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Review

Modulation of gut microbiota by bioactive compounds for prevention and management of type 2 diabetes

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia and insulin resistance. Gut microbiota (GM) are specific groups of microbes colonized in the gastrointestinal (GI) tract. They profoundly influence health, disease protection, and associated with metabolic activities, and play a vital role in the production of functional metabolites from dietary substances. Dysbiosis of GM has been linked to the onset of T2DM and can be altered to attain eubiosis by intervention with various nutritional bioactive compounds such as polyphenols, prebiotics, and probiotics. This review presents an overview of the evidence and underlying mechanisms by which bioactive compounds modulate the GM for the prevention and management of T2DM.

1. Introduction

Diabetes is a chronic metabolic disorder characterized by hyperglycemia. The long-term effect of hyperglycemia causes the malfunctioning of several vital organs in the body, causing multiorgan failure and death [1,2]. According to the International Diabetes Federation (IDF), 463 million people were affected with diabetes in 2019, and the number is expected to increase up to 700 million by 2045 [3]. Diabetes is classified broadly into three types based on the underlying causes. Type 1 diabetes is characterized by the destruction and damage of β-cells due to autoimmune response, leading to suppression or absence of production of insulin [4]. Type 2 diabetes (T2DM) is characterized by hyperglycemia and loss of insulin sensitivity in insulin-responsive tissues such as skeletal muscle and adipose tissue [5]. Type 3 diabetes, known as gestational diabetes, is caused temporally during pregnancy or Alzheimer's disease [6]. T2DM is an expanding global public health and economic burden, closely linked to the macro and microvascular complications leading to cardiomyopathy, nephropathy, neuropathy, etc., causing death and significant economic loss [7]. T2DM is caused by interactions between intrinsic (genetic or hereditary), and extrinsic factors such as changes in the lifestyle, a lack of physical activity, and stress factors [5]. A choice of a healthy diet and regular physical activities forms a group of primary and long-term and sustainable, effective measures for the management of T2DM. Additionally, depending upon the individual's age and physical fitness, lifestyle changes have been shown to complement antidiabetic treatment's efficacy and contribute to lowering the drug dosage [8–10] (Fig. 1).

The variety of gut functions is regulated by the interactions between bioactive compounds of the food and gut microbiota (GM). GM plays an essential role in controlling the fermentation and absorption of dietary nutrients such as SCFAs (Short Chain Fatty Acids) [11,12]. The GM is distributed throughout the GI (gastrointestinal) tract, and their type and activities are linked to various pathophysiological effects, including the development of T2DM [13]. Several metagenomic studies have found that dysbiosis in the GM directly influences the development of T2DM by affecting the gut permeability, inflammation, immune system, and energy metabolism [14–19]. Therefore, modulation of the GM by bioactive compounds has gained substantial momentum in recent years for finding suitable bioactive compounds or their formulation that have prophylactic and or curative potential on T2DM. Several studies in the recent past described the cross-talk between diet, GM, and the host in the context of metabolic disorders such as diabetes, obesity, and cardiovascular diseases [20–24]. An article by Lazar et al., (2019) [22] highlights the importance of prebiotics and probiotics in modulating the GM and thus indicating their preventive effect on the onset of diabetes and obesity. Other studies have also shown that prebiotics and probiotics

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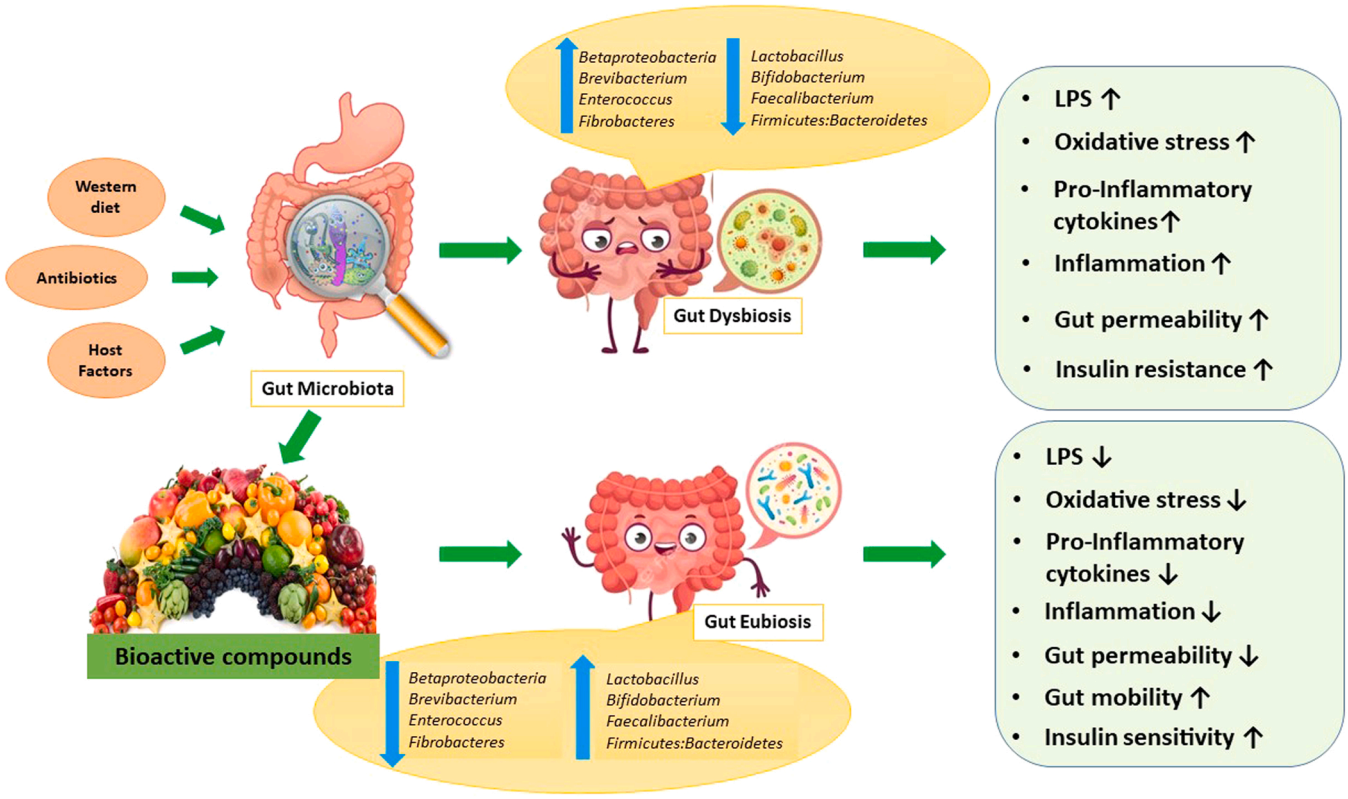

Fig. 1. The figure represents the relationship among the food-derived bioactives, gut microbiota, and risk factors associated with the development of insulin resistance and T2DM. The long-term consumption of the western diet, the overuse of antimicrobials (antibiotics), and contribution from host factors including age, sedentary lifestyle, etc., cause gut dysbiosis, which subsequently causes increased levels of bacterial lipopolysaccharide, -oxidative stress, -the release of pro-inflammatory cytokines, -gut inflammation, and gut permeability. All these changes over a period of time cause the development of insulin resistance and T2DM. On the other hand, bioactive compounds from a healthy diet positively influence the maintenance of gut eubiosis, which causes attenuation in the above-described pathological changes in the gut with concurrent improvement in insulin sensitivity and gut mobility, thus benefiting the prevention and management of T2DM.

have a favorable impact on eubiosis over dysbiosis and thus can be exploited to prevent and treat T2DM [20,22,25,27,28]. Further, previous studies also describe strategies of modulation of GM by antimicrobial agents, bariatric surgery and its implications in managing metabolic disorders [21]. On the other hand, studies also implicate how pharmacological, surgical and nutritional interventions for T2DM impact the GM [23]. This review article provides the update and summarizes the interaction between dietary bioactive compounds, GM, and T2DM. In addition, the article also focuses on three key questions: how different types of diet affect the GM populations, how changing the dietary pattern leads to gut dysbiosis linked to T2DM condition, and how bioactive compounds modulate the GM population help in preventing and managing the T2DM. Further, we have compiled most studies done in experimental models and humans based on the bioactive compounds from different sources modulating the gut population having anti-diabetic properties.

2. T2DM and diet interactions

A popular quote says, *"you are what you eat*". T2DM is caused by the cumulative effect of lifestyle changes and physical inactivity together with genetic susceptibility [26]. The incidence of T2DM is high in people who consumed a diet rich in high fat and sugar compared to the traditional diet [27]. Further, long-term eating of white rice [28], potatoes [29], fried foods [30], red and processed meat [31], sugar-sweetened beverages, and packaged fruit juices [32] increases the risk of getting T2DM. Therefore, consumption of healthy foods such as whole grains, nuts, yogurt, green leafy vegetables, fruits, coffee, green tea which contain bioactive compounds that lower down risk of T2DM has gained the attention of the public as well as researchers [17,33–37]. Furthermore, consumption of foods rich in ω− 6 polyunsaturated fatty acids [38], dietary fiber [39], magnesium [40], zinc [41], vitamin D [42], selenium [43] lower risk of T2DM. Additionally, Koppes et al. (2005) [44] and other studies [45,46] have observed that moderate alcohol consumption can lower the risk of T2DM. Changing the dietary pattern, including lowering the fat consumption together with lifestyle modifications, can be an effective way for prevention as well as therapy for T2DM [27].

3. Gut microbiome

The gut microbiome refers to the set of genomes of all microorganisms in the gut. The GM refers to a specific microbial population in the gut [46,47]. The interplay between GM and host physiology influences the host's metabolic phenotype, stress response [48]. The equilibrium between the microbial diversity is a prerequisite to maintaining the host homeostasis, including energy metabolism, immunity response, inflammation, and brain-gut axis [19]. The dysbiosis in the GM may contribute to the onset of chronic conditions, including irritable bowel diseases, colorectal cancer, obesity, diabetes, metabolic syndrome, allergy, depression, and anxiety [21,49]. The factors that influence host intestinal microbiota are genetics, lifestyle, diet, and environmental factors [50]. Therefore, balancing the composition of GM is critical to preventing metabolic diseases [51–53].

3.1. Location, composition, and function

The microbiota is present on every surface of the human body, from the skin to genitourinary, GI, and respiratory tracts [51]. The GI tract is sterile at birth but gradually becomes colonized by various microbial

Table 1
Location, composition and function of GM.

GI region	Microbiota	Function of Microbiota	Reference
Stomach	***Firmicutes*****:** *Lactobacillus,Veillonella*, ***Proteobacteria***: *Helicobacter*	***Bacteroidetes*****:** It digest complex polysaccharides, degraded complex O-glycans yielding Volatile Short-chain fatty acids (SCFAs) which is an energy source for host, regulating intestinal epithelial cell growth and differentiation, stimulates immune system ***Firmicutes*****:** It release butyrate as end product and promote intestinal epithelial health, promote host immune homeostasis ***Actinobacteria*****:** some of them have probiotic effects, protect against pathogens through competitive exclusion, immune modulation, bile salt hydrolase activity, also have the ability to adhere to mucus as well as intestinal epithelium. ***Proteobacteria*****:** less health benefit, serve as a potential diagnostic signature of dysbiosis and risk of diseases.	[51,54,57,103,108–114]
Duodenum	***Firmicutes*****:** *Bacilli*, *Streptococcaceae*, ***Actinobacteria***: *Actinomycinaeae*, *Corynebacteriaceae*		
Jejunum	***Firmicutes*****:** *Bacilli*, *Streptococcaceae*, ***Actinobacteria*****:** *Actinomycinaeae*, *Corynebacteriaceae*		
Ileum	***Firmicutes*****:** *Bacilli*, *Streptococcaceae*, ***Actinobacteria*****:** *Actinomycinaeae*, *Corynebacteriaceae*		
Colon	***Firmicutes*****:** *Lachnospiraceae*, ***Bacteroidetes*****:** *Bacteroidetes*		
Epithelial surface	***Firmicutes*****:** *Clostridium*, *Lactobacillus*, *Enterococcus*		
Mucus layer	***Firmicutes*****:** *Clostridium*, *Lactobacillus*, *Enterococcus*		
Intestinal lumen	***Bacteroidetes:*** *Bacteroides*, ***Actinobacteria*****:** *Bifidobacterium*, ***Firmicutes*****:** *Streptococcus*, *Clostridium*, *Lactobacillus*, *Enterococcus*, *Ruminococcus* ***Proteobacteria***: *Enterobacteriacea*		

species and becomes the GM [13]. There is a notable spatial variation in the composition of GM in the GI tract. GM colonizes heavily in the GI tract, starting with the small concentration in the stomach followed by duodenum, jejunum, ileum, and colon (almost 70% of all microbes) as listed in Table 1. Human gut microbiota is anaerobic, and most belong to the phyla *Firmicutes* (~60%), *Bacteroidetes* (~15%), and *Actinobacteria* (~15%) followed by, *Verrumicrobia* (~2%), *Proteobacteria* (~1%), and *Methanobacteriales* (~1%) [49,50]. Table 1 depicts the spatial distribution of the GM, along with their functions.

3.2. Effect of diet on GM

The human diet is very complex, having nutrients as well as food-derived bioactive compounds. Hence, dietary patterns are considered the key elements of human health. Changes in the dietary pattern influence GM's composition [56,57]. Alternative dietary patterns or miss management in the dietary component may harm the healthy microorganisms in GM. Several studies have revealed that diet-induced GM dysbiosis is linked to the onset of T2DM and obesity [19,49,58].

The components present in the diet affects GM by various mechanism, as shown in the Table 2. *Bifidobacteria*, *Clostridium*, and *Bacteroidetes* decrease if carbohydrate content in the diet decreases [59,60]. Similarly, increases in the dietary fiber content increase the short-chain fatty acid (SCFA) producing bacteria in the GM [61]. On the other hand, the western diet showed a more significant reduction in GM diversity due to lesser dietary fiber content [62]. Several studies have shown that the Mediterranean diet that is intrinsically rich in polyphenols has been found to lower the risk of T2DM and obesity [63,64]. Table 2 depicts the different types of dietary patterns and how they affect the population of healthy microbes in GM. Diet with high carbohydrates, fiber, protein has shown a positive impact on the person's health, as it acts as an energy source, helps in the production of SCFAs, production of microbial metabolites, and helps in increasing butyrate-producing bacteria. While, the keto diet, western diet, and high-fat diet cause a decrease in gut microbiota including *Bifidobacteria*, *Bacteroidetes* which will lead to the disease condition [59–61].

3.3. Diabetes and GM

Gut microbiota is an environmental factor responsible for controlling energy metabolism, body weight, proinflammatory activity, bile acid metabolism, insulin resistance, and modulating gut hormones [65,66]. The imbalance in the GM causes dysbiosis, which is associated with the onset of T2DM, insulin resistance, and obesity [19,23,24,53,67]. Several studies have revealed significant differences in the two most abundant phyla of GM i.e., *Firmicutes* and *Bacteroidetes*, where the ratio of *Firmicutes* to *Bacteroidetes* increased in people with diabetes as compared to healthy persons [67,68]. On the other hand, *Bifidobacteria, Akkermansia, Prevotella, and Faecalibacterium* have a positive effect on host metabolism and a negative influence on diabetes. Cani et al. (2007) [65] reported the contribution of *Bifidobacteria* towards the improvement of mucosal barrier function and reduction in low-grade chronic inflammation.*Bifidobacteria* also improves glucose tolerance and insulin sensitivity [69]. Hippe et al. (2016) [70] have found decreased levels *Faecalibacterium prausnitzii* in feces contributing to inflammation and poor glucose homeostasis. Similarly, Tap et al. (2015) [61] have studied the effect of *Prevotella* on the host diabetic phenotype, where it increased glucose metabolism by enhancing glycogen storage. Table 3 describes the effect of dysbiosis on diabetes and the contribution of the GM for controlling diabetes. Studies in mice show that alternation in GM can lead to diabetes. Some of the studies show that *Bifidobacteria*, *Bacteroidetes* contribute toward the improvement of mucosal barrier function, reduce inflammation, improve glucose tolerance, reduce oxidative stress which will ultimately help in controlling diabetes. Whereas, increase in *Lachnospiraceae* will contribute toward the development of T2DM, by increasing blood glucose levels and decreasing insulin levels in plasma. And studies in human shows that, *Bifidobacterium*, *Faecalibacterium prausnitzii, Akkermansia muciniphila, Prevotella* played a pivotal role in controlling diabetes. As shown in Table 3, the decreases in *Bifidobacterium, Faecalibacterium*, *Akkermansia, Prevotella* is associated with the diabetes condition.

Table 2
Effect of diet on GM.

Type of diet	Effect on microbiota	Mechanism	Reference
Low Carbohydrates	*Bifidobacteria*↓ *Clostridium* ↓ *Bacteroidetes* ↓	It acts as energy source for microbiota and support microbial growth in the colon. It releases short-chain fatty acids that will help in regulation of gene expression by affecting host energy expenditure and storage.	[59,60]
High fiber	*Bacteroidetes* ↑ *Actinobacteria*↑ *Firmicutes* to *Bacteroidetes* ratio↓	It help in production of SCFAs which will further regulate the expression of genes related to glycan and lipid metabolism	[61] [2,3]
High protein diet	*Bacteroidetes* ↑, *Lactobacillus*↑, *Bifidobacteria* ↑, *Firmicutes* ↓	Microbiota digest the undigested protein and produced metabolites which are responsible for metabolism, immune system and nervous system.	[115–117]
High-fat diet	*Bacteroidetes*↓ *Firmicutes* ↑ Proteobacteria ↑	It results in impairments in colonic epithelial integrity and barrier function which is associated with the development of Insulin resistance and type 2 diabetes. Increased plasma LPS levels	[118,119]
Keto diet	Dysmicrobism	As microbiota need carbohydrates as energy source, which are diminished in this type of diet	[120]
Western diet	*Clostridium innocuum*↑, *Eubacterium dolichum*↑, *Catenibacterium mitsuokai*↑, *Enterococcus* spp. ↑ and *Bifidobacteria*↓, *Bacteroidetes*↓	High fat and digestible saccharides: mostly absorbed in duodenum, leaving very few substrate for colonic bacteria.	[62,118]
High Mediterranean diet	*Bacteroidetes* ↑ *Firmicutes* ↑ *Actinobacteria* ↑	Help in increasing beneficial butyrate-producing bacteria which impart a positive metabolic influence.	[9,63,64]

3.4. Mechanisms of GM on host metabolism

Gut microbiota is responsible for initiating, controlling, and manipulating the host's overall metabolic processes such as energy metabolism, metabolic endotoxemia, maintenance of gut permeability, and host immune system [66]. The interaction of GM and host metabolic changes linked to the onset of T2DM has been studied by various researchers and is presented in Table 4. The metabolites produced by the GM during the fermentation of complex carbohydrates i.e., SCFAs and bile acids, initiate several metabolic pathways that regulate glucose absorption, insulin sensitivity, and inflammation in the host [11,22,72,73]. There are three types of SCFAs i.e., acetate, propionate, and butyrate, produced by bacteria present in the colon [55]. *Bacteroidetes* phylum is known to produce acetate and propionate, while *Firmicutes* phylum produces butyrate by fermenting dietary fibers [74]. The SCFAs help to regulate energy expenditures, glucose homeostasis, and hepatic lipogenesis, which have a substantial impact on T2DM and obesity.

Gao et al. (2009) [75] have found that butyrate reduces insulin sensitivity in high-fat-fed diabetic mice by promoting energy expenditure and inducing mitochondria function. Acetate ingestion in T2DM rats reduces lipogenesis in adipose tissues and the liver. It improves glucose tolerance by inhibiting the transcription factor ChREBP (Carbohydrates-Responsive Element-Binding Protein), which is required for the conversion of glucose to fatty acids in the liver [76]. The diet-derived propionate improves the function of β-cells and promotes insulin secretion through the protein kinase C- dependent pathway [77]. Tolhurst et al. (2012) [78] have found that acetate and propionate influence the L-cells to release GLP-1 (Glucagon-Like Peptide-1) and PYY (Peptide YY hormone), which stimulate insulin secretion, glucose uptake in the muscle and decrease glucagon production in the pancreas. Understanding GM and host metabolism could be the potential strategy for controlling T2DM by modulating the GM of the host.

4. Bioactive compounds: relation with GM and T2DM

Bioactive compounds are phytochemicals such as polyphenols, anthocyanin, flavonoids, carotenoids, alkaloids, and tannins found in various plant parts, including leaf, bark, root, and have functional benefits to maintain normal health. Fruits and vegetables are also a substantial source of several bioactive compounds. Bioactive compounds like phenolics, flavonoids, alkaloids, anthocyanin possess significant antidiabetic properties by increasing α-glycosidase inhibiting activity, improving glucose tolerance by activating the P13K/Akt and inhibiting JNK in signaling, improving serum lipid levels, and reversing the insulin resistance by upregulating the expression levels of insulin receptor and glycolytic enzymes and by down regulating the expression of insulin receptor substrate-1 and gluconeogenesis enzymes [79]. Foods loaded with bioactive compounds have to pass through various metabolic processes in the body where it finds the space to macerate themselves and release the potential bioactive compounds. Microorganisms are always considered as a sustainable approach to macerate phytochemicals from the foods by fermentation process [80]. As the GI tract contains trillions of GM, the GI tract suits as an appropriate site where the bioactive compounds can be extracted after intake and utilized prominently in several metabolic processes [81]. Several studies have shown a two-way relationship between bioactive compounds and GM [82]. GM plays a crucial role in modulating the production, bioavailability, and biological activities of bioactive compounds, particularly after the intake of food containing high-molecular-weight polyphenols. Furthermore, bioactive compounds might be converted by the colonic GM to metabolites such as SCFAs and bile acids that can affect the intestinal ecology and influence host health by participating in the several metabolic pathways [11,12]. On the other hand, the bioactive compounds supplied to the GM by the various dietary pattern modulates the composition of GM, due to the action of aromatic metabolites [82–85]. In recent years, research focus has shifted towards the modulation of GM by bioactive compounds to combat metabolic diseases such as diabetes and obesity [69,86–90].

Studies have shown that bioactive compounds modulate the composition of microflora either by selective prebiotic effects or antimicrobial effects against the pathogenic bacteria in the gut [82,91–94]. The modulation of colonic microbiota may contribute to control the T2DM, although the mechanisms regarding the antidiabetic action have not been clearly explained. Studies [95–98] have found that allicin modulates the *Firmicutes* to *Bacteroidetes* ratio, consequently maintain glucose homeostasis and insulin sensitivity. Saponin reduces the *Firmicutes* to *Bacteroidetes* ratio, which again beneficial in controlling T2DM [99]. Protocatechuic acid elevated GLP-1 secretion, and serum insulin, also improved insulin resistance by reducing the *Firmicutes* to *Bacteroidetes* ratio [100]. The contradictory results have been found by other studies [101] where the flavonoids from green seaweed increased the *Firmicutes* to *Bacteroidetes* ratio but decreased blood glucose level and improved insulin sensitivity, which might be due to other microflora niches in the ecology of GM [82].

Bifidobacterium spp. enhances the expression of proteins involved in the insulin-signaling pathway and expression of adiponectin hormone, which regulates the blood glucose level and decreases inflammatory adipokines [102]. Cani et a. (2007) [65] reported that *Bifidobacterium* spp. significantly increased the extraction of energy and fat storage, also reduced the expression levels of TNF-α and LPS (lipopolysaccharides) in diabetic models. In addition, *Bifidobacterium* spp. reduced endotoxemia and inflammation and also improved glucose tolerance and insulin

Table 3
GM dysbiosis and interlinkage with diabetes.

Change in GM	Effect on diabetes	References
Studies in Experimental mice		
Firmicutes ↓, *Bacteroidetes* ↑, *Bifidobacteria* ↑	• improved glucose tolerance, • help in secretion of GLP-1 from L-cells • reduction of low grade inflammation and oxidative stress.	[121]
Bifidobacteria ↑	• contribute toward the improvement of mucosal barrier function by increasing the production of endogenous GLP-2 • improved tight junctions • decreased plasma LPS concentrations • reduction in low grade inflammation • oxidative stresses	[65]
Lachnospiraceae↑	• contribute toward the development of type 2 diabetes by increasing fasting blood glucose levels, - decreasing insulin in plasma.	[122]
Studies in human		
Firmicutes (*Clostridia*)↓ *Bacteroidetes* ↑ *Proteobacteria*↑, *Bacteroides*- versus class *Clostridia* and *C. coccoides* ↑	• Gram negative bacteria, made up of Lipopolysaccharides, which is known as a potent stimulator of inflammation and cause diabetes.	[123,124]
Bifidobacterium spp. ↓ *Clostridium leptum* ↑, *Bacteroides vulgatus*↓	Role of *Bifidobacterium* spp. in host metabolism: • improved glucose tolerance, • mucosal barrier function, • glucose-induced insulin and • normalized inflammatory tone which lead to diabetes.	[65,69]
Faecalibacterium prausnitzii ↓	Role of *Faecalibacterium prausnitzii* in host metabolism: • Block NF-κB activation • Inhibit secretion pro-inflammatory mediators • Improve glucose and lipid homeostasis	[70,109, 125]
Clostridiales sp. SS3/4 ↓, *Eubacterium rectale* ↓, *Faecalibacterium prausnitzii* ↓, *Roseburia intestinalis* ↓, *Roseburia inulinivorans* ↓, *Bacteroides caccae* ↑, *Clostridium hathewayi*↑, *Clostridium ramosum* ↑, *Clostridium symbiosum* ↑, *Eggerthella lenta* ↑ and *E. coli* ↑	This led to type 2 diabetes, as this cultures is mainly: • associated with membrane transport of sugars, • transportation of branched-chain amino transport, • metabolism of methane, • degradation of xenobiotics, • metabolism and reduction of sulfate	[126]
Akkermansia muciniphila ↓ *Clostridiaceae* ↑, *Enterococcus casseliflavus* ↑, *Butyrivibrio* ↓, *Bifidobacterium* ↓, *Megasphaera* ↓	Role of *Akkermansia muciniphila* (mucin degrading bacteria) in host metabolism • stimulates the secretion of glucagon like peptide from the L-cells that suppress glucagen secretion, • improve intestinal permeability, • ingestion of carbohydrate, • improved insulin secretion, • Protect against pathogens.	[127,128]
	SCFAs producing bacteria: • improved insulin secretion.	
	Role of *Bifidobacterium* in host phenotype: • improve of mucosal barrier function improved tight junctions • decreased plasma LPS concentrations • reduction in low grade inflammation • oxidative stresses	
Clostridium clostridioforme ↑, *Lactobacillus gasseri* ↑, *Streptococcus mutans* ↑	• lead to diabetes, mainly associated with fasting glucose, HbA1c, insulin plasma triglycerides.	[129]
Prevotella ↑	Increase in *Prevotella*:	[61]
Firmicutes ↓, *Bacteroidetes* ↑, *Bifidobacteria* ↑	• improve glucose metabolism by promoting glycogen storage • contribute toward the production of butyrate which further help in the secretion of GLP-1 from L-cells that changes the metabolic function	[130]

↑ shows increase in GM, ↓ shows decrease in GM

secretion by promoting the synthesis and secretion of incretin and GLP-1 [103]. Hence, the increase in the *Bifidobacterium* spp. by certain bioactive compounds helps to control T2DM. Studies have been reported that berberine, polyphenols, phenolic acids such as gallic acid and ellagic acid increase the levels of *Bifidobacterium* spp. which helps to maintain T2DM (Table 5). Similarly, *Lactobacillus* spp. Improved glucose tolerance and normalized inflammatory tone by reducing LPS and also increased the production of SCFAs and inhibited the pathogenic gut microflora, which might be beneficial for maintaining the T2DM [104, 105]. Table 5 depicts that the various bioactive compounds increase the

Table 4
Effect of GM on host diabetic phenotype.

Function of GM	Mechanism	Effect on diabetes	References
Energy metabolism	SCFA-GPR41/43 Pathway	Gut microbiota ferment indigestible complex carbohydrates and produced monosaccharides, secondary bile acids and short chain fatty acids. SCFAs include: butyrate (activate GPR41), propionate (activate both GPR41 and GPR43), and acetate (activate GPR43). SCFAs act as a signaling molecules and bind to the G-protein coupled receptors GPR43 and GPR41 and played a major role by supressing insulin signaling and decreased storage of lipid in the adipocytes, increase the oxidation of lipids which will lead to increase in energy expenditure.	[131] [7]
	ChREBP/SREBP-1c Pathway	GM regulate the lipogenesis in liver (production of triglyceride) by controlling two transcription factors i.e., carbohydrate response element binding protein (ChREBP) and sterol response element binding protein 1c (SREBP-1c) which improves glucose absorption and insulin levels.	[67,132]
	AMPK Pathway	GM help to increase the AMPK activity by production of SCFAs. AMPK inhibits lipid and glycogen synthesis and stimulates glucose uptake, glycolysis, fatty acid oxidation.	[75, 133–135]
	FIAF Pathway	GM influence the host metabolism by supressing the expression of fasting –induced adipose factor (FIAF) which ultimately arrest the Microbiota influence the host by supressing the expression of fasting –induced adipose factor (FIAF) which will further supress the lipoprotein lipase (LPL) inhibitor. Hereby increase the activity of LPL will improve the uptake of fatty acids and triacylglycerol accumulation in adipocytes.	[136,137]
Metabolic endotoxemia	Low grade inflammation	High LPS level will form a complex (LPS- binding proteins & the CD14 co-receptor) which is recognized by Toll-like receptor 4, triggering an inflammatory response through Complex signaling pathway by the activation of NF-kB pathway and subsequently expression of proinflammatory cytokines. The activation of NF-kB pathway may also have impaired insulin signaling, which can lead to insulin resistance. LPS also creates a metabolic endotoxemia that cause damage to the mucosal integrity and increase intestinal permeability, also reducing the expression of epithelial tight junction proteins.	[137,138]
Gut permeability	GLP-2 dependent mechanism	Microbiota will help in increasing the production of endogenous GLP-2 and improved the gut barrier functions by a GLP-2 dependent mechanism and hence improves the gut barrier function.	[139,140]
Immune system	Toll-like receptor 5	Toll-like receptor 5 (TLR5) is a component that activated the innate immune system which help to fight against the infection, exhibit hyperphagia, hyperlipidemia, hypertension, increased adiposity and insulin resistance	[141,142]

level of *Lactobacillus* spp. in GM to control the T2DM. Table 5 shows that allicin, flavanols, alkaloids, betacyanins, protocatechuic acid, phlorizin, polyphenols increases the *Akkermansia* spp. in the GM. The antidiabetic action of *Akkermansia* spp. has been described by various researchers. It is a mucin degrading bacteria, helps in preserving the mucus layer thickness, thereby decreasing gut permeability and leakage of LPS [106]. It also improves insulin resistance by inhibiting JNKI and activating P13K signaling pathways [107]. Xie et al. (2018) [100] also noticed that *Akkermansia* spp. promotes the secretion of GLP-1 from the L-cells to suppress glucagon secretion.

Furthermore, a number of microflora in the GM are modulated by the particular bioactive compounds, which is presented in Table 5. The potential antidiabetic action of GM modulation by bioactive compounds is attributed to increases in the levels of *Bifidobacterium* spp. *Lactobacillus* spp. *Akkermansia* spp., as well as to the reduction in the *Firmicutes* to *Bacteroidetes* ratio. Hence, the particular bioactive compounds having the ability to modulate the gut ecosystem could be beneficial for use as preventive and therapy of T2DM.

The major predictor of human gut microbiota composition is diet. Scientific evidence supports the importance of diet and its composition in modulating gut microbiota. The long-term consumption of the western diet, the overuse of antimicrobials (antibiotics), and host factors including age, sedentary lifestyle, etc., cause gut dysbiosis which, subsequently causes increased levels of bacterial lipopolysaccharide, oxidative stress, the release of pro-inflammatory, gut inflammation, and permeability. All these changes over a period of time cause the development of insulin resistance and T2DM. On the other hand, bioactive compounds from the healthy diet positively influence the maintenance of gut eubiosis, which causes attenuation in the above-described pathological changes in the gut with concurrent improvement in insulin sensitivity and gut mobility, thus benefiting prevention and management of T2DM. In addition to these factors, the influence of specific micronutrients in the diet, frequency in consumption of western diet etc. on GM requires further investigations. Therefore, more studies are required to elucidate the complex interactions between bioactive compounds in the diet, GM, and on the onset and progression as well as prevention and management of T2DM.

5. Conclusion

T2DM is expanding as a most dangerous metabolic disorder after obesity, which invites various health-related risks. The global health organizations and disease control boards have declared the severity of T2DM and advised to take preventive and curative therapeutic measures to control this metabolic disorder. Several research studies conducted in past decades proved that T2DM is mainly caused by a combination of unhealthy dietary patterns and relative inactivity of insulin. The systemic investigations concerning diet-induced T2DM conclude on the importance of GM and its role to prevent T2DM. Various species of GM like *Firmicutes, Bacteroidetes, Lactobacillus*, and *Bifidobacterium* play a vital role to control T2DM. Several scientific evidence stated that lifestyle changes and dietary patterns might affect the healthy GM, which causes GM dysbiosis, responsible for the T2DM. Recently researchers have proved that diet-induced GM dysbiosis can be solved by incorporating dietary supplements such as polyphenols, prebiotics, and bioactive compounds. Several systematic studies have recently supported the antioxidative and antimicrobial effects of bioactive compounds on GM, ultimately increasing the ratio of healthy GM. Various in vitro and in vivo studies proved that GM's modulation by bioactive compounds helps prevent T2DM by improving glucose homeostasis, improving insulin sensitivity, and increasing the production of short-chain fatty acids. However, more studies are required to elucidate the intricate relationship between dietary factors including the role of specific micro and macronutrients, combination of bioactive compounds, mechanism of their action on GM, interactions among GM, the role of microbial metabolites, bioaccessibility, and bioavailability of bioactive compounds, the host factors, such as age, gender, stress, etc., and their impact on the onset as well as prevention and management of T2DM.

CRediT authorship contribution statement

Basista Rabina Sharma: Literature search, Writing – original draft. **Swarna Jaiswal**: Addition of literature, editing and language and grammatical corrections. **P.V. Ravindra**: Conceptualization, Supervision, Final draft preparation.

Data availability

Data will be made available on request.

Table 5
Modulation of GM by bioactive compounds for controlling the T2DM.

Bioactive compounds	Sources	Effect on GM	Anti-diabetic mechanisms	References
Anthocyanin	Strawberry	*Bifidobacterium* ↑, *Lactobacillus* ↑, *Verrucomicrobia* ↓,	• Improved lipid, glucose metabolism, insulin resistance, gut barrier function, • reduce low grade inflammation and stimulate the host immune system	[143]
	Blueberries, Cherries,	*Bifidobacterium* spp. ↑, *Lactobacillus- Enterococcus* spp. ↑	• Decreased blood glucose level • Increased the expression of adiponectin • Decreased Inflammatory adipokines • Improved gut barrier function	[102,144, 145]
Hesperdin and naringin	Citrus fruit	*Bifidobacterium* spp. ↑, *Lactobacillus* spp. ↑, *Enterobacteria* ↓	• Improved glucose homeostasis • Improved insulin sensitivity • Increase the production of SCFAs	[105]
Flavanoids	E. prolifera	*Bacteroidetes* ↑, *Firmicutes* ↓, *Lachnospiraceae* group and Alisties ↑,	• Decreased blood glucose levels • Improve glucose tolerance (by activating the P13K/Akt and inhibiting JNK in signaling pathway)	[101] [4,5]
1-Deoxynojirimycin (Alkanoids)	Mulberry Leaves	*Lactobacillus* ↑, *Lachnospiraceae* NK4A136 group↑, *Oscillibacter* ↑, *Alistipes* ↑, *Lachnospiraceae* ↑, *Bifidobacterium*↑, *Ruminococcaceae UCG-014*↓, *Weissella*↓, *Ruminococcus* ↓, *Prevotellaceae Ga6A1 group* ↓, *Anaerostipes* ↓, *Klebsiella* ↓, *Prevotellaceae UCG-001*↓ *and Bacteroidales S24–7 group*↓	• Decreased serum glucose and insulin levels • Improved serum lipid levels and reversed insulin resistance by upregulating the protein expression of insulin receptor glycolysis enzymes (GK, PK and PFK) and by down regulating the protein expression of insulin receptor substrate-1 and gluconeogenesis enzymes (PCB, PEPCK, FBPase and G-6-Pase).	[146]
Alkaloids, polyphenols	Mulberry leaves and Oat bran	*Firmicutes*: *Bacteroidetes*↑, *Bacteroidales* S-247 group ↓, *Escherichia Shigella* ↓, *Alistipes* ↑, *Ruminiclostridium*↑	• Improved glucose metabolism by regulating insulin receptor and GK expressions and by down regulating PCB, PEPCK, PDCK expression.	[147]
Berberine		*Bifidobacterium* spp. ↑	• Increased the extraction of energy and fat storage • Reduced the expression levels of TNF-α and LPS • Reduced endotoxemia and inflammation, Improved glucose tolerance and insulin secretion by promoting the synthesis and secretion of incretin and GLP-1.	[65,148]
Polyphenols	Cranberry	*Akkermansia* ↑	Mucin degrading bacteria: • Preserved the mucus layer thickness • Decreasing gut permeability &Leakage of LPS	[106]
	Enteromorpha prolifera	*Akkermansia*↑,*Alistipes and Turicinbacter*↓	• Improved insulin resistance by inhibiting JNKI and activating P13K signaling pathway	[107]
	Wild Blueberry	*Bifidobacterium* ↑, *Lactobacillus acidophilus* ↑, *Eubacteria* ↑	• Decreased blood glucose level • Increased the expression of adiponectin • Decreased Inflammatory adipokines • Improved gut barrier function	[102,149]
	Green tea, Oolong tea, black tea	*Bifidobacterium* spp. ↑, *Lactobacillus- Enterococcus* spp. ↑, *Bacteroides* ↓, *Clostridium Histolyticum* ↓	• Increase the production of SCFAs • Inhibit pathogenies species • Improved glucose tolerance and insulin secretion • normalized inflammatory tone.	[104,150, 151]
	Red wine	*Bifidobacterium* spp. ↑, *Lactobacillus* spp. ↑,	• Improved glucose tolerance and insulin secretion • Normalized inflammatory tone • Increase the production of SCFAs, • Inhibit the adhesion of pathogen.	[104,152]
Allicin	Garlic	p_*Firmicutes*: p_*Bacteroidetes* ↓, f-*Lachnospiraceae* ↑, g-*Akkermansia* ↑, g-*Lactobacillus* ↑, *Lachnospiraceae* ↑, *Ruminococcaceae* ↑	• Maintains glucose homeostasis, • Improves insulin sensitivity, • Regulate glucose metabolism	[95–98]
Berberine	European barberry, goldenseal, goldthread, Oregon grape, and tree turmeric	*Blautia* ↑, *Allobaculum* ↑, *Streptococcus* ↓, *Prevotella* ↓	• Improves insulin secretion by producing SCFA such as acetate and propionate	[78, 153–155]
β-glucan	Oats, Barley, Mushroom	*g-Bifidobacterium*↑, *g-Blautia* ↑, *p-Actinobacteria* ↑	• Increase the production of SCFAs such as acetate, propionate which influence the L-cells to release the peptide GLP-1 and PYY • Stimulate insulin secretion	[17,78,156, 157]
Flavonols	Green tea leaves, Red wine, Cocoa, Cranberry	*Lactobacillus* ↑, *Bifidobacterium* ↑, *p-Bacteroidetes* ↑, *Akkermansia* ↑	• Increase glucose tolerance • Increase insulin secretion	[106,158, 159]
Baicalein	Tuber aestivum. Oroxylum indicum, Scutellaria baicalensis, Scutellaria lateriflora	*Bacteroidales* ↑, *Bacteroides* ↑, *Prevotellaceae* ↑ *Alloprevotella* ↑, *Butyricimonas* ↑, *Arabacteroide* ↑,	• Increase the production of SCFAs • Improved insulin resistance, lipid metabolism, • Decreased blood glucose, • Decreased circulating LPS and systemic inflammation	[160,161]
Catechin	Rhododendron groenlandicum	*Clostridium perfringens* ↓, *Clostridium difficile* ↓, *Lactobacillus-Enterococcus* spp. ↑ *Bifidobacterium* spp. ↑	• Reduced intestinal endotoxin levels • Improve mucosal barrier function • Lower serum glucose • Increase expression of insulin signaling proteins • Improved adipokine	[65,102, 150,162, 163]

(*continued on next page*)

Table 5 (*continued*)

Bioactive compounds	Sources	Effect on GM	Anti-diabetic mechanisms	References
Alkaloids	Rhizomz Coptidis	*Sporobacter termitidis* ↑, *Alcaligenes faecalis* ↑, *Akkermansia muciniphila* ↑, *E. coli* ↓, *Desulfovibrio* C21_c20 ↓, *Parabacteroides* ↓	Improved: • Insulin sensitivity • Glucose homeostasis • Blood lipids	[164]
Gallic acid, ellagic acid	Pomegranate by-product	*Bifidobacterium* spp. ↑, *Lactobacillus* spp. ↑, *Clostridium coccoides* ↓: *Eubacterium rectale* group and *C. Histolyticum* group	• Increase the production of SCFAs • Inhibit pathogenic species • Increased the activity of α-glucosidase • Improved glucose tolerance • Improved insulin secretion.	[104,165]
Ellagitannins	Pomegranate	*Bifidobacterium* spp. ↑, *Lactobacillus* spp. ↑, *B. fragilis* ↓, *Clostridia* ↓, *Enterobacteriaceae* ↓	• Inhibits LPS induced inflammation • Improved glucose tolerance & insulin secretion, • Normalized inflammatory tone • Increase the production of SCFAs • Inhibit the adhesion of pathogen.	[166–168]
Betacyanins	Red pitaya	*Akkermansia* ↑, *Firmicutes/ Bacteroidetes* ↓	• Improved Hepatic steatosis • Improved insulin resistance • stimulates the secretion of glucagon like peptide from the L-cells that suppress glucagen secretion	[127,169]
Saponin	Polygonatum kingianum	*Firmicutes* ↑, *Bacteroidetes* ↓, *Proteobacteria* ↓	• Decreased blood glucose and LPS, • Improved glucose metabolism • Increase the production of SCFAs	[99]
Protocatechuic acid	Alpinia oxyphylla	*Bacteroidetes* to *Firmicutes* ↑, *Akkermansia* ↑, *Helocobacter* ↓	• Elevated GLP-1 secretion & serum insulin • Improved insulin resistance &renal function • decreased blood glucose level	[100]
Triterpenoid	Potentilla discolour Bunge	*Firmicutes / Bacteroidetes* ↓, *Proteobacteria*↑	• Improves Insulin resistance, • Protect pancreatic β-cells • decreased LPS, • decreased pro-inflammatory cytokines, Reduced expression of TLR4. • Increased expression of GPR41& GPR43	[170,175]
Phlorizin	Apple, Strawberr, pomegranate	*Akkermansia muciniphila* ↑, *Prevotella* ↑	Prevent metabolic syndrome, Decreased: • weight gain • energy intake • serum LPS • insulin resistance	[171]
Lycopene	Tomato, Morringa oleifera	*Proteobacteria* ↓, *Bifidobacterium* ↑, *Lactobacillus* ↑	Improved: • LPS-induced insulin resistance Mitochondrial dysfunction, • Hepatic inflammation, • Gut barrier function	[172–174, 176]

↑ shows increase in GM, ↓ shows decrease in GM.

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Conflict of interest statement

We declare no competing interests.

Data availability

Data supporting this systematic review are from previously reported studies and datasets, which have been cited at appropriate places in the text.

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