Microbial cell factories for bio-based biodegradable plastics production

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SUMMARY
The misuse of petroleum-based plastics has resulted in serious environmental pollution and resource wastage. Biodegradable plastics can be used as green substitutes for traditional plastics. Here, we discuss the feasibility and technical bottlenecks in developing microbial cell factories for the production of biodegradable plastics from lignocellulosic wastes. First, we introduce the basic properties of the main biodegradable plastics on the market, including poly(lactic acid), poly(hydroxyalkanoate), and poly(butylene adipate-co-terephthalate). We then demonstrate the feasibility of synthesizing petroleum-based biodegradable plastic monomers from bio-based raw materials and propose strategies to further advance their commercial production through metabolic engineering and synthetic biology. We also analyze the main challenges facing the current development of bio-based biodegradable plastic biosynthesis technology. Finally, we discuss the current major lignocellulose bioconversion processes and explore ways to further improve the utilization efficiency of the main carbohydrates in lignocellulosic hydrolysates by microorganisms, from the perspectives of sugar transport, sugar assimilation, and carbon catabolite inhibition.

INTRODUCTION
Since its invention in the 19th century, plastics have been widely used in all aspects of our lives because of their light weight, durability, and anti-corrosion properties. The annual consumption of plastics per capita has been reported to exceed 140 kg. However, although the large-scale use of plastics is convenient for our lives, it also causes serious environmental pollution. The misuse of plastics generates a large amount of plastic wastes, of which less than 10% can be recycled, and most of which is directly discharged into the natural environment. Traditional plastics are stable in the environment for a long time, and the first plastic sample ever made has not degraded yet. This means that the adverse effects of plastics on the environment remain over the long term. However, some plastics are degraded in the natural environment through physical or chemical processes to form microplastics that can enter animals and even human bodies through food chains. A recent study reveals that microplastic components can indeed be detected in human blood. Therefore, there is an urgent need for safe and environmentally friendly novel materials to replace traditional plastic to solve a series of environmental problems.

Biodegradable plastics are excellent alternatives to conventional plastics, with material properties similar to those of plastics and the ability to be rapidly degraded by microorganisms into CO2, water, or usable compost. However, compared to traditional plastics, the production costs of biodegradable plastics are still relatively high, which limits their further applications. In addition, many biodegradable plastics are petroleum-based ones, which may cause problems such as resource consumption during the production processes. Even the current raw materials for bio-based plastics are mostly derived from food crops, which may occupy valuable agricultural resources. Therefore, the current biodegradable plastics market urgently requires new, low-cost, and sustainable substrates.

Waste-derived lignocellulosic biomass is an alternative to traditional petroleum-based feedstocks. The global annual amount of lignocellulosic biomass obtained from wastes such as straw and wood chips can reach 150 billion tonnes. Lignocellulosic biomass wastes, whether they are directly discharged or incinerated, have adverse effects on the environment. Therefore, recycling of lignocellulosic biomass is a green process. From a cost perspective, waste-derived lignocellulosic biomass is more economical
than the current major bio-based feedstocks and, therefore, has potential advantages in cost control. This substrate is also renewable and does not require additional resources. Production of biodegradable plastics from lignocellulosic biomass is challenging. On the one hand, lignocellulose has a very stable structure and is difficult to be degraded by green and efficient processes. On the other hand, some petroleum-based biodegradable plastics cannot be efficiently synthesized from lignocellulose hydrolysates. However, with the development of metabolic engineering and synthetic biology techniques, exciting breakthroughs have been made in these areas. In recent years, efficient bio-based synthesis processes for several monomers of petroleum-based biodegradable plastics, such as 1,4-butanediol and adipic acid, have been successively established. In addition, the participation of microorganisms makes the degradation process of lignocellulose green and efficient. Therefore, the use of microbial cell factories to produce biodegradable plastics from lignocellulosic biomass represents a promising green plastic approach.

Here, we comprehensively demonstrate the promising prospects of using microbial cell factories to produce degradable plastics from lignocellulose. Through metabolic engineering and a rational design of synthetic biology, microbial cell factories can process lignocellulosic biomass and new green materials, thereby building a circular production system for biodegradable plastics (Figure 1). In this system, energy and carbon are retained to the greatest extent possible, thereby revolutionizing the interaction between humans and nature in the production of plastics. Through a comprehensive review of current bio-based production processes for biodegradable plastics and lignocellulose bioconversion, we profile the essential issues and future development directions in this field.

![Figure 1. Resource recycling economic scheme based on bio-based biodegradable plastics](image)
The microbial cell factory converts agricultural waste-derived lignocellulosic biomass into biodegradable plastics in an environmentally friendly manner. Agricultural wastes are recycled in the form of novel materials. Waste biodegradable plastics are biodegraded into compost to support crops, recycling this carbon back into nature.
PROPERTIES AND APPLICATIONS OF BIODEGRADABLE PLASTICS

Biodegradable plastics are polymeric materials that can be degraded using microorganisms. Under the right conditions, most biodegradable plastics can be completely degraded into carbon dioxide and water in a relatively short period of time, reducing long-term environmental pollution. Therefore, biodegradable plastics are considered green alternatives to traditional plastics. To date, a variety of biodegradable plastics have been discovered or invented, such as poly(lactic acid) (PLA), poly(hydroxyalkanoate) (PHA), and poly(butylene adipate-co-terephthalate) (PBAT) (Figure 2). These polymers, which include both bio-based and petroleum-based plastics, show significant differences in thermal stability, mechanical properties, and degradation rates and have the potentials to replace traditional plastics in different applications (Table 1).

Poly(lactic acid)

PLA is a promising biodegradable plastic that is polymerized from lactic acid monomers. It has mechanical properties similar to those of polystyrene and can be regarded as its green alternative. PLA has good processability and can be processed using various methods such as injection molding, blow molding, and thermoforming. Therefore, it is suitable for packaging materials and containers. At the same time, PLA is also a material with good biocompatibility, and thus, it has important applications in biomedicine. It is worth noting that the lactic acid monomer of PLA is a chiral molecule with 2 configurations: D and L. Based on the chirality of the monomers, PLA can be divided into pure poly(l-lactic acid) (PLLA), pure poly(d-lactic acid) (PDLA), and poly(DL-lactic acid). The chirality of the lactic acid monomer significantly influences the properties of PLA. Studies have shown that mixing PLLA with PDLA can significantly affect the crystallinity and melting point of PLA, thereby broadening the application range of this biodegradable plastic.

Poly(hydroxyalkanoate)

PHA is a class of biosynthesized intracellular polyesters that are natural constituents of many organisms. PHA production is entirely dependent on biosynthesis, the polymer is regarded as one of the
most classic bio-based plastics. To date, more than 150 PHAs polymerized from (R)-hydroxy fatty acids of varying lengths have been discovered. These PHAs can be divided into 3 groups based on the number of carbon atoms in their polymer monomers. PHAs with 3–5 monomeric carbon atoms are called short-chain-length PHAs (SCL PHAs). PHAs with 6–14 and over 14 monomeric carbon atoms are referred to as medium-chain-length PHAs and long-chain-length PHAs, respectively. Currently, the mainstream PHAs on the market are SCL PHAs, including the most well-known poly(β-hydroxybutyrate) (PHB) and poly(hydroxybutyrate-co-valerate) (PHBV). PHB is the earliest discovered PHA, which has good biodegradability and biocompatibility but poor mechanical properties. To enhance the application value of PHA, PHBV was subsequently developed with lower crystallinity, higher tensile strength, and greater toughness. However, the mechanical properties of PHBV still lag behind those of traditional plastics, which limits the application range of this polymer. Compared with SCL PHAs with poor toughness, PHAs with longer carbon chains generally have better mechanical properties but are more difficult to synthesize. Owing to their good biocompatibility, PHAs have many applications in biomedicine. In addition, PHAs can be used to produce biodegradable agricultural mulches.

### Poly(butylene adipate-co-terephthalate)

PBAT is an aliphatic polyester compound that is polymerized from 1,4-butanediol, adipic acid, and terephthalic acid. Owing to its excellent mechanical properties, similar to those of low-density polyethylene, PBAT has gradually become one of the best biodegradable plastics in the market. Toughness is an advantage of PBAT; its percentage of breaking elongation can reach 700%, and its tensile strength is also high. However, the poor thermal performance of PBAT and the high production cost limit the wide application of this material. At present, the application of plastic PBAT is concentrated in the fields of biomedicine, agriculture, and food, and it can be used to make agricultural mulch and food packaging bags. With the development of low-cost and efficient bio-based synthesis processes, the production cost of PBAT is expected to be further reduced, thereby further enhancing its market competitiveness compared to traditional plastics.

### BIO-BASED PRODUCTION FOR BIODEGRADABLE PLASTICS AND THEIR MONOMERS

Establishing efficient biosynthetic pathways is the core technology for developing microbial cell factories for biodegradable plastics. Except for PHAs, both PLA and PBAT require the synthesis of monomers and polymerization by other methods; however, techniques for directly synthesizing PLA have recently been developed. Lactic acid, adipic acid, 1,4-butanediol, and terephthalic acid are the main compounds involved in the polymerization of these biodegradable plastics. The ease of synthesizing these compounds by microorganisms and the degree of development of the corresponding biosynthetic technologies vary, as do the major challenges in their synthesis. Here, we divide the development of bio-based synthesis technologies for compounds into 5 stages (Figure 3). The compounds in the first stage cannot be synthesized from carbohydrate substrates by microbial fermentation and can only be produced by petroleum-based synthetic processes. In the second stage, compounds have relatively effective biosynthesis pathways

| Plastic | Mechanical property | Thermal stability | Commercial production process | Future perspective |
|---------|---------------------|-------------------|------------------------------|-------------------|
| PLA     | High tensile strength, low toughness | Moderate, better thermal stability of PLLA mixed with PDLA | Bio-based production of lactic acid and polymerization by chemical methods | Direct bio-based production of PLA, commercial production of PLA from lignocellulosic wastes |
| PHA     | Relatively poor mechanical property of PHB, better mechanical properties of PHAs with longer carbon chains | Overall low, various thermal stabilities of PHA with different carbon chain lengths | Direct bio-based production of PHAs | Commercial production of PHAs with longer carbon chains, commercial production of PHAs from lignocellulosic wastes |
| PBAT    | Moderate tensile strength, high toughness | Relatively low | Petroleum-based production of adipic acid, 1,4-butanediol, and terephthalic acid and polymerization by chemical methods | Commercial bio-based production of adipic acid and terephthalic acid |

PLA, poly(lactic acid); PHA, poly(hydroxyalkanoate); PBAT, poly(butylene adipate-co-terephthalate); PLLA, poly(L-lactic acid); PDLA, poly(D-lactic acid).
and production processes, but parameters such as the final titer, yield, productivity, and raw material costs have not yet reached commercial standards. For compounds in the third stage, commercial production has been successfully achieved; however, efficient production processes using lignocellulosic wastes as substrates have not yet been established. With improvements in the lignocellulose fermentation process, the compound is in the fourth stage, which can support the fermentation process using this renewable and cheap biomass as a substrate; however, this production process is not yet ready for real industrial applications. When the compound is in the fifth stage, the processes of producing biodegradable plastics from lignocellulosic wastes become fully mature and can enter the market to replace the traditional production mode.

The main problems faced by compounds at different stages are different; therefore, the technical means required to complete industrial upgrading are also different. For first-stage compounds, bioinformatics-based pathway-prediction algorithms as well as metabolomics-based metabolic network reconstruction may be helpful for the development of new biosynthetic pathways. In addition, high-throughput mining and directed evolution of key enzymes also facilitate the development of new biosynthetic pathways for the production of such compounds. For second-stage compounds, with systems metabolic engineering, improving the carbon metabolism flux of the synthetic pathway, providing sufficient cofactors and ATP, and enhancing the synthesis and secretion pathways of the products may promote their commercial production. For third-stage compounds, efficient utilization of xylose, co-utilization of mixed carbon sources, and tolerance to lignocellulosic hydrolysates are the core issues. For fourth-stage compounds, further improvement of the lignocellulose fermentation process through fermentation engineering and coupling of the microbe-mediated lignocellulose degradation process is key to commercialization. Terephthalic acid is currently in the first stage. Adipic acid, PLA, and most PHAs are in the second stage.
1,4-Butanediol, PHBV, and poly(3-hydroxybutyrate-co-4-hydroxybutyrate) (P34HB) are in the third stage. Lactic acid and PHB are in the fourth stage. No compound has yet reached the fifth stage, which means that efficient lignocellulosic biomass conversion processes need to be urgently developed.

**PLA and lactic acid**

Lactic acid, the monomer of PLA, is an organic acid that exists widely in nature and can be naturally synthesized by a large number of microorganisms. The pyruvate reduction reaction catalyzed by lactic acid dehydrogenase is the main pathway for lactic acid synthesis, and the configuration of lactic acid is completely determined by the enzyme (Figure 5). Various lactic acid bacteria that can efficiently produce L-lactic acid and D-lactic acid have been screened from nature, including *Bacillus coagulans*, *Sporolactobacillus inulinus*, *Sporolactobacillus terrae*, and *Lactobacillus delbrueckii*, which are widely used in the commercial production of lactic acid. In addition, lactic acid has also been efficiently synthesized from a variety of lignocellulosic biomasses, with final titers exceeding 100 g/L (Table 2). Therefore, the lactic acid production from lignocellulosic wastes holds great promise.

The production of lactic acid is accompanied by a decrease in pH value. Therefore, there are multiple economic and environmental advantages to developing a lactic-acid-production process at a low pH value or even without adding neutralizers. Presently, acid-tolerant *Saccharomyces cerevisiae* has been successfully transformed into an efficient lactic acid producer, which has certain application prospects. Knockout of the by-product synthesis pathway, knockout of the lactic acid utilization pathway, enhancement of the...
glycolysis pathway, and overexpression of heterologous lactate dehydrogenase are common strategies for transforming S. cerevisiae into lactic acid producers with remarkable results. However, because of the impact of lactic acid on the growth of microorganisms, the current low-pH lactic-acid-production process is less efficient than the traditional lactic-acid-production process in many aspects such as final concentration, conversion rate, and fermentation cost. The accumulation of lactic acid causes intracellular acidification and brings about many negative effects, including ATP consumption, reactive oxygen species (ROS) accumulation, membrane perturbation, and dysregulation of some metabolic pathways. Microbial cells usually respond to these adverse effects through the export of lactic acid and global regulation of cellular metabolic networks, and several studies have been successful in improving lactic acid tolerance in S. cerevisiae. With increasing research on the mechanism of lactic acid tolerance, the lactic acid production is expected to be further improved.

PLA polymers can also be produced directly from microbial cells via a pathway similar to that of PHAs (Figure 5). Using the evolved propionyl-CoA transferase and PHA synthase, lactic acid in microbial cells is first converted to lactyl-CoA and then polymerized to PLA, thereby circumventing the complex and expensive chemical polymerization of lactic acid. However, limited by the substrate specificity of propionyl-CoA transferase and PHA synthase, the yield of PLA per dry cell weight is much lower than that of PHB, which greatly increases production costs. At present, 1-step production of PLA by microbial cells is far from meeting the needs of industrial production, but these problems may be solved by enzyme engineering and synthetic biology.
Directed evolution of enzymes is expected to enhance the specificity of propionyl-CoA transferase and PHA synthase for lactic acid and lactyl-CoA, thereby improving the PLA production. However, some complex synthetic bio-regulatory elements can also be applied in the biosynthesis of PLA to adjust the ratio of D- and L-type monomers and improve the mechanical properties of the polymer products.

Poly(hydroxyalkanoate)

PHA is a family of natural polyesters accumulated by many microorganisms as storage units of energy and carbon sources. PHB is the most-studied PHA family member due to its effective synthesis from sugar-derived metabolite acetyl-CoA (Figure 5). The supply of metabolic flux toward acetyl-CoA is, thus, of most importance for the PHB synthesis. Fermentation under oxygen-limiting conditions can reduce the loss of acetyl-CoA via the tricarboxylic acid cycle (TCA cycle), resulting in a significant increase in the PHB production. In addition, manipulating the division pattern and morphology of microbial cells also demonstrates promising improvement for the PHB accumulation with fast cell growth and an enlarged cell volume. A recent study has also developed the self-flocculation fermentation process to address simplified separation of PHB-enriched cells. Currently, PHB has been successfully produced as a commercial product. Moreover, more efforts have been made to demonstrate the potential of the cost-effective PHB production from lignocellulosic wastes (Table 2). However, the low production titer and yield of PHB from lignocellulosic biomass still remain a challenge. In addition, the brittle nature of PHB also limits its commercial use in various areas. Therefore, the synthesis of PHAs with applicable mechanical properties for diverse applications has generated extensive attention.

The incorporation of 3-hydroxyvaleric acid (3HV) units into PHB, which forms a PHBV random co-polymer consisting of 3-hydroxybutyrate (3HB) and 3HV, can significantly improve the flexibility with improved tensile strength and elongation at break. Particularly, the synthesis of PHBV can be achieved by recombinant microbes using glucose as a sole carbon source and mixed carbon sources containing glucose and propionic acid (Figure 5). In addition, co-polymers that consist of 3HB and 4-hydroxybutyrate (4HB), namely P34HB, and a 3-hydroxypropionate unit, namely poly(3-hydroxybutyrate-co-3-hydroxypropionate), have also been efficiently synthesized from glucose (Figure 5). More importantly, the hyperproduction of P34HB has been achieved by recombinant Halomonas spp. grown on glucose and structure-related carbon sources, including gamma-butyrolactone and 1,4-butanediol. Notably, a low-cost PHA-manufacturing industrial platform, termed “next-generation industrial biotechnology,” has been developed successfully.

Table 2. Processes for biodegradable plastics from lignocellulose biomass

| Method | Substrate | Strain | Titer | Yield | Reference |
|--------|-----------|--------|-------|-------|-----------|
| Lactic acid | | | | | |
| SHF | Banana peduncles hydrolysate | Bacillus coagulans | 26.6 g/L | 0.90 g/g | Azaizeh et al. 126 |
| SHF | Sugarcane hydrolysate | Bacillus coagulans | 46.5 g/L | 0.88 g/g | Azaizeh et al. 126 |
| SHF | Carob hydrolysate | Bacillus coagulans | 51.4 g/L | 0.83 g/g | Azaizeh et al. 126 |
| SSF | Corn stover | Pediococcus acidilactici | 139.0 g/L | N/A | Han et al. 127 |
| SSF | Corn cob residue | Bacillus coagulans | 79.1 g/L | 0.76 g/g | Jiang et al. 39 |
| SSF | Beech wood | Lactobacillus delbrueckii subsp. bulgaricus | 62 g/L | 0.69 g/g | Karnouri et al. 128 |
| CBP | Beech wood | Lactobacillus pentosus | 19.8 g/L | 0.85 g/g | Shahab et al. 11 |
| PHB | | | | | |
| SHF | Hardwood hydrolysate | Paraburkholderia sacchari | 34.5 g/L | 0.15 g/g | Dietrich et al. 50 |
| SHF | Mixed substrate containing straw cellulose extract liquid | Halomonas campaniensis | ~49.0 g/L | N/A | Yue et al. 129 |
| SHF | Wheat straw hydrolysate | Corynebacterium glutamicum | 16.2 g/L | 0.13 g/g | Jin et al. 130 |
| SHF | Corn stover hydrolysate | Cupriavidus necator | 2.1 g/L | N/A | Li et al. 131 |
| SSF | Waste office paper | Cupriavidus necator | 4.2 g/L | N/A | Al-Battashi et al. 132 |

CBP, consolidated bioprocessing; PHB, poly(β-hydroxybutyrate); SHF, separate hydrolysis and fermentation; SSF, simultaneous saccharification and fermentation.
both in the lab and in pilot scale using 5-m$^3$ and 20-m$^3$ bioreactors, respectively. Additionally, a synthesis platform of versatile PHA co-polymers with short-, medium-, and long-chain length co-monomers, which exhibit better mechanical properties than PHB with promising applications, has been constructed based on beta-oxidation-defected *Pseudomonas* spp.

**Adipic acid**

Adipic acid is an important dicarboxylic acid and a monomer of PBAT. The production of adipic acid via microbial fermentation is challenging. The reverse adipate-degradation pathway is currently the most important adipic acid biosynthesis pathway (Figure 4) and has been successfully applied in *Escherichia coli*,* Corynebacterium glutamicum*, and *S. cerevisiae*. However, the process of adipic acid production from glucose is underperforming, with very low yields and final titers. The most successful adipic acid biosynthesis process reported thus far was completed by Zhao et al. using a heterologous reverse adipate-degradation pathway derived from *Thermobifida fusca* to produce adipic acid with a final titer of up to 68 g/L from glycerol. Overexpression of the key rate-limiting enzyme Tfu_1647 has been shown to be very important for the efficient production of adipic acid. Strategies such as elimination of by-product pathways and succinyl-CoA consumption pathways have also been used to improve adipic acid production. Based on this work, Zhou et al. relieved the dependence of adipic acid production on inducers by replacing the promoter, thus reducing production costs.

Glycerol is not an ideal renewable substrate, and glucose can be obtained from lignocellulose hydrolysates, making adipic acid production from glucose attractive. Compared with glucose, glycerol provides more reducing power. Zhao et al. reported that adipic acid fermentation performs better under low-dissolved-oxygen conditions. The TCA cycle is usually preferred by microorganisms under aerobic conditions, whereas it is reversed to reductive TCA pathway under oxygen-limited conditions. Therefore, succinyl-CoA may be primarily synthesized via the reductive TCA pathway, leading to better adipic acid production under oxygen-limited conditions. Synthesis of succinyl-CoA via the reductive TCA pathway prevents carbon loss in the form of CO$_2$ at the expense of reducing power. The reducing power provided by glycerol can support cells to synthesize adipic acid through the reduced TCA pathway, but when glucose is used as a substrate, there is insufficient reducing power, which may be responsible for the inefficient production of adipic acid from glucose. Solving the problem of a small supply of reducing power is the key to the development of the adipic acid biosynthesis technology, which may be solved by the efficient synthesis of cofactors from sources such as the pentose phosphate pathway.

Glycerol provides more reducing power. Therefore, succinyl-CoA may be primarily synthesized via the reductive TCA pathway, leading to better adipic acid production under oxygen-limited conditions. Thus, adipic acid production from glycerol is more efficient than from glucose. Solving the problem of a small supply of reducing power is the key to the development of the adipic acid biosynthesis technology, which may be solved by the efficient synthesis of cofactors from sources such as the pentose phosphate pathway.

Recent studies have achieved better results by enhancing the activities of key enzymes in the adipic acid synthesis pathway, such as 5-carboxy-2-pentenoyl-CoA reductase and adipyl-CoA synthetase. Improving the activities of key enzymes through directed evolution may also be a way to upgrade the adipic acid biosynthesis technology. The accumulation of adipic acid causes intracellular acidification and brings about many negative effects similar to lactic acid. In addition, adipic acid itself affects the growth of many microorganisms without lowering the pH value, which may be another challenge to be overcome to achieve high adipic acid production. In addition, there is currently no effective process for producing adipic acid from xylose in lignocellulose hydrolysates, which is another development direction for adipic acid biosynthesis.

**1,4-Butanediol**

1,4-Butanediol is a synthetic monomer used for PBAT. Although no microorganisms that can naturally produce 1,4-butanol have been found, several biosynthetic pathways of this compound have been developed with metabolic engineering technology. In 2011, Genomatica reported a 1,4-butanol synthesis pathway using α-ketoglutarate or succinyl-CoA in the TCA cycle as a precursor, which is currently the most efficient pathway (Figure 4). The biosynthetic pathway predicted by the SimPheny Biopathway Predictor software supported the production of 18 g/L of 1,4-butanol from glucose in *E. coli*. The final titer and yield of 1,4-butanol increased to 125 g/L and 0.40 g/g, respectively, in subsequent years through strategies such as limiting TCA circulating flux, eliminating by-product pathways, and directed evolution to increase the activity of key enzymes. This production process has been successfully commercialized, but its theoretical yield is only 0.5 g/g, which significantly increases the production costs. Two molecules of CO$_2$ are produced for every molecule of 1,4-butanol synthesized via this pathway, which is the main reason for the low theoretical yield. The synthesis of succinyl-CoA via the reductive TCA pathway can circumvent carbon loss but cannot provide sufficient reducing power. The bio-based production of succinic acid...
acid requires the introduction of CO₂. Therefore, the CO₂ generated during the production of 1,4-butanediol can be recycled by coupling the succinic acid production process. 1,4-Butanediol has low toxicity to microbial cells, and 6% 1,4-butanediol has a significant effect on the growth of E. coli. In addition, the hydroxypyruvate-CoA transferase Cat2 in the 1,4-butanediol biosynthesis pathway is inhibited by high concentrations of 1,4-butanediol, thereby limiting the conversion of 4HB to 1,4-butanediol. The production of 1,4-butanediol was successfully improved by using the 1,4-butanediol-tolerant Cat2 variant, suggesting that it is important to enhance the 1,4-butanediol tolerance.

Although the production of 1,4-butanediol from glucose has been successful, the current production of 1,4-butanediol from xylose is relatively low. In 2016, Tai et al. reported a synthetic pathway based on a non-phosphorylative metabolism that utilizes xylose to produce 1,4-butanediol (Figure 4). Through this pathway, E. coli produced 12 g/L of 1,4-butanediol using a mixed carbon source of glucose and xylose, and the yield of 1,4-butanediol from xylose was 0.26 g/g. The synthesis of 1,4-butanediol by the non-phosphorylative metabolism pathway also results in carbon loss, resulting in a theoretical yield of only 0.6 g/g. In addition, the non-phosphorylative metabolism pathway consumes reducing power and requires other pathways to synthesize nicotinamide adenine dinucleotide (NADH). The main components of lignocellulosic hydrolysates are glucose and xylose; therefore, combining the two pathways mentioned earlier may help develop a fermentation process for the production of 1,4-butanediol from lignocellulosic biomass. However, NADH supply and carbon loss remain core issues that limit the production costs.

**Terephthalic acid**

Terephthalic acid is a PBAT monomer. As a traditional petroleum-based compound, terephthalic acid is difficult to synthesize directly from bio-based carbohydrate substrates, which is a key bottleneck limiting the bio-based production of PBAT. The precursor of terephthalic acid, p-xylene, can be produced from biomass by fermentation, whereas the conversion of p-xylene to terephthalic acid can be achieved by engineered E. coli. Other studies have reported the direct chemical production of terephthalic acid from lignin and its derivatives. However, these methods have multiple problems such as low efficiency and high costs. Currently, although the conversion of isobutanol to p-xylene is achieved by chemical methods, the production of isobutanol from glucose and the conversion of p-xylene to terephthalic acid can be achieved by biosynthetic methods. Therefore, finding an enzyme that can catalyze the conversion of isobutanol to p-xylene is the key to realizing the total biosynthesis of terephthalic acid.

**DEVELOPMENT OF A COST-EFFECTIVE LIGNOCELLULOSE BIOCONVERSION PROCESS**

Lignocellulosic biomass is a renewable resource widely distributed in nature. Every year, a large number of lignocellulosic wastes are produced worldwide, including agricultural and forest wastes. The production of biodegradable plastics from these wastes has the potential to reduce the cost of raw materials and eliminate the environmental pollution associated with the disposal of these wastes. Lignocellulose has a very stable structure, consisting of cellulose, hemicellulose, and lignin, of which 60%–90% by weight are cellulose and hemicellulose. In general, lignocellulose biomass needs to undergo a 2-step process of pretreatment and saccharification to obtain hydrolysates whose main components are monosaccharides. Pretreatment is a key step in the degradation of lignocellulose that releases cellulose and hemicellulose from its stable structure. Chemical pretreatment methods are the most commonly used lignocellulose pretreatment techniques, including acid or alkali pretreatment. Such pretreatment methods are highly efficient, but consume additional energy and have potential environmental pollution risks. Pretreated lignocellulose also needs to be converted into soluble monosaccharides through a saccharification process, which is usually enzymatic hydrolysis. Cellulases and hemicellulases produced by microorganisms play key roles in the saccharification process. Cellulase includes endoglucanase, cellobiohydrolase, and β-glucosidase. Hemicellulase includes glycoside hydrolase and sugar esterase.

Pretreatment is an important process to destroy the highly ordered structure of lignocellulosic biomass. However, the pretreatment process produces inhibitors such as organic acids, furans, and phenols. These inhibitors not only affect the subsequent enzymatic hydrolysis process but also affect microbial growth and product biosynthesis. Therefore, cellulases, hemicellulases, and microbial cells need to be able to tolerate these inhibitors. Formic acid and acetic acid are the main organic acid inhibitors. Improving the tolerance of microorganisms to formic acid and acetic acid is mainly achieved through the engineering of transporters and regulators. Hydroxymethylfurfural and furfural-converting reductases are important targets for improving tolerance toward furans. These inhibitors are diverse and generally have complex
effects on microbial cells; therefore, it is very difficult to construct a common microbial chassis into super microbes that can tolerate all these inhibitors. In contrast, screening for strains with superior tolerance to multiple inhibitors is attractive.

Lignocellulosic hydrolysates are rich in glucose and xylose and can be used to produce biodegradable plastics and their monomers (Table 2). However, this process is cumbersome and requires the collaborative participation of multiple factories responsible for pretreatment, degrading enzyme preparation, saccharification, and product synthesis, which significantly increase the production costs. At the same time, the use of chemical pretreatment methods increases environmental pollution and energy consumption, thus greatly reducing the advantages of lignocellulosic substrates. Therefore, in some studies, integration of the multiple steps in separate hydrolysis and fermentation (SHF) has been attempted, which successively established simultaneous saccharification and fermentation (SSF) and consolidated bioprocessing (CBP) (Figure 6). Among them, CBP not only integrates the pretreatment, saccharification, and product synthesis steps but also replaces the chemical pretreatment method with an environmentally friendly microbial pretreatment method to fully exploit the advantages of lignocellulose.

**Figure 6. Production models of 3 lignocellulose bioconversion processes**

SHF contains 4 steps of pretreatment, enzyme preparation, saccharification, and fermentation. SSF integrates saccharification and fermentation, while CBP integrates all 4 steps in 1 bioreactor. CBP, consolidated bioprocessing; SHF, separate hydrolysis and fermentation; SSF, simultaneous saccharification and fermentation.

Separate hydrolysis and fermentation

The microbial fermentation process that directly uses lignocellulose hydrolysates as substrates is called SHF. Stability and efficiency are the main advantages of SHF because all steps of the separation can be conducted under optimal conditions. SHF has minimal requirements for microbial strains, namely, the ability to efficiently produce target compounds from mixtures of monosaccharides. However, the continuous accumulation of sugar substrates during isolated saccharification can inhibit the activities of cellulase and hemicellulase, thereby reducing hydrolysis efficiency and leading to incomplete hydrolysis of lignocellulose. This inhibitory effect is an important bottleneck for SHF as it limits the production of lactic acid, succinic acid, and PHB (Table 2).
Simultaneous saccharification and fermentation

SSF integrates saccharification and microbial fermentation processes, reduces equipment costs, and simplifies the process. More importantly, monosaccharides obtained by hydrolysis can be directly utilized by microorganisms, thereby avoiding the inhibition of hydrolase activity. Efficient production of lactic and succinic acids can be achieved by SSF, demonstrating the effectiveness of this improved process (Table 2). However, SSF has higher requirements for microbial strains and needs to adapt to the catalytic conditions of cellulase and hemicellulase. The optimum temperature for cellulase and hemicellulase is usually above 50°C, and thus, microorganisms with higher optimum growth temperatures are more suitable for SSF. This high-temperature fermentation also provides the additional advantages of resistance to bacterial contamination, lower heat-exchange costs, and possibility of improving reaction efficiency. Many lactic-acid-producing strains, such as *B. coagulans* and *Bacillus licheniformis*, are able to grow above 50°C, thus enabling the efficient production of lactic acid by SSF. However, SSF does not fully utilize the advantages of microbial resources. It relies on chemical pretreatment methods and isolated saccharification enzymes during the production process, which is not an ideal lignocellulosic biomass bioconversion technology.

Consolidated bioprocessing

Microbial resources are treasure troves of nature and have strong potentials for efficient conversion of lignocellulosic biomass. Scientists have identified the microbial communities responsible for lignocellulose degradation in lignocellulose-rich forest soils, and lignocellulose-degrading microorganisms can also be found in the gut microbiomes of herbivores or wood-eating insects. The direct utilization of biomass via microorganisms has multiple advantages, such as reducing the environmental pollution caused by chemical pretreatment and enhancing the utilization efficiency of substrates. CBP takes full advantage of the ability of microbial cells to degrade lignocellulose and integrates almost all the steps of lignocellulose conversion with microbial fermentation. This process can directly convert milled lignocellulosic biomass into target compounds and may represent the ultimate form of lignocellulosic processing. At present, this strategy has been applied to both lactic acid and succinic acid fermentation and shows the potential to establish a platform for short-chain fatty acid synthesis. However, none of these studies addressed the inefficiency of CBP: Yields and titers of the target products are low. This has led to certain questions regarding the economic viability of CBP. However, a recent study achieved efficient dicarboxylic acid fermentation through CBP, where crushed corncob was directly converted into 110 g/L of C4-diacyds, including 105 g/L of malic acid and 5.4 g/L of succinic acid. The efficient lignocellulose-degrading strain *Myceliophthora thermophila* was used as a chassis cell for metabolic engineering and exhibited excellent lignocellulose fermentation performance after rational metabolic reprogramming. This result suggests that the ability of microorganisms to degrade lignocellulose is less easily conferred than that of the product-synthesis pathway. Therefore, screening for microbial chassis with excellent lignocellulose degradation abilities, growth performance with high temperatures, and ability to support efficient genetic modification is key to improve the CBP process.

IMPROVEMENT IN CO-UTILIZATION OF PENTOSE AND HEXOSE

The major constituents of lignocellulose hydrolysates are readily available carbohydrates of pentose and hexose, including glucose, xylose, and arabinose. These carbohydrates can be transported into microbial cells by sugar transporters and subsequently assimilated into intracellular components via carbon metabolic pathways. To construct a microbial cell factory that can perform efficient lignocellulose bioconversion, it is necessary to maximize the utilization efficiency of pentose and hexose by the microorganisms. On the other hand, the vast majority of microorganisms have a carbon catabolite repression (CCR) response when utilizing mixed sugars, which limits the utilization efficiency of microorganisms to nonglucose carbon sources and is also a key factor limiting lignocellulose bioconversion.

Utilization of hexose

Hexose (glucose) is the dominant component of lignocellulosic biomass hydrolysates, and glucose is the preferred carbon source for most microorganisms. The Embden-Meyerhof-Parnas (EMP) glycolysis pathway is the most important glucose assimilation pathway. After 9 reaction steps, 1 molecule of glucose is converted into 2 molecules of pyruvate, and 2 molecules of ATP and 2 molecules of NADH are simultaneously generated (Figure 7). The utilization efficiency of glucose can be significantly improved by enhancing the expression of enzymes in the EMP pathway, such as glyceraldehyde-3-phosphate
dehydrogenase, phosphofructokinase, and pyruvate kinase, thereby increasing the yield of microbial fermentation. In addition, glucose can be utilized by microbial cells through the pentose phosphate pathway or the Entner-Doudoroff (ED) pathway (Figure 7). The pentose phosphate pathway is an efficient way to generate nicotinamide adenine dinucleotide phosphate (NADPH), which can synthesize 2 such molecules at the expense of 1 carbon molecule. By coupling with glucose-6-phosphate isomerase, the pentose phosphate pathway completely converts 1 molecule of glucose into 6 molecules of CO2 while generating 12 molecules of NADPH. Therefore, it can be applied in the synthesis of products with a higher degree of reduction and can be used to provide additional reducing power. The ED pathway is widely distributed in Gram-negative bacteria. Compared with the EMP pathway, the ED pathway converts glucose into pyruvate and glyceraldehyde-3-phosphate through only 4 reaction steps and can synthesize 1 molecule of NADPH instead of NADH. The ED pathway is widely distributed in Gram-negative bacteria. Compared with the EMP pathway, the ED pathway converts glucose into pyruvate and glyceraldehyde-3-phosphate through only 4 reaction steps and can synthesize 1 molecule of NADPH instead of NADH. However, the energy-production efficiency of the ED pathway is lower than that of the EMP pathway, and glyceraldehyde-3-phosphate must be coupled with the EMP pathway for conversion to pyruvate. Taking advantage of its shorter reaction path, in a recent study, the ED pathway was integrated into lactate-producing strains, and the production of L- and D-lactic acid was successfully improved.

In addition to the intracellular glucose-assimilation pathway, glucose transport is an important factor limiting the efficiency of glucose utilization. In bacteria, the transport of glucose occurs mainly through the phosphotransferase system (PTS), which is composed of the phosphohistidine carrier protein (HP) and enzyme I in the cytoplasm and carbohydrate-specific EII ATP-binding cassette (ABC) component in the cell membrane. This type of bacteria-specific sugar transport system can simultaneously achieve
highly-efficient glucose transport and phosphorylation. However, PTS requires phosphoenolpyruvate as a precursor to phosphorylate glucose and convert the former to pyruvate; therefore, it is coupled with the last step of the reaction in the EMP pathway. Some products use phosphoenolpyruvate or intermediates upstream of phosphoenolpyruvate in the EMP pathway as precursors; therefore, the transport of glucose through the PTS may have an impact on the biosynthesis of these products. To solve this problem, the synthesis of lysine, succinic acid, 1,3-propanediol, and other products was successfully accomplished by replacing PTS with a non-PTS glucose transporter and glucokinase.

Utilization of pentose

In addition to glucose, pentose is another major component of lignocellulosic biomass hydrolysates, mainly xylose and arabinose. Currently, microorganisms mainly utilize pentoses through 3 assimilation pathways: the pentose phosphate pathway, the xylulose-1-phosphate or ribulose-1-phosphate pathway, and the nonphosphorylated pathway (Figure 7). In the first 2 pathways, xylose and arabinose are first isomerized to xylulose and ribulose, respectively. Xylulose and ribulose can be further phosphorylated to xylulose-5-phosphate and ribulose-5-phosphate, respectively, and finally converted to fructose-6-phosphate and glyceraldehyde-3-phosphate through the pentose phosphate pathway in a molar ratio of 2/1. Both fructose-6-phosphate and glyceraldehyde-3-phosphate are intermediates of the glycolytic pathway and can be further converted to pyruvate or other products via the glycolytic pathway. In addition, xylulose and ribulose can be phosphorylated to xylulose-1-phosphate and ribulose-1-phosphate, respectively, which are subsequently cleaved to glycolaldehyde and dihydroxyacetone phosphate (DHAP) through a 1-step reaction. DHAP is an intermediate product of the glycolytic pathway, and glycolaldehyde can be converted to other 2-carbon compounds, such as glycolic acid and ethylene glycol. Unlike the first 2 pathways, the assimilation of pentose by the nonphosphorylating pathway does not require ATP-dependent phosphorylation, but a 3-step reaction converts xylose and arabinose to 2-keto-3-deoxyxylulonate and 2-keto-3-deoxyarabononate, respectively. 2-Keto-3-deoxypentanoate can be converted to pyruvate and glycolaldehyde via the Dahms pathway or to α-ketoglutarate via the Weimberg pathway. Similar to the second route, the Dahms pathway is suitable for the biosynthesis of pyruvate precursors and 2-carbon compounds. The Weimberg pathway can directly generate the TCA cycle intermediate, α-ketoglutarate, which has potential applications in the synthesis of many TCA cycle intermediate derivatives. In fact, 1,4-butanediol can be directly synthesized from pentose via a nonphosphorylating pathway, showing the value of the nonphosphorylating pathway. However, neither of these 2 nonphosphorylating pathways can generate ATP and need to obtain energy from NADH through oxidative phosphorylation; therefore, they are not suitable for oxygen-limited fermentation conditions.

In addition to the pentose-assimilation pathway, the lack of efficient pentose transporters is a key factor limiting pentose utilization. Unlike glucose, the pentose transporters discovered thus far are mainly non-PTS transporters, including transporters of the ABC transporter family and the major facilitator superfamily transporter family. In addition, some common chassis microorganisms, such as S. cerevisiae, lack efficient and specific pentose transporters, which become key factors limiting the efficiency of pentose utilization. Therefore, some studies have been devoted to mining and heterologous expression of transporters that can efficiently and specifically utilize pentose in S. cerevisiae.

Co-utilization of hexose and pentose

CCR is a mechanism that fully utilizes carbon sources to promote growth in mixed carbon source environments, allowing microorganisms to preferentially utilize preferred carbon sources and inhibiting the utilization of other carbon sources. Glucose is the preferred carbon source for most microorganisms. Lignocellulosic biomass hydrolysate is a mixture of various carbon sources, and the presence of glucose inhibits the utilization of pentose sugars. Currently, there are 2 main modes of CCR in bacteria. CCR in E. coli is mainly controlled by the phosphorylation state of ElIAac in the PTS system. When the medium contains higher concentrations of glucose, ElIAac is mainly in an unphosphorylated state because the phosphate groups are cascaded for glucose phosphorylation. Unphosphorylated ElIAac leads to low levels of intracellular cyclic AMP (cAMP), thereby inhibiting the expression of a large number of catabolic genes that require activation by the cAMP receptor protein. In addition, unphosphorylated ElIAac directly blocks the transport of nonpreferred carbon sources. In Bacillus subtilis, CCR is mainly achieved through regulation of the global regulator CcpA. HPr interacts with CcpA in the presence of glucose, inducing the latter to bind the catabolite responsive element (cre), which in turn controls the activation of 85 genes and the repression of 250 genes. Although the mechanisms of these 2 CCRs are completely different,
they are both directly related to the PTS system. Therefore, some studies have knocked out the PTS system in bacteria and transported glucose and other nonpreferred carbon sources through non-PTS transporters, thereby circumventing the CCR response. The PTS system is absent in the eukaryotic microorganism S. cerevisiae, but CCR is still present. CCR in S. cerevisiae is mainly achieved through global regulation mediated by 2 signal transduction transducers, Snf1 and Gcn2. In addition, pentoses are transported by nonspecific transporters in S. cerevisiae; therefore, the presence of glucose competitively inhibits pentose transport. Several recent studies have significantly reduced the effects of CCR in S. cerevisiae by expressing novel heterologous pentose transporters. In addition, some studies circumvent the CCR response by directly transporting cellodextrin or cellobiose into cells for intracellular hydrolysis.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Conversion of lignocellulosic wastes into biodegradable plastics via microbial cell factories is an attractive biotechnological approach. Here, we briefly review related works in recent years and propose future research suggestions in this field. Currently, the main biodegradable plastics on the market include PHA, PLA, and PBAT. PHA and PLA are recognized as bio-based plastics and have relatively mature biobased synthesis processes. The next step is to improve the production efficiency of lignocellulosic wastes as substrates. In addition, PHB occupies a mainstream position in the PHA market, but its mechanical properties are not satisfactory. Therefore, it is crucial to develop an industrial production process to obtain PHA with improved mechanical properties. On the other hand, researchers have also recently attempted to develop processes for generating PLA polymers directly from microbial cells, representing a new direction in this field. Through a biosynthetic pathway similar to PHA, PLA can be synthesized in 1 step, avoiding the subsequent polymerization process. However, the yield and molecular weight of PLA obtained through direct biosynthesis are currently low and cannot meet industrial requirements. However, further research is expected to provide a breakthrough in this issue.

A commercial bio-based synthesis process for 1,4-butanediol, which is a monomer of the petroleum-based polymer PBAT, has been established using glucose as a substrate. However, there is a lack of an efficient 1,4-butanediol production process from pentose or lignocellulose, which limits the synthesis of PBS from lignocellulose wastes. Therefore, developing processes for the efficient synthesis of 1,4-butanediol using pentose or lignocellulose hydrolysates as substrates has become a focus of future research in this field. Relatively effective biosynthetic pathways have been developed for adipic acid, another monomer of PBAT, but the current titters and yields do not meet the requirements of industrialization. Metabolic analysis of synthetic pathways enables the discovery of key bottlenecks that limit the efficiency of the synthesis of these products, such as insufficient reducing power and carbon loss. Next, these bottlenecks need to be overcome through systems metabolic engineering strategies. Terephthalic acid, the monomer of PBAT, cannot be biosynthesized from carbohydrates using microbial fermentation methods. This may require the development of new synthetic pathways and the expansion of the substrate scope of existing enzymes.

The efficient utilization of lignocellulose resources is another major challenge, including developing efficient lignocellulose bioconversion processes and improving the utilization efficiency of carbon sources in lignocellulose hydrolysates by microorganisms. The pretreatment and degradation of lignocellulose is key to limiting its biotransformation. The existing SHF and SSF processes rely on high-temperature and high-pressure chemical pretreatment methods, which incur additional costs and potential environmental and energy problems. With the gradual maturity of the CBP process, the participation of microbial cells makes the hydrolysis of lignocellulose greener and more sustainable, which may be a future development trend. Improving the utilization efficiency of carbon sources by microorganisms is a key factor in improving the entire fermentation process; however, CCR, which represses pentose utilization in the presence of glucose, has become the key limiting factor of the co-utilization of pentoses and hexoses in lignocellulose hydrolysates. In addition, the assimilation pathway and transport efficiency of nonpreferred carbon sources (mainly pentoses) by some microorganisms are low, which is another major challenge for lignocellulose utilization. These issues can be ameliorated by transporter engineering, metabolic engineering, and methods that alter the global regulation of microbial cells, requiring continued efforts by researchers.

At present, the biodegradable polymer-production strains and the lignocellulosic hydrolysate-transforma-
tion strains are not consistent. More specifically, some microbial characteristics with industrial or metabolic advantages, such as acid resistance, high-temperature resistance, high osmolarity resistance, and high-efficiency synthetic reducing power, are also often distributed in different strains. From the perspective
of industrial applications, integrating these excellent characteristics into the same microorganism can significantly simplify the production process and reduce production costs. The rapid development of synthetic biology in recent years has made it possible to construct such superior microbial cell factories with these features and properties in the same chassis in a modular fashion. We believe that, with further technological developments, the use of microbial cell factories to convert lignocellulosic wastes into biodegradable plastics will gradually replace the traditional petroleum-based plastics market, especially in the fields of food packaging and agricultural mulching films.

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AUTHOR CONTRIBUTIONS

X.H., J.L., and S.T. wrote the manuscript. P.X. and F.T. critically revised the manuscript. All authors made substantial contributions to the conception and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Filiciotto, L., and Rothenberg, G. (2021). Biodegradable plastics: standards, policies, and impacts. ChemSusChem 14, 56–72.
2. Rhodes, C.J. (2018). Plastic pollution and potential solutions. Sci. Prog. 101, 207–260.
3. Law, K.L., and Thompson, R.C. (2014). Oceans. Microplastics in the seas. Science 345, 144–145.
4. Leslie, H.A., van Velzen, M.J.M., Brandsma, S.H., Vethaak, A.D., Garcia-Vallejo, J.J., and Lamoree, M.H. (2022). Discovery and quantification of plastic particle pollution in human blood. Environ. Int. 163, 107199.
5. Moshood, T.D., Nawani, G., and Mahmud, F. (2021). Sustainability of biodegradable plastics: a review on social, economic, and environmental factors. Crit. Rev. Biotechnol. 16, 1–21.
6. Aversa, C., Barletta, M., Gisario, A., Pizzi, E., Prati, R., and Vesco, S. (2021). Design, manufacturing and preliminary assessment of the suitability of bioplastic bottles for wine packaging. Polym. Test. 100, 107227.
7. Vigneswari, S., Noor, M.S.M., Amelia, T.S.M., Balakrishnan, K., Adrian, A., Bhubalan, K., Amirul, A.A.A., and Ramakrishna, S. (2021). Recent advances in the biosynthesis of polyhydroxyalkanoate from lignocellulosic feedstocks. Life 11, 807.
8. Lorenci Woiciechowski, A., Dalmas Neto, C.J., Porto de Souza Vandenbergh, L., de Carvalho Neto, D.P., Novak Sydney, A.C., Letti, L.A.J., Karp, S.G., Zevillos Torres, L.A., and Soccol, C.R. (2020). Lignocellulosic biomass: acid and alkaline pretreatments and their effects on biomass recalcitrance – conventional processing and recent advances. Bioresour. Technol. 304, 122848.
9. Burgard, A., Burk, M.J., Osterhout, R., Van Dier, S., and Yim, H. (2016). Development of a commercial scale process for production of 1,4-butanediol from sugar. Curr. Opin. Biotechnol. 42, 118–125.
10. Zhao, M., Huang, D., Zhang, X., Koffas, M.A.G., Zhou, J., and Deng, Y. (2018). Metabolic engineering of Escherichia coli for producing adipic acid through the reverse adipate-degradation pathway. Metab. Eng. 47, 254–262.
11. Shahab, R.L., Luttenbacher, J.S., Brethauer, S., and Studer, M.H. (2018). Consolidated bioprocessing of lignocellulosic biomass to lactic acid by a synthetic fungal-bacterial consortium. Biotechnol. Bioeng. 115, 1207–1215.
12. Kulkarni, R.K., Moore, E.G., Hegyeli, A.F., and Leonard, F. (1971). Biodegradable poly(lactic acid) polymers. J. Biomed. Mater. Res. 5, 169–181.
13. Brandl, H., Gross, R.A., Lenz, R.W., and Fuller, R.C. (1988). Pseudomonas oleovorans as a source of poly(beta-hydroxyalkanoate) for potential applications as biodegradable polyesters. Appl. Environ. Microbiol. 54, 1977–1982.
14. Herrera, R., Franco, L., Rodríguez-Galán, A., and Fuentes, J. (2002). Characterization and degradation behavior of poly(butylene adipate-co-terephthalate). J. Polym. Sci. A. Polym. Chem. 40, 4141–4157.
15. Balakrishnan, H., Hassan, A., Wahit, M.U., Yussuf, A.A., and Razak, S.B.A. (2010). Novel toughened poly(lactic acid) nanocomposites: mechanical, thermal and morphological properties. Mater. Des. 31, 3289–3298.
16. Auras, R., Harte, B., and Selke, S. (2004). An overview of polylactides as packaging materials. Macromol. Biosci. 4, 835–864.
17. Singhvi, M.S., Zinjarde, S.S., and Gokhale, D.V. (2019). Poly(lactic acid): synthesis and biomedical applications. J. Appl. Microbiol. 127, 1612–1626.
18. Shao, J., Xiang, S., Bian, X., Sun, J., Li, G., and Chen, X. (2015). Remarkable melting behavior of PLA stereocomplex in linear PLLA/PDLA blends. Ind. Eng. Chem. Res. 54, 2246–2253.
19. Tsuji, H., and Ikada, Y. (1996). Blends of isotactic and atactic polylactides: 2. Molecular-weight effects of atactic component on crystallization and morphology of equimolar blends from the melt. Polymer 37, 395–402.
20. Keskin, G., Kızılı, G., Bechelany, M., Pochat-Bohatier, C., and Oner, M. (2017). Potential of polyhydroxyalkanoate (PHA) polymers family as substitutes of petroleum based polymers for packaging applications and solutions brought by their composites to form barrier materials. Pure Appl. Chem. 89, 1841–1848.
21. Urtuviu, V., Villegas, P., González, M., and Seeeger, M. (2014). Bacterial production of the biodegradable plastics polyhydroxyalkanoates. Int. J. Biol. Macromol. 70, 208–213.
22. Tan, G.Y., Chen, C.L., Li, L., Ge, L., Wang, L., Razaad, I., Li, Y., Zhao, L., Mo, Y., and Wang, J.Y. (2014). Start a research on biopolymer polyhydroxyalkanoate (PHA): a review. Polymers 6, 706–754.
23. Park, S.J., Kim, T.W., Kim, M.K., Lee, S.Y., and Lim, S.C. (2012). Advanced bacterial polyhydroxyalkanoates: towards a versatile and sustainable platform for unnatural tailor-made polymers. Biotechnol. Adv. 30, 1196–1206.
24. Hanggi, U.J. (1995). Requirements on bacterial polyesters as future substitute for conventional plastics for consumer goods. FEMS Microbiol. Rev. 16, 213–220.
25. Abe, H., and Doi, Y. (2002). Side-chain effect of second monomer units on crystalline morphology, thermal properties, and enzymatic degradability for random
26. Wampfler, B., Ramsauer, T., Rezzonico, S., Huscher, R., Köhling, R., Thony-Meyer, L., and Zinn, M. (2010). Isolation and purification of medium chain length poly(3-hydroxyalkanoates) (mcl-PHA) for medical applications using nonchlorinated solvents. Biomacromolecules 11, 2716–2723.

27. Pegu, E.I., Stokes, J., and McGuinness, G.B. (2013). Electroporin composites of PHBV, silk fibroin and nano-hydroxyapatite for bone tissue engineering. Mater. Sci. Eng. C Mater. Biol. Appl. 33, 4905–4916.

28. Brodhagen, M., Peyron, M., Miles, C., and Inglis, D.A. (2015). Biodegradable plastic agricultural mulches and key features of microbial degradation. Appl. Microbiol. Biotechnol. 99, 1039–1056.

29. Jian, J., Xiangbin, Z., and Xianbo, H. (2020). An overview on synthesis, properties, and applications of poly (butylene-adipate-co-terephthalate)-PBAT. Adv. Indusical Eng. Polym. Res. 3, 19–26.

30. Nagajaran, V., Mira, M., and Mohanty, A.K. (2013). New engineered biocomposites from poly(3-hydroxybutyrate-co-3-hydroxyvalerate). (PHBV)poly (butylene adipate-co-terephthalate) (PBAT) blends and switchgrass: fabrication and performance evaluation. Ind. Crops Prod. 42, 461–468.

31. Ferreira, F.V., Cividanes, L.S., Gouveia, R.F., and Lona, L.M. (2019). An overview on properties and applications of poly (butylene adipate-co-terephthalate)-PBAT based composites. Polym. Eng. Sci. 59, E7–E15.

32. Sander, M. (2019). Biodegradation of polymeric mulch films in agricultural soils: concepts, knowledge gaps, and future research directions. Environ. Sci. Technol. 53, 2304–2315.

33. Layu, S., Dusseau, S., Verbeke, J., Rigouin, C., Guo, Z., Fatarova, M., Bellvert, F., Borsenberger, V., Bressy, M., Nicaud, J.M., et al. (2020). Engineering the yeast Torraria (polymyxa for production of polyactic acid homopolymer. Front. Bioeng. Biotechnol. 8, 954.

34. Wang, J., Wang, C., Liu, H., Ji, H., Chen, H., and Wen, J. (2018). Metabolomics assisted metabolic network modeling and network wide analysis of metabolites in microbiology. Crit. Rev. Biotechnol. 38, 1106–1120.

35. Yim, H., Haselbeck, R., Niu, W., Pujol-Baxley, C., Burgard, A., Boldt, J., Khadurina, J., Trawick, J.D., Osterhout, R., Stephen, R., et al. (2011). Metabolic engineering of Escherichia coli for direct production of 1, 4-butanediol. Nat. Chem. Biol. 7, 445–452.

36. Bornscheuer, U.T., Hauer, B., Jaeger, K.E., and Schwaneberg, U. (2019). Directed evolution empowered redesign of natural proteins for the sustainable production of chemicals and pharmaceuticals. Angew. Chem. Int. Ed. Engl. 58, 36–40.

37. Mohd Fadzil, F.I., Mizuno, S., Hiroe, A., Nomura, C.T., and Tsuge, T. (2018). Low carbon concentration feeding improves medium-chain-length polyhydroxyalkanoate production in Escherichia coli strains with defective β-oxidation. Front. Bioeng. Biotechnol. 6, 178.

38. Koller, M., and Mulkerjee, A. (2022). A new wave of industrialization of PHA biopolymers. Bioengineering (Basel) 9, 74.

39. Jiang, S., Xu, P., and Tao, F. (2019). Lactic acid production by Bacillus coagulans through simultaneous saccharification and fermentation of lignocellulosic corncob residue. Bioresour. Technol. Rep. 6, 131–137.

40. Dietrich, K., Oliveira-Filho, E.R., Dumont, M.J., Gómez, J.G., Taciro, M.K., Silva, L.F.d., Ots, V., and Rio, L.F.D. (2020). Producing PHB production with an industrially scalable carbon source. Ind. Crops Prod. 154, 112703.

41. Abedi, E., and Hashemi, S.M.B. (2020). Lactic acid production – perspective producing microorganisms and substrates sources-state of art. Helyon 6, e04974.

42. Han, X., Huang, K., Tang, H., Ni, J., Liu, J., Xu, P., and Tao, F. (2019). Steps toward high-performance PLAs: economical production of d-lactate by a newly isolated Sporoactobacillus terrestr strain. Biotechnol. J. 14, e1800056.

43. Xu, K., and Xu, P. (2014). Efficient calcium lactate production by fermentation coupled with crystallization based in situ product removal. Bioresour. Technol. 163, 33–39.

44. Wang, L., Zha, B., Li, F., Xu, K., Ma, C., Tao, F., Li, Q., and Xu, P. (2011). Highly efficient production of d-lactate by Sporoactobacillus sp. CASD with simultaneous enzymatic hydrolysis of peanut meal. Appl. Microbiol. Biotechnol. 89, 1009–1017.

45. Tashiro, Y., Kaneko, W., Sun, Y., Shibata, K., Hischier, R., Köhling, R., Thoney-Meyer, L., and Zinn, M. (2010). Isolation and characterization of medium chain length polyhydroxyalkanoate (mcl-PHA) for medical applications using nonchlorinated solvents. Angew. Chem. Int. Ed. Engl. 50, 178–182.

46. Baek, S.H., Kwon, E.Y., Kim, Y.H., and Hahn, J.S. (2016). Metabolic engineering and adaptive evolution for efficient production of d-lactic acid in Saccharomyces cerevisiae. Appl. Microbiol. Biotechnol. 100, 2737–2748.

47. Song, J.Y., Park, J.S., Kang, C.D., Cho, H.Y., Yang, D., Lee, S., and Cho, K.M. (2011). Continuous d-lactic acid production by a novel tolerant lactic Lactobacillus delbrueckii subsp. lactis QU 41. Appl. Microbiol. Biotechnol. 89, 1741–1750.

48. Baek, S.H., Kwon, E.Y., Kim, Y.H., and Hahn, J.S. (2016). Metabolic engineering and adaptive evolution for efficient production of d-lactic acid in Saccharomyces cerevisiae. Appl. Microbiol. Biotechnol. 100, 2737–2748.

49. Peetemans, A., Foulqué-Moreno, M.R., and Thevelein, J.M. (2021). Mechanisms underlying lactic acid tolerance and its influence on lactic acid production in Saccharomyces cerevisiae. Microb. Cell 8, 111–130.

50. Tan, C., Tao, F., and Xu, P. (2022). Direct carbon capture for the production of high-performance biodegradable plastics by cyanobacterial cell factories. Green Chem. 24, 4470–4483.

51. Choi, S.Y., Cho, J.I., Lee, Y., Park, S., and Lee, S.Y. (2019). Biocatalytic synthesis of poly(lactate) and its copolymers by engineered microorganisms. Methods Enzymol. 627, 125–162.

52. Ren, Y., Ling, C., Hajnal, I., Wu, Q., and Chen, G.Q. (2018). Construction of Halomonas bluephagenesis capable of high cell density growth for efficient PHA production. Appl. Microbiol. Biotechnol. 102, 4499–4510.

53. Ma, H., Zhao, Y., Huang, W., Zhang, L., Wu, F., Ye, J., and Chen, G.Q. (2020). Rational flux–tuning of Halomonas bluephagenesis for co-production of bioplastic PHB and ectoine. Nat. Commun. 11, 3513.

54. Tang, R., Weng, C., Peng, X., and Han, Y. (2020). Metabolic engineering of Cupivarius necator with improved chemoautotrophic growth and PHB production under oxygen-limiting conditions. Metab. Eng. 61, 11–23.

55. Wu, H., Fan, Z., Jiang, X., Chen, J., and Chen, G.Q. (2016). Enhanced production of polyhydroxybutyrate by multiple dividing E. coli. Microb. Cell Fact. 15, 128.

56. Zhao, H., Zhang, H.M., Chen, X., Li, T., Wu, Q., Ouyang, Q., and Chen, G.Q. (2017). Novel T7-like expression systems used for Halomonas Metab. Eng. 39, 128–140.

57. Ling, C., Giao, Q.G., Shuai, B.W., Song, K.N., Yao, W.X., Jiang, X.R., and Chen, G.Q. (2019). Engineering self-flocculating Halomonas campanensis for wastewaterless open and continuous fermentation. Biotechnol. Bioeng. 116, 805–815.

58. Chen, Y., Chen, X.Y., Du, H.T., Zhang, X., Ma, Y.M., Chen, J.C., Ye, J.W., Jiang, X.R., and Chen, G.Q. (2019). Chromosome engineering of the TCA cycle in Halomonas bluephagenesis for production of copolymers of 3-hydroxybutyrate and 3-hydroxyvalerate (PHBV). Metab. Eng. 54, 60–82.

59. Ye, J., Huo, D., Che, X., Jiang, X., Li, T., Chen, J., Zhang, H.M., and Chen, G.Q. (2018a). Engineering of Halomonas bluephagenesis for low cost production of poly(3-hydroxybutyrate-co-3-hydroxybutyrate) from glucose. Metab. Eng. 47, 143–152.

60. Meng, D.C., Wang, Y., Wu, L.P., Shen, R., Chen, J.C., Wu, Q., and Chen, G.Q. (2019). Production of poly(3-hydroxypropionate) and poly(3-hydroxybutyrate-co-3-hydroxypropionate) from glucose by engineering Escherichia coli. Metab. Eng. 29, 189–195.
61. Zhang, L., Ye, J.W., Zhang, X., Huang, W., Zhang, Z., Lin, Y., Zhang, G., Wu, F., Wang, Z., Wu, Q., and Chen, G.Q. (2022). Effective production of Poly(3-hydroxybutrate-co-4-hydroxybutyrate) by engineered Halomonas bluephagenesis grown on glucose and 1, 4-Butanediol. Bioreesour. Technol. 355, 127270.

62. Ye, J., Huang, W., Wang, D., Chen, F., Yin, J., Li, T., Zhang, H., and Chen, G.Q. (2018b). Pilot scale-up of poly(3-hydroxybutrate-co-4-hydroxybutyrate) production by Halomonas bluephagenesis via cell growth adapted optimization process. Biotechnol. J. 13, e1800074.

63. Li, M., Ma, Y., Zhang, X., Chen, X., Ye, J.W., and Chen, G.Q. (2022). Tailor-made polyhydroxyalkanoates by reconstructing Pseudomonas Entomophila. Adv. Mater. 33, e2102766.

64. Ning, Y., Liu, H., Zhang, R., Jin, Y., Yu, Y., Deng, L., and Wang, F. (2022). Research progress on the construction of artificial pathways for the biosynthesis of adipic acid by engineered microbes. Fermentation 8, 393.

65. Shin, J.H., Andersen, A.J.C., Achterberg, P., and Olsson, L. (2021). Exploring functionality of the reverse β-oxidation pathway in Corynebacterium glutamicum for production of adipic acid. Microb. Cell Fact. 20, 155.

66. Zhang, X., Liu, Y., Wang, J., Zhao, Y., and Deng, Y. (2020). Biosynthesis of adipic acid in metabolically engineered Saccharomyces cerevisiae. J. Microbiol. 58, 1065–1075.

67. Yu, J.L., Xia, X.X., Zhong, J.J., and Qian, Z.G. (2014). Direct biosynthesis of adipic acid from a synthetic pathway in recombinant Escherichia coli. Biotechnol. Bioeng. 111, 2580–2586.

68. Zhou, Y., Zhao, M., Zhou, S., Zhao, Y., Li, G., and Deng, Y. (2020). Biosynthesis of adipic acid by a highly efficient induction-free system in Escherichia coli. J. Biotechnol. 314-315, 8–13.

69. Hao, T., Li, G., Zhou, S., and Deng, Y. (2021). Engineering the reductive TCA pathway to dynamically regulate the biosynthesis of adipic acid in Escherichia coli. ACS Synth. Biol. 10, 632–639.

70. Yang, J., Lu, Y., Zhao, Y., Bai, Z., Ma, Z., and Deng, Y. (2019). Site-directed mutation to improve the enzymatic activity of S-carboxy-2-pentenoyl-CoA reductase for enhancing adipic acid biosynthesis. Enzyme Microb. Technol. 125, 6–12.

71. Yang, J., Wei, Y., Li, G., Zhou, S., and Deng, Y. (2020). Computer-aided engineering of adipyl-CoA synthetase for enhancing adipic acid synthesis. Biotechnol. Lett. 42, 2693–2701.

72. Karlsson., E., Mapelli, V., and Olsson, L. (2017). Adipic acid tolerance screening for potential adipic acid production hosts. Microb. Cell Fact. 16, 20.

73. Guo, H., Liu, H., Jin, Y., Zhang, R., Yu, Y., Deng, L., and Wang, F. (2022). Advances in research on the bio-production of 1, 4-butanediol by the engineered microbes. Biochem. Eng. J. 185, 108478.

74. Ahn, J.H., Seo, H., Park, W., Seok, J., Lee, J.A., Kim, W.J., Kim, G.B., Kim, K.J., and Lee, S.Y. (2020). Enhanced succinic acid production by Mannheimia employing optimal malate dehydrogenase. Nat. Commun. 11, 1970.

75. Szmidt-Middleton, H.L., Ouellet, M., Adams, P.D., Keasling, J.D., and Mukhopadhyay, A. (2013). Utilizing a highly responsive gene, yh/H, in E. coli based production of 1, 4-butanediol. Chem. Eng. Sci. 103, 68–73.

76. Tai, Y.S., Xiong, M., Jambutathan, P., Wang, J., Wang, C., and Zhang, K. (2016). Engineering nonphosphorylative metabolism to generate lignocellulose-derived products. Nat. Chem. Biol. 12, 247–253.

77. Peters, M.W., Taylor, J.D., Jenni, M., Manzer, L.E., and Henton, D.E. (2010). Integrated Process to Selectively Convert Renewable Isobutanol to P-Xylene.

78. Luo, Z.W., and Lee, S.Y. (2017). Biotransformation of pyreline into terethaphelic acid by engineered Escherichia coli. Nat. Commun. 8, 15689.

79. Tang, D., Huang, X., Tang, W., and Jin, Y. (2021). Lignin-to-chemicals: application of catalytic hydrolysis of lignin to produce phenols and terethaphelic acid via metal-based catalysts. Int. J. Biol. Macromol. 190, 72–85.

80. Bhatia, L., Sarangi, P.K., Singh, A.K., Prakash, A., and Shadangi, K.P. (2022). Lignocellulose-to-bio-terenthaphelic acid biomass for biohydrogen production: future challenges and bio-economic perspectives. Biofuel. Bioprod. Biorefin. 16, 838–858.

81. Huber, G.W., Iborra, S., and Correa, A. (2006). Synthesis of transportation fuels from biomass: chemistry, catalysts, and engineering. Chem. Rev. 106, 4044–4098.

82. Liu, C., and Wyman, C.E. (2003). The effect of particle size on the fermentation of lignocellulose stover. Ind. Eng. Chem. Res. 42, 5409–5416.

83. Shahabazuddin, M., Sarat Chandra, T., and Studer, M.H. (2020). A heterogeneous microbial consortium producing short-chain fatty acids from lignocellulose. Science 369, eabb1214.

84. Ferreira, R.G., Azzoni, A.R., and Freitas, S. (2017). Lignin-to-chemicals: application of recombinant L-lactic acid. Chembiochem 17, 1491–1494.

85. Wilhelm, R.C., Singh, R., Eltis, L.D., and Mohn, W.W. (2019). Bacterial contributions to delignification and lignocellulose degradation in forest soils with metagenomic and quantitative stable isotope probing. ISME J 13, 413–429.

86. Ceja-Navarro, J.A., Karam, U., Bill, M., Hao, Z., White, R.A., III, Arellano, A., Ramanculova, L., Filley, T.R., Bony, T.D., Conrad, M.E., et al. (2019). Gut anatomical properties and microbial functional assembly promote lignocellulose deconstruction and colony subsistence of a wood-feeding beetle. Nat. Microbiol. 4, 864–875.

87. Peng, X., Wilken, S.E., Lankiewicz, T.S., Gilmore, S.P., Brown, J.L., Henske, J.K., Swift, C.L., Salamay, A., Barry, K., Grigoriev, I.V., et al. (2021). Genomic and functional analyses of fungal and bacterial consortia that enable lignocellulose breakdown in gut goat microbiomes. Nat. Microbiol. 6, 499–511.

88. Lu, J., Li, Y., Jiang, Y., Wu, M., Xu, B., Zhang, W., Zhou, J., Dong, W., Xin, F., and Jiang, M. (2020). Consolidated bioprocessing of hemicellulose-enriched lignocellulose to succinic acid through a microbial cocultivation system. ACS Sustain Chem. Eng. 8, 9035–9045.

89. Gandini, C., Tarranan, L., Kalemassi, D., Pessione, E., and Mazoili, R. (2017). Recombinant Lactococcus lactis for efficient conversion of cellobextrins into L-lactic acid. Biotechnol. Bioeng. 114, 2807–2817.

90. Shahab, R.L., Brethauer, S., Davey, M.P., Smith, A.G., Vignolini, S., Lutterbacher, J.S., and Studer, M.H. (2020). A heterogeneous microbial consortium producing short-chain fatty acids from lignocellulose. Science 369, eabb1214.

91. Li, J., Lin, L., Sun, T., Xu, J., Liu, Q., and Tian, C. (2020). Direct production of commodity chemicals from lignocellulose
using Myceliophthora thermophila. Metab. Eng. 61, 416–426.

97. Madhavan, A., Srivastava, A., Kondo, A., and Bisaria, V.S. (2012). Bioconversion of lignocellulose-derived sugars to ethanol by engineered Saccharomyces cerevisiae. Crit. Rev. Biotechnol. 32, 22–48.

98. Ruiz-Villafán, B., Cruz-Bautista, R., Manzo-Ruz, M., Passari, A.K., Villarreal-Gómez, K., Rodríguez-Sanoja, R., and Sánchez, S. (2022). Carbon catabolite regulation of secondary metabolite formation, an old but not well-established regulatory system. Microb. Biotechnol. 15, 1058–1072.

99. Görke, B., and Stülke, J. (2008). Carbon catabolite repression in bacteria: many ways to make the most out of nutrients. Nat. Rev. Microbiol. 6, 613–624.

100. Suo, Y., Fu, H., Ren, M., Liao, Z., Ma, Y., and Wang, J. (2018). Enhanced butyric acid production in Clostridium tyrobutyricum by overexpression of rate-limiting enzymes in the Embden-Meyerhof-Parnas pathway. J. Biotechnol. 272–273, 14–21.

101. Tsuge, Y., Yamamoto, S., Kato, N., Suda, M., Vertès, A.A., Yukawa, H., and Inui, M. (2015). Overexpression of the phosphofructokinase encoding gene is crucial for achieving high production of d-lactate in Corynebacterium glutamicum. Appl. Microbiol. Biotechnol. 99, 4679–4689.

102. Becker, J., Klopportegge, C., Zelder, O., Heinzle, E., and Wittmann, C. (2005). Amplified expression of fructose 1, 6-bisphosphatase in Corynebacterium glutamicum decreases in vivo flux through the pentose phosphate pathway and l-lysine production on different carbon sources. Appl. Environ. Microbiol. 71, 8587–8596.

103. Yuan, X., Mao, Y., Tu, S., Lin, J., Shen, H., Yang, L., and Wu, M. (2021). Increasing NADPH availability for xylitol production via pentose-phosphate-pathway gene overexpression and Embden-Meyerhof-Parnas-pathway gene deletion in Escherichia coli. J. Agric. Food Chem. 69, 9625–9631.

104. Borodina, I., Schöller, C., Eliasson, A., and Nielsen, J. (2005). Metabolic network analysis of Streptomyces tenebrarius, a Streptomyces species with an active enterodoudoroff pathway. Appl. Environ. Microbiol. 71, 2294–2302.

105. Tsuge, Y., Kato, N., Yamamoto, S., Suda, M., Jojima, T., and Inui, M. (2019). Metabolic engineering of Corynebacterium glutamicum for hyperproduction of polymer-grade L- and d-lactic acid. Appl. Microbiol. Biotechnol. 103, 3381–3391.

106. Gosset, G. (2005). Improvement of Escherichia coli production strains by modification of the phosphoenolpyruvate sugar phosphotransferase system. Microbiol. Cell Fact. 4, 14.

107. Xu, J.Z., Yu, H.B., Han, M., Liu, L.M., and Zhang, W.G. (2019). Metabolic engineering of glucose uptake systems in Corynebacterium glutamicum for improving the efficiency of L-lysine production. J. Ind. Microbiol. Biotechnol. 46, 937–949.

108. Zhang, X., Jantama, K., Moore, J.C., Jarboe, L.R., Shannum, K.T., and Ingram, L.O. (2009). Metabolic evolution of energy-conserving pathways for succinate production in Escherichia coli. Proc. Natl. Acad. Sci. USA 106, 20180–20185.

109. Larma, S., Seol, E., and Park, S. (2020). Development of Klebsiella pneumoniae J2B as microbial cell factory for the production of 1,3-propanediol from glucose. Metab. Eng. 62, 116–125.

110. Li, X., Chen, Y., and Nielsen, J. (2019b). Harnessing xylose pathways for biofuels production. Curr. Opin. Biotechnol. 57, 56–65.

111. Pereira, B., Li, Z.J., De Mey, M., Lim, C.G., Zhang, H., Hoeltgen, C., and Stephanopoulos, G. (2016). Efficient utilization of pentoses for bioproduction of the renewable two-carbon compounds ethylene glycol and glycolate. Metab. Eng. 34, 80–87.

112. Cabulong, R.B., Lee, W.K., Bañares, A.B., Ramos, Y., and Zhao, G. (2020). Biochemical routes for uptake and conversion of xylose by microorganisms. Biotechnol. Biofuels 13, 21.

113. Nijland, J.G., and Driessen, A.J.M. (2020). Engineering of pentose transport in Saccharomyces cerevisiae for biotechnological applications. Front. Bioeng. Biotechnol. 8, 464.

114. Nair, A., and Sarma, S.J. (2021). The impact of carbon and nitrogen catabolite repression in microorganisms. Microbiol. Res. 251, 126831.

115. Bettenbrock, K., Sauter, T., Jaehreis, K., Kremling, A., Lengerer, J.W., and Gilles, E.D. (2007). Correlation between growth rates, ELIAcrr phosphorylation, and intracellular cyclic AMP levels in Escherichia coli K-12. J. Bacteriol. 189, 6891–6900.

116. Homburg, C., Bommer, M., Wügge, S., Hobie, C., Beck, S., Dobbeke, H., Deutscher, J., Licht, A., and Schneider, E. (2017). Inducer exclusion in Firmicutes: insights into the regulation of a carbohydrate ATP binding cassette transporter from Lactobacillus casei BL23 by the signal transducing protein P-Scr46-HPr. Mol. Microbiol. 105, 25–45.

117. Detert Oude Weme, R., Seidel, G., and Detert, O. (2015). Probing the regulatory effects of specific mutations in three major binding domains of the pleiotropic regulator CopA of Bacillus subtilis. Front. Microbiol. 6, 1051.

118. Wacker, J., Ludwig, H., Reif, I., Blencze, H.M., Detsch, C., and Stülke, J. (2003). The regulatory link between carbon and nitrogen metabolism in Bacillus subtilis regulon of the gltAB operon by the carboxylate control protein CopA. Microbiology (Read.) 149, 3001–3009.

119. Yemen, J., Kim, D.G., Jung, M.Y., Saratale, G.D., and Oh, M.K. (2017). Metabolic engineering of Enterobacter aerogenes for 2,3-butanediol production from sugarcane bagasse hydrolysate. Bioresour. Technol. 245, 1567–1574.

120. Peter, G.J., Durning, L., and Ahmed, A. (2006). Carbon catabolite repression regulates amino acid permeases in Saccharomyces cerevisiae via the TOR signaling pathway. J. Biol. Chem. 281, 5546–5552.

121. Bueno, J.G.R., Borelli, G., Corrêa, T.L.R., Fiamenghi, M.B., José, J., de Carvalho, M., de Oliveira, L.C., Pereira, G.A.G., and Dos Santos, L.V. (2020). Novel xylose transporter Cs4130 expands the sugar uptake repertoire in recombinant Saccharomyces cerevisiae strains at high xylose concentrations. Biotechnol. Biofuels 13, 145.

122. Galazka, J.M., Tian, C., Beeson, W.T., Martínez, B., Glass, N.L., and Cate, J.H.D. (2010). Celloextrin transport in yeast for improved biofuel production. Science 330, 84–88.

123. Chen, G.Q., and Jiang, X. (2018). Next generation industrial biotechnology based on extracellular bacteria. Curr. Opin. Biotechnol. 50, 94–100.

124. Chen, G.Q., and Liu, X. (2021). On the future fermention. Microb. Biotechnol. 14, 18–21.

125. Azaiez, H., Abu Tayeh, H.H., Schneider, R., Klönglkaew, A., and Venus, J. (2020). Production of lactic acid from carob, banana and sugarcane lignocellulosic biomass. Molecules 25, 2956.

126. Han, X., Hong, F., Liu, G., and Bao, J. (2018). An approach of utilizing water-soluble carbohydrates in lignocellulosic feedstock for promotion of cellulolitic l-lactic acid production. J. Agric. Food Chem. 66, 10225–10232.

127. Kamaouri, A., Asimakopoulou, G., Kalogiannis, K.K., Lappas, A., and Topakas, E. (2020). Efficient d-lactic acid production by Lactobacillus delbrueckii subsp. bulgaricus through conversion of organosolvent pretreated lignocellulosic biomass. Biomass Bioenergy 140, 105672.

128. Yue, H., Ding, C., Yang, T., Chen, X., Chen, Y., Deng, H., Wu, Q., Chen, J., and Chen, G.Q. (2014). A seawater-based open and continuous process for polyhydroxyalkanoates production by recombinant Halomonas campaniensis LS21 grown in mixed substrates. Biotechnol. Biofuels 7, 108.

129. Jin, C., Li, J., Huang, Z., Han, X., and Bao, J. (2022). Engineering Corynebacterium glutamicum for synthesis of poly(3-hydroxybutyrate) from lignocellulose biomass. Bioresour. Biotechnol. 119, 1598–1613.

130. Li, M., Eskridge, K., Liu, E., and Wilkins, M. (2019a). Enhancement of polyhydroxybutyrate (PHB) production by 10-fold from alkaline pretreatment liquor
with an oxidative enzyme-mediator-surfactant system under Plackett-Burman and central composite designs. Bioresour. Technol. 281, 99–106.

132. Al-Battashi, H., and Sivakumar, N. (2022). High-solid loading enzymatic hydrolysis of waste office paper for poly-3-hydroxybutyrate production through simultaneous saccharification and fermentation. J. Polym. Environ. 30, 3045–3054.