



Microbiota-accessible carbohydrates (MACs) as novel gut microbiome modulators in noncommunicable diseases

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ABSTRACT

The gut microbiota has a significant role in human health and is affected by many factors. Diet and dietary components have profound impacts on the composition of the gut microbiome and largely contribute to the change in bacterial flora. A high-fiber diet increased dietary fiber (DF) fermentation and the production of short-chain fatty acids (SCFAs), which increased the number of microorganisms. Microbiota-accessible carbohydrates (MACs), a subgroup of fermentable carbohydrates such as DF, are defined as indigestible carbohydrates metabolized by microbes. These carbohydrates are important components to sustain the microbial environment of the complicated digestive tract and avoid intestinal dysbiosis. Each MAC has a unique property and can therefore be used as a sensitive output microbiota modulator to support host homeostasis and modulate health. In addition to the overall health-developing effects, MACs are thought to have a promising effect on the prevention of non-communicable diseases (NCDs), which are major health problems worldwide. The aim of the manuscript was to describe microbiota-accessible carbohydrates and summarize their effects on gut modulation and NCDs.

1. Introduction

The gut microbiota is a dynamic, complex, and spatially heterogeneous ecosystem inhabited by numerous microorganisms, including archaea, bacteria, viruses, and fungi, that interact with each other and the host [1]. 25 different taxa, roughly 2000 genera, and 5000 species have been identified in the gut microbiota [2]. The gut microbiome plays pivotal roles in host immunity, digestion of nutrients, intestinal endocrine function, regulation of neurological signal transmission, elimination of toxins, and the production of numerous compounds that affect the host [3]. While the formation and proliferation of the intestinal microbiome begin at birth, changes in its composition are primarily influenced by genetic, nutritional, and environmental factors [4]. A deeper understanding of the variables influencing the makeup and functionality of this microbial community is necessary given the significance of the gut microbiota for human health [5]. The gut microbiota can be modulated to improve human health and treat or prevent diseases [4].

One of the key points influencing the homeostasis of the gut microbiota is the diet [6]. The microbial ecology in the intestine is significantly shaped by the diet. Due to variations in the availability of macronutrients and micronutrients in the intestine, dietary alterations can have a direct impact on the composition and functionality of the gut microbiota [7]. However, the most determining factor in healthy or unhealthy nutrition is the quality and content of the diet rather than the amount of food consumed [8].

Diet can alter intestinal pH, intestinal permeability, and bacterial metabolites, and therefore inflammation in addition to promoting

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the growth of specific bacterial groups [8,9]. Food components can modify the immune system in the host by directly influencing the barriers to gut bacteria populations and host metabolites. Each food component directly affects the health of the host by altering the intestinal epithelial barrier, commensal bacteria, and subsequently cell immunophenotypes and their pro- or anti-inflammatory responses [8].

It is well-known that dietary fiber (DF) has a significant effect on the gut microbiota [10]. According to the commonly recognized definition derived by the Codex Alimentarius Commission (CAC) in 2009, DFs are carbohydrate polymers with three or more monomeric units DFs are carbohydrate polymers with three or more monomeric units, which are neither digested nor absorbed in the small intestine [11,12]. A high-DF diet promotes the production of short-chain fatty acids (SCFAs) as a result of DF fermentation, leading to an increase in microbial diversity [7]. Through DFs fermentation, various intestinal bacterial populations can mediate inflammatory functions via SCFAs and endogenous signals to reduce inflammation [13].

A new classification regarding DFs, microbiota-accessible carbohydrates (MACs), are dietary substances that the gut microbiota uses and are crucial in determining the composition of the intestinal microbial ecology [8]. Sonnenburg et al. coined the concept of "microbiota-accessible carbohydrates", which are essentially equivalent to fermentable DFs and are defined as carbohydrates that can be used as growth substrates by intestinal microorganisms that have the necessary enzymatic capacity [14]. This definition excludes insoluble DFs, as they cannot be used by the gut microbiota [15]. MACs are the main source of energy for colonic bacteria [14,16]. MACs can modify the composition and function of the gut microbiota. They can also be used as "gut microbiota modulators" to improve the health of the host [17,18].

Non-communicable diseases (NCDs), commonly known as chronic diseases, are conditions that typically last for a significant amount of time and are brought on by a confluence of genetic, physiological, environmental, and behavioral variables. NCDs, such as obesity, Type 2 diabetes (T2DM), cardiovascular disease, and cancer, cause more than 70.0% of annual global deaths [19]. The 2030 Agenda for Sustainable Development also recognizes NCDs as a major challenge for sustainable development [20].

Nutrition is a key part of keeping people healthy and free of NCDs for longer periods [21]. MACs may also have a promising effect on chronic diseases and immune system [17]. The aim of this review article was to describe MACs and summarize their effects on gut modulation and NCDs.

2. Diet and gut microbiota

The influence of nutrition on gut microbiota modulation is widely accepted. It is well established that nutrition influences microbiota-related disease processes and health-promoting activities [22,23]. There is a mutual relationship between the gut microbiota and diet. Hence, dietary variables rank among the most potent influences on the structure and function of the microbiota [24]. The diet can impact the composition and diversity of the gut microbiota [25]. The effects of dietary changes on microbiota can be both short-term and long-term and vary between individuals [26].

Dietary choices cause differences in the composition of the gut microbiota. While the Western pattern diet reduces the intestinal microbial phyla and genera diversity, the Mediterranean diet positively affects the host's immune functions, as well as microbiota diversity and stability [27]. The composition and functionality of the microbiota can also be altered by nutrients, bioactive substances, and certain dietary patterns, with either good or negative impacts on human health [28]. High consumption of animal proteins, saturated fats, refined carbohydrates, and salt encourage the growth of pathogenic bacteria, which may affect the intestinal barrier and reduce the diversity and function of microorganisms [27]. In contrast, consumption of fruits and vegetables, plant proteins, polyphenols, n-3 fatty acids and DFs provides health benefits through the modulation of the gut microbiota [2].

2.1. What are MACs? What is the difference between DF and MACs?

Nondigestible fermentable carbohydrates (NDFCs), a diverse group of polysaccharides and oligosaccharides that are resistant to digestion and absorption by the host, are metabolically available to the gut microbiota. Prebiotics, fermentable DFs, and MACs, collectively known as nondigestible fermentable carbohydrates (NDFCs), effectively modulate the gastrointestinal microbiome. Although there is no exact distinction between them, these concepts are different from each other [29]. Similar to the varying definitions of DF, prebiotics also have varying definitions. In 2016, the International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus panel recommended "a substrate that is selectively used by host microorganisms while conferring a health benefit" as a definition for prebiotics, and this definition is still in use [30]. However, definitions of prebiotics that are incorrect and based on outdated scientific views also exist [29,31–33].

Most prebiotic carbohydrates are DFs, although not all DFs are considered prebiotics, according to modern criteria [29,34,35]. The classification of DFs as prebiotics is complicated, since a DF that acts as a prebiotic in one host may not act as a prebiotic in another host [30]. Thus, a precise distinction between prebiotic DFs and non-prebiotic DFs is impossible [33]. Many classifications have been created for DF that take into account solubility, viscosity, and fermentability [36]. On the other hand, the fermentability of foods can also change as a result of some food processing techniques [37,38]. This makes it difficult to give a clear definition and to distinguish between terms [33].

Although there is no universally accepted definition of DF, many definitions imply that each form of DF plays a part in controlling the composition of the gut microbiota, which in turn significantly influences host metabolism [39]. Dietary fiber is defined as edible plant parts or analogous carbohydrates that are difficult for humans to digest and absorb in the small intestine, with full or partial fermentation occurring in the large intestine [40]. DFs, such as arabinoxylans, galacto-oligosaccharides (GOS), inulin, and oligofructose, support the growth of various beneficial microorganisms while suppressing potentially damaging ones [41].

The functionality and therapeutic advantages of many forms of DF have been studied. However, the optimal types, amounts, and sources of DFs to be consumed for therapeutic effects are still questionable. Although uncertainties regarding DF intake, a daily intake of 25–35 g of DF for adults is recommended in most countries [42].

Most of the plant polysaccharides are structurally complex [43]. In general, the more complex the polysaccharide, the more enzymes are needed to break it down. This requires "carbohydrate active enzymes". However, the human genome encodes 17 glycoside hydrolases (GH) and does not contain polysaccharide lyase (PL). As a result, glycans such as fructo-oligosaccharides (FOS), inulin, lignin, pectin, resistant starch, and inulin reach the large intestine undigested.

The gut microbiome compensates for the lack of GH and PL that are not encoded by the human genome. The gut microbiome can encode 130 GH families and 22 PL families [44]. Glycoconjugates, oligosaccharides, and polysaccharides are broken down into fermentable monosaccharides by these enzymes. A complicated cross-feeding metabolic network is started by fermentation during secondary breakdown, which produces acetate, propionate, formate, butyrate, lactate, and succinate [9]. One of the main jobs of the fecal and colonic microbiota is DF fermentation, which is also a significant source of SCFAs, the products of fermentation. According to current evidence, SCFAs play a key role in how soluble DFs promote health [36].

On the other hand, MACs are carbohydrates that can be fermented or "accessed" by an individual's microbiota and used metabolically by gut microbes [14]. MACs can be consumed through a diet or be derived from the host [29]. Dietary MACs can come from a range of sources, including plants, animal tissue, or food-borne microorganisms found in food and must be metabolizable by microbiota [14]. A lack of dietary MACs causes a microbial community to become dependent on endogenous MACs derived from the host, such as mucin glycans [45] (Fig. 1).

Whether or not an NDFC is regarded as a MAC is not just dependent on its physical and chemical properties. This is because the gastrointestinal microbiota of an individual host also should have the enzymatic capacity to metabolize said NDFC [29]. For example, cellulose is not digested by gut microorganisms and is not a MAC [45]. MACs are various oligosaccharide and polysaccharide groups that have significant structural heterogeneity and have various effects on microbial ecology [24].

Because each individual's microbiome determines which carbs are metabolized, the amount of dietary MACs contained in a certain food source varies between individuals [14]. For example, while genes associated with the metabolism of the algal polysaccharide porphyran are expressed in the microbiomes of Japanese individuals, these gene expressions are rarely observed in individuals from North America and Europe. Thus, porphyran would be regarded as a MAC for individuals who host a microbial strain that can metabolize porphyran in their guts, but it would not be regarded as a MAC for individuals who do not have adaptations for metabolizing seaweed [46]. Therefore, the concept of MAC is relevant for efforts aimed at personalizing human nutrition, which can provide individually customized dietary recommendations with the goal of including certain NDFCs known to be accessible by a person's gastrointestinal microbiota [29].

The availability of MACs largely determines the composition and function of the gut microbiota [47]. Each MAC has unique

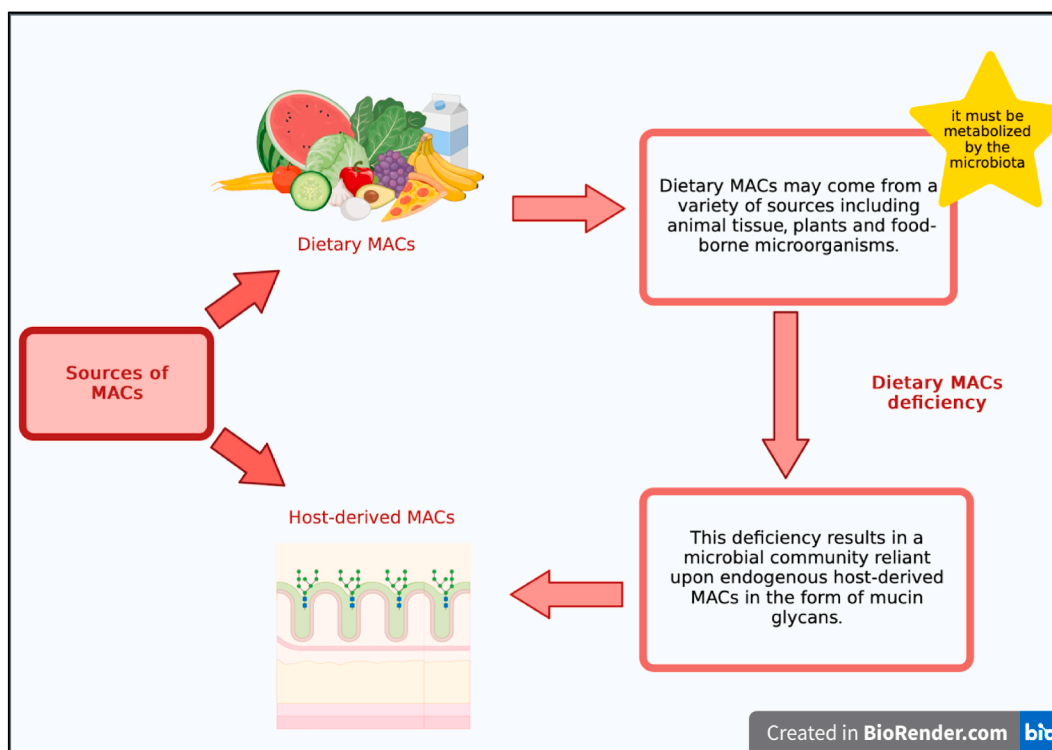


Fig. 1. Main sources of MACs.

properties and can be used as a sensitive microbiota modulator to support host homeostasis [18]. The intake of different MACs has been associated with the proliferation of different microorganisms. For example, fructans, polydextrose, FOS, and GOS are associated with intestinal *Bifidobacteria* and *Lactobacilli* proliferation. On the other hand, resistant starch is associated with *Ruminococcus*, *Eubacterium rectale*, and *Roseburia* proliferation [48]. Because intestinal bacteria vary in their ability to use different MACs as a food source, the effect of MACs on gut microbiota and host physiology varies depending on the type of MAC. However, it remains unclear how each MAC affects the gut microbiota and regulates host physiology [18].

MACs are a resource that modulate the proportion of microbial taxa in the gut. They are also used in the production of metabolic products such as SCFAs [26]. These carbohydrates are functional components that help maintain the microbiome of the complex gastrointestinal tract and prevent intestinal dysbiosis [49].

MACs are the main source of energy for colonic bacteria, and abundance of MACs helps proliferate beneficial bacteria [16]. MACs act as selective agents that can change the microbiota's composition, and they also determine the microbiota's functionality and metabolic output [14]. The main mechanisms of action of MACs are believed to be increasing the production of SCFAs and modulating the gut microbiome [50]. These mechanisms are extremely dependent on the individual host microbiota and persist as long as carbohydrates are consumed [47].

The available data suggest that changes in microbiota composition and diversity caused by dietary MAC are related to host health. Although the mechanisms underlying the connection between microbiota diversity and health remain unknown, it is believed that SCFAs may serve as a possible intermediary of this connection [14]. SCFAs, which are produced by the fermentation of MACs in the colon, serve as intermediaries in various pathways, including local, immune, and endocrine effects, as well as microbiota-gut-brain communication [51].

3. Short-chain fatty acids

The primary metabolite of MAC fermentation in the colon is called SCFAs, which is a fatty acid with a carbon chain length ranging from one to six carbon atoms. In the intestine, 500–600 mmol of SCFAs are produced per day, depending on the amount of fiber in the diet. Acetate (C2), propionate (C3), and butyrate (C4) are the most commonly produced SCFAs in the lumen of the large intestine [52]. Other SCFAs, such as formate, caproate, and valerate, are produced in smaller quantities [53]. Based on the microbiota composition, substrate, and intestinal transit time, each SCFAs's quantity and relative ratio vary [50]. However, in general, the ratio of acetate, propionate, and butyrate in the colon is respectively 60:20:20 [54]. The fermentation of fiber into SCFAs in the colon reduces pH, increases fecal acidification and promotes the growth and taxonomic diversity of the gut microbiome [51]. The SCFAs profile of the human gut is shaped by microbial species. The production of propionate and acetate in the intestine is correlated with the presence of Bacteroides species, whereas butyrate is predominantly produced by Firmicutes [55].

Following their production in the colon, SCFAs that are specifically derived from the intestine are absorbed by the host epithelium. SCFAs are absorbed from the intestinal lumen through two mechanisms: SCFAs can be taken up by epithelial cells by simple diffusion. However, larger amounts of SCFAs can be absorbed into cells through active transport via monocarboxylate transporter 1 (MCT-1) and, to a lesser extent, through sodium-bound monocarboxylate transporter 1 (SMCT-1) [53,56].

SCFAs function as a crucial metabolic fuel because they can be used to create glucose and lipids, which the host uses as energy sources after being absorbed by host cells [53]. SCFAs are used in citric acid cycles and mitochondrial β -oxidation after being absorbed by colonocytes [57]. This provides colonocytes with a crucial source of energy. Butyrate is the primary source of energy for colonocytes. Its anti-inflammatory effects also contribute to maintaining intestinal homeostasis [51]. SCFAs also affect host insulin sensitivity and appetite regulation, and they can help prevent diet-related insulin resistance and obesity. SCFAs can also be used as a substrate for the synthesis of gluconeogenesis and cholesterol [53].

In the cecum and proximal colon, where colonocytes use them as a source of energy, there is a high concentration of SCFAs. However, through the portal vein, SCFAs can enter the peripheral circulation and affect the liver and other tissues [25]. Only a small portion of SCFAs is included in the systemic circulation and reaches other tissues [58]. Although SCFAs are included in the peripheral circulation in small amounts, it is now known that they function as signaling molecules and control various biological processes [25]. SCFAs are associated with various physiological processes, ranging from the regulation of blood pressure and circadian rhythms to natural and adaptive immunity [53,59,60].

SCFAs can have direct or indirect effects on cellular processes such as cell growth, differentiation, and gene expression. SCFAs also act as ligands for G-protein-coupled receptors (GPCRs), including G-protein-coupled receptor 41 (GPR41), G-protein-coupled receptor 43 (GPR43), and G-protein-coupled receptor 109A (GPR109A), and possess anti-inflammatory properties [51]. The activation of these receptors has greatly varying effects depending on the cell in which they are expressed. For example, SCFAs binding to GPCR receptors on enteroendocrine cells induces the secretion of intestinal hormones including glucagon-like peptide 1 (GLP1), aminobutyric acid (GABA), serotonin (5-HT), and peptide YY (PYY), which promotes the indirect signal transmission to the brain via systemic circulation or vagal pathways, whereas the signal transmission in pancreatic cells results in increased insulin secretion [61].

SCFAs also regulate histone deacetylase (HDAC) activity, which affects nuclear factor kappa B (NF- κ B) inhibition [62]. SCFAs exert a wide range of effects on T-cell function by directly promoting the differentiation of natural T cells into regulatory T cells (Treg), T helper cell 1 (Th1), and T helper cell 17 (Th17), and indirectly inhibiting the differentiation of natural T cells into T helper cell 2 (Th2) [16]. Through GPR43, SCFAs affect the differentiation of Treg cells and the production of interleukin-10 (IL-10). They also regulate the function of dendritic cells (DC) [62]. By regulating the levels of metabolites and components associated with microbiota, including SCFAs and endotoxins, butyrate inhibits the expression levels of interleukin-1 (IL-1), interleukin-6 (IL-6), and Monocyte chemoattractant protein-1/Chemokine (CC-motif) ligand 2 (MCP1/CCL2) in the liver, as well as Toll Like Receptor 4 (TLR4) in adipose tissue

[63]. Butyrate also affects the anti-inflammatory cytokine production, plasma B -cell proliferation, and antibody production [64]. It also supports the immune system’s natural defense against pathogenic bacteria by activating antimicrobial molecules [65]. These functions of SCFAs affect their immunomodulatory potential and maintain a balance between pro- and anti-inflammatory processes [58].

SCFAs, whose circulating concentrations can be efficiently manipulated by diet, have both direct and indirect effects on the brain [53]. SCFAs can modulate the enteric nervous system, which affects intestinal motility and the gut-brain axis [65]. SCFAs can influence blood-brain barrier (BBB) integrity by upregulating the expression of tight junction proteins after passing through endothelial cells’ MCTs [61].

Mucin-2 glycoprotein (MUC2) secretions constitute the main component of the colonic mucus layer, which is a dynamic and chemically complicated structure [66]. The mucus layer of the colon is an alternate source of host-derived glycans and contributes to the colonization of bacteria in the human intestine [67]. This layer functions as a physical barrier to protect the host from the intestine’s high bacterial load [68]. Mucus and mucin glycosylation play a key role in shaping the microbiota and mediating host health by allowing the selection of the most suitable microbial species [69]. A compromised intestinal barrier may allow microbial metabolites to pass from the intestine into the systemic circulation, which can lead to metabolic diseases [68].

SCFAs have significant effects on the mucosal homeostasis of the intestine. By inducing intracellular or extracellular processes, SCFAs have positive effects on intestinal epithelial cells (IECs) and immune cells [51]. They fortify intestinal barrier integrity by supporting epithelial cell function [65]. SCFAs affect the inflammatory activation of absent in melanoma 2 (AIM2) and Nucleotide-binding oligomerization domain-like receptor 3 (NLRP3), which impacts the generation of interleukin-18 (IL-18) and improves epithelial barrier function. The secretion of IL-18 and the inflammatory activation of Nucleotide-binding oligomerization domain-like receptor 6 (NLRP6) regulate the synthesis of intestinal antimicrobial peptides (AMPs) [62]. SCFAs improve intestinal health through various local effects, including preserving intestinal barrier integrity, mucus production, and protection against inflammation, as well as reducing the risk of colorectal cancer [64]. The mechanisms of action of SCFAs are summarized in Fig. 2.

- a. Following intestinal bacterial hydrolysis or fermentation of MACs, SCFAs are absorbed by colonocytes either by passive diffusion or by active transport via MCTs (MCT1 or SMC1). SCFAs are the main energy source for colonists and contribute to ATP production.
- b. The increase of SCFAs in the lumen increases the abundance of *Akkermansia muciniphila*. An increase in mucin and mucus synthesis has protective effects on tight junction integrity. The production of SCFAs increases the activation of NLRP3, resulting in the activation of GPR43 on epithelial cells, which increases the production of the epithelial healing cytokine IL-18. Additionally, ATP contributes to tight junction integrity.
- c. Through the stimulation of receptors on the membrane, SCFAs promote secretion of gut hormones such as GLP1, PYY, GABA and 5-HT. On the other hand, SCFAs inhibit HDAC.

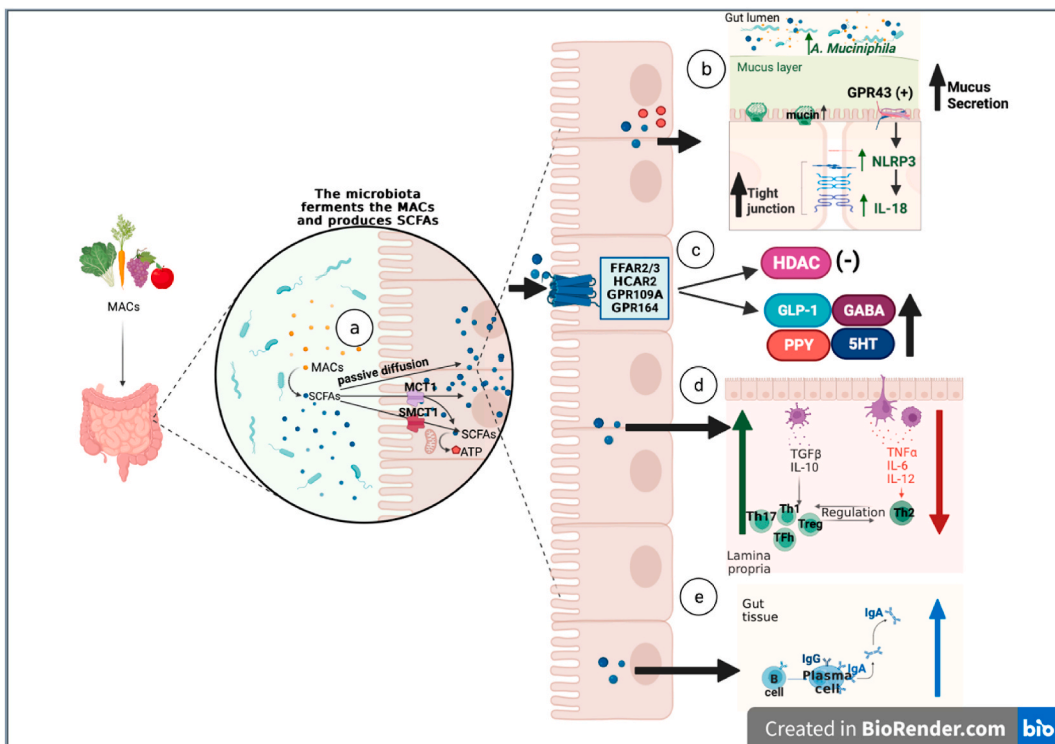


Fig. 2. Metabolic functions of short-chain fatty acids (SCFAs).

- d. SCFAs stimulate the release of IL-10 and inhibit the release of TNF- α , IL-6, and IL-12. However, it increases the growth of Treg, Th1, Th17, and Tfh and decreases Th2 development.
- e. SCFAs contribute to the direct activation of B cells and the production of IgA and IgG. Additionally, it leads to the plasma cell-mediated production of IgA.

(MACs: Microbiota-accessible carbohydrates, SCFAs: Short chain fatty acids, MCT: H + -linked monocarboxylate transporters, MCT1: Monocarboxylate transporter 1, SCMT1: Sodium dependent monocarboxylate transporter 1, NLRP3: Nucleotide-binding oligomerization domain 3, GPR43: G-protein-coupled receptor 43, IL-18: Interleukin 18, GLP1: Glucagon-like peptide 1, PYY: Peptide YY, GABA: γ -aminobutyric acid, 5-HT: Serotonin, HDAC: Histone deacetylases, IL-10: Interleukin 10, TNF- α : Tumor necrosis factor alpha, IL-6: Interleukin 6, IL-12: Interleukin 12, Treg: Regulatory T cell, Th1: T helper 1 cell, Th17: T helper 17 cell, Tfh: T follicular helper cell, Th2: T helper 2, IgA: Immunoglobulin A, IgG: Immunoglobulin G).

4. Amounts of MACs in diets

The diet composition, particularly the availability of MACs, has a significant effect on the gut microbiota [16]. It is thought that dietary MAC-induced changes in microbiota composition and diversity are linked to host health [50]. Fig. 3 summarizes the metabolic changes caused by low MAC intake and high MAC intake via diet.

4.1. Low MAC diets

The gut microbiome is resistant to short-term degradation. It seems likely that microbiome adaptation can be largely reversed on short-term scales. On the other hand, a consequence of long-term and intergenerational low uptake of MAC also leads to a decrease in bacterial diversity and an irreversible loss of bacterial strains [14]. In a prior study, it was observed that changes in mice’s microbiota, which were hosting strains found in human microbiota and fed with a diet low in MACs, were largely reversible within a single generation. However, a low-MAC diet over several generations causes a progressive loss of diversity that cannot be recovered by reintroducing dietary MACs [70]. Another study similarly showed that a diet with a low MAC content resulted in a reduction in a large number of specific bacterial taxa and reduced diversity, this effect persisting even after reintroduction of MACs [71]. Although comparable research on people has not been undertaken, it is known that, similar to mice, consuming a diet low in MACs lowers the diversity of bacteria in the human microbiome [16].

The changes caused by the modern lifestyle affect in the function and composition of microbiota [72]. In addition to the loss of microbial species across generations in industrialized countries, the lack of MACs required to feed this community causes severe

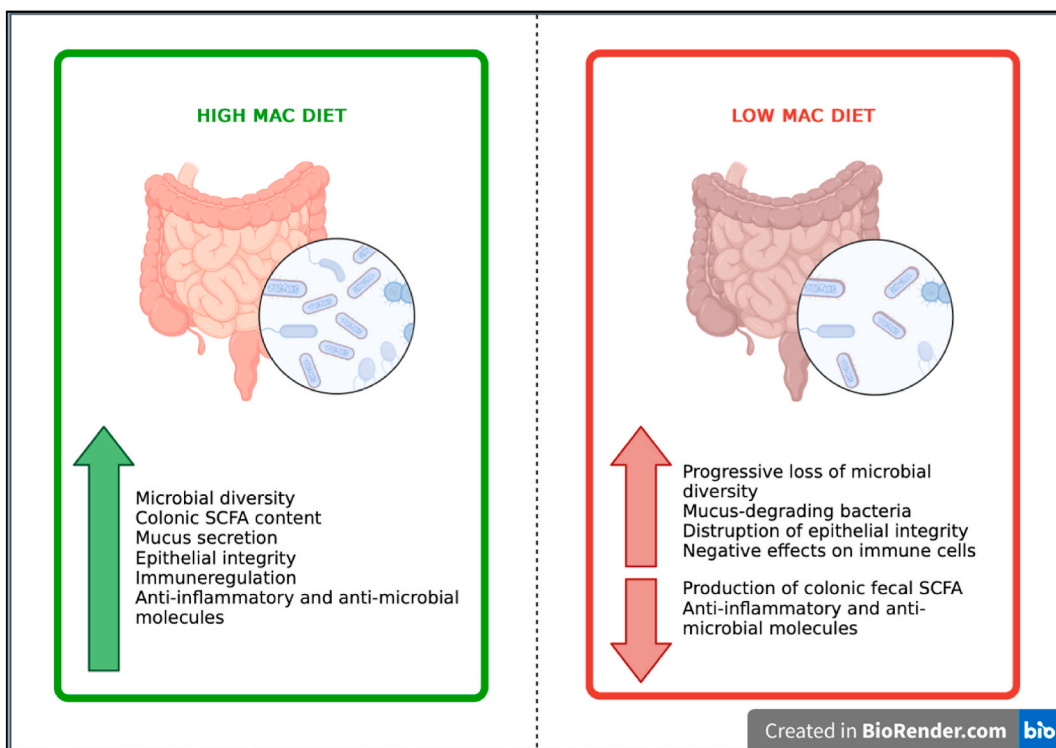


Fig. 3. Certain Changes in Gut Microbiota by the high MAC diet and the low MAC diet.

functional changes, such as a decline in SCFAs production [14]. Low MAC consumption has harmful effects not only on the gut microbiota but also on the entire host. Low MAC consumption facilitates the development of diseases and increases mortality [70].

The gut microbiomes of cities and industrialized societies are different from those of traditional societies, according to data collected over time. It is observed that traditional societies have higher intestinal microbial diversity than urban-industrialized societies and have a lower rate of NCDs [70,73,74]. For example, the Yanomami subjects of South America are a group of people who live in a relatively isolated and remote area. Their microbiome has the most bacterial diversity and genetic functions ever found in a human group. Dietary practices in industrialized societies may eliminate potentially useful microorganisms and their encoded functions [75]. It has been shown that the Tanzanian Hadza, a hunter-gatherer community, has a higher microbial richness and diversity than the Italian urban groups [76]. In a study, the fecal microbiota of children from Europe and children from a remote African village in Burkina Faso, where the diet is high in DF and similar to the diets of early human settlements, have been compared. It has been revealed that the gut microbiota of the two groups differ significantly [73]. In another study, fecal samples were acquired from traditional agrarian and hunter-gatherer communities in Peru and from an urban-industrialized population in the United States of America. It was shown that the rural groups had higher levels of microbial richness [77]. In one study, the fecal microbiota of adults in two non-industrialized regions of Papua New Guinea was compared with that of a community in the United States. Researchers found that the Papua New Guineans hosted microbial communities with higher bacterial diversity, very different species abundance profiles and bacterial lineages, and lower interpersonal variation [74].

Changes in the microbiota induced by MACs can directly affect epithelial integrity. In low MAC environments, certain bacteria use the mucus layer as an energy source and disrupt the epithelial barrier by thinning the mucus layer. The overgrowth of bacteria that metabolize mucus and the decrease in bacteria that metabolize MAC decrease intestinal bacterial diversity [16]. Therefore, diets deficient in MACs cause the inner mucus layer to get thinner due to reduced MUC2 production, and bacteria can pierce deeper into the epithelium. This could lead to the mucosal barrier disruption, which in turn increases inflammation and susceptibility to pathogens [78]. This MAC-induced condition has been associated with increased sensitivity to *Citrobacter rodentium*, a pathogen that targets the epithelium, which indicates the importance of dietary MACs in fighting against gastrointestinal infections [66].

To maintain intestinal homeostasis, IECs create a physical and metabolic barrier between the host tissue and commensal microorganisms. Secretory IECs support this function through secretion of mucins and antimicrobial peptides [79]. Epithelial integrity has paramount importance for both intestinal and host health. SCFAs production modulates epithelial cells and the immune system [80]. Low MAC consumption causes impaired epithelial integrity and is associated with epithelial cytokine expression changes [16,81].

MACs can affect both bacterial-epithelial and epithelial-immune interactions [82]. An important consequence of low MAC consumption is a decrease in SCFAs production [29]. Low SCFAs production leads to decreases in the release of anti-inflammatory cytokines, whereas the release of pro-inflammatory cytokines increases [83]. Epithelial damage is caused by the production of pro-inflammatory cytokines (such as IL-1, interleukin-17 (IL-17), tumor necrosis factor alpha (TNF- α), or interferon gamma (INF- γ)) by natural and adaptive inflammatory cells that infiltrate the lamina propria (LP) [51]. Low SCFAs production also disrupts the activation of GPR43 on epithelial cells, which in turn increases the production of the pro-Th2 cytokine thymic stromal lymphopoietin (TSLP) while decreasing activation of NLRP3 and, ultimately, decreases the production of the epithelium-healing cytokine IL-18 [16]. In one study, mice fed a diet low in MACs had increased epithelial TSLP expression, which triggered an immune response and allergies. In the aforementioned study, this effect was reversed with the administration of a diet high in MACs [84]. On the other hand, mice fed with a MAC-free diet produced significantly less IL-18 [85,86].

Low IL-18 production caused by diets low in MACs can also affect immune cells. SCFAs deficiency disrupts Treg, Th1 cells, and Th17 cells while increasing Th2 cells. SCFAs deficiency also interferes with the production of IgA and immunoglobulin G (IgG) by reducing the direct activation of B cells and the indirect stimulation of T follicular helper cells (Tfh) [16].

In a mice model, it has been observed that diets low in MACs exacerbate gout and that acetate promotes recovery from neutrophilic inflammation via GPR43. This condition has been linked to enhanced neutrophil apoptosis mediated by caspase in mice [87,88]. Mice that produce low amounts of SCFAs due to low MAC consumption or microbial insufficiencies have poorer homeostatic and pathogen-specific antibody responses and are more sensitive to pathogens [89]. The amount of MAC in the diet changes the composition of intestinal and lung microbiota, particularly by changing the ratio of Firmicutes to Bacteroidetes. A diet containing low DFs/MACs reduces SCFAs levels and exacerbates allergic airway disease [90]. A higher consumption of SCFAs or MACs relieves this immune deficiency and lowers the severity of inflammation [89,90].

In comparison to a high-MAC diet, the most consistent effects of a low-MAC diet include a rise in Proteobacteria and a decrease in Bacteroidetes, as well as a reduction in bacterial diversity [84,89].

4.2. High -MAC diets

Increased dietary MAC consumption has been associated with the composition and diversity of microorganisms [14]. Increased dietary MAC consumption, sourced from a healthy diet and processed foods, supports the increase in beneficial microorganisms [91]. An umbrella review examined the associations between 14 dietary interventions and cardiovascular risk factors. It has been cited as the most important dietary intervention of the MAC recommendation [17].

Diets high in MACs can change the composition of the microbiota in humans within days or weeks [55]. Previous studies also support the idea that MACs have a role in modulating the gut microbiota [92,93]. It has been shown that feeding mice white button mushrooms high in DF for six weeks increased the number of *Ruminococcaceae* and *Lachnospiraceae* in the mouse fecal microbiome [94]. A high consumption of MAC has been linked to an increase in the fecal abundance of Bacteroidetes, particularly *Prevotella*, and the eradication of Firmicutes in children who are otherwise healthy. Children who have high MAC consumption also have greater

amounts of SCFAs, which is connected with a lower prevalence of fecal infections, including *Escherichia* and *Shigella*, in their guts [95]. *Clostridioides difficile* can be suppressed by adding a complex mixture of MACs to the diet or by adding inulin alone as a source of MAC for a simplified diet [96].

SCFAs affect the T lymphocytes of the developing fetal immune system, resulting in a tolerogenic condition and a decreased risk of asthma in the baby [92]. The activation of T cells that produce Th1, Th17, and IL-10 by acetate and butyrate may play a crucial role in the protective effects of high MAC consumption against *Citrobacter rodentium* infections [97]. In one study, it was concluded that the methanolic extract of *Hemidesmus indicus* protected against oxidative stress, hyperlipidemia, and liver damage [98]. In another study, IgA production was shown to be significantly increased in mice fed with a diet containing a high amount of MACs compared to mice fed with a MAC-free diet. The production of TFh, IgA, and B cells in the intestine all increased in response to high MAC consumption [84].

In mice, high DF/MAC consumption improves oral tolerance and protects against food allergies. High DF/MAC consumption changes intestinal microbial ecology and increases the production of SCFAs, especially butyrate and acetate [84]. High-DF or acetate content suppresses the expression of genes in the embryonic lungs of mice that are associated with both human asthma and mouse allergic reactivity [99].

In a previous study, a diet rich in MACs was found to strengthen the endurance exercise capacity in mice. In contrast, antibiotic administration and a low-MAC diet modulated muscle fuel availability and impaired exercise capacity [93]. In another study, the effect of high MAC consumption on the microbiota-gut-brain axis as well and the cognitive performance of mice with obesity caused by a high-fat diet was evaluated. High MAC intake by the aforementioned mice has prevented gut microbiota dysbiosis, disruption of the colonic mucus barrier, endotoxemia, and cognitive impairment. It has also decreased systemic and colonic inflammation and an increase in serum SCFAs levels [100].

In addition to studies on high MAC intake through diet, other studies that increase the amount of MACs in foods have also been conducted. For example, whole grains have low MAC content. However, food processing affects the availability of carbohydrates to the microbiome, and processing can increase the MAC content in whole grains [101,102]. Baking bread is the most popular method of cereal preparation [103]. In a previous study, sourdough bread and other breads were found to enhance the amount of beneficial microorganisms belonging to the families *Ruminococcaceae* and *Lachnospirae* that ferment complex carbohydrates into SCFAs. Increased resistant starch content combined with small changes in the cell wall matrix caused by sourdough bread baking increased MAC quality, both in terms of complexity and variety [100].

5. MACs and certain non-communicable diseases (NCDs)

The majority of global annual deaths are caused by NCDs, and the incidence of these diseases is increasing. Healthy nutrition and modulation of dietary content can have a positive effect on combating the global burden of NCDs [104]. Defining a framework for

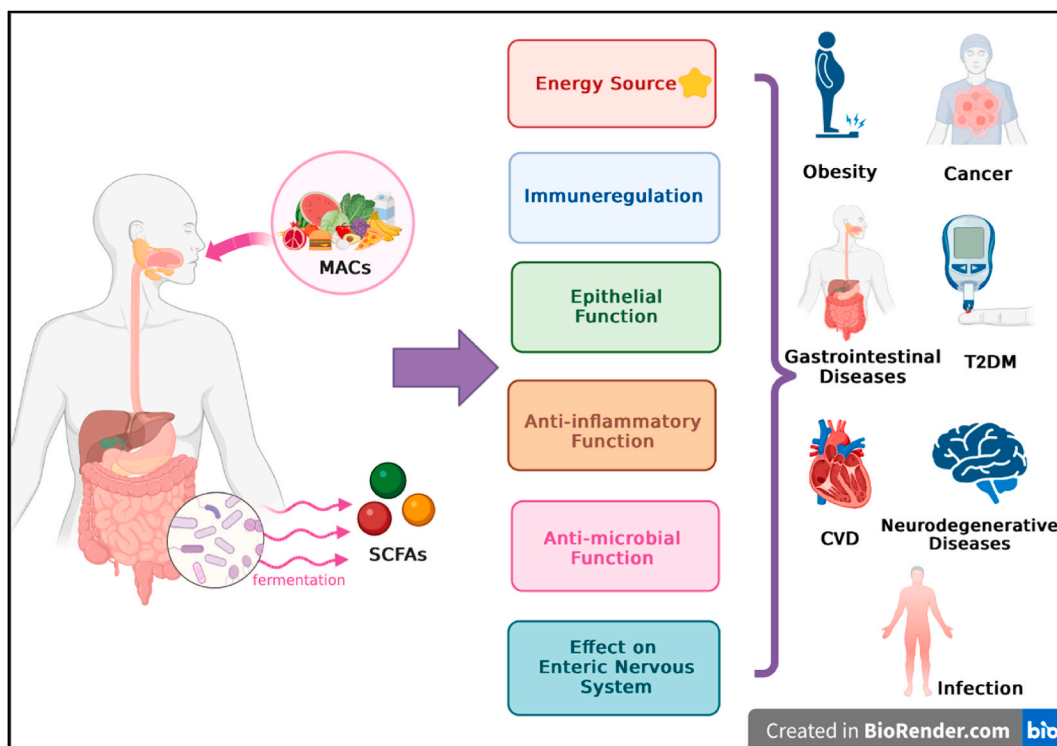


Fig. 4. MACs and their promising effects on non-communicable diseases (NCDs).

nutrition research is the initial step in efforts to lower the risk of diet-related chronic diseases. Dietary patterns are a valuable nutritional assessment method for examining the association between food and the risk of chronic disease at the population level [105]. The content and variety of MACs in the diet has gradually decreased, particularly because of Westernization and the transition to foods rich in refined simple sugars [106,107]. Many factors associated with dysbiosis, such as the modern lifestyle and increased intestinal permeability, facilitate bacterial translocation in the host [6,16]. It is thought that the dysbiotic microbiota that is proliferating due to lower MAC levels may exacerbate the development of NCDs [16]. Dysbiotic microbiota, which is associated with NCDs, also leads to a substantial decrease in intestinal microbial biodiversity [6]. Because of this mutual interaction, low microbial diversity also contributes to obesity and diabetes [108]. It is thought that by regulating the microbiota in the gut, one might gradually improve the host's metabolic and immunological functioning, hence assisting in the prevention of chronic diseases or in the improvement of their symptoms [109]. Higher abundances of MAC-digesting bacteria and the resulting increase in SCFAs have positive effects [108]. MACs also have preventive effects in chronic diseases, based on their synergism with other nutritional components in regulating intestinal function [109]. Additionally, MACs have effects that improve the main metabolic risk factors associated with NCDs, which are increased blood pressure, overweight or obesity, hyperglycemia, and hyperlipidemia (Fig. 4) [110,111].

5.1. Obesity

The gut microbiota of obese and lean people are different in composition, suggesting that microbiome dysbiosis play a role in changes in body mass index [112]. Obese and lean human subjects have different microbiota compositions. Obese subjects had a higher *Firmicutes/Bacteroidetes* ratio and *Actinobacteria* ratio, less diversity, and different representations of bacterial genes and metabolic pathways [113].

Compared to lean mice, the intestinal microbiome of obese mice has a larger number of enzymes that degrade carbohydrates that cannot be digested by the host. This enzyme richness increases SCFAs production [110,114]. Microbial products such as SCFAs, can regulate appetite, lipogenesis, gluconeogenesis, inflammation, and other metabolic activities [115]. SCFAs have a significant impact on the inflammation caused by obesity. SCFAs affect appetite through substrates for lipid storage and G-protein-coupled receptor signaling, in addition to serving as the main source of energy for colonocytes [110]. A systematic review of seven human clinical trials with a total of 246 obese cases and 198 healthy controls demonstrated that obese subjects had higher amounts of fecal acetate, propionate, butyrate, and other SCFAs than lean subjects [116]. There are contradictory findings concerning the association between SCFAs and obesity in the literature [117]. For example, in a number of interventional studies, it has been observed that high SCFAs levels was positively correlated with weight loss and insulin sensitivity, modulated through the activation of PYY and GLP-1 by SCFAs [118]. PYY modulates appetite and satiety by either delaying gastric emptying or inhibiting neuropeptide Y (NPY) and stimulating proopiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus (ARC) [119]. On the other hand, it has been suggested that the regulating effects of SCFAs on appetite and energy expenditure become ineffective in the context of obesity, so that obese people do not benefit from high levels of SCFAs [117].

According to a study, L-arabinose and sucrose, two MACs that affect diet-related obesity and gut microbiota metabolism, work together on certain bacteria, such as *Bacteroides*, to synergistically increase acetate and propionate concentrations in the intestine, thereby preventing diet-related obesity [18]. Acetate can directly modulate satiety through a primary mechanism in the central nervous system, whereas propionate can influence body weight regulation through sympathetic nervous system activity and activation of intestinal gluconeogenesis [119]. It has been shown in inulin intervention studies in obese children that inulin reduced overall fat masses and body weight gain [120].

MACs that complement the fight against malfunction offer a promising approach to improving Westernized dietary patterns and preventing obesity-related neurodegenerative diseases [110]. It has been suggested that adding DF to existing food products is an effective way to boost MAC content, microbiome diversity, and fermentation end product output [121].

5.2. Type 2 diabetes (T2DM)

Substantial evidence suggests that the gut microbiota play a role in T2DM [17]. The microbiota composition of T2DM patients and healthy controls differs significantly [122]. T2DM patients' gut microbiota and fecal metabolites are characterized by an abundance of *Proteobacteria*, a much higher ratio of *Firmicutes/Bacteroidetes* than in healthy individuals, and significantly irregular SCFAs concentrations [123]. In one of the first large-scale microbiota investigations conducted on persons with T2DM, it was found that T2DM patients had significantly decreased abundance of butyrate-producing bacteria, such as *Roseburia intestinalis* and *Faecalibacterium prausnitzii*, compared with healthy controls. Additionally, it was found that the microbiota of T2DM patients included a much larger number of harmful bacteria, such as *Desulfovibrio*, *Clostridiales*, and *Bacteroides caccae* [15,124]. Another study found that people with diabetes have lower levels of butyrate-producing bacteria and a higher frequency of opportunistic infections [124]. The abundance of *Bifidobacteriaceae* and the diversity of gut microbiota have been found to be significantly lower in T2DM patients than in healthy subjects, and although GOS consumption has not improved the glucose tolerance of these patients, it has significantly improved their *Bifidobacteriaceae* infections [125].

Dietary intervention in patients with T2DM modulates the gut microbiota and improves glucose control [126]. Generally, the role of DF in physically encasing/retaining nutrients is linked to the main mechanism of action of MACs in the regulation of blood glucose in patients with T2DM. This slows the rate of digestion of plant tissues and reduces the increase in blood glucose [127,128]. According to the available studies, MAC consumption improves glycemic control, blood pressure, blood lipid concentrations, obesity, and inflammation in patients with T2DM patients. These effects may be attributable to SCFAs, the primary bacterial byproducts of

MAC fermentation. SCFAs can decrease metabolic inflammation, improve glycemic control and modulate satiety, preventing the progression of T2DM [17]. One study has shown that increasing the amount of indigestible carbohydrates reaching the intestines may be sufficient to improve T2DM patients' metabolic parameters [129]. The consumption of a diet with high DF/MAC content can decrease body weight and improve hemoglobin A1c (HbA1c) levels [130]. SCFAs can activate the secretion of both GLP-1 and PYY by enteroendocrine L-cells [131]. Through increased GLP-1 production, this increases glucose usage and insulin sensitivity, reducing HbA1c. SCFAs also reduce microbes that produce metabolically harmful compounds such as indole and hydrogen sulfide [129,131]. Another study found that a milk powder supplement fortified with inulin and resistant dextrin improved islet B cell function, decreased blood glucose, and reduced blood pressure in elderly T2DM patients compared with the placebo group [132]. The results of the aforementioned studies provide supporting evidence that consuming a diet rich in DFs/MACs may have positive effects on T2DM diagnoses and the course of the disease [17].

5.3. Cardiovascular diseases

It has been reported that patients with T2DM patients have a greater incidence of hypertension. Hypertension is a serious risk factor for cardiovascular disease, which is linked to mortality and morbidity in patients with DM patients [133]. Prior research has shown that a 10 mmHg reduction in systolic blood pressure reduces the risk of cardiovascular disease by 20%, heart failure by 28%, stroke by 27%, and the chance of mortality from any cause [134]. According to a meta-analysis conducted in 2015, people who ate a high-DF diet had reductions in both their systolic and diastolic blood pressure, with the latter effect being more pronounced in people who consumed more beta-glucan [135]. A similar study compared the serum cholesterol levels and blood pressure of participants who consumed high amounts of soluble viscous DF with those receiving a placebo. As a result of the study, decreases in blood pressure and cholesterol levels were observed in the group with high soluble viscous DF consumption [130].

In other meta-analyses and an umbrella review, it has been shown that high DF consumption improves cardiovascular risk factors. The correlation between MACs and cardiovascular risk factors was supported by evidence ranging from moderate to high quality. Increased consumption of MAC reduces LDL and TG levels while increasing HDL levels [17]. In a study conducted on the psyllium- and placebo-administered groups of patients, a decrease in total cholesterol, TG, and LDL levels, and an increase in HDL levels were observed in the psyllium group, whereas no significant changes were observed in the placebo group [136]. Consumption of psyllium effects intravascular processing of lipoproteins by decreasing the cholesteryl ester transfer protein activity through changes in VLDL composition [136,137]. It is well known that oats can prevent induced hyperlipidemia in rats and humans. In a study, oat flakes were found to positively affect the lipid metabolism of rats fed a high-fat diet. In the aforementioned study, four different types of oats exhibited distinct nutritional qualities and hypolipidemic effects. β -Glucan extracted from the Bayou-1 variety of said oats were the most effective in preventing serum lipid levels from increasing [138].

There is growing evidence that SCFAs may play a role as a metabolic tool in the prevention and treatment of obesity and obesity associated cardiometabolic risk factors, such as insulin resistance [119]. SCFAs have the ability to improve adipose tissue's lipid storage capacity, which in turn lowers the amount of circulating TG and prevents ectopic fat storage. SCFAs may also reduce inflammation in adipose tissue, possibly via lowering levels of CRP and TNF- α as well as downregulating ectopic fat deposits in non-adipose tissues, all of which are related to insulin resistance remission [17].

Glutathione (GSH), a marker of oxidative stress, plays a crucial role in detoxifying oxygen radicals and can prevent cellular damage resulting from oxidative stress. Reduced GSH levels have been linked to cardiovascular disease [139]. A study has shown that mice fed with resistant starch have higher circulating GSH levels, suggesting that they may be exposed to less oxidative stress [140].

5.4. Gastrointestinal diseases

Diseases related to intestinal metabolism have become an important public health problem due to their widespread prevalence and harmful effects. Functional oligosaccharides promote the proliferation of probiotics, regulate immunological responses, and increase SCFAs production by enabling the metabolism of intestinal bacteria [141]. High psyllium intake can alleviate the symptoms of chronic constipation and reduce body weight, glycemic, and cholesterol levels in patients with T2DM and chronic constipation [136]. In one study, the symptoms, glycemia lipids, and weight of chronic constipation patients with T2DM who consumed high amounts of flaxseed or psyllium were compared with those of patients who took a placebo. Because of the aforementioned study, both nutritional substances provide positive effects to constipated patients with T2DM, but flaxseed is superior to psyllium when it comes to relieving constipation and managing weight, glycemic, and lipid levels. However, these benefits of flaxseed and psyllium were not sustained over the long term [142].

The decreased diversity of the gut microbiota in patients with inflammatory bowel diseases (IBD) patients is a significant feature [143]. The modern Western diet is also considered an environmental factor in the cause of IBD [144]. Functional oligosaccharides may regulate inflammatory cytokines to alleviate intestinal diseases [141]. Evidence suggests that inulin's ability to modify intestinal barrier function and deliver anti-inflammatory benefits through modulating dysbiosis of the gut microbiota and metabolic butyrate help alleviate colon inflammation [143].

The mucus layer in the colon is an early barrier that bacteria must infiltrate. A microbiota that is not adequately supplied with DF results in the thinning of this barrier, indicating that DF consumption has significant implications on susceptibility to gastrointestinal pathogens. In this context, patients with IBD patients have higher levels of mucolytic bacteria [66]. *Bifidobacterium* and other symbiotic bacteria ferment indigestible oligosaccharides, which result in the production of SCFAs, vitamins, and various other small molecules beneficial to the structural integrity of the intestinal epithelial barrier [141]. Prebiotics increase the secretion of GLP-2 by increasing

L-cell activity and *Akkermansia muciniphila* count, which can strengthen the intestinal barrier and improve intestinal tight junctions. Prebiotics can also increase endogenous 2-arachidonoylglycerol (2-AG) levels and reduce systemic inflammation and metabolic endotoxemia by increasing *Akkermansia muciniphila* counts [145]. Peptic polysaccharides (PPSs) can efficiently manage the dysbiosis of the gut microbiota, which is one of the anti-IBD modes of action. Additionally, PPSs increase the diversity of gut microbiota while decreasing the intestinal bacterial load [143].

Ulcerative colitis, a type of IBD, is characterized by the infiltration of inflammatory cells into the colon mucosa. According to the available evidence, GOS may reduce the harm caused by colitis [146]. Patients with ulcerative colitis who received 2.8-g GOS per day for six weeks showed an improvement in stool consistency and a reduction in the incidence and severity of loose stools [147]. GOS treatment inhibits the activation of the NF- κ B signaling pathway, significantly decreasing the secretion of IL-6, IL-13, IL-18, and IL-33, as well as the expression of mRNA in the colon, and induces a Th17/Treg imbalance by regulating the intestinal flora. All of these findings suggest that GOS protect mice from dextran sulfate sodium-induced colitis [146]. In clinical trials, FOS and inulin have improved the course of IBD, possibly by repairing intestinal penetrations or through direct interactions with gut microbes or immune cells [148]. Efforts to identify optimal combinations of DF to be consumed and the minimum intake required for restoring the integrity and elasticity of the colonic mucus layer are of critical importance [66].

5.5. Neurodegenerative diseases

The human gut microbiome can have a big effect on the activity of the central nervous system in a number of ways. These include the physiological effects of microbiota, changes in the way the intestinal barrier works, and changes in the activity of neurons in the periphery. The gut-brain axis controls immunological activity, which is considered a crucial component of neurodegenerative diseases [149]. Research on the gut-brain axis suggests that the gut microbiota plays a significant role in the coordination of brain development and behavior, and that metabolites that are mediated by the gut microbiota are a primary regulator of these interactions [150].

Lipopolysaccharide (LPS) is the primary component of gram-negative bacteria's outer cell wall and is modulated by stress via changes in the gut microbiota [151]. LPS has triggered BBB degradation, which has been linked to a number of neurodegenerative diseases [152]. Toll-like receptors (TLRs) identify LPS and signal for the production of inflammatory cytokines such TNF α , IFN γ , and IL-6, which impact the hypothalamic-pituitary-adrenal (HPA) axis and its metabolites [153]. By crossing the BBB and altering neurotransmitter metabolism, LPS affects the activation of the HPA axis, the disruption of synaptic plasticity, activation of afferent nerve DFs, and the development of depression [154]. Decreases in tight junction proteins increase BBB permeability, but high MAC intake can correct this deficit [100].

Eucommia cortex polysaccharide (EP) intake effectively inhibits intestinal dysbiosis, thereby reducing neuroinflammation and serum endotoxin. Additionally, high EP consumption lowers the levels of glutamic acid and quinolinic acid in the hippocampus and aids in treating metabolic syndrome, which is a result of an obesogenic diet. The recovery of adult behavioral impairments and neurogenesis deficits in mice on an obesogenic diet has been facilitated by these effects [150].

The high consumption of MAC significantly increases the abundance of the Bacteroidetes phylum and decreases the abundance of the Proteobacteria phylum. Studies indicate that High MAC intakes improve the diversity and composition of the gut microbiota, which may contribute to the prevention of cognitive decline in mice fed a high-fat, low-DF diet [100]. Resistant dextrin increased the abundance of *Bifidobacterium*. *Bifidobacterium* and *Lactobacillus* metabolize glutamate to generate GABA, which can alter the expression of GABA receptors in key brain regions associated with central nervous system stress. Additionally, *Bifidobacterium* can improve mental health by increasing tryptophan levels, a precursor of serotonin, which increases the availability of serotonin [154]. PYY is associated with anxiety, and it can increase resistant dextrin GLP2 and PYY neuropeptide levels, which can improve anxiety [154,155]. It has also been reported that some types of inulin are antidepressant-like in behavioral patterns of depression [156].

5.6. Cancer

Even though cancer is caused by plenty of factors, diet is an important modifiable risk factor. DFs have been known for a long time as an essential dietary component that can influence cancer risk. DFs and colorectal cancer (CRC) have been the subject of much research [157]. There is conflicting information about the link between DF intake and the risk of colorectal adenoma (CRA), which is a precursor to colorectal cancer. A meta-analysis of case-control and cohort studies has been used to look into this link. This meta-analysis backs up the idea that a high intake of DF, especially DF from fruits and grains, is linked to a lower risk of CRA [158].

It has been indicated that fecal SCFAs concentrations are not correlated with the presence of adenomas or carcinomas, have poor predictive ability, and do not aid in the diagnosis of a person with one of these lesions [159]. SCFAs induce apoptosis in cancerous cells, regulate tumor suppressor gene expression via histone deacetylase inhibition and regulate cellular glucose metabolism [160]. On the other hand, comparing the fecal SCFAs concentrations of healthy people with those of people with carcinoma or adenoma showed that there is no link between fecal SCFAs concentrations and tumor load or the bacteria in the feces [159].

MAC-microbiota interactions can affect the colonic environment and prevent and control cancer independently from the potential effects of SCFAs [157]. Low MAC intake may result in intestinal mucosa glycans as a food source by microorganisms [161]. This weakens the epithelial mucosa, increases the microbial invasion of commensal bacteria, and triggers inflammation in gnotobiotic mice's epithelial cells [66]. Similarly, mice fed a Western diet low in DF showed increased microbial infiltration and changed MUC2 protein levels in the mucus layer [162]. Although it has not been proven that these changes are directly related to cancer, individuals with ulcerative colitis have an increased risk of developing CRC ranging from 2% to 18%, depending on the duration of the disease [163]. The literature indicate that MAC-mediated microbiota interactions may alter mucus production and mucosal immune responses

to anti-inflammatory and, subsequently, tumor suppressor profiles. However, the significance of these mechanisms in human populations has not yet been determined [157].

The results of studies examining the association between cereal DF consumption and the risk of various types of cancer have been inconsistent. Although cereal DF consumption significantly reduces the risk of gastrointestinal and head and neck cancer, it did not significantly reduce the risk of breast and colorectal cancer. On the other hand, no relationship has been found between female and genitourinary cancers and cereal DF consumption [164].

Inflammation, insulin resistance, hyperinsulinemia, and increased concentrations of circulating adrenergic or estrogenic hormones can stimulate prostate carcinogenesis. It has been shown that MAC intake plays a potentially protected role against prostate carcinogenesis through direct or indirect modulation of these mechanisms [165].

The biological mechanisms by which MAC exerts its anticarcinogenic effects are not yet fully understood, despite important developments regarding the role of microbiomes [166].

6. MACs and *Clostridioides difficile* infection

Clostridioides difficile (CD) is an opportunistic diarrheal pathogen. The most important risk factor for *Clostridioides difficile* infection (CDI) is the dysbiosis of the gut microbiota, which is typically brought on by antibiotic use. Hence, methods targeted at understanding and reducing CD pathogenesis may include treatments aimed at positively altering the composition and function of the gut microbiome [167].

Dietary fat increases the mortality rate related to CD [96]. In one study, the introduction of exogenous pig mucin glycans decreases host mucus consumption in the lack of dietary MACs and suppresses CD abundance [168]. Diets containing MAC mixtures such as inulin, xanthan gum, FOS have also been used to reduce CD burden below detection levels. This effect can also be observed by adding a complex mixture of MACs to the diet or adding inulin alone as a source of MAC for a simplified diet [96]. MACs are a particularly productive avenue for diet-oriented studies on CD. Inulin and FOS have different effects on CD loads in mice. There is a possibility that sources of MAC that eliminate CDI may not do so in a different microbiome and host [167]. The health effects of MACs are summarized in Table 1.

7. Conclusions

The gut microbiota is important due to its regulatory roles in health and disease. Dietary variables are among the most effective modulators of microbiota composition and function due to the reciprocal interaction between nutrition and gut microbiota. MACs are defined as carbohydrates that can be digested by bacteria. MACs are the primary energy source for colonic bacteria, and abundance of MACs promotes the proliferation of beneficial bacteria. Each MAC has unique properties and can be used as a sensitive microbiota modulator to support host homeostasis. Most of the effects of MACs on metabolism occur through SCFAs mechanisms. SCFAs serve as mediators in multiple pathways, such as intestinal homeostasis, endocrine effects, immunoregulation, and microbiota-gut-brain

Table 1
Summary of the health effects of MACs.

MACs	Health Effects	References
L-arabinose and Sucrose	<ul style="list-style-type: none"> • Influences body weight regulation • Activates intestinal gluconeogenesis 	[119]
Inulin and Resistant dextrin	<ul style="list-style-type: none"> • Improves islet B cell function • Decrease blood glucose • Reduces blood pressure 	[132]
Psyllium	<ul style="list-style-type: none"> • Reduces body weight • Regulates glycemic and cholesterol levels • Positively effective for chronic constipation 	[135]
B-Glucan	<ul style="list-style-type: none"> • Prevents elevated serum lipid levels 	[138]
Resistant starch	<ul style="list-style-type: none"> • Increases circulating GSH levels 	[140]
Inulin	<ul style="list-style-type: none"> • Modifies the intestinal barrier function • Provides anti-inflammatory benefits 	[143]
Pectic polysaccharides	<ul style="list-style-type: none"> • Modulates dysbiosis of the gut microbiota • Modulates the dysbiosis of the gut microbiota • Increases the diversity of gut microbiota 	[143]
Galacto-oligosaccharides (GOS)	<ul style="list-style-type: none"> • Improves in stool consistency • Reduces in the incidence and severity of loose stools • Inhibits the activation of the NF-kb signaling pathway Decreases the secretion of IL-6, IL-13, IL-18, and IL-33 	[146,147]
Eucommia cortex polysaccharide (EP)	<ul style="list-style-type: none"> • Inhibits intestinal dysbiosis • Reduces neuroinflammation • Reduces serum endotoxin 	[150]
Resistant dextrin	<ul style="list-style-type: none"> • Improve immune system function • Improve biomarkers of inflammation/anti-inflammation and mental health in T2DM patient 	[154]
Inulin, Xanthan gum and Fructo-oligosaccharides (FOS)	<ul style="list-style-type: none"> • Reduces CD burden below detection levels 	[167]

communication. MACs show health-enhancing effects with these metabolic functions. MACs are also effective on metabolic risk factors such as increased blood pressure, obesity, hyperglycemia, and hyperlipidemia. MACs are also thought to have positive effects on preventing NCDs and slowing down the course of disease. Based on the current data, it is thought that high MAC-containing diet consumption and personalized nutrition will have an impact on microbiota modulation and health.

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Data availability statement

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Abbreviations

2-AG	2-arachidonoylglycerol
5-HT	Serotonin
AIM2	Absent in melanoma 2
AMPs	Antimicrobial peptides
ARC	Arcuate nucleus
BBB	Blood-brain barrier
CCL2	Chemokine (CC-motif) ligand 2
CD	<i>Clostridioides difficile</i>
CDI	<i>Clostridioides difficile</i> infection
CRA	Colorectal adenoma
CRC	Colorectal cancer
CRP	C-reactive protein
DC	Dendritic cells
DF	Dietary fiber
EP	Eucommia cortex polysaccharide
FOS	Fructo-oligosaccharides
GABA	Aminobutyric acid
GLP-1	Glucagon-like peptide-1
GLP-2	Glucagon-like peptide-2
GOS	Galacto-oligosaccharides
GPCRs	G-protein-coupled receptors
GPR109A	G-protein-coupled receptor 109A
GPR41	G-protein-coupled receptor 41
GPR43	G-protein-coupled receptor 43
GSH	Glutathione
HbA1c	Hemoglobin A1c
HDAC	Histone deacetylase
HDL	High-density lipoprotein
HPA	Hypothalamic-pituitary-adrenal
IBD	Inflammatory bowel diseases
IECs	Intestinal epithelial cells
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL-1	Interleukin-1

IL-6	Interleukin-6
IL-10	Interleukin-10
IL-13	interleukin 13
IL-17	interleukin-17
IL-18	Interleukin-18
IL-33	interleukin 33
INF- γ	interferon gamma
ISAPP	International Scientific Association of Probiotics and Prebiotics
LDL	Low-density lipoprotein
LP	lamina propria
LPS	Lipopolysaccharide
MACs	Microbiota-accessible carbohydrates
MCP1	Monocyte chemoattractant protein-1
MCT-1	Monocarboxylate transporter 1
MUC2	Mucin-2 glycoprotein
NCDs	Non-communicable diseases
NDFCs	Nondigestible fermentable carbohydrates
NF-kB	nuclear factor kappa B
NLRP3	Nucleotide-binding oligomerization domain-like receptor 3
NLRP6	Nucleotide-binding oligomerization domain-like receptor 6
NPY	Neuropeptide Y
POMC:	Proopiomelanocortin
PPSs	Peptic polysaccharides
PYY	Peptide YY
SCFAs	Short-chain fatty acids
SCMT-1	Sodium-bound monocarboxylate transporter 1
T2DM	Type 2 diabetes
Tfh	T follicular helper cells
TG	Triacylglycerol
Th1	T helper cell 1
Th17	T helper cell 17
Th2	T helper cell 2
TLR4	Toll Like Receptor 4
TLRs	Toll-like receptors
TNF- α	Tumor necrosis factor alpha
Treg	regulatory T cells
TSLP	Thymic stromal lymphopoietin
VLDL	Very low-density lipoprotein

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2023.e19888>.

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