



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

Yan Shi¹, Dun Si¹, Xinfeng Zhang, Donghong Chen^{**}, Zhigang Han^{*}

State Key Laboratory of Subtropical Silviculture, Zhejiang A&F University, Hangzhou, 311300, China

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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; Márquez-López 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 López, 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 sprout. 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

* Corresponding author.

** Corresponding author.

E-mail addresses: 1018802810@qq.com (Y. Shi), nsr_einston@163.com (D. Si), zhangxf@zafu.edu.cn (X. Zhang), chendh212@163.com (D. Chen), hanzg@zafu.edu.cn (Z. Han).

¹ These authors contributed to this paper equally.

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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 (30.96), 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 6Gfructosyltransferase (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, and are broken down by fructan exohydrolases (FEH) (Pérez-López and Simpson, 2020).

One of the simplest form of fructans is inulin, which consists of $\beta(1-2)$ -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

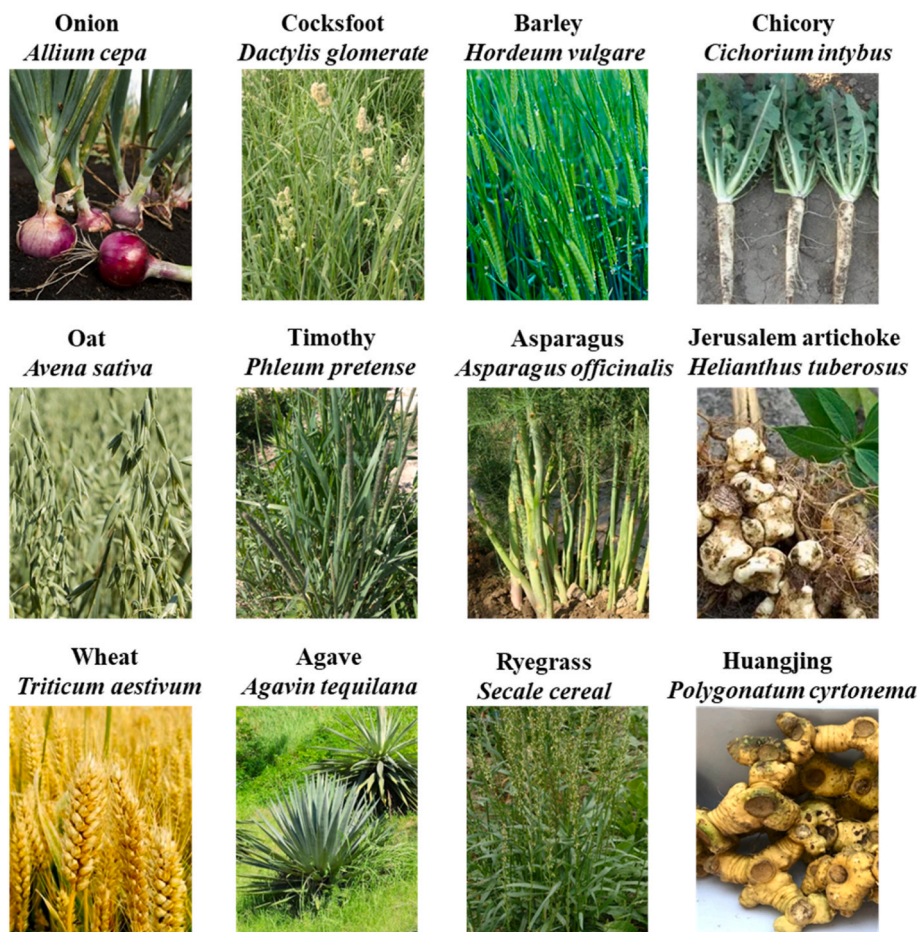


Fig. 1. Representative species containing different fructans structure.

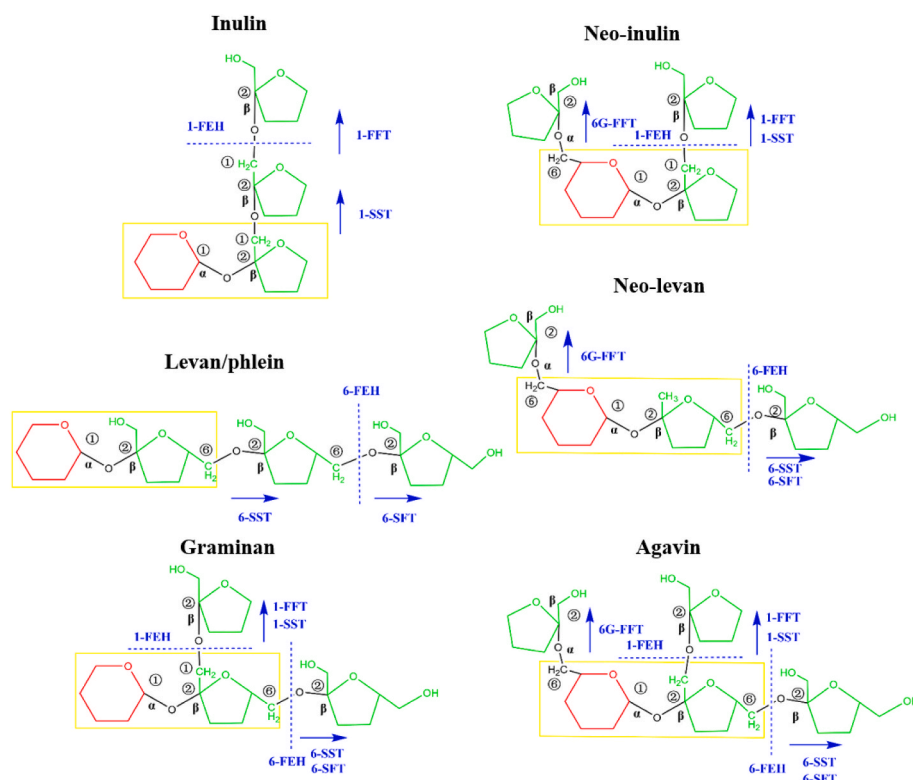


Fig. 2. Schematic representative structure of plant fructans.

Table 1

Summary of degree of polymerizaion 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)
<i>Agave tequilana</i>	Agavin	3–23	NA	(Suárez-González et al., 2016; Mellado-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)
<i>Curcuma kwangsiensis</i>	Levan	30–31	NA	(Dong et al., 2015)
Jerusalem artichoke	Inulin	3–61	NA	(Jiao et al., 2018; Luo et al., 2018; Maicaurkaew et al., 2017)
<i>Smallanthus sonchifolia</i>	Inulin	3–7	NA	(Contado et al., 2015)
<i>Codonopsis pilosula</i>	Inulin	3–18	6	Fu et al. (2018)
<i>Gomphrena marginata</i>	Levan	3–41	NA	(Joaquim et al., 2018)
<i>Platycodon grandiflorus</i>	Inulin	3–11	NA	(Pang et al., 2019)
Onion	Inulin- and neoseries-type	3–20	NA	(Oku et al., 2022; Oku et al., 2019; Downes and Terry, 2010)
<i>Avena sativa</i>	Fructooligosaccharides	3–7	NA	(Matsui et al., 2018)
<i>Campanula rapunculoides</i>	Inulin	3–20	NA	(Matsui et al., 2018)
<i>Asparagus officinalis</i> L.	Inulin- and neoseries-type	3–17	NA	(Witzel and Matros, 2020)
<i>Polygonatum cyrtonema</i>	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)
<i>Phleum pratense</i>	Levan	3–72	NA	(Kagan et al., 2022; Pérez-López and Simpson, 2020)
<i>Dactylis glomerata</i>	Levan	3–60	NA	(Kagan et al., 2022; Ince et al., 2014)
<i>Agave salmiana</i>	Agavin	7–30	~19	Plascencia et al. (2022)

sucrose 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

Table 2
Potential benefit of fructans for human health.

Fructans structure	Plant sources	Function type	Function mechanism	Reference
Inulin-type fructans	<i>Cichorium intybus</i>	Modification of the gut microbiota	Increased relative abundance of the Bifidobacterium genus from (mean \pm SEM) 5.3% \pm 5.9%–18.7% \pm 15.0%	Reimer et al. (2020)
Inulin-type fructans	<i>Codonopsis pilosula</i>	Modification of the gut microbiota	Stimulation effect on Lactobacillus and pH reduction of medium	Fu et al. (2018)
Inulin-type fructans	<i>Asparagus cochinchinensis</i>	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	<i>Polygonatum cyrtoneura</i>	Modification of the gut microbiota	Promoted growth of Bifidobacterium and Lactobacillus strains	Zhang et al. (2021)
Inulin	<i>Cichorium intybus</i>	Modification of the gut microbiota	Increased Bifidobacterium and Anaerostipes abundances, while decreased Bilophila numbers	Vandeputte et al. (2017)
Inulin	<i>Cichorium intybus</i>	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	<i>Lobelia chinensis</i>	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	<i>Sechium edule</i>	Hypocholesterolemic effects	Significantly decreased cholesterol, serum triglycerides, serum LDL, and serum VLDL	Bandyopadhyay et al. (2021)
Inulin-type fructans	<i>Codonopsis pilosula</i>	Anti-inflammatory effects	Reduced the expression of inflammatory factors such as TLR4, NF- κ B, TNF- α and IL-6	Meng et al. (2020)
Carboxymethylation and sulfation modified fructans	<i>Anemarrhena asphodeloides</i>	Antioxidant activity	Increased DPPH and hydroxyl radical scavenging activity	Zhang et al. (2020)

acceptors such as 1-kestose, 6-kestose and 6G-kestotriose (Tamura et al., 2009; Van den Ende et al., 2011; Lammens et al., 2012). Neo-levefructans are formed through transfer of fructose residues to the glucose 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 neo-levefructans by 1-FFT and 6-SFT, respectively (Lasseur et al., 2011; Rao et al., 2011). In plants, levan is commonly found in grasses, including *Dactylis glomerata* and *Phleum pratense*, whereas neo-levefructans are found in a few Poales order species (e.g., oat and ryegrass).

Graminan and agavin structures are the special types combining both inulin and levan, 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 (DTTHGGT) of the fructan biosynthesis genes, revealing 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, CiMYB17, is able to activate both fructosyltransferase (1-SST, 1-FFT) and fructans exohydrolase (1-FEH1, 1-FEH2) genes, via binding to the DTTHGGT cis-elements (Wei et al., 2017). In fructans degradation pathway, CiMYB5 and CiMYB3 have been identified to regulate the expression of 1-FEH genes in chicory (Wei et al., 2017). However, CiMYB3 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. cyrtoneura*, providing a new question as for how carbohydrate 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 (Haouazine-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

CWINs from higher plant 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 (Ritsem 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

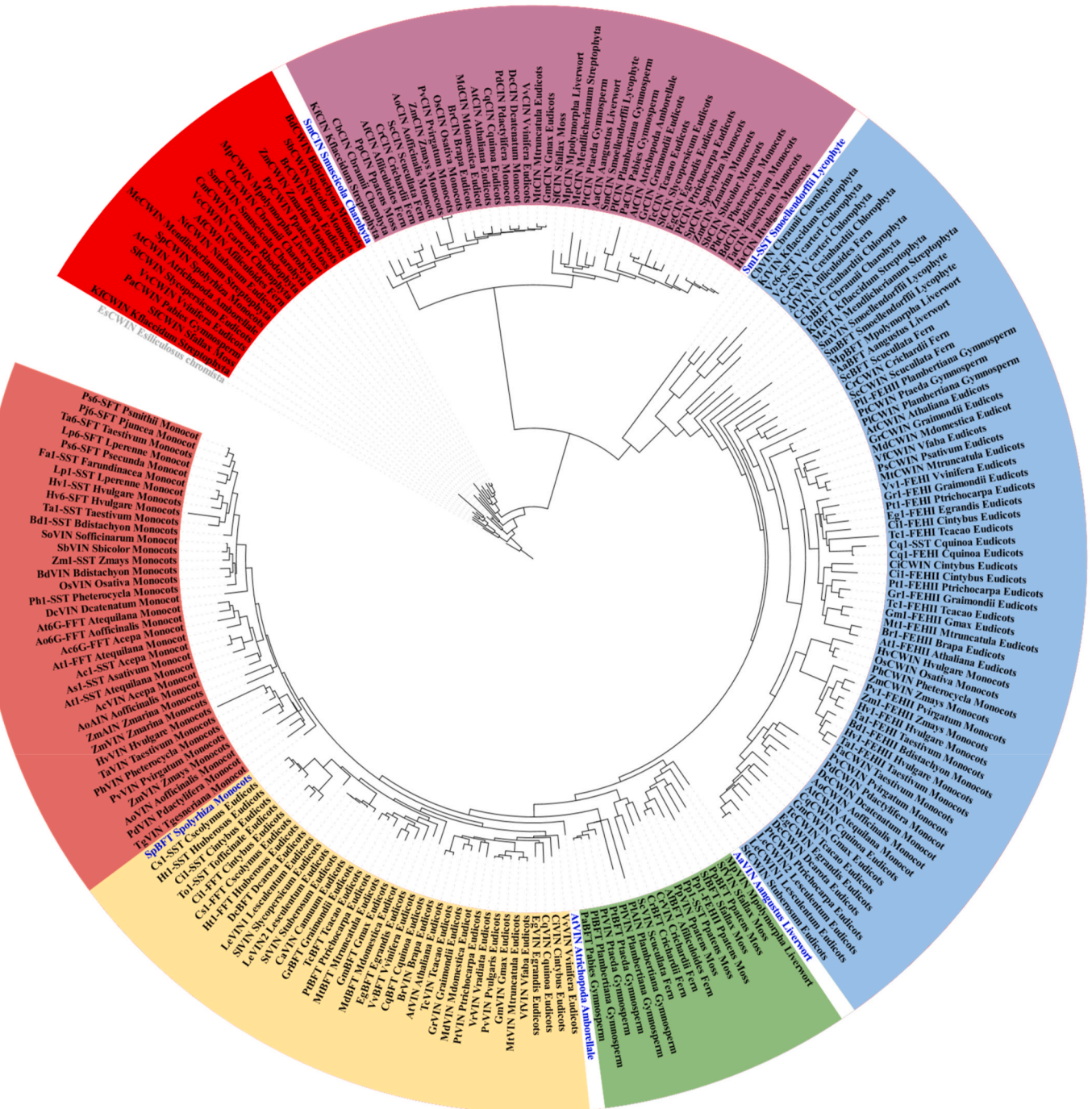


Fig. 3. Evolutionary and phylogenetic analysis of invertase genes in plant and algal species. The amino acid sequence of invertases that have been experimental verification was used as database sequences; Query sequence in Table S1 were selected by the criteria of E-value $< 10^{-10}$ using BLASTP. The sequences were aligned with MAFFT (<https://mafft.cbrc.jp/alignment/software/>) and the phylogenies constructed with the RAXML-PPC2 on XSEDE (<http://www.phylo.org/>). *Ectocarpus siliculosus* was used as the outgroup (the species are shaded) and the root of the tree, and the Interactive Tree of Life resource (<http://www.itol.embl.de>) was used to draw the phylogenetic tree.

more similar to other invertases from monocots than to the fructosyltransferases from dicots. The At1-FFT from monocot *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 *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 *Cichorium intybus* (Vandeputte et al., 2017; Reimer et al., 2020), *Agave tequilana* (Márquez-Aguirre et al., 2013; Padilla-Camberos et al., 2018; Sáyago-Ayerdi et al., 2021), *Agave salmiana* (Castillo Andrade et al., 2019; Daniel et al., 2022; Martínez-Martin et al., 2022), *Codonopsis pilosula* (Fu et al., 2018), *Asparagus cochinchinensis* (Sun et al., 2020), and *Polygonatum cyrtoneura* (Zhang et al., 2021), selectively stimulate the growth of beneficial bacteria such as *Prevotella*, *Megamonas* and *Bifidobacterium*, improving health with human colon (Sun et al., 2020) (Table 2). For instance, a diet supplemented with *Agave species* fructans in an animal model stimulated the growth of *Bifidobacterium* and *Lactobacillus* and inhibited growth of *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 *Bifidobacterium* and help reduce the dietary fiber gap prevalent in modern life (Hiel et al., 2019; Teferra, 2021; Reimer et al., 2020). In a double-blind trial in which *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 *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-Martin et al., 2022).

4.1.2. Short chain of fat 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 *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 hypocholesterolemic 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 *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-Ayerdi 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 commensal 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

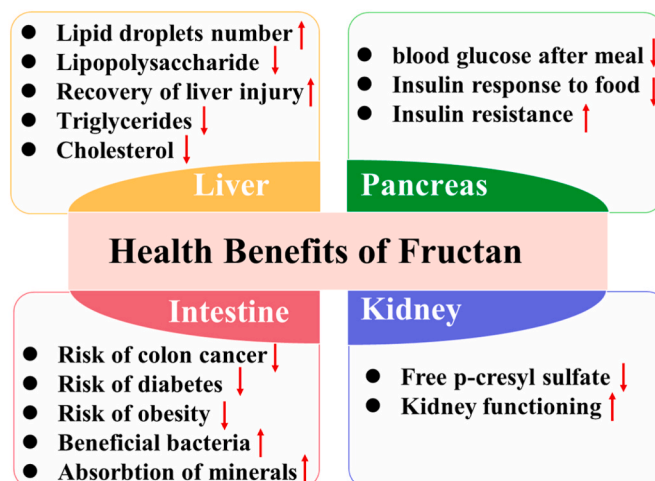


Fig. 4. The health benefits of plant fructans.

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; Valenlia 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- κ B, 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-cresyl 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 (Østerberg 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 allotetraploid 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; Østerberg et al., 2017). Thus, domestication of perennials is in the breeding pipeline. Huangjing is a perennial plant with natural polyploidization. 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 CWINs, CINs, VINs and FT from lower to higher plants. These advances provide new opportunities to select fuctans-rich wild plants and improve the domestication using biotechnological approaches. A representative wild species, *Polygonatum cyrtoneuma* has been attracting huge interest in China, which fulfils 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

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