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REVIEW

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Effects of natural mono- and di-saccharide as alternative sweeteners on inflammatory bowel disease: a narrative review

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ABSTRACT

Objectives: The incidence of inflammatory bowel disease (IBD) is increasing globally, and excessive added sugar consumption has been identified as one of the contributing factors. In the context of IBD, it is essential to explore functional sweeteners that can improve metabolic health and minimize the risk of IBD-related symptoms. This review article aims to shed light on the effects of natural mono- and di-saccharides as alternative sweeteners, specifically focusing on potential benefits for IBD.

Methods: A comprehensive literature review was performed using PubMed and Google Scholar databases with articles published after the year 2000. The search terms 'IBD', 'added sugar', 'sweeteners', 'mono-saccharide', and 'di-saccharide' were combined to retrieve relevant articles. A total of 21 manuscripts, aligning with the objectives of the study, were selected. Papers focusing on artificial or high-intensity sweeteners were excluded to ensure relevant literature selection.

Results: Multiple studies have emphasized the association between the high consumption of added sugars such as simple sugars and the increased risk of developing IBD. This is suggested to be attributed to the induction of pro-inflammatory cytokine productions and dysbiosis of the gut microbiota. Consequently, there is a growing demand for safe and functional sweeteners, in particular mono- and di-saccharides, that can serve as alternatives for IBD patients. Those functional sweeteners regulate inflammation, oxidative stress, and Intestinal barrier protection, and restore microbiome profiles in various IBD models including cells, animals, and humans.

Conclusions: Understanding these mechanisms resolves the link between how sugar consumption and IBD, and highlights the beneficial effects of natural alternative sweeteners on IBD when they were administered by itself or as a replacement for simple sugar. Further, exploration of this relationship leads us to recognize the necessity of natural alternative sweeteners in dietary planning. This knowledge could potentially lead to more effective dietary strategies for individuals with IBD.

KEYWORDS monosaccharide, disaccharide, sucrose, alternative sweetener, inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD) is known as a chronic inflammatory disease that primarily impacts the gastrointestinal (GI) tract and induces immune system disorder [1]. The primary manifestations of IBD consist of two distinct conditions: Crohn's Disease (CD) and ulcerative colitis (UC). The CD has the potential to affect any part of the gastrointestinal tract and exhibits transmural involvement. Colonoscopy findings associated with CD include skip lesions, cobblestoning, ulcerations, and strictures. On the other hand, UC typically occurs exclusively in the colon and affects only the mucosa and submucosa. Classic colonoscopy findings for UC involve pseudopolyps and continuous areas of inflammation [1]. Accumulating evidence suggests that both the incidence and prevalence of IBD are dramatically increasing worldwide [2]. Estimations indicate that around 1.3% in the United States (US) are affected by IBD. In North America, the CD incidence rates vary between 0 and 20.2 per 100,000 individuals per year, while for UC they range from 0 to 19.2 per 100,000 individuals per year. The prevalence rates range from 25.9 to 318.5 cases per 100,000 individuals for CD and from 37.5 to 248.6 cases per 100,000 individuals for UC [3, 4]. In comparison to Western countries, South Korea has a lower prevalence of IBD. However, there is a gradually increasing trend in the incidence rate of the disease in the country. Over the past 10 years in South Korea, the number of patients with IBD has increased by 66.5%, with 68,524 patients reported in 2018 compared to 41,163 patients in 2009 [5]. IBD patients have various symptoms including include weight loss, diarrhea, bleeding, and abdominal pain accompanied by persistent inflammatory responses on the mucosal surface [6]. Inflammation in IBD can be triggered by a variety of factors, including harmful environmental factors, bacterial infections, and external toxic chemicals. This inflammatory response leads to the dysfunction and cell death in normal cells within the affected tissues [7]. The microbiome composition in individuals with IBD is typically different from that of healthy individuals, characterized by variations in specific microbial species or groups and overall community. These changes in the microbiome are considered influential factors in the progression of IBD [8]. Therefore, it is crucial to characterize the risk factors that contribute to the increased incidence of IBD in modern society and explore strategic factors that can reduce IBD symptoms related to inflammation and microbiome.

It's well known that excessive consumption of added sugar has been linked to various dysfunctions in tissues and organs. It is known to contribute to weight gain, type 2 diabetes, insulin resistance, cardiovascular diseases, non-alcoholic fatty liver disease, and systemic inflammation [9, 10]. Food and Drug Administration highly recommends individuals restrict their consumption of added sugars to no more than 10% of their total daily calorie intake. It highlights the significance of reducing the consumption of added sugars in order to promote general health [11]. In modern society, excessive added sugar consumption has been recognized as one of the associated factors to the increased incidence of IBD and a significant risk factor for the development of IBD [12-15]. Polysaccharides obtained from many plants, animals, and microorganisms in nature, such as pectin, chitosan, and fructan, have been shown to exert a positive therapeutic effect on IBD [16, 17]. However, Hou *et al.* [12] found that a high intake of both mono- and di-saccharides was linked to an increased risk of developing CD. Furthermore, natural sweeteners have emerged as popular and safer sweeteners compared to artificial sweeteners, which are chemically synthesized compounds having intensely sweet without calories, in the U.S. market [18]. Unlike artificial sweeteners, natural sweeteners have a more positive track record and are associated with fewer health complications and diseases [18]. They offer a viable substitute for simple sugar, prioritizing the well-being of individuals [18]. Therefore, it is necessary to identify natural sweeteners among the mono-saccharides and di-saccharides, which can be used as alternative sugars and determine their effects on IBD.

This study aims to systematically review 1) current evidence regarding the association between IBD and added sugars, 2) the valid data showing the current research status of natural alternative sweeteners, especially mono-saccharides and di-saccharides, 3) natural alternative sweeteners-mediated various physiological mechanisms contributing to the development/progression of IBD. This comprehensive literature review will provide nutritional knowledge and support individuals with IBD. Hence, this will suggest future research directions of using natural alternative sweeteners as a potential therapeutic reagent in improving IBD.

Methods

To review the existing research papers on IBD and its relationship with added sugar or natural alternative sweeteners, electronic databases were utilized through the internet. Google Scholar and PubMed were used as search engines, and the data were extracted in April 2023 and papers published after the year 2000 were included. Using the aforementioned search engines, papers containing the keywords 'IBD' or 'inflammation related to IBD' in their titles, abstracts, or keywords were initially selected as the primary target. Subsequently, a secondary search was conducted using additional keywords such as 'added sugar', 'alternative sweetener', 'monosaccharide', and 'disaccharide' to summarize the effects and mechanisms of added sugar and natural alternative sweeteners among the retrieved papers. The following criteria were used to exclude certain papers from the search results: i) Non-peer-reviewed papers such as books or conference proceedings, ii) papers for which the full text was not available, iii) papers written in languages other than English, iv) papers that had redundant or overlapping information regarding the mechanisms studied, v) papers that focused on artificial sweeteners, vi) papers that investigated high-intensity sweeteners. These papers were excluded to ensure the reliability and relevance of the selected literature. A total of 21 papers were used to delineate the link between IBD and added sugar or natural alternative sweeteners, in particular mono-saccharides and di-saccharides. These papers were selected specifically to review the impact of added sugar or alternative sweeteners on IBD.

Narrative review

1. IBD

1) Inflammation related to IBD

Research has demonstrated that abnormalities in the epithelial layer play a vital role in the development of mucosal inflammation [6]. The response characterized by abnormalities in the epithelial layer is seen as a critical factor contributing to the progression of inflammation in IBD [7]. Major players in inflammatory response in IBD include IFN-γ, IL-1β, IL-6, TNF-α, and nitric oxide (NO), which are produced by macrophages, monocytes, and leukocytes. These inflammatory mediators contribute to the chronic inflammation and affects the pathogenesis and progression of the disease IBD [19]. Furthermore, previous studies revealed that inducible NOS (iNOS) and cyclooxygenase-2 (COX-2) were notably increased by pro-inflammatory cytokines in inflammatory disease [20, 21]. Therefore, reducing inflammatory factors is very important strategy in improving immune-related diseases like IBD. Furthermore, targeting pro-inflammatory cytokines, iNOS, and COX2 will drive the most effective way in ameliorating inflammatory diseases.

During the development of inflammation, macrophages play a prominent role in the immune system's response against pathogens. The secretion of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNFα by macrophages, which are the most common leukocytes in the colon, is an essential mechanism for promoting inflammation and combating pathogens during the immune response [22]. Macrophages can differentiate into two types, each playing a significant role in the pathogenesis of IBD. The "M1 type" macrophages are classically activated and are responsible for promoting the secretion of pro-inflammatory cytokines. On the other hand, the "M2 type" macrophages are alternatively activated and contribute to the production of anti-inflammatory cytokines involved in immunoregulation and tissue repair [22]. Consequently, an enhanced polarization of macrophages toward the M2 phenotype is an important mechanism for improving symptoms of colitis.

2) Microbiome related to IBD

The gut microbiota is widely recognized for its ability to provide numerous benefits to the host, including protection against pathogens, contribution to metabolism, nutrient absorption, and modulation of the immune system. In addition, the microbiome

Table 1. Summary of the added sugars on inflammatory bowel disease (IBD)

Study design	Types of added sugars	Effects	References
In vitro	High-fructose corn syrup	• Generation of reactive oxygen species (ROS), which in turn activate the nuclear factor-κB (NF-κB) signaling pathway	[32]
In vivo	Glucose and fructose	• Increased bloody diarrhea and weight loss and architectural distortion in the colon in dextran sodium sulfate (DSS)-induced colitis	[14]
	Sucrose	• Increased inflammatory phenotypes of colitis such as epithelial damage and inflammatory M1 macrophage phenotype and delayed recovery of colitis induced by DSS	[33]
Epidemiology	Mono- and di-saccharides	• A high intake of both mono- and di-saccharides was linked to an increased risk of developing Crohn's disease	[12]
	High-sugar diet including sugar and soft drinks	• An increased risk of ulcerative colitis particularly when they had a low intake of vegetables and a positive correlation with IBD incidence	[13, 34]
Microbiome	Glucose and fructose	• Changes in gut microbiota composition and an increased abundance of mucus-degrading bacteria *Akkermansia muciniphila* and *Bacteroides fragilis* in *Il10*$^{-/-}$ mice	[14]
	Sugar	• Increased osmotic load and a higher fermentation rate by the colonic microbiota causing abdominal pain and various intestinal dysfunctions in several *in vivo* rat and mouse model	[9, 15]
	High-sucrose diet	• Altered *Bacteroidetes*/*Firmicutes* ratio with an elevated in *Bacteroidetes* and *Verrucomicriobia* and decreased *Firmicutes* accompanied in hyperlipidemia-induced Wistar rat	[36]
	Fructose	• Elevated presence of *Parasutterella* and *Blautia*, but reduced *Intestinimonas* levels in the gut microbiota in Sprague-Dawley rats	[37]

is intricately connected to humans; it establishes a range of symbiotic relationships with host and contribute to the maintaining host health [23]. The gastrointestinal tract harbors varying numbers of bacteria at different locations. Dysbiosis refers to an imbalance or disruption in the number, composition, and functioning of the gut microbiome. It occurs when there are changes in the normal microbial communities, leading to an abnormal or unhealthy state of the host [23]. The composition of the microbiome in IBD patients is known to be altered compared to that of healthy individuals. IBD patients often exhibit differences in the abundance and diversity of specific microbial species or groups, as well as changes in the overall microbial community structure. These alterations in the microbiome composition are believed to play a role in the development and progression of IBD. The pathogenesis of IBD may occur due to a dysfunction of the mucosal immune system, leading to an altered immune response against the gut flora symbiosis. In individuals with IBD, there is a disruption in the delicate balance between the immune system and the gut microbiota, which can result in an abnormal immune response such as chronic inflammation in the gastrointestinal tract. This dysregulation of the mucosal immune system is suggested to contribute to the development and progression of IBD [8]. Therefore, enhancing the altered microbiome is an important strategy in the treatment of IBD. It is necessary to provide Interventions which targets the microbiome can restore a healthy microbial composition and function in the gut, which may ultimately alleviate inflammation and improve symptoms in individuals with IBD.

In conclusion, research strongly underscores the crucial roles inflammation and alterations in the gut microbiome play in the onset and progression of IBD. Fig. 1 clearly illustrates the key characteristics of IBD-related inflammation, such as persistent inflammation, epithelial cell damage, immune system dysregulation, infiltration of immune cells, and associated microscopic changes. As we transition to the next section of our review, we will focus on the role of added sugars as an environmental factor influencing IBD. A comprehensive review of the current literature will shed light on the effects of added sugar intake on IBD development, its potential impact on inflammatory responses, and its interactions with gut microbiota.

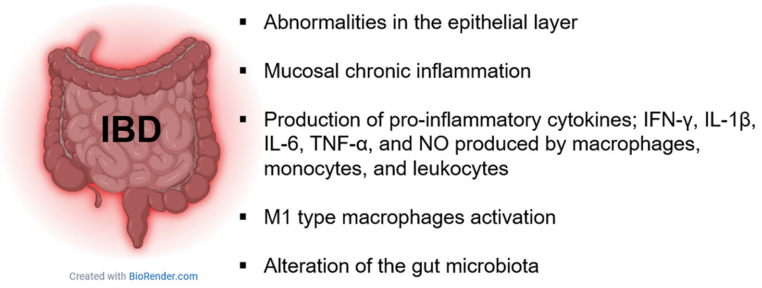

Fig. 1. Characteristics of inflammatory bowel disease. Inflammatory bowel disease (IBD) is a chronic condition characterized by recurring episodes of inflammation in the gastrointestinal tract. The key characteristics of IBD-related inflammation include: Persistent inflammation, epithelial cell damage, immune system dysregulation, infiltration of immune cells, and microscopic changes.

Table 2. Summary of the effects of natural mono- and di-saccharides on inflammatory bowel disease (IBD)

Types	Sweeteners	Effects	References
Mono-saccharides	L-Arabinose	• Enhances the intestinal environment and supports the growth of beneficial probiotic bacteria	[40]
		• Leads to an acidic intestinal environment for the growth and proliferation of beneficial probiotic bacteria, including *Bifidobacterium* and *Lactobacillus*	[41]
		• Suppresses dextran sodium sulfate (DSS)-induced inflammatory activation by reducing proinflammatory cytokines and phosphorylated p38 Mitogen-activated protein kinases (MAPKs) and p65 nuclear factor-κB (NF-κB) in DSS-induced colitis mouse model	[39]
	Mannose	• Protects gut microbiota by increasing in the Bacteroidetes to Firmicutes ratio	[43]
		• Alleviates the symptoms of DSS-induced colitis and *Il (interleukin)-10*$^{-/-}$ spontaneous colitis	[44]
		• Preserves lysosomal function, leading to enhanced mitochondrial metabolism and the formation of tight junctions in the epithelial layer	[44]
	L-Fucose	• Suppresses macrophage M1 polarization and suppress the activation of NLRP3 inflammasome and NF-κB by down-regulating pro-inflammatory cytokines	[47]
Di-saccharides	Leucrose	• Improves pro-inflammatory mediators, reduces myeloperoxidase (MPO) activity, and decreases MCP-1, TNFα, IL-1β, iNOS, and COX2 expression levels.	[50]
		• Enhances M2 macrophage polarization via regulation JAK1/STAT6 in RAW 264.7 macrophage cells.	[50]
	Turanose	• Reduces lipopolysaccharide (LPS) - and glucose-induced inflammation in RAW 264.7 macrophage cells by suppressing inflammatory cytokines and NO production.	[54]
		• Attenuates miR-21 and histone acetylation associated with inflammatory responses in DSS-induced colitis mouse model.	[55]
Honey		• Inhibits the colonic inflammation trinitrobenzene sulfonic acid (TNBS)-induced colonic damage in a rat model by improving anti-oxidant parameters.	[57]
		• Alleviates ulcerative colitis induced by DSS by improving intestinal inflammation and oxidative stress resistance, and reducing the microbiota populations of *Bacteroides, Corynebacterium,* and *Proteus* species.	[58]

2. Added sugars

Added sugars refer to caloric sweeteners that are incorporated into foods as ingredients during food processing, cooking, or when added directly to food at the table [25]. Examples of added sugars include brown sugar, cane sugar, all types of syrups, dextrose, sucrose, glucose, fructose, high-fructose corn syrup, and other sweeteners we usually add during food processing [25]. The majority of added sugars commonly used in food processing are composed of mono- or di-saccharides. It is the basic unit of carbohydrates and includes sugars such as glucose, and fructose. On the other hand, a di-saccharide is a sugar molecule composed of two mono-saccharide units linked together through a glycosidic bond. Examples of di-saccharides include sucrose (glucose + fructose), lactose (glucose + galactose), and maltose (glucose + glucose) [26]. Mono-saccharides and di-saccharides are generally considered less beneficial for health compared to polysaccharides, which are complex carbohydrates and are

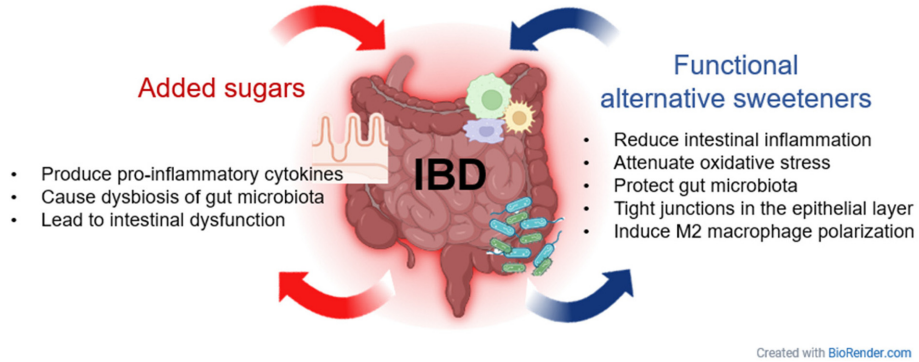

Fig. 2. Mechanism of added sugars and functional alternative sweeteners in inflammatory bowel disease. The potential mechanisms of action of added sugars and functional alternative sweeteners in the context of inflammatory bowel disease (IBD). The figure highlights the effects of functional alternative sweeteners described in the manuscript on key processes involved in IBD pathogenesis and management. Detailed mechanisms were described in table 1 and 2.

composed of long chains of mono-saccharide units, due to their quick digestion and absorption. Mono-saccharides and di-saccharides can result in insulin resistance, obesity, metabolic disease and other diseases [10, 26].

In 2016, the American Heart Association (AHA) issued guidelines recommending individuals to limit their intake of added sugars to no more than 6-9 teaspoons per day [27]. This guideline emphasizes the importance of limiting the amount of added sugars in one's diet for overall health and well-being [11]. However, the average per-person consumption of sweeteners in the US was reported to be around 22 teaspoons per day [28]. In South Korea, according to the 7th Korea National Health and Nutrition Examination Survey (2018), the average daily consumption of total sugars was 58.9 g. When comparing by gender, men had a higher total sugar intake with an average of 63.4 g, while women consumed an average of 54.4 g [29]. When considering the contributions of major food groups to the total intake of total sugars, processed foods accounted for 56.8%, fruits for 24.9%, dairy products for 5.7%, and other natural food sources for 12.5% of the total sugar intake. It is noteworthy that more than half of the total sugar consumption came from processed foods. Looking at the major sources of sugar intake through processed foods, sugar itself was the highest contributor with 4.9 g, followed by carbonated beverages with 3.5 g, coffee with 3.3 g, bread with 3.2 g, and fruit/vegetable drinks with 2.9 g [30]. Therefore, it is essential to study and conduct research on alternative sweeteners that can reduce or replace the added sugar in processed foods such as snacks, coffee, and meals.

1) Added sugar consumption related to IBD

RAW 264.7 macrophages are widely utilized as a model system to investigate various cellular and molecular processes related to macrophage biology, inflammation, and immune responses [31]. In RAW 264.7 macrophages, it has been observed that high-fructose corn syrup (HFCS; consists of 55% fructose and 45% glucose or glucose polymers), a commonly used added sugar in food and beverages, stimulates the production of proinflammatory cytokines [32]. It investigated the effects of simple sugars (glucose and fructose) on colitis development in mice [14]. A high sugar diet (50% sucrose)increases inflammatory phenotypes of colitis such as epithelial damage and promotes inflammatory M1 macrophage phenotype resulting in delayed recovery of colitis induced by DSS [33]. Wild-type mice and *Il10*$^{-/-}$ mice fed high glucose exhibited worsened colitis compared to those without sugar treatment. Short-term consumption of high glucose or fructose led to changes in gut microbiota composition and an increased abundance of mucus-degrading bacteria *Akkermansia muciniphila* and *Bacteroides fragilis* [14]. Furthermore, a human study based on the national health survey data in the US found a positive correlation between consuming regular soda and cookies rich in added sugars and IBD incidence in human study [34]. Within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, individuals who consumed high levels of added sugar and soft drinks had an increased risk of UC, particularly when they had a low intake of vegetables [13]. In terms of the relationship between

mono- and di-saccharides and microbiome, it was found that western diets characterized by high saturated fat and refined added sugar intake have been linked to the dysbiosis of the gut microbiota [35]. Dysbiosis in the gut microbiota can occur due to changes in the number, composition, or quality of the microbial community. These alterations can disrupt the various physiological functions performed by the gut microbiota, leading to imbalances and dysregulation. Furthermore, male Wistar rats treated with a high-sucrose diet for 4 weeks dramatically altered *Bacteroidetes/Firmicutes* ratio with an elevated in *Bacteroidetes* and *Verrucomicriobia* and decreased *Firmicutes* accompanied by increasing serum triglycerides and cholesterol levels [36]. The high intake of fructose was linked to an elevated presence of *Parasutterella* and *Blautia*, while *Intestinimonas* levels were reduced in the gut microbiota [37]. The accumulation of added sugar in the colon can result in an increased osmotic load and a higher fermentation rate by the colonic microbiota causing abdominal pain and various intestinal dysfunctions [15].

These studies strongly suggest the correlation between high consumption of added sugars including sucrose, HFCS, glucose, and fructose and IBD development by aggravating pro-inflammatory cytokines and dysbiosis of gut microbiota. The need for functional sweeteners that can be safely used by IBD patients as an alternative is emerging, and research in this area is gradually increasing. This narrative review will provide a summary of the effects of natural alternative sweeteners in mitigating symptoms and progression in IBD patients. This understanding has the potential to drive the development of more effective dietary strategies for IBD patients.

3. Natural functional sweeteners against IBD; mono- and di-saccharide

To review the underlying mechanisms of natural mono-saccharides and di-saccharides which were proven to have beneficial effects on IBD. First, we sought to summarize the effects of mono-saccharide on IBD. L-Arabinose is a natural mono-saccharide, a five-carbon aldose, obtained from plants or fibers, and it possesses diverse functional characteristics [38]. Administration of L-arabinose 400 mg/kg b.w. significantly suppressed DSS-induced IBD by reducing inflammatory activation such as suppressing proinflammatory cytokines and phosphorylated p38 MAPK and p65 NF-κB in the DSS-induced colitis mouse model [39]. Importantly, it selectively inhibits the activity of sucrase in the intestine, which mitigates the negative impact of sucrose breakdown in the context of IBD. Additionally, it enhances the intestinal environment and supports the growth of beneficial probiotic bacteria [40], which may potentially have preventive effects on IBD. In addition, L-arabinose has been found to have a positive impact on the intestinal environment by influencing the levels of metabolites in the cecum *in vivo*. It promotes the synthesis and production of organic acids and short-chain fatty acids (SCFA), leading to an acidic intestinal environment. This acidic environment is conducive to the growth and proliferation of beneficial probiotic bacteria, including *Bifidobacterium* and *Lactobacillus* [41].

Mannose is a type of sugar belonging to the group of carbohydrates known as aldohexoses (mono-saccharide). It is structurally similar to glucose but differs in the configuration of its carbon-2 position. Specifically, mannose is an epimer of glucose at carbon-2 [42]. Interestingly, Mannose has been found to alleviate the symptoms of DSS-induced colitis and $Il10^{-/-}$ spontaneous colitis in mouse models by safeguarding the integrity of the intestinal epithelial barrier. Mechanistic investigations have shown that mannose preserves lysosomal function by trafficking of lysosomal enzymes. It acts as a recognition marker that allows these enzymes to bind to specific receptors on the lysosomal membrane, facilitating their transport into the lysosome. Investigations have found that the administration of mannose during the early stages of life protected from diet-induced obesity in mice. Mannose supplementation promotes an increase in the *Bacteroidetes* to *Firmicutes* ratio within the gut microbiota, which is commonly observed in individuals with a lean body phenotype. This protective effect is believed to be due to alterations in the composition of gut microbiota [43]. As a result, Mannose enhances mitochondrial metabolism and the formation of tight junctions in the epithelial layer [44].

L-Fucose (6-deoxy l-galactose) is a natural monosaccharide present in mammals and also presents in its free form in human breast milk as a human milk monosaccharide [45]. L-Fucose plays a crucial role in the development of the immune and nervous systems and contributes to cognitive function and the formation of memories, in particular for infants [46]. It is

demonstrated that L-Fucose has beneficial effects in alleviating DSS-induced acute colitis by inhibiting macrophage M1 polarization. The M1 macrophages are considered activated macrophages which are responsible for promoting the secretion of pro-inflammatory cytokines [22]. As a result, L-Fucose suppresses the activation of NLRP3 (Nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing 3) inflammasome and NF-kB by down-regulating pro-inflammatory cytokines [47].

Next, we observed the effects of di-saccharides on IBD. For example, sucrose isomers are composed of glucose and fructose like sucrose but have different linkages. Leucrose (D-glucosyl-α(1-5)-D-fructopyranose), a naturally occurring sucrose isomer found in honey and pollen, possesses a sweetness that is approximately 40 to 50% compared to sucrose [48]. A previous study conducted a sub-acute toxicological investigation lasting 13 weeks in dogs and rats and found no evidence of any toxic side effects associated with leucrose consumption [49]. Supplementation with leucrose as sucrose substitute resulted in improvements in pro-inflammatory mediators in DSS-induced colitis mice, as evidenced by reduced myeloperoxidase (MPO) activity and decreased expression levels of MCP-1, TNFα, IL-1β, iNOS, and COX2. Moreover, leucrose supplementation enhanced M2 macrophage polarization via regulation JAK1/STAT6 in RAW 264.7 macrophage cells in the DSS-induced colitis *in vivo* model [50].

Another natural sucrose isomer is turanose (di-saccharide). Turanose (D-glucopyranosyl-α(1-3)-D-fructopyranose) is present in honey and exhibits a sweetness level of less than 50% compared to sucrose [51, 52]. Toxicity studies have demonstrated that the No Observed Adverse Effect Level (NOAEL) is 7 g/kg/day, indicating that turanose is a safe sugar for both short-term and long-term use [53]. Replacing glucose with turanose at different percentages (50%, 75%, and 100%) was found to reduce LPS- and glucose-induced inflammation in RAW 264.7 macrophage cells. This reduction was attributed to the suppression of inflammatory cytokines and NO production [54]. It is shown that DSS administration markedly elevated miR-21 expression accompanied by increased pro-inflammatory responses such as elevated levels of TNF-α, IL-1, and IFN-γ [55]. Interestingly, Turanose intervention profoundly attenuated miR-21 and histone acetylation associated with inflammatory responses in the DSS-induced colitis mouse model [55].

Honey is considered one of the most popular natural sweeteners worldwide. Honey, a natural food with both nutritional and medicinal properties, has been enjoyed among consumers for many years. Honey predominantly consists of sugars, glucose (34%), fructose (41%), and sucrose (1-2%) [56]. In recent years, extensive research using different approaches, including chemical assays, *in vitro* models, and *in vivo* models, has provided solid evidence confirming the anti-inflammatory properties of honey. In terms of IBD studies, oral administration of Manuka honey 5 g/kg b.w. and 10 g/kg b.w. significantly inhibited the colonic inflammation in TNBS-induced colonic damage in rat models by improving anti-oxidant parameters [57]. Polyphenol-enriched honey was found to alleviate UC induced by DSS. The honey restored antioxidant levels, and reduced colonic apoptosis and inflammatory cytokines such as IL-6, TNF-α, and TGF-β1. Moreover, honey was effective in improving intestinal inflammation, oxidative stress resistance, and reducing the microbiota populations of *Bacteroides, Corynebacterium*, and *Proteus* species [58].

Discussion

This narrative review demonstrates the meaningful association between excessive consumption of added sugar and the development and progression of IBD, highlighting the potential of natural functional sweeteners as alternatives having beneficial effects of inflammation, gut microbial composition, protection of the intestinal barrier, and immune modulation, all of which contribute to the potential alleviation of IBD symptoms (Table 1). However, the overall effects of natural alternative sweeteners on IBD are currently limited in human studies, with most of the research conducted at the cellular or animal model level. There is a need for further intervention studies involving IBD patients to establish a more definitive evaluation of their efficacy. In addition, the functional natural sweeteners discussed in this review are not widely used in the food industry.

Continued research is necessary to stimulate interest and urge the food industry to develop functional sweetener products specifically designed for IBD patients.

This review study provided comprehensive insights on the effects of added sugar, particularly mono-saccharides and di-saccharides on IBD that have been studied so far, highlighting areas that require further investigation and emphasizing the need for systematic analysis. However, it is important to acknowledge certain limitations in the existing evidence, including small sample sizes, short study durations, and a dearth of clinical studies. Therefore, further research is warranted to gain a comprehensive understanding of the long-term effects of natural alternative sweeteners on IBD, encompassing inflammation and the gut microbiome. Future investigations should involve larger cohorts of individuals with IBD and extended assessment periods to summarize the effects of natural alternative sweeteners on IBD more comprehensively. Additionally, the focus of current investigation was primarily on mono-saccharides and di-saccharides among various natural sweeteners including poly-saccharides and oligosaccharides. Therefore, the evaluation of other natural sweeteners' efficacy in IBD is needed in the future. Future research should consider evaluating the efficacy of a broader range of natural sweeteners, including poly-saccharides, and comparing their efficacies with that of mono-saccharides and di-saccharides which were discussed in this study. Overall, the systematic examination of these natural alternatives provides valuable insights into the detrimental effects of excessive added sugar intake in IBD and highlights the need for continued research and development of functional sweeteners that can safely support the well-being of IBD patients.

Conclusion

Utilizing natural alternative sweeteners as functional replacements for detrimental mono-saccharides and di-saccharides can have advantageous effects in the management of IBD (Fig. 2). These sweeteners have been found to have varying effects on reducing inflammation and oxidative stress, regulating macrophage polarization, and improving gut microbiota. However, the current evidence related to functional alternative sweeteners on IBD is limited to cellular and animal studies, and more intervention studies involving IBD patients are needed for a definitive evaluation of their efficacy. Further research should also explore a wider range of natural sweeteners, including poly-saccharides, and compare their effects with mono-saccharides and di-saccharides. Such endeavors will yield more robust evidence and contribute to a deeper comprehension of the potential advantages and limitations of natural alternative sweeteners in the prevention and treatment of IBD.

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Conflicts of Interest

There are no financial or other issues that might lead to conflict of interest.

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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