Plant fructans: Recent advances in metabolism, evolution aspects and applications for human health

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ABSTRACT

Fructans, fructose polymers, are one of the three major reserve carbohydrate in plants. The nutritional and therapeutic benefits of natural fructans in plants have attracted increasing interest by consumers and food industry. In the course of evolution, many plants have developed the ability of regulating plant fructans metabolism to produce fructans with different structures and chain lengths, which are strongly correlated with their survival in harsh environments. Exploring these evolution-related genes in fructans biosynthesis and de novo domestication of fructans-rich plants based on genome editing is a viable and promising approach to improve human dietary quality and reduce the risk of chronic disease. These advances will greatly facilitate breeding and production of tailor-made fructans as a healthy food ingredient from wild plants such as huangjing (Polygonatum cyrtonema). The purpose of this review is to broaden our knowledge on plant fructans biosynthesis, evolution and benefits to human health.

1. Introduction

Fructans are significant for both plant development and human diet (Jin et al., 2017). Most plants store starch or sucrose as reserve carbohydrates. But about 15% of flowering plant species store fructans (Vijn and Smeekens, 1999). As a type of dietary fiber, fructans, together with protein, fat, carbohydrates, vitamins, minerals and water, are listed by the World Health Organization as the “seven major nutrients” necessary for the human body (Matsui et al., 2018). Fructans are low in calories and have a sweet taste, which can increase the secretion of satiety hormones, regulate intestinal bacteria, and improve constipation (Schaafsma and Slavin, 2015). In recent years, fructans-based functional foods have also been industrially developed and utilized due to the increasing attention to emphasis on healthy diet.

Plant fructans are fructose polymers derived from sucrose and stores in vacuoles (Darwen and John, 1989; Peukert et al., 2014; Marquez-Lopez et al., 2022). They often act as a long-term carbohydrate in the specialized organs of perennial plants, the taproot of chicory (Cichorium intibus), the rhizome of Polygonatum cyrtonema, the stem of Agave species, the bulb of tulip (Tulipa gesneriana) and onion (Allium cepa) (Fig. 1) (Ritsema and Smeekens, 2003b; Mancilla-Margalli and Lopez, 2006; van Arkel et al., 2013; Van den Ende and El-Esawe, 2014). As structurally flexible and high soluble sugars, plant fructans play a key role in plant regrowth after defoliation and sprouting. In addition, fructans enable plants to survive in harsh environments such as chilling and dry climates by associating with cell membranes (Van Der Meer et al., 1994; Ritsema and Smeekens, 2003a; Van den Ende, 2013; Si and Zhu, 2021).

Fructans are fructose-linked molecules and thus are not digested in human stomach or small intestine; However, they can be fermented by bacteria in the large intestine, producing short-chain fatty acids (SCFAs) (Bach Knudsen, 2015; Fu et al., 2019). Therefore, fructans can efficiently regulate blood glucose and reduce the risk of obesity (Wan et al., 2020). Fructans are also used as popular prebiotics to help reduce the risk of cancer, promoting the probiotic activity of homologate bifidobacterium and lactobacilli and the absorption of minerals in human (Sanders et al., 2019). These known benefits have made fructans to become a popular ingredient during the development of plant-based functional foods.

Wild plants rich in fructans have attracted great attention from crop breeders. Domestication of the rich variety of nutritious and functional plants is considered to have enormous potential in agricultural and food...
industry (Siddique et al., 2021). *P. cyrtonema* is a traditional wild plant with dual purposes as food and medicine for around 2000 years in China. Current research showed that rhizome of *P. cyrtonema* does not contain starch, but is rich in fructans, which makes the plant highly suitable for domestication (Si and Zhu, 2021). Traditionally, development of commercial crops is the result of long-term domestication including natural and human selection, which is a time-consuming and labor-intensive process (Eshed and Lippman, 2019; Yu et al., 2021). The recently developed genome editing technology has become a robust approach for targeted gene editing in a wide array of plants in just a few generations (Yu et al., 2021). Domestication of fructans-rich wild plants with traditional or genome editing methodology will be a novel approach for improving human dietary choices for prevention and control of chronic disease such as diabetes and cancer.

2. Fructans structures and metabolism in plants

Plant fructans chain lengths range from three up to around one hundred fructose units, mainly including inulin, neo-inulin, levan, neo-levan, graminan, agavin structures (Fig. 2) (Mancilla-Margalli and López, 2006; Ahmed and Rashid, 2019; Pérez-López and Simpson, 2020). The length, or degree of polymerization (DP) of fructans, can vary with species or time of year, and plants rich in fructans could be used as a source for developing functional foods (Table 1). Chicory contains the longest average DP (20.96), whereas wheat shows low average DP (4.4–7.3) (Van Loo, 2007; Verspreet et al., 2013; Ribeiro et al., 2022). vegetables garlic and leek bulb display average lengths of DP 8–10 (Muir et al., 2007). Agave tequilana containing a special fructan agavin shows a range of DP 3–30 (Arrizon et al., 2010; Mellado-Mojica and López, 2012; Suárez-González et al., 2016). The huge diversity of DP in these species indicates the great complexity of fructan metabolism in plants. However, most of the plant species could reach 20 of DPs whereas average DPs of cereal crops are less than 10, suggesting cereal crops tend to accumulate low DP fructans. In addition, fructan DP is a decisive factor that promotes the growth of specific carbohydrate-degrading bacteria (Reimer et al., 2020; Sun et al., 2020) (Table 2). Fructans with low DP are more easily fermentable by a wider range of bacteria species, including probiotic bifidobacteria and lactobacilli, than larger fructan molecules (Muir et al., 2007). Nevertheless, long-chain fructans seem to produce a more prolonged prebiotic effect in time. Therefore, how to make use of tailor-made fructans based on genes or enzymes of fructan metabolism from plants is still a question.

Sucrose in yellow frame including glucose (red) and fructose (green); fructosyltransferase in blue color, sucrose:sucrose 1-fructosyltransferase (1-SST), fructans:fructans 1-fructosyltransferase (1-FFT), sucrose:fructans 6-fructosyltransferase (6-SFT), fructans:fructans 6G-fructosyltransferase (6G-FFT), 1-fructanexohydrolase (1-FEH), 6-fructanexohydrolase (6-FEH), sucrose:sucrose 6-fructosyltransferase (6-SST).

The diversity in the structure or DP of fructans across plant species is caused by the different combinations of the enzymes in fructan biosynthesis (Pérez-López and Simpson, 2020). Commonly, fructans are biosynthesized by fructosyltransferase (FT) including 1-SST, 1-FFT, 6-SST/6-SFT, and 6G-FFT, 1-fructanexohydrolase (1-FEH), 6-fructanexohydrolase (6-FEH), sucrose:sucrose 6-fructosyltransferase (6-SST).

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One of the simplest form of fructans is inulin, which consists of β(1–2)-linked fructose style synthesized by 1-SST and 1-FFT (Kusch et al., 2009; Wei et al., 2017). 1-SST is responsible for the conversion of

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**Fig. 1.** Representative species containing different fructans structure.
Inulin to 1-kestose. 1-FFT is able to use 1-kestose or other high polymerization fructans as fructose donors, and fructans or sucrose as fructose acceptors, which determines the length of inulin in plants. Chicory and Jerusalem artichoke are representative species of inulin. Neo-inulin in Liliaceae (e.g. onion and asparagus) has typical $\beta(2\rightarrow6)$ linking fructose with glucose of sucrose synthesized by 6G-FFT. The levan structures include levan and neo-levan, both having the basic linear $\beta(2\rightarrow6)$-linked fructose structure attached to sucrose. Levan fructans are synthesized by species-specific enzyme 6-SST/6-SFT which preferentially transfers the fructosyl unit of sucrose to a wide variety of plant fructans.

### Table 1
Summary of degree of polymerization in different plant species.

| Plant species                  | Fuctan structure | Degree of polymerization (DP) | Average degree of polymerization | Reference                                      |
|--------------------------------|------------------|-------------------------------|----------------------------------|-----------------------------------------------|
| Chicory                        | Inulin           | 3–67                          | 30.96 (Verspreet et al., 2012; Vandeputte et al., 2017) |
| Agave tequilana                | Agavin           | 3–23                          | NA                               | (Suárez-Gonzáles et al., 2016; Melado-Mojica and López, 2012) |
| Wheat                          | Graminan         | 3 to > 10                     | 4.4–7.3 (Verspreet et al., 2012, 2013; Ribeiro et al., 2022) |
| Barley                         | Graminan; inulin | 3–10                          | NA                               | (Matsui et al., 2018; Nemeth et al., 2014) |
| Ryegrass                       | Neo-levan        | 3–65                          | 9.1 (Abeynayake et al., 2015; Ispiryan et al., 2019) |
| Curcuma kwangsiensis           | Levan            | 30–31                         | NA                               | (Jiao et al., 2018; Luo et al., 2018; Maicaurkaew et al., 2017) |
| Jerusalem artichoke            | Inulin           | 3–61                          | NA                               | (Contado et al., 2015) |
| Smallanthus sonchifolia        | Inulin           | 3–7                           | NA                               | (Fu et al., 2018) |
| Codonopsis pilosula            | Inulin           | 3–18                          | 6 (Joaquim et al., 2018) |
| Gomphrena marginata            | Levan            | 3–41                          | NA                               | (Pang et al., 2019) |
| Platycodon grandiflorus        | Inulin           | 3–11                          | NA                               | (Oku et al., 2022; Oku et al., 2019; Downes and Terry, 2010) |
| Onion                          | Inulin- neoseries-type | 3–20                              | NA                               | (Matsui et al., 2018) |
| Avena sativa                   | Fructooligosaccharides | 3–7                     | NA                               | (Matsui et al., 2018) |
| Campanula rapunculoides        | Inulin           | 3–20                          | NA                               | (Matsui et al., 2018) |
| Asparagus officinalis L.        | Inulin- neoseries-type | 3–17                              | NA                               | (Wirzel and Matros, 2020) |
| Polygonatum cyrtomum           | Neo-inulin       | 3–28                          | 6 or 10 (Han et al., 2021) |
| garlic                         | Neo-inulin       | NA                            | −10 (Muir et al., 2007) |
| leek                           | Neo-inulin       | NA                            | −8 (Muir et al., 2007) |
| Phleum pratense                | Levan            | 3–72                          | NA                               | (Kagan et al., 2022; Pérez-López and Simpson, 2020) |
| Asparagus glomerata            | Levan            | 3–60                          | NA                               | (Kagan et al., 2022; Ince et al., 2014) |
| Agave salmiana                 | Agavin           | 7–30                          | −19 (Plascencia et al., 2022) |

Fig. 2. Schematic representative structure of plant fructans.
acceptors such as 1-ketose, 6-ketose and 6G-kestotriose (Tamura et al., 2009; Van den Ende et al., 2011; Lammens et al., 2012). Neo-levan fructans are formed through transfer of fructose residues to the gli moiety of sucrose to form a 6G-kestose catalyzed by 6G-FFT (Lasseur et al., 2006). 6G-kestose can be further elongated to form neo-inulin and levan, having both β(2–1) linkages, whereas neo-levans are found in a few Poales order species (e.g., oat and ryegrass).

Graminans and agavins structures are the special types combining both inulin and levans, having both β(1–2) fructose and β(2–6) fructose residues. Graminans are widely found in plant species belonging to Poales order, such as wheat and barley. Compared with graminans, agavins contain more β(2–6) fructose chains attached to fructose, mainly existing in Agave species.

Fructans exohydrolases (FEHs) are known to cause fructans breakdown that may be specific for β(2–6) or β(2–1) linkages or act on both (Pérez-López and Simpson, 2020). The 1-FEH is responsible for the breakdown of inulin-type fructans with only β(2–1) linkages, while the 6-FEH degrades levan-type fructans exhibiting β(2–6) linkages (Kooiker et al., 2013). Fructans with β(2–1) and β(2–6) linkages can be hydrolyzed by the 1&6-FEH that exhibited a preferred activity for bifurcose (Kawakami et al., 2005; Tamura et al., 2011).

Although fructan metabolism enzymes are thought to be transcriptionally regulated, the transcription mechanism of fructans accumulation and stress signaling is still unclear. Recently, a R2R3-MYB transcription factor, TaMYB13, has been characterized as a transcriptional activator with the DNA-binding motifs (DTHGGT) of the fructan biosynthesis genes, unveiling fructosyltransferase genes co-expression mechanism driven by transcription factor (Xue et al., 2011; Kooiker et al., 2013). Interestingly, another recently identified chicory R2R3-MYB factor, CbMYB17, is able to activate both fructosyltransferase (1-SST, 1-FFT) and fructans exohydrolase (1-FEH1, 1-FEH2) genes, via binding to the DTHGGT cis-elements (Wei et al., 2017). In fructan degradation pathway, CbMYB5 and CbMYB3 have been identified to regulate the expression of 1-FEH genes in chicory (Wei et al., 2017). However, CbMYB3 transcripts only showed similar co-induction with FEH genes in cold-treated hairy roots but the correlation with expression of 1-FEH genes was less consistent during different stress exposures and hormone treatments, indicating these R2R3-MYB regulators are expected to cooperatively or antagonistically regulate the expression of 1-FEH genes in a stress-dependent manner.

In addition, Jin et al. discovered a mechanistic model of starch and fructans synthesis in barley, whereby a dual-promotor gene encodes two functionally distinct transcription factors, SUSIBA1 of 30 kDa and SUSIBA2 of 62 kDa, repressing the synthesis of fructans and activating the synthesis of starch, respectively (Jin et al., 2017). SUSIBA1 serves as a repressor that directly suppresses the synthesis of fructans, whereas SUSIBA2 is an activator that promotes the synthesis of starch, generating an autoregulatory system for the synthesis of carbon allocation. Interestingly, abundant fructans were accumulated instead of starch in rhizome of P. cyrtonema, providing a new question as how carbohydrates allocation is regulated (Si and Zhu, 2021).

### 3. Evolutionary aspects of fructans synthesis

The causes explaining the vast diversity of fructans structures and chain lengths in plants are currently unknown. Plants may have evolved to grasp highly complex and diversified mechanisms for fructan biosynthesis for different physiological needs or as a consequence of the different evolutionary origins of fructans biosynthesis.

Biochemical and molecular experiments showed fructosyltransferases evolved from invertases by relatively few mutational changes (Wan et al., 2018). Cell wall and vacuole invertases are acid invertases, which are also called β-fructofuranosidases breaking dis- or oligosaccharides from fructose residues (Sturm, 1999; Lammens et al., 2009; Ruan, 2014). The acid invertases belong to the glycoside hydrolase family (GH) 32 (Lombard et al., 2014). Cytoplasmic invertases (CIN), vacuole invertases (VIN) and cell wall invertases (CWIN) are converting enzymes localized in the cell membrane, vacuole and cell wall species, respectively, that hydrolyze sucrose into glucose and fructose for use in plant life (Wan et al., 2018). Compared with acid invertases, the alkaline/neutral invertases (CINs) that lack glycosylated activities and N-terminal signal peptide, specifically hydrolyze sucrose and fall in the GH100 family (Sturm, 1999; Lombard et al., 2014). CINs are likely to act in a different mechanism from acid invertases.

Sequence comparisons of plant invertases showed a common evolutionary origin for vacuolar and cell wall invertases (Unger et al., 1994). It is also possible that they originated from duplication of a common ancestral gene, which may have occurred before the divergence of monocots and dicots (Haouzine-Takvorian et al., 1997). In addition, it was previously hypothesized that plant VINs evolved from CWINs (Ji et al., 2005). Recently an evolutionary study showed that

### Table 2: Potential benefit of fructans for human health.

| Fructans structure | Plant sources | Function type | Function mechanism | Reference |
|--------------------|---------------|---------------|-------------------|-----------|
| Inulin-type fructans | Cichorium intybus | Modification of the gut microbiota | Increased relative abundance of the Bifidobacterium genus from (mean ± SEM) 5.3% ± 5.9%–18.7% ± 15.0% | Reimer et al. (2020) |
| Inulin-type fructans | Codonopsis pilosula | Modification of the gut microbiota | Stimulation effect on Lactobacillus and pH reduction of medium | Fu et al. (2018) |
| Inulin-type fructans | Asparagus cochinchinensis | Modification of the gut microbiota | Decreased the pH value, increased total short-chain fatty acids, stimulated the growth of Prevotella, Megamonas and Bifidobacterium while suppressed the growth of Haemophilus | Sun et al. (2020) |
| Fructans | Polygonatum cyrtonema | Modification of the gut microbiota | Promoted growth of Bifidobacterium and Lactobacillus strains | Zhang et al. (2021) |
| Inulin | Cichorium intybus | Modification of the gut microbiota | Increased Bifidobacterium and Anerostiguiites abundances, while decreased Bilipohila numbers | Vandeputte et al. (2017) |
| Inulin | Cichorium intybus | Anti-tumor effects | Increased the relative abundances of key commensal microbes and their short-chain-fatty-acid metabolites, and led to enhanced recall responses for interferon-γ, CD8+ T cells | Han et al. (2021) |
| Inulin-type fructans | Lobelia chinesis | Anti-obesity effects | Reduced total cholesterol and triglyceride levels in serum and liver tissues, while reduced weight gain caused by a high-fat diet | Zhang et al. (2020) |
| Inulin and oligofructose | Sechium edule | Hypoholestremic effects | Significantly decreased cholesterol, serum triglycerides, serum LDL, and serum VLDL | Bandyopadhyay et al. (2021) |
| Inulin-type fructans | Codonopsis pilosula | Anti-inflammatory effects | Reduced the expression of inflammatory factors such as TLR4, NF-κB, | Meng et al. (2020) |
| Carboxymethylfructan and sulfation modified fructans | Anemarrhena asphodeloides | Antioxidant activity | Increased DPPH and hydroxyl radical scavenging activity | Zhang et al. (2020) |
CWINs from higher plants shared a common ancestor with VINs from lower plant species (Wan et al., 2018). In contrast, our phylogenetic analysis showed VINs evolved from CINs, whereas CINs are more closely related to CWINs (Table S1; Fig. 3). Thus, we proposed a novel evolution model of invertases whereby CWINs, CINs, VINs evolved from lower to higher plants corresponding to the emergence of the plant organ cell wall, cytoplasm, and vacuole.

The phylogenetic tree also suggested that plant fructosyltransferases evolved from vacuolar invertases, whereas fructans exohydrolases are more closely related to cell-wall invertases (Ritsema and Smeekens, 2003a). Our results indicated ancestral genes of 1-SST and 6-SFT were from Sm1-SST in Lycophyte plants. Fructosyltransferases and vacuolar invertases from monocots occur in clade separate from those of the dicots, indicating that plant fructans genes evolved independently after the divergence of monocotyledons and dicotyledons (Wei and Chatterton, 2001). However, our results revealed fructosyltransferase in both monocots and dicots were from a common origin gene AtVIN in basal angiosperm *Amborella trichopoda*. The 6-SFT genes from monocots were

![Fig. 3. Evolutionary and phylogenetic analysis of invertase genes in plant and algal species.](image-url)
more similar to other invertases from monocots than to the fructosyl-transferases from dicots. The At1-FFT from monocot \textit{A. tequilana} was more similar to Ac6G-FFT than to fructosyltransferases from monocots. Hv6-SFT from barley showed higher similar protein sequences with Ta1-SST from wheat rather than Ta6-SFT. Similar phenomenon were also found eudicots \textit{Jerusalem artichoke} (van der Meer et al., 1998). These results suggested that different functional enzymes are sometimes more closely clustered than those that catalyze the same reaction but originate from different species (Ritsema and Smeekens, 2003a).

These evolution advances provide new insights into fructan metabolism and new advances in elucidating carbon allocation by the predictive function of invertases.

4. Fructans application by human

4.1. Potential benefits in human health

4.1.1. Modification of the gut microbiota

Many studies report that gut microbiome dysbiosis is responsible for several somatic and neurological diseases, including inflammatory bowel disease, obesity, nonalcoholic fatty liver disease, type 2 diabetes mellitus (Delzenne et al., 2015; Harakeh et al., 2016; Pascal et al., 2017; Zhao et al., 2018; Sharma and Tripathi, 2019) and Alzheimer’s disease (Wu et al., 2017; Kim et al., 2021). Dietary interventions with fructans have become one of the main strategies to modulate the composition and function of the gut microbiota (Carbonero, 2021; Vandeputte et al., 2017; Hiel et al., 2019). Several studies have demonstrated that fructans sourced from \textit{Cichorium intybus} (Vandeputte et al., 2017; Reimer et al., 2020), \textit{Agave tequilana} (Márquez-Aguirre et al., 2013; Padilla-Camberos et al., 2018; Sáyago-Ayerdí et al., 2021), \textit{Agave salmiana} (Castillo Andrade et al., 2019; Daniel et al., 2022; Martínez-Martín et al., 2022), \textit{Codonopsis pilosula} (Fu et al., 2018), \textit{Asparagus cochinchinensis} (Sun et al., 2020), and \textit{Polygonatum cyrtomena} (Zhang et al., 2021), selectively stimulate the growth of beneficial bacteria such as \textit{Prevotella}, \textit{Megamonas} and \textit{Bifidobacterium}, improving health with human colon (Sun et al., 2020) (Table 2). For instance, a diet supplemented with \textit{Agave} species fructans in an animal model stimulated the growth of \textit{Bifidobacterium} and \textit{Lactobacillus} and inhibited growth of \textit{Clostridium} in the large intestine (Castillo Andrade et al., 2018, 2019; Castillo Andrade et al., 2021; Martínez et al., 2022). Clinical trials also show that consumption of inulin-rich vegetables or snack bars increase the ratio of \textit{Bifidobacterium} and help reduce the dietary fiber gap prevalent in modern life (Hiel et al., 2019; Tefera, 2021; Reimer et al., 2020). In a double-blind trial in which \textit{Agave salmiana} fructans were added to children’s diets, it has been demonstrated that those children who supplemented with fructans had a more considerable weight gain, an increased number of lactic acid bacteria, and a decreased concentration of volatile organic compounds (Daniel et al., 2022). Furthermore, interventions that add fructans from \textit{Agave salmiana} to probiotic yogurt have been reported to increase the abundance of intestinal microbiota and stimulate the growth of beneficial bacteria in overweight or obese children (Martínez-Martín et al., 2022).

4.1.2. Short chain of fatty acids (SCFAs) production

A growing body of work suggests that SCFAs are crucial modulators of different metabolic pathways in human (Koh et al., 2016; Salamone et al., 2021). SCFAs prevent the establishment of potentially pathogenic intestinal microbes in balancing the colonic microflora towards a healthier condition in human (Pool-Zobel, 2005; Hermes et al., 2009). SCFAs, produced during the fermentation by the intestinal flora, improve the gut environment and stimulate the growth of colonic mucosa, thereby increase the absorption of minerals (Wan et al., 2020). Fructans are metabolized by the beneficial microbiota in the large intestine and thereby produce the major SCFAs (Ahmed and Rashid, 2019; Gupta et al., 2019). These beneficial flora and small molecules deliver potential therapeutic benefits in human liver, pancreas, intestine and kidney (Fig. 4).

Inulin-type fructans have been studied for several decades. They are fermented by beneficial bacteria in the large intestine or colon, producing SCFAs (acetate, propionate, butyrate) that are rapidly absorbed in the colon to provide additional energy to the host and improve the functioning of gastrointestinal microflora i.e., lactobacilli and bifidobacteria (Mulabagal et al., 2009; De Filippo et al., 2010). The production of SCFAs is strongly associated with the fructan dose, especially the composition of acetate, propionate and butyrate. For instance, a 12.5% dose of \textit{Agave salmiana} fructans produces higher concentration of butyric acid and total SCFA than doses of 0 and 10% (Castillo Andrade et al., 2019).

4.1.3. Anti-obesity effects and lipid metabolism

Inulin-type fructans have attracted considerable attention in the treatment or intervention of overweight and obesity, which significantly reduce total cholesterol and triglyceride levels in serum and liver tissues, while reducing weight gain caused by a high-fat diet (Zhang et al., 2020) (Table 2). Inulin-type fructans also increase lipid droplets number, reduce fat mass, lipopolysaccharide, triglycerides, cholesterol, and free fatty acids in liver, and it have been further demonstrated to provide potential protective effects against acute liver injury (Dehghan et al., 2014; Duan and Yu, 2019). Furthermore, inulin and oligofructose can inhibit triglyceride synthesis to exert hypcholesterolemic effects by reducing lipogenesis and favoring the production of SCFAs (Ahmed and Rashid, 2019; Bandyopadhyay et al., 2021). In addition, the ingestion of fructans in \textit{A. tequilana} enhanced the decrease in BMI, total body fat and triglycerides in obese individuals, which showed the great potential in human health (Padilla-Camberos et al., 2018; Sáyago-Ayerdí et al., 2021).

4.1.4. Anti-tumor effects

Several studies have reported the anti-tumor effects of fructans (Han et al., 2021; Li et al., 2020). For instance, orally administered inulins increase the relative abundances of key commensals microbes and their short-chain-fatty-acid metabolites, and enhance recall responses for interferon-γ + CD8+ T cells (Han et al., 2021) (Table 2). In addition, inulin enhanced the anti-tumor efficacy of anti-programmed cell death protein-1 (a-PD-1) therapy (Han et al., 2021). It has also been reported that inulin limited tumor growth and enhanced the efficacy of a MEK inhibitor against melanoma in syngeneic mouse models (Li et al., 2020).

4.1.5. Anti-diabetic effects

Fructans are important components of dietary fiber and contribute to beneficial function for diabetic patients via modulation of the gut

- Lipid droplets number
- Lipopolysaccharide
- Recovery of liver injury
- Triglycerides
- Cholesterol
- blood glucose after meal
- Insulin response to food
- Insulin resistance

Fig. 4. The health benefits of plant fructans.
microbiota (Regina et al., 2006; Struck et al., 2014; Zhao et al., 2018; Kim et al., 2021). In addition, fructan-type plant polysaccharides, reduce postprandial blood glucose and suppress insulin response to foods (Anastasovska et al., 2012; Lightowler et al., 2018; Nishimura et al., 2015). *Lactobacillus plantarum* 1058 (ATCC 8014) and IN supplements is reported to lower hyperglycemia, insulin resistance and hyperlipidemia, reduce oxidative stress and increase the insulin and leptin levels in the hypothalamus of T2DM rats (Man et al., 2021; Valenìa et al., 2018).

Therefore, the fructans may regulate blood glucose levels in dual way.

4.1.6. Others

Inulin-type fructans isolated from *Codonopsis pilosula* can exert anti-inflammatory activities in a manner of reducing the expression of inflammatory factors such as TLR4, NF-κB, TNF-α and IL-6 (Meng et al., 2020) (Table 2). Furthermore, fructans modified by carboxymethylation and sulfation have potent scavenging effects on DPPH and hydroxyl radicals (Zhang et al., 2020). In addition, it has been shown that a diet supplemented with *Agave salmiana* fructans contributes to suppress inflammation in epithelial cells through reducing the concentration of TNF-α and strengthening the mucosa layer (Castillo Andrade et al., 2018; Castillo Andrade et al., 2021). Recently studies also found fructans reduce serum total & free p-creosl sulfate in chronic kidney disease patients and improve kidney function (Ahmed and Rashid, 2019; Ramos et al., 2019).

4.2. Accelerating the domestication of fructans-rich crops

Currently crop breeders focus on wild plants or neglected crops that consist of a larger extent on environmental sustainability, low input, and high nutritional/functional value (Österberg et al., 2017; Siddique et al., 2021). Utilization of the health-promoting properties of fructans has become a focus of modern crop breeding for the purpose of improved human diet. Therefore, domestication of these crops is a viable and promising approach to meet human’s healthy needs.

Traditionally, domestication of wild plants into commercially available crops requires a long period of time spanning from hundreds or even thousands of years. But the recently developed genome editing technologies provide a new efficient way to accelerate the domestication by precisely editing the target genes (Yu et al., 2021). A clear accelerated *de novo* domesticated path by combining the advantages of wild allo-tetraploid rice genome sequencing and editing for creating novel crops were demonstrated. These promising techniques have become useful tools in the plant breeding toolbox when domesticating new crops.

Perennial plants typically have more-advanced root systems which not only allows them to be less reliant on fertilizer and water supply but also contribute to preservation of soil quality (Kantar et al., 2016; Österberg et al., 2017). Thus, domestication of perennials is in the breeding pipeline. Huangjing is a perennial plant with natural polyplidization. It has a large cultivation area and features great tolerance to various environments (Chen et al., 2021). The nutritional value of Huangjing is characterized with high abundance of non-starch polysaccharides and fructans, but very low amount of starch, creating an opportunity for plant breeders to apply genome editing approaches to create varieties of Huangjing with higher yield, allowing easier processing, giving better taste with higher nutrition. Therefore, Huangjing may be a promising candidate species for domestication to fight chronic and hidden hunger (Chen et al., 2021).

5. Conclusions and future perspectives

In conclusion, fructans are a fructose-based polymer that has great nutritional and health potential for promoting human health, including prebiotics effects, reducing the risk of colon cancer, obesity and diabetes and so forth. This review systematically summarizes the fructans structure, functional enzymes and evolution aspects in fructans metabolism. Additionally, by adopting evolutionary analysis, we add new opinions related to the origin and evolution of invertases including CWIs, CINs, VINs and FT from lower to higher plants. These advances provide new opportunities to select fructans-rich wild plants and improve the domestication using biotechnological approaches. A representative wild species, *Polygonatum cyrtomema* has been attracting huge interest in China, which fulfills as nutritional and functional diet especially for diabetes and elderly. Domestication of these fructans-rich plants would promote the diversity of agriculture and fill the current gaps between crop production and utilization of crop nutritional and functional values.

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CRediT authorship contribution statement

Yan Shi: Conceptualization, charts and, Writing – original draft. Dun Si: final, Writing – review & editing, table and charts. Xinfeng Zhang: final, Writing – review & editing. Donghong Chen: final, Writing – review & editing. Zhigang Han: Conceptualization, charts and, Writing – original draft, final, Writing – review & editing, table and charts, All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crfs.2023.100595.

References

Abeynayake, S.W., Ritseroldt, T.P., Jonaviciene, K., Byrne, S., Asp, T., Boedt, B., 2015. Fructan metabolism and changes in fructan composition during cold acclimation in perennial ryegrass. Front. Plant Sci. 6, 329.

Ahmed, W., Rashid, S., 2019. Functional and therapeutic potential of inulin: a comprehensive review. Crit. Rev. Food Sci. Nutr. 59, 1-13.

Anastasovska, J., Avra, T., Sanchez-Carson, G.J., Parkinson, J.R.C., Toubly, K., Gibson, G.R., Nadkarni, N.A., So, P.W., Goldstone, A.P., Thomas, E.L., Hankir, M.K., Van Loo, J., Modi, N., Bell, J.D., Frost, G., 2012. Fermentable carbohydrate alters hypothalamic neuronal activity and protects against the obesogenic environment. Obesity 20, 1016-1023.

Arrizón, J., Morel, S., Guchaedler, A., Monsan, P., 2010. Comparison of the water-soluble carbohydrate composition and fructan structures of Agave tequilana plants of different ages. Food Chem. 122 (1), 123–130.

Bach Knudsen, K.E., 2015. Microbial degradation of whole-grain complex carbohydrates and impact on short-chain fatty acids and health. Adv. Nutr. 6 (2), 206-213.

Bandopadhyay, B., Mandal, M., Mandal, N.C., 2021. Partial characterization of novel inulin-like prebiotic fructooligosaccharides of Scichium edule (Jacq.) Sw. (Cucurbitaceae) tuberous roots. J. Food Biochem. 45, e13764.

Carbonero, F., 2021. Plant-based foods and the gut microbiome: a research profile of Agave salmiana fructans as gut health
promotes: prebiotic activity and inflammatory response in Wistar healthy rats. Int. J. Biol. Macromol. 136, 785–795.

Castillo Andrade, A.D., Kaland, C., Godínez-Hernández, C., Ruiz-Cabrera, M.A., Fuentes-Ahumada, C., García-Chávez, E., Grajales Lagunes, A., 2018. Physiomebotanical effects of Agave salmiana fructans evaluated in Wistar rats. Int. J. Biol. Macromol. 108, 1300–1309.

Castillo Andrade, A.D., Fei, M., Rosenquist, S., Jin, L., Gohil, S., Sandström, P., Pachikian, B.D., Kalala, G., Broers, V., Zamariola, G., Chang, B.P.I., Fu, Y.P., Li, L.X., Zhang, B.Z., Paulsen, B.S., Yin, Z.Q., Huang, C., Feng, B., Chen, X.F., Duan, G.L., Yu, X.B., 2019. Isolation, purification, characterization, and antioxidant activity of grape seed procyanidins. J. Funct. Foods 57, 703–729.

Kawakami, A., Yohida, M., Van den Ende, W., 2005. Molecular cloning and functional characterization of a novel 6-α-FEI from wheat (Triticum aestivum L.) preferentially degrading small glycans like bifurcanose. Gene 358, 93–101.

Kim, Y., Jean, S.H., Ju, I.G., Gee, M.S., Do, J., Oh, M.S., Lee, J.K., 2021. Transplantation of gut microbiota derived from Alzheimer’s disease mouse model impairs memory function and gene expression in C57BL/6 mice. Brain Behav. Immun. 96, 357–365.

Koh, A., De Vadder, F., Kovatcheva-Datchary, P., Backhed, F., 2016. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 165, 1323–1345.

Kooner, M., Jerath, D., Glasson, D., McIntyre, C.L., Xue, G.P., 2013. TaMYB13-1, a R2R3 MYB transcription factor, regulates the fructan synthetic pathway and contributes to enhanced fructan accumulation in bread wheat. J. Exp. Bot. 64, 3681–3696.

Kuch, U., Greiner, S., Steininger, H., Meyer, A.D., Corbibère-Diviale, H., Hams, K., Rausch, T., 2009. Dissecting the regulation of fructan metabolism in chicory (Cichorium intybus) hairy roots. New Phytol. 184, 127–140.

Lammens, W., Van Roy, K., Savelkoul, K., Rahimis, A., Van den Ende, W., 2009. Structural insights into glycoside hydrolase family 32 and 68 enzymes: functional implications. J. Exp. Bot. 60, 727–740.

Lammens, W., Le Roy, K., Yu, S., Verguurnen, R., Rahimis, A., Van Laere, A., Sterk, S. V., Van den Ende, W., 2014. Characterization and prebiotic activity in vitro of inulin-type fructan from Codonopsis pilosula roots. Carbohydr. Polym. 193, 212–220.

Gupta, N., Jangid, A.K., Pooja, D., Kulhari, H., 2019. Inulin: a novel and stretchy polysaccharide to explore for biomedical and nutritional applications. Int. J. Biol. Macromol. 132, 852–863.

Han, K., Nam, J., Xu, J., Sun, X., Huang, X., Anisahumou, O., Achreja, A., Jeon, J.H., Puresly, B., Kamada, N., Chen, G.Y., Nagrath, D., Moon, J.J., 2021. Generation of systemic antitumour immunity via the in situ modulation of the gut microbiome by orally administered inulin gel. Nat. Biomed. Eng. 5, 1377–1388.

Haouzine-Takovirian, N., Tymowska-Lalanne, Z., Takovirian, A., Tregear, J., Lejene, B., Lecharny, A., Kreis, M., 1997. Characterization of two members of the Arabidopsis thaliana gene family, at beta-fruct, and at beta-fruct,4 coding for vascular invertases. Gene 197, 239–251.

Harakeh, S.M., Khan, I., Kumosani, T., Barbara, E., Almasoudi, S.B., Bahjii, S.M., Affadou, S.M., Ajibmoore, G.M.A., Azhar, E.I., 2016. Gut microbiota: a contributing factor to obesity. Front. Cell. Infect. Microbiol. 6, 95.

Hermes, R.G., Mlost, F., Wyazaki, M., Nofarais, M., Gomez de Segura, A., Gau, J., Pérez, J.F., 2009. Effect of dietary level of protein and fiber on the productive performance and health status of piggies. J. Anim. Sci. 87, 3566–3577.

Hile, S., Beltran, L.A., Kravchenko, A., de Young, L.B., Kalasa, G., Chang, B.P.L., Kambashi, B., Rodriguez, J., Cani, P.D., Neya, S.R., Thissen, J.P., Luminet, O., Bindelle, J., Delzenne, N.M., 2019. Effects of a diet based on inulin-rich vegetables on gut microbiota. JSFA reports 2, 264.

Hinojosa, A., Javier, R., Delgado-Hinojosa, A., Carrasco, G., Ochoa, A., Malavé, L., 2016. A chronobiological method to monitor fructan catabolism in two cool-season grasses fermented by mixed bovine ruminal microflora. J. Sci. Food Agric. 20, 264–271.

Kantar, M.B., Tyl, C.E., Borm, K.M., Zhang, X., Jumpers, J.M., Kaser, J.M., Schendel, R.R., Eckberg, J.G., Runck, B.C., Bunzel, M., Jordan, N.J., Stupar, R.M., Marks, M.D., Anderson, J.A., Johnson, G.A., Skaar, C.C., Schoonvuss, M., Ismail, B., Heimpell, G.E., Wyse, D.I., 2016. Perennial grass and oilseed crops. Annu. Rev. Plant Biol. 67, 634–655.
Ribeiro, M., Ferreira, D., Siopa, J., Rodríguez-Quijano, M., Nunes, F.M., 2022. Natural
Salamone, D., Rivellese, A.A., Vetrani, C., 2021. The relationship between gut
Ramos, C.I., Armani, R.G., Canziani, M.E.F., Dalboni, M.A., Dolenga, C.J.R., Nakao, L.S.,
Ruan, Y.L., 2014. Sucrose metabolism: gateway to diverse carbon use and sugar
Ritsema, T., Smeekens, S., 2003a. Fructans: beneficial for plants and humans. Curr. Opin.
Pool-Zobel, B.L., 2005. Inulin-type fructans and reduction in colon cancer risk: review of
Pascal, V., Pozuelo, M., Borruel, N., Casellas, F., Campos, D., Santiago, A., Martinez, X.,
Padilla-Camberos, E., Barragán-Alvarez, C.P., Díaz-Martínez, N.E., Rathod, V., Flores-
Fernández, J.M., 2018. Effects of agave fruagtes (Agave tequilana Weber var. azul) on body fat and serum lipids in obese. Plant Food Food Nutr. 73, 34–39.
Pang, D., Huang, C., Cao, X., and oxidative stress in human cancer cells. Front.
Pascal, V., Poumard, M., Nañez, V., Casellas, F., Campos, D., Martinez, X., Varela, E., Sarrabayrouse, G., Machiels, K., Vermeire, S., Sokol, H., Guarner, F.,
Oku, S., Ueno, K., Sawazaki, Y., Maeda, T., Shimura, H., 2022. The possible role of fructan in the gut microbiota. Gut 66, 1968–1978.
Oku, S., Ueno, K., Tsuruta, Y., Jitsuyama, Y., Suzuki, T., Shimura, H., 2022. Functional characterization and vacuolar localization of fructan exohydrolase derived from onion (Allium cepa). J. Exp. Bot. 73 (14), 4908–4922.
Oku, S., Ueno, K, Kawazaki, Y., Maeda, T., Jitsuyama, Y., Suzuki, T., Shimura, H., 2019. Functional characterization and anti-inflammatory activities of inulin-type fructan from barley grains. Plant Cell 26, 3728–3741.
Matros, A., 2014. Spatio-temporal dynamics of fructan metabolism in developing barley plants. J. Exp. Bot. 65, 1073–1086.
Meng, Y., Xu, Y., Chang, C., Qiu, Z., Hu, J., Wu, Y., Zhang, B., Zheng, G., 2020. Extraction, characterization and anti-inflammatory activities of an inulin-type fructan from Codonopsis pilosula. Int. J. Biol. Macromol. 163, 1077–1086.
Muñoz, I., Shephard, S.J., Rose, O., Rose, B., Barbre-Sloss, E., Gibson, P.R., 2007. Fructan and free fructose content of common Australian vegetables and fruit. J. Agric. Food Chem. 55, 6619–6627.
Mulabagal, V., Wang, H., Ngouajio, M., Nair, M.G., 2009. Characterization and quantification of health beneficial anthocyanins in leafy chicory (Cichorium intybus) varieties. Eur. Food Res. Technol. 230, 47.
Nemeth, C., Andersson, A.A.M., Andersson, R., Mangelsen, E., Sun, C., Per, Åman., 2014. Randomized crossover trial. Am. J. Clin. Nutr. 111, 1286–1297.
Oku, S., Ueno, K., Oku, S., Ueno, K., Sawazaki, Y., Maeda, T., Jitsuyama, Y., Suzuki, T., Shimura, H., 2022. 2020 a novel inulin-type fructan from Asparagus cochinchinensis and its beneficial impact on human intestinal microbiota. Carbohydr. Polym. 247, 116761.
Tomura, K., Kawakami, A., Sanada, Y., Tase, K., Komatsu, T., Yoshida, M., 2009. Cloning and functional analysis of a fructosyltransferase cDNA for synthesis of highly polymerized levan in Pheum pretense L.). J. Exp. Bot. 60, 893–905.
Tomura, K., Sanada, Y., Tase, K., Komatsu, T., Yoshida, M., 2011. Pp6-FEH1 encodes an enzyme for degradation of highly polymerized levan and is transcriptionally induced by defatol in timothy (Phleum pretense L.). J. Exp. Bot. 62, 4321–4329.
Tefera, T.F., 2021. Possible actions of inulin as prebiotic polysaccharides: a review. Front. Food. Nutr. 2 (4), 407–416.
Unger, C., Hardegger, M., Liendhard, S., Sturm, A., 2016. cDNA cloning of carrot (Daucus carota) soluble acid beta-fructofuranosidase and comparison with the cell wall isoenzyme. Plant Physiol. 140, 1351–1357.
Velasco, E., Sarrabayrouse, G., Machiels, K., Vermeire, S., Sokol, H., Guarner, F.,
Ritsema, T., Delaune, M.C., Lemaire, S., Gommes, M., Martínez-López, M., Azpiroz, P.A.P., Cruz-Rubio, J.M., Martínez-Gallardo, N.A., Díez-Mateos, I.C., Díez-Leyva, J.F., 2016. Differential fructan accumulation and expression of fructan biosynthesis pathway of Jerusalem artichoke. Plant J. 15, 489–497.
Varela, E., Sarrabayrouse, G., Machiels, K., Vermeire, S., Sokol, H., Guarné, F.,
Michau, C., 2017. Accelerating the domestication of new crops: feasibility and approaches. Trends Plant Sci. 22, 1785–1794.
Vitrac, T., Gili, A., Dumas, F., Chantrel, P., Arouet, A.A., 1989. Comparison of the bioactivity of Pp6-FEH1 gene of Pheum pretense L. with those of other agave species. J. Agric. Food Chem. 37, 360–365.
Vitrac, T., Gili, A., Dumas, F., Chantrel, P., Arouet, A.A., 1989. Comparison of the bioactivity of Pp6-FEH1 gene of Pheum pretense L. with those of other agave species. J. Agric. Food Chem. 37, 360–365.
Yu, H., Lin, T., Meng, X., Da, H., Zhang, J., Liu, G., et al., 2021. A route to de novo domestication of wild allotetraploid rice. Cell 184 (5), 1156–1170.
Zhang, J., Chen, H., Luo, L., Zhou, Z., Wang, Y., Guo, T., Yang, L., Peng, T., Wu, M., 2021. Structures of fructan and galactan from Polygonatum cyrtonema and their utilization by probiotic bacteria. Carbohydr. Polym. 267, 118219.
Zhang, J., Li, Z., Zhou, L., Bao, J., Xu, J., 2020. The modifications of a fructan from Anemarrhena asphodeloides Bunge and their antioxidant activities. Int. J. Biol. Macromol. 164, 4435–4443.

Zhang, X., Hu, P., Zhang, X., Li, X., 2020. Chemical structure elucidation of an inulin-type fructan isolated from Lobelia chinensis lour with anti-obesity activity on diet-induced mice. Carbohydr. Polym. 240, 116357.
Zhao, L., Zhang, F., Ding, X., Wu, G., Lam, Y.Y., Wang, X., Fu, H., Xue, X., Lu, C., Ma, J., Yu, L., Xu, C., Ren, Z., Xu, Y., Xu, S., Shen, H., Zhu, X., Shi, Y., Shen, Q., Dong, W., Zhang, C., 2018. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science (New York, N.Y.) 359 (6380), 1151–1156.