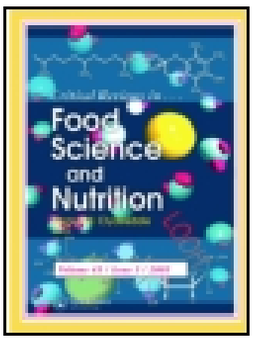

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REVIEW

A critical review of the relationship between dietary components, the gut microbe *Akkermansia muciniphila*, and human health

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ABSTRACT

The human gut contains trillions of microorganisms with a great diversity that are associated with various health benefits. Recent studies have reported an increasing correlation between diet, gut microbiota, and human health, indicating rapid development in the field of gut health. Diet is an important factor that determines the gut microbiota composition. The gut comprises great diversities of microbes involved in immune modulation and other functions. In particular, *Akkermansia muciniphila* is a mucin-degrading bacterium is believed to have several health benefits in humans. Several studies have evaluated the prebiotic effects of various dietary components on *A. muciniphila* and their association with various ailments, such as diabetes mellitus, atherosclerosis, and cancer. Hence, this review aims to provide a plausible mechanistic basis for the interactions between dietary components, and *A. muciniphila* and for the therapeutic benefits of this interaction on various illnesses.

KEYWORDS

Prebiotics; gut microbiota; *Akkermansia muciniphila*; diabetes; cancer

Introduction

Beneficial dietary and lifestyle changes can prevent and control notable disorders (Hou et al. 2017), such as type 2 diabetes mellitus (T2DM) (90%), coronary heart disease (CHD) (80%), colorectal cancer (CRC), and stroke (70%) (Everitt et al. 2006). The increase in the prevalence of chronic diseases such as cardiovascular diseases (CVD), T2DM, and respiratory diseases, is associated with the westernization of global foods and unhealthy lifestyle habits. Adapting a healthy diet can be an aid in treating various diseases. For example, adaptation to the Mediterranean diet has significant protective effects over CVD, stroke, cancer, T2DM, hypertension, Parkinson's and Alzheimer's diseases (Sofi et al. 2008). By providing important nutrients to the body, diet improves the state of health and reduces the risk of disease recurrence. The consumed food is primarily digested in the stomach, whereas the undigested diet is digested in the colon with the help of gut microbiota. The composition of the gut microbial community is greatly influenced by the type of diet (Alou et al. 2016). Importantly, the gut microbiota produces potent metabolites from the diet (Li et al. 2018). These metabolites possess a strong immune potential to combat various diseases, such as cancer and diabetes. The health status, genetics, and mode of delivery at birth are the various factors that can influence the population of microbiota, but diet remains the most decisive factor that constantly influences the gut microbiota from infancy to old age (Rodríguez et al. 2015). Notably, some bacterial species supplemented with diet can alter the gut microbiota composition; e.g. in one study, a 10-g/kg dietary supplementation of *Clostridium butyricum* altered the microbiota composition by significantly decreasing the population of *Clostridiales* and increasing that of *Selenomonadales*. This, in turn, increased the acetate production required for butyrate production (Zhang et al. 2018).

The major phyla of gut microbiota are Firmicutes and Bacteroidetes, followed by Actinobacteria and Verrucomicrobia (Jandhyala et al. 2015). *Akkermansia* is an important genus of the Verrucomicrobia phylum. *A. muciniphila* is a mucin-degrading, gram-negative, oval-shaped, non-motile, and strictly anaerobic bacteria (Derrien et al. 2004) found in the small intestinal epithelial crypts and mucus layer (Reunanen et al. 2015). Its proportion among the total gut microbiota is 3–5% and its population reduces in certain medical conditions, such as obesity (Karlsson et al. 2012; Dao et al. 2016).

Several studies have shown that *A. muciniphila* supplementation can be used to treat inflammatory bowel disease (IBD) or appendicitis (van Passel et al. 2011). Changes in the population of *A. muciniphila* occur in certain diseases; e.g. a recent study reported that *A. muciniphila* population decreases in patients with severe appendicitis. Another study showed reduced *A. muciniphila* population in the intestinal tract of IBD patients (van Passel et al. 2011). In addition to exerting beneficial effects on inflammation, *A. muciniphila* can reduce the burden of hyperlipidemia or obesity. In a recent study, mice fed with a high-fat diet (HFD) followed by *A. muciniphila* supplementation

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reported that *A. muciniphila* reduced the fat burden of the mice (Zhao et al. 2017). Another study showed that *A. muciniphila* abundance, insulin sensitivity, and metabolic status are interlinked (Roopchand et al. 2015). A high abundance of *A. muciniphila* in the gut microbiota was seen in healthy adults.

The field of gut microbiota research has garnered much interest because of its importance in human health, nutrition, and well-being. Our previous review on gut microbiota focused on beta-glucan and its action over different pathological conditions via the regulation of gut microbiota (Jayachandran et al. 2018). Our another study focused on the potential of edible mushrooms to regulate gut microbiota and modulate various diseases mechanisms (Jayachandran et al. 2017). Hence, in this review, we have particularly focused on the beneficial bacterial species *A. muciniphila* and its association with various dietary components involved in the regulation of the various diseases. Overall, we have reviewed several studies and discussed the efficacy of various dietary components, their ability to modulate the *A. muciniphila* abundance and the therapeutic effects of their interaction.

Human host and its beneficial partner-gut microbiota

The gut microbial community in humans plays a key role in the metabolism of the host and has received much attention for its potential in treating various diseases (Shreiner et al. 2015). The number of bacterial cells in the gastrointestinal tract (GIT) is considered higher than the total number of the host cells. The gut microbes contain various beneficial genes, and the total number of bacterial genes also outnumber the total number of host genes by 100 times (Bull and Plummer 2014). The studies on the human gut microbiome and its impact on human health and various diseases are based on the following functions: nutrition, host metabolism, physiology, and immune response. Among the gut microbiota, the population of anaerobe microbes outnumbers that of the facultative anaerobes and, in particular, aerobic microbes by 100 fold (Jost et al. 2012). To date, approximately 50 bacterial phyla have been detected in the gut, with Bacteroidetes and Firmicutes being the major phyla. It is considered that the gut contains approximately 1000 microbial, species-level phylotypes (Bhagawati et al. 2018).

Microbial colonization of the human gut initiates at birth (Nagpal and Yamashiro 2018). Wide interindividual variations with a simple microbial composition are observed during the first year of life. The initial stage of the gut colonization plays an important role in shaping the gut microbiota composition in adult life. (Dreyer and Liebl 2018). The microbiota composition varies along the GIT through the stomach and duodenal contents (10–103 bacteria/g), small intestine contents (104–107 bacteria/g), and large intestine (1011–1012 bacteria/g) that show the highest abundance. The gut microbiota plays key roles in immune support, host metabolism, and regulation of the gut-brain axis (Mayer et al. 2015). In some cases, the gut microbiota can perform metabolic functions that cannot be performed by the human host because the gut microbiota possesses 100 times higher number of genes than the host, which could code for various enzymes. Other important functions of the gut microbiota include synthesis of some vitamins, amino acids and bile biotransformation (Rowland et al. 2018). The gut microbiota is also involved in the digestion of various nondigestible dietary components, such as resistant starch, large polysaccharides, cellulose, pectin, hemicellulose, alcohols, and sugars (Flint et al. 2012).

The epithelial layer of the intestine forms a clear boundary between the external environment and the host immune system (Moens and Veldhoen 2012). The host immune system is regulated by continuous interaction between the intestinal microbiota and dietary metabolites. The gut mucosal immune system plays an important role in the prevention of various diseases and is tightly regulated by the presence of numerous health-promoting beneficial bacteria in the intestinal epithelium. The gut microbes also play an important role in controlling signals to the brain (hormonal, neural, and immunological signaling), referred to as the gut-brain axis (Carabotti et al. 2015). Studies have reported that the concentrations of most bacterial metabolites are directly proportional to the concentration of dietary proteins. One study have tested three doses (18%, 15%, and 12%) of crude dietary proteins showed that the abundances of Clostridiaceae_1, *Ruminococcaceae*, *Spirochaetaceae*, *Christensenellaceae*, and *Bacterodales_S24-7* decreased and those of some other species increased. Overall, the study indicated that dietary proteins play a significant role in altering the bacterial community (Chen et al. 2018). A recent study reported that dietary amino acids are also utilized by the gut microbiota. Some bacterial species can produce its own amino acids, and there exists a bidirectional exchange of amino acids between the host and gut microbiota. Hence, the availability or unavailability of certain amino acids can affect the abundance of those amino acid-synthesizing bacteria. The presence or absence of those bacterial species can alter various signaling pathways and mainly regulates the mucosal immunity and intestinal homeostasis. Amino acid metabolism plays a key role in the survival, and proliferation of the gut microbes and competition between them (Ma and Ma 2019). One study revealed that stress also affects the gut microbiota composition (Foster and McVey Neufeld 2013). Stress alters the integrity of the gut epithelium as well as peristalsis, mucin production, and secretions, which in turn alters the population and function of the bacterial community.

Is *A. muciniphila* a rescuer?

The *A. muciniphila* population is inversely correlated with various disease conditions (Cani and De Vos 2017). *A. muciniphila* uses mucin as the source of carbon, nitrogen, and energy required for growth. It was first isolated from the fecal sample using mucin. It inhabits the surface of the intestinal epithelium coated with mucin for protection and

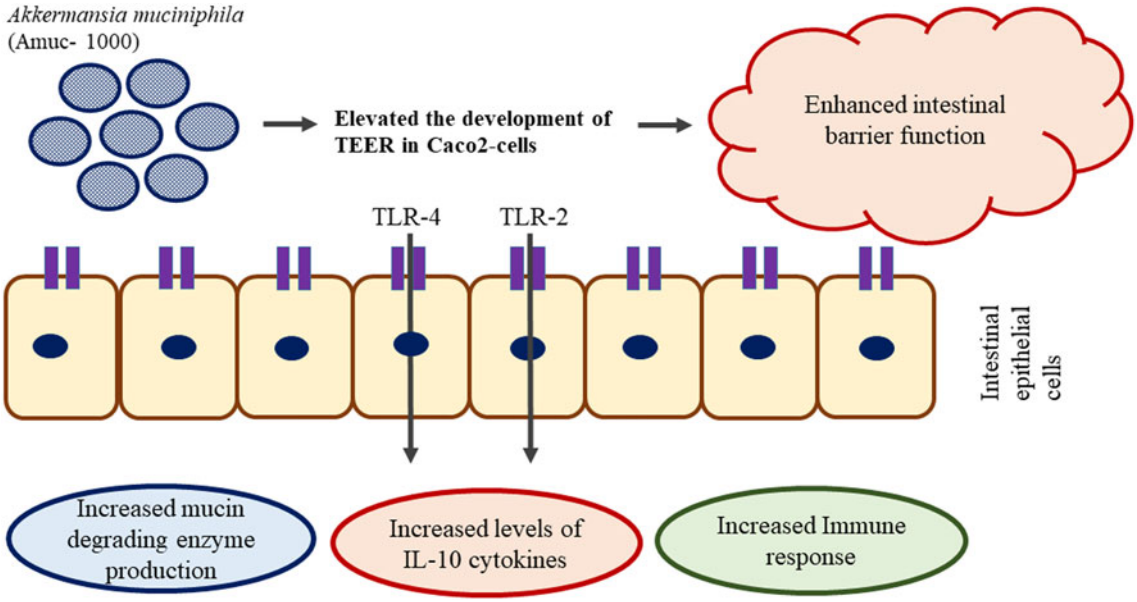

Figure 1. The mechanism underlying improvement in intestinal barrier functions and immune response stimulation by *A. muciniphila*.

maintenance of gut barrier functions and immune response (Ottman et al. 2017) (Figure 1). It accounts for approximately 3% of the total microbial population in the colon of a healthy human (Png et al. 2010; De Vos 2017). *A. muciniphila* can produce enzymes required for mucin digestion; hence, its key function is to degrade the mucin present in its surrounding (Collado et al. 2007; Tailford et al. 2015; Desai et al. 2016; Ganesan et al. 2018). *A. muciniphila* also plays the role of a rescuer in various disease states. In the following sections, we discuss the involvement of *A. muciniphila* and various diets in the prevention of several ailments.

Combined actions of diet and *A. muciniphila* on various disease conditions

Diet plays a significant role in the alterations of gut microbiota diversity. It can increase or decrease some to several species. Various studies have reported evidence showing that the diet influences gut microbiota composition. One such study evaluated the effects of dietary fiber gap on human gut microbiota. Fiber gap is generally referred to as the low-fiber diet. The consumption of a low-fiber diet can reduce gut microbiota and its beneficial metabolites, such as short-chain fatty acids (SCFAs). SCFAs play a significant role in mucosal immunity and metabolism and prevent inflammation (Han et al. 2017). Several diets can increase the abundance of beneficial bacterial species *A. muciniphila*. The presence of the adequate *A. muciniphila* ensures the protection of the intestinal epithelium as well as protections against several disease conditions. Several pathological conditions are associated with the increase or decrease in *A. muciniphila population*, such as IBD, DM, obesity, atherosclerosis and some types of cancer (Schneeberger et al. 2015; De la Cuesta-Zuluaga et al. 2018). Using shotgun metagenomics sequencing and high-throughput 16S rRNA gene sequencing a recent study showed that black raspberry rich diet modulated the gut microbiota in C57BL/6J mice. It was found to increase the *A. muciniphila* population and regulate various functions of the gut microbiome, such as oxidative stress, vitamin synthesis, carbohydrate, and aromatic amino acid metabolism (Tu et al. 2018). Notably, the interaction between the diet and *A. muciniphila* enhanced amino acid synthesis and vitamin synthesis and upregulated the expression of genes encoding for antioxidative enzymes. It is widely accepted that oxidative stress is an important factor for various disease conditions. Black raspberry also increases programed cell death, which is crucial for inhibiting carcinogenesis. We have discussed the role of diet and microbiota in producing various metabolites and affecting pathological conditions. In the following section, we elaborately discuss the impacts of various diets and their components on *A. muciniphila* and its health benefits (Table 1).

Diet, A. muciniphila, and DM

Hyperglycemia is the general characteristics of DM and it occurs due to deficient insulin secretion from the pancreatic beta-cells or inefficient utilization of the available insulin (American Diabetes Association 2009). T2DM, the most common type of DM is a chronic metabolic disorder with a globally increasing prevalence. With the increase in population and aging, the number of T2DM cases has increased from 108 million (1980) to 422 million (2014) (WHO 2016). It has been projected that DM will be the seventh leading cause of death in 2030. Several treatment methods are available for T2DM including the synthetic antidiabetic drugs such as thiazolidinediones, sulfonylureas, biguanides, and glucosidase inhibitors (Chaudhury et al. 2017). Although the availability of various synthetic drugs reduces the burden of the disease, they have adverse effects. Hence, the use of herbal medicines and diet-derived phytochemicals for treating DM is recommended. Diets rich in active phytochemicals with various health-promoting properties play a significant role in diabetes management (Craig 1999; Slavin

Table 1. Effects of different diet on human health via regulating the gut microorganism *A. muciniphila*.

Diet sources	Animal model and disease condition	Beneficial changes achieved	Action on *A. muciniphila*	References
Concord grape polyphenols	C57BL/6J mice; obesity/ diabetes mellitus	Reduced weight gain, reduced adiposity, attenuation of inflammation, regulation of iNOS and GluT2. Regulates triglyceride storage and gut barrier functions	Increased abundance of *A. muciniphila* with a decrease in Firmicutes and Bacteroidetes	Roopchand et al. 2015
Cranberry extract	C57BL/6J mice; T2DM	Weight control, reduced visceral fat, liver weight regulation, oxidative stress and inflammation suppression with increased insulin sensitivity	*A. muciniphila* population has been raised	Anhe et al. 2015
Table grapes	C57BL/6J mice; obesity	The mRNA expression of peroxisome proliferator-activated receptor gamma 2, fatty-acid-binding protein 4, sterol-CoA desaturase 1, and Gpat1 was lowered	The increased *A. muciniphila* along with the decreased levels of Bilophila wadsworthia-specific dissimilatory sulfite reductase gene (dsrA-Bw), and sulfidogenic *Desulfobacter* spp.	Baldwin et al. 2016
Dietary flavonols/ procyanidins	C57BL/6J mice; obesity/ metabolic syndrome	Reduced weight gain, reduced inflammation, and improved gut permeability	Increased abundance of *A. muciniphila* with a decrease in Firmicutes and Bacteroidetes	Masumoto et al. 2016
Berberine	$Apoe^{-/-}$ mice; atherosclerosis	Reduced metabolic endotoxemia, inflammation, atherosclerotic lesions, and increased expression of tight junction proteins	Increased prevalence of *A. muciniphila* and increased gut barrier functions	Zhu et al. 2018
Walnuts	Mice; cancer	Lower dosage has shown higher inhibitory effects on carcinogen induced cancer	Walnut consumption reshape the microbial community and the increased the abundance of *A. muciniphila*	Nakanishi et al. 2016

and Lloyd 2012; Leitzmann 2016). Several studies have elucidated the mechanisms underlying the effects of different phytochemicals on diabetes. Recent studies have focused on the role of the gut microbiota in digestion and synthesis of crucial metabolites from diets.

A recent study on dietary polyphenols has shown that they can promote the growth of *A. muciniphila* in the gut and consequently attenuate the HFD-induced metabolic syndrome in mice (Roopchand et al. 2015). In that study, 1% Concord grape polyphenols (GPs) along with an HFD were provided to C57BL/6J mice. Mice fed with HFD alone showed increased body weight and adiposity in addition to increased levels of inflammatory cytokines and persistent insulin resistance. The oral supplementation of GPs to the HFD-fed mice considerably diminished the effects of HFD prevented weight gain, and reduced adiposity. Serum levels of various inflammatory markers, such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) were reduced, and the regulation of glucose metabolism was improved. GPs also positively regulated the expression of various intestinal markers, such as TNF-α, IL-6, inducible nitric oxide synthase, glucose transporter 2. GPs also regulated the expression of genes involved in the intestinal barrier function and regulated triglyceride storage. GP supplementation also increased the levels of proglucagon, the precursor protein involved in insulin production and gut barrier integrity. This further characterized the role of *A. muciniphila* in disease management and evaluated the changes in its population. The fecal samples of the different groups of mice were analyzed for the presence of *A. muciniphila*. Interestingly, the fecal samples of GP-fed mice showed an increased *A. muciniphila* population with a decreased Firmicutes to Bacteroidetes ratio. Overall, the findings suggest that GPs can alter the gut microbial community, reduce intestinal inflammation and regulate glucose intolerance (Figure 2). They also suggest that the alterations in gut microbiota community, in particular, the increase in *A. muciniphila* maybe in part responsible for changes in the intestinal gene expression that helped maintain the intestinal epithelial integrity, and reduce inflammation. This further reduced fat deposition, increased glucose absorption, and regulated insulin secretion. Because grapes are consumed worldwide for its several health benefits (Imran et al. 2017), this study supports the health benefits of grapes, especially in terms of GPs and their role in enhancing *A. muciniphila* population.

Another similar study used C57BL/6J mice to investigate how gut microbiota alters the pathophysiology of diet-induced T2DM. The mice were given a chow or high-fat/ high-sugar (HFHS) diet, in addition to cranberry extract (CE) to alleviate T2DM. A 200-mg/kg body weight of CE was orally supplemented to mice for 8 weeks. Phenolic acids, flavanols, anthocyanins, and proanthocyanins are the major polyphenol contents of the CE extract. It is widely accepted that polyphenols can efficiently attenuate the pathological condition associated with DM. Consistent with this finding, this study revealed that the CE reduced the HFHS diet-induced weight gain, visceral obesity, liver weight, triglyceride accumulation, and oxidative stress, and inhibited inflammation. Insulin resistance is a hallmark of T2DM, and the CE was found to improve the insulin sensitivity of cells. The intestinal triglyceride levels also reduced, in addition to reduced intestinal oxidative stress and NF-κB activation. The metagenomic results established the role of the association between the CE and *Akkermansia* in combating

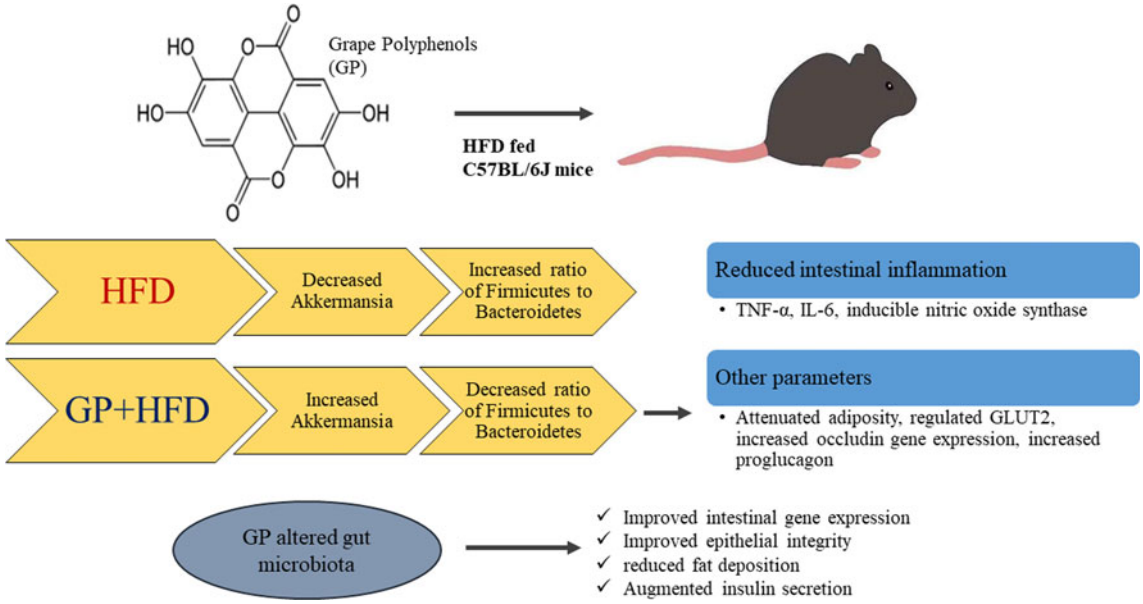

Figure 2. Effects of dietary polyphenols on *A. muciniphila* population and other changes in HFD fed C57BL/6J mice.

T2DM. The results suggest that the *Akkermansia* population increased due to the supplementation of CE, which thus shows potential to be used for treating T2DM. The increased abundance of the *A. muciniphila* population upon CE supplementation reduced lipopolysaccharide levels and effectively prevented intestinal inflammation. This increase in the Akkermansia population might be adequate to preclude the negative metabolic phenotype associated with obesity-driven dysbiosis. Overall, this study revealed that CE is effective in reducing diet-mediated obesity, liver steatosis, and insulin resistance in obese mice, which suggests that fruit polyphenols, due to their prebiotic effects, may prevent obesity and T2DM in association with gut microbiota (*A. muciniphila*) (Anhe et al. 2015).

Diet, A. muciniphila, and obesity

Grapes intended for intake while fresh are referred to as table grapes. One study on mice fed a high-fat butter-rich diet showed that the consumption of table grapes can inhibit adiposity and its related conditions by altering the gut microbiota population. In brief, C57BL/6J mice were fed an HFD in addition to 3% and 5% grapes for 11 weeks. The results revealed significantly reduced total body and inguinal fat in both 3% and 5% grape-fed groups. The 5% grape-fed HFD group exhibited lower liver weight, triglyceride levels, and glycerol-3-phosphate acyltransferase (Gpat1) expression compared with the 5% control groups. The mRNA levels of peroxisome proliferator-activated receptor gamma 2, fatty-acid-binding protein 4, sterol-CoA desaturase 1, and Gpat1 were lower in the livers of 3% grape-fed HFD group than in the 3% control group. However, grape feeding did not significantly affect the levels of inflammatory and lipogenesis markers. The 3% grape diet reduced the populations of dissimilatory sulfite reductase gene containing *Bilophila wadsworthia*, and sulfidogenic *Desulfobacter* spp. and increased that of *A. muciniphila* (Baldwin et al. 2016). The results also showed that Bifidobacterium, Lactobacillus, and Allobaculum populations are negatively correlated with adiposity. In particular, comparison *A. muciniphila* population is negatively correlated with HFD. This finding indicates that the abundance of *A. muciniphila* plays a role in the prebiotic-mediated reduction in obesity.

Shen et al. (2017) proved that the anti-obesity effects of capsaicin are related to the changes in the gut microbiota community. During their experimental period of 9 weeks, the mice were fed either with an HFD or HFD with capsaicin. The results revealed that the capsaicin plus HFD reduced weight gain and improved glucose tolerance. It also increased the abundance of *A. muciniphila* population, whereas decreases that of the Proteobacteria members. Capsaicin also elevated the mucin 2 gene expression. Overall, these results indicate that capsaicin is beneficial in alleviating the HFD-induced obesity by altering the gut microbiota community (Shen et al. 2017).

Another study showed that dietary flavanols/procyanidins are associated with a reduced risk of developing obesity and metabolic syndrome. Fruits, especially apples, provide major sources of polyphenols and particularly procyanidins (Boyer and Liu 2004). In this study, C57BL/6J mice fed with a high-fat/high-sucrose diet showed that 0.5% polyphenol administration for 20 weeks improved obesity and regulated lipid metabolism by controlling the expression of related genes. The polyphenol treatment diminished weight gain, reduced inflammation, and improved gut permeability. In addition, metabolic urine profiling performed using high-performance liquid chromatography–quadrupole time-of-flight/mass spectrometry demonstrated that polyphenol treatment decreased the levels of endogenous metabolites associated with insulin resistance. Polyphenol administration also noticeably diminished the Firmicutes/Bacteroidetes ratio and increased the abundance of *Akkermansia* by eight times, as observed by microbial 16S rRNA gene sequencing of the cecum. Taken together, the results of these studies indicate

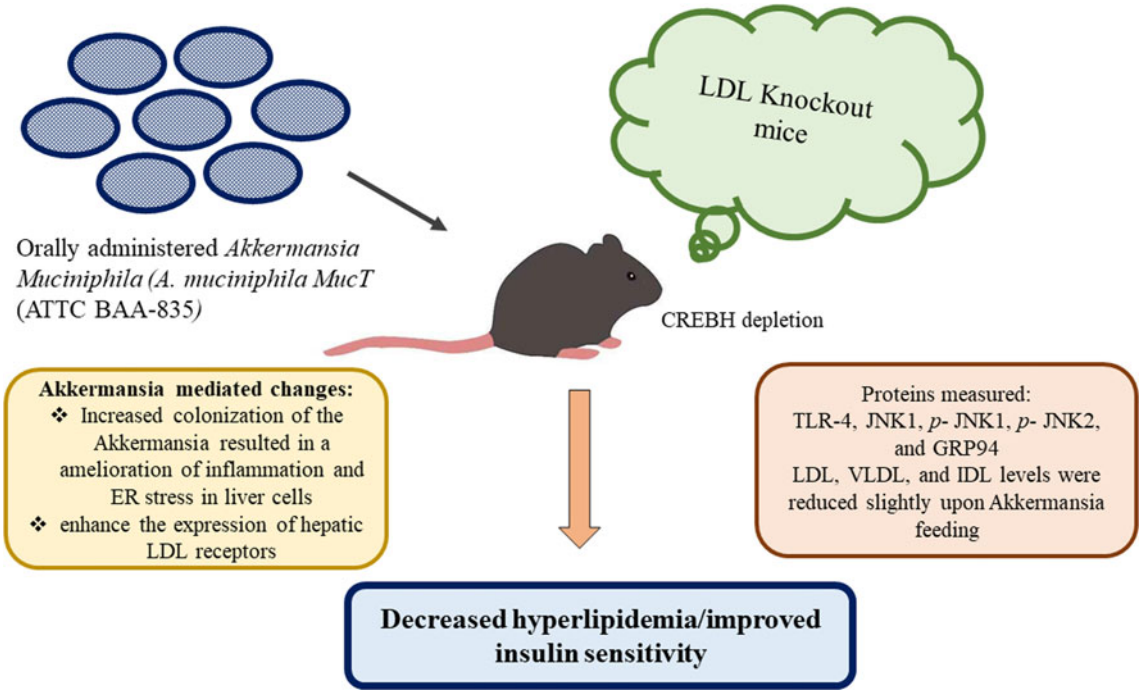

Figure 3. The mechanism underlying the reduction in triglyceride levels by a combination of *A. muciniphila* in genetically induced hyperlipidemia.

that the *A. muciniphila* population is considerably affected by diet and exerts beneficial effects on DM and obesity. The increase in the *Akkermansia* population by polyphenols resulted in increased gut barrier functions and improved intestinal permeability of lipopolysaccharides. Thus the gut microbiota is directly or indirectly involved in the prevention of obesity in HFD-fed mice. Further studies on the role of *A. muciniphila* and its metabolites could promote the development of diet based diabetes management therapies targeting gut microbiota (Masumoto et al. 2016). Notably, oral supplementation of *A. muciniphila* in experimental mice was also found to induce changes such as alleviation of ER stress and inflammation (decreased hyperlipidemia) (Figure 3) (Zhao et al. 2017), and pasteurized *A. muciniphila* supplementation to Wistar rats inhibited T2DM (Figure 4) (Plovier et al. 2017).

A recent study on gut microbiota associated changes upon feeding of prebiotics to obese diabetic mice showed interesting results. The study used two animal models: genetically (ob/ob) obese and HFD-fed diabetic obese mice. The animals were treated with prebiotics and normal diet. Pyrosequencing of the 16S rRNA, phylogenetic microarrays, and quantitative PCR assays for the ob/ob mice that received prebiotic feeding showed reduced Firmicutes population and augmented Bacteroidetes population. The prebiotic feeding also improved various other parameters, e.g. its increased L-cell number, plasma glucagon-like peptide-1 levels, and intestinal proglucagon mRNA expression, and improved glucose tolerance. Prebiotic treatment also reduced low-grade inflammation, oxidative stress parameters, and fat-mass development. The obese mice showed increased Verrucomicrobia population. In particular, *A. muciniphila* is acknowledged as the major species of Verrucomicrobia family. The results indicate that prebiotic mediated alteration in gut microbiota modulation restores blood glucose maintenance, and increases leptin sensitivity in obese and diabetic mice (Everard et al. 2011).

Diet, A. muciniphila, and atherosclerosis

Atherosclerosis is a disorder in which the arteries are blocked due to plaque build-up caused by high cholesterol (Tomkin and Owens 2012). The atherosclerotic process involves the accumulation of lipid, oxidation of low-density lipoprotein, and modification of macrophages loaded with cholesterol into foam cells, which further induce chronic inflammation in the blood vessels and surrounding tissues, results in thrombosis (Rafieian-Kopaei et al. 2014). Several studies on diets with atheroprotective properties have recently been conducted. A diet devoid of fat, cholesterol, and sugars is the prerequisite for managing atherosclerosis. Berberine is a plant alkaloid with several medicinal activities and used in Chinese medicine (Neag et al. 2018). Various plant sources are rich in berberine, such as goldenseal, coptis or golden thread, Oregon grape, barberry, and tree turmeric (Chander et al. 2017). A recent study on berberine showed that it could increase the abundance of *Akkermansia* in the gut and mitigate HFD-induced atherosclerosis in $ApoE^{-/-}$ mice. The mice were given either a normal chow diet or HFD in addition to berberine administered with drinking water at a dose of 0.5 g/L for 14 weeks. The total microbiome community was estimated by a 16S rRNA sequencing. Mice fed with berberine showed an efficient reduction of atherosclerotic lesions induced by HFD and an increased abundance of *Akkermansia* spp. HFD induces metabolic endotoxemia, and inflammation and berberine supplementation in these mice decreased endotoxemia and the expression of various pro-inflammatory cytokines.

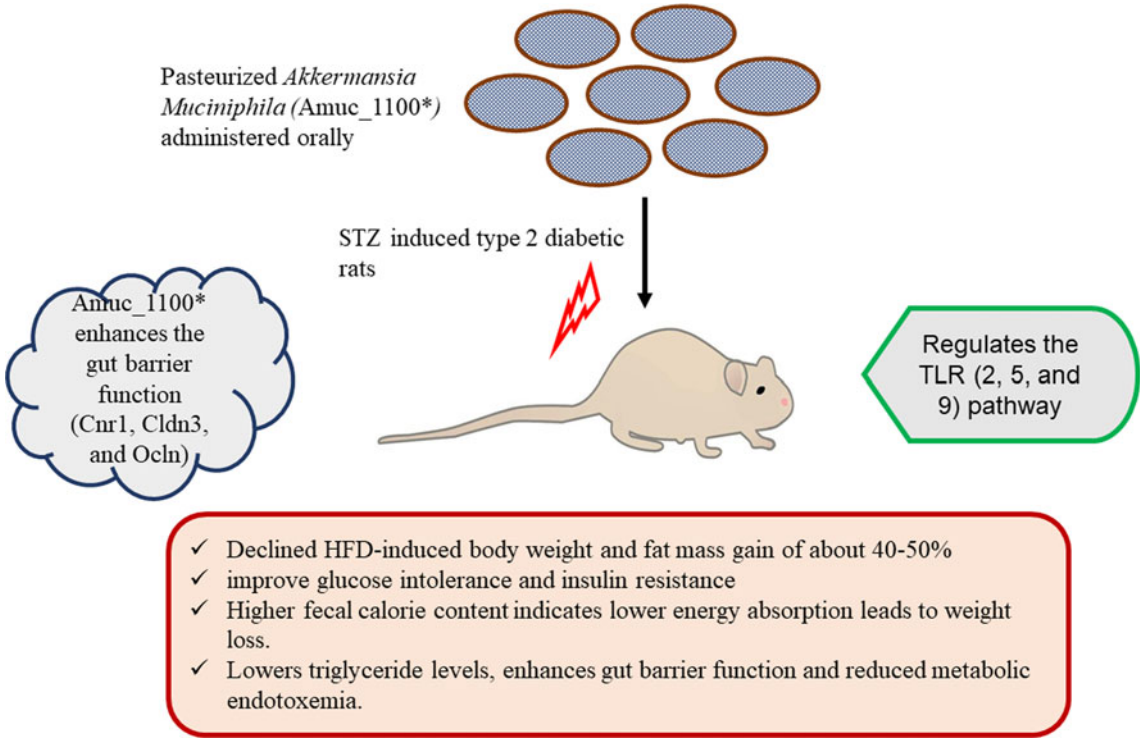

Figure 4. The action of orally administered *A. muciniphila* on rats with streptozotocin-induced diabetes.

In contrast, the expression of tight junction proteins and the thickness of the mucus layer increased upon berberine treatment, indicating improved gut barrier functions in HFD-fed mice. Thus, the study demonstrated that berberine mediated changes in the gut microbiota population, especially in terms of increasing the *Akkermansia* population (Zhu et al. 2018). This proves that gut microbiota plays an important role in the anti-atherosclerotic effects of berberine. In-Depth sequencing analysis of the gut bacteria involved may provide some interesting results.

Another similar study examined the antiatherosclerotic effects of resveratrol on gut microbial abundance. Resveratrol was found to reduce the trimethylamine-N-oxide (TMAO)-mediated atherosclerosis in ApoE-/- mice. Results also suggested that resveratrol decreased the TMAO via changes in the gut microbiota population. Resveratrol enhances bile acid (BA) deconjugation and fecal excretion by increasing the Lactobacillus and Bifidobacterium population. TMAO inhibits the liver BA synthesis, thus promoting atherosclerosis. Overall, the results of this study indicate that resveratrol prevents TMAO-mediated atherosclerosis by reducing the TMAO levels and increasing BA secretion (Chen et al. 2016).

Diet, A. muciniphila and cancer

Similar to DM, cancer remains one of the most dreaded diseases for several decades and the leading cause of mortality worldwide (Ma and Yu 2006). In recent years, several foods and food constituents have been studied for their inhibitory effects on carcinogenesis. Foods such as grape, turmeric, garlic, blueberry, raspberry, green tea, cabbage, broccoli, and mushrooms have been shown to exhibit strong anticancer activity (Béliveau and Gingras 2007). Several studies have found that phytochemicals derived from various dietary sources inhibit cancer either directly by acting on tumor cells or indirectly by creating a condition that does not support cancer growth.

Some enzymes can neutralize carcinogen by reducing their potential or by promoting its excretion. The action of chemopreventive phytochemicals mainly targets this enzyme system. Some types of phytochemicals inhibit tumor growth by inducing apoptosis (programed cell death) (Kumi-Diaka et al. 2004; Kumar et al. 2016). To provide oxygen and nutrients to the newly formed tumor cells, tumor cells initiate the formation of new blood vessels- a process referred to as angiogenesis (Nishida et al. 2006; Rajabi and Mousa 2017). The phytochemicals that possess antiangiogenic properties can act as better chemopreventive agents (Jeong et al. 2011; Kadioglu et al. 2013). Colorectal, breast, and lung cancers are the predominant types of cancers, all of which are characterized by inflammation (Coussens and Werb 2002). Several inflammatory conditions can predispose patients to develop cancer, which explains the significant association between inflammation and carcinogenesis.

Some studies have assessed microbial abundance in different types of cancers. One such notable cancer is colorectal carcinoma (CRC), one of the most commonly diagnosed malignancies. Many factors can cause CRC, such as a diet rich in processed meat and chronic inflammation of the GIT. Recent studies have shown that changes in the gut microbiota population are also a causative factor for the development of CRC (Gagnière et al. 2016; Gao et al. 2017). In the following section, we discuss various studies that evaluated how a diet can regulate the microbial population and exert beneficial effects on CRC.

One study has investigated how walnut consumption can prevent colon cancer by influencing the microbial community. In group 1, the mice were fed standard diet along with 9.4% walnuts composed of 15% total fat, and in group 2, the mice were fed a complete western diet, along with 7% walnuts composed of 10.5% total fat. The results revealed that walnuts at higher concentration exhibited a lower inhibitory effect than the other dosage because of the pronounced alterations in the oleic acid levels in the body due to the high oleic acid content in the walnuts (18.8%). Several studies have reported that oleic acid can promote weight loss and possess anticancer activity (Lim et al. 2013: Owen et al. 2004). Others have shown that oleic acid can inhibit inflammatory cytokines and prostaglandin production in human glioblastoma cells (Lamy et al. 2016). The levels of oleic acid and palmitic acid have been found to be low in cancerous tissues. Overall, these data suggest that oleic acid plays an important role in cancer prevention. Walnut consumption also altered the abundance of gut microbiota based on the gender of the mice. The diversity and abundance of the gut microbiome were significantly reduced by the carcinogen, especially in male mice. The consumption of walnut-supplemented diets was found to influence various phylotypes. In particular, walnut consumption can reshape the gut microbial community by increasing the abundance of *A. muciniphila* a mucin-degrading bacteria known for its ability to attenuate intestinal inflammation by virtue of its mucosal barrier functions (Nakanishi et al. 2016). This study is the first of its kind to report the effects of the diet-induced changes in the gut microbiota in combating cancer.

Various studies have described the role of *A. muciniphila* in CRC development. One related study compared the fecal samples of healthy volunteers with those of CRC patients and found that higher butyrate concentrations in the fecal samples of healthy individuals and higher acetate concentrations in those of CRC patients. In addition, GC-MS profiling revealed higher concentrations of amino acids in the fecal samples of CRC patients and higher levels of conjugated BA, ursodeoxycholic acid, and poly and monounsaturated fatty acids in those of healthy individuals. Correlative analysis studies have suggested the existences of some relationship between metabolites and certain bacterial species. Overall, the results demonstrated no significant difference in the total bacterial community, but the population of the butyrate-producing bacteria reduced and that of *A. muciniphila*, increased 4 folds in CRC samples (Weir et al. 2013), indicating that *A. muciniphila* plays an important role in CRC development.

Diet, A. muciniphila, and IBD

The immune system performs various actions to protect the host from the invasion of various foreign bodies. Occasionally, the body's immune system attacks the parts of the digestive system by causing inflammation; this condition is referred to as IBD. IBD is classified into two major types: Crohn's disease (CD) and ulcerative colitis (UC) (Carter et al. 2004). IBD results in evident morbidity; although not associated with mortality, IBD impairs the quality of life. Adaptation to the western lifestyle, increased awareness of IBD and improvement in the detection methods have increased the global prevalence of IBD over the past few decades. The severity of the inflammation and location of the disease determines the clinical presentation of IBD. IBD is characterized by several symptoms, such as diarrhea, abdominal pain, bloody mucoid stool, and rectal bleeding (Wehkamp et al. 2016). The examination of fecal samples of IBD patients shows an increased abundance of mucosa-associated bacteria. In a study on mucosa-associated bacteria in CD and UC, the population of the total mucosa-associated bacteria increased 1.9 fold in CD and 1.3 fold in UC. In particular, *Ruminococcus gnavus* population increased by 4-fold, *R. torques* population increased by 100-fold, *A. muciniphila* population reduced several folds in CD and in UC. Overall, the results state that the gut microbiome, especially *A. muciniphila*, plays a vital role in IBD development, as evident by the alterations in its abundance (Png et al. 2010).

Diet plays an important role in preventing inflammatory diseases. Diets containing low-fermentable oligosaccharides, monosaccharides, disaccharides, and polyols are well known for their protective effects against various inflammatory processes (Varju et al. 2017). Food such as legumes, including lentil, chickpea, bean, chicory, brussels sprout, onion, and cabbage are known to have anti-inflammatory activities. Diet affects IBD, indirectly via the formation of various active metabolites with strong anti-inflammatory properties. For example, ingested stachyose and raffinose reaches the colon undigested and is metabolized in the colon with the help of gut microbiota. The gut microbiota produces many active SCFAs such as acetate, butyrate, and propionate. In particular, butyrate, a four-carbon SCFA is produced from the dietary fibers in the lower intestine by gut microbiota. The main function of butyrate is as a histone deacetylase inhibitor. Butyrate exerts beneficial effects on intestinal homeostasis, inflammation prevention, immunity, and energy metabolism. It is a potent anti-inflammatory agent that can inhibit various pro-inflammatory cytokines such as IL-8, IL-6, IL-1β, and TNF-α. The major action of butyrate over the host metabolism occurs via the gut-brain axis. Butyrate protects gut health and prevents obesity (Liu et al. 2018). In our previous review on gut microbiota, we discussed the various functions of SCFAs (Jayachandran et al. 2017). However, further studies are warranted to clarify the exact role of *A. muciniphila*, active metabolite conversion from the diet, and how diet influences the population of *A. muciniphila*.

Future perspectives on diet-mediated changes in *A. muciniphila* and its impacts on health

Previous studies on the gut microbiota have mainly investigated the abundance at phylum/genus-level and to some extent at species-level in different age groups such as infants, adults, and elders. Further analysis of species-level functional behaviors of microbes in the gut microbiota is warranted. Several methods are available to study the human gut

microbiota. One such method is constraint-based modeling (Bauer and Thiele 2018). The genome-scale metabolic model is used to present the metabolic information of an organism in constraint-based modeling (Baart and Martens 2012). Metabolic models are used to interpret the genotype-phenotype interactions in a single species. These metabolic models are also used to study microbial communities for determining the inter-species interactions and their objective functions in a multispecies system such as the human gut microbiota. Metagenomics is a sequencing-based technique widely used to study the functional features of the genomic sequences of different microbe's (Handelsman 2004). Still, several beneficial microbes have not been studied at the genomic level, and interaction between various diets, microbiota composition, and human health needs to be investigated further using advanced techniques. In addition, investigation of the interactions between different microbial species will elucidate the reason behind the changes in the abundance of particular species.

Conclusions

There is a growing appreciation of the role of diet and other environmental factors in modulating the composition and metabolic activity of the human gut microbiota, which in turn can affect human health (Conlon and Bird 2014). In recent decades, various studies have investigated the role of gut microbiota in diet-based therapy and prevention of various disorders. Hence, this review provides a useful overview of the available evidence and advances in the field of diet-based disease prevention with a focus on *A. muciniphila* present in the gut microbiota. Overall, this review covers the effects of different diets and on gut microbiota, in particular, A. muciniphila. We have summarized the results of various studies, including the changes that occur in the microbiota population and how they influence DM, obesity, atherosclerosis, cancer, and IBD. The various gene-sequencing methods, such as PacBio single-molecule real-time sequencing, ion semiconductor sequencing, and Illumina genome analyzer, in addition to metagenomics, could enhance the credibility of the gut microbiota research and strengthen the evidence of its benefits to human health.

Abbreviations

A. muciniphila	*Akkermansia muciniphila*
CD	Crohn disease
CE	cranberry extract
CRC	colorectal cancer
dsrA-BW	Bilophila wadsworthia-specific dissimilatory sulfite reductase gene
GEM	genome-scale metabolic model
GIT	gastrointestinal tract
Gpat1	glycerol 3-phosphate acyltransferase 1
HFD	high fat diet
HFHS	high fat high sugar
IBD	inflammatory bowel disease
IL-6	interleukin-6
LF	low fat
mRNA	messenger ribonucleic acid
MUC2	mucin 2
NFkB	nuclear factor kappa B
PCR	polymerase chain reaction
PP	polyphenols
rRNA	ribosomal ribonucleic acid
SCFA	short-chain fatty acids
T2DM	type 2 diabetes mellitus
TNF-alpha	tumor necrosis factor alpha
UC	ulcerative colitis

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