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Transforming orange waste with yeasts: bioprocess prospects

Transformando resíduos de laranja com leveduras: perspectivas de bioprocessos

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ABSTRACT

It is mandatory to make the circular economy a reality, developing ways of transforming waste into valuable products. In this context, investigating the biotechnological potential of different residues is most welcome. This review analyzes how orange waste can be used as biorefinery feedstock to produce different bioproducts using yeasts as the major biocatalysts. In addition to the current orange market, its pectin-rich biomass is described in detail, aiming to elucidate how yeast cells can convert it into ethanol, xylitol, polyphenols, and organic acids (some of them, volatile compounds). Genetic, metabolic, and evolutionary engineering are also analyzed as biotechnological tools to improve the existing processes. Finally, this review also addresses the potential employment of fruit-dwelling yeasts in biorefining pectin-rich biomasses such as orange wastes. All the data presented herein lead to the conclusion that these residues could already be used for noble purposes.

Keywords: biomass; pectin; sugar; fermentation; bioproducts.

RESUMO

Para tornar a economia circular uma realidade, é obrigatório desenvolver formas de transformar resíduos em produtos de valor. Nesse contexto, investigar o potencial biotecnológico de diferentes resíduos é bastante desejável. Esta revisão analisa como os resíduos de laranja podem ser usados como matéria-prima de biorrefinaria para produzir diferentes bioprodutos utilizando leveduras como principais biocatalisadores. Além do mercado atual da laranja, a biomassa da fruta, rica em pectina, é descrita detalhadamente, visando elucidar como as células de levedura podem convertê-la em etanol, xilitol, polifenóis e ácidos orgânicos (alguns deles, compostos voláteis). As engenharias genética, metabólica e evolutiva também são analisadas como ferramentas biotecnológicas para melhorar os processos já existentes. Finalmente, esta revisão também aborda o potencial emprego de leveduras isoladas de frutas no biorrefinamento de biomassas ricas em pectina, como resíduos de laranja. Todos os dados aqui apresentados levam à conclusão de que esses resíduos já poderiam estar sendo aproveitados para fins nobres.

Palavras-chave: biomassa; pectina; açúcar; fermentação; bioprodutos.

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Introduction

the vast majority of the countries in all continents signed the Paris Agreement, thus committing to reduce carbon dioxide emissions. In fact, to meet such an idealized agreement, CO_2 emissions must be reduced by 43% by 2030 (United Nations Climate Change, 2023). Although this goal frequently appears in many politicians' speeches, the truth is little has been done for it to be reached. Undoubtedly, without a fast and disruptive change of our linear economy model to a circular one, humanity will not avoid the serious consequences of severe climate change.

Ironically, the countries that historically have contributed less to the greenhouse effect suffer the most from climate change and are most likely to reverse this catastrophic scenario. This is the case of Brazil, whose energetic matrix is majorly renewable, besides having a huge potential to put a circular economy into practice. This is especially due to the possibility of employing its commodities production residual chain into second-generation bioprocesses (Alves Júnior et al., 2023).

Orange is one of the leading Brazilian commodities. In the Systematic Survey of Brazilian Agricultural Production, carried out by the Brazilian Institute of Geography and Statistics [*Intituto Brasileiro de Geografia e Estatística*] (IBGE, 2022), Brazil produced 16.9 million tons of orange in 2022. According to the Brazilian Ministry of Agriculture, around 80% of this production results in industrialized juices, with the European Union as their primary buyer. More than 67% of worldwide orange juice production happens in Brazil, which places the country in the spotlight for orange production and processing (Food and Agriculture Organization of the United Nations, 2021). However, around 50% of the mass of processed fruits consists of waste, including peels, pomace, and seeds (Gaind, 2017; de la Torre et al., 2019; Šelo et al., 2021).

Nevertheless, as a negative impact, all this production accounts for the country's fourth largest generation of residual biomass. According to the National Solid Waste Plan (Ministério do Meio Ambiente, 2022), orange cultivation generates 8.8 million tons of waste annually in Brazil. This amount is only behind sugarcane (201.4 million tons of waste generated annually), soybeans (41.8 million tons/year), and corn (29.4 million tons/year). Orange waste, however, unlike the other three mentioned, ends up being underused. This is mainly due to its high moisture content and the high cost of drying, which makes transportation and storage difficult and makes it unfeasible to burn it to generate heat or electrical energy. Obviously, this waste can be destined for composting, where it increases the organic load of the soil and functions as a source of nutrients. Nevertheless, this alternative can reduce the soil's pH, negatively affecting the process (Ruiz and Flotats, 2014). Because of this, the pomace and peel of this fruit, when used, are primarily intended only for dietary supplementation for cattle and goats (Oloche et al., 2019; Guzmán et al., 2020). Controversially, though, this biomass imparts a bitter taste to animal food, and studies in the literature point to a potential generator of diseases in cattle (Bampidis and Robinson, 2006; de la Torre et al., 2019).

On the other hand, these residues can fortunately have much more profitable and environmentally sustainable destinations if used in second-generation (2G) biorefineries. In these industrial environments, several agro-industrial wastes and by-products of agricultural production, including orange peels and pomace, can be transformed into a myriad of bioproducts through the metabolism of microorganisms such as yeast (Fenner et al., 2022; Tadioto et al., 2022; Scapini et al., 2023b). In this context, this review presents the state of the art and analyzes the biotechnological potential of orange waste in 2G biorefineries with fermentative processes driven by yeast. Literature was searched on the basis of previous studies and experiences of the authors, who have been working in the field for the last few years. The references were chosen according to their relevance to this study's subject. Also, foundational articles were sometimes used as jumping-off places, leading to more recent articles that cited them.

Orange Wastes: a Pectin-Rich Substrate

Orange waste contains biopolymers and bioactive compounds, such as proteins, carbohydrates, lipids, lignin, polyphenols, and natural dyes, which can be recovered and applied in the production of food, pharmaceutical products, and cosmetics. Furthermore, some of these components can be converted into several high-value chemical products, such as bioplastics, functional materials, and biofuels (Fazzino et al., 2021; Talekar et al., 2023). Oranges also display several bioactive phenolic compounds such as hesperidin, naringin, quercetin, rutin, gallic acid, caffeic acid, p-coumaric acid, and chlorogenic acid (Singh B. et al., 2020; Ortiz-Sanchez et al., 2023; Vadalà et al., 2023). These compounds can benefit human health, mainly because they have antioxidant, anti-inflammatory, anticancer and antidiabetic activities (Andrade Barreto et al., 2023; Ortiz-Sanchez et al., 2023).

On the other hand, to transform fruit waste into different bioproducts from the metabolism of yeast cells, attention must be paid to the carbohydrates present in these substrates, initially in the form of three polysaccharides: cellulose, hemicellulose, and pectin, whose concentrations vary according to the source of biomass used (Scapini et al., 2023a). On average, orange residues are composed (on dry-weight basis) of 18.1% of cellulose, 13.1% of hemicellulose, and 28.5% of pectin (Vadalà et al., 2023).

Cellulose is a homopolysaccharide of glucose, and hemicellulose is a heteropolymer whose composition varies according to the plant species, although it is mostly represented by xylan, a polysaccharide of xylose. Pectin, in turn, is formed by a linear chain of galacturonic acid molecules (which may or may not be methylated) linked together through ß-1,4 glycosidic bonds and branched chains composed mainly of galactose, rhamnose, arabinose, and xylose (Figure 1) (Bai et al., 2019; Brandon and Scheller, 2020; Zdunek et al., 2021).

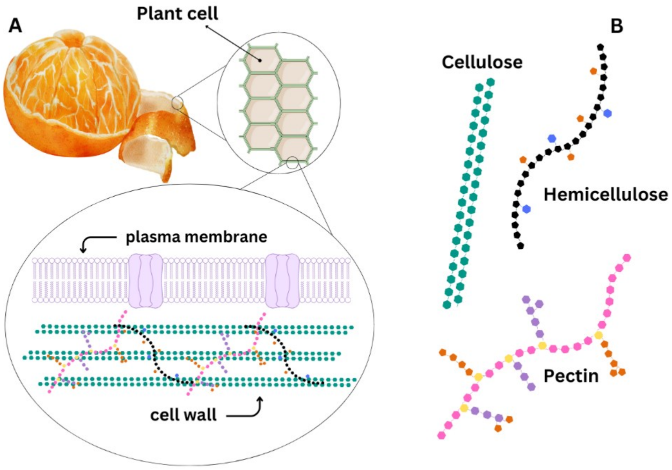

Figure 1 – Plant cell walls' polysaccharides. (A) Cellulose, hemicellulose, and pectin are interconnected in orange peel's plant cell walls. (B) Cellulose is a homopolysaccharide of glucose (green hexagons), and hemicellulose has a main branch of xylose (black pentagons) in which arabinose (orange pentagons) and glucuronic acid (blue hexagons) molecules are attached. Pectin is mainly composed of galacturonic acid (pink hexagons), rhamnose (yellow hexagons), galactose (purple hexagons), and arabinose (orange pentagons).
Source: adapted from Cosgrove (2005), Phyo et al. (2017), Bai et al. (2019), Brandon and Scheller (2020) and Zdunek et al. (2021).

The percentage of pectin tends to be lower in the so-called lignocellulosic biomasses, such as the woody structures of trees and sugarcane residues, and higher in residual biomasses such as fruit bagasse and peels (especially orange), as stated above. These residual biomasses are, therefore, called pectin-rich biomasses. In them, the lignin content hardly exceeds 2% of the dry weight, which makes their pretreatment (the process prior to hydrolysis and fermentation) more economical than that of lignocellulosic biomasses, where the percentage of lignin can exceed 30% (Venkatanagaraju et al., 2020; Paliga et al., 2022).

Biotechnological Potential of Orange Residues

For the sugars available in residual plant biomasses to be metabolized by yeast cells, the polysaccharides must be initially hydrolyzed. Several alternatives to this initial process, also called saccharification, have been proposed to improve the availability of carbon sources for fermentation. However, the method currently recognized as the most viable does not only seek the hydrolysis of biomass separately from the fermentation process, but rather the combination of both, which is known as Simultaneous Saccharification and Fermentation (SSF). SSF allows sugars released with the hydrolysis of polysaccharides to be readily metabolized by microbial cells (Panda and Maiti, 2024). In contrast, the conventional separate hydrolysis and fermentation (SHF) process allows the introduction of an intermediate detoxification step. This step aims to remove possible inhibitors, optimizing the operational conditions independently for each stage of the process (Widmer et al., 2010).

Although the chemical hydrolysis of polysaccharides is possible, enzymatic methods have been more widely used due to higher yields and less formation of toxic products (Bonatto et al., 2023). Cellulose and xylan hydrolysis have been extensively studied, given the interest in enabling ethanol production from lignocellulosic residues such as straw and sugarcane bagasse (by-products of first-generation ethanol production), which have negligible concentrations of pectin. On the other hand, assuming the use of residual fruit biomass, the pectin concentration is significantly higher, as already pointed out above. In this case, the hydrolysis of this last polysaccharide becomes predominant in enabling the desired biotransformation (Scapini et al., 2023c). Still, it is important to highlight that the enzymatic hydrolysis of xylan present in orange residues can be harnessed to generate Xylooligosaccharides, molecules with great potential as functional food ingredients (Ávila et al., 2020; Martins and Goldbeck, 2023). In this context, for example, Martins and Goldbeck (2023) demonstrated that the integration of pectin production, Xylooligosaccharides, and bioenergy (with biogas production from free sugars and cellulose) could be an alternative to achieve the economic viability of orange waste-based biorefineries (see section 4).

In the Fungi kingdom, pectin hydrolysis depends on the synergistic action of enzymes that, together, are called pectinases, namely polymethylgalacturonate esterase, polygalacturonate lyase, endo-polygalacturonase, and exo-polygalacturonase. While the first removes the methyl ester groups from galacturonic acid, the last three are responsible for depolymerization. Endo-polygalacturonase promotes internal breaks randomly, and exo-polygalacturonase breaks from the ends of the pectin molecule. Polygalacturonate lyase catalyzes the cleavage of ß-1,4 bonds in an endo or exo manner by trans elimination. The total hydrolysis of pectin releases especially the monosaccharides D-galacturonic acid, D-galactose, L-rhamnose, L-arabinose, and D-xylose (Satapathy et al., 2020; Bassim Atta and Ruiz-Larrea, 2022; Paliga et al., 2022).

After hydrolysis, the yeast employed in the process must be capable, as already mentioned, of metabolizing the sugars arising from the breakdown of polysaccharides. Depending on the metabolic routes they will follow, the products obtained can differ, as described below.

Bioethanol production

A profitable and environmentally sustainable destination for the residual orange biomass is the production of second-generation ethanol (2G ethanol). This residual plant biomass is rich in pectin, a heteropolysaccharide that, when hydrolyzed, mainly releases the sugars galacturonic acid, galactose, rhamnose, arabinose, and xylose (Paliga et al., 2022). Therefore, ethanol production from this substrate depends on the action of microorganisms capable of metabolizing the aforementioned carbohydrates via fermentation.

D-galacturonic acid is the primary pectic sugar, accounting for approximately 70% of pectin (Grassino et al., 2018; Vaez et al., 2021; Frempong et al., 2022). Within the Kingdom Fungi (which includes yeasts), the metabolism of this hexose initially depends on its reduction to L-galactonate, in a reaction catalyzed by the enzyme galacturonate reductase, which depends on the coenzymes NADPH or NADH as electron donors (Figure 2). Subsequently, galactonate dehydratase generates 2-keto-3-deoxy-L-galactonate, which is later converted to pyruvate and L-glyceraldehyde by the enzyme deoxygalactonate-aldolase (Richard and Hilditch, 2009; Biz et al., 2016). While L-glyceraldehyde is reduced to glycerol by glyceraldehyde reductase, pyruvate can be a. transformed into Acetyl-CoA and enter the Krebs Cycle if the metabolism is respiratory, or b. decarboxylated to acetaldehyde, which is finally reduced to ethanol, through alcoholic fermentation. In addition to these enzymes, for yeasts to metabolize galacturonic acid, a transporter must also be present on their plasma membrane (Protzko et al., 2019).

Among the pectic sugars, the most widely fermented by yeast is D-galactose. For galactose to be metabolized, it initially enters cells through membrane transporters of the *HXT* family. In the cytoplasm, this hexose is converted to glucose-6-phosphate via the Leloir Pathway. This pathway comprises three sequential reactions: phosphorylation of galactose by galactokinase, generating galactose-1-phosphate that is subsequently isomerized, by galactose-uridyltransferase, to glucose-1-phosphate, which, finally, is converted to glucose-6-phosphate in a reaction catalyzed by phosphoglucomutase (Leloir, 1951; van Maris et al., 2006). Glucose-6-phosphate then follows the glycolytic pathway until pyruvate, which ends up being converted to ethanol during alcoholic fermentation (Figure 2).

Unlike most sugars, L-rhamnose and L-arabinose are more common in nature than their D isomers. In yeast capable of metabolizing L-rhamnose, it is initially oxidized by the enzyme rhamnose dehydrogenase to L-rhamnon-1,4-lactone, which is subsequently converted to L-rhamnonate by rhamnon-lactonase (Figure 2). This second product of the pathway is then dehydrated by rhamnonate dehydratase, generating 2-keto-3-deoxy-L-rhamnonate, which is finally cleaved into pyruvate and lactaldehyde by an aldolase (Twerdochlib et al., 1994). Although L-arabinose is a pentose metabolized by a large number of yeast species, few of them are capable of fermenting it (i.e., they preferentially respire this sugar), and this fermentation is generally of low yield (Gong et al., 1981; Dien et al., 1996). In these yeasts, L-arabinose is initially reduced to L-arabitol, which is then oxidized to L-xylulose by the action of arabinose reductase and arabinitol dehydrogenase, respectively (Figure 2). L-xylulose is isomerized to D-xylulose in two sequential reactions catalyzed by the enzymes xylulose reductase and xylitol dehydrogenase. Finally, D-xylulose, after being subsequently phosphorylated, enters the Pentose-Phosphate Pathway (PPP) to generate Glycolytic-Pathway intermediates and, subsequently, ethanol from pyruvate (Stambuk et al., 2008).

Indeed, several studies have shown that it is feasible to produce ethanol from orange wastes. Oberoi et al. (2010), for example,succeeded in producing ethanol from orange peel powder (OPP) with a yield of 0.46 g/g on a substrate-consumed basis and a volumetric productivity of 3.37 g/L/h. Interestingly, the authors submitted the OPP to two subsequent acid hydrolysis processes at an optimum pH of 5.4 and temperature of 34°C.

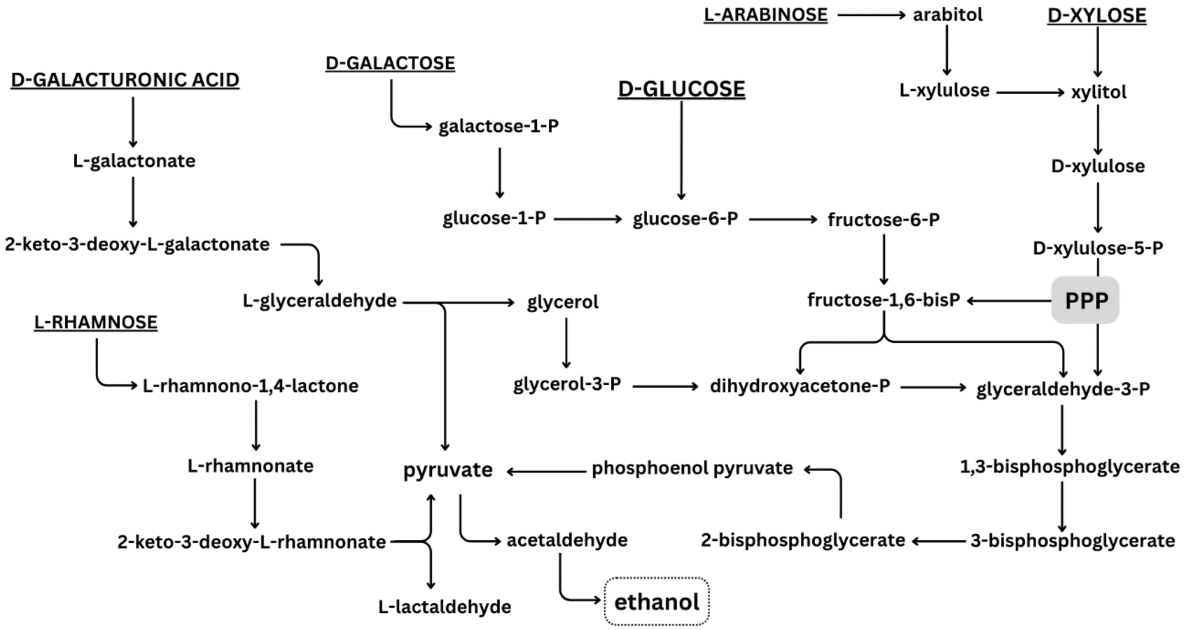

Figure 2 – Yeast metabolic pathways from the main sugars in orange waste to ethanol. The most prevalent monosaccharides in cellulose, hemicellulose, and pectin are in underlined uppercases. Phosphate groups in each molecule are represented by "P". The acronym PPP stands for the pentose-phosphate pathway.

Similarly, Joshi et al. (2015) obtained 41 g/L of ethanol from 380 g/L of total carbohydrate after a 48-h fermentation with an inoculum size of 20% (v/v) with the strain *Saccharomyces cerevisiae* NCIM3495. However, despite the high ethanol titer achieved, it should be noted that the amount of available sugar could have rendered an even higher amount of the final product. The same holds for the results found by Jha et al. (2019), whose fermentations did not allow more than 50% of the sugar available to be consumed, and by Vadalà et al. (2023), who observed that ~14% of citrus-waste hydrolysate sugar content was not consumed by yeast cells. This incomplete sugar conversion is probably due to the incapacity of *S. cerevisiae* to ferment many of the orange biomasses' sugars. Fortunately, many strategies to overcome this issue have been developed, as addressed in section 4.

Xylitol production

Among sugars found in orange wastes, D-xylose is one of the most well-studied. As well as other monosaccharides, xylose initially needs to be transported from the extracellular environment to the interior of yeast cells to enable fermentation. Once inside the cell, this pentose must be reduced to xylitol, which is then oxidized to xylulose before following the PPP (Figure 2). However, for yeast cells to efficiently ferment xylose, there must be a redox balance in these first two reactions of xylose metabolization, which are catalyzed by Xylose reductase (XR) and Xylitol dehydrogenase (XDH), respectively. While the latter uses NAD^+ as a coenzyme (which is reduced to NADH), the former can make use of both NADH and NADPH (which are oxidized to NAD^+ or $NADP^+$), depending on the isoenzyme present. In those yeasts whose XR uses a coenzyme different from XDH, an imbalance may interrupt the metabolization of xylose so that yeast cells end up accumulating xylitol (Alves Júnior et al., 2022).

Xylitol is a five-carbon polyol classified as a natural sweetener (Lenhart and Chey, 2017). Therefore, this compound can also be applied in areas of extreme importance for human subsistence, such as the food and pharmaceutical industries (Kumar et al., 2022). It also helps prevent cavities, osteoporosis, and infections, and there are also reports of anti-cancer effects (Xu et al. 2019; He et al. 2021).

The demand in the xylitol market is growing, requiring this product to be obtained in a sustainable and economical way, as it is produced by the chemical hydrogenation of xylose, which is extremely expensive (Grembecka et al., 2014). To reduce high costs, several biotechnological methods for generating xylitol from lignocellulosic and pectic biomass from fruit waste have been studied (Mathew et al., 2018). Many wild yeasts have the potential to accumulate xylitol from the xylose available to the cells. In fact, since several yeasts display the redox imbalance mentioned above, yeast-based xylitol production may become a trend in the biorefinery context (Tadioto et al., 2022; Albarello et al., 2023; Vargas et al., 2023).

Organic acids

Organic acids are a group of mostly weak acids whose solubility in water relies on the size of their hydrocarbon chain (the smaller the particle size, the easier it is to dissolve). They can be produced naturally by the living beings. These acids are high-value-added products with important applications in the food, pharmaceutical, and chemical industries. The impacts of producing these compounds, which are primarily made from fossil resources, have instigated the development of biotechnological routes, since they are more sustainable, less harmful to the environment, and economically more viable than the conventional method. Metabolic engineering and synthetic biology are biotechnological tools employed to develop high-performance microorganisms capable of producing organic acids with elevated conversion rates (Du et al., 2011; Liu et al., 2017).

The microbial production of organic acids has some obstacles in its synthesis, as bacteria are normally not tolerant to low pH conditions, which often makes industrial processes very costly. Yeasts naturally have greater resistance to acidic pH, but their yield in the process is lower. As a result, several studies have been seeking a more sustainable way to produce organic acids, and one of the ways is to use fruit waste as biomass as feedstocks (Hong et al., 2012; Tran and Zhao, 2022).

Some examples of organic acids that are part of the wide range of chemical products in different types of industries are Citric Acid (used as a food additive), Lactic Acid (production of polymers, drinks, and foods), Acetic Acid, better known as vinegar (solvent and polymers), Succinic Acid (as building blocks and as a replacement for anhydrous maleic acid), Oxalic Acid (complexing agent) among many others. Most studies present the production of these compounds using the yeast *S. cerevisiae* (Panda et al., 2016).

Phenolic compounds

Phenolic compounds are described as bioactive substances, that is, compounds that provide health benefits and are present in different fruits and vegetables. The quantity and structure of these compounds vary according to the plant matrix, being more present in fruit seeds than in their edible portions (Soong and Barlow, 2004; Rabetafika et al., 2014). In foods and beverages, phenolic compounds are directly linked to attributes such as color, bitterness, astringency, aroma, and oxidative stability (Angelo and Jorge, 2007).

One of the options for managing fruit processing industry waste is the recovery of bioactive compounds in the byproducts. Oranges stand out due to their high global consumption and a significant amount of bioactive compounds such as hesperidin, naringin, naringenin, and quercetin — substances that can be applied in the food, cosmetic, and mainly pharmaceutical industries (Madeira and Macedo, 2015; Fierascu et al., 2020). Among these compounds, flavonoids constitute the main subgroup, and their antioxidant activity has been reported in several studies (Jayaprakasha et al., 2001; Soong and Barlow, 2004; Babbar et al., 2015; Romero-Díez et al., 2018). The flavonoids most present in citrus fruit residues are naringin and hesperidin, presenting many health benefits such as the ability to prevent cancer, suppress carcinogenesis, and induce cell apoptosis (Meiyanto et al., 2012).

Fruit waste has a highly diverse microbiota. Yeasts have been isolated from these substrates and are applied in fermentation processes precisely on these residues, as they can metabolize the available carbohydrates and generate distinct phenolic compounds (Noori et al., 2022; Makopa et al., 2023). Bioactive compounds are naturally present in fruits, so just consuming them is beneficial for people. However, studies have reported that the bioaccessibility (absorption capacity of the human body's gastrointestinal system) of these compounds is higher after yeast fermentation, facilitating their access to systemic circulation. With this in mind, scientists are working to ensure that these microorganisms act on waste recovery to increase the production of phenolic compounds (Stinco et al., 2020; Coelho et al., 2021; Macêdo et al., 2023). Indeed, the growing demand for these compounds cannot be supplied by purifying them from plant sources, requiring larger-scale production, which can be fulfilled through the fermentation of wastes by yeast (Tadioto et al., 2023).

Pectin Oligosaccharides

Although the complete hydrolysis of a given polysaccharide is usually the primary goal (once free monosaccharides are more easily converted into fermentation products), sometimes a partial depolymerization may be desirable. This is the case of Pectin Oligosaccharides (POSs), which are obtained through incomplete pectin hydrolysis processes. Depending on the pectin source, POSs may include products such as oligogalacturonides, galactooligosaccharides, arabinooligosaccharides, rhamnogalacturonooligosaccharides, and arabinogalactoligosaccharides (Concha Olmos and Zúñiga Hansen, 2012; Gullón et al., 2013; Gómez et al., 2016).

Because of their lower mass and lower degree of polymerization, POSs display better water solubility and, consequently, higher bioavailability than natural pectin (Kong et al., 2023). In fact, recent papers have shown different human health benefits after POSs consumption, namely prebiotic effect and antioxidant and anti-inflammatory properties. Since they can be metabolized by beneficial gut bacteria, POSs stimulate these microorganisms' growth, which improves the host immune system (Babbar et al., 2016; Montilla et al., 2022). POSs have also been linked to improvements in cholesterol and glucose blood levels, toxins binding and removal, and anticancer and antimetastatic effects (Minzanova et al., 2018; Zhu et al., 2019; Singh R.P. et al., 2020; Zaitseva et al., 2020).

Interestingly, yeast can also work in the production of POSs through their pectin lyases, which cleave pectin glycosidic bonds at the fourth carbon, releasing hydrogen from the fifth carbon, and producing unsaturated 4,5-unsaturated oligogalacturonides (Yadav et al., 2023). Pectin lyase activity has been reported in the following yeast species: *Pichia pinus* (Moharib et al., 2000), *Cystofilobasidium capitatum* (Nakagawa et al., 2005), *Kluyveromyces wickerhamii*, *Stephanoascus smithiae*, *Pichia anomala* (da Silva et al., 2005), *Wickerhamomyces anomalus*, *Saccharomycopsis fibuligera*, and *Pichia kudriavzevii* (Haile and Kang, 2019). Additionally, genetically-engineered *Pichia pastoris* strains have shown to be well-succeeded in POS production, yielding oligogalacturonides (Yang et al., 2020) and rhamnogalacturonan (Normand et al., 2012) as major products.

Besides Pectin: Hemicellulose and Cellulose Exploration

In addition to the abundant pectin structure found in orange waste, there is a broader scenario where cellulose and hemicellulose structures can be explored. These structures constitute the matrix of the waste (Figure 1), and offer potential for conversion into bioproducts of interest, expanding the possibilities beyond pectin (Patsalou et al., 2020; Tsouko et al., 2020). For example, Patsalou et al. (2020) investigated the conversion and recovery of four bioproducts from citrus waste: essential oils, pectin, succinic acid, and fertilizer.

In this situation, the remaining solids rich in hemicellulose and cellulose can be recovered and utilized as raw material in other integrated pathways. The composition is abundant in sugars such as glucose, xylose, and arabinose, which can be converted into high and medium value-added bioproducts. These integrated conversion scenarios are noteworthy in the industrial sector due to the volume and characteristics of the waste generated. Citrus waste, owing to its high carbohydrate and low lignin content, can be exploited for the production of biofuel and bioproducts without requiring pretreatments with high concentrations of chemicals and substantial energy consumption. Consequently, pectin-free solid waste can be used to produce food additives, organic acids, biofuels, and agricultural inputs. Thus, assessing consecutive routes for producing bioproducts from this waste can be an approach to make these processes economically viable on a large scale.

Oligosaccharides can be derived from the hydrolysis of the hemicellulose structure present in orange waste. Similarly to what has been described above for POSs, these hemicellulose-derived oligosaccharides are prebiotics of significant interest in the food industry and can be prepared through autohydrolysis, acid hydrolysis, or enzymatic hydrolysis of the hemicellulose-rich fraction (Cho et al., 2020; Martins and Goldbeck, 2023). Therefore, following the extraction of pectin, it is feasible to explore this conversion route. The hydrothermal process for extracting the pectin structure has been previously reported to preserve 60% of the xylan content, enabling enzymatic conversion to xylooligosaccharides (XOS). This process also facilitates the conversion of solid waste into energy, allowing for the design of a self-sufficient plant in accordance with the principles of the circular economy and biorefineries (Martins and Goldbeck, 2023).

The utilization of this waste in the biofuel production chain is a viable strategy, primarily due to the high carbohydrate that remains in the solid residue. Biohydrogen, biogas and ethanol are among the most explored processes. Saadatinavaz et al. (2021) evaluated citrus waste for possible production routes of biomethane, acetone, butanol, biohydrogen, ethanol, acetic acid, and butyric acid. Hydrothermal pretreatment unit operations were common to all routes, and under optimized conditions, the estimate was a production of 4,560 kJ of energy through sustainable processes (Saadatinavaz et al., 2021). Additionally, in an integrated context, pectin, bioethanol, and methane were produced from citrus waste, enhancing the total economic value of the products by 75 times compared to the approach of managing the waste solely for anaerobic digestion (Vaez et al. 2021).

In addition to bioenergy, the pectin-free solid residue can be exploited for conversion into various bioproducts. Recently, researchers utilized these residues to produce natural red colorant using the fungus *Talaromyces amestolkiae* (titer 2.75 g/L) (Lima et al., 2023). The enzymatic production of xylanases and cellulases was also evaluated, offering a potential route for recovery (Lima et al., 2023). Another innovative approach for this waste involves its conversion into bioplastics. A recent study explored this scenario using a cyanobacterial culture, demonstrating that citrus waste hydrolysates could serve as an alternative culture medium for polyhydroxybutirate (PHB) accumulation (Mishra and Panda, 2023). Arabino-oligosaccharides, glucose-rich hydrolysate, and polylactic acid (PLA) have also been successfully obtained from different fractions of citrus waste (tangerine peel) (Jang et al., 2022). Additionally, bacterial cellulose has been obtained from pectin-free citrus waste, with the remaining solid predominantly composed of cellulose and hemicellulose (Tsouko et al., 2020). Alternatively, non-biological conversion processes, such as the development of biofilms using residual pulp and peels post hydrothermal pre-treatment of the waste, have been explored as well (Santos et al., 2023).

Integrating processes to obtain various bioproducts presents an interesting alternative for orange waste. After pectin removal, the remaining solids, typically rich in cellulose and hemicellulose, offer endless possibilities. Whether through thermal, chemical, or enzymatic hydrolysis, these pathways can provide alternative routes for obtaining a diverse range of bioproducts and bioenergy. The scalability of these processes on an industrial level not only reduces waste generation but also establishes ecologically sustainable processes.

Improving Bioconversion from Pectin-Rich Wastes

Despite the vast potential of orange waste as feedstock for multi-product biorefineries, some challenges must be overcome to achieve highly efficient conversion of orange residues into valuable products. In this sense, the biotechnology field displays some tools that may offer improved alternatives according to the bioprocess aim. Interestingly, many of these improvements can be reached by engineering or prospecting the biocatalysts. The following sections address some of these strategies, considering yeasts as the main employed biocatalyst. It should be noted, though, that due to the limitation of optimization studies with oranges, other fruits were considered in this review, considering that they are all plant-waste material and pectin-rich biomasses. Thus, we are assuming that these similarities allow us to extrapolate many of the advances obtained with other fruits' waste to the orange residue scenario.

Yeast genetic and metabolic engineering

One of the fields where genetic engineering is heavily exploited is the development of robust strains for biofuel production. Plant-residual biomasses are widely available renewable resources and viable alternatives for the development of biorefinery processes. However, a pretreatment step is essential to break the recalcitrant structure of these biomasses into cellulose, hemicellulose, and pectin in order to improve enzyme access and saccharide solubilization. This initial stage leads to the formation of inhibitory compounds, which include weak acids and furan aldehydes (Vanmarcke et al., 2021). In this sense, to ensure a sustainable process, integrating research has been developed to identify determinants of tolerance, (over)expression of genes involved in the tolerance response, and the use of a robust microorganism capable of tolerating these stressors, which includes genetic engineering (Baptista et al., 2021). Noteworthily, Cámara et al. (2022) carried out a huge data mining process of *S. cerevisiae* mutants (designed to increase tolerance to inhibitory compounds) that led to overexpression or deletion of approximately 4,000 unique genes, mostly for tolerance to compounds such as acetic acid, formic acid, and furans.

In addition to being used to improve tolerance to inhibitory compounds, genetic engineering has also been applied to enable yeast to metabolize different components (generated during the lignocellulosic biomass pretreatment and hydrolysis steps) that are not directly utilized by most yeasts — e.g., *S. cerevisiae* and the non-assimilation of pentoses like xylose (van Maris et al., 2006; Moysés et al., 2016). In fact, in the ethanol industry, the co-fermentation of pentose and hexose by simultaneous saccharification processes and microbial metabolism is an important strategy to improve ethanol production yields and ensure the development of a competitive and economically viable second-generation biorefinery (Liu et al., 2022).

Saccharomyces cerevisiae is the model industrial microorganism used to produce ethanol. For this reason, it is generally used as an ideal host cell for genetic engineering to perform simultaneous assimilation of glucose and other sugars (Wang et al., 2018). In addition, *S. cerevisiae* is generally recognized as a safe (GRAS) organism, which enables it to be widely used for pharmaceuticals and food. Thus, it ends up being the most commonly used yeast to produce these compounds and in applications as a host for metabolic engineering strategies (Pereira et al., 2019; Feng et al., 2022). This can be seen from the studies presented in Table 1. Not limited to *S. cerevisiae*, other microorganisms have also been reported as hosts for metabolic engineering because they exhibit characteristics like high tolerance to fermentation inhibitors, act under low pH conditions, and are more tolerant to high temperatures, such as the *Issatchenkia orientalis* (Lee et al., 2022).

Table 1 – Metabolic and genetic engineering strategies for production of high value-added chemicals from pectin-derived sugars.

Compound	Yeast	Strategies	Substrate/Residue	Main results	Reference
Ethanol	*S. cerevisiae*	Implementation of nine repair fragments to establish the fungal d-GalUA pathway using CRISPR/Cas9 in the reference strain Gly (able to utilize glycerol efficiently via a NAD-dependent pathway)	Minimal medium with galacturonic acid (the main pectic sugar) and glycerol	Maximum specific galacturonic acid consumption rate of 0.23 g g_{CDW}^{-1} h^{-1} 0.48 ± 0.06 C-mol C-mol_{s}^{-1} ethanol yield	Perpelea et al. (2022)
Phenylalanine	Indigenous yeast and *S. cerevisiae* AWRI796	Yeast was exposed to toxic phenylalanine analogs	Chardonnay grape juice	*ARO4* and *TYR1* mutations – 20-fold increase in 2-phenylethanol and 2-phenylethyl acetate production	Cordente et al. (2018)
Oligogalacturonides	*Pichia pastoris*	The gene (GAQ40478.1) encoding endo-polygalacturonase (AnPG28A) from *Aspergillus niger* was expressed in *P. pastoris*	Mandarin and orange peel wastes	The best oligogalacturonides yield were 26.1%.	Yang et al. (2020)
Ethanol	*S. cerevisiae*	Industrial strain with CRISPR-Cas9-directed integration of cellulase genes	Orange peel	Ethanol yields: 7.53 g L^{-1} and 0.151 g g^{-1} orange peel	Yang et al. (2018)

As the polymeric matrix of pectin has a complex structure, pectin-rich residues present particular challenges in hydrolysis and fermentation. Depending on the pretreatment and hydrolysis process, d-galacturonic acid is one of the quantitatively most abundant monomers, negatively affecting yeast growth and fermentation (Martins et al., 2020; Perpelea et al., 2022). Given these considerations, the use of d-galacturonic acid in *S. cerevisiae* has been the focus of some recent studies (Protzko et al., 2018; Perpelea et al., 2022). An engineered strain was able to consume d-galacturonic acid with the reported maximum specific rate of 0.23 g g_{CDW}^{-1} h^{-1} in minimal synthetic medium when glycerol was added under aerobic conditions. Adding glycerol in pectin-rich hydrolysates was seen to bring an additional advantage by increasing the available carbon that can be converted into ethanol. It was shown that ethanol production from the co-fermentation of d-galacturonic acid and glycerol is a realistic opportunity, given the yield obtained from this strategy (0.48±0.06 C-mol $\text{C-mol}_{substrate}^{-1}$) (Perpelea et al., 2022). Furthermore, *S. cerevisiae* has also been modified to directly ferment orange peel extract, through the expression of a cellulase complex (Yang et al., 2018).

As the production of ethanol from lignocellulosic biomass has already been commercialized, research has been developed to expand the use of the substrate and to produce chemical compounds in addition to ethanol, such as organic acids (Perpelea et al., 2022; Stovicek et al., 2022). Dicarboxylic acids for example, are found at very low levels as yeast products. However, the concentrations can be improved by using metabolic engineering. Metabolic engineering strategies lead to relevant yields of dicarboxylic acids (malic and succinic acid) from xylose as a carbon source (Kang et al., 2022; Stovicek et al., 2022).

The development of cell factories has been created either as alternative routes to the chemical ones or to improve the efficiency of biochemical pathways naturally present in microorganisms. For example, the production of gastrodin — a phenolic glycoside — was achieved using *S. cerevisiae* as a host of a compatible glycosyltransferase that recognizes 4-hydroxybenzyl alcohol as a substrate, and then applying a simultaneous chromosomal integration strategy of CAR^{syn}, $PPTcg\text{-}1^{syn}$, $AsUGT^{syn}$, $ubiC^{syn}$, and *ARO4K229L* into the yeast chromosomal rDNA. The authors demonstrated that the engineered strain produced a much higher level of gastrodin (175 times more than the original gastrodin-producing strain) (Yin et al., 2020).

Metabolic engineering can also be an interesting strategy in phenolic production when challenges surround the scaling-up by natural biochemical pathways. This is the case of resveratrol production, a polyphenolic compound of great importance mainly in the medical field and health products (Feng et al., 2022). Efforts have been made to develop cell factories capable of efficiently producing these compounds, as in the study conducted by Li et al. (2016), which applied the pull-push-block metabolic engineering strategy for overexpression of the resveratrol biosynthesis pathway in *S. cerevisiae*, resulting in a concentration of 800 mg L^{-1} of the compound in fed-batch fermentation using glucose as substrate. More recently, other strategies have been applied to yeasts such as *Yarrowia lipolytica*, which is a versatile yeast applied to the production of organic acids, and whose metabolic engineering has been demonstrated to be able to increase levels of phenolic compounds (Gu et al., 2020; He et al., 2020; Sáez-Sáez et al., 2020; Yuan et al., 2020).

Another efficient possibility of increasing yeast resistance to inhibitor compounds is applying laboratory adaptive evolution. This approach approximates a process of evolution by natural selection through the application of restrictive conditions for microbial propagation in the laboratory, inducing the expression of a phenotype best suited to the hostile environment (Barrick and Lenski, 2013; Menegon et al., 2022). It was recently reported that exposure of yeast to toxic phenylalanine analogs induced mutation in two genes of the aromatic amino acid biosynthetic pathway, *ARO4* and *TYR1*, leading to overproduction of 2-phenylethanol and 2-phenylethyl (Cordente et al. 2018).

Thus, although little explored, metabolic engineering and laboratory adaptive evolution will progressively allow the construction of more robust strains for application in industrial flows. This scenario may expand the variety of chemicals produced, making microbial cells economically feasible for integrated biorefinery systems (Baptista et al., 2021).

Indigenous yeasts on fruits: transforming their substrate into bioproducts

Many species have already been isolated from different environments, and represent a still little-explored resource, offering innovation for biotechnological development in several fields (Nandal et al., 2020). Indigenous microorganisms from diverse environments may present interesting characteristics for industrial processes, and it is of scientific interest to explore biological resources that enable the development of new strategies. Many researchers examine and characterize different yeast species that exhibit relevant characteristics, such as high tolerance to the saline environment, toxic compounds, high temperatures, and high substrate concentration, and that can produce certain bioproducts with high efficiency. In this context, when it comes to plant environments, yeast isolation may lead to the effective production of volatile organic compounds (Fenner et al., 2022).

There is a wide diversity of microorganisms inhabiting fruits and vegetables, which are interesting substrates for yeast prospecting. In fact, among the microorganisms indigenous to these environments, yeasts are the dominant populations (10^5 a 10^7 CFU g^{-1}) (Pimentel et al., 2021). These microorganisms play an important role in ecological relationships, which explains their abundance in these environments. Considering the prospection of fruit-dwelled yeasts, it is possible to explore the products resulting from these ecological relationships that can be highly lucrative, mainly by the fermentative capacity and metabolite production of commercial interest (Pimentel et al., 2021; Fenner et al., 2022). In addition, fermentative processes conducted by indigenous yeasts can result in better adaptation to environmental factors as well as enhanced volatile compound profiles (Macêdo et al., 2023).

The increase in studies isolating yeast to produce volatile compounds and other bioproducts has been essential for the understanding of genetic diversity, as well as for the advances in the consolidation of commercial products, which is mainly directed to the food and beverage field (Amorim et al., 2018; Rêgo et al., 2020; Pimentel et al., 2021; Macêdo et al., 2023). Besides, the production of volatile organic compounds from yeast has also been widely evaluated as a biocontrol mechanism in agriculture. Several yeast species isolated from fruit exhibited the potential to control pathogenic fungi through the production of volatile organic compounds (see Table 2). As noted, the recovery of these compounds can be valuable for a wide range of applications.

Besides the relevance of yeast prospecting for the knowledge of the role of flavorings produced in food or the mechanism of action in biocontrol, the difference in the diversity of microorganisms is also a factor that affects the performance of autochthonous yeasts when used on substrates from which it was isolated. It has been demonstrated that yeast performance is enhanced when using fermentation media that have similarity to the source of the natural habitat of these organisms (Pimentel et al., 2021; Macêdo et al., 2023), as it is the case of fruit residues. Moreover, the microorganisms present in the residues can be different with the change of the environment, being strongly dependent on intrinsic parameters, such as carbohydrate and protein content and pH, and extrinsic parameters, such as climatic conditions and harvesting periods (Pimentel et al., 2021). In summary, there is a scenario where yeasts isolated from fruit and fruit residues are currently related to the identification of flavorings in food and beverage (mostly) and biocontrol in agriculture. Fortunately, this can be exploited in bioprocesses by fermentation of orange wastes to recover volatile organic compounds, providing a wide range of opportunities for biotechnology expansion.

Recently, Macêdo et al. (2023) evaluated the yeasts *Hanseniaspora opuntiae* and *Issatchenkia terricola*, isolated from umbu-cajá, and *H. opuntiae*, isolated from soursop, in the fermentation of soursop and umbu-cajá pulp. Higher metabolic activity of the yeast strains was observed in the media produced with the fruit pulps from which the yeasts were isolated. All strains were able to ferment the pulp, increasing the production of acetic acid and the concentration of phenolics (Macêdo et al., 2023).

Another interesting result for the production of volatile compounds by yeast isolated from fruits was presented by Rêgo et al. (2020), which demonstrated that fermentation can be directed to the production of specific volatile compounds from indigenous yeasts in cashew juice. When co-inoculating *Torulaspora delbrueckii* and *Hanseniaspora opuntiae* with *Saccharomyces cerevisiae*, the production of 2-propenoic acid and 3-phenyl-ethyl ester was detected, whereas this compound was not observed in simple fermentation (only with *S. cerevisiae*). The manuscript also identified 18 other volatile compounds from the mentioned yeasts in simple fermentation and co-fermentation (Rêgo et al., 2020). These results supported the proposition that autochthonous microorganisms may be more adapted to the matrix and better able to carry out fermentative processes (Pimentel et al., 2021), being interesting in the prospection for industrial expansion.

Table 2 – Recent studies evaluating the production of volatile compounds by yeasts isolated from fruit, with their respective applications.

Yeast	Isolation site	Target compound	Application	Reference
Aureobasidium pullulans	The surface of 'Redhaven' peaches (Italy)	1-Propanol, 2-methyl 1-Butanol, 3-methyl Butanoic acid, 2-oxo Limonene Phenethyl alcohol	Biocontrol of postharvest fungal pathogens	di Francesco et al. (2015); Mari et al. (2012)
Clavispora lusitaniae AgL21	Lemon Packinghouse (Argentina)	Ethyl acetate Isoamyl acetate 3-methyl butanol Phenethyl alcohol	Biocontrol of fungal pathogens	Pereyra et al. (2021, 2022)
Hanseniaspora vineae	Cashew apple fruit (Brazil)	Octanoic acid β-farnesene Decanoic acid 2-phenyl acetate Acetophenone Acetic acid	Production of cashew wine	Rêgo et al. (2020)
Hanseniaspora opuntiae	Soursop and umbu-cajá (Caatinga Biome fruits, Brazil)	Ethanol Acetic acid Succinic acid 3-methyl-1-butanol α-terpineol Aldehyde Isobutyric acid	Produce fermented pulps	Macêdo et al. (2023)
Meyerozyma caribbica	Pineapple pulp and peel	Gallic acid Catechin Ferulic acid Vanillin Resveratrol Coumaric acid	Functional fermented beverage	Amorim et al. (2018)
Sporidiobolus pararoseus YCXT3	Healthy leaf of strawberry (China)	2-ethyl-1-hexanol 2-hexyl-1-decanol, 2,6,10-trimethyl-dodecane Pentadecane Tetradecane 1-chloro-octadecane	Biocontrol of postharvest fungal pathogens	Huang et al. (2012)
Torulaspora delbrueckii	Cashew apple fruit (Brazil)	Isoamyl alcohol Phenylethyl alcohol Decanoic acid 3-methyl-1-pentanol Dodecanoic acid Acetic acid Benzoic acid	Production of cashew wine	Rêgo et al. (2020)
Wickerhamomyces anomalus Disva 2	Grape berry surface	Ethyl acetate Ethyl butyrate Isoamyl acetate Ethyl hexanoate Isobutanol Amylic alcohol Isoamyl alcohol	Biocontrol of postharvest fungal pathogens	Oro et al. (2014, 2018)
Pichia galeiformis BAF03	Lemon fruit surface (China)	Ethanol Acetic acid 3-methyl-1-butanol 3-methyl-1-butanol acetate Benzaldehyde Pentyl propanoate Benzeneacetaldehyde Phenylethyl alcohol	Biocontrol of citrus green mold (*Penicillium digitatum*)	Chen et al. (2020)

Continue...

Table 2 – Continuation.

Yeast	Isolation site	Target compound	Application	Reference
Pichia fermentans JT-1-3	Soil of research center (China) for citrus fruits (orange and lemon)	3-methyl-1-Butanol 2-methyl-1-Butanol Phenylethyl Alcohol Ethyl 9-hexadecenoate Linoleic acid ethyl ester 4-ethyl-2-methoxy-Phenol 4-ethyl-Phenol Limonene	Production of kiwifruit wine	Zhong et al. (2020)
Candida parapsilosis strains (IFM 48375 and NRRL Y-12969)	Orange bagasse (Brazil)	Ethanol	Fermentation of Citrus Pulp of Floater (an industrial residue from manufacturing of orange juice)	Cypriano et al. (2018); Tsukamoto et al. (2013)

Laboratory, semi-industrial, and industrial scale experiments

Several laboratory experiments have been developed to i. optimize industrial conditions, ii. enable technology transfer, and iii. ensure the production of chemicals in an integrated manner at the commercial level. It should be noted that, in addition to the efforts to optimize processes with different waste biomasses, there is a need to bring laboratory research closer to industrial demands. To this end, numerous efforts have been made to develop microbial cell factories to drive scaling-up.

Moreover, it is necessary to consider the concentration of the final product for the industry reality. For example, terpenoid production carried out in batch fermentations is at mg L^{-1}, which has no commercial significance. On the other hand, fermentation in a bioreactor with a fed-batch mode of operation can provide titers on the grams per liter scale and higher yields (Carsanba et al., 2021). For this purpose, the industrial production of compounds, e.g., terpenoids, is conducted in fed-batch mode, as it combines advantages of both batch and continuous fermentation modes. Fed-batch in 2 L bioreactors conducted simulating the industrial process of β-farnesene production by Amyris Inc. using a recombinant *S. cerevisiae* strain resulted in yields above 97% after a six-days fermentation (Carvalho et al., 2022). The same discussion can be extended to phenolics, such as resveratrol. Recently, in a fed-batch process, concentrations of approximately 800 $mg{\cdot}L^{-1}$ were achieved with glucose and ethanol as substrate using the strain S. cerevisiae ST4990 (Li et al., 2016).

Strategies to optimize the production of high-value-added compounds are also explored, either by adapting fermentative processes (e.g., co-culture) or operationalization. It has been demonstrated that co-fermentation methods can improve other processes, such as with indigenous yeasts (*Hanseniaspora guilliermondii*) and *S. cerevisiae*, which in co-culture significantly improved the content of polyphenols and aromatic compounds (Xu et al., 2022).It is important to highlight that xylitol is already a large-scale product, being mostly produced from lignocellulosic biomass and chemical routes (Grand View Research, 2017). However, in recent decades, biological routes have gained ground in industries, and research efforts have driven these advances. For instance, to produce xylitol from lignocellulosic biomass using biological route, the yeast *S. cerevisiae* PE-2-GRE3 (yeast engineered for xylitol production, with overexpression of *GRE3* gene from *Pichia stipitis*) and an enzyme cocktail of cellulases and hemicellulases were used in simultaneous saccharification and fermentation process and showed interesting conversion results (Baptista et al., 2020). In addition to engineered organisms, native yeasts have been identified and evaluated for their ability to accumulate xylitol, especially yeasts of the genera *Spathaspora* and *Scheffersomyces*, which have been essential to promote advances in the fermentation and production processes in single or co-culture, besides enabling the identification of genes of interest for metabolic engineering (Hickert et al., 2013; Farias and Maugeri-Filho, 2021; Neitzel et al., 2022; Scapini et al., 2022).

Conclusion

The most significant and recent findings about the biotechnological potential of orange wastes, as low-cost feedstocks, and yeasts, as a microbial cell factory, were highlighted in this review. Although for decades yeasts have shown an impressive competence in being genetically engineered, we showed that nature on its own can offer us indigenous strains with the ability to produce the most distinct and valuable bioproducts. This has been the case of fruit-isolated yeasts, which naturally work as fruit-decomposing microbes, thus showing an innate capacity to consume and transform residual biomasses.

According to the literature reviewed, at least twenty-one yeast species isolated from natural environments are capable of being employed in citrus-waste-based biorefineries. Cellulose, hemicellulose, and pectin hydrolysates have sugars that can be transformed into ethanol, xylitol, and volatile organic compounds by those yeasts. Moreover, in a multiproduct context, biorefineries may concomitantly produce bioactive polyphenols and terpenes that can be of interest to pharmaceutical companies and food industry. Last but not least, some indigenous yeasts display hydrolytic enzymes that can be used to generate xylan- and pectin-derived oligosaccharides, which also have been proven to benefit human health.

Finally, our review shows that, in this scenario, the current flagship is probably process scaling up. It is time to go from the laboratory to semi-industrial environments. Many laboratory-tested and -analyzed strategies now must be optimized on larger scales to make fruit-waste-based biorefineries real.

Authors' Contributions

MINUSSI, G. A.: writing – original draft, writing – review & editing. SANTOS, A. A. dos: writing – original draft, writing – review & editing. SCAPINI, T.: writing – original draft, Writing – review & editing. BONATTO, C.: writing – original draft, writing – review & editing. FENNER, E. D.: writing – original draft, writing – review & editing. DRESCH, A. P.: writing – original draft, writing – review & editing. SANTOS, B. C. S. dos: writing – original draft, writing – review & editing. BENDER, J. P.: writing – original draft, writing – review & editing. ALVES JÚNIOR, S. L.: conceptualization, supervision.

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