summarized in Table 2. Along with the beneficial effects on host metabolism including prevention or reduction of diabetes and obesity, it is known that polysaccharide like inulin, β- glucan oligosaccharides and soy fibers induce a shift in the gut microbiome to favor advantageous effects [88-90]. Certain natural dietary supplements (eg. green tea) that are traditionally known and used for their antidiabetic and anti-obesity effects are believed to be exhibiting these effects via alkaloids and flavonoids. However, recent studies show that the polysaccharide contents of green tea play a significant role in beneficial effects against obesity and diabetes [91,92]. Resistant starch from maize and Yacon syrup has also been reported to decrease food intake and appetite while increasing the plasma levels of hunger reducing and satiety promoting gut hormones like PYY and GLP-1 [93]. Considering these evidences and current paradigm about the beneficial effects of dietary fibers and polysaccharides, it is reasonable to speculate that polysaccharides could be explored and exploited for their use for both preventative and therapeutic measures against metabolic diseases like obesity, diabetes and cardiovascular events, as most of the studies have been performed on both healthy models as well as in the models of metabolic diseases.

Table 2: Summary of findings about the biological efficacies of polysaccharides against various metabolic diseases

S#	Source	Polysaccharides	Biological activity	Major findings	Ref.
1	Pistachio	Water-soluble polysaccharides	Antioxidant and antihypertensive	Pistachio polysaccharide have the potential to inhibit angiotensin converting enzyme (ACE; a blood pressure regulator) **in-vitro** and it is a promising candidate for future application for natural ACE inhibitory and antioxidant activities.	[116]
2	Almond	Water-soluble polysaccharides	Antioxidant and antihypertensive	Almond polysaccharide also have the potential to inhibit ACE and antioxidant activities **in-vitro.**	[116]
3	Tea	Polysaccharide	Antidiabetic	Tea polysaccharides exhibit high α-glucosidase inhibitory and antioxidant activity **in vitro and also in vivo (mice),** that can be beneficial for hyperglycemia treatment in diabetes.	[117]
			Antioxidant	Antioxidant properties of tea polysaccharides can be exploited for chronic diseases including diabetes, obesity and oxidative stress related disorders.	
			Anti-obesity	Polysaccharides and polyphenols suppressed body weight increase and fat accumulation and also improved blood lipid and antioxidant levels, along with effectively reducing serum leptin levels, inhibiting the absorption of fatty acids and markedly reducing the expression levels of the IL-6 and TNF-α gene in white adipose tissue of **rats**. Furthermore, polysaccharides and polyphenols were synergistic in reduction of serum leptin levels and in anti-inflammatory activity.	[91]
4	*Psyllium* (*Plantago psyllium*)	Husk fiber	Anti-diabetic and hypocholesterolemic	*Plantago psyllium* husk fiber feeding to Albino **rats** for 7 weeks reduced blood glucose and cholesterol levels.	[118]
5	Basil seed (*Ocimum basilicum* Linn)	AEOBS: aqueous extraction (gum)	Antidiabetic	AEOBS reduces blood glucose levels in diabetic **rats**, with improvements in body weight, serum electrolytes, and hematological indices, along with increased pancreatic islets.	[119]
6	Fenugreek seeds (*Trigonella foenum graecum* L.)	Sub-fraction rich in fibers	Antidiabetic	The addition of fiber rich sub fraction of fenugreek seeds to insulin treatment decreases hyperglycemia, glycosuria, plasma glucagon, somatostatin levels and hyperglycemic response to the oral glucose tolerance test in diabetic **dogs.**	[120]

7	Jerusalem artichokes and chicory	Inulin type fructans (commercially available) Oligofructose	Anti-dyslipidemia	Prebiotic supplementation reduces plasma total cholesterol, LDL-cholesterol, triglycerides and increased HDL-cholesterol concentrations in diabetic **human.**	[121]
			Anti-diabetic	Inulin and oligofructose reduces plasma cholesterol and triglycerides and decreases fat accumulation in liver and reduced hepatic steatosis in **rodents.**	[89]
			Anti-obese/diabetes	Daily intake of oligofructose decreases energy intake, epididymal fat mass, body-weight gain, glycaemia, endotoxemia, adipose tissue pro-inflammatory cytokines, glucose tolerance and glucose-induced insulin secretion and intestinal permeability in **humans and rodents**.	[122]
8	Pumpkin	Protein-bound polysaccharide (PBPP)	Antidiabetic	PBPP increases serum insulin, reduced the blood glucose with improvements in glucose tolerance of glucose in diabetic **rats** in dose dependent manner.	[123]
9	Yacon syrup	Fructo-oligosaccharide	Anti-obesity/ diabetes	Daily intake of Yacon syrup by obese and slightly dyslipidemic **pre-menopausal women** produced a significant decrease in body weight, waist circumference, body mass index and fasting serum insulin, by increasing defecation frequency, satiety sensation and serum LDL-cholesterol levels.	[124]
		Galacto-oligossacharide (GOS)	Microbiome dysbiosis and metabolism	12-week supplementation of Yacon's GOS to **overweight or obese prediabetic men and women** selectively increased fecal Bifidobacterium species abundance, without significant changes in insulin sensitivity and energy metabolism.	[125]
10	Maize	High amylose resistant starch (RS)	Anti-obese/diabetes	The consumption of 15–30 g/d high-amylose maize resistant starch improves insulin sensitivity in **men**.	[126]
			Body fat patterning and central appetite regulation	Dietary RS significantly impacts on adipose tissue patterning by decreasing adipocyte size, glucose and insulin metabolism, as well as affecting hypothalamic neuronal appetite regulation in **mice**.	[93]
			Anti-obese and energy metabolism	RS potentially reduced adiposity and weight gain in obesity-prone (OP) and obesity-resistant (OR) male rats, by reducing energy intake, and changes in gut hormones and large bowel carbohydrate fermentation.	[127]
			Insulin sensitivity and metabolic syndrome	Consumption of resistant starch improves insulin sensitivity in **human subjects with the metabolic syndrome.**	[128]
			Anti-obese/diabetes	Rats fed fermentable RS had increased cecal weights and plasma gut hormones e.g. peptide YY (PYY) and glucagon like protein-1 (GLP-1), gene transcription of PYY and proglucagon, short-chain fatty acids in cecal contents of **rats.**	[129]
11	Oatrim	β-Glucan	Anti-hyperglycemic	Consumption of foods containing moderate amounts of Oatrim fibers improves postprandial insulin release and glucose levels in **normal and overweight women.**	[130]
12	Oat and barley grains	β-Glucan	Preventive and therapeutic against metabolic syndrome	β-glucan improves postprandial glucose and insulin responses, and improve insulin sensitivity both in diabetic and nondiabetic **humans.**	[90]

13	Fruit of *Lycium barbarum* L. (Wolfberry)	Acidic polysaccharide (LBP-s-1)	Hypoglycemic	LBP-s-1 exhibit hypoglycemic and insulin-sensitizing activities via increasing glucose metabolism and insulin secretion and promoting pancreatic β cell proliferation in **mice.**	[92]
14	Apple	Thinned young apple polysaccharide (TYAP)	Anti-obese/diabetes	TYAP attenuates high fat diet induced obesity and associated hepatic metabolic disorder by activating the hepatic mitochondrial respiratory function in **mice**.	[131]
15	Artemisia Iwayomogi	Oligosaccharide	Anti-obese/ dyslipidemia	Orally feeding of Artemisia Iwayomogi oligosaccharide not only has triglyceride and cholesterol reducing effects, but also reduces body weight and abdominal adipose tissue weights in obese **rats**.	[132]
16	*Physalis alkekengi* L**.**	A water-soluble polysaccharide (PPSB)	Hypoglycemic activity in diabetic rats	PPSB oral administration to alloxan-induced diabetic **rats** reduces blood glucose levels, and increase the body weight of diabetic mice compared with alloxan-induced diabetic control group.	[133]
17	*Solanum lycocarpum* fruits or fruta-de-lobo (wolf-fruit)	Polysaccharides	Anti-obese/diabetes	The main component of *Solanum lycocarpum* St**.-**Hil fruit as a traditional antidiabetic and cholesterol lowering medicine is polysaccharides. Therefore,I t is concluded that the anti-obesity and antidiabetic activity of the this medicine is related to its polysaccharides contents.	[134]
18	Wheat	Arabinoxylan	Hypoglycemic	Postprandial glucose and insulin responses improves upon ingestion of Arabinoxylan-rich fiber in **human subjects**.	[135]
			Anti-obese/diabetes	Arabinoxylan feeding increased circulating satiety inducing gut hormones (peptide YY and glucagon-like peptide-1), decreased insulin resistance, body weight gain and fat mass with improved gut barrier function in **mice.**	[136]
19	Soy pods	Activated soy pod fiber (ASPF)	Absorption of dietary fat in mice	**Mice** fed high fat diet with 15% ASPF did not gain body fat, with decreased absorption of calories into the gut, with decreased plasma concentrations of the anti-inflammatory cytokine e.g. IL-10 and fecal excretion of triglycerides increased, which was associated to decreased bile acid secretion. A shift in abundances of microbiota in 10 genera was observed. *Flavonifractor*, *Barne-siella, Bacteroides, Oscillibactor* and *Alistipes,* were significantly increased but *Parabacteroides*, *Ruminococcus, Hydrogenoanaerobacterium, Akkermansia* and *Lactococcus* were significantly decreased in feces from 'HFD-fed group.	[88]
20	*Acacia senegal*	Arabic gum	Anti-obese/diabetes	The total body weight gain, insulin level, fasting blood glucose concentrations were significantly decreased in Arabic gum treated **mice** in comparison with high fat diet or glucose treated mice.	[137]
			Anti-nephropathic	Arabic gum treatment decreased blood pressure and proteinuria in diabetic **mice**.	[138]
			Anti-obesity in healthy adult females	Significant reduction in BMI by 0.32 and body fat percentage by 2.18% following regular intake of 30 g/day Arabic gum for 6 weeks was observed in **adult female**.	[139]

Mechanisms of Polysaccharides to Modulate Gut Microbiome and Benefit Metabolic Health

Indigestibility of carbohydrates or polysaccharides in foods is one of the most important parameters determining their health effect on the host. Some polysaccharides are completely or partly broken down during the gastrointestinal tract digestion process; however, the ones that are not digested by human digestive enzymes are considered bulking agents and pass through the gut. These bulking agents dilute or bind to toxins and carcinogens in the intestine and physically remove them from the body as they move down the large intestine, and exhibit significant benefiting effects on the host. Indigestible but fermentable carbohydrates entering the large intestine are broken down and fermented (metabolized) by the residing micro-flora and the metabolites (eg. SCFAs) produced from this process confer a direct effect on colon function and the host health [2,3]. Polysaccharide fermentation by the gut microbiota yields energy for microbial growth as well as for intestinal cells including colonocytes mainly by producing metabolites like SCFA [4,94]. In addition, mixed gases (CO_2, methane and hydrogen), lactate, formate, ethanol and some heat are also produced as a by-product of this fermentation process [95]. The ratio of fecal SCFAs produced upon polysaccharide fermentation into the human gut are in the order of: acetate (CH_3COOH) > propionate (CH_3CH_2COOH) ≥ butyrate ($CH_3CH_2CH_2COOH$) [96-98]. The concentration and proportion of these SCFAs is closely proportional to the amount of non-digestible polysaccharides available in the diet that reaches the colon [4]. The health benefits of a polysaccharides generally depends on the type and concentration of SCFAs enhanced in the region of the intestinal tissues where fermentation and SCFAs production takes place [2,4]. The major fraction of acetate is known to be included in lipid biosynthesis and hepatic gluconeogenesis, whereas propionate is primarily known to enter in hepatic gluconeogenesis flux. Butyrate is the major energy source for colonocytes, which provides approximately 70% of daily energy. The free form of these SCFAs exhibit several biological functions that can alter several physiological mechanism(s) in human body (Figure 3).

Selected indigestible but fermentable oligosaccharides or polysaccharides function as prebiotics. Prebiotics are defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a specific number of bacteria in the colon, and thus improving host health" [5]. Fermentation and the prebiotic effect of a fiber/ polysaccharides depends on its chemical composition of sugar moieties, solubility, chain length, degree of branching, particle size, porosity and presence of other dietary components like proteins and lipids [2]. For example, SCFA-producing bacterial population increases upon dietary fibers/ polysaccharides that help in reducing obesity and diabetes [99,100].

Gut microbiome and its fermentative properties control several nutrient sensing and enteric neuroendocrine mechanism(s) that regulate whole body metabolism. Gut microbiome metabolite like butyrate is known to enhance GLP-1 production that results to decrease obesity and diabetes in several rodent models [101]. On the same time, gut microbiome metabolites induced upon polysaccharide consumption are known to decrease ghrelin levels and ultimately reduce food intake via manipulating gut-brain axis [102,103]. Microbiome and its metabolites impact adipose tissue to reduce lipolysis by suppressing Fiaf and LPL and ultimately result in decreased fat storage [104,105]. Dietary fibers/ polysaccharide feeding lowers adiposity via lipolysis due to the gene expression pattern changing in white adipose tissue (by acting on PPARγ and G-coupled receptors protein), decreasing adipogenesis and increasing metabolic response to hormones such as leptin [72].

The microbiome changes are explained by the modulation of microbial communities that are over grown in favorable conditions (i.e., feeding of dietary fibers) versus other communities are suppressed in identical conditions [106,107]. Suppression of certain bacterial communities i.e., *Bacteriodetes* and increase in Firmicutes are known to be contributing in the pathology of obesity and diabetes in animal models and humans. However, this gives an opportunity to target these microbial species to reverse their proportion that can help in improving host metabolic function. Dietary fibers/polysaccharides are one of the efficient modulators of gut microbiome communities to help host metabolic health. In addition, certain bacteria species are also known to modulate immune function; for example: *Bifidobacteria*, *Faecalibacterium* and *Akkermansia* are interesting bacteria known for their anti-inflammatory properties and benefits in diabetes and weight gain [71,108-112]. Polysaccharide feeding dramatically increases the population of these bacterial species in several animal models and humans.

A plethora of literature is coming recently suggesting several parallel mechanisms connecting gut microbiota and metabolic diseases, and how dietary fibers/polysaccharides feeding can modulate gut microbiome-metabolic axis to reduce insulin resistance and adiposity [12,113,114]. These mechanisms include regulation of satiety, inflammation (metabolic endotoxemia), endocannabinoid system (eCB) and barrier function of intestine, regulation of bile-acid and cholesterol metabolism, effect on adipose tissue, production of SCFA and metabolism of choline [76,82,115]. Dietary polysaccharides are known to impact these pathways via modulation of gut microbiome via suggested pathways and indicate that the consumption of dietary polysaccharides can ameliorate metabolic diseases by diverse mechanisms (Figure 4).

Conclusions and Future Perspectives

Growing epidemic of metabolic diseases warrants development of novel and effective preventive and therapeutic strategies. Recent research findings are approving the relationship between gut microbiota and metabolic diseases beside other important factors such as diets and lifestyle. Dietary polysaccharides have received significant attention as functional biomaterials for manipulating the gut microbiome. Indigestible but fermentable polysaccharides, defined as prebiotics, can stimulate the growth and activity of beneficial bacteria in the colon. Therefore, inclusion of polysaccharides in diet influences

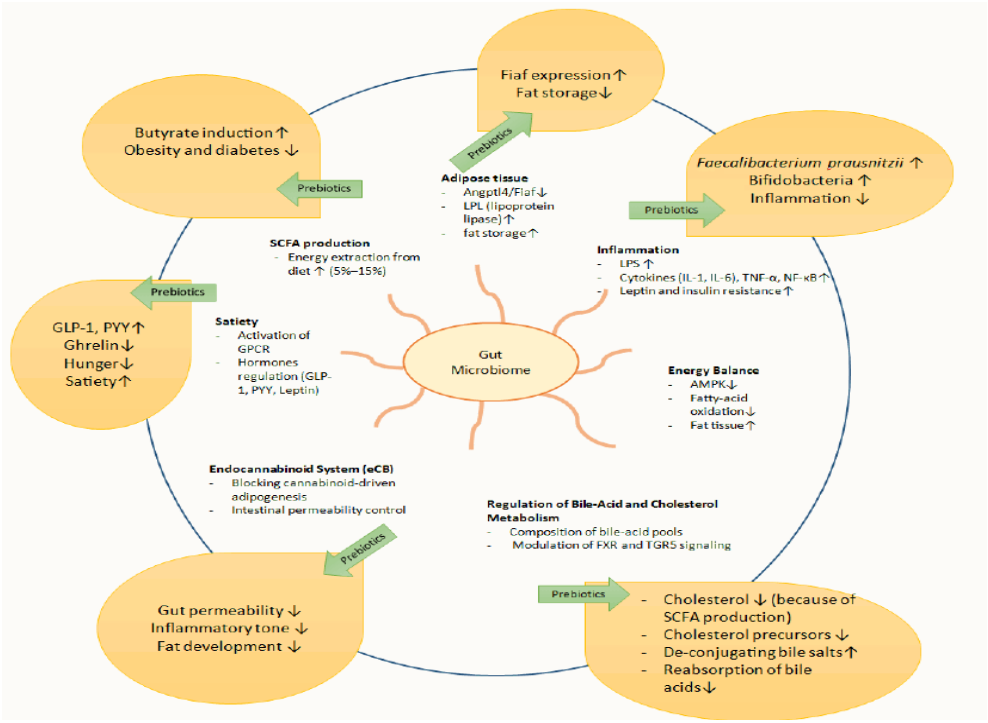

Figure 4: Mechanisms link gut microbiome-prebiotic interactions to modulate host metabolism and their effects on miscellaneous mechanisms of metabolic regulation.

Non-digestible oligosaccharides (prebiotics) manipulation gut microbiome than involves in modulation of pathological pathways of obesity and diabetes i.e. adipose tissue, inflammation, energy balance, bile acid and cholesterol metabolism, eCB, satiety and SCFA production (details in Figure 2) in beneficial manner, that further manipulate the gene expression, bacterial colonization and physiological function to reduce metabolic burden into the host body. Overall these changes contribute in reduction of obesity and diabetes.

the host metabolism, fat accumulation and insulin resistance. There are a lot of scientific studies confirming the positive effects of polysaccharides from various plant sources, as value-added products, on metabolic syndrome. In spite of multiple suggested mechanisms and accumulating data, a clear pathway of actions and the relationship between dietary polysaccharides consumption and human metabolism is not well established. Therefore, more research in this area is needed to determine the structural features of functional polysaccharides, accurate dosage for therapeutic applications, gut microbiota and metabolites changes in the intestine as well as to decipher the mechanism-of-action occurring in the gut upon the consumption of these polysaccharides.

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