Biotechnology Advances 37 (2019) 107397

Contents lists available at ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

From lignocellulosic residues to market: Production and commercial potential of xylooligosaccharides

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ARTICLE INFO

Keywords:
Prebiotic
Xylooligosaccharides
Lignocellulosic residues
Production processes

ABSTRACT

The updated definition of prebiotic expands the range of potential applications in which emerging xylooligosaccharides (XOS) can be used. It has been demonstrated that XOS exhibit prebiotic effects at lower amounts compared to others, making them competitively priced prebiotics. As a result, the industry is focused on developing alternative approaches to improve processes efficiency that can meet the increasing demand while reducing costs. Recent advances have been made towards greener and more efficient processes, by applying process integration strategies to produce XOS from costless lignocellulosic residues and using genetic engineering to create microorganisms that convert these residues to XOS. In addition, collecting more *in vivo* data on their performance will be key to achieve regulatory claims, greatly increasing XOS commercial value.

1. Introduction

Due to the increasing of health consciousness, consumers today are driven to the use of natural products as preventive medicine, pivoting their food preferences towards healthier and sustainably sourced options, including functional food, *i.e.* products holding health benefits apart from nutrition (Aragon et al., 2013; Adebola et al., 2014; Samanta et al., 2015; Kaprelyants et al., 2017). The current health-based consumer trends explain the revenues decline of fast food outlets (Market Mogul, 2017) and the increasing demand of functional ingredients, such as prebiotics, presently marketed beyond the traditional digestive health and functions, as for instance sugar/fat replacement, taste/texture enhancement, weight management, mineral absorption and immune health improvement (Samanta et al., 2015; Zhao et al., 2017). In fact, consumers prefer healthy food products and are willing to pay more for them (Forbes, 2015).

Recently, the International Scientific Association for Probiotics and Prebiotics (ISAPP) updated the definition of prebiotics (Gibson et al., 2017), to "a substrate that is selectively utilized by host microorganisms conferring a health benefit", on the understanding that the host can be human or animal. Besides considering potential prebiotic substances other than non-carbohydrates, namely plant polyphenols, the current definition expands it to include applications to extra-intestinal sites, namely vagina and skin, thus allowing for different application categories other than food.

The global prebiotic ingredients market is estimated at USD 4.07 billion in 2017, and it is expected to reach a value of USD 7.37 billion by 2023, registering a Compound Annual Growth Rate (CAGR) of 10.4% (MarketsandMarkets™, 2018), with the Asia-Pacific (APAC) region including China, India and Japan, expecting the highest gains at over 9.5% (The Market Watch, 2018).

In particular, prebiotic xylooligosaccharides (XOS) present a remarkable potential as food ingredients due to their price competitiveness compared to other prebiotics (AIDP Inc., 2017), heat and pH stability (Courtin et al., 2009), organoleptic properties (Aachary and Prapulla, 2011) and multi-dimensional effects on human health and livestock (Aachary et al., 2015).

The industry is presently focused on developing different processes for XOS production with increased efficiency and high-income to fulfil the market needs. However, the production of XOS is still more expensive than other prebiotics. Recent advances have been made towards greener and more efficient processes, namely by using renewable, cheap and abundant lignocellulosic residues as raw material and applying integration process strategies that can be further included on biorefinery processes.

The main goals of this review are (a) to highlight the main aspects that allow the XOS commercial potential to stand out from the competition; (b) to provide key measures for increasing XOS commercial value; (c) to identify emerging and high-impact XOS production approaches from lignocellulosic residues.

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https://doi.org/10.1016/j.biotechadv.2019.05.003
recibido en 23 octubre 2018; recibido en versión revisada en 7 abril 2019; aceptado en 4 mayo 2019
Available online 07 May 2019
0734-9750/

2. XOS as emerging prebiotics

2.1. Physicochemical properties

Generally, XOS are oligosaccharides composed by chains of xylose residues, linked through β-(1,4)-xylosidic bonds, which can be decorated with different side groups (*e.g.* α-d-glucopyranosyl uronic acid or its 4-*O*-methyl derivative, acetyl groups, or arabinofuranosyl residues) forming branched structures (Coelho et al., 2016). They are mainly produced by xylan hydrolysis, the major constituent of hemicellulose polysaccharides that are present in plant cell walls (Carvalho et al., 2013). The xylan hydrolysis can be performed, for instance, by xylanases (more detailed information on XOS production in Section 3).

Depending on the xylan source and production process, XOS vary greatly in degree of polymerization (DP), side groups and their pattern of substitution on the xylose chain, along with the types of linkages (Samanta et al., 2015; Belorkar and Gupta, 2016). In particular, the DP can vary from 2 to 10 xylose units (Moure et al., 2006).

XOS can be naturally present in honey, fruits, vegetables and others but not in sufficient amounts to exhibit prebiotic effects (Samanta et al., 2015), which explains the need of their production at industrial scale from xylan-rich materials, such as lignocellulosic biomass. Besides presenting acceptable organoleptic properties, XOS exhibit temperature (up to 100 °C) and acidity (pH 2.5 to 8) stability in a higher range than inulin and FOS (Aragon et al., 2013; Mano et al., 2018), hence making them potential food ingredients.

2.2. Biological properties

XOS are classified as non-digestible oligosaccharides, passing through the upper gastrointestinal (GI) tract without being digested, thus reaching the lower intestine to be primarly metabolized by probiotic bacteria (Aachary and Prapulla, 2011; Gibson et al., 2017; Sophonputtanaphoca et al., 2018). Therefore, XOS present multidimensional properties and effects which make them suitable for food and health applications (Fig. 1).

When compared with other well stablished prebiotics, namely inulin and FOS, XOS showed higher resistance to digestion and ability to stimulate the growth of bifidobacteria (Palframan et al., 2003; Hsu et al., 2004) and to produce lactate in a higher extent (Rycroft et al., 2001), not exhibiting toxicity or negative effects on human health (Aachary and Prapulla, 2009). Additionally, they hold acceptable organoleptic properties and stability, and can potentially be used as emulsifying, stabilizing and fat replacer agents (Courtin et al., 2009; Mano et al., 2018). Given these unique features, as well as other beneficial effects on health, *e.g.* prevention of colon cancer (Aachary et al., 2015), XOS have been incorporated in several functional foods and animal feed, nutraceuticals and cosmetics (Moure et al., 2006; Ayyappan et al., 2016; Gao et al., 2017; Gupta and Mehra, 2017; Abasubong et al., 2018; Guo et al., 2018; Ferrão et al., 2018; Zhang et al., 2018).

Furthermore, XOS are also reported to present other beneficial effects, namely in the prevention of diabetes (Yang et al., 2015), neurotoxicity (Krishna et al., 2015) and colon inflammation (Femia et al., 2010; Lin et al., 2016), which have gained attention from the medical and pharmaceutical industries (Fig. 1). Additionally, XOS also have interesting properties for the cosmetic industry. Their antioxidant and moisturizing capacity, together with the ability to restore microflora are clearly valorized in a cosmetic product (Moure et al., 2006; Valls et al., 2018). Nevertheless, application of XOS in cosmetics has been poorly explored probably due to the previous 'prebiotic concept' (prebiotic action limited to the GI tract). However, the recent update of the prebiotic definition (application to extra-intestinal sites) is likely to gather the interest of the cosmetic industry.

Recently, several patents have been granted on a wide range of applications in which XOS are used, *e.g.* detoxification beauty jelly (CN107397171B, 2018), weight loss food (CN106107293B, 2017), nutritional formula for cancer patients (CN104814375B, 2018), odor reducing feed for pigs (BE1023808B1, 2017), microencapsulation (CN105831784B, 2018), constipation treatment (CN105053778A 2015; CN106361741B, 2017).

2.3. Market potential and regulatory considerations

Although XOS have been used in the APAC region for a while

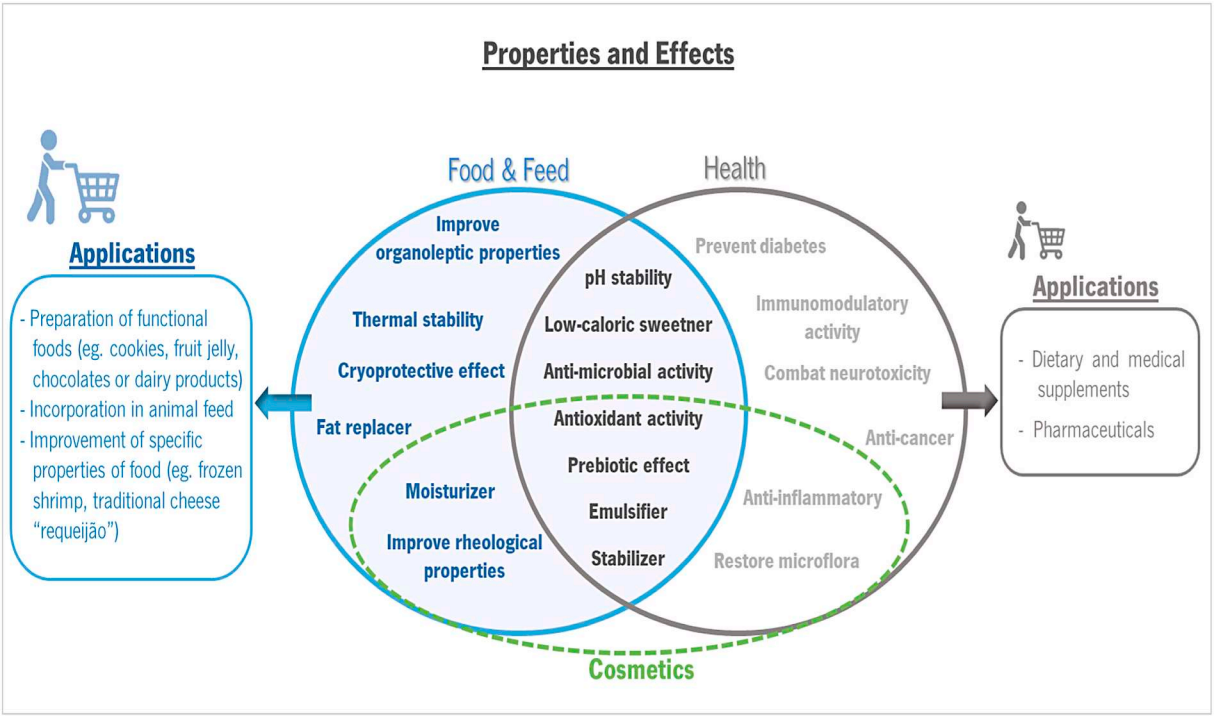

Fig. 1. Main properties and effects reported for XOS which can be considered interesting features for different marketable areas.

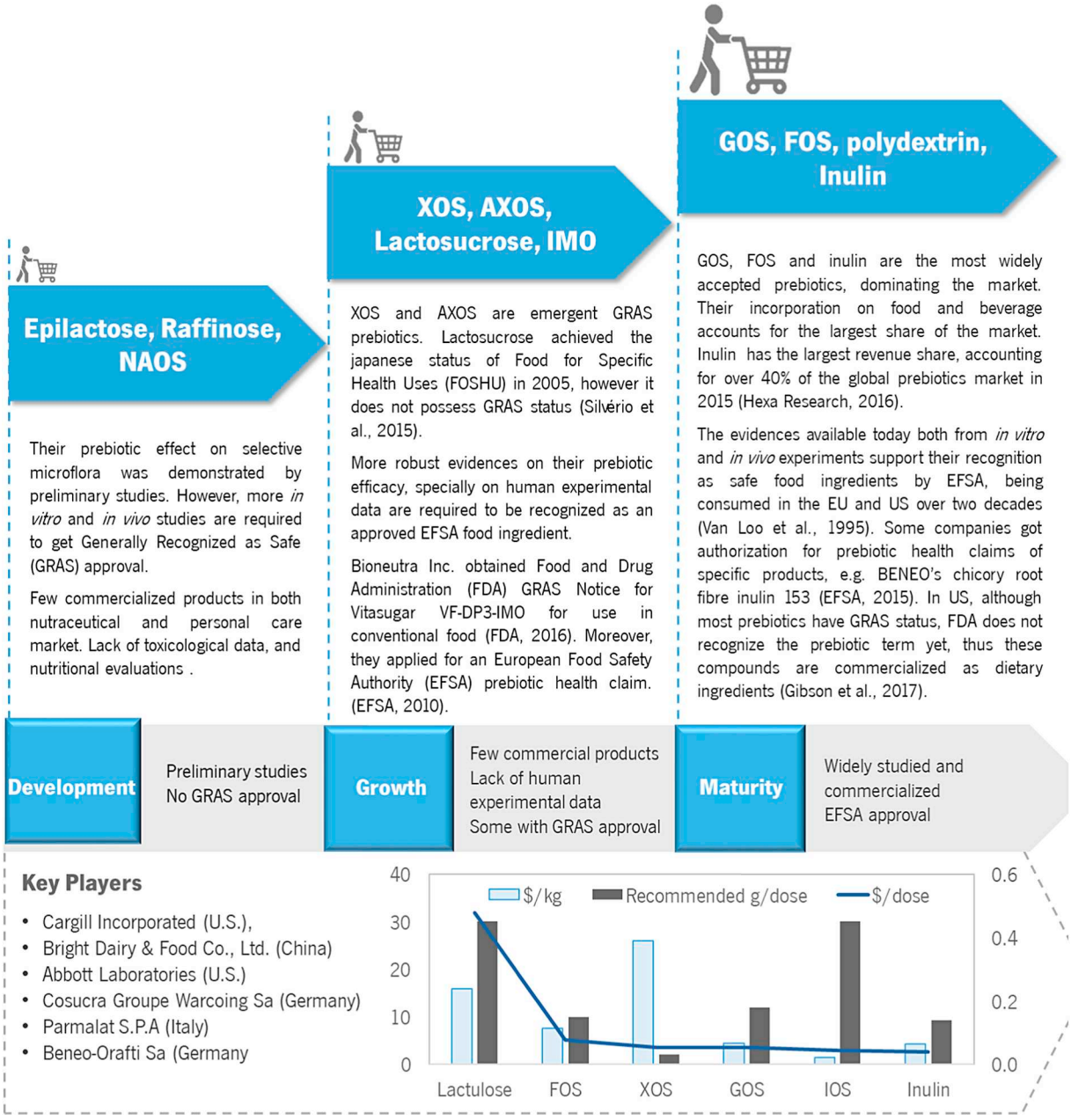

Fig. 2. Prebiotics positioning in market stages according to their level of development. Abbreviations: NAOS, neoagarooligosaccharides; XOS, xylooligosaccharides; AXOS, arabinoxylooligosaccharides; IMO, isomaltooligosaccharide; GOS, galactooligosaccharides; FOS, frutooligosaccharides; IOS, Isooligosaccharide. EFSA Panel on Dietetic Products and Nutrition and Allergies (NDA), 2010; Food and Administration, 2016; Hexa Research, 2016; Silvério et al., 2015.

(Aachary and Prapulla, 2011), they are categorized as 'emerging prebiotics' (Lin et al., 2016), especially in other regions as North America and Europe, based on the health claims obtained comparing to other established prebiotics, such as inulin (Fig. 2). Fig. 2 highlights the XOS position comparing to other prebiotics regarding market volume and selling price, respectively.

In North America, XOS have received up to now two FDA GRAS notifications for use in food, no infant food mentioned, GRN 458 (FDA, 2013), and for wheat bran extract containing XOS and arabinoxylooligosaccharides (AXOS), GRN 343 (FDA, 2010). Recently, XOS enzymatically produced from corncob by Longlive Europe Food Division Ltd. were evaluated by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) obtaining the status of save as a novel food (NF) pursuant to Regulation (EU) 2015/2283 (EFSA, 2018).

Given the stage of the XOS market, it is expected that regional regulatory approval will greatly determine its evolution, which in turn will strongly depend on the research and development (R&D) investment. Since the human experimental data on XOS and AXOS are scarce, we consider that providing substantial evidences of the XOS prebiotic efficacy will be key to obtain health claims approvals and consequently to increase XOS commercial value.

According to a new Global Info Research (GIR) study, the worldwide market for XOS is expected to grow from 93 million US$ in 2017 to 130 million US$ in 2023, at a CAGR of approximately 5.3% (The Market Reports, 2018). Longlive, Kangwei, Hfsugar are three of the top XOS manufacturers (The Market Reports, 2018), nonetheless competition is expected to greatly increase and R&D and innovation will be key to boost XOS demand, especially to obtain health claims approval which naturally favor the consumers' acceptance (Benson et al., 2018). However, XOS are considered the most competitively priced prebiotic

ingredient in terms of price per recommended dose given their lower requirement to achieve the prebiotic effect, 1.4–2.8 g/day (Finegold et al., 2014) (Fig. 2). XOS will expectably compete for market share as their potential and multidimensional benefits are more widely communicated and factually substantiated.

3. Production of xylooligosccharides from lignocellulosic residues

Although XOS are recognized as competitive emerging prebiotics, their production costs significantly limit their wide adoption, being costlier than other prebiotics, particularly because commercial xylan is an expensive substrate and difficult to obtain. Therefore, industry has been challenged to develop alternative production processes with high-efficiency and high-income to attend the market needs. For instance, the use of lignocellulosic biomass as raw materials has been considered a potential strategy to reduce the production costs as they are costless, renewable and abundant.

Lignocellulosic biomass, such as agro-residues, is mainly composed by cellulose, hemicellulose and lignin: cellulose is composed by a chain of glucose molecules with hydrogen bonds between different layers of the polysaccharides forming a crystalline conformation; hemicellulose mainly constituted by xylan is the key target for XOS production; and lignin confers structure to the plant, being composed by three major phenolic components, namely p-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol (Dutta and Wu, 2014).

There has been a great interest in the exploitation of agro-residues, which are the most widely available renewable resource on earth (Chapla et al., 2012; Kumar and Satyanarayana, 2015). The use of agro-residues that not compete for food supply is an economically advantageous strategy for the production of value-added compounds (Somerville et al., 2010). Particularly, they can reduce the cost of a microbial fermentation process, by reducing the production medium cost, which represents approximately 60% of the upstream cost of a fermentation process (Lotfy, 2007). Moreover, using agro-residues also entails environmental benefits, since it assists the management of billions of tons of residues generated annually (Kumar and Satyanarayana, 2015), thus representing a boon to all concerned authorities (Samanta et al., 2015). However, the use of agro-residues also presents meaningful challenges, as variable composition, seasonality and spoilage risk during storage (Batidzirai et al., 2016). Additionally, depending on the chemical composition, the residues can be more or less suitable for XOS production. Residues with higher amounts of xylan and low amounts of lignin are better options. Corncob, wheat straw and sugar cane bagasse are examples of abundant residues with interesting xylan/lignin ratios (Danish et al., 2015). In particular, AIDP Inc. uses corncob to produce XOS by enzymatic hydrolysis and sells the product as PreticX (AIDP Inc, 2017).

3.1. Chemical and auto-hydrolysis versus enzymatic hydrolysis

XOS can be produced from raw lignocellulosic residues using chemical, auto-hydrolytic, enzymatic processes or a combination thereof (Kumar and Satyanarayana, 2015; Carvalho et al., 2013) (Fig. 3).

Chemical or auto-hydrolytic processes present several disadvantages, namely product contamination by undesired by-products, including toxic compounds such as furfural and hydroxymethylfurfural (HMF); low control over the DP; high downstream costs (Bian et al., 2014); generally, requires the use of noxious chemicals and consequently specific and more robust equipment.

Chemical and auto-hydrolysis generate XOS with a wide range of polymerization (from DP2 to DP20) (Kaprelyants et al., 2017; Li et al., 2018), while enzymatic processes generate mostly low-DP XOS (from DP2 to DP4) (Carvalho et al., 2015; Kaprelyants et al., 2017; Sukri and Sakinah, 2018). It is well known that low-DP XOS present a higher prebiotic potential (Okazaki et al., 1990; Moura et al., 2007; Ho et al., 2018), hence being more suitable for food-related and pharmaceutical applications (Vázquez et al., 2000). Particularly xylobiose (X2), has been reported to present the strongest prebiotic activity among the xylose polymers, leading to higher growth of *Bifidobacterium* and *Lactobacillus* strains (Okazaki et al., 1990; Palframan et al., 2003; Moura et al., 2007. Furthermore, X2 is also 0.3–0.4 times sweeter than sucrose (Park et al., 2017), contributing to the sweetness potency of XOS, thus presenting high industrial interest as a health-promoting bulk sweetener ingredient.

The enzymatic process is more environment-friendly, operating at milder conditions without the use of noxious chemicals, and thus more compatible with the perspective of a biodegradable process. Additionally, the use of xylanolytic enzymes presents high efficiency and specificity, allowing a higher control over DP and a reduced production of undesired xylose and other by-products is obtained (Akpinar et al., 2007).

Nonetheless, since xylan is mostly present as a xylan-lignin matrix, XOS are generally produced by a combination of methods involving a two-step approach (Carvalho et al., 2013; Faryar et al., 2015). The first step includes pretreatment of the lignocellulosic biomass to remove lignin and cellulose, increasing concentration of xylan, or the xylan extraction itself by solubilization, which may be further purified by precipitation. This initial step to obtain soluble xylan can be performed in many ways and comprise multiple process stages, depending on the method and residue. The most common methods are autohydrolytic, chemical or enzymatic, in particular pretreatments with alkaline solutions are largely used and considered one of the most efficient in terms of xylan recovery without degradation. The second step consists in the xylan hydrolysis by xylanolytic enzymes (Chapla et al., 2012; Rico et al., 2018), such as *endo*-1,4-β-xylanases (EC 3.2.1.8) and endo-1,3-β-xylanases (EC3.2.1.32).

The xylanolytic enzyme systems in nature comprise endo-xylanase or xylose releasing enzymes (Mamo et al., 2013), *exo*-xylanase and/or β-xylosidase, and debranching enzymes (Aachary and Prapulla, 2011). For the production of XOS, only the endo-acting enzymes are of interest and these can be found in the glycoside hydrolase families (GH) 5, 8, 10, 11 and 43 based on sequence conservation. Moreover, enzyme preparations with low exo-xylanase and/or β-xylosidase activity are desired to avoid the production of xylose (Vázquez et al., 2000). Xylanases have been isolated from many different fungi and bacteria (Manisha and Yadav, 2017), however the majority of the commercial xylanolytic preparations are currently produced by the genetically modified *Trichoderma* or *Aspergillus* strains (Mussatto and Teixeira, 2010).

Nonetheless, the economic viability of XOS production from lignocellulosic residues may be compromised by the low yields associated to the pretreatment step and by the cost of producing or purchasing commercially available xylanases (Reddy and Krishnan, 2016a). Hence, recent advances towards greener and more efficient processes have been reported, for instance the use of raw lignocellulosic residues without pretreatment and integration process strategies, such as direct fermentation.

3.2. Future trends on XOS production

As shown in Fig. 3, the number of publications on enzymatic hydrolysis to produce XOS comparing with other processes in the last two years, clearly demonstrates that enzymatic hydrolysis leads the research on XOS production, highlighting the awareness of the scientific community towards the advantages of this production process approach. In particular, within the enzymatic production, different strategies have been carried, namely immobilization of enzymes, genetic modification of xylanases, enzymatic cocktails and heterologous production of xylanases.

Interestingly, the increasing number of publications about XOS production under the biorefinery concept and/or through process integration approach strengths the current effort to reduce XOS

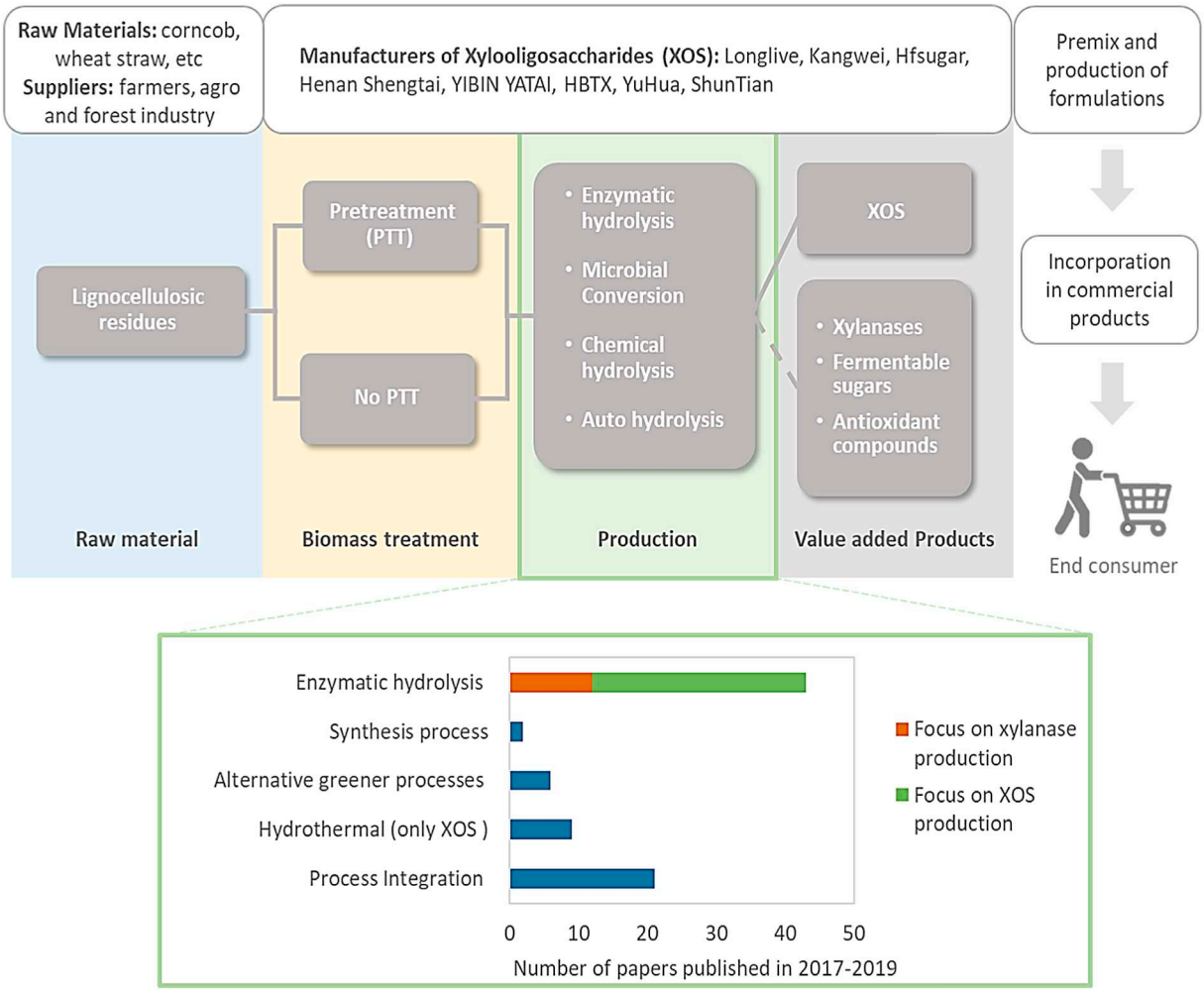

Fig. 3. Methods of xylooligosaccharides production from lignocellulosic residues.

production costs. Within this notion, the direct fermentation of lignocellulosic biomass by microorganisms to produce XOS encloses a remarkable potential mainly due to process simplification. Nevertheless, only few reports focus on this strategy. We anticipate the increasing use of synthetic biology tools to create super-microorganisms that will work as integrative cell (bio)factories able to directly convert raw lignocellulosic biomass into XOS. On the other hand, the use of genetic modified microorganisms (GMOS) may be hampered due to regulatory issues, particularly in Europe.

Table 1 summarizes the yields of XOS produced (mg) per gram of xylan, $Y_{XOS/xylan}$ (mg/g), that have been recently reported for enzymatic hydrolysis of agro-residues with and without pretreatment. Purohit et al. (2017) reported both the highest yield and the lowest production time, using a magnetic cross-linked xylanase aggregate developed from *Acinetobacter pittii* MASK 25 xylanase to hydrolyze milled rice straw. This study clearly reinforces the importance of sophisticated genetic strategies to increase the process efficiency.

The yields seem to significantly depend on the substrate and production process, ranging approximately between 100 mg/g and 800 mg/g. Nonetheless, Reddy and Krishnan (2016a), da Silva Menezes et al. (2018), Palaniappan et al. (2017) and Purohit et al. (2017) reported similar yield values using corncob, 670–720 mg/g, though the production times vary greatly (from 1 to 30 h), emphasizing the importance of using suitable residues and xylanase sources. Moreover, it is noteworthy that the majority of the processes include a first step of residue pretreatment, therefore the $Y_{XOS/xylan}$ values showed in Table 1 do not represent the overall production process yield (Faryar et al., 2015; Reddy and Krishnan, 2016a; Mathew et al., 2018; Palaniappan et al., 2017; Rajagopalan et al., 2017; Salas-Veizaga et al., 2017; Seesuriyachan et al., 2017; Liu et al., 2018; Singh et al., 2018), except for the ones reported by Amorim et al. (2018, 2019b), Purohit et al. (2017) and da Silva Menezes et al. (2018).

Purohit et al. (2017) and da Silva Menezes et al. (2018) used direct enzymatic hydrolysis of rice straw and corn cobs, and rice husk, respectively. These agro-residues were previously milled, but no other conventional pre-treatment was applied.

Amorim et al. (2018, 2019b) used an integrated process approach based on the production of XOS through direct fermentation of non-pretreated agro-residues by suitable microorganisms. The authors compared the use of direct fermentation with the application of commercial enzymes, concluding that direct fermentation is an advantageous approach to hydrolyze brewers' spent grain (BSG) and produce AXOS. In fact, this is a very promising strategy to reduce the production cost of these compounds given that by not requiring the production/purchase of enzymes and by reducing the number of steps involved in the process, it may potentially benefit the overall production yield.

Furthermore, the direct fermentation process allows to produce a mixture containing high amounts of XOS and low content of xylose, due to the microorganism preference for readily available sugars, which are first consumed before XOS degradation. Thus, this approach also holds the potential of reducing the downstream cost.

On the contrary, the production process yield may significantly decrease when the yields of both pretreatment, and enzyme production and purification (when not using a commercial enzyme) are considered,

Table 1
Xylooligosaccharides (XOS) production using enzymatic hydrolysis and direct fermentation of the substrate.

Substrate	Pretreatment (PTT)	Biocatalyst	Time (h)	$Y_{XOS/xylan}$[a] (mg/g)	DP[c]	Reference
Brewers' spent grain	No PTT	Commercial xylanase from *Trichoderma longibrachiatum*	12	444.3	X2-X5	Amorim et al. (2019b)
		Trichoderma reesei	72	326.2	X2-X5	
		Recombinant *B. subtilis* 3610	12	463.41	X2-X6	Amorim et al. (2018)
Mahogany	Thermal PTT (121 °C for 15 min) with 0.05 N NaOH	*Clostridium* sp. BOH3 xylanase	12	572[b]	X2-X5	Rajagopalan et al. (2017)
Mango xylan				504[b]	X2-X3	
Pretreated corn cob	Ultra-high pressure PTT	*Streptomyces thermovulgaris* TISTR1984 xylanase	18	106.6[b]	X2-X4	Seesuriyachan et al. (2017)
Sugarcane bagasse	Aqueous ammonia PTT	β-xylosidase-free xylanase of *B. subtilis* KCX006	30	670.0[b]	X2-X4	Reddy and Krishnan (2016a)
Quinoa Stalks	Akaline extraction (0.5 M NaOH at 80 °C)	*Rhodothermus marinus* RmXyn10ACM	12	12.6	X2-X6	Salas-Veizaga et al. (2017)
Arecanut husk	Two stage alkali PTT	endo-1, 4-β-xylanase M1 from *Trichoderma viridea*	24	351	X2-X4	Singh et al. (2018)
Rice straw	Milled at particle size < 2 mm	Magnetic cross-linked xylanase aggregate developed from *Acinetobacter*	1	841[b]	X2,X3, X5/X6	Purohit et al. (2017)
Corn cobs		*pittii* MASK 25 xylanase		691[b]		
Wheat bran	Enzymatic and thermal PTT	Pentopan (1,4-β- xylanase from *Thermomyces lanuginosus)*	24	228[b]	X2-X6	Mathew et al. (2018)
		Neocallimastix patriciarum NpXyn11A	8	186[b]	X3-X4	
Corncobs	Steam explosion using acidic electrolyzed water	*Paenibacillus barengoltzii* (PbXyn10A) xylanase	12	750	X2-X4	Liu et al. (2018)
Rice husk	Milled	*Aspergillus nidulans* XynC A773	24	690	X3-X6	da Silva Menezes et al. (2018)
Wheat bran	Washing with 50 mM sodium acetate buffer at pH 5.5 and alkali extraction	Recombinant *Bacillus amyloliquefaciens* xylanase A	24	161.4	X2-X6	Liu et al. (2017)
Wheat straw	Alkaline extraction (2% NaOH at 80 °C, 90 min)	*Bacillus halodurans* S7 endoxylanase A mutated at K80R	7	397.7[b]	X2, X3	Faryar et al. (2015)
Finger millet seed coat	Defatted, de-starched and water-extracted (25 °C during 8 h)	Commercial xylanase from *Thermomyces lanuginosus*	5	720	X2, X3	Palaniappan et al. (2017)

[a] Yields are represented in terms of amount XOS per amount of xylan, $Y_{XOS/xylan}$ (mg/g).
[b] Calculated from text information and converted to appropriate units.
[c] Degree of Polymerization.

thus compromising the economic viability of the process. Palaniappan et al. (2017) reported one of the highest Yxos/xylan values, however the low yields of xylan extraction (5.8 ± 0.03 and 4.8 ± 0.07 g per 100 g for rice bran and finger millet seed coat, respectively) after being de-starched were not accounted which would significantly decrease the actually reported yield. Besides, a commercial enzyme was used which definitely impacts the production cost.

The same analysis can be done to the yields reported by Rajagopalan et al. (2017) which would decrease to 441.6 mg/g (substrate - mahogany) and 315.5 mg/g (substrate - mango sawdust) if the xylan extraction yields have been accounted. Additionally, the production and purification of the *Clostridium sp.* BOH3 xylanase requires 2 days which naturally has an impact on costs. The authors reported one of the highest $Y_{xos/xylan}$ values, however as explained, if the xylan extraction yields from mahogany (77.2%) and mango sawdust (62.6%) are considered, the yields values are similar to the ones reported by Amorim et al. (2018). Again, if the overall process yield and production time accounted for the xylanase production and purification, this would have a major impact on the costs. Likewise, Reddy and Krishnan (2016a) reported a production time that does not include the time required to produce the β-xylosidase-free xylanase from *B. subtilis* KCX006 (36 h). Contrariwise, the single-step fermentation yields correspond to the overall production process and respective production time. Therefore, it is important to hold a critical vision while carefully drawing comparisons between process yields reported in different studies, particularly when comparing two step processes with direct fermentation, which represent a potentially advantageous strategy to greatly decrease production costs.

Additionally, other process integration approaches have been reported based on co-production of XOS and other value added products as shown in Fig. 3.

Reddy and Krishnan (2016b) and da Silva Menezes et al. (2017) used solid-state fermentation for the co-production of xylanase and XOS from several agro-residues, using *Bacillus subtilis* KCX006 and *Aspergillus brasiliensis*, respectively. However, low yields of XOS were obtained under the optimal conditions, 24.92 mg/g using wheat bran and groundnut oil-cake (Reddy and Krishnan, 2016b), and 14.48 mg/g using rice rusk (da Silva Menezes et al., 2017). The optimization of xylanase production by fermentation requires specific process conditions, distinct from the ones for the optimization of XOS production (Amorim et al., 2019b), including different optimal fermentation times, which probably explains the low yields of XOS obtained.

Chen et al. (2019) used pretreated reed scraps of reed pulp mill to co-produce XOS (144 mg/g) and glucose (304 mg/g) by xylanase and cellulase hydrolysis. Similarly, Zhang et al. (2017) reported the co-production of XOS (139.8 mg/g), glucose (328.1 mg/g), cellobiose (25.1 mg/g) and xylose (147.8 mg/g) from raw corncob by pre-hydrolysis with acetic acid followed by enzymatic hydrolysis. Besides the use of commercial enzymes, this approach may involve a more complex downstream process which may represent a limitation for the economic viability of the process.

Wu et al. (2017) studied the synergistic action of recombinants xylanase (AnXyn11A) and feruloyl esterase (AnFaeA) for the co-production of XOS and ferulic acid from de-starched wheat bran. The authors observed that the XOS yield was double (0.85 ± 0.04 mg/ml) when compared with the single enzyme action (0.48 ± 0.02 mg/ml).

The main bottlenecks of the described co-production approaches are the need for production/purchase of enzymes and the increased complexity of the downstream process.

On the other hand, the XOS production by direct fermentation also presents meaningful challenges, due to its viability greatly depends on the type of residue and microorganism used. Only residues with high ratio of xylan/lignin and microorganisms holding the enzymatic machinery required to degrade lignocellulosic biomass will be suitable for the process.

Amorim et al., 2019b performed a screening of residues to assess the potential of XOS production by direct fermentation and more than half of the tested residues did not present relevant XOS potential when fermented by *T. reesei* or *T. viride*. The authors selected BSG as the most suitable substrate. In fact, BSG is an attractive residue, being the most abundant by-product of the brewing industry, with an annual worldwide production of 39 million tons (Vitanza, 2016). Moreover, after being exposed to the brewing process, BSG present a lignin matrix less recalcitrant which is favorable to the fermentation process.

BSG was also directly fermented by *Bacillus subtilis* containing the xylanase gene *xyn2* from *Trichoderma reesei* coupled with a secretion tag endogenous to *B. subtilis* (Amorim et al., 2018). The authors identified different process steps ruled by the metabolic behavior of *B. subtillis*, namely from 0 to 4 h, the free sugars present in the medium were consumed; at 12 h, the highest accumulation of XOS and lowest amount of monosaccharides was found; from 16 to 32 h, the degradation of XOS occurred. This metabolism dynamics of the microorganism is one of the main advantages of the direct fermentation approach since it allows to minimize the amount of undesired monosaccharides. This fact considerably simplifies the downstream process, which generally represents up to 80% of the total production costs (Urmann et al., 2010). Furthermore, the solid residues originated by this direct fermentation process, namely biomass and BSG, potentially can be further used as raw materials in other processes within the biorefinery concept, for instance to extract antihypertensive peptides (Amorim et al., 2019a), recover sugars and produce energy.

Since the direct fermentation of agro-residues is a promising approach, it would be advantageous in future research (a) to explore the potential of new agro-residues holding a favorable chemical composition towards XOS production and (b) to increase their potential use through process optimization, namely by testing different process strategies that can minimize mass transfer/mixing limitations generally associated with the use of these residues. Possible strategies include optimizing the amount of substrate and the agitation rate; operating in fed-batch mode; using mixing auxiliaries, such as glass spheres; optimizing the fermentation process in bioreactors with a suitable design; performing solid state fermentation (SST). In particular, SST can potentially improve the concentration of XOS and co-product xylanase (Fig. 3) as Reddy and Krishnan (2016a) reported using *Bacillus subtilis* KCX006.

High temperatures were found to favor the direct fermentation of BSG (Amorim et al., 2018, 2019b), (a) enabling the xylan-lignin matrix opening, which increases the accessibility to xylanases; (b) releasing free sugars from BSG, which are important during the first stage of the microorganism growth; (c) reducing the medium viscosity, thus improving the bulk mixture. For all these reasons, it would be interesting to evaluate the performance of thermophile xylanase-producer microorganisms for direct fermentation.

Additionally, several debranching enzymes (*e.g.* arabinofuranosidases, acetylxylan esterases, galactosidases) support the xylan hydrolysis by cutting its side elements attached, therefore increasing the *endo*-xylanases accessibility to the main xylose chain (Coelho et al., 2016). On the other hand, the activity of beta-xylosidases is not desirable, since it promotes XOS degradation, increasing the amount of free xylose (Reddy and Krishnan, 2016b). Thus, possible interesting strategies to improve a microorganism performance by genetic manipulation would include the knockout of the beta-xylosidase gene and insertion of debranching enzymes genes, hence equipping the microorganism with an advantageous enzymatic machinery, in order to directly compete with the reported approaches that consider the use of commercial enzymatic cocktails for XOS production from agro-residues (Azelee et al., 2016).

4. Conclusions

XOS are emerging prebiotics with a huge market potential in several applications given their physicochemical and biological properties.

They stand out from the competition due to their low recommended daily dose to achieve a prebiotic effect, making them price competitive. However, additional *in vivo* experimental data is required to attain important regulatory status in order to increase their commercial value.

Importantly, XOS can be produced from alternative low-cost substrates leading to the reduction of their production costs. Indeed, it is expected the continuous increased development of integrated production strategies using lignocellulosic residues as raw materials, including direct fermentation, as well as the use of genetic engineering to generate super-microorganisms able to directly convert lignocellulosic biomass to XOS and other added value components. These novel production strategies can be further integrated on biorefinery processes.

Acknowledgments

CA, SCS and LRR acknowledge their grants (UMINHO/BPD/4/2019, SFRH/BPD/88584/2012 and SFRH/BSAB/142873/2018) from University of Minho and Portuguese Foundation for Science and Technology (FCT). The study received financial support from FCT under the scope of the strategic funding of UID/BIO/04469/2019 unit; COMPETE 2020 (POCI-01-0145-FEDER-006684), through national funds and where applicable co-financed by the FEDER, within the PT2020 Partnership Agreement; the Project FoSynBio (POCI-01-0145-FEDER-029549) and Lignozymes (POCI-01-0145-FEDER-029773). The authors also acknowledge BioTecNorte operation (NORTE-01-0145-FEDER-000004) funded by the European Regional Development Fund under the scope of Norte2020 - Programa Operacional Regional do Norte.

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