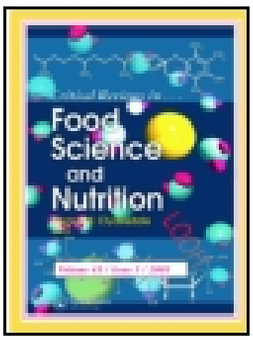

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REVIEW

Prebiotic inulin as a treatment of obesity related nonalcoholic fatty liver disease through gut microbiota: a critical review

Yaolian Hu, Jun He, Ping Zheng, Xiangbing Mao, Zhiqing Huang, Hui Yan, Yuheng Luo, Jie Yu, Junqiu Luo, Bing Yu, and Daiwen Chen

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ABSTRACT

The microbial-derived products, including short chain fatty acids, lipopolysaccharide and secondary bile acids, have been shown to participate in the regulation of hepatic lipid metabolism. Previous studies have demonstrated that prebiotics, such as oligosaccharide and inulin, have abilities to change the concentration of microbial-derived products through modulating the microbial community structure, thus controlling body weight and alleviating hepatic fat accumulation. However, recent evidence indicates that there are individual differences in host response upon inulin treatment due to the differences in host microbial composition before dietary intervention. Probably it is because of the multiple relationships among bacterial species (e.g., competition and mutualism), which play key roles in the degradation of inulin and the regulation of microbial structure. Thereby, analyzing the composition and function of initial gut microbiota is essential for improving the efficacy of prebiotics supplementation. Furthermore, considering that different structures of polysaccharides can be used by different microorganisms, the chemical structure of processed inulin should be tested before using prebiotic inulin to treat obesity related nonalcoholic fatty liver disease.

KEYWORDS

Hepatic fat content; Individual differences; lipid metabolic disorders; physicochemical characterization; precision prebiotic

1. Introduction

Nonalcoholic fatty liver disease (NAFLD), including simple nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), characterized by an excessive hepatocyte triglyceride accumulation, is a risk factor for hepatocellular carcinoma (HCC) (Brunt et al. 2015; Lambertz et al. 2017). The epidemic of obesity leads to an increased prevalence of liver cancer worldwide, in which patients with obesity are more likely to develop fatty liver and liver damage (Porras et al. 2018; Younossi et al. 2019). There are many factors influencing the initiation and progression of obesity, including genetic, environmental and commensal microbial factors (Murea, Ma, and Freedman 2012). Increasing evidence shows that gut microbiota plays a critical role in controlling obesity and NAFLD (Duranti et al. 2017; Soderborg et al. 2018; Vallianou, Stratigou, and Tsagarakis 2018). Some bacterial species are closely related with the increased energy harvest in host, and the bacterial metabolites, such as lipopolysaccharide (LPS) or secondary bile acids (BAs), have also been reported to involve in the occurrence of lipid metabolic disorder in liver (Cani et al. 2012; De Preter et al. 2011; Duranti et al. 2017; Yang et al. 2019). Importantly, the microbiota living in the host gut is very plastic, implying that it can be easily shaped by dietary pattern and components (Zmora, Suez, and Elinav 2019). Thus, researchers believe that the changes in diet can modulate gut microbial structure and subsequently influence the development of obesity related metabolic diseases.

A considerable amount of studies showed that the use of prebiotic, probiotic and fecal microbiota transplantation (FMT), aiming to optimize intestinal microbial structure, can ameliorate the harmful bacteria-induced lipid metabolism disorder (Leylabadlo et al. 2020; Meng et al. 2020). Inulin, a fermentable linear polysaccharide consisting of fructan and glucose, has been considered as a high-quality prebiotic (Kelly 2008; van der Beek et al. 2018). According to the amounts of the sugar monomers, namely degree of polymerization (DP), inulin can be classified into short-chain inulin ($2 < DP < 25$) and long-chain inulin ($10 < DP < 60$), and native inulin (directly extracted from plants, a mixture with DP ranging 2-60) (He et al. 2017; Van Loo 2004). Inulin supplementation in mice fed high-fat or high-sugar diets has been reported to alleviate fat accumulation through regulating the gut microbiota (Bianchi et al. 2019; Druart et al. 2013). Inulin can selectively promote the growth of *Bifidobacterium* and *Lactobacillus*, and these beneficial bacteria help decrease blood cholesterol content and reduce body weight gain (Buclaw 2016; Kumar et al. 2012; Pachikian et al. 2013). Wiele et al. (2007) presented that inulin (DP ranging 2-60) addition elicited a greater inhibitory effect on the opportunistic pathogens in the descending colon vessel and a higher bifidobacterial count than the supplementation of prebiotic oligofructose (DP ranging 2-20).

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Additionally, inulin remains undigested in small intestine but can be fermented to the short chain fatty acids (SCFAs), referring primarily to acetate, propionate and butyrate (Louis, Flint, and Michel 2016). These fermentation products have also been shown to alleviate NASH in mice in a AMPK-dependent manner (Song et al. 2019; Wang et al. 2019a). Thus, inulin intervention appears as a promising potential treatment for lipid metabolism disorder. However, several studies demonstrated that SCFAs possessed some detrimental effects, as an example, the fructose-derived acetate was a substrate of hepatic acetyl-CoA synthesis, contributing to energy accumulation and fatty liver disease occurrence (Serino 2019; Tirosh et al. 2019; Zhao et al. 2020). Furthermore, recent researches indicated that the physiological response varied significantly upon prebiotic intervention among different obese patients (Holmes et al. 2020; Kolodziejczyk, Zheng, and Elinav 2019; Rodriguez et al. 2020). This may be explained through analyzing the composition of gut microbiota before the dietary supplementation (Cantu-Jungles and Hamaker 2020). Rodriguez et al. (2020) demonstrated that the efficacy of native inulin supplementation may be modified by the pre-intervention gut microbiota composition, implying that the individual variation should be taken into consideration in patients when treated with native inulin for metabolic diseases. Due to the unique glycan preferences by different bacteria, dietary fibers had varying impacts between individuals on gut microbiota composition and microbial metabolites (Hamaker and Tuncil 2014; Riviere et al. 2018). Besides, inulin with different DP was utilized by different bacterial genera (De Vuyst and Leroy 2011; Falony et al. 2009a). For example, the inulin with a DP of 15 increased the number of *Bifidobacterium* and *Lactobacillus* compared to inulin DP 10 or inulin DP 24, and elevated the productions of propionate and butyrate (Han et al. 2014). These studies suggest that inulin intervention is difficult to treat precisely metabolic disorder via modulating the gut microbiota. The researchers need to have a comprehensive understanding of the structure characteristics of inulin and the physiological status of the subjects before dietary intervention. In this review, based on the key words of "inulin" and "metabolism", a total of 650 articles between 1970 and July 2020 were searched from web of science core collection, and key articles were analyzed with aid of Mendeley Desktop based on their content. We focus on the roles of gut microbiota and its metabolites in progressions of the obesity-related metabolic diseases such as NAFLD. The biological effects of inulin and the connection between these effects and DP of inulin will be discussed in this article. Considering the physiological features of individuals, this article provides an outlook for treating the metabolic diseases through personalized nutrition.

2. The microbiota and its metabolites in obesity and NAFLD

Compared to those normal body weight individuals, excess energy in obese patients gets to be stored as fat in hepatocytes, which easily lead to an accumulation of fat in liver (Moreira et al. 2018; Schwimmer et al. 2019). Increasing evidence supports a central role of gut microbiome in promoting energy intake and NAFLD development in obese patients (Moreira et al. 2018; Schwimmer et al. 2019; Soderborg et al. 2018). A study by Gordon et al. published in 2004 showed that feeding a high-fat diet (HFD) did not lead to obesity in germ-free mice (Bäckhed et al. 2004). In 2006, they further found that the obesity phenotypes were transferred between individuals by FMT, suggesting that gut microbiota plays a causal role in controlling the obesity (Turnbaugh et al. 2006). The carbohydrate-active enzymes (CAZymes) encoded by the genes belong to Actinobacteria, Firmicutes and Bacteroidetes have been shown to participate in the fermentation of indigestible carbohydrates, and the fermentation products can provide energy for the body (Flint et al. 2012). As an example, the high ratio of Firmicutes to Bacteroidetes have been associated with an enhanced capacity for energy harvest in host (Turnbaugh et al. 2006). However, Schwiertz et al. (2010) presented that compared to lean subjects, obese subjects show a higher proportion of Bacteroidetes. These findings engendered the controversy concerning the roles of the ratio of Firmicutes to Bacteroidetes in development of obesity. In addition, indigestible carbohydrates can be fermented to produce the metabolites (e.g., SCFAs) in gut through microbial fermentation, and these microbially produced SCFAs are easily absorbed into the portal vein (Koh et al. 2016). SCFAs in blood circulation, such as propionate and acetate, have been reported to act as precursors for gluconeogenesis or lipogenesis (den Besten et al. 2013).Kindt et al. (2018) found that compared to germ free mice, dietary fiber-derived acetate has been involved in hepatic synthesis of fatty acids in specific pathogen-free mice. Some evidence also demonstrated that acetate and propionate were significantly positively correlated with BMI and fasting insulinemia, and these results were consistent with *Kindt*'s study (Perry et al. 2016; Salazar et al. 2015). However, controversially, previous studies have indicated that SCFAs are capable of decreasing hepatic lipid content and reducing risk factors related with obesity in a SCFAs receptors-dependent way (Canfora, Jocken, and Blaak 2015; Weitkunat et al. 2015). Such discrepancies between these research results are likely due to the fact that the effects of SCFAs in the gut on cells function are different from that in the circulatory system (Macfarlane and Macfarlane 2011).

Other microbial-derived products including LPS, bacteria-derived ethanol and secondary bile acid, like SCFAs, are also the key media of communication between gut microbiota and host (Canfora et al. 2019; Tremaroli and Bäckhed 2012). These microbial-derived products, as mediators, can be involved in the regulation of host metabolism, and once gut barrier damage occurs, an increase in intrahepatic secondary bile acids and LPS can induce and promote liver lipid disorders (Carpino et al. 2020; Chopyk and Grakoui 2020). The composition of gut microbiota in obese patients is characterized by a high number of *Escherichia coli* and *Bilophila*, which are often accompanied with

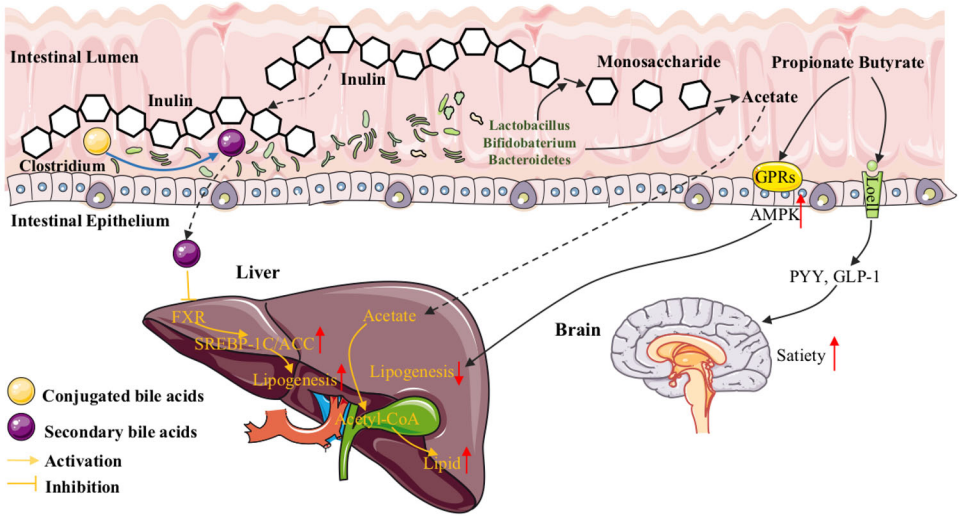

Figure 1. Proposed Mechanisms for the Effects of Inulin on Hepatic Lipogenesis. Inulin is quickly and extensively metabolized to monosaccharide and SCFAs (e.g., acetate, propionate and butyrate) by gut microorganisms such as Lactobacillus, Bifidobacterium and Bacteroidetes. Acetate is a substrate of hepatic acetyl-CoA synthesis, contributing to hepatic lipogenesis. However, SCFAs, especially propionate and butyrate, can stimulate the secretion of PYY and GLP-1 via GPR41 and GPR43, controlling appetite and energy intake in host. The elevated SCFAs levels can also inhibit the expression of lipogenesis gene ACC and its regulatory protein SREBP-1c through activating GPRs-AMPK pathway. On the other hand, inulin may be able to regulate the production of secondary bile acid via the secondary bile acids producer, then affecting the expression of hepatic FXR and lipogenesis gene ACC. GPRs, G protein-coupled receptors; PYY, peptide YY; GLP-1, glucagon-like peptide 1; FXR, farnesoid X receptor; AMPK, adenosine monophosphate (AMP)-activated protein kinase; ACC, acetyl-CoA carboxylase; SREBP-1c, sterol regulatory element binding protein-1c.

impaired gut barrier function (Sanz, Santacruz, and Gauffin 2010; Thaiss 2018; Tilg et al. 2020). The liver is linked to the gut through the portal circulation, and once disruption of gut barrier occurs, pathogen-associated molecular patterns (PAMPs) such as LPS would be release into the portal vein (Schnabl and Brenner 2014; Seki and Schnabl 2012). Carpino et al. (2020) noted that LPS localization in human hepatocytes was higher in patients with NAFLD when compared with the healthy group. An increased LPS content in hepatocytes was associated with a higher expression of pNF-κB through a TLR4-mediated pathway, facilitating the transition from fatty liver to NASH (Carpino et al. 2020). In addition to LPS, secondary bile acids are another important risk factor for NSAH and HCC (Jia, Xie, and Jia 2018; Jiao et al. 2018). Bile acids, synthesized from hepatic cholesterol, are classified as primary bile acids and secondary bile acids, and gut microbiota can convert primary bile acids to secondary bile acids (Gérard 2013). Jiao et al. (2018) suggested that an increased abundance in *Escherichia coli* and *Bilophila*, which belong to taurine metabolizing bacteria, can help the deconjugation of the taurine conjugates of primary bile acids, contributing the production of secondary bile acids. In liver, secondary bile acids, including lithocholic acid (LCA) and deoxycholic acid (DCA), have been reported to increase fatty acid synthesis and reduce fatty acid oxidation through the inhibition of bile acid receptor Farnesoid X receptor (FXR) (Jiao et al. 2018; Mouzaki et al. 2016). Hepatic FXR is thought to decrease the expression of sterol regulatory element binding protein-1c (SREBP-1c) and acetyl-CoA carboxylase (ACC) in liver (Chávez-Talavera et al. 2017; Molinaro, Wahlström, and Marschall 2018). However, the effects of secondary bile acids on intestinal FXR are still controversial in human and animal studies (Kliewer and Mangelsdorf 2015; Long, Gahan, and Joyce 2017; Schubert et al. 2017). Some results have pointed out that secondary bile acids have an activation effect on FXR in the intestine, then triggering hepatic fat synthesis pathway via FXR-fibroblast growth factor-15/19 (FGF-15/19) (Kliewer and Mangelsdorf 2015; Long, Gahan, and Joyce 2017; Schubert et al. 2017). Anyway, it is an established fact that secondary bile acids are positively correlated with liver fat content (Jiao et al. 2018). Those results indicate that gut microbiota and its products are closely involved in the pathogenesis or treatment of NAFLD.

3. How to degrade prebiotic inulin by the gut microbiome

Prebiotics, most of which refer to non-digestible carbohydrate polymers consisting of unbranched or branched sugar chains, such as high-fermentable dietary fibers, are able to be fermented by gut microbiota (Gibson et al. 2017; Nicolucci and Reimer 2017). The microbial fermentation products, as an energy and carbon sources, can be utilized selectively for the growth of beneficial bacteria (Cockburn and Koropatkin 2016; Joglekar et al. 2018). Thus, the gut microbial community structure could be purposefully regulated via providing microbiota-accessible carbohydrates (MACs), subsequently optimizing microbial community structure (Cockburn and Koropatkin 2016; Joglekar et al. 2018). Inulin, as a well-recognized prebiotic, can be degraded by *Bifidobacteria* or *Bacteroides* (Figure 1), and promotes the growth of *Bifidobacteria* (Kolida, Tuohy, and Gibson 2002; Slavin 2013). In a randomized, double blind, parallel and placebo-controlled trial, the researchers noted that inulin-type fructans, the fructans mixtures with different DP, increased the number of *Bifidobacterium adolescentis*, *Bifidobacterium longum* and *Bifidobacterium pseudocatenulatum* in obese women, then human subjects showed an

improved fat mass percentage (Salazar et al. 2015). The correlation analyses showed that improved host metabolic markers in the gut of subjects were significantly closely related to a high abundance of beneficial bacteria such as *Bifidobacterium spp* (Salazar et al. 2015). These data demonstrate that the modification of inulin on gut microbiota are involved in the regulation of host fat content. However, in recent years, clinical studies have suggested that prebiotic inulin does not invariably increase the number of beneficial bacteria, and these trials do not present consistent results across individuals (Bouhnik et al. 2004; Healey et al. 2016; Healey et al. 2018; Rios-Covian et al. 2013). Some researchers presented that inulin supplementation affected differently gut microbiota composition of individuals due to distinct pre-intervention gut microbiota characteristics (Chijiiwa et al. 2020; Kolida, Meyer, and Gibson 2007; Rodriguez et al. 2020). The gut microbiota, which contains multiple fructan polysaccharide utilization loci (PULs) on the baseline, tended to be changed after inulin intervention (Bolam and Sonnenburg 2011; Sonnenburg et al. 2010). This means that it is essential to learn how gut microbiota break down prebiotics before using prebiotics to regulate the microbiota.

Most gut bacteria species possess polysaccharide-processing genes, which has been described as PULs, and they have the capacity to express CAZymes degrading non-digestible carbohydrates (Hamaker and Tuncil 2014). However, previous studies suggested that not all microbial community members (they have the capacity to process dietary polysaccharides) could benefit from polysaccharide metabolites (Cantu-Jungles and Hamaker 2020; Falony et al. 2009a). One reason is that there are the differences in glycan-degrading abilities of distinct species, which have been shown to be related with these differences in CAZymes encoded by PULs between bacterial species (Koropatkin, Cameron, and Martens 2012; Sonnenburg et al. 2010). Hamaker et al. presented that a type of dietary fiber, containing a variety of sugars, linkage types, and branching patterns, belonging to highly specific fibers that are accessed and utilized only by a narrow group of bacteria (Cantu-Jungles and Hamaker 2020). However, another low-specificity fiber such as inulin and fructooligosaccharides, would be degraded by many bacteria, leading to competitive pressure within the intestine (Cantu-Jungles and Hamaker 2020). Increased competitive pressure in turn was capable of affecting easily the niche of microbes, and the lower glycan-degrading abilities may cause the lack of their competitiveness for some microbes (Ferreiro et al. 2018). In a vitro coculture model, Falony et al. (2009b) found that compared to *Bifidobacterium longum*, *Roseburia inulinivorans* hardly use inulin (average DP $>$ 23) due to a lack of competitiveness. In 2019, Patnode and colleagues developed a method for tracking fiber digestion, using forward genetic screens and artificial food particles, and they explored the mechanisms how gut microorganisms compete with each other for dietary fiber (Patnode et al. 2019). For example, researchers found that the abundance of *Bacteroides vulgatus* increased upon omission of *Bacteroides cellulosilyticus* in the presence of pea fiber (Patnode et al. 2019). They identified that both the proteins encoded by *B. vulgatus* PUL27 and by *B. cellulosilyticus* PUL6 could be responsible for the degradation of pea fiber, but there was a non-redundant glucan degradation ability of *B. cellulosilyticus* (Patnode et al. 2019). This demonstrates that the negative interactions between *B. cellulosilyticus* and *B. vulgatus* may be caused by the differences in glucan-degradating CAZymes encoded by PUL between the two strains. Chung et al. (2016) found that pH value also plays an important role in controlling interspecies competition, and the proportion of *Faecalibacterium prausnitzii* 16S rRNA gene copies fell while the proportion of Bacteroidetes sequences increased with the increasing of pH value in the inulin-fed fermenters. In addition to the competition mentioned above, there is also a cross-feeding system between gut symbionts (Boger, van Bueren, and Dijkhuizen 2018; Turroni et al. 2018). In vitro assays, it revealed that when leaving *Bacteroides dorei* out of the microbial consortium using inulin as carbon source, the other 10 species showed a decrease in their abundance, and the amount of residual inulin also increased, suggesting that *B. dorei* is important for inulin degradation and the growth of the consortium (Gutiérrez and Garrido 2019). Inulin is a linear polymer molecule with mainly beta-2,1 linked fructan chain attached to glucose, and *B. vulgatus* lacks the enzyme necessary for inulin degradation (Rakoff-Nahoum, Foster, and Comstock 2016; Slavin and Feirtag 2011). Rakoff-Nahoum, Foster, and Comstock (2016) demonstrated that *B. ovatus*-derived inulin breakdown products were able to be used by *B. vulgatus*. Collectively, these results demonstrate that the interactions between resident microbial communities, such as interspecies competition and the cross-feeding, can affect the changes of microbial community structure upon inulin supplementation. The initial gut microbiota varies widely among individuals, which may determine the degradation of inulin, gut microbiota changes and the efficacy upon inulin intervention (Holmes et al. 2020). A new finding provides evidence that compared to non-responders, who refer to a part of obese patients with no anthropometric or metabolic changes on native inulin treatment, the gut microbiota of responders was characterized by a higher abundance of *Akkermansia* and *Butyricicoccus* before the dietary intervention (Rodriguez et al. 2020). This underlines the importance of individuality of gut environment. However, Rodriguez et al. (2020) found that the abundance of *Akkermansia*, the major determinants of responders, was decreased during inulin intervention, implying that the initial number of *Akkermansia* and *Butyricicoccus* were not key drivers to improve metabolic health. In the future, the exact mechanism of which needs to be further explored.

4. Inulin affects host lipid metabolism via SCFAs

Numerous studies in animal and human models have reported the positive effects of inulin on lipid profile and energy homeostasis (Delzenne et al. 2002; Kaden-Volynets et al. 2019; Nicolucci et al. 2017). Song et al. (2019) presented that hepatic steatosis in obese mice fed native inulin was alleviated, moreover, feeding native inulin increased the

abundance of *Prevotellaceae UCG 001* and decreased the abundance of *Alistipes*, *Anaerotruncus and Family XIII UCG001* in genetically obese mice (leptin gene deficient mice). According to the results of the correlation analysis, *Prevotellaceae UCG 001* had a significant positive correlation with the AMPK signaling pathway in cecum, which may contribute to the low level of serum total cholesterol (TC) and the ratio of TC to high-density lipoprotein cholesterol (HDL-C) (Song et al. 2019). *Prevotellaceae* in gut are well known to produce SCFAs, indicating that inulin can increase the number of SCFAs-producing bacteria and then the level of intestinal SCFAs (Li et al. 2019). AMPK in cecum is able to be phosphorylated and activated when SCFAs recognized and bound to short-chain fatty acid receptors (GPR41/FFAR3 and GPR43/FFAR2), and the activation of AMPK signaling can trigger the process of fatty acid oxidation and inhibit fatty acid synthesis in liver or adipose tissue (Sharma et al. 2018; Song et al. 2019). A study utilizing MDG-1, an inulin type fructan (average molecular weight = 3400 Da) extracted from *Ophiopogon japonicas*, also showed that 8% MDG-1 treatment increased the relative abundance of SCFA-producing bacteria and stimulated the production of SCFAs in HFD-fed mice (Wang et al. 2019b). The researchers presented that elevated SCFAs levels inhibited the expression of lipogenesis gene *ACC* and its regulatory protein SREBP-1c through activating GPRs-AMPK pathway, then preventing lipid accumulation in liver and inhibiting the process of NAFLD (Wang et al. 2019b). Besides, SCFAs, especially propionate, can stimulate the secretion of gut hormones peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) via GPR41 and GPR43, affecting appetite and energy intake in host (Brooks et al. 2017). Brooks et al. (2017) noted that HFD supplemented with 7.5% inulin reduced the percentage of body weight change and liver triglyceride content in high-fat diet-induced obesity mice, however, this protective effect was lost in FFAR2 knock-out mice. The further analysis showed that circulating PYY was increased following inulin supplementation in WT but not Ffar2-/- mice, suggesting that the ability of inulin to reduce food intake and prevent weight gain is dependent on FFAR2 (Brooks et al. 2017). These results indicated that inulin had the capacity to exert positive effects on obesity-related lipid metabolism disorders through activating SCFAs receptor and its related signaling pathways (Figure 1).

However, several researchers noted that some SCFAs which were absorbed into the blood, as energy substrate can participate in carbohydrate synthesis (Kindt et al. 2018; Weitkunat et al. 2015). Isken et al. (2010) noted that compared to insoluble fiber, long-term consumption of soluble fiber increased body weight and hepatic triacylglycerol contents, which probably result from host energy imbalance that there are increasing available energy substrates SCFAs due to soluble fiber fermentation. There seems to be an increasing concern that prebiotic inulin may affect the normal lipid metabolism in liver. Interestingly, inulin-type fructans generated lower rates of SCFA production compared to rhamnose in an in vitro fermentation model (Reichardt et al. 2018). A human feeding study, aiming to describe the fermentation of three dietary fibers, also noted that resistant starch from potatoes, not inulin, ranked the highest for the production of fecal total SCFA and butyrate (Baxter et al. 2019). The baseline abundance of *Ruminococcus bromii* may be responsible for increasing butyrate production (Baxter et al. 2019). These results demonstrated that the health promoting effects of inulin intervention may be less consistent across individuals, highlighting the importance of initial gut microbiota in personalized nutrition. Additionally, in 2019, Chambers et al. (2019) presented that unlike acetate, which are directly involved in acetyl-CoA synthesis, propionate has been proven to inhibit hepatic *de novo* lipogenesis. Supplementation with inulin-propionate ester (IPE), a dietary compound which delivers propionate to the colon and augments colonic propionate concentration, may attenuate acetate-induced hepatic lipid accumulation (Chambers et al. 2019). 20 g/day inulin supplementation in adults with NAFLD increased intrahepatocellular lipid, whereas no changes occurred in IPE-supplemented patients (received 14.6 g inulin with 5.5 g bound propionate) (Chambers et al. 2019). IPE has also been demonstrated to stimulate the release of PYY and GLP-1 and suppress appetite, thus preventing weight gain (Chambers et al. 2019; Chambers et al. 2015). These results indicate that IPE, aiming to increase propionate not acetate concentration, provide a novel tool in the treatment of NAFLD.

5. Inulin regulates lipid metabolism through other pathways rather than SCFAs-mediated pathways

Some evidence noted that inulin can also regulate lipid metabolism through other pathways rather than SCFAs-mediated pathways (Dehghan et al. 2014; Yang et al. 2019). An accretion of serum LPS always occurs in NASH patients, which accompanied by LPS induced-inflammation (Sharifnia et al. 2015). According to recent studies, inulin-treated rodents exhibited a low abundance of *Desulfovibrio*, *Mucispirillum and Ruminiclostridium_6 abundance*, which produce LPS (Zhang et al. 2018). Dehghan et al. (2014) further demonstrated that compared to the control group, supplementation with high-performance inulin, a high-molecular weight prebiotic (DP > 10), decreased the serum LPS level in patients with type 2 diabetes, improving inflammatory status associated with obesity. Besides, secondary bile acid was reported to aggravate the metabolic disorders (Jiao et al. 2018). Notably, dietary fiber, as platforms, can bring conjugated bile acids and gut bacteria into close proximity, subsequently increase the production of secondary bile acid (Makki et al. 2018). In 2018, an unexpected study reported by Singh et al. (2018) noted that dysbiotic mice fed soluble fibers, such as inulin (DP > 23), pectin and fructooligosaccharides (DP: between 2 and 8), exhibited an increased concentrations of secondary bile acids in the circulatory system, following by the occurrence of HCC. Surprisingly, the negative effect of soluble fibers on liver function was not observed in germ-free nor antibiotics-treated mice (Singh et al. 2018). Toll-like receptor 5 deficient (T5KO) mice has been proposed as an animal model

of microbiota-dependent metabolic syndrome (Vijay-Kumar et al. 2010). To further elucidate the mechanism by which inulin induces HCC, T5KO mice treated with vancomycin was used, which would deplete preferentially Gram-positive bacteria, including *Lachnospiraceae*, *Ruminococcaceae*, *Bifidobacteria* and *Clostridium cluster XIVa* (Singh et al. 2020). These microorganisms can express bile hydrolase or 7 α-hydroxylase, contributing to synthetize secondary bile acids (Scott et al. 2014). Singh et al. (2020) presented that with the decrease of the secondary bile acids producer, the concentrations of DCA and LCA were decreased in serum, thus preventing the progression of HCC in T5KO mice fed inulin (DP $>$ 23). This implies that abnormal test results might be obtained when subjects show a high abundance of secondary bile acids producer during inulin treatment. Overall, current findings provide support for the view that the beneficial effects of inulin, which refer to selectively affect the growth of some beneficial bacteria, are essential for improving host lipid metabolism. Based on this, synbiotic, a combination of probiotics and prebiotics such as *Lactobacillus*-inulin synbiotic, may be considered a promising treatment for metabolic diseases (Ke et al. 2019; Tajadadi-Ebrahimi et al. 2014).

6. What needs to do before dietary inulin intervention

While data on the contradictory effects of inulin on lipid metabolism have been presented in emerging literature above, the metabolic changes of subjects upon inulin intervention are definitely related with the regulation of inulin on gut microbiota (Chambers et al. 2019; Singh et al. 2018). Current evidence demonstrates that many factors, including the physiological conditions of the animals and the physicochemical characteristics of dietary fiber, can affect dietary fiber fermentation and their functional effects (Chen et al. 2017; van de Wiele et al. 2007; Van Loo 2004). As mentioned above, inulin is divided into different types of inulin by its DP, and DP variations lead to differences in its solubility and fermentability (Van Loo 2004). Inulin with different DP can stimulate different bacterial strains, which may cause the varying metabolic responses among animals or human (De Vuyst and Leroy 2011). A study on effects of low-performance inulin (LPI: DP $\leq$ 9) and high-performance inulin (HPI: DP $\geq$ 23) on liver injury of obese mice demonstrated that LPI increased the abundance of *Barnesiella*, *Bacteroides*, and *Parabacteroides* compared to HPI, whereas the abundance of secondary bile acids producer *Clostridium XIVa* was decreased in mice fed LPI (Du et al. 2020). The researchers noted that LPI treatment leaded to reduce the excessive accumulation of liver fat, which may be mediated by improved gut microbiota structure (Du et al. 2020). Chen et al. (2017) noted that due to prolonged fermentation, long-chain ($10 <$ DP < 60) but not short-chain inulin ($2 <$ DP < 25) can ameliorate diabetes through improving gut integrity and barrier function. The researchers further evaluated the attenuating effects of long-chain inulin-type fructans ($10 <$ DP < 60) on pancreatitis induced by caerulein in mice, which indicated that a slower fermentation rate of long-chain inulin would ensure more endurable protective effect against inflammation of remote organs compared with short-chain inulin (He et al. 2017; Van Loo 2004). These existing research results show the importance of analyzing the physicochemical properties of prebiotic before dietary intervention (Zhu et al. 2017). Recently, an inconsistent study showed that both inulin ($2 <$ DP < 60) and short-chain inulin (average DP $= 4$) reduced body weight and serum lipid level in obese mice (Zhu et al. 2019), the result indicated presented that the regulatory effect of inulin on the lipid metabolism may be closely related with an optimized microbial community structure instead of chain length, however, this is an area that requires further investigation.

In addition to DP, as noted above, individual differences, especially the differences in the microbial ecology before dietary intervention, also play key roles in the efficacy of dietary fiber (Hjorth et al. 2020; Rodriguez et al. 2020). Similar to Rodriguez's research, Chijiiwa et al. (2020) support that there is a clear separation between inulin-responders and non-responders before the dietary intervention, and the metabolic response to inulin among obese patients can be predicted due to a subset of specific bacteria. This means that in order to predict the personalized response to diet, some effective technical tools are needed to evaluate the microbiome features of dietary-responders (Nunes-Alves 2016; Wan and Jena 2019). At present, direct sequencing of the 16S rRNA gene in bacterial detection can provide taxonomic (e.g. composition) information by using reference genomes (Goodrich et al. 2014). Metagenomic sequencing provides information regarding all genes present in the sample (e.g., composition and function), but the high cost of metagenomic sequencing prohibits its widespread use (Jovel et al. 2016). In addition, metabonomics, such as transcriptome, proteomics, phosphoproteomics or lipid metabonomics, are able to be used to find biomarker metabolites (Garcia-Perez et al. 2017; Pedersen et al. 2018; Tang et al. 2019; Xiong et al. 2017). Chijiiwa et al. (2020) developed a single-cell genome sequencing technique, which would provide single bacterial genetic information and identify specific bacteria responsible for inulin fermentation independent of reference genomes. The researchers established that two *Bacteroides* draft genomes (IMSAGC_001 and IMSAGC_004), both of which possess inulin PULs such as susC/D homolog pairs and so on, play a vital role in the degradation of inulin (Chijiiwa et al. 2020). According to these microbiome features, dietary responsiveness among obese patient can be predicted, which are required for treatments of lipid metabolic disorders via designing personalized diet (Kolodziejczyk, Zheng, and Elinav 2019; Mendes-Soares et al. 2019; Zeevi et al. 2015). However, it is still difficult to combine host microbial structure with personal lifestyle or genetic factors when dealing with big data (Loughman and Staudacher 2020). This could be feasible if you simply determine whether there are characteristic bacteria or metabolites in the host. Altogether, in order to precisely improve the metabolism disturbance, there is a need

for designing personalized diets based on the physiological characteristics of metabolic disorder patients, combined with the physicochemical characteristics of dietary fiber (Chijiiwa et al. 2020; Van Loo 2004). Besides, it is essential for verifying the effect of personalized diet through large-scale prospective experiment before clinical application, and in this process, in vivo and in vitro experiments should also be conducted to explore how the target bacteria or metabolites cause physiological changes in host (Noureddin et al. 2020; Rodgers and Collins 2020).

7. Conclusion

The gut microbiota and microbial-derived products have been proven to be relevant to hepatic lipid metabolism balance. Inulin, as a prebiotic, can be degraded by gut microorganisms, subsequently regulating the microbial composition and the concentration of microbial-derived products. Thus, inulin supplement may be a novel approach to the treatment of metabolic diseases. However, there are diverse relationships among gut microorganisms due to their differences in glycan-degrading abilities, which will affect the degradation of polysaccharides. This may lead to an unexpected result that individuals with different initial gut microbiota respond differently to dietary inulin intervention when aiming to modulate microbiota structure. In addition, the chemical structure of inulin may also determine its efficacy. Thus, targeting therapy for obesity related NAFLD would require to pay more attention to on the initial gut microbiota and the mechanism how gut microbiota degrade prebiotic. Based on the data from analyzing initial gut microbiota, combining with physicochemical properties of dietary supplement, it is possible to develop more precise treatment for the patients with NAFLD.

Conflict of interest

There are no conflicts of interest to declare.

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Data availability statement

Data Sharing Is Not Applicable To This Article As No New Data Were Created Or Analyzed In This Study.

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