Chapter 5
Biotech Green Approaches to Unravel the Potential of Residues into Valuable Products

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Inamuddin, A. Asiri (eds.), *Sustainable Green Chemical Processes and their Allied Applications*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-42284-4_5

Abbreviations

ATPS	Aqueous two-phase systems
CCR	Carbon catabolite repression
cmc	Critical micelle concentration
COS	Chitooligosaccharides
CRISPR-Cas9	Clustered regularly interspaced short palindromic repeats-associated caspase 9 endonuclease
CSL	Corn step liquor
DNA	Deoxyribonucleic acid
E24	Emulsifying index
epPCR	Error-prone polymerase chain reaction
FOS	Fructooligosaccharides
GOS	Galactooligosaccharides
IMO	Isomaltooligosaccharides
NGS	New-generation sequencing
OMW	Olive mill wastewater
PCR	Polymerase chain reaction
PEG	Polyethylene glycol
PUF	Polyurethane foam
RL	Rhamnolipid
SmF	Submerged fermentation
SSF	Solid state fermentation
ST	Surface tension
STR	Stirred tank reactor
XOS	Xylooligosaccharides

5.1 Introduction

Green chemistry and sustainability principles are the basis to develop alternative strategies for a rational use of resources (preferably renewable) within a closed-looped system and with limited generation of waste, aiming to overcome the current challenges related with industrial progress, impact on environment, and economic growth (Winans et al. 2017; Sheldon and Woodley 2018). These strategies are well aligned with the circular economy concept that includes the well-known 3Rs (reduce, reuse, recycle) (Vea et al. 2018). Bioeconomy involves the use of biotech processes to sustainably produce and convert renewable biological resources and waste streams into valuable products across several economic sectors, including food, feed, bio-based products, and bioenergy. Merging the circular economy and bioeconomy concepts is a priority (Aguilar et al. 2018). A circular economy without added-value and wealth generation as well as a noncircular bioeconomy will not be widely adopted and accepted by society.

Biotech processes are a good fit to the green chemistry principles, namely, in what concerns reduced waste, atom economy, low toxicity, safe water-based processes, use of mild conditions leading to energy efficiency, renewable feedstock (e.g., enzymes), reduced derivatization, catalysis, real-time analysis, and inherently safer processes (Sheldon and Woodley 2018). In addition to being cost-effective and environmentally friendly, usually these strategies are considered sustainable as they are based on the use of natural resources at rates that do not excessively deplete supplies on the long term, and residues are generated at lower rates than the ones at which they can be readily assimilated by the environment (Graedel 2002). Remarkable advances in biotechnology, bioinformatics, metabolic engineering and molecular, systems, and synthetic biology made this possible. High-throughput DNA sequencing unraveled hundreds of microbial genome sequences which are currently available, opening countless opportunities for the identification of a target gene through bioinformatics analysis (data mining). In addition, DNA synthesis became affordable and feasible; thus with the sequence retrieved from databases it is easy to get the gene synthesized, cloned into an adequate chassis (host microorganism), and further produced at industrial scales in a cost-efficient manner. Two decades ago, the low number of enzymes available dictated the process conditions which often had to be adjusted as there were no other alternatives. Using in vitro directed evolution it is nowadays possible to create libraries of mutant enzymes to be further screened for enhanced properties (Denard et al. 2015) and engineered to specifically match predefined process requirements (e.g., activity, specificity, stability), leading to bioprocesses that are truly sustainable by design (Bommarius et al. 2011; Illanes et al. 2012). Actually, through protein engineering not only the optimization of existing enzymes but also the assembly of entirely new pathways and reactions using systems and synthetic biology principles has been possible. Site-directed mutagenesis enables the creation of point mutations by replacing an amino acid at a predetermined site in the protein by the other canonical amino acids. Hence, it can be used to rationally design an enzyme given that its three-dimensional structure and mechanism is known. Alternatively, if that structural information is missing, random mutagenesis can be used. This can be achieved using the error-prone polymerase chain reaction (epPCR) which has been extensively used to generate mutant enzymes (Chen and Arnold 1993; Moore and Arnold 1996). DNA shuffling that enables the in vitro homologous recombination of pools of selected mutant genes by random fragmentation and PCR reassembly (Stemmer 1994) led to several advances in this topic. Indeed, this procedure of random mutagenesis, recombination, and screening can be repeated until the desired mutant phenotypes are generated, for instance, the ability of an enzyme to catalyze a non-natural substrate under severe operational conditions (Renata et al. 2015; Sun et al. 2016). The exciting new gene editing tool CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats-associated caspase 9 endonuclease) and its further developments are broadening even more the protein engineering possibilities (Doudna and Charpentier 2014). For instance, tools like EvolvR that constantly vary all nucleotides within a tunable window length at user-defined loci will allow advancing genetic strategies in organisms/systems that do not easily and effectively

integrate homology-directed oligonucleotides. Additionally, these tools will likely simplify the fast development of valuable phenotypes through accelerated and parallelized mutagenesis and selection cycles. Using engineered DNA polymerases targeted to loci via CRISPR-guided nickases, EvolvR directly generates mutations (Halperin et al. 2018).

Additionally, the diversity of unexplored microorganisms and communities that inhabit the planet makes possible the continuous screening and discovery of promising biocatalysts. Metagenomics has emerged as an innovative and strategic approach to explore these unculturable microorganisms through the analysis of DNA extracted from environmental samples (Batista-García et al. 2016). Functional metagenomics involving the direct cloning and heterologous expression of environmental DNA without prior knowledge of its sequence is a useful technique to discover novel and promising enzymes. The total genomic DNA is extracted from the microbial communities present in a given sample and further used to construct metagenomics libraries. A functional screening is then performed to retrieve the most robust catalysts for different industrial applications. After identification of the genes involved in the biosynthesis of the enzymes, the most promising biocatalysts can be characterized and further engineered for a desired application. Successful examples of this approach have been reported (Ko et al. 2013; Rabausch et al. 2013; Wang et al. 2016; Zafra et al. 2016).

Besides the potential use of protein engineering strategies, there are other optimizations at the level of the substrate, culture medium, and reactor design that can greatly enhance cost-effectiveness and efficiency, thus contributing to the processes sustainability. In addition, emergent downstream solutions are expected to lead not only to purer added-value products but also to lower amounts of waste and effluent streams, as well as to a lower use of hazardous solvents, hence with a less negative impact on the environment. All these topics will be further detailed in the next subsections.

In the latest years, the European Union has been strongly committed in promoting a sustainable growth based on bioeconomy, through a change toward the use of renewable resources and environmentally friendly processes to produce energy. Mandatory regulatory rules to effectively accomplish greenhouse gas reductions and to diminish risks related to zones of carbon stock and high biodiversity value have been established. Overall, this urged the search for cleaner and more resource-efficient alternatives that simultaneously produce less waste and generate economic value. The biorefinery concept is well positioned to overcome such needs and to provide interesting solutions (Sheldon and Woodley 2018). A biorefinery is grounded on the use of renewable raw materials to produce several bio-based products, chemicals, and biofuels (Elbersen et al. 2012; Gullon et al. 2012). Industrial and agro-food residues and wastes are considered renewable feedstock that are rich in valuable compounds (Devesa-Rey et al. 2011; Lin et al. 2014) that can be reused and recycled to produce energy or other products (e.g., enzymes, bulk chemical, prebiotics, biosurfactants, biopolymers), thus setting the foundations for the circular bioeconomy (Wysokinska 2016).

In order to effectively base the European growth on a sustainable and rational use of resources, it is essential that all those existing resources suitable for a biorefinery

processing are properly identified and quantified. For instance, the amount of food waste currently produced is a global concern and the development of sustainable green technologies is crucial (Dahiya et al. 2018). Bioprocesses like acidogenesis, fermentation, methanogenesis, solventogenesis, photosynthesis, oleaginous process, and bioelectrogenesis, among others, can be used for food waste valorization either alone or integrated (Lin et al. 2014). On the other hand, many residues have already a commercial use, as, for example, sawdust that is generated in the wood production process and is used to make fibreboard or some crop residues that are used for animal feed or in some agricultural activities. Consequently, only a portion of those wastes (around 225 million tons/year) can indeed be used in biorefineries. These wastes include crop residues (around 122 million tons/year), municipal waste (gardens, food, paper, and wood) (around 63 million tons/year), and forestry residues (around 40 million tons/year) (Searle and Malins 2013). Mapping of resources available and other potential uses from a biorefinery perspective is an unmet need (Scoma et al. 2016). A significant percentage of available residues are comprised by agriculture and forestry residues that could potentially contribute to satisfy global energy needs (De Wit and Faaij 2010; Scarlet et al. 2010). Nevertheless, agriculture residues are heterogeneous and are produced seasonally. Therefore, residues generated in industrial processes (e.g., citrus pulp, spent coffee grounds, winery residues, olive mill wastewater (OMW), corn steep liquor (CSL), seafood waste, and brewer spent grain, among others) comprise an alternative renewable source and an opportunity for process economy improvement, new market opportunity development, and innovation.

5.2 Metagenomics Approaches to Unravel Novel Biocatalysts and Microorganisms

Microbial ecosystems are viewed as enormous reservoirs of genetic diversity, representing the largest proportion of biomass on Earth, although only 0.1–1% microorganisms are cultivable from any given niche (Handelsman et al. 1998). The discovery and characterization of this vast microbial and metabolic diversity has been possible due to culture-independent method advances. To unlock the genetic diversity contained within microbiomes, analysis of nucleic acids, proteins, and lipids using molecular approaches, such as genetic fingerprinting, metagenomics, and a combination study of the meta-omics techniques, revealed to be very useful (Bragg and Tyson 2014; Panigrahi et al. 2019). Currently, metagenomics is accepted as the most promising methodology for identifying enzymes with novel (bio)catalytic activities (so-called biocatalysts), by exploring the genetic material of whole microbial communities (the metagenome), as if it were a single large genome in an environmental sample. In addition, the rapidly expanding field of omics-mediated survey (e.g., genomics, transcriptomics, proteomics, and metabolomics, among others) coupled with an enhanced repertoire of bioinformatics tools has revolutionized the ability to analyze microbial communities, providing access to the diversity of taxonomically and phylogenetically relevant genes, catabolic genes, and whole operons and cor-

relation of genomes with particular functions in the environment (Béjà et al. 2000; Aguiar-Pulido et al. 2016; Ameen and Raza 2017). This knowledge has a wide range of potential applications under the areas of systems biology and biodiversity (Allen and Banfield 2005; DeLong 2005; Maruthamuthu 2017) and to produce novel natural products for several biotechnological and therapeutic applications (Montella et al. 2016; Maruthamuthu 2017).

5.2.1 Metagenomics on the Road for Green Chemistry

Metagenomics is the most successful tool for uncovering novel biocatalysts with great applicability and potential in green sustainable technologies for the industrial production of relevant chemicals (Castilla et al. 2018). Ahmad et al. (2019) reported that between 2014 and 2017, 332 metagenome-sourced enzymes were identified and characterized. These consist of one β-agarase, nitrilase, exonuclease, and acylase; two epoxides; four transferases; six proteases, amylases, chitinases, and phosphatases/phytases; 19 oxidoreductases, 118 cellulases/hemicellulases; and 161 esterases/lipases. Various environmental substrates can be explored using metagenomics, including marine waters and sediment, soil, compost, activated sludge, and animal rumen, among others (Montella et al. 2016; Berini et al. 2017; Ahmad et al. 2019; Castilla et al. 2018). For instance, enzymes naturally adapted to the constraints of certain industrial processes have been identified in extreme environments, namely, halotolerant esterases and glycoside hydrolases, thermostable lipases, or even psychrophilic DNA polymerases (Ufarte et al. 2015; DeCastro et al. 2016). With the application of these enzymes and others yet to be discovered, the future of green chemistry looks very promising.

The greatest advantage of metagenomics is that no prior knowledge of the DNA sequence is required and several different screening strategies may be applied. The critical step is the extraction of the environmental DNA. Any protocol needs to be optimized for each environmental sample and no protocol can provide an accurate determination of species distribution. Hence, different protocols for genomic DNA extraction can be employed and the DNA pools can be mixed to maximize the number of different species represented, thus increasing the final level of metagenomics diversity (Delmont et al. 2011). Moreover, some adjustments may be included in the protocol, like enrichment of the sample in the target microorganisms to improve the specificity of the sample's DNA (Jiao et al. 2006), although most of studies use the non-enrichment approach to preserve the natural diversity and relative abundance of microbial communities (Montella et al. 2016).

Metagenomics screening can be function-based or sequence-based. Function-based screening is a straightforward way to identify novel biocatalysts and biochemical mechanisms that have desired industrial functions. This technique is based on the principle of discriminating biochemical activities of the reactions catalyzed by enzymes and the detection of novel functional genetic elements with different functions from the known enzymes (Ahmad et al. 2019). Numerous

novel enzymes and bioactive compounds that have potential commercial applications were identified through functional screening, such as hydrolases, oxidoreductases, transferases, or catabolic enzymes with environmental cleanup purposes (Sjöling and Cowan 2008; DeCastro et al. 2016; Madhavan et al. 2017). This strategy involves the creation of metagenomics libraries where genomic DNA extracted from environmental samples is directly cloned in a suitable vector like phage, plasmid, cosmid, fosmid, or bacterial artificial chromosome. Subsequently, the ligated product is transferred into a suitable host to evaluate the expression of the target enzyme. Cosmid and fosmid libraries are the most commonly used because of their stability, their capacity to accept large fragments, and their feasibility of transduction (Montella et al. 2016) and also because they enable recovering of full-length genes, gathering information on their genetic context in natural sources, and unveiling cocktails of synergistic activities that degrade complex substrates (Berini et al. 2017). The common function-based screening strategy is assaying enzyme activities by harvesting a metagenomics library on agar plates incorporated with dyes and substrates of target enzymes. This technique provides a simple and straightforward approach to identify novel biocatalysts that function under diverse conditions (Simon and Daniel 2011) and even though the low throughput, a large number of unique enzymes from various environments have been successfully isolated (Ngara and Zhang 2018). Despite the great potentialities of functional screening, there are constraints limiting its success; the hit rate (probability) of identifying a particular gene depends on multiple elements that are inextricably linked to each other including the host-vector system, size of the target gene, the efficiency of heterologous gene expression, and screening conditions employed. Nevertheless, several strategies to overcome these drawbacks are being evaluated (Batista-García et al. 2016).

The sequence-based screening can be achieved by either the homology-based screening of libraries or the direct large-scale sequencing of extracted DNA, using engineered degenerate primers from highly conserved target regions in PCR or probes for hybridization (Batista-García et al. 2016). Most metagenomics studies involving high-throughput sequencing adopt either an amplicon-based or a shotgun-based approach using next-generation sequencing (NGS) technology. NGS technologies are enabling the sequencing of thousands of genomes in parallel (Montella et al. 2016). A number of sequencing platforms are currently available, offering varying levels of sequence coverage and depth (Goodwin et al. 2016). The collected data offer an insight into the potential function of the population while also aiding direct gene mining for biotechnological applications (Aguiar-Pulido et al. 2016). These techniques already proved to be useful to find enzymes with high activity and efficiency leading to the identification of several novel enzymes such as bacterial laccases, dioxygenases, nitrite reductases, hydrogenases, hydrazine oxidoreductases, or chitinases from various ecosystems (DeCastro et al. 2016; Berini et al. 2017; Madhavan et al. 2017; Ahmad et al. 2019). The continuous development of bioinformatics tools suggests that the shotgun strategy will be more suitable than the function-based screening or amplicon sequencing for the discovery of novel target genes from environmental DNA (Montella et al. 2016).

5.2.2 *Novel Metagenomics Biocatalysts on the Market*

The whole process of finding novel biocatalysts and also the optimization of the efficiency of the processes is very expensive and time-consuming. Also, independently of the novelty of the sequence encoding an enzyme, the key is its application. Novel enzymes such as oxygenases, esterases, and laccases with very diverse origins have been highlighted for their competence to degrade pollutants such as nitriles, lindane, styrene, naphthalene, aliphatic and aromatic carbohydrates, organophosphorus, or plastic materials (Ufarte et al. 2015). Nevertheless, very few cases of new environmental biocatalyst products have been yet patented and translated to market (Berini et al. 2017). Some examples of patented enzymes obtained through metagenomics for application on green chemistry include nitrile hydratases (EP2369009A3), laccases (GB01P006EP), cellulases (EP04015680.4), an esterase able to degrade terephthalate esters (component of bioplastics) (WO 2007017181), and cow rumen-derived esterases (EP04015920.4) (Ngara and Zhang 2018).

5.3 Synthetic Biology Approaches to Construct Microbial Cell Factories Able to Degrade Agro-industrial Wastes

Society still depends on fossil fuels and other petrochemicals that are nonrenewable and contribute to the global climate change. Besides, the reliance on the extraction from plants of essential compounds such as drugs, foods, and cosmetics, among others, is also not environmentally friendly and demands valuable resources such as water and high area of arable land. In addition, the slow and seasonal growth of the plants, in combination to the small amounts produced in some cases, can cause a serious supply depletion (Jullesson et al. 2015). Taking all this into account, new sustainable and greener processes ought to be developed. Synthetic biology allows to design, construct, and engineer parts, devices, systems, and organisms with useful, predictable, and novel functions by applying engineering principles (Weber and Fussenegger 2012). Nowadays, the design and construction of biological systems to produce drugs (Westfall et al. 2012; Paddon and Keasling 2014; Rodrigues et al. 2015a, b, c; Couto et al. 2017; Rodrigues et al. 2017a; Kung et al. 2018; Abdallah et al. 2019), biofuels (Lee et al. 2008; Majidian et al. 2018), biosensors (Rodrigues et al. 2014; Rodrigues et al. 2017a; Rodrigues and Rodrigues 2017b; Kim et al. 2018), and added-value products such as natural fibers (Bowen et al. 2018) became a routine (Rodrigues and Rodrigues 2017a; Rodrigues et al. 2017b). However, the success of industrial synthetic biology strategies depends not only on the ability of getting products in high concentrations but also in an economically viable manner of using renewable and inexpensive feedstock (Protzko et al. 2018). Sustainable feedstock cannot compete directly or indirectly with food production and should include waste lignocellulose derived from agriculture and forestry residues and by-products from fruit and vegetable processing processes (Fig. 5.1).

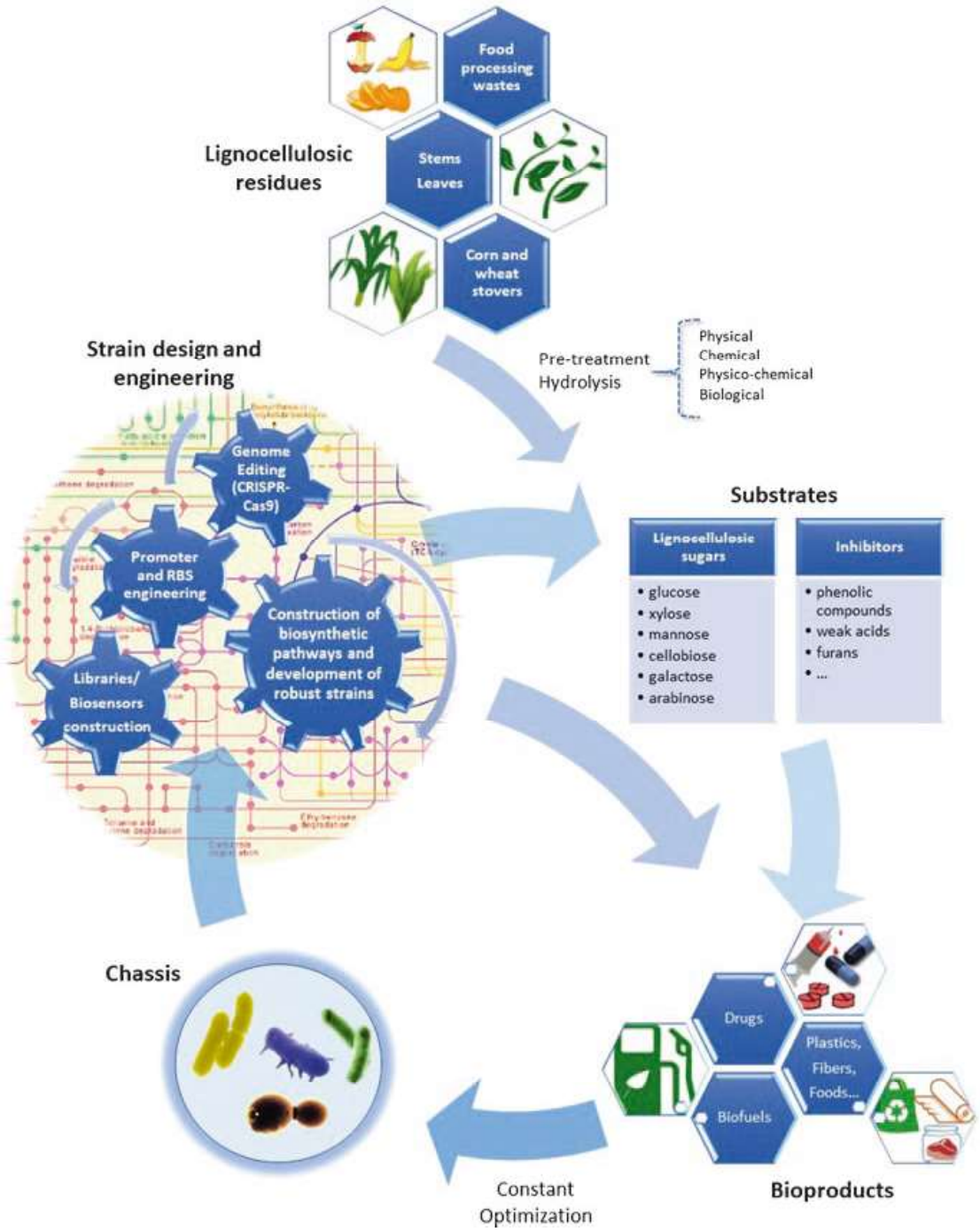

Fig. 5.1 Overview of synthetic biology approaches to produce added-value products from lignocellulosic residues. A selected chassis is engineered using parts retrieved from databases and literature. After the parts/pathway(s) assembly, the engineered strain is used to degrade the lignocellulosic residues or to directly convert the lignocellulosic sugars into the envisaged (bio)product. The chassis can be continuously optimized until the productivity of the target added-value product meets the expected level

As previously mentioned, lignocellulosic residues are the most abundant renewable source of sugars. Lignocellulose is mostly composed of cellulose, hemicellulose, lignin, and pectin. Its hydrolysis results in a mixture of sugars that includes hexoses (glucose, mannose, and galactose), pentoses (xylose and arabinose), and uronic acids (galacturonic acid). Glucose is the hexose present in higher amount and the only monomer present in cellulose. Hemicellulose contains different sugar monomers with xylose usually being the one present in higher concentration. Simultaneous co-fermentation of these carbon sources is required for the efficient production of compounds derived from lignocellulosic residues. Many microbes (e.g., *Saccharomyces cerevisiae* and *Zymomonas mobilis*) cannot naturally metabolize xylose or other pentoses (Kim et al. 2010). Even microorganisms that are able to metabolize xylose, such as *Escherichia coli*, experience repression from glucose – carbon catabolite repression (CCR). Therefore, diauxic growth is observed – pentose consumption only occurs after glucose exhaustion (Görke and Stülke 2008). Using metabolic engineering and synthetic biology, several organisms have been engineered to confer them the ability to metabolize simultaneously different sugars (hexoses and pentoses) (Eiteman et al. 2008; Kim et al. 2010; Xia et al. 2012; Flores et al. 2019; Paula et al. 2019). For example, *E. coli* was engineered to use only one sugar through several different gene deletions. The use of a consortium of different *E. coli* strains was able to use simultaneously glucose, xylose, and arabinose (Eiteman et al. 2008; Xia et al. 2012; Flores et al. 2019). In a different study, the deletion of *ptsG* gene that encodes a subunit of glucose transporter and plays a central role in CCR, in combination to the (over)expression of genes related to xylose degradation, allowed *E. coli* to co-utilize both glucose and xylose (Jung et al. 2015; Chae et al. 2018). The deletion of key enzymes in the competing pathways using synthetic biology tools such as CRISPR-Cas9 also allows to increase the titers (Wang et al. 2018; Abdelaal et al. 2019;). In addition, *E. coli* metabolic pathway for xylose and/or arabinose consumption was constructed in *Z. mobilis* and *S. cerevisiae* (Lawford and Rousseau 2002; Hahn-Hägerdal et al. 2007). Xylose assimilation in these organisms has been achieved by inserting xylose isomerase or xylose reductase-xylitol dehydrogenase pathways (Cunha et al. 2019), being these pathways found in anaerobic fungi and naturally xylose-utilizing bacteria, respectively (Hahn-Hägerdal et al. 2007). In the arabinose case, *araABD* genes from different sources were tested throughout the years and it was concluded that they were effective in arabinose consumption but only in combination with adaptive evolution (Caballero and Ramos 2017). Since these organisms do not have specific transporters for xylose or arabinose (Kim et al. 2010), transporters were also engineered (Li et al. 2016a, b; Caballero and Ramos 2017; Wang et al. 2019). More recently, Protzko et al. (2018) engineered *S. cerevisiae* to use both glucose and galacturonic acid from citrus peel waste (pectin-rich biomass) as carbon sources and to produce meso-galactaric acid, a building block used in the production of numerous compounds (nylon, plastic monomers). The expression of the heterologous transporter, GatA, from *Aspergillus niger* was essential.

In addition to introduce pathways to consume the sugars from lignocellulosic residues, other issues need to be considered, such as the presence of inhibitory by-products (fermentation inhibitors). These by-products that include phenolic compounds, furans, and acids are produced during the lignocellulose pretreatment and reduce the microorganism growth. Therefore, the engineering of stress response regulators can be of utmost importance to increase tolerance to these by-products (Paula et al. 2019). Transcription factors are transcriptional regulatory proteins that allow the organism to use the available nutrients without wasting energy. Several studies proved that the overexpression or inactivation of specific transcription factors can increase *S. cerevisiae* resistance to acids and ethanol (Li et al. 2017; Balderas-Hernández et al. 2018). Synthetic biology also provides new tools, such as promoter engineering, to improve the expression in biological systems. Synthetic promoters are designed to optimize expression levels. For example, Hector and Mertens (2017) designed a synthetic hybrid promoter in *S. cerevisiae* controlled by xylose presence/absence. For that purpose, they constructed a promoter that combined *Ashbya gossypii* TEF promoter and the operator sequence (*xylO*) for binding the XylR repressor. This new hybrid promoter was repressed in the absence of xylose. The generation of promoter libraries is also a synthetic biology approach that can be very useful to find new promoters that allow an appropriate expression level (Rodrigues et al. 2014; Rodrigues and Rodrigues 2017a; Rodrigues and Rodrigues 2017b). For example, Redden and Alper (2015) used this strategy to construct short synthetic yeast promoters that maintain a strong function. For that purpose, the authors identified minimal core elements and minimal upstream activating sequences and combined them to obtain short and strong constitutive and inducible promoters.

Synthetic biology can also have a major role in the use of lignocellulose wastes to produce added-value compounds by designing trees with customized lignin. Lignin, the complex polymer that confers mechanical support to the plant, acts as major impediment to industrial processing due to the high energy demand needed to break it down. Yang et al. (2013) used synthetic biology tools in *Arabidopsis thaliana* to replace some promoters of key lignin genes in order to decrease the lignin content without the collapsing of the vessels. In a different study (Tsuji et al. 2015), the introduction of LigD enzyme from bacterium *Sphingobium* sp. in *A. thaliana* allowed to alter the lignin structure according to the design due to the enzyme ability to oxidize α-hydroxyl groups in β-O-4 units in lignin to α-keto analogues that are chemically more labile. More recently, the curcumin biosynthetic pathway was introduced in *A. thaliana* and curcumin and other phenylpropanoids produced were incorporated into the cell wall (Oyarce et al. 2019). This allowed to significantly increase the saccharification efficiency after chemical treatment of the heterologous *A. thaliana* as compared to the wild type. All these strategies can be used in the future to enhance the lignocellulosic biomass processing efficiency.

5.4 Bioprocess Development: Trends in Bioreactor Design and New Engineering Approaches

Another important aspect to be considered in the development of a sustainable development evolution of a bio-industry is the process engineering. In bioreactor design two main issues should be addressed, namely, the optimization of volumetric productivity and the efficient use of the starting material and/or catalyst (Andri et al. 2010). Additionally, the control of some parameters and variables addition, it is also essential to control some parameters and variables in order to ensure the optimal conditions for the reaction system, being the most relevant the dissolved oxygen concentration, medium pH, temperature and mixing (Zhong 2010; Caramihai and Severin 2013; Sofía et al. 2018).

In the last decades, research efforts have been concentrated on bioreactor design and engineering to overcome the main problems with mixing, mass, and heat transfer (Mitchell et al. 2000; Ferreira et al. 2017). Different bioreactor configurations have been developed, being the most common the stirred tank reactor (STR). In 2017, Guneser et al. (2017) studied the production of D-limonene, a flavor compound, by *Rhizopus oryzae* and *Candida tropicalis* using OMW as raw material in a 5-L STR. A maximum D-limonene concentration of 87.73 mg/kg was attained. Although the STR is the most commonly used bioreactor at an industrial scale, nowadays a variety of bioreactor type and configurations have been explored and developed such as airlift bioreactors and bubble columns (Chisti and Moo-Young 1987; Werner et al. 2018). The production of β-carotene and single cell oil with *Rhodotorula glutinis* from cellulose hydrolysate was studied by Yen and Chang (2015). The authors compared the cultivation of this oleaginous yeast in an airlift and STR bioreactors and observed that the highest lipid content (34.3%) was obtained in the airlift, as well as the highest biomass concentration. However, the highest β-carotene content was achieved in the STR (1.2 mg/g). Currently, fermentation processes can be classified as submerged fermentation (SmF) or solid state fermentation (SSF). In SmF, microorganisms are cultivated in a liquid nutrient medium (Pandey 2003; Singhania et al. 2009). Instead, SSF comprises the microbial growth in a solid substrate in the absence of free water (Pandey et al. 2000; Singhania et al. 2009).

In fact, SSF approach allows the valorization of unexploited biomass and offers the possibility of using residues and wastes as substrates, helping in solving some environmental issues (Soccol et al. 2017). SSF has many advantages comparing to traditional SmF such as higher yields and product titers, easier downstream process, reactors with smaller volumes, and lower energy and cost requirements (Singhania et al. 2009; Manan and Webb 2017). One of the key factors in the design of a SSF process is the selection of the microbial host. Filamentous fungi are the dominant microorganisms used in SSF since this technique simulates their natural environment, as well as their mycelia growth (Farinas 2015). However, the utilization of yeasts (e.g., *Pichia pastoris*, *Kluyveromyces marxianus*, *S. cerevisiae*) and some bacterial cultures (e.g., *Bacillus subtilis*, *B. thuringiensis*, and *Clostridium thermo-*

cellum) have also been described in SSF processes (Singhania et al. 2009; López-Pérez and Viniegra-González 2015). Another important aspect in this process is the substrate selection. The most common residues applied in SSF include starchy substrates as rice, oats, cassava, and wheat bran, among others, that are rich in carbohydrates (Soccol et al. 1994; El-Shishtawy et al. 2014); substrates with protein such as oil cakes (e.g., soybean, coconut, sesame, sunflower, and olive oil cakes) (Ali et al. 2012; Paithankar and Rewatkar 2014); cellulosic or lignocellulosic substrates that include sugarcane bagasse, corncob, barley husk, barley straw, and wood (Elegbede and Lateef 2017; Martínez-Avila et al. 2018b; Sadh et al. 2018); and substrates rich in soluble sugars that are mostly produced in fruit industries such as sugar beets and sugar beet pulp, molasses, and grape pomace (Zeng et al. 2018; Teles et al. 2019). Palm oil mill and OMW, organic wastes and textile wastes, and tea, coffee, and cassava wastes have also been used as substrates in SSF as an alternative mean of waste valorization integrated in the biorefinery concept (Lopes et al. 2016; Hu et al. 2018; Mejias et al. 2018). Usually these residues and wastes provide the nutrients and the carbon necessary for microbial growth, in addition to be a solid support for microbial growth and nutrient adsorption. Nevertheless, sometimes it is also necessary to additionally supplement the medium with macro- and micronutrient essentials for an optimum microbial growth (Pandey 2003; Farinas 2015).

In the last decade, SSF has been applied in the production of a broad range of metabolites, such as organic acids, enzymes, secondary metabolites, biofuels, flavors, pigments, and phenolic compounds (Kumar et al. 2003; Cavalcanti et al. 2005; Gadhe et al. 2011; Try et al. 2017; Martínez-Avila et al. 2018a; Mejias et al. 2018). Table 5.1 presents a summary of the most recent studies (last 4 years) regarding the production of some added-value molecules by SSF.

Bioreactor design for SSF is another important research area under development (Ashok et al. 2018). In SSF, the bioreactors employed can be classified according to the mixed system used and the type of aeration (Durand 2003; Spier et al. 2011). In the last years, bioreactors such as packed beds (Khanahmadi et al. 2006; Melikoglu et al. 2015), multilayer packed beds (Shojaosadati and Babaeipour 2002), rotating drum bioreactors (Saithi and Tongta 2016), column bioreactors (Linde et al. 2007; Salum et al. 2010), column-tray bioreactors (Ruiz et al. 2012), magnetic rotating biological contactors (Saha 1997), fixed beds (Castro et al. 2015), and tray systems (Khanahmadi et al. 2004), among others, have been used in SSF processes. The most commonly used bioreactors for SSF are the static bioreactors such as Erlenmeyer flasks, trays, fixed bed, or packed bed bioreactors, being their main advantage its simplicity (Durand 2003). Tray bioreactors are chambers or rooms, with air circulation and controlled humidity and temperature, in which different recipients laid with the substrate are placed. Usually, the top of the tray is open and the bottom is perforated to allow air convection (Durand 2003). The scale-up of this system is simple; however it needs large areas, since it is performed by increasing the number of trays, is intensive labor, and is a non-sterile process, which makes the contamination control difficult. Another bottleneck in these systems can occur with oxygen transfer, which is strongly affected by substrate bed height and bioreactor design. Oliveira et al. (2017b) compared the lipase production by SSF of olive pom-

Table 5.1 Overview of the production of some added-value molecules by solid state fermentation (SSF) in the recent years

Products	Strain	Substrate/support	Concentration/ activity	Bioreactor	Reference
Enzymes					
Amylase	*Bacillus amyloliquefaciens*	Orange peels and cheese whey	220 U/mL	Flask	Uygut and Tanyildizi (2018)
	Bacillus sp. *BBXS-2*	Wheat straw	6900 U/g	Flask	Qureshi et al. (2016)
	Bacillus cereus and *B. thuringiensis*	Wheat brain	14.5 U/mL	Flask	Abdullah et al. (2018)
Xylanase	*Aspergillus tubingensis* FDHN1	Sorghum straw	5177.23 U/g	Static flask	Adhyaru et al. (2016)
	Aspergillus awamori IOC-3914	Palm kernel cake and palm pressed fiber	134.2 U/g	Tray-type bioreactor	Oliveira et al. (2018)
	Aspergillus oryzae		27.2 U/g		
	Aspergillus niger		18.8 U/g		
Cellulase	*Trichoderma reesei CECT 2114*	Rice bran, rice husk, rice straw	1.317 U/g	Flask	Darabzadehet al. (2019)
Laccase	*Funalia trogii IFP0027*	Rice straw	172.74 U/g	Flask	Li et al. (2019)
Lipase	*Burkholderia cenocepacia*	Sugarcane bagasse, sunflower seed, and olive oil	72.3 U/g	Flask	Liu et al. (2016)
	Rhizomucor miehei	Babassu cake	30 U/g	Fixed-bed bioreactor	Ávila et al. (2018)
	Rhizomucor miehei	Cottonseed meal	93 U/g	Tray-type bioreactor	Aguieiras et al. (2018)
Phytase	*Aspergillus ustus*, *Aspergillus niger* van Tieghem, *Trichoderma atroviride*, *Trichoderma koningii*, *Trichoderma harzianum Rifai*, *Bacillus subtilis*, *Bacillus megaterium*, *Bacillus amyloliquefaciens*, *Aspergillus niger*	Cassava bagasse, soybean bran, wheat bran, sorghum, and maize distiller dried grains with solubles	0.33–2.03 U/ $mg_{protein}$	Flask	Barbosa et al. (2019)

Products	Strain	Substrate/support	Concentration/ activity	Bioreactor	Reference
Pigments					
Astaxanthin	*Sporidiobolus salmonicolor* (ATCC 24259), *Yamadazyma guilliermondii* (ATCC 90197), *Yarrowia lipolytica* (ATCC 24060), *Xanthophyllomyces dendrorhous* (ATCC 24202)	Wheat wastes	109.23 μg/g	Flask	Dursun and Dalgiç (2016)
β-Carotene	*Blakeslea trispora* MTCC 884	Fruit and vegetable waste (orange, carrot, and papaya peels)	0.127 mg/mL	Flask	Kaur et al. (2019)
Organic acids					
Oxalic acid	*Trichoderma asperellum* MG323528	Corn stover	27.55 mg/g	Flask	Al-Askar et al. (2018)
Citric acid	*Aspergillus niger MTCC 281*	Brewer's spent grain	0.22 %	Flasks	Pathania et al. (2018)
Fumaric acid	*Aspergillus oryzae*	Wheat bran	0.54 mg/g	Flask	Jiménez-Quero et al. (2017)
Flavor and fragrances					
2-Phenylethanol	*Kluyveromyces marxianus*	Sugarcane bagasse	16 mg/g	Flask	Martínez-Avila et al. (2018a)
γ-Decalactone	*Yarrowia lipolytica W29*	Castor oil	196 mg/L	Forced aeration mini-reactor	Try et al. (2017)
			75 mg/L	Small-headspace bottle	
6-Pentyl-α-pyrone	*Trichoderma asperellum* G7	Sugarcane bagasse	85.1μg/g	Flask	Hamrouni et al. (2019)

ace using a tray-type bioreactor and a novel pressurized bioreactor. In the latter one, the increase in the total pressure was used as a tool to enhance the oxygen solubility in the media, improving the oxygen transfer rate (Belo et al. 2003). The authors observed a twofold increase in the lipase production using the pressurized bioreactor (126 U/g), at a pressurized aeration of 200 and 400 kPa, when compared with the tray-type bioreactor (61 U/g). Another interesting bioreactor for SSF is the packed bed bioreactor. The main attractive features of this bioreactor are its easier operation and the possibility of continuous operation, besides allowing the in situ extraction of enzymes (Ganguly and Nandi 2015). Oliveira et al. (2017a) studied the lipase production by *Aspergillus ibericus* MUM 03.49 in a packed bed bioreactor. The authors used SSF of olive pomace and wheat brain, and after the process optimization an enzyme activity of 223 U/g (dry basis) was obtained after 7 days of fermentation. Another relevant concept to consider on bioreactor design for SSF is the use of continuous or intermittent agitation in order to decrease the heterogeneity of the solid medium and improve the oxygen transfer to the microorganism. The application of a rotating drum bioreactors was described by Saithi and Tongta (2016) in phytase production with *A. niger* from soybean meal. In this bioreactor, agitation is applied by a rotating system tumbling the solid medium. The authors reported a phytase activity of 580 U/g substrate dry weight.

Generally, the most common operation mode applied in SSF systems is the batch process where all nutrients are added before the cultivation starts and remain in the bioreactor until the end of fermentation. However, this approach has several issues mainly due to the problems with mass and heat transfer in the solid-liquid-gas interphases, thus making the scale-up of a SSF process very challenging (Lonsane et al. 1985). Therefore, it is necessary to develop alternative operational strategies to overcome these limitations and enhance the SSF performance. Semicontinuous operation allows the substrate supplementation with partial feeding or sequential batch of nutrients. This is an interesting approach that has been used to control the microorganism growth rates (Cerda et al. 2017; Martínez-Avila et al. 2019). This feature was explored by Martínez-Avila et al. (2019). The authors compared the 2-phenylethanol and 2-phenethyl acetate production by *K. marxianus* using fed-batch and sequential-batch strategies in a SSF process with sugarcane bagasse as substrate, supplemented with L-phenylalanine. The authors observed that in the fed-batch strategy it was possible to increase the production of both flavors in 12.5%. Moreover, in the sequential-batch the production was also increased in 2.4% compared to the batch. Cheirsilp and Kitcha (2015) compared the lipid production using different cellulolytic oleaginous fungi and compared its production in SSF using a fed-batch strategy with intermittent feeding and a repeated-batch strategy. Comparing to the batch experiments, with this approach it was possible to increase the lipid yield from 79.9 to 86.6 mg/g dry substrate. Nevertheless, the industrial applications of SSF are still limited mainly due to the necessity for continuous inoculum production that becomes expensive and time-consuming and the low productivity inherent to the repeated-batch operation. A continuous SSF process can potentially overcome these bottlenecks. Lagemaat and Pyle (2004) firstly described a SSF process operating in a mixed continuous mode without an inoculation feed.

The authors cultivated *Penicillium glabrum* on tannin-rich model substrate for tannase production, attaining concentrations that range from 50 to 140 μmol (min/gPUF).

Another important feature that has been applied in SSF is the utilization of co- or mixed-culture systems. In fact, most studies with SSF reported the application of a single strain for (bio)production or bioconversion of the desired metabolite (Qiao et al. 2018; Martínez-Avila et al. 2019). However, the substrate utilization in a monoculture processes is often limited to more simple substrates (Lin et al. 2011). On the other hand, the utilization of two or more microorganisms that are cultured together in the same medium (co-culture strategies) allow the utilization of more complex substrates, as lignocellulosic and agriculture residues, as well as mixtures of substrates with different compositions (Lin et al. 2011). Co-cultures appear to be advantageous over single microorganism ones since with this approach it will be possible to use the metabolic abilities of all involved strains in the co-culture setup (Yao and Nokes 2013). The production of cellulase and hemicellulase from various agriculture residues using single and co-cultures of *A. niger* and *Trichoderma reesei* and SSF technology was studied by Dhillon et al. (2011). They observed that the utilization of mixed cultures allowed a higher cellulase activity (3106.34 IU/$g_{dry\ substrate}$) when compared to the activities attained with single cultures. These experiments demonstrated the potential of co-cultivation as an alternative strategy to produce enzymes in a competitive way from cheaper substrates. In fact, SSF has a high potential to be a more economical industrial process than SmF. However, although SSF industrial applications are well established for certain traditional processes in oriental countries, their use in western countries is still very limited. The main drawback is that a simple and practical automated fermenter for SSF processes has not yet been developed. In fact, the main constraints for SSF scale-up are still the selection of the microbial host, the bioreactor system employed, and substrate/support used.

5.5 Green and Sustainable Downstream Processing of Biomolecules Using Aqueous Two-Phase Systems

Aqueous two-phase systems (ATPSs) have been widely described as a versatile and promising separation/recovery tool in biotechnology. These biphasic systems are formed when aqueous solutions of two different constituents are mixed above certain critical conditions, namely, concentration and temperature. Typically, the equilibrium phases are constituted mostly by water (>70%) and each one is enriched in a specific component. Depending on the type of ATPS prepared, the predominant component in each equilibrium phase may significantly differ. ATPSs formed by two polymers (such as dextran and polyethylene glycol (PEG)) or a polymer and a salt (such as PEG-Na_2SO_4) constitute the classical systems. However, other alternative biphasic systems have been proposed using surfactants (Cordisco et al. 2016),

alcohols (Xu et al. 2017), organic acids (Saravanan et al. 2008), carbohydrates (Silva et al. 2007), ionic liquids (Lee et al. 2017), or deep eutectic solvents (Xu et al. 2015). The main advantages reported for the use of ATPSs in the recovery of biomolecules include the simplicity of operation, rapid separation, relative low cost and energy consumption, ease to scale up, high selectivity, ability to be coupled with different extraction techniques, biocompatibility of most of the constituents, and the high water content in both equilibrium phases (Phong et al. 2018). Since water is the main component of ATPSs, a gentle environment is generated for the efficient recovery and separation of biological compounds without compromising their integrity. Furthermore, some compounds frequently used in ATPS formation, such as polyols (sorbitol or xylitol), polymers (PEG or dextran), and surfactants (Tween or Triton) are known for their additional capacity to stabilize the structure and activity of several biological constituents (Silva et al. 2018). ATPSs offer innumerous advantages in biomolecule recovery when compared to the classical liquid-liquid extraction using organic solvents which can present several environmental issues and toxicity and frequently promote the damage of biological products. However, to increase the potential of ATPSs as a green and sustainable downstream strategy it is important to use phase-forming components with proven biocompatibility and biodegradability and preferably with the ability to be reused and recycled. In the last decade, several studies have been focused on the recyclability and environmental impact of ATPSs. Several phase-forming constituents from natural origin such as choline derivatives, salts derived from organic acids, or carbohydrates have been proposed (Li et al. 2012; Kalaivani and Regupathi 2013; Ramalakshmi et al. 2014). Also, several strategies have been adopted to recycle the phase-forming components such as the application of thermo-separating polymers (Leong et al. 2016) or the preparation of successive ATPSs to achieve an efficient back-extraction of the target product and the regeneration of the most expensive components (Cláudio et al. 2014). Some practical examples of the successful applications of ATPSs as greener and eco-friendly alternatives for the extraction and recovery of different biological compounds will be further discussed below.

5.5.1 Extraction of Natural Products from Plants or Animal Tissues

Higher yield and/or purity has been reported for the extraction of several phytochemicals using ATPSs when compared with the traditional extraction procedures. Mejía-Manzano et al. (2019) improved the extraction of the natural anticancerigen pristimerin from *Mortonia greggii* root bark previously ground using an ethanol-Na_3PO_4 ATPS. The extraction of pro-anthocyanidins (catechin, epicatechin, and procyanidin B2) from powdered grape seeds was also significantly raised using the ethanol-$(NH_4)_2SO_4$ ATPS with the ionic liquid 1-hexyl-3-methylimidazolium tetrafluoroborate ($[C_6mim]BF_4$) as adjuvant (Ran et al. 2019). Additionally, the use of

ultrasonic-assisted ethanol-$(NH_4)_2SO_4$ ATPSs proved to be an effective strategy for the extraction of curcumin from powdered *Curcuma longa* rhizomes (Xu et al. 2017). In all these examples, the natural products were extracted to the ethanol-rich phase. However, less organic solvent was consumed, shorter extraction time was required, and safer methodologies were developed when compared to the traditional solvent extraction.

The extraction of enzymes directly from animal tissues was also reported using ATPSs. Tjerneld et al. (1987) studied the affinity extraction of lactate dehydrogenase from pig muscle using polymer-polymer ATPS composed of Aquaphase PPT and PEG 8000. Boland et al. (1991) performed pilot-scale trials to extract superoxide dismutase from bovine liver using PEG 1550-potassium phosphate buffer ATPS. Although these strategies were described as economically favorable and presenting efficient use of space and time, they are not commonly used. Alternatively, previous crude extracts from animal tissues and/or animal tissue processing residues can be prepared and the target biomolecules be further recovered through ATPSs (Sripokar et al. 2017).

5.5.2 *Recovery and Purification of Biomolecules from Alternative Fermentation Broths and Industrial Residues*

The recovery and separation of several enzymes/proteins from synthetic fermentation broths using ATPSs has been extensively studied (Iqbal et al. 2016) with recognized advantages over the conventional methodologies (Aguilar et al. 2006; Moreira et al. 2013). However, product recovery from fermentation broths composed of agro-industrial residues is generally described as a more difficult task. Fermentation media containing residues are considered a cheaper and sustainable approach to obtain some biomolecules, but these fermentation media are also more complex in composition and impurities which can make the downstream process difficult. ATPSs have demonstrated likewise potential for product recovery from these alternative fermentation broths. Some examples of enzymes recovered and partially purified from fermentation broths containing agro-industrial residues include esterase from *A. pullulans*, cellulase from *Schizophyllum commune*, laccase from *Peniophora cinerea*, or keratinolytic protease from *Serratia marcescens* which were produced in fermentation broths containing OMW (Lemes et al. 2019), wheat bran (Kumar et al. 2018), CSL (Moreira et al. 2013), and feather meal (Bach et al. 2012), respectively. Furthermore, ATPSs can also contribute for the direct valorization of industrial by-products and residues. The extraction and recovery of added-value products such as enzyme/proteins from cheese whey (Anandharamakrishnan et al. 2005), tannery wastewater (Raja and Murty 2013), salted egg white (Jiang et al. 2019), or brewery yeast waste (Léon-González et al. 2016) have been effectively achieved using different PEG-salt ATPSs.

5.5.3 Process Integration

ATPSs have enormous potential for process integration. The simultaneous mechanical cell disruption and extraction of intracellular proteins from yeasts has been successfully reported (Rito-Palomares and Lyddiatt 2002; Gurpilhares et al. 2015). Furthermore, extractive fermentation for the production and in situ product recovery can be performed in ATPSs to improve the production yield and reduce both the costs and the operation time. Pullulan production by *A. pullulans* through extractive fermentation in PEG 4000-Dextran 500 ATPS effectively integrated the upstream and downstream processes for continuous production and proved to be environmentally friendly, reliable, and reproducible (Badhwar et al. 2019). The extractive fermentation using a thermo-separating ATPS to obtain polyhydroxyalkanoates from *Cupriavidus necator* contributed to reduce the costs and environmental impact and increase the productivity and purity of the target product (Leong et al. 2019). The scale-up of the extractive fermentation process using a thermo-separating ATPS to a bench-scale bioreactor allowed the increase of the production and recovery yield of *Burkholderia cepacia* lipase (Show et al. 2012). Also, extractive bioconversions using enzymes and whole cells as biocatalysts have been performed in ATPSs. The simultaneous synthesis and recovery of cyclodextrins in PEG 3000-potassium phosphate buffer ATPS using *Bacillus cereus* cyclodextrin glycosyltransferase proved to be a cost- and time-saving technique in repetitive batch process (Lin et al. 2016). The hydrolysis of poly-ε-caprolactone by *B. cepacia* lipase in PEG 3000-potassium phosphate ATPSs was optimized and allowed 80% recovery of hydrolyzed product in the top phase (Chew et al. 2015). Also, lactose was successfully hydrolyzed by β-galactosidase from bacteria, yeast, and fungi in polymer-polymer ATPSs (Chen and Wang 1991). The whole cells of recombinant *E. coli* expressing penicillin acylase were also used as biocatalysts for penicillin G hydrolysis in PEG 6000-potassium phosphate ATPSs allowing the recovery of the target product in the top phase and the reuse of the biocatalyst in ten cycles (Liao et al. 1999).

5.5.4 Aqueous Two-Phase Flotation

This technique combines solvent sublation with aqueous two-phase extraction (Bi et al. 2009). Basically, the surface-active compounds present in an aqueous solution are adsorbed on bubble surfaces of an ascending gas stream and further collected in the top phase of the system. The mass transfer by bubble adsorption is reported as more effective than the mechanical vibration frequently used in conventional liquid-liquid extraction. Aqueous two-phase flotation has been applied for the recovery and concentration of penicillin G from *Penicillium chrysogenum* (Bi et al. 2009), puerarin from *Puerariae* (Bi et al. 2010), baicalin from *Scutellaria baicalensis* Georgi (Bi et al. 2013), proteins from wet microalgae (Phong et al. 2017), betacyanins from peel and flesh of *Hylocereus polyrhizus* (Leong et al. 2018), or lipase

from *B. cepacia* (Sankaran et al. 2018a). Process integration of fermentation and liquid biphasic flotation was also reported and this approach enabled the acceleration of product formation, improved the production yield, and facilitated the downstream processing (Sankaran et al. 2018b). Compared with solvent sublation and liquid-liquid extraction, the combined strategy of aqueous two-phase flotation presented clear advantages in separation efficiency, providing high concentration coefficients and reducing the consumption of organic solvents (Bi et al. 2013).

5.6 Valorization of Agro-industrial Residues Through the Production of Added-Value Compounds: Case Studies

5.6.1 Xylooligosaccharides (XOS)

From an economic and environmental point of view, the use of agro-residues is an attractive approach for the production of bioactive compounds that offer potential health benefits, among other added-value (bio)products (Chapla et al. 2012; Linares-Pastén et al. 2018). As a consequence of the negative impact *of globalization*, the current food processing technologies are leading to a decrease of nutrients and functional properties of food products (Adamberg et al. 2014). Additionally, the people's lifestyles have significantly changed, including their eating behaviors, which in turn are related to their health and morbidity. The high prevalence of diet-related chronic diseases worldwide including diabetes mellitus, cardiovascular disease, stroke, and hypertension (WHO 2017, 2018) has increased the consumer awareness for the prevention of these diseases. In this sense, the consumers have shifted their attention toward healthier food options, even when these are more expensive (Liu et al. 2017b).

Among several bioactive molecules being studied, prebiotics have been the focus of many studies due to their broad range of beneficial effects on human and animal health (Ashwini et al. 2019). The prebiotic definition was recently reviewed by the International Scientific Association for Probiotics and Prebiotics to "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (Gibson et al. 2017), including human and animal hosts. Several mechanisms promoted by the use of prebiotics have been linked to health benefits. The most widely reported phenomenon is the selective fermentation of prebiotics by beneficial gut bacteria, such as bifidobacteria and lactobacilli, which are known producers of short-chain fatty acids, such as acetate, propionate, and butyrate (Gibson and Roberfroid 1995; Hutkins et al. 2016). Added to the selective growth stimulation of beneficial gut microflora, the use of prebiotics has been related with cholesterol lowering, enhanced mineral absorption, immune modulation, pathogen exclusion, glucose homeostasis, anticarcinogenic properties, and antioxidant, among others (Samanta et al. 2015; Gibson et al. 2017). Prebiotics have been employed in a wide range of applications including food and beverage processing, dietary supplements, animal

feed (Mano et al. 2018), and less explored cosmetics applications (Bockmühl et al. 2007). In fact, the increased demand of prebiotics in the past years has been reflected on the significant growth of global prebiotic market which is expected to reach nearly 6.0 billion $ by 2022 (Gaurav 2017). Oligosaccharides are the most widely reported and stabilized type of prebiotics. In particular, inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS) dominate the market (Global Market Insights Inc. 2017). These compounds are classified as established prebiotics in the market (Fig. 5.2), according to the number of commercial applications and regulatory status, while isomaltooligosaccharides (IMO), chitooligosaccharides (COS), and xylooligosaccharides (XOS) are considered as emerging ones.

The development of more cost-effective, simple, and green technology for the production of prebiotics is currently a major concern. At the present, the production strategies that better meet those criteria are enzymatic hydrolysis (including isolated and immobilized enzyme biocatalysis) and the whole-cell fermentation, using abundant and cheap agro-residues as substrates, e.g., cheese whey, molasses, corncob, and orange straw, among others (Fig. 5.2). Besides the direct use as substrates for prebiotics production, these agro-residues have also been widely explored for

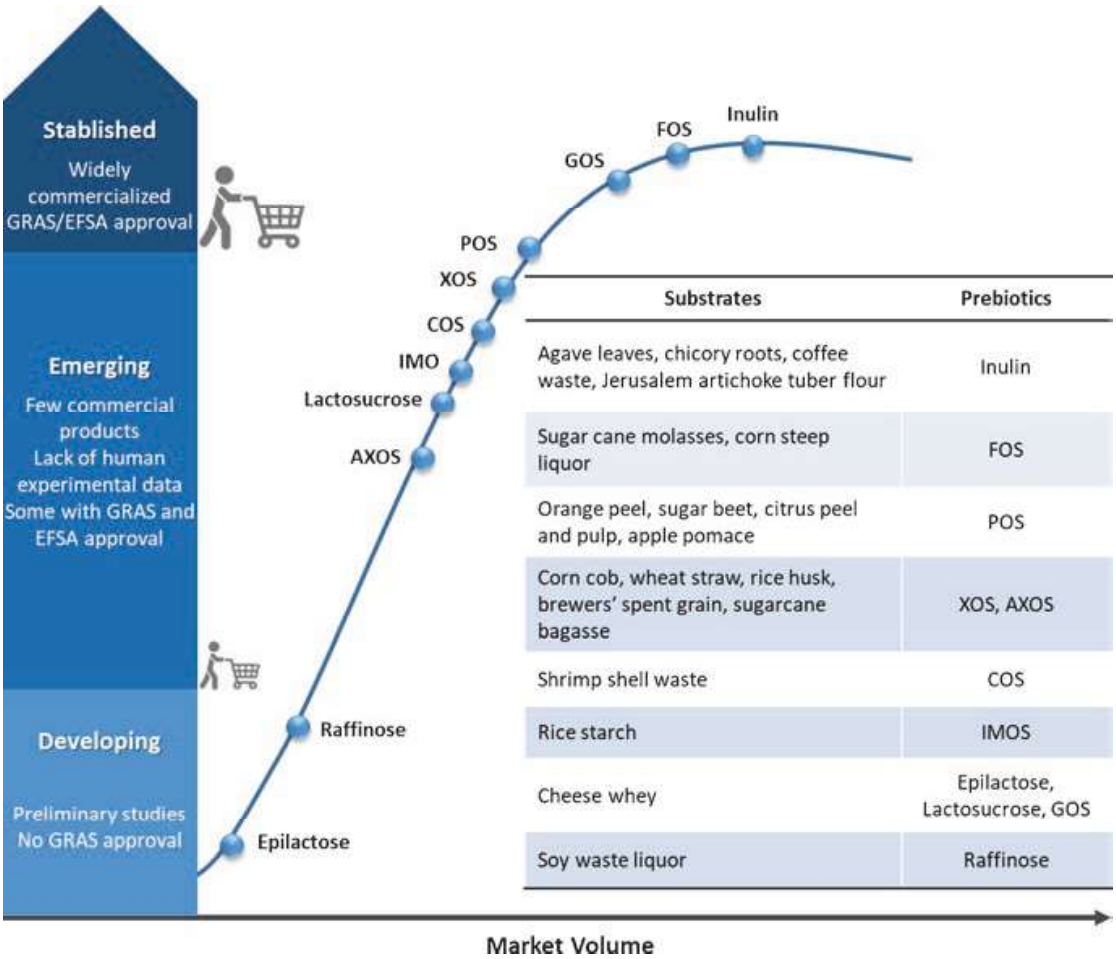

Fig. 5.2 Prebiotics positioning in the market and possible substrates for their production. *Abbreviations*: *AXOS* arabinoxylooligosaccharides, *IMO* isomaltooligosaccharides, *COS* chitooligosaccharides, *XOS* xylooligosaccharides, *POS* pectin oligosaccharides, *GOS* galactooligosaccharides, *FOS* fructooligosaccharides

enzyme production, which in turn are applied on production processes of prebiotics. For instance, sugar molasses and cassava husk, cheese whey, wheat bran, and corncob have been used for the microbial production of β-fructofuranosidase and fructosyltransferase (Babu et al. 2008; Fernandes et al. 2017), ß-galactosidase (Barbosa et al. 1985; Cardoso et al. 2017), and xylanase (Narang et al. 2001; Khanahmadi et al. 2018), which can be further applied on the production of FOS, GOS, and XOS, respectively.

XOS have raised particular interest to both industry and academy, especially because these compounds can be produced from lignocellulosic agro-residues. XOS are oligomers composed of a main chain of xylose residues linked through (β1,4)-linkages, which can present different side elements attached, including acetyl groups, arabinose, and glucuronic acids (Kumar and Satyanarayana 2011). These compounds present a remarkable potential as food ingredients being considered one of the most promising emerging prebiotics. Indeed, XOS stand out due to their price competitiveness, pH and temperature stability, organoleptic properties (Courtin et al. 2009), resistance to digestion (Amorim et al. 2019a), and a broad range of beneficial effects on human and animal health (Aachary et al. 2015) with a lower recommended dose, 2 g/day (Yang et al. 2015), when compared to other prebiotics. Due to the increasing market demand of XOS (The Market Reports 2018), the industry is currently motivated on developing alternative production approaches of XOS, such as the use of agro-residues, in order to reduce costs, while improving efficiency and sustainability. XOS can be obtained from xylan which is the major constituent of hemicelluloses present in the lignocellulosic biomass (Aragon et al. 2013; Samanta et al. 2015). XOS have been produced by different techniques, including chemical, auto-hydrolytic, enzymatic, and fermentation processes or a combination of these techniques (Carvalho et al. 2013; Kumar and Satyanarayana, 2015; Amorim et al. 2018). The XOS production by chemical or auto-hydrolytic processes may encounter several disadvantages, as the production of undesired products, in particular toxic compounds (e.g., furfural and hydroxymethylfurfural), which increases the costs of the downstream process (Bian et al. 2014). Other common limitations are the use of toxic chemicals and more expensive and robust equipment operating at more extreme conditions and low control over the degree of polymerization (DP) (Bian et al. 2014). On the contrary, the enzymatic process is considered a greener approach, being better aligned with the perspective of biosustainability. It does not require the use of harmful chemicals, operates at milder conditions, presents high specificity and efficiency and low production of undesired by-products, and allows a higher control over DP (Akpinar et al. 2007). The enzymatic hydrolysis is currently considered a more efficient and environmentally friendly (Carvalho et al. 2013) for XOS production, especially for food applications. However, the lignocellulosic biomass generally comprises a xylan-lignin matrix structure (Samanta et al. 2012), reducing the xylan accessibility to enzymes. Hence, XOS are mainly obtained by combined methods, usually in a two-step process (Table 5.2). The first step, usually known as pretreatment, includes the pretreatment of the lignocellulosic residue in order to obtain soluble xylan or to reduce the amount of lignin from the residue, followed by the second step of xylan hydrolysis

by xylanases (Carvalho et al. 2013). The limitations of this approach rely on the low yields of the pretreatment step added to the cost of producing or purchasing xylanases, which may compromise the economic viability of the process (Reddy and Krishnan, 2016a).

Recent advances have been done on the development of more integrated production approaches, as the single-step fermentation of lignocellulosic residues by microorganisms and the co-production of XOS and other added-value products (Table 5.2). The single-step fermentation is a promising strategy, in the sense that, by not including the purchase or production of enzymes and by reducing the process stages, it may reduce the production cost and benefit the overall XOS production yield. This approach was successfully applied for the production of AXOS from brewers' spent grain by submerged fermentation (Amorim et al. 2018, 2019b). A mixture composed by a high amount of XOS and low concentration of monosaccharides, mainly xylose, was obtained, since the free sugars in the medium are assimilated by the microorganism before starting the step of XOS degradation. In this context, single-step fermentation also may allow to reduce downstream costs. Furthermore, the authors concluded that the use of single-step fermentation was more advantageous than the application of commercial enzymes. Nevertheless, this approach is fraught with different challenges. Besides the great influence of the type of microorganism and agro-residue used on the economic feasibility of this approach, the cross-reactivity with cellular metabolites, the suboptimal use of cofactors that may be used in other metabolic networks, and the decomposition of substrates and products through competing cellular reactions may contribute to lowering the XOS production yield (Sheldon and Woodley 2018). Reddy and Krishnan (2016b) and da Silva Menezes et al. (2017) applied single-step solid state fermentation to co-produce XOS and xylanase using different agro-residues (Table 5.2). However, the authors reported low yields of XOS, which may be explained by the diversion between the specific optimal process conditions required for XOS and xylanase production, including different optimal fermentation times (Amorim et al. 2019b).

5.6.2 Biopolymers

Polymers constitute a versatile group of compounds that perform essential functions in our society, being their production estimated in more than 180 million tons per year. The application of these compounds includes fields such as food, textile, paper, painting, pharmaceutics, cosmetics, and petroleum industries, among others, where they are used as emulsifiers, stabilizers, or thickening agents (Sharma et al. 2013; Mehta et al. 2014; Wu et al. 2016). For instance, in food industries, polymers enhance the rheology, texture, viscosity, flavor release, appearance, or water control of juices, fruit pulps, chocolates, jellies, desserts, margarine, yoghurts, bakery products, frozen foods, or sauces. In the petroleum industry, they are applied to enhance oil production from oil fields that exhibit low productivities by improving the water-

Table 5.2 Valorization of different agro-residues for xylooligosaccharide (XOS) production and other added-value products using greener bioprocess approaches

Agro-residue	Pretreatment (PTT)	Bioprocess	Biocatalyst	Products	Reference
Areca nut husk	Alkali PTT (two-step process)	EH	*Trichoderma viride* endo-1,4-β-xylanase M1	XOS	Singh et al. (2018)
Brewers' spent grain	No PTT	EH	Commercial xylanase (*Trichoderma longibrachiatum*)		Amorim et al. (2019b)
		SmF	*Trichoderma reesei*		
			Wild-type and recombinant *Bacillus subtilis* 3610		Amorim et al. (2018)
Corncob	Steam explosion with acidic electrolyzed water	EH	*Paenibacillus barengoltzii* (PbXyn10A) xylanase		Liu et al. (2018)
	Ground and prehydrolysis with acetic acid		Commercial cellulase (*Trichoderma reesei*)	XOS, cellobiose, glucose, and xylose	Zhang et al. (2017)
	Ultrahigh-pressure PTT		*Streptomyces thermovulgaris* TISTR1984 xylanase	XOS	Seesuriyachan et al. (2017)
Finger millet seed coat	De-starch and water extraction		Commercial xylanase (*Thermomyces lanuginosus*)		Palaniappan et al. (2017)
Mahogany	Thermal PTT with NaOH		*Clostridium* sp. BOH3 xylanase		Rajagopalan et al. (2017)
Mango					
Quinoa stalks	Alkaline extraction		*Rhodothermus marinus* RmXyn10ACM		Salas-Veizaga et al. (2017)
Reed scraps	Liquid hot water		Commercial xylanase and cellulase	XOS and glucose	Chen et al. (2019a, b)
Rice husk	No PTT	SSF	*Aspergillus brasiliensis*	Xylanase and XOS	da Silva Menezes et al. (2017)

(continued)

Table 5.2 (continued)

Agro-residue	Pretreatment (PTT)	Bioprocess	Biocatalyst	Products	Reference
Rice straw	Milling	EH	Aggregate of magnetic crosslinked xylanase (*Acinetobacter pittii* MASK 25)	XOS	Purohit et al. (2017)
Sugarcane bagasse	Ammonia PTT		β-Xylosidase-free xylanase of *Bacillus subtilis* KCX006		Reddy and Krishnan (2016a)
Wheat bran	Thermal and enzymatic PTT		1,4-β-Xylanase (*Thermomyces lanuginosus*) and *Neocallimastix patriciarum* NpXyn11A		Mathew et al. (2018)
	Sodium acetate buffer washing and alkali extraction		Recombinant *Bacillus amyloliquefaciens* xylanase A		Liu et al. (2017a)
	De-starch		Recombinants xylanase and feruloyl esterase	XOS and ferulic acid	Wu et al. (2017)
Groundnut oil cake and wheat bran	Finely ground	SSF	*Bacillus subtilis* KCX006	XOS and xylanase	Reddy and Krishnan (2016b)
Wheat straw	Alkaline extraction	EH	Recombinant *Bacillus halodurans* S7 endoxylanase	XOS	Faryar et al. (2015)

Abbreviations: *EH* enzymatic hydrolysis, *SmF* submerged fermentation, *SSF* solid state fermentation

flooding performance during tertiary oil recovery operations (Niknezhad et al. 2015; Salah et al. 2015; Couto et al. 2019). Nowadays, the global market is dominated by synthetic polymers (polyacrylamides) and biopolymers extracted from plants (gums, cellulose, pectins, starch) or algae (alginate, carrageenan, agar). Biopolymers of microbial origin exhibit better environmental compatibility and biodegradability than the synthetics, and their production is faster when compared with those obtained from plants (Assis et al. 2014; Ai et al. 2015; Antunes et al. 2017).

Microbial biopolymers display a broad variety of chemical structures, which results in different physicochemical and rheological properties. Furthermore, they usually exhibit high viscosifying activity at low concentration, high solubility, high water retention capacity, stability at extreme temperatures, pHs and salinities, resistance to shear degradation, and compatibility with many polysaccharides and salts. Consequently, they represent a promising alternative for application in several fields (Savvides et al. 2012; Gunasekar et al. 2014; Li et al. 2016a, b). Another advantage of microbial biopolymers is the possibility of producing them from renewable

resources. Furthermore, several microbial biopolymers exhibit distinctive biological activities that are not present in their synthetic counterparts, including antitumor, antimicrobial, antioxidant, or prebiotic activities. Therefore, some of them can be incorporated in high-value products, including functional foods and medical devices (Antunes et al. 2015; Salah et al. 2015; Wu et al. 2016).

Despite all these advantages, the application of microbial biopolymers is limited as a result of the high costs associated to their production. In the recent years, the search for new molecules with improved rheological properties has increased due to the growing demand for new biopolymers; at the same time, cost-effective and more efficient production processes have been developed to make biopolymers more accessible to the industry. Several microbial biopolymers, such as xanthan gum, pullulan, gellan gum, scleroglucan, dextran, or levan, are already commercialized for application in medicine, food industries, cosmetics, and the petroleum industry (Sharma et al. 2013; Li et al. 2016a, b; Couto et al. 2019). Xanthan gum, synthesized by *Xanthomonas campestris* (a Gram-negative bacterium), is the microbial biopolymer with the highest production volume. Due to the extraordinary performance of xanthan gum, it is mainly used in the food industry, but also in the petroleum and textile industries. Its annual worldwide production is around 30 kilotons, corresponding to a market of 360 million €. However, its price (3500–4500 €/ton) is high when compared with the synthetic polymers (Savvides et al. 2012; Salah et al. 2015; Li et al. 2016a, b).

The high production costs of microbial biopolymers are mostly due to the price of the culture media, in particular the carbon sources. Traditional substrates, including sucrose, glucose, or fructose (400–600 €/ton), in which concentration in the culture medium can achieve 200 g/L, can represent up to one-third of the total production costs (Ai et al. 2015; Niknezhad et al. 2015; Li et al. 2016a, b; Antunes et al. 2017). Therefore, the use of alternative inexpensive substrates is crucial to reduce the price of the final product. Accordingly, several wastes and by-products generated by agricultural and industrial processes are being evaluated as low-cost carbon and nitrogen sources for the production of biopolymers by different microorganisms. Some examples are summarized in Table 5.3. Among the different alternative carbon sources stands out molasses, an inexpensive residue (85–150 €/ton) resulting from the extraction of sugar from dates, sugar beet, or sugarcane. Molasses is the residual syrup from the final crystallization stage, from which further crystallization of sugar is uneconomical. This residue is rich in carbohydrates (between 40 and 70% (w/w)), but is also an important source of micronutrients (vitamins, minerals, and organic acids) (Banik et al. 2007; Joshi et al. 2008; Al-Bhary et al. 2013; Ai et al. 2015; Gudiña et al. 2015a). Accordingly, this residue from the sugar industries is commonly used as a suitable alternative source of carbon for the biosynthesis of xanthan gum, gellan gum, and welan gum (Table 5.3). Another important alternative carbon source is raw glycerol, the main by-product from biodiesel production. Each liter of biodiesel results in the production of approximately 0.12 kg of glycerol. It is estimated that the production of this residue (around 15 million m^3 per year) will grow in the upcoming years as a result of a higher production of biodiesel. Raw glycerol contains impurities (e.g., organic compounds, salts), which avoids its use

in food or pharmaceutical-related applications, being a low-cost source of carbon for the biosynthesis of added-value compounds by different microorganisms (de Faria et al. 2011; Sousa et al. 2012; Assis et al. 2014; de França et al. 2015; Cruz et al. 2018). Cheese whey is a residue generated by the dairy industry in large amounts that contains a high concentration of lactose. It represents about 85–95% of the milk's volume and its worldwide production is around 140 million tons per year. Besides lactose, it also contains soluble proteins, minerals, lactic acid, and fats.

The high oxygen demand of this residue makes necessary its treatment before being discharged into the environment (Savvides et al. 2012; Antunes et al. 2015; Niknezhad et al. 2015). CSL is a by-product generated by the corn wet milling industry. This inexpensive (40 €/ton) and abundant liquid residue contains proteins, vitamins, amino acids, and minerals and represents an excellent nitrogen source for the growth of microorganisms in many industrial processes (Sharma et al. 2013; Mehta et al. 2014; Gudiña et al. 2015a, b). The applicability of CSL as a low-cost source of nitrogen for the synthesis of microbial biopolymers has also been demonstrated (Table 5.3).

The use of some of these residues to produce added-value compounds can contribute to reduce the negative impact associated to their disposal into the environment. Some of these residues have been successfully used as substrates to synthesize biopolymers without the need of performing previous pretreatments, which reduces the costs associated to their use (Banik et al. 2007; Sharma et al. 2013; Assis et al. 2014; Antunes et al. 2015, 2017). However, in other cases, specific pretreatments are necessary in order to remove growth inhibitors or to breakdown complex carbohydrates into simple reducing sugars, which increases the overall production costs (Kalogiannis et al. 2003; Göksungur et al. 2011; Savvides et al. 2012; Gunasekar et al. 2014; Ai et al. 2015; Li et al. 2016a, b; Wu et al. 2016). In some cases, even using low-cost carbon sources, it was necessary to add expensive nitrogen sources (e.g., tryptone, yeast extract) to the culture medium, which results in high production costs (Banik et al. 2007; Göksungur et al. 2011; Gunasekar et al. 2014; Niknezhad et al. 2015; Wu et al. 2016). However, in some cases it was possible to design culture media containing residues as sole ingredients (Mehta et al. 2014; Li et al. 2016a, b). The results shown in Table 5.3 demonstrate that the replacement of expensive nutrients by low-cost residues can result in the biosynthesis of high amounts of biopolymer (40–88 g/L). Furthermore, in some cases, that production was achieved in 24 h. The variability observed among the biopolymer productions obtained (Table 5.3) can be due to the different degree of purification achieved in the different works, which is not always reported, and make the comparison among the different studies difficult. Nevertheless, according to several authors, the use of agricultural and industrial wastes as low-cost substrates to produce microbial biopolymers can reduce their production costs between 50 and 75%, making their production processes more cost-effective (Sharma et al. 2013; Mehta et al. 2014; Salah et al. 2015; Wu et al. 2016). However, this can have a negative impact on the properties of the product obtained, or it can be necessary to apply additional downstream purification steeps to obtain a compound with a similar purity to those obtained using synthetic culture media.

Table 5.3 Biopolymer production using different agricultural and industrial by-products and residues as substrates

Biopolymer	Strain	Substrate	[BP] g/L	Productivity (g/L/day)	Reference
Xanthan gum	*Xanthomonas campestris* NCIM 2954	Hydrolyzed tapioca pulp	7.1	2.4	Gunasekar et al. (2014)
	Xanthomonas campestris ATCC 13951	Sugar beet molasses	53.0	53.0	Kalogiannis et al. (2003)
	Xanthomonas campestris NRRL B-1459	Palm date juice	43.3	43.3	Salah et al. (2015)
	Xanthomonas campestris LRELP-1	Kitchen waste hydrolysate	11.7	2.8	Li et al. (2016a, b)
	Xanthomonas campestris 2103	Raw glycerol	5.6	1.1	Assis et al. (2014)
	Xanthomonas campestris ATCC 13951	Cheese whey	28.0	7.0	Savvides et al. (2012)
	Xanthomonas campestris PTCC1473	Cheese whey	16.4	8.2	Niknezhad et al. (2015)
Pullulan	*Aureobasidium pullulans* P56	Hydrolyzed potato starch	19.2	4.1	Göksungur et al. (2011)
	Aureobasidium pullulans CJ001	Hydrolyzed potato starch	36.2	9.0	Wu et al. (2016)
	Aureobasidium pullulans RBF 4A3	Corn steep liquor	88.6	22.1	Sharma et al. (2013)
	Aureobasidium pullulans RBF 4A3	Corn steep liquor + de-oiled Jatropha seed cake + jaggery	66.2	22.1	Mehta et al. (2014)
Welan gum	*Alcaligenes* sp. ATCC 31555	Sugarcane molasses	41.0	8.2	Ai et al. (2015)
Gellan gum	*Sphingomonas paucimobilis* ATCC 31461	Molasses	13.8	6.9	Banik et al. (2007)
FucoPol	*Enterobacter* A47	Cheese whey	6.4	2.0	Antunes et al. (2015)
		Out-of-specification tomato paste	8.7	2.9	Antunes et al. (2017)

[BP] biopolymer concentration

5.6.3 *Biosurfactants*

Surfactants or surface-active compounds are an outstanding class of chemicals that are present in most of the products used in our daily life. These compounds are included in the formulation of cleaning products (e.g., laundry formulations, detergents), paints, pesticides, herbicides, cosmetic products, and pharmaceutical products and are also used in agriculture, paper, textile, food, and petroleum industries, among others (Gudiña et al. 2016; Chen et al. 2018; Cruz et al. 2018). Surfactants are amphiphilic compounds containing at least one hydrophilic and one hydrophobic moiety that accumulate at interfaces between fluid phases with different degrees of polarity (e.g., oil–water, air–water interfaces). Due to their amphiphilic structure, surfactants reduce both surface and interfacial tensions and decrease the repulsive forces that exist between different phases, which makes easier the mixture of immiscible phases. Consequently, surfactants allow the formation of dispersions, emulsions, and foam, being indispensable in applications that require the stabilization of emulsions or foam, lubrication, the solubilization of immiscible compounds, or phase dispersion (Moshtagh et al. 2018; Chen et al. 2019a, b; Pérez-Armendáriz et al. 2019).

More than 15 million tons of surfactants are produced per year, and these figures are expected to increase up to 24 million tons, corresponding to a market of 37300 million € per year by 2020 (Markets and Markets 2015). Currently, the vast majority of surfactants commercialized are chemically synthesized from petrochemical resources and are only partially biodegradable. Due to the ubiquity of surfactants in daily life, questions regarding their environmental impact in the long term constitute a growing concern. Consequently, the demand for eco-friendly and sustainable surfactants has grown in recent years (Sathi-Reddy et al. 2016; Roelants et al. 2019). The market for these environmentally friendly surface-active compounds is projected to grow at a CAGR of 5.5%, from 1600 million € in 2017 to more than 2400 million € by 2024, with consumption exceeding 540 kilotons (Grand Market Insights Research 2018).

Surfactants of biological origin (i.e., biosurfactants) are attracting significant interest as a potential alternative to the synthetic ones in many fields. Among them, microbial biosurfactants (synthesized by bacteria, yeasts, and filamentous fungi) are particularly attractive to replace the chemical surfactants in a wide variety of applications, given their unique properties and the possibility of large-scale sustainable production using renewable substrates. The performance of the microbial biosurfactants is similar or even better comparing with the synthetic ones; their effectiveness is not lost at extreme salinities, temperatures, and pH values; and they exhibit higher biodegradability and lower toxicity comparing with the conventional synthetic surfactants (Cruz et al. 2018; Pérez-Armendáriz et al. 2019; Roelants et al. 2019). According to their chemical structure, microbial biosurfactants can be classified as glycolipids, lipopeptides, phospholipids, fatty acids, and neutral lipids, being glycolipids and lipopeptides the most widely studied (Gudiña et al. 2013; Roelants et al. 2019).

Regarding the lipopeptide biosurfactants, the hydrophobic domain consists in a fatty acid of variable length, whereas the hydrophilic moiety is a peptide ring comprising seven or ten amino acids. Lipopeptide biosurfactants are mainly synthesized by species belonging to the genus *Bacillus*. Among the broad spectrum of lipopeptide biosurfactants identified until now, surfactin, produced by *B. subtilis* strains, is one of the most effective. This lipoheptapeptide reduces the surface tension of water from 72 mN/m to values as low as 26 mN/m; the concentration at which the formation of micelles is initiated (critical micelle concentration, *cmc*) can be as low as 10 mg/L; furthermore, it also exhibits a high emulsifying activity (Al-Wahaibi et al. 2014; Gudiña et al. 2015b; Moshtagh et al. 2018; Chen et al. 2019a, b).

Among the glycolipid biosurfactants, rhamnolipids, synthesized mainly by *Pseudomonas aeruginosa*, are the most studied. Rhamnolipids are classified in mono-rhamnolipids and di-rhamnolipids, according to the number of rhamnose molecules that constitute their hydrophilic domain. The hydrophobic domain consists of two (or more rarely one) β-hydroxy fatty acids; the chain length of those fatty acids varies between 8 and 24 carbons, and they can be saturated or unsaturated. To the date, more than 60 different rhamnolipid congeners have been reported. Different congeners differ in their surface and emulsifying activities, solubilities, and *cmcs*. These glycolipid biosurfactants are usually synthesized as mixtures of different congeners, in which composition depends on the microorganism used and is also affected by the culture medium and other parameters such as the pH and the concentration of oxygen. Rhamnolipids reduce the surface tension to values around 28 mN/m and exhibit high emulsifying activities, and their *cmcs* are between 10 and 200 mg/L (depending on the rhamnolipid congeners) (Abdel-Mawgoud et al. 2008; Gudiña et al. 2015a; Chen et al. 2018).

Besides the properties described above, rhamnolipids and surfactin also exhibit antimicrobial, antifungal, antiviral, and antitumor activities, which are not present in their synthetic counterparts; this contributes to increase their value and their potential applications (Gudiña et al. 2013; Duarte et al. 2014). Despite their outstanding properties, the commercialization of microbial biosurfactants will be only possible if their production costs are reduced to make them competitive with the synthetic surfactants. The main obstacles to achieve this objective are the relatively low amounts of biosurfactants usually produced and the high price of the culture media used. The price of chemical surfactants such as sodium lauryl sulfate is around 1–2 €/kg, whereas the sales price of sophorolipids (a glycolipid biosurfactant), the cheapest and most widely available microbial biosurfactant, is around 30 €/kg. In the case of rhamnolipids (95% purity) and surfactin (98% purity), the current market price is in the range of thousands of euros per gram (Roelants et al. 2019). As a result, a limited number of companies commercialize microbial biosurfactants, usually incorporated in high-value products such as cosmetics. Some examples are Rhamnolipid Companies, AGAE Technologies, TOYOBO, Logos Technologies, Evonik Industries, and KANEKA.

The culture medium contributes significantly (up to 50%) to the total production costs of microbial biosurfactants. The expensive synthetic media commonly used for their production can be replaced by low-cost agricultural and industrial by-

products or wastes in order to make their production economically viable and increase their competitiveness in the market. Furthermore, the valorization of these residues as substrates for the production of added-value compounds reduces the environmental impact caused by their disposal (Al-Bhary et al. 2013; Lan et al. 2015; Gudiña et al. 2016; Ozdal et al. 2017; Chen et al. 2018). As it can be seen in Tables 5.4 and 5.5, several agricultural and industrial residues and by-products have been used to produce surfactin and rhamnolipids by different microorganisms. Most of these residues are the same previously described for the production of biopolymers. In most of the cases, these residues were used as alternative carbon sources, which means that nitrogen sources (organic or inorganic), salts, micronutrients, or other supplements have to be added to the media, increasing the costs of the production process. However, in some cases it was possible to design culture media that contain as sole ingredients agricultural and industrial residues, without the addition of other nutrients (Nitschke and Pastore 2006; Joshi et al. 2008; Gudiña et al. 2015a, 2015b, 2016). In the case of rhamnolipids, a considerable number of residues associated with the extraction or the consumption of different vegetable oils have been used as alternative carbon sources (Table 5.4). These residues contain different long-chain fatty acids that stimulate the biosynthesis of rhamnolipids by *P. aeruginosa* (Gudiña et al. 2016; Samykannu and Achary 2017; Pérez-Armendáriz et al. 2019). Waste cooking oils are generated in large amounts during food preparation and their disposal represents an environmental problem. Therefore, their use as substrates to produce biosurfactants is an environmentally friendly and cost-effective strategy. However, the use of these water-immiscible substrates made difficult the subsequent recovery and purification processes. A particular residue is OMW, an effluent generated during the extraction of olive oil. In the Mediterranean countries, around 30 million m^3 of OMW are generated each year. OMW is rich in long-chain fatty acids, but also contains phenolic compounds, carbohydrates, tannins, pectins, organic acids, and minerals. OMW is a hazardous waste, being toxic for microorganisms, aquatic ecosystems, and plants. Consequently, the bioconversion of OMW into rhamnolipids is an interesting strategy from an environmental and economic point of view. Furthermore, the only cost associated to the use of this residue is the handling and transportation cost (Ramírez et al. 2015; Gudiña et al. 2016). As it can be seen in Table 5.4, high amounts of rhamnolipids (up to 13 g/L) have been produced using different agricultural and industrial residues as substrates.

However, the productivities reported in the different works are difficult to compare, since different methods can be used to quantify the rhamnolipid concentrations. For instance, the use of colorimetric methods can indicate rhamnolipid concentrations up to nine times higher than the real ones (Ramírez et al. 2015). The variability observed in the amount of surfactin produced in the different studies (Table 5.5) is due to the different purification processes applied, which results in products with different purity. The promising future of microbial biosurfactants depends on the exploitation of abundant and inexpensive agricultural and industrial residues together with the improvement of the culture conditions to increase the current production yields.

Table 5.4 Rhamnolipid production by *Pseudomonas aeruginosa* strains using different agricultural and industrial by-products and residues as substrates

Substrate	Strain	[RL] g/L	Time (h)	ST (mN/m)	E_{24} (%)	cmc (mg/L)	Reference
Molasses (1%, v/v)	2B	4.97	96	29	84	100	Aparna et al. (2012)
Sugarcane molasses (10%, w/v) + corn steep liquor (CSL) (10%, v/v)	#112	3.19	96	29	54	30	Gudiña et al. (2015a)
Sugarcane molasses (10%, w/v) + CSL (10%, v/v) + olive oil mill wastewater (25%, v/v)	#112	5.12	168	29	58	13	Gudiña et al. (2016)
Raw glycerol (2%, v/v)	P6	7.54[a]	144	–	–	–	El-Housseiny et al. (2016)
Orange peels (3%, w/v)	MTCC 2297	9.18[a]	192	31	73	–	George and Jayachandran (2009)
Sunflower oil refinery waste	LBI	7.50[a]	72	34	83	120	Benincasa and Accorsini (2008)
Soybean oil refinery waste (2%, w/v)	LBI	11.70[a]	144	26	55	51	Nitschke et al. (2008)
Coconut oil cake (1.5%, w/v) + coconut oil sludge (2%, w/v)	AMB AS7	5.53[a]	60	31	88	50	Samykannu and Achary (2017)
Mango kernel oil (1%, v/v)	DR1	2.80	72	30	73	80	Sathi-Reddy et al. (2016)
Olive oil mill wastewater (10%, w/v)	PAO1	0.19	192	33	–	–	Ramírez et al. (2015)
Waste cooking oil (40 g/L)	SWP-4	13.93[a]	60	24	59	27	Lan et al. (2015)
Waste cooking coconut oil (2%, w/v)	D	3.55[a]	168	24	71	–	George and Jayachandran (2013)
Waste cooking olive/ sunflower (1:1, v/v) oil (40 g/L)	47T2	8.10[a]	96	32	90	108	Haba et al. (2003)
Waste cooking canola oil (3%, v/v)	MK307837	3.58[a]	336	–	–	–	Pérez-Armendáriz et al. (2019)
Kitchen waste oil (2%, w/v)	–	2.47[a]	120	–	58	56	Chen et al. (2018)
Waste cooking oil (5.2%, w/v) + chicken feather peptone (0.9%, w/v)	OG1	13.31[a]	168	–	80	–	Ozdal et al. (2017)

[RL] rhamnolipid concentration, *ST* surface tension, E_{24} emulsifying index, *cmc* critical micelle concentration

[a]Rhamnolipids were quantified as rhamnose equivs alents through colorimetric methods

Table 5.5 Surfactin production by *Bacillus subtilis* strains using different agricultural and industrial by-products and residues as substrates

Substrate	Strain	[Surf] g/L	Time (h)	ST (mN/m)	E_{24} (%)	cmc (mg/L)	Reference
Molasses (16%, v/v)	BS5	1.12	60	25	–	–	Abdel-Mawgoud et al. (2008)
Molasses (5%, w/w)	R1	–	72	29	–	–	Joshi et al. (2008)
Date molasses (8%, w/v)	B20	2.29	24	27	–	–	Al-Bhary et al. (2013)
Date molasses (2%, w/v)	B30	0.30	12	26	50	–	Al-Wahaibi et al. (2014)
Raw glycerol (2%, v/v)	LAMI005	0.44	72	29	–	28	Sousa et al. (2012)
Raw glycerol (2%, v/v)	ICA56	1.29	54	28	90	25	de França et al. (2015)
Raw glycerol (5%, v/v)	LSFM-05	0.93	72	29	67	72	de Faria et al. (2011)
Raw glycerol (5%, v/v)	ATCC 6633	0.79	72	35	38	1500	Cruz et al. (2018)
Potato peels (2%, w/v)	DM-03	2.04	48	34	55	140	Das and Mukherjee (2007)
Cashew apple juice (67%, v/v)	LAMI005	0.32	72	30	67	63	Oliveira et al. (2013)
Corncob hydrolysate (80%, v/v) + feather hydrolysate waste (1%, v/v)	BS-37	0.52	72	–	–	–	Chen et al. (2019a, b)
Brewery wastewater (7%, v/v)	N3-1P	0.66	72	27	63	107	Moshtagh et al. (2018)
Corn steep liquor (10%, v/v)	#573	1.31	48	30	55	30	Gudiña et al. (2015b)
Cassava wastewater	LB5a	3.00	48	26	74	33	Nitschke and Pastore (2006)

[Surf] surfactin concentration, *ST* surface tension, E_{24} emulsifying index, *cmc* critical micelle concentration

5.7 Conclusion

Nowadays, all stakeholders and society in general recognize that it is urgent for the humanity, environment, and progress the study and implementation of alternative strategies for the rational use of resources and zero-waste generation. Among these strategies, the design of new, sustainable, and green biotechnological processes encloses a great promise. The possibility of using microorganisms (single or microbial consortia) and/or enzymes (crude, pure, or mixtures) able to degrade complex

substrates (such as the C5 compounds derived from lignocellulosic residues) to produce added-value products (as the ones herein discussed, functional food ingredients, biopolymers, and biosurfactants, among others) is unique to these strategies. The recent developments of the omics techniques (e.g., metagenomics), gene editing (CRISPR-Cas9), sequencing (speed, costs, and accuracy), metabolic engineering, synthetic biology, and bioinformatics make, in principle, possible to improve and/or create any organism for any given purpose, opening great opportunities under the circular bioeconomy and biorefinery concepts. In addition, new bioreactors and production techniques together with new recovery strategies are expected to greatly contribute to the development of cost-effective and productive processes. Nevertheless, in order to assure a sustainable and rational use of resources (viz., residues from different origins) by these bioprocesses, it is crucial to map and deeply characterize all existing resources, as well as to develop integrated processes that are versatile enough to deal with the resources heterogeneity and availability (related to their sazonality in some cases). Several agricultural, forestry, and industrial residues remain underused and these comprise an extremely interesting alternative to fossil resources and a great opportunity for the development of an innovative bioeconomy.

Acknowledgements C.A. and A.C. acknowledge their grants (UMINHO/BPD/4/2019 and UMINHO/BPD/37/2018, respectively) from Portuguese Foundation for Science and Technology (FCT). The study received financial support from FCT under the scope of the strategic funding of UID/BIO/04469/2013 unit, COMPETE 2020 (POCI-01-0145-FEDER-006684), and the projects FoSynBio (POCI-01-0145-FEDER-029549) and Lignozymes (POCI-01-0145-FEDER-029773). The authors also acknowledge BioTecNorte operation (NORTE-01-0145-FEDER-000004) and the project MultiBiorefinery (POCI-01-0145-FEDER-016403) funded by the European Regional Development Fund under the scope of Norte2020—Programa Operacional Regional do Norte.

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