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Research review paper

Engineering yeast cell factories to produce biodegradable plastics and their monomers: Current status and prospects

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ABSTRACT

Traditional plastic products have caused serious environmental pollution due to difficulty to be degraded in the natural environment. In the recent years, biodegradable plastics are receiving increasing attention due to advantages in natural degradability and environmental friendliness. Biodegradable plastics have potential to be used in food, agriculture, industry, medicine and other fields. However, the high production cost of such plastics is the bottleneck that limits their commercialization and application. Yeasts, including budding yeast and non-conventional yeasts, are widely studied to produce biodegradable plastics and their organic acid monomers. Compared to bacteria, yeast strains are more tolerable to multiple stress conditions including low pH and high temperature, and also have other advantages such as generally regarded as safe, and no phage infection. In addition, synthetic biology and metabolic engineering of yeast have enabled its rapid and efficient engineering for bioproduction using various renewable feedstocks, especially lignocellulosic biomass. This review focuses on the recent progress in biosynthesis technology and strategies of monomeric organic acids for biodegradable polymers, including polylactic acid (PLA), polyhydroxyalkanoate (PHA), polybutylene succinate (PBS), and polybutylene adipate terephthalate (PBAT) using yeast cell factories. Improving the performance of yeast as a cell factory and strategies to improve yeast acid stress tolerance are also discussed. In addition, the critical challenges and future prospects for the production of biodegradable plastic monomer using yeast are also discussed.

1. Introduction

Plastic products have been widely used in everyday life and various industries. Due to the difficulty of degradation, traditional plastic products made from petroleum refinery can easily cause serious environmental pollution and become a global threat (MacLeod et al., 2021). Biodegradable plastic is a type of product that meets the performance requirements of users and does not change its performance during storage. After use, it can be broken down into environmentally friendly substances (water, carbon dioxide, and biomass) under certain natural environmental conditions, thus achieving the goal of environmental protection. On the other hand, biodegradable plastics (biodegradable polymers) can be degraded and utilized by natural microorganisms (bacteria, fungi, and algae), and some can be synthesized by biorefinery (Haider et al., 2019; Thakur et al., 2022; Zhou, 2022). Biodegradable plastics have the advantages of being environmentally friendly and renewable, and could potentially be used in a wider range of applications, such as agriculture, environment, food, medicine, and etc. (Filiciotto and Rothenberg, 2021; Lambert and Wagner, 2017; Reddy et al., 2013; Thakur et al., 2022). Bioplastics are plastics that are either bio-

Abbreviations: AA, adipic acid; BD, butanediol; CDW, cell dry weight; DHA, dihydroxyacetone; LA, lactic acid; LDH, lactate dehydrogenase; PBAT, polybutylene adipate terephthalate; PBS, polybutylene succinate; PCL, polycaprolactone; PDC, pyruvate decarboxylase; PLA, polylactic acid; PHA, polyhydroxyalkanoate; PHB, polyhydroxybutyrate; PPC, polypropylene carbonate; PYC, pyruvate carboxylase; SA, succinic acid; SDH, succinate dehydrogenase; TCA, tricarboxylic acid cycle; TPA, terephthalic acid; XDH, xylitol dehydrogenase; XK, xylose kinase; XR, xylose reductase; YPD, yeast extract peptone dextrose..

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based, biodegradable or both. Nowadays, bioplastics represent less than 1 % of more than 367 million tons of plastics produced annually. Production of biodegradable plastics is expected to increase to nearly 7.59 million tons by 2026 (Bioplastics market development update, 2021). Comprehensive research into efficient and cost-effective microbial cell factories biosynthesis technology for these biodegradable plastics is urgently needed.

Studies on production of biodegradable plastics have received increasing attention. As of 20 January 2023, 70,586 publications can be searched in Web of Science using "biodegradable polymers" as the subject. These publications include many reviews introducing the use, detection methods and degradation mechanisms of biodegradable plastics. Of these publications, there are more than 100 articles that focus on the biosynthesis of biodegradable plastics, including applications of biotechnology in their production.

Structurally, commonly used biodegradable plastics include polylactic acid (PLA), polyhydroxyalkanoate (PHA), polybutylene succinate (PBS), polybutylene adipate terephthalate (PBAT), poly caprolactone (PCL), polyvinyl alcohol (PVA), and polypropylene carbonate (PPC) (Jambunathan and Zhang, 2016; Lomwongsopon and Varrone, 2022; Roy Chong et al., 2022). The PHB and various monomers, such as cis, cis-muconic acid, lactic acid, succinic acid, and 1,4-butanediol, have been studied for biosynthesis of biodegradable plastics through sustainable microbial fermentation. PHB can be produced by bacteria, yeast *Saccharomyces cerevisiae*, and plants (Jambunathan and Zhang, 2016; Jayakody et al., 2022). 1,4-butanediol can be produced by designed *Escherichia coli* through systems-based metabolic engineering approach (Yim et al., 2011). Lactic acid and succinic acid can be produced in yeast *S. cerevisiae* (Jayakody et al., 2022). Due to different structures and synthesis mechanisms, degradable plastics have different properties and characteristics (Ilyas et al., 2020; Reddy et al., 2013) (*Comparison of biodegradable materials PLA, PBAT, PHA and PBS*, 2020). Table 1 lists the characteristics and physical properties of four types of biodegradable plastics PLA, PHA, PBS, and PBAT. The structures of the biosynthetic monomers for PLA, PHA, PBS and PBAT are shown in Fig. 1.

In recent years, studies on bioproduction of biodegradable plastics in microorganisms have made significant progress (Abdel-Rahman et al., 2013; Jayasekara et al., 2022), and various biodegradable plastic monomers produced by bacteria and yeasts have also been reported (Chen, 2010; Yang et al., 2021). For example, a variety of types of PHAs can be directly synthesized by numerous native bacteria (Sangkharak and Prasertsan, 2012) and engineered yeasts (Ylinen et al., 2021, 2022). In addition, PLA can be directly produced by engineered *E. coli* (Yang et al., 2010) and the nonconventional yeast *Yarrowia lipolytica* (Lajus et al., 2020). However, generally, production of biodegradable polymers normally requires the synthesis of monomers and the subsequent polymerization (Han et al., 2022). During organic acid fermentation, the decreased pH normally has an inhibitory effect on the metabolic activities of host cells. To neutralize the acids, $CaCO_3$, $Ca(OH)_2$, NaOH, KOH, or NH_4OH have been added during the fermentation processes. However, the neutralization of acid during fermentation easily leads to salt accumulation, as well as microbial contamination and increased separation costs (Chung et al., 2017; Thoma et al., 2021; Tsuge et al., 2015). Comparing with bacteria, yeast is known to grow and survive at relatively lower pH levels. Therefore, yeasts are better candidates as host cells to produce organic acids (Porro and Branduardi, 2017). Therefore, the related studies on yeast are receiving increasing attention.

Yeast is a unicellular fungus with various advantageous characteristics for industrial applications. These features include tolerance to low pH, absence of bacteriophage contamination, and amenability to genetic manipulation (Malubhoy et al., 2022; Rajkumar et al., 2016; Zhang et al., 2017). The budding yeast *S. cerevisiae* is a classic organism for the synthesis of bioplastics and plastic organic acid monomers (Liu et al., 2022a; Thakur et al., 2022). In addition, non-conventional yeasts, with specific properties, are also emerging as suitable hosts for the production of organic acids for industrial applications (Fatma et al., 2020; Li et al., 2020).

Several published reviews have summarized metabolic engineering strategies of biopolymers and synthetic monomers produced by various engineered microbes. The engineered microorganisms in these reviews are mainly microalgae (Roy Chong et al., 2022) and prokaryotic microorganisms, such as *E. coli* (Yang et al., 2021), *Actinobacillus succinogenes*, *Basfia succiniciproducens*, and *Mannheimia succiniciproducens* (Wang et al., 2022; Zhou, 2022). However, so far there has been limited reviews focusing on production of bioplastics using yeasts as cell factories. Studies on P3HB (Poly(3-hydroxybutyrate)) (Zhou, 2022) and monomeric organic acid LA (Augustiniene et al., 2022; Liu et al., 2022a), SA (Liu et al., 2022b), citric fumaric acid, and itaconic acid (Di Lorenzo et al., 2022) have been summarized and discussed. A systematic and comprehensive review of the biosynthesis of biopolymers and monomers using yeasts as cell factories will benefit further development of robust yeast cell factories for bioplastic production.

In this review, we present aspects of current developments on metabolic routes and the genetic engineering synthesis strategies of monomeric organic acids for four types of promising biodegradable plastics PLA, PHA, PBS, and PBAT in yeast (Fig. 1 and Table 1). We emphasize and predict an integrated strategy for efficient production of biodegradable plastic monomers in yeast.

2. Synthesis of biodegradable plastics and monomer organic acids by yeast

2.1. Synthesis strategies of lactic acid (LA) in yeast

Currently, PLA is one of the most promising biodegradable materials and has wide application prospects in biomedicine, food packaging, electronics, and electrical appliances, etc. (Casalini et al., 2019; Singhvi et al., 2019). PLA is produced from biomass feedstocks such as corn, wheat, potato, sugar cane, sugar beet and straw through biological fermentation to form lactic acid and subsequent chemically polymerization. Recently, recombinant bacteria were reported to convert glucose directly into PLA in vivo using CoA transferase and engineered PHA synthase (Huang et al., 2021; Choi et al., 2019). However, so far there has been no report on PLA producing yeast, either in nature or

Table 1
Characterization and physical properties of PLA, PHA, PBS, and PBAT biodegradable plastics.

Name	Thermo-stability	Film-forming	Hardness	Mechanical strength	Hydrolysis resistance	Tm (°C)	Tensile strength (MPa)	Flexural strength (MPa)	Flexural Modules (GPa)	Biosynthetic monomer
PLA	++	−	+++	++	−	140–152	53	92	3.4	LA
PHA	+++	++	−	+++	+++	75–180	20–65	No	No	SCL or MCL PHAs
PBS	+++	++	o	+++	+++	114	31	35	0.63	SA and 1,4-BD
PBAT	+++	++	−	+++	+++	110–120	20	3.1	0.08	TPA, AA, and 1,4-BD

+++ best, ++ better, + medium, o not good, − bad, −-worse, No No data.
Abbreviation: AA, Adipic Acid; 1,4-BD, 1,4-Butanediol; LA, Lactic acid; MCL, Medium-Chain-Length; SCL, Short-Chain-Length; SA, Succinic acid; TPA, Terephthalic Acid (Ilyas et al., 2020). The structures of the monomers have been shown in Fig. 1.

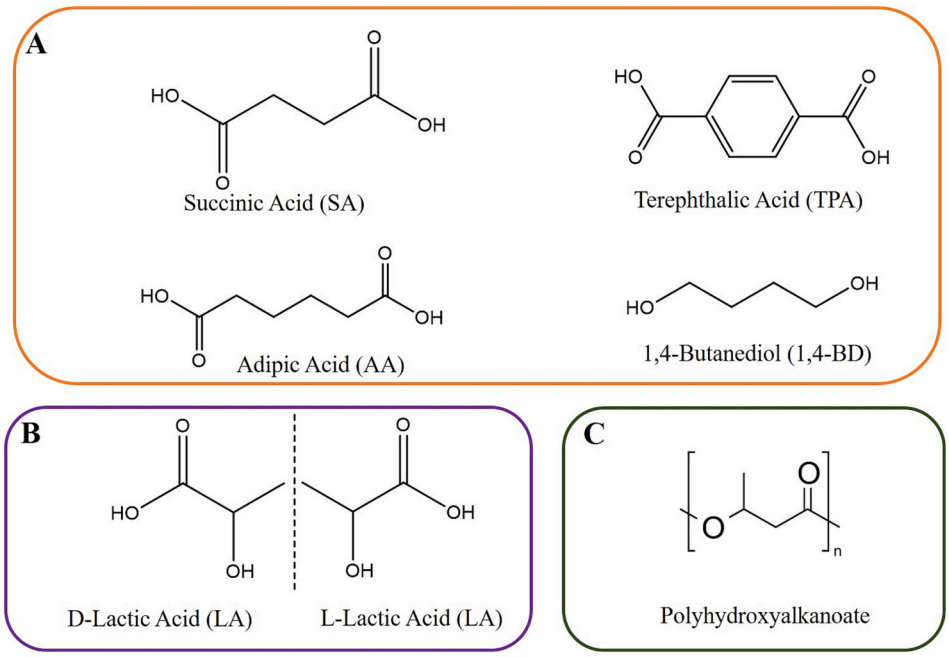

Fig. 1. Biobased monomers structures for PLA, PBS, and PBAT (A), schematic diagram of optical isomers of (+)-lactic acid (LA) and (−)-LA (B), and structure for PHA (C).
Abbreviation: PBAT, Polybutylene adipate terephthalate; PBS, Polybutylene succinate; PHA, Polyhydroxyalkanoate; PLA, Polylactic acid.

developed by genetic engineering.

The synthetic monomer of PLA is LA (lactic acid, 2-hydroxypropanoic acid) with the molecular formula $C_3H_6O_3$, which can be obtained by chemical synthesis or microbial fermentation. LA is a chiral molecule (Fig. 1B) that can exist in two enantiomeric forms: L- or D- LA. Chemical synthesis results in a racemic mixture. LA production by microbial fermentation can not only solve the problem of racemic mixtures, but also eliminate environmental pollution caused by intermediate molecules (de Franca et al., 2022; Datta and Henry, 2006). Microbial fermentation has become the main route for L-LA production (Liu et al., 2022a).

The fermentation efficiency of LA mainly depends on the LA production strains, different substrates and fermentation methods and technologies (Abdel-Rahman et al., 2013). LA can be produced by a variety of microorganisms, including bacteria, fungi, yeast, cyanobacteria, and algae (Abdel-Rahman et al., 2013; Huang et al., 2021). The microorganisms have been used to achieve the highest yield, productivity, and optical purity of either L- or D- LA, along with the modes of fermentation (Augustiniene et al., 2022). Most yeast strains have strong environmental tolerance to low pH (pH = 3.0–7.0) to produce LA (Abdel-Rahman et al., 2013; Pangestu et al., 2022). Several yeast genera have been engineered to produce LA, including *Saccharomyces* (Baek et al., 2016a; Jang et al., 2021; Watcharawipas et al., 2021), *Zygosaccharomyces* (Kuanyshev et al., 2021), *Candida* (Bellasio et al., 2015; Koivuranta et al., 2014;), *Pichia* (Melo et al., 2018; Park et al., 2018), and *Kluyveromyces* (Bianchi et al., 2001).

Saccharomyces and *Zygosacchromyces* can produce LA with glucose as substrate (Baek et al., 2016a; Jang et al., 2021; Lee et al., 2015; Novy et al., 2018; Valli et al., 2006; Watcharawipas et al., 2021). Genetically modified *S. cerevisiae* can produce LA using xylose as substrate (Novy et al., 2018; Turner et al., 2015), and metabolically engineered *S. cerevisiae* can produce LA utilizing fructose and sucrose as substrate (Gao et al., 2009). *C. sonorensis* can convert the substrate xylose D-xylose into LA by heterologous expression of lactobacillus L-lactate dehydrogenase (ldh) (Koivuranta et al., 2014). The substrates of LA synthesis by *Pichia* spp. include glycerol (Melo et al., 2018), and methanol (Yamada et al., 2019). Several yeasts from different genera can synthesize LA by using different sugar substrates (glucose, fructose, sucrose, xylose, lactose, etc.). The synthesis strategies of LA in yeast mainly including expression of biosynthesis enzyme, regulation monocarboxylate transporters, and lowering competition pathway (Fig. 2 and Table 2).

2.1.1. *Expression of LA biosynthesis enzyme*

For LA biosynthesis, and the gene *LDH* encoding lactate dehydrogenase enzyme that catalyzes pyruvate to LA, has been heterologously expressed in various engineered yeasts (Fig. 2). In the engineered *S. cerevisiae* BTCC3 LA2, an exogenous *LDH* gene (GenBank accession number MF582630.1) from *Lactobacillus casei* was introduced after disruption of the pyruvate decarboxylase gene *PDC1* and *PDC5* genes (Pangestu et al., 2022). An *LpDLDH* gene (GenBank accession number: MW574957) from *Leuconostoc pseudomesenteroides* was expressed in engineered *S. cerevisiae* ASc-d789M after deletion of *GPD1*, *GPD2* and *DLD1* and downregulation of ethanol pathway gene *ADH1* (Watcharawipas et al., 2021). In engineered *Z. bailii* NRRL Y7239, *ADE2* was deleted and *LDHA* from *Rhizopus oryzae* was site-specifically integrated into the *PDC1* gene locus (Kuanyshev et al., 2021). In engineered *S. cerevisiae* BK01, an evolution of the parental strain *S. cerevisiae* SR8LDH expressing the *LDH* gene (NCBI reference sequence NC_006814.3) from *Lactobacillus acidophilus*, LA production was increased (Jang et al., 2021; Kim et al., 2019). In engineered *Pichia pastoris* X-33, the bovine lactic acid dehydrogenase (XP_002492397) gene (*LDHb*) was expressed with interruption of the *PDC* gene (Melo et al., 2018). In engineered *S. cerevisiae* IBB14LA1–5, a gene *pfLDH* from *Plasmodium falciparum* was integrated at locus of the *PDC1* and *PDC5* gene (Novy et al., 2018). In engineered *Pichia kudriavzevii* DKA, *PDC1* was replaced with the *D-LDH* from *Lactobacillus plantarum* (Park et al., 2018). In engineered *S. cerevisiae* JHY5330, deleted genes *DLD1*, *GPD1*, *GPD2*, and a monocarboxylate transporter jen1, and overexpression of a transcriptional activator *HAA1*, an *LDHA* gene (LEUM_1756) from *Leuconostoc mesenteroides* subsp. *mesenteroides* ATCC 8293 was expressed, and the production of LA was increased (Baek et al., 2016a). In engineered *P. kudriavzevii* DKA, *PDC1* was replaced by *D-LDH* from *Lactobacillus plantarum* (Park et al., 2018). In engineered *S. cerevisiae* SR8L, an *LDHA* gene from *Rhizopus oryzae* was overexpressed under the control of

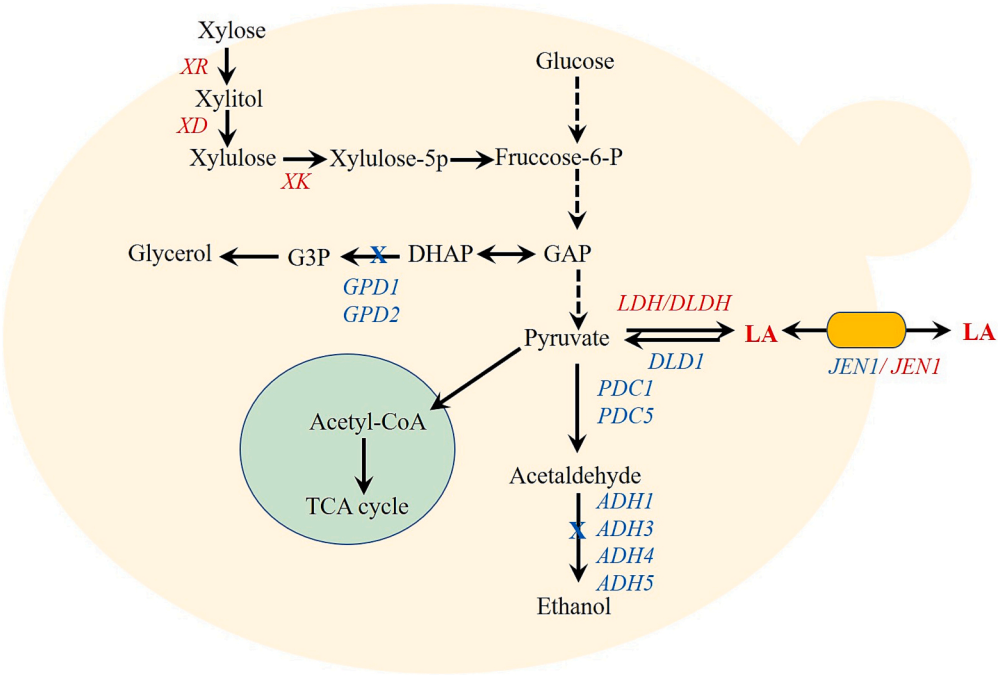

Fig. 2. The metabolic synthesis pathways of L/D-lactic acid in engineered yeast. The genes have been expressed in red italic; the genes have been deleted in blue italic. Lines: Black dotted line, multiple steps pathways; Black solid line, one step pathway. Abbreviation: A-ALD, acetylating acetaldehyde dehydrogenase; ADH: alcohol dehydrogenase; DHAP, dihydroxyacetone phosphate; DLD1, D- lactate dehydrogenase; GAP, glycealdehyde-3-phosphate; G3P, glycerol-3-phosphate; GPD1 and GPD2, Glycerol-3-phosphate dehydrogenases; JEN1: monocarboxylate transporter; LA, Lactic Acid; LDH, lactate dehydrogenase; PDC, Pyruvate decarboxylase; TCA, tricaboxylic acid cycle; XD, xylitol dehydrogenase; XK, xylulose kinase; XR, xylose reductase (Augustiniene et al., 2022; Baek et al., 2016a; Bianchi et al., 2001; Koivuranta et al., 2014; Liu et al., 2022a; Turner et al., 2015; Zhu et al. 2022). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the *PGK1* promoter through integration of the expression cassette in the chromosome (Turner et al., 2015). In engineered *C. sonorensis* 169, deleted xylose reductase and xylitol dehydrogenase encoding genes and overexpressing xylulokinase gene from *S. cerevisiae*, two copies of the gene *LDHL* from *Lactobacillus helveticus* were integrated (Koivuranta et al., 2014). In engineered *K. lactis* BM3-12D lacking the single pyruvate decarboxylase gene (*KlPDC1*), an *LDH* gene from bovine was expressed to produce LA (Bianchi et al., 2001). Zhu et al. (2022b) found that *LcLDH* from L. *casei*, *BoLDH* from bovines, and *RoLDH* from *Rhizopus oryzae*, were used to replace the coding region of *PDC1* in the chromosome of *S. cerevisiae* and LA production was increased to 12.4 g/L, 15.3 g/L, and 9.8 g/L, respectively, which were 21.5-, 26.8-, and 16.8-fold higher than yields of the control strain. The future research on *ldhs* from different sources how to affect quantity of LA production is highly suggested to further explore (Table 2).

2.1.2. Regulation monocarboxylate transporters increase the LA production

In LA-producing *S. cerevisiae* strains, monocarboxylate transporter jen1 and ady2 can downregulate LA production and are unstable in the presence of glucose, but upregulate LA production and are stable on xylose (Turner et al., 2019). In engineered *S. cerevisiae* JHY5330, with deletion of the genes *DLD1*, *GPD1*, *GPD2* and a monocarboxylate transporter jen1, and overexpression of a transcriptional activator *HAA1*, an *LDHA* gene (LEUM_1756) from *Leuconostoc mesenteroides subsp. mesenteroides* ATCC 8293 was expressed and LA production was increased (Baek et al., 2016a). However, the engineered *S. cerevisiae* S.c-NO.2–100 in the medium containing glucose, expression of monocarboxylate transporters was beneficial to the production of LA (Zhu et al., 2022b). Therefore, the effect of transporters expression on organic acid production deserves further study.

2.1.3. Lowering competition pathway for LA production

Furthermore, in engineered yeasts, the LA biosynthesis strategy has been implemented through blocking other metabolic pathways of pyruvate, such as deleting or inactivating glycerol synthesis pathway genes *GPD1* and *GPD2*, ethanol synthesis pathway genes *PDC1* and *ADH1*, TCA pathway gene *PDH*, and *DLD1* involved in biosynthesis conversion from LA (Fig. 2). By deleting or attenuating competing pathways (for glycerol and ethanol) and introducing heterologous *LDHs* through the LA biosynthetic pathway in metabolically engineered yeast strains, LA production was efficiently increased (Fig. 2). By expressing the highly stereospecific D-lactate dehydrogenase gene (*ldhA*, LEUM_1756) from *Leuconostoc mesenteroides* ATCC 8293 in *S. cerevisiae* and deleting main pyruvate decarboxylase gene (*PDC1*), alcohol dehydrogenase gene (*ADH1*), and glycerol-3-phosphate dehydrogenase genes (*GPD1* and *GPD2*), the engineering strain produced 112.0 g/L D-lactate with a yield of 0.80 g/g glucose and a productivity of 2.20 g/L/h (Baek et al., 2016a; Liu et al., 2022a); In *K. lactis* with deletion of *PDC1* and heterologous expression of the *LDH* gene, the yield of LA reached 0.85 g/g glucose (Bianchi et al., 2001); In *C. sonorensis* with two copies of the *ldhL* gene and a xylose isomerase encoded by *XYLA* from *Piromyces* sp., and xylulokinase encoding gene *XKS1* from *S. cerevisiae,* L-LA of 31.0 g/L was obtained from D-xylose medium (Koivuranta et al., 2014). Redox balance can influence metabolic flux. Cytosolic NADH (Nicotinamide adenine dinucleotide) is oxidized by two external (cytosolic) mitochondrial membrane-bound NADH dehydrogenases encoded by the *NDE1* and *NDE2* genes. In *S. cerevisiae*, deletions of *NDE1* and *NDE2* genes increased the amount of NADH available in the cytosol, resulting in improved L-LA production (Lee et al., 2015).

2.2. Synthesis strategies of polyhydroxyalkanoate (PHA) in yeast

PHA is a microbial polyester containing 3-, 4-, 5- and 6-hydroxycarboxylic acids. PHA is synthesized by microorganisms under certain environmental conditions (unbalanced nutrition or metabolism, limited O, N, P, S or trace elements). PHA is non-toxic, fully biosynthesized, and biodegradable and is considered one of the most promising bioplastics to replace traditional plastics. According to the number of carbon atoms in the monomer, PHA is divided into short chain length (SCL) PHAs with a monomer carbon chain length of 3–5 and medium chain length (MCL) PHAs with monomer carbon chain length of 6–14 (Ansari et al., 2021). Hydroxyalkanoates have a rich structural variation with alkyl to benzyl. However, hydroxyalkanoates as monomers do not usually occur alone and most microorganisms do not produce hydroxyalkanoates but PHA (Chen, 2010; Zhou, 2022). Yeasts lack endotoxins and PHA depolymerases that can be found in many bacterial strains. Yeast cellular compartments allow the separation of different precursors into distinct locations, increasing the possibilities of modifying the PHA

Table 2
Synthesis strategies of LA by yeast *S. cerevisiae* and non-conventional yeasts.

Strains	Substrates	Strategies	Product titer (g/L)	Yield (g/g)	Productivity (g/L/h)	Culture Conditions	References
S. cerevisiae BTCC3 LA2	Bagasse hydrolysate	Introducing an exogenous *LDH* gene after disrupting the *PDC1* and *PDC5* genes	L-LA (25.3)	0.51 g/g glucose	1.69	Shake flask, 90 rpm	Pangestu et al., 2022
S. cerevisiae S.c-NO.2–100	Medium with 1.95 g/L SC or SC-Ura, 90 g/L glucose, 3.4 g/L YNB, and 5 g/L $(NH4)_2SO_4$	Expressing monocarboxylate transporters *JEN1*	L-LA (121.5)	0.81 g/g glucose	1.69	Bioreactor, Batch, 200 rpm	Zhu et al. 2022b
S. cerevisiae ASc-d789M	Semi-defined media	Overexpressing *LpDLDH* and deleting *GPD1*, *GPD2* and *DLD1*, as well as downregulation of ethanol pathway gene *ADH1* using the L-methionine	D-LA (40.0)	0.81 g/g glucose	0.81	Bioreactor, Fed-batch, 0.5 VVM, 500 rpm	Watcharawipas et al., 2021
S. cerevisiae BK01	Acetate-rich buckwheat husk hydrolysates	Expressing the xylose oxidoreductase pathway derived from *Pichia stipitis* (*XYL1, XYL2*, and *XYL3*), Δald6, adaptive laboratory evolution on xylose, expressing the *LDH* gene from *Lactobacillus acidophilus.*	L-LA (119.0)	0.72 g/g glucose	–	Shake flask, 80 rpm	Jang et al., 2021; Kim et al., 2019
S. cerevisiae IBB14LA1–5	Complex media (10 g/L yeast extract) supplemented with either glucose or xylose at 50 g/L	Integrating *pfLDH* from *Plasmodium falciparum* at the *PDC1* and *PDC5* genes	L-LA (−)	0.68 g/g glucose	1.77	Bioreactor, 100–1000 rpm	Novy et al., 2018
S. cerevisiae JHY5330	YPD medium containing 100 g/L glucose with 50 g/L of $CaCO_3$	Expressing *LDHA* gene (LEUM_1756) from *Leuconostoc mesenteroides* subsp. mesenteroides ATCC 8293; deleting *DLD1* and a monocarboxylate transporter *JEN1*; deleting *GPD1* and *GPD2* genes, and overexpression of a transcriptional activator gene *HAA1*	D-LA (112.0)	0.80 g/g glucose	2.2	Shake flask, Fed-batch, 170 rpm	Baek et al., 2016a
S. cerevisiae SP7	Modified YP medium: 60 g/L glucose, 20 g/L yeast extract, 20 g/L peptone	Expressing *LDH* gene, deleting *PDC1*, L-lactate cytochrome-c oxidoreductase gene *CYB2*, *GPD1*, and isoenzymes of the external NADH dehydrogenase (*NDE1* and *NDE2*)	L-LA (117.0)	0.58 g/g glucose	–	Bioreactor, Fed-batch, 320 rpm	Lee et al., 2015
S. cerevisiae SR8L	YP medium containing 80 g/L of xylose	Overexpressing *LDHA* from *Rhizopus oryzae* under the control of the *PGK1* promoter through integration of the expression cassette in the chromosome	LA (49.1)	0.60 g/g xylose	0.47	Bioreactor, 200 rpm	Turner et al., 2015
S. cerevisiae H5531	SC medium	Expressing engineered PHA synthase PhaC1437 Ps6–19, propionyl-CoA transferase Pct540Cp, acetyl-CoA acetyltransferase PhaA, and acetoacetyl-CoA reductase PhaB1	PDLA (0.06) LA-3HB (0.36)	- -	- -	Shake flask, 220 rpm	Ylinen et al., 2021
Zygosaccharomyces bailii NRRL Y7239	YPD medium	Deleting of *ADE2* and site-specific integration of *Rhizopus oryzae ldhA* into the *PDC1* locus	LA (35.0)	0.35 g/g glucose -	–	Shake flask,100 rpm	Kuanyshev et al., 2021
P. pastoris X-33	YPD medium	Inserting the bovine *LDHb* concomitantly with the interruption of pyruvate decarboxylase gene *PDC*	LA (−)	0.65 g/g glucose	–	Bioreactor, Batch, 200 rpm	Melo et al., 2018
P. kudriavzevii DKA	YPD medium	Replacing *PDC1* with *D-LDH* from *Lactobacillus plantarum*	D-LA (154.0)	0.72 g/g glucose	4.16	Bioreactor, Fed-batch, 350 rpm, 1 vvm	Park et al., 2018
C. sonorensis 169	D-xylose medium	Integrating two copies of the gene *LDHL* from *Lactobacillus helveticus* into its genome, deleting xylose reductase and xylitol dehydrogenase encoding genes and overexpressing xylulokinase encoding gene from *S. cerevisiae*	L-LA (30.8)	0.57 g/g D-xylose	–	Shake flask,100 rpm	Koivuranta et al., 2014
*K. lactis*BM3-12D	SM supplemented with 5% (wt/vol) glucose, 2% (vol/vol) ethanol	Expressing *LDH* from bovine and lacking the single pyruvate decarboxylase gene *KlPDC1*	LA (60.0)	0.85 g/g glucose	–	Bioreactor, 400 rpm	Bianchi et al., 2001

Abbreviation: LA, lactic acid; LDH, lactate dehydrogenase; SM, Synthetic medium; PDC, pyruvate decarboxylase; YPD or YEPD, yeast extract peptone dextrose medium.

polymerization process and the final monomer compositions. PHA can be synthesized in several microorganisms (Chen, 2010; Koller, 2022; Tan et al., 2021). To develop a more efficient PHA system, yeast, insect cells, transgenic plants and other eukaryotic systems are being used to synthesize PHA. Polyhydroxybutyrate (PHB) is the earliest biosynthesis and the simplest structure of PHA (Leaf et al., 1996). *S. cerevisiae* synthesized PHB by heterologous expression of PHB synthase gene (*phbC*) from *Alcaligenes eutrophus* (Leaf et al., 1996), which is the first report that yeast produces PHA. In the biosynthesis of PHB, yeast, especially *S. cerevisiae*, could be an alternative production host because of good

inhibitor tolerance to weak acids and phenolic compounds, and it does not depolymerize the produced PHB (Portugal-Nunes et al., 2017).

2.3. Expression biosynthesis enzyme of polyhydroxybutyrate (PHB)

Biosynthesis of PHB in engineered yeast has been based on the following pathway: An acetyltransferase (PhaA) merges two acetyl-CoA molecules into one acetoacetyl-CoA. Acetoacetyl-CoA reductase (PhaB1) converts Acetoacetyl-CoA to 3-Hydroxybutyryl-CoA, and then PHA synthase (PhaC1) adds covalently to the growing polymer chain (Fig. 3) (Ylinen et al., 2022). In engineered yeasts, *phaA*, *phaB1*, and *phaC1* genes were expressed to produce PHB (Table 3) (Biernacki et al., 2017; Kocharin et al., 2012; Li et al., 2017a, 2017b; Portugal-Nunes et al., 2017; Sandstrom et al., 2015; Ylinen et al., 2021). In the engineered strain *S. cerevisiae* TMB4425, by heterologous expression of acetyl-CoA acetyltransferase (*phaA*), NADPH-linked acetyl-CoA reductase (*phaB*), and poly(3-hydroxybutyrate) polymerase (*phaC*) from *Ralstonia eutropha* H16, the production of PHB can be significantly increased up to a 2.7-fold increase (Kocharin et al., 2012); Constructed by integrating the PHB pathway (*phaA*, *phaB1*, and *phaC1* genes) from *Cupriavidus necator*, β-glucosidase gene *GH1–1* from *Neurospora crassa*, the cellobiose phosphorylase gene *CBP* from *Ruminococcus flavefaciens* cellodextrin, and transporter gene *CDT-1* from *N. crassa*, the PHB producing *S. cerevisiae* strain utilized cellobiose and produced PHB (Ylinen et al., 2022). Two recombinant *S. cerevisiae* strains TMB4443 expressing an NADPH-dependent acetoacetyl-CoA reductase and *XR* and TMB4425 expressing an NADH-dependent acetoacetyl-CoA reductase and a mutated *XR* were used to synthesize PHB (Portugal-Nunes et al., 2017; Sandstrom et al., 2015). The genes for β-ketothiolase, NADPH-dependent acetoacetyl-CoA reductase, and PHB synthase gene were inserted into the chromosome in *Y. lipolytica* C1AB (Li et al., 2017a, 2017b). Over-expressing PHA pathway genes for β-ketothiolase, acetoacetyl-CoA reductase, PHAs synthase and the *phasin* gene in *A. adeninivorans* AAMS_bktBp, PHB was produced (Biernacki et al., 2017).

2.4. Synthesis of the polybutylene succinate (PBS) monomer in yeast

PBS is a biodegradable, heat-resistant material. It is a plastic polymer synthesized by chemical condensation of 1,4-butanediol (BD) and succinic acid (SA) (Jambunathan and Zhang, 2016). The monomer is derived from fossil fuels or renewable resources. 1,4-BD, monomer for PBS and PBAT, is widely used in many chemical syntheses and served as an important chemical raw material. Among the 1,4-BD producing microorganisms, to our knowledge there is no report on the production of 1,4-BD in yeast (Guo et al., 2022). *Y. lipolytica* and *Issatchenkia orientalis* are non-conventional yeasts characterized by biosafety and robustness. Many strains of *Y. lipolytica* and *I. orientalis* can metabolize glucose to synthesize SA (Babaei et al., 2019; Cao et al., 2020; Fatma et al., 2020; Xiao et al., 2014). SA is a metabolic intermediate of the tricarboxylic acid (TCA) cycle in microbial cells. With the development of molecular biology, many engineered *Y. lipolytica* strains have been reported to produce SA. Selection of fermentation strains with an efficient strategy mode and their cultivation parameters will increase the efficiency of SA biosynthesis (Fig. 4).

2.5. Synthesis strategies of succinic acid (SA) monomer in yeast

2.5.1. Expression biosynthesis enzyme of SA

There are three major metabolic pathways of SA biosynthesis in microorganisms, e.g., in yeast: (1) reductive branch of the TCA cycle (Tricarboxylic acid cycle, rTCA), also known as reverse TCA, (2) oxidative TCA cycle (oTCA), (3) glyoxylate bypass cycle (Fig. 4) (Jiang et al., 2021; Li et al., 2021; Liu et al., 2022b). Succinate dehydrogenase (SDH) is involved in conversion of succinate to fumarate in the oTCA

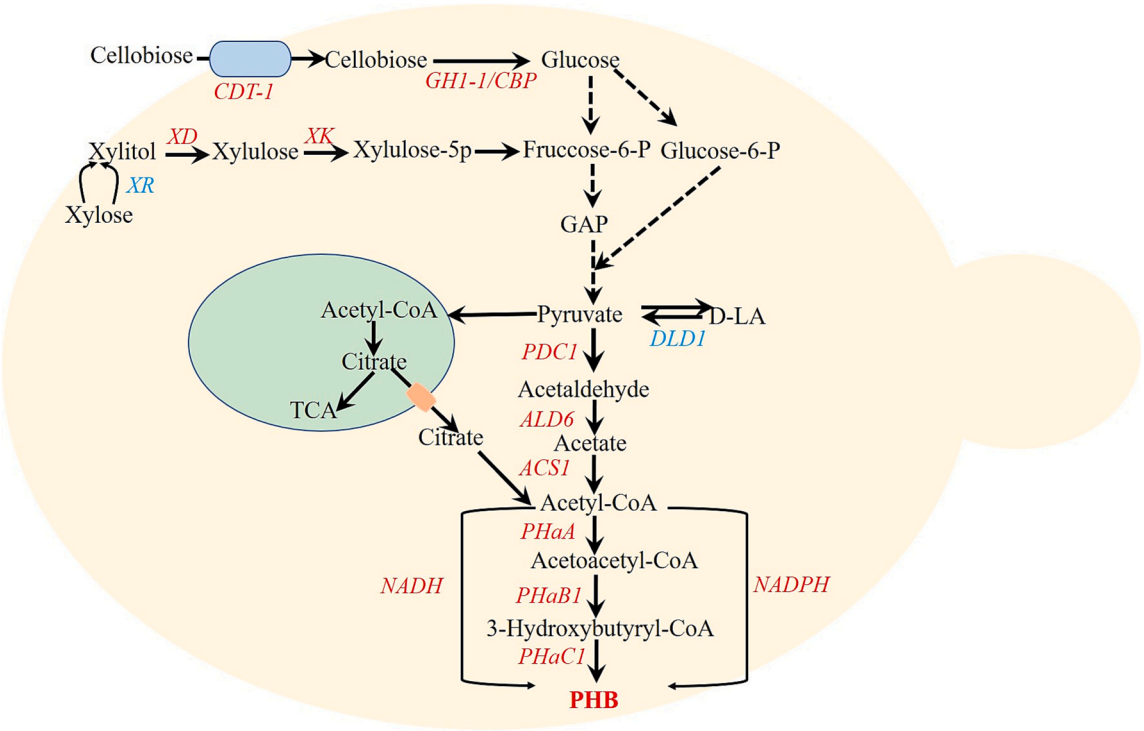

Fig. 3. Biosynthetic pathway of polyhydroxybutyrate (PHB) in yeast. The genes have been expressed in red italic; the genes have been deleted in blue italic. Lines: Black dotted line, multiple steps pathways; Black solid line, one step pathway. Abbreviations: ACS, acetyl-CoA synthase; ALD, aldehyde dehydrogenase; CBP, cellobiose phosphorylase; CDT-1,cellodextrin transporter; DLD1, D- lactate dehydrogenase; GAP, glycealdehyde-3-phosphate; GH1–1, β-glucosidase; PDC, pyruvate decarboxylase; PhaA, acetyl-CoA acetyltransferase; PhaB, acetoacetyl-CoA reductase; PhaC, PHA synthase; PHA, polyhydroxyalkanoate; XD, xylitol dehydrogenase; XK, xylulose kinase; XR, xylose reductase (Sandstrom et al., 2015; Li et al. 2017; Ylinen et al., 2022). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Synthesis strategies of PHA by yeast *S. cerevisiae* and non-conventional yeasts.

Strains	Substrates	Strategies	Product titer (g/L)	Yield (g/g)	Productivity (g/L/h)	Culture Conditions	References
S. cerevisiae PHB_cbp	SC-URA media with 35 g/L cellobiose	Expressing PHB pathway genes from *Cupriavidus necator*, cellodextrin transporter gene *CDT-1* from *Neurospora crassa,* and β-glucosidase gene *GH1–1* from *N. crassa* or cellobiose phosphorylase gene *CBP* from *Ruminococcus flavefaciens*	PHB (−)	37.40 mg/g cellobiose	10.5 mg/L/h	Bioreactor, Batch, 600 rpm	Ylinen et al., 2022
S. cerevisiae H5531	SC medium	Expressing engineered PHA synthase PhaC1437 Ps6–19, propionyl-CoA transferase Pct540Cp, acetyl-CoA acetyltransferase PhaA, and acetoacetyl-CoA reductase PhaB1	PDLA (0.06) LA-3HB (0.36)	- -	- -	Shake flask, 220 rpm	Ylinen et al., 2021
S. cerevisiae TMB4443	Yeast Base (YB) media	Expressing an NADPH-dependent acetoacetyl-CoA reductase and a wild-type *S. stipitis XR* with preferential use of NADPH.	PHB (0.012)	1.00 mg/g glucose	–	Shake flask, 180 rpm	Portugal-Nunes et al., 2017
S. cerevisiae TMB4425	Yeast Base (YB) media	Expressing an NADH-dependent acetoacetyl-CoA reductase and a mutated *XR* with a balanced affinity for NADPH/NADH.	PHB (0.073)	13.80 mg/g glucose	–		
S. cerevisiae TMB4443	YNB xylose medium (13.4 g/L Yeast nitrogen base, 50 g/L xylose)	PHB producer gene from *Cupriavidus necator* were introduced in recombinant *S. cerevisiae* 3043 capable of pentose utilization by introduction of the fungal genes for xylose utilization from the yeast *Scheffersomyces stipites*	PHB (0.1017)	1.99 mg/g xylose	–	Bioreactor, 300 rpm	Sandström et al. 2015
S. cerevisiae SCKK006	Synthetic dextrose (SD) medium	With a plasmid containing the PHB pathway genes coding for acetyl-CoA acetyltransferase (phaA), NADPH-linked acetoacetyl-CoA reductase (phaB) and poly(3-hydroxybutyrate) polymerase (phaC) from *Ralstonia eutropha* H16	PHB (0.043)	6.09 mg/g ethanol	–	Bioreactor, Batch	Kocharin et al., 2012
Y. lipolytica C1AB	Medium with 13.4 g/L yeast nitrogen base or complex medium (10 g/L yeast extract and 20 g/L peptone) supplemented with 50 g/L sodium acetate	The genes for β-ketothiolase, NADPH-dependent acetoacetyl-CoA reductase, and PHB synthase gene were inserted into the chromosome	PHB (7.4)	–	–	Bioreactor, Fed-batch, 200–800 rpm	Li et al. 2017
Arxula adeninivorans AAMS_bktBp	YPD medium	Overexpressing PHA pathway genes for β-ketothiolase, acetoacetyl-CoA reductase, PHAs synthase and the phasin gene	PHB/PHBV (11.6)	–	–	Bioreactor, Fed-batch	Biernacki et al., 2017

Abbreviation: SC, synthetic complete medium; TCA, tricarboxylic acid cycle; PHA, polyhydroxyalkanoate; PHB, polyhydroxybutyrate; YNB, yeast nitrogen base; YPD or YEPD, yeast extract peptone dextrose medium.

cycle. To produce SA via oTCA, in several engineered *Y. lipolytica* strains, *SDH* gene was deleted to produce SA (Billerach et al., 2021; Li et al., 2019; Li et al., 2018a; Li et al., 2017a, 2017b; Xi et al., 2021). In the engineered strain *Y. lipolytica* ST8578 constructed by Babaei et al. (2019), the promoter sequence of gene *SDH* was truncated, and the SDH activity was reduced by 77%, but the growth of the strain in glucose medium was unaffected. In the mediumwith pH of 5, the strain produced 35.3 g/L SA with a yield of 0.26 g/g glucose and a productivity of 0.60 g/L/h, respectively (Table 4).

The microbial production of SA via the rTCA pathway is a process potentially accompanied by net-fixation of carbon dioxide. According to the types of CO_2-fixing enzymes ie PPC (phosphoenolpyruvic acid (PEP) carboxylase), PCK (PEP carboxykinase), PYC (pyruvate carboxylase), MAE (malic enzyme), there are four types of rTCA (Liu et al., 2022b). During the PYC-rTCA pathway in the biosynthesis of SA from pyruvate, there are four enzymes, pyruvate carboxylase catalyzing pyruvate to oxaloacetate, malate dehydrogenase (mdh) catalyzing oxaloacetate to malate, fumarate hydratase (fum) catalyzing malate to fumarate, fumarate reductase (frd) catalyzing fumarate to succinate (Fig. 4). The enzymes endogenous peroxisomal malate dehydrogenase (MDH3), the cytosolic fumarase from *Rhizopus oryzae* (RofumR), and the peroxisomal fumarate reductase from *Trypanosoma brucei* (TbFRDg) are involved in rTCA pathway to synthesize SA in engineered *S. cerevisiae* (Malubhoy et al., 2022). To produce SA via rTCA pathway, *S. cerevisiae* UBR2 CBS -DHA-SA-AnDCT-02 (2)-PYC2oe, derived from *S. cerevisiae* UBR2 CBS -L-G3P-SA-AnDCT-02, overexpressing *PYC2* and *genes MDH1/2/3*, *FUM1*, and *FRD* can convert pyruvate to SA in the cytosol and dicarboxylic acid transporter *DCT-02* from *Aspergillus niger,* produced 35.0 g/L of SA (Malubhoy et al., 2022; Rendulic et al., 2022; Xiberras et al., 2020). Yan et al. (2014) reconstructed PYC-rTCA pathway in *S. cerevisiae*, and the engineered strain showed a 19.3-fold increase in SA production in shaken flasks, rising from 0.32 g/L to 6.17 g/L. Via the PCK-rTCA pathway in the biosynthesis of SA from PEP, the *ScPCK* from *S. cerevisiae* and the endogenous succinyl-CoA synthase beta subunit gene *YlSCS2* were overexpressed in *Y. lipolytica*, resulting in the production of 110.7 g/L SA with a yield of 0.53 g/g glycerol (Cui et al., 2017). Although high productivities and yields of SA can be achieved through rTCA biosynthesis pathways, some drawbacks still exist with using these pathways, such as their slow carbon throughput, limitation of NADH availability and poor cell growth (Liu et al., 2022b).

2.5.2. Regulation of transporters increase the SA production

Because mitochondrial carriers and C4-dicarboxylic acid transporters can increase SA secretion, Jiang et al. (2021) expressed the

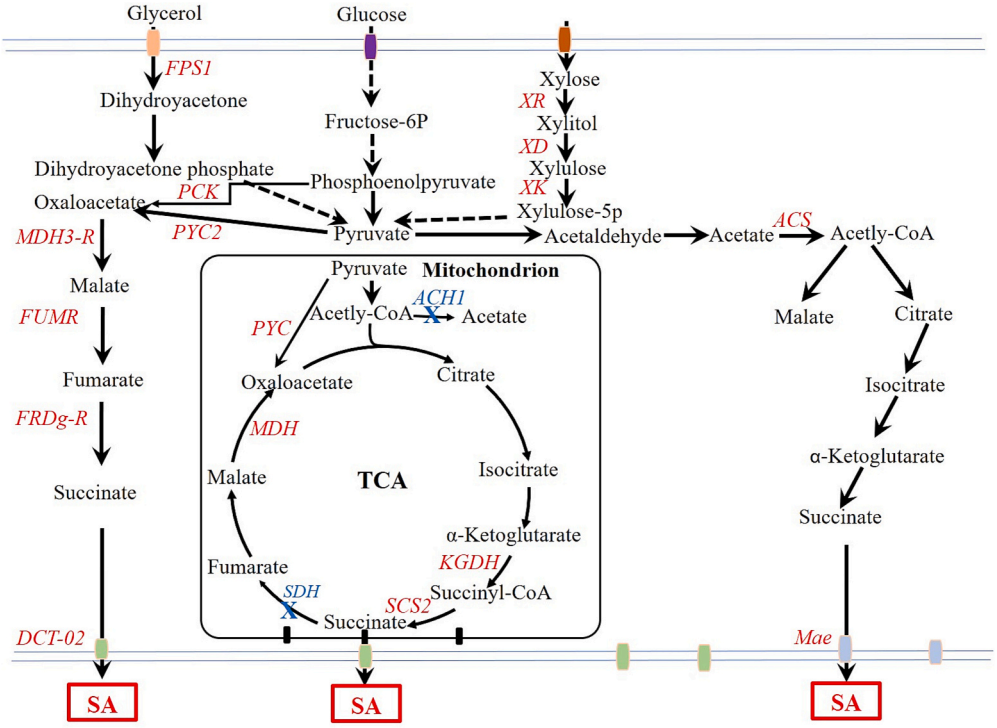

Fig. 4. Biosynthesis process of succinic acid (SA) in yeast. The genes have been expressed in red italic; the genes have been deleted in blue italic. Lines: Black dotted line, multiple steps pathways; Black solid line, one step pathway. Abbreviations: DCT-02 dicarboxylic acid transporter; FPS1, plasma membrane aquaglyceroporin protein; FRDg-R, glycosomal fumarate reductase; FUM, fumarase; KGDH, α-ketoglutarate dehydrogenase; Mae, C4-dicarboxylic acid transporter; MDH, malate dehydrogenase; PCK, phosphoenolpyruvate carboxykinase; PYC, pyruvate carboxylase; SCS, succinyl-CoA synthase; SDH, succinate dehydrogenase complex; XD, xylitol dehydrogenase; XK, xylulose kinase; XR, xylose reductase (Jiang et al., 2021; Li et al., 2018a; Li et al., 2019; Liu et al., 2022b; Malubhoy et al., 2022; Prabhu et al., 2020; Xiberras et al., 2020). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

transporter SpMae1 from *Schizosaccharomyces pombe* and optimized the biosynthetic pathway process of SA in *Y. lipolytica* PGC62-SYF-Mae and the strain produced 101.4 g/L SA with 0.37 g/g glucose and 0.70 g/L/h productivity, respectively (Jiang et al., 2021). *S. cerevisiae* UBR2 CBS-DHA-SA-AnDCT-02 expressing the dicarboxylic acid transporter DCT-02 from *A. niger* produced 10.7 g/L SA with a yield 0.22 g/g glycerol (Xiberras et al., 2020). *S. cerevisiae* SA-Dct-02 expressing the transporter Dct-02 from *A. niger* and produced 29.3 g/L SA (Rendulic et al., 2022). *P. kudriavzevii* is also known for the industrial production of various organic acids, especially SA. Expression of the carboxylate transporters PkJEN2–1 and PkJEN2–2 helped *P. kudriavzevii* CY902 to improve the SA production to 3.2 g/L titer (Table 4) (Xi et al., 2021).

2.6. Synthesis of polybutylene adipate terephthalate (PBAT) monomer in yeast

Among the biodegradable polymers, PBAT, a fully biodegradable polymer, has received worldwide attention due to its unique properties, including high flexibility, ductility and toughness (Table 1) (Jian et al., 2020; Lule and Kim, 2021). PBAT, an aromatic aliphatic copolymer, has been synthesized by polycondensation reaction of monomers 1,4-BD, adipic acid (AA) and terephthalic acid (TPA) using general polyester manufacturing technology. The biosynthesis of PBAT is one of the most promising and economical techniques.

2.6.1. Synthesis of AA in yeast

Biobased AA, an important platform chemical in industry, is a promising alternative to the current petrochemical route. In *E. coli,* AA production has been greatly improved by various synthetic biology and metabolic engineering strategies (Yu et al., 2014), with adipate at 57.6 g/L (Zhou et al., 2020). However, there is very little research on AA biosynthesis in yeast cells (Fig. 5 and Table5). *Candida tropicalis* KCTC 7212, which lacks the acyl-CoA oxidases *AOX* genes, was able to obtain AA of 12.1 g/L with a productivity of 0.10 g/L/h under optimal agitation speed, pH and substrate methyl laurate (Ju et al., 2020). In *Thermobifida fusca* B6, AA was produced from acetyl-CoA and succinyl-CoA via five reaction steps catalyzed by β-ketothiolase (Tfu_0875), 3-hydroxyacyl-CoA dehydrogenase (Tfu_2399), 3-hydroxyadipyl-CoA de-hydrogenase (Tfu_0067), 5-carboxy-2-pentenoyl-CoA reductase (Tfu_1647), and adipyl-CoA synthetase (Tfu_2576–7). Reverse adipate degradation pathway (RADP) genes (*Tfu_0875*, *Tfu_2399*, *Tfu_0067*, *Tfu_1647*, and *Tfu_2576-7*) from *T. fusca* were co-expressed in *S. cerevisiae*, and AA of 10.1 mg/L was achieved under optimal conditions (Zhang et al., 2020). The enoate reductases (ERs) gene from *Bacillus coagulans* was expressed in *S. cerevisiae*, and the biosynthesis of AA from glucose was demonstrated (Fig. 5 and Table 5) (Raj et al., 2018). Therefore, the exploration of AA synthesis in yeast is of great importance and innovation.

2.6.2. Synthesis of TPA in yeast

TPA (terephthalic acid) is a key raw material to produce polyesters, which are commercially required in large quantities for adhesives, beverage containers, fibers, films and paints. The biocatalytic synthesis of aromatic dicarboxylic acid is of current interest due to its mild reaction conditions and substrate specificity (He et al., 2022). However, to our knowledge, there is no report on the biosynthesis of TA in yeast.

3. Performance improvement of yeast cellular factory

Yeast is a unicellular eukaryotic fungus with completely different properties from those of bacteria. Nucleus, Golgi apparatus, mitochondria, endoplasmic reticulum, vacuole, and cytoskeleton are important components in yeast (Compagno et al., 2014; Montes de Oca et al., 2016). *E. coli* and *S. cerevisiae*, as model microorganisms, with the advantage and convenience of genetic and genome-editing tools, and well-annotated genomics, metabolomics, and fluxomic data, have been extensively developed for the bio-based production of various organic acids (Liu et al., 2021; Xiao et al., 2017; Yang et al., 2021). Among the cellular factories exploited for the commercial-scale production of monomeric organic acids, yeast strains have been attractive compared to bacteria due to their robustness at low pH values and convenient downstream processing (Rendulic et al., 2022; Wahl et al., 2017). However, these model microorganisms are not able to produce all the desired products for practical applications due to the limitation of different carbon sources, high tolerance to the substrates as well as the

Table 4
Synthesis strategies of SA by yeast *S. cerevisiae* and non-conventional yeasts.

Strains	Substrates	Strategies	Product titer (g/L)	Yield (g/g)	Productivity (g/L/h)	Culture Conditions	References
S. cerevisiae SA-Dct-02	$CaCO_3$ buffered medium	Expressing transporter Dct-02 from *Aspergillus niger*	SA (29.3)	0.42 g/g glycerol	–	Shake flask, Batch, 200 rpm	Rendulic et al., 2022
S. cerevisiae UBR2 CBS -DHA-SA-AnDCT-02 (2)-PYC2oe	Synthetic glycerol medium with ammonium sulfate	Overexpressing *PYC2* and DHA pathway genes in engineered *S. cerevisiae* UBR2 CBS -L-G3P-SA-AnDCT-02	SA (35.0)	0.81 g/g glycerol	–	Bioreactor, Aerobic batch	Malubhoy et al., 2022
S. cerevisiae UBR2 CBS -L-G3P-SA-AnDCT-02	Synthetic medium containing 75.6 g/L glycerol	Expressing three genes *MDH1/2/3*, *FUM1*, and *FRD* that encoding protein can convert oxaloacetate to SA in the cytosol and dicarboxylic acid transporter DCT-02 from *A. niger*	SA (10.7)	0.22 g/g glycerol	–	Shake flask, Batch, 200 rpm	Xiberras et al., 2020
Y. lipolytica PSA02004PP	Acetate as the sole carbon source	Expressing acetyl-CoA synthase	SA (12.2)	0.33 g/g acetate	–	Bioreactor, Feb-batch, 400 rpm, 2.0 vvm	Narisetty et al., 2022
Y. lipolytica PGC62-SYF-Mae	YPD medium	Screening mitochondrial carriers and C4-dicarboxylic acid transporters to enhance SA secretion	SA (101.4)	0.37 g/g glucose	0.70	Bioreactor, Feb-batch	Jiang et al., 2021
Y. lipolytica PGC202	Chemically defined medium (CM) containing initially 40 g/L glycerol.	Deleting succinate dehydrogenase gene *Ylsdh5*, acetyl-coA hydrolase gene *Ylach1*, followed by incorporating *S. cerevisiae* pyruvate carboxykinase *Scpck* gene and overexpressing the succinyl-CoA synthetase gene *Ylscs2*	SA (33.0)	0.12 g/g glycerol	0.57	Bioreactor, Feb-batch	Billerach et al., 2021
P. kudriavzevii CY902	YPD medium	Expression *PkJEN2–1* transporting a-ketoglutarate disrupted the *SDH* complex subunit gene *SDH5* in the parental DURA3 strain	SA (3.2)	–	–	Shake flask, 250 rpm,	Xi et al., 2021
Y. lipolytica PSA02004	OFMSW hydrolysate	Originated from the engineered *Y. lipolytica* PGC01003	SA (54.4)	0.44 g/g OFMSW hydrolysate	0.82	Bioreactor, Fed-batch, two stage pH	Stylianou et al., 2021
Y. lipolytica PSA02004	Crude xylose-rich hydrolysate derived from SCB	Overexpressing pentose pathway cassette comprising *XR*, *XDH*, and *XK* gene	SA (22.3)	0.19 g/g xylose	–	Bioreactor, Fed-batch, 600 rpm, aeration rate at 2.0 L/min	Prabhu et al., 2020
Y. lipolytica ST8578	YPG or YPD	Truncating the promoter of *SDH1* gene, overexpressing the genes in the glyoxylate pathway and the oxidative TCA branch, and expressing phosphoenolpyruvate carboxykinase from *Actinobacillus succinogenes*	SA (35.3)	0.26 g/g glucose	0.60	Bioreactor, Fed-batch, 1vvm	Babaei et al., 2019
Y. lipolytica PSA02004	Fruit and vegetable waste (FVW) hydrolysate	Originated from the engineered *Y. lipolytica* PGC01003 by adaptive evolution	SA (140.6)	–	0.69	In situ fibrous bed bioreactor (isFBB), Fed-batch	Li et al., 2018b
Y.lipolytica PGC01003	60 g/L crude glycerol	Deleting succinate dehydrogenase *YLsdh5* to interfere its function of oxidizing SA to fumaric acid in TCA cycle	SA (209.7)	0.45 g/g glycerol	–	In situ fibrous bed bioreactor (isFBB), Fed-batch	Li et al., 2018a
Y. lipolytica PGC202	YPG medium	Overexpressing phosphoenolpyruvate carboxykinase gene *ScPCK* from *S. cerevisiae* and endogenous succinyl-CoA synthase beta subunit *gene YlSCS2*	SA (110.7)	0.53 g/g glycerol	–	Bioreactor, Fed-batch, 600 rpm, 2 vvm	Cui et al., 2017
Y.lipolytica Y3753	YPG medium	–	SA (55.3)	0.34 g/g glucose	2.6	Bioreactor, Batch, 700 rpm	Bondarenko et al., 2017
Y.lipolytica PGC202	isFBB with 3% tryptone (*w/v*) and 60 g/L glucose-containing MFW hydrolysate	Deleting of the CoA-transferase gene and overexpressing of the succinyl-CoA synthase beta subunit gene and phosphoenolpyruvate carboxykinase gene from *S. cerevisiae*	SA (71.6)	0.43 g/g glucose	–	Bioreactor, Fed-batch, 600 rpm	Li et al., 2019
Y. lipolytica PSA02004	YPD medium and food waste hydrolysate	Adaptive evolution strategy via cell immobilization from the strain PGC01003	SA (87.9)	0.56 g/g glucose	0.70	Bioreactor, Batch, 600 rpm, aeration rate at 2.0 L/min	Yang et al., 2017

Abbreviation: SA, succinic acid; SCB, sugarcane bagasse; OFMSW, organic fraction of municipal solid waste; YPD or YEPD, yeast extract peptone dextrose medium; YPG, yeast extract peptone glycerol medium.

desired products, tolerance to different stress factors such as pH, temperature and oxidative stress (Cao et al., 2020; Fatma et al., 2020; Suthers et al., 2020). In addition, research on non-model yeasts as cellular factories has attracted the attention of researchers in recent years (Li et al., 2020).

3.1. *S. cerevisiae* as cellular factory to produce monomer organic acid

S. cerevisiae, as a model yeast, has been involved in the synthesis of different monomer organic acids. In the last five years, the situation of monomer organic acids production by yeasts including *S. cerevisiae* has

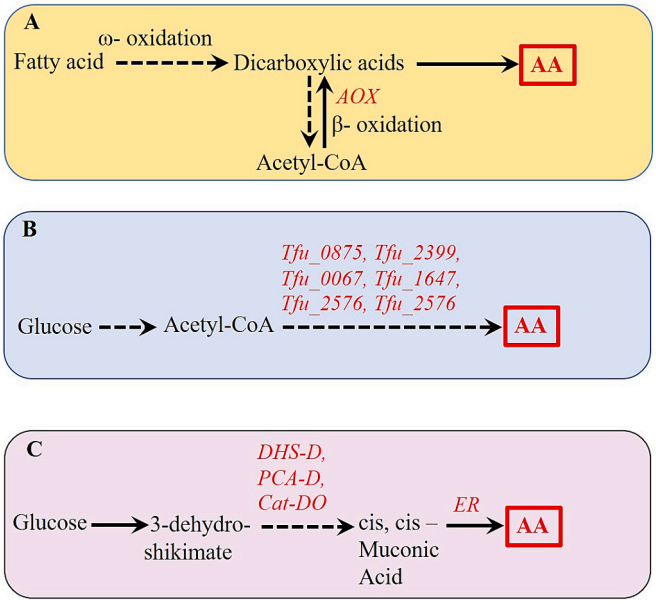

Fig. 5. The putative biosynthesis pathway for adipic acid (AA) in yeast. Lines: Black dotted line, multiple steps pathways; Black solid line, one step pathway. The genes have been expressed in red italic. A: The synthetic pathway of adipic acid by β-oxidation in *Candida tropicalis* (Ju et al., 2020). B: In *S. cerevisiae*, metabolic engineering to yield AA by heterologous co-expression of *Thermobifida fusca* reverse adipate degradation pathway (Tfu RADP) genes (*Tfu_0875*, *Tfu_2399*, *Tfu_0067*, *Tfu_1647*, and *Tfu_2576-7*) (Zhang et al., 2020). C: AA biosynthesis from glucose in *S. cerevisiae* by heterologous co-expression of *DHS-D, PCA—D, Cat-DO*, and *ER* gene. Abbreviations: DHS-D, 3-dehydroshikimate dehydratase; PCA—D, protocatechuate decarboxylase; Cat-DO, catechol 1,2 -dioxygenase; ER, enoate reductase (Raj et al., 2018). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

been investigated (Tables 2–5). The strain *S. cerevisiae* BTCC3 was used as a production platform for L-LA using real lignocellulosic hydrolysate (Pangestu et al., 2022); *S. cerevisiae* BK01 synthesized LA using acetate-rich buckwheat husk hydrolysates (Jang et al., 2021); *S. cerevisiae* ASc-d789M produced D-LA using semi-defined media (Watcharawipas et al., 2021); *S. cerevisiae* IBB14LA1_5 produced LA using complex media (10 g/L yeast extract) supplemented with either glucose (YG) or xylose (YX) at 50 g/L each (Novy et al., 2018). Poly (D-lactic acid) (PDLA) and copolymer P(LA-3HB) were produced in the *S. cerevisiae* H5531 (Ylinen et al., 2021). *S. cerevisiae* strains TMB4443 and TMB4425 produced PHB in YB medium (Portugal-Nunes et al., 2017). SA was produced in three different engineered *S. cerevisiae* strains, *S. cerevisiae* SA-Dct-02, *S. cerevisiae* UBR2 CBS -DHA-SA-AnDCT-02 (2)-PYC2oe, and *S. cerevisiae* UBR2 CBS -L-G3P-SA-AnDCT-02, respectively (Malubhoy et al., 2022; Rendulic et al., 2022; Xiberras et al., 2020). Engineered *S. cerevisiae* AA-2 produced AA in YPD medium (Zhang et al., 2020), and engineered *S. cerevisiae* ADP2 produced AA in YSC medium (Raj et al., 2018).

3.2. Non-conventional yeasts as cellular factories to produce monomer organic acid

In recent years, strong acid-tolerant phenotypes have received increasing attention, these non-conventional yeasts such as *A. adeninivorans*, *Zygosaccharomyces bailii*, *C. sonorensis*, *Y. lipolytica*, *R. toruloides*, *Kluyveromyces lactis, P. kudriavzevii, P. pastoris*, *I. orientalis*, and *C. tropicalis* have been exploited for various organic acids applications (Tables 2–5) (Fatma et al., 2020; Li et al., 2020). The engineered *Z. bailii* NRRL Y7239 produced LA (Kuanyshev et al., 2021); *P. pastoris* can grow in media containing only methanol as a carbon source, and can utilize crude glycerol, engineered *P. pastoris* X-33 produced LA (Melo et al., 2018); *P. kudriavzevii* DKA from *P. kudriavzevii* NG7 isolated from grape skins, produced D-LA (Park et al., 2018). *Y. lipolytica* is an obligate aerobic, oleaginous yeast that can grow on a wide range of substrates, including carbohydrates, alkanes, fatty acids and triglycerides. Engineered *Y. lipolytica* C1AB showed promising PHB producing ability when acetate was used as the carbon source (Li et al., 2017b). The non-conventional yeast *A. adeninivorans* AAMS_bktBp produced PHB/PHBV organic acids (Biernacki et al., 2017). Six yeast strains *Y. lipolytica* PSA02004PP (Narisetty et al., 2022), *Y. lipolytica* PGC62-SYF-Mae (Jiang et al., 2021), *Y. lipolytica* PGC202 (Billerach et al., 2021; Cui et al., 2017), *Y. lipolytica* PSA02004 (Li et al., 2019; Prabhu et al., 2020; Stylianou et al., 2021; Yang et al., 2017), *Y. lipolytica* ST8578 (Babaei et al., 2019), and *Y. lipolytica* PGC01003 (Yang et al., 2017) produced SA under different fermentation conditions. The unconventional yeast *P. kudriavzevii* CY902 produced SA (Xi et al., 2021), the engineered *C. tropicalis* ΔAOX4::AOX5 produced AA from short and long chain fatty acids after deletion of the acyl-CoA oxidase gene *AOX* (Ju et al., 2020).

3.3. Fermentation optimization and selection of substrate for yeast monomer organic acid

As a platform cell factory, yeast offers several desirable industrial properties, including fast growth, efficient anaerobic glucose

Table 5
Synthesis strategies of AA by yeast *S. cerevisiae* and non-conventional yeasts.

Strains	Substrates	Strategies	Product titer (g/L)	Yield (g/g)	Productivity (g/L/h)	Culture Conditions	References
S. cerevisiae AA-2	YPD medium	Co-expressing genes of reverse adipate degradation pathway gene *Tfu_0875*, *Tfu_2399*, *Tfu_0067*, *Tfu_1647*, and *Tfu_2576-7* from *Thermobifida fusca* (Tfu RADP)	AA (0.01009)	–	–	Bioreactor, Batch and Fed-batch, 400 rpm, ventilation volume 2 L/min	Zhang et al., 2020
S. cerevisiae ADP2	Yeast Synthetic Complete (YSC) medium	Expressing the *B. coagulans* enoate reductases *ER*	AA (0.00259)	–	–	Media bottles	Raj et al., 2018
C. tropicalis ΔAOX4::AOX5	G1 medium (6.7 g/L yeast nitrogen base, 3.0 g/L yeast extract, 3.0 g/L ammonium sulfate, 1.0 g/L potassium phosphate monobasic, 1.0 g/L potassium phosphate dibasic, 75 g/L glucose)	Deficient of acyl-CoA oxidases gene *AOX*	AA (12.1)	–	0.1	Bioreactor, Fed-batch, 1000 rpm, methyl laurate of 3% (w/v)	Ju et al., 2020

Abbreviation: AA, adipic acid; AOX, acyl-CoA oxidase; YPD, yeast extract peptone dextrose medium.

metabolism, high ethanol productivity, high yield, insensitivity to bacteriophage infection and high tolerance to environmental stresses such as high ethanol concentration, low pH and low oxygen levels.

The *S. cerevisiae* strains were capable of xylose utilization by introducing *Scheffersomyces stipitis* xylose utilization genes, with a PHB yield of 1.99 ± 0.15 mg/g xylose obtained (Sandstrom et al., 2015). *S. cerevisiae* used cellobiose as carbon source to produce PHB by expressing the *phaA, phaB1,* and *phaC1* genes under the Tet-On synthetic transcription factor system (Ylinen et al., 2021, 2022). Compared to *S. cerevisiae*, *Y. lipolytica* is an obligate aerobic, oleaginous yeast which can grow on broad substrates, and can provide sufficient acetyl-COA, that is the precursor of PHB product (Li et al., 2017b). The PHB production by strain *Y. lipolytica* with expression of β-Ketothiolase, NADPH-dependent acetoacetyl-CoA reductase, and PHB synthase, was increased to 7.4 g/L (Li et al., 2017b). In *Y. lipolytica*, tailor-made PHAs, medium-chain-length PHA (mcl-PHA) were produced (Rigouin et al., 2019). In the non-conventional yeast *Arxula adeninivorans*, by genetic modification and optimization of culture conditions, poly (hydroxybutyrate-*co*-hydroxyvalerate) (PHB-V) (10.8 g/L) was produced (Biernacki et al., 2017).

Via the selection in the repeated-batch bioreactor mode, Bondarenko et al. (2017) optimized the fermentation conditions of the patented strain *Y. lipolytica* VKPM Y3753, derived from *Y. lipolytica* VKPM Y-3314 (with an inactivated *SDH*2 gene), by multi-step mutagenesis using nitrosoguanidine and subsequent two-stage selection (Sineokii et al., 2013). SA production of 55.3 g/L was achieved with a productivity of 2.60 g/L/h (Bondarenko et al., 2017). Li et al. (2018a) used agricultural residues through the in situ fiber bed bioreactor (isFBB) and optimized fermentation conditions, including initial crude glycerol concentration, quantity of sugarcane bagasse, and aeration, in *Y. lipolytica* PGC01003 from *Y. lipolytica* Po1f (deleting the *YLsdh5* gene), SA production reached 209.7 g/L. By feeding glucose-rich mixed food waste to *Y. lipolytica* PGC202, a succinate dehydrogenase-deficient strain, in isFBB fermentation with optimal nitrogen source and initial glucose concentration, SA production reached 71.6 g/L (Li et al., 2019); Billerach et al. (2021) found that SA yield and specific production rate in strains PGC01003 and PGC202 were increased due to nitrogen limiting flux instead of nitrogen deficiency. In PGC01003, the SA production reached 19.0 g/L with 0.23 g/g glycerol yield, and 0.23 g/L/h productivity; In PGC202, SA production reached 33.0 g/L with 0.12 g/g glycerol yield and 0.57 g/L/h productivity. The engineered yeast *Y. lipolytica* PSA02004 produced 54.4 g/L SA with 0.44 g/g glucose yield and 0.82 g/L/h productivity by using urban organic biological waste in a two-step pH regulation strategy with optimal initial carbon source concentration and volumetric oxygen transfer coefficient (Stylianou et al., 2021). The optimized waste hydrolysate from mixed fruit and vegetables as medium, fermentation conditions of *Y. lipolytica* PSA02004 originated from the engineered *Y. lipolytica* PGC01003 (*Ylsdh5* gene knocked out) were optimized by *is*FBB and fed-batch fermentation, SA production of 140.6 g/L titer with productivity of 0.69 g/L/h was achieved (Li et al., 2018b).

The deletion of the CoA transferase gene *Ylach* eliminated the formation of acetic acid and improved SA production and cell growth. Inactivation of *SDH* is beneficial for *Y. lipolytica* to produce SA. However, the reduced ability of the strain to metabolize glucose affects the application of the strain. Yang et al. (2017) used an adaptive evolution strategy in the engineered strain *Y. lipolytica* PSA02004 with *YlSDH5* deletion, the utilization rate of glucose was improved, and the SA production in YPD (Yeast Extract Peptone Dextrose) medium and food waste hydrolysate medium was 65.7 g/L and 87.9 g/L, respectively. By overexpressing xylose reductase gene *XR*, xylol dehydrogenase gene *XDH*, and xylose kinase gene *XK*, *Y. lipolytica* PSA02004 used xylose as the sole carbon source to synthesize SA with a yield of 22.3 g/L (Prabhu et al., 2020). Recombinant *Y. lipolytica* PSA02004PP expressing acetyl-CoA synthase produced 12.2 g/L SA when the strain was grown in high concentrations of acetate as the sole carbon source (Narisetty et al., 2022).

Currently, there is limited research on mixed culture of yeast and other microorganisms for production of monomeric organic acid. To our knowledge, one literature found that the synthesis of LA was higher in the co-culture of *Kluyveromyces marxianus* with *Lactobacillus delbrueckii* than in the independent culture of three single strains when cheese whey was used as substrate (Plessas et al., 2008).

3.4. Biomass feedstocks for yeast bioplastic production

One of the promising applications of yeast cell factory is to utilize renewable biomass as feedstocks to produce fuels, chemicals, and biomaterials (Rosenboom et al., 2022; Sheldon, 2014). However, so far there are only few relevant reports on yeast bioplastic production, which were summarized in Table 6. Among the studies, yeast strain *C. lignohabitans* CBS 10342 can produce LA when straw, miscanthus, sawdust, shrub cuttings and wood chips containing 30% (*w*/w) spruce and 70% (w/w) beech as lignocellulosic biomass substrate (Bellasio et al., 2015). *S. cerevisiae* SR8 LDH and BTCC3 can produce LA when spent coffee grounds (SCG) generated after coffee extraction and sterile-filtered sugarcane bagasse hydrolysate as biomass substrates during fermentation, respectively (Kim et al., 2019; Pangestu et al., 2022). Studies showed that *Y. lipolytica* can utilize various biomass feedstocks (sugarcane bagasse, glucose-rich mixed food waste, fruit and vegetable waste, agricultural waste, and organic fraction of municipal solid waste) to produce SA (Li et al., 2018a, 2018b, 2019; Stylianou et al., 2021). In addition, *S. cerevisiae* can produce SA by utilizing *Eucalyptus globulus* lignosulfonate stream (Stovicek et al., 2022). Considering the abundance and low-cost nature of biomass, production of bioplastics using biomass as substrates by yeast cell factories deserves in-depth investigation.

Table 6
Yeast monomeric organic acid production on biomass feedstocks.

Strains	Biomass Feedstocks	Products	References
C. lignohabitans CBS 10342	Straw, miscanthus, sawdust, shrub cuttings and wood chips containing 30% (*w*/w) spruce and 70% (w/w) beech as lignocellulosic biomass.	LA	Bellasio et al., 2015
S. cerevisiae SR8 LDH	Spent coffee grounds (SCG) generated after coffee extraction	LA	Kim et al., 2019
S. cerevisiae BTCC3	Sterile-filtered sugarcane bagasse hydrolysate	LA	Pangestu et al., 2022
Y. lipolytica PGC01003	Sugarcane bagasse with crude glycerol	SA	Li et al., 2018a
Y. lipolytica PGC202	Glucose-rich mixed food waste (MFW) hydrolysate consisting of rice, noodles, meat and vegetables; Fruit and vegetable waste (FVW) consisting of apples, pears, oranges, potatoes, cabbages, lettuce and taros; Agricultural waste (AW) including sugarcane bagasse, wheat straw and corn stalk	SA	Li et al., 2019
Y. lipolytica PSA02004	The glucose-containing FVW hydrolysate composed of apples, pears, oranges, potatoes, cabbages, lettuce and taros and 4% corn steep liquor (CSL)	SA	Li et al., 2018b
Y. lipolytica PSA02004	Organic fraction of municipal solid waste (OFMSW)	SA	Stylianou et al., 2021
S. cerevisiae	*Eucalyptus globulus* lignosulfonate stream (60%, *v*/v)	SA	Stovicek et al. 2022

3.5. Improvement strategies of yeast acid stress tolerance

Despite the promising future of biomass for yeast bioplastic production, high production cost remains a major challenge, just like what is being faced by lignocellulosic fuel ethanol production (Raj et al., 2022). Inhibitors in lignocellulosic biomass commonly repress yeast fermentation (Zhao et al., 2016). On the other hand, in the production process of microbial organic acids, acid stress is unavoidable for microorganisms. Yeast, as a significant microbial cell factory, has been employed to produce organic acids due to its unique characteristics such as tolerance to low pH and osmolarity (Gao et al., 2021; Xu et al., 2022). Normally, yeast thrive at pH ranging from 4.0 to 6.0, and recent studies reported an *S. cerevisiae* mutant that thrived at pH = 2.3 (Sun et al., 2023). However, during high titer organic acids production, acid stress is still unavoidable for the yeast cells. On the other hand, yeast bioproduction can be affected by multiple stress conditions, which include high temperature, nutrient starvation, as well as inhibitors, including acetic acid, formic acid, furfural, and so on that present in lignocellulosic hydrolysate (Zhao et al., 2016). To improve the stress tolerance of yeast, biochemical and molecular mechanism of yeast stress tolerance have been studied (Chen et al., 2022; Zhang et al., 2019a) and reviewed (Deparis et al., 2017; Takagi, 2021; Zhao and Bai, 2009). Acid stress is a key factor limiting the production of organic acids during yeast fermentation. The yeast acid tolerance mechanisms can be used to enhance the biosynthesis of organic acids, but also protect yeast from contamination by other microorganisms during the fermentation during fermentation under low pH conditions. The following strategies have been reviewed for the improvement of organic acid yield and acid tolerance of yeast strains.

3.5.1. Screening natural and mutated acid-tolerant strains

Microorganisms isolated from acidic environments may have the potential for organic acid production and high acid pH tolerance. After selection, excellent natural acid-tolerant strains can be used for industrial production of organic acid. Therefore, screening acid-tolerant strains as promising chassis strains is the key to further metabolic engineering of yeast strains to improve organic acid production. The isolation of stress-tolerant yeasts from environmental sources, including from industrial processes can prove advantageous for yeast fermentations (Basso et al., 2008; Walker and Basso, 2020). Carbon dioxide concentration can be used to optimize the industrial fermentations of yeast (Guadalupe-Daqui et al., 2023). Although relevant studies have only been performed in bacteria, similar strategies can be employed using yeast. For example, high throughput screening (HTS) method has been developed to screen lactic-acid bacteria with desirable traits, including acid production and osmotic stress tolerance. The strains were cultured in 96-well microplates and growth was monitored using Plate Butler® robotic systems. The growth data obtained was analyzed using a microplate package to obtain maximum growth rates and OD values. The high-throughput method with colloidal calcium carbonate agar plate-based screening has also been developed for screening lactobionic acid (LBA) producing microorganisms. The high-throughput method (Zhu et al., 2022a) and colloidal calcium carbonate agar plate-based screening method (Oh and Eom, 2022) can be used to screen acid-producing yeast strains. In addition to simple growth detection, biosensor-based HTS methods have been developed to select yeast strains that efficiently produce octanoic acid (Baumann et al., 2021), pyruvate acid (Luo et al., 2017), and cis, cis-muconic acid (Jensen et al., 2021). Tolerance formation is a complex process and mechanism involving large number of factors, including stress proteins, transcription factors, efflux pumps, altered membrane composition, stress-adapted energy metabolism, chemical detoxification, and the accumulation of small-molecule chaperons and the compatible solutes (Nicolaou et al., 2010). For example, the *S. cevisiae* transcriptional regulator War1 involved in weak acid response and the acid responsive PDR12 promoter were used to develop an organic acid biosensor to detect varying levels of para-hydroxybenzoic acid (PHBA) production (Williams et al., 2017). Positive-feedback, ratiometric biosensor expression improved the efficiency of high-throughput screening for metabolite producers in yeast (Adeniran et al., 2015). Biosensor-based screening has significantly increased the efficiency of selection. However, this method requires a suitable biosensor that is specific and operates in the meaningful range, which may require considerable effort. The biosensor-based method can be used to screen not only natural isolates but also laboratory adapted strains (Adeniran et al., 2015).

3.5.2. Metabolic engineering and genetic modification

Studies on the mechanisms of acid stress response and tolerance in yeast are benefiting organic acid production in yeast strains. The cell wall integrity (CWI), high osmolarity glycerol (HOG) and Ca^{2+}/calcineurin signaling pathways provide the post-translational activation of transcription factors required to promote cell wall maintenance and regeneration to survive acidic pH stress (Ribeiro et al., 2022). Stress tolerance is regulated by a coordinated process involving many transcription factors (Dawes and Perrone, 2020). Overexpression or knockout of many genes involved in the response to low pH can lead to changes in acid tolerance in yeast. For example, in an early study, overexpression of *CTT1* in *S. cerevisiae* improved acid tolerance and organic acid production (Abbott et al., 2009). Overexpression of the transcription factor gene *ECM22* can increase ergosterol levels in *S. cerevisiae*, resulting in improved tolerance to lactic acid stress (Ferraz et al., 2022). Our previous study demonstrated that the de novo purine biosynthesis genes are useful targets for metabolic engineering of lactic acid stress tolerance in yeast (Zhang et al., 2019a). In *S. cerevisiae*, many genes are involved in lactic acid tolerance (Peetermans et al., 2021). The strain in which the four genes *dse2*, *scw11*, *eaf3* and *sed1* are deleted together can increase lactic acid resistance and productivity (Suzuki et al., 2013). Changes in the expression of single genes *GSF2* (Baek et al., 2016b), *HAA1* (Baek et al., 2016a), *SSB1* (Lee et al., 2016), *SAM2* (Dato et al., 2014), *ESBP6* (Sugiyama et al., 2016) can alter lactic acid tolerance in *S. cerevisiae*.

Similar studies have also been carried out in non-conventional yeasts. For example, in *C. glabrata*, overexpression of *CgAMD1* encoding AMP deaminase (AMD1) in AMP metabolism can improve acid tolerance and pyruvate fermentation performance of the strain at pH = 4 (Wu et al., 2018). Deletion of *CgADE13*, which encodes adenylosuccinate lyase in AMP metabolism, can increase pyruvate productivity and improve acid tolerance of *C. glabrata* (Chen et al., 2018).

The critical genes that can improve acid tolerance and acid production provide a basis for further investigation of acid tolerance mechanisms and regulation of organic acid production in yeast strains.

3.5.3. Adaptive laboratory evolution (ALE) experiments

Adaptive laboratory evolution (ALE) is a useful approach to generate evolved microbial strains with desired properties under specific growth conditions (Dragosits and Mattanovich, 2013; Mavrommati et al., 2022). Using the ALE approach, several *S. cerevisiae* strains with improved organic acid tolerance to low pH were obtained (Fletcher et al., 2017). The extent of selective pressure and the nature of the acid were shown to be important factors in directing the evolutionary path of low pH tolerance in *S. cerevisiae* strains (Fletcher et al., 2017). Kildegaard et al. (2014) obtained *S. cerevisiae* strains tolerant to a heterologous product (3-HP) using an ALE strategy, and the experimental result provides insights into possible mechanisms for product toxicity and detoxification. By using short-term adaptation strategy and ALE in *S. cerevisiae*, strains were obtained for tolerance to at pH = 3.7 with acetic acid and lignocellulosic hydrolysate inhibitors during ethanolic fermentation (Narayanan et al., 2016). The above HTS method can be used to screen mutants obtained from the ALE, and the mechanisms underlying the improved tolerance and production can be further elucidated using multi-omics analyses. This knowledge can then be further used to breed strains with improved production (Zhang et al., 2019b).

The addition of substrates from external sources is also used to improve acid stress tolerance strategies in yeast. In *S. cerevisiae*, the comparative transcriptome analysis results suggested that the up-regulated vitamin B1 and B6 biosynthesis contributed to the low pH tolerance (Wu et al., 2022). In our group's study, the addition of zinc sulphate improved the acid tolerance of cells (Wan et al., 2015). The addition of exogenous substrates can efficiently improve strain acid tolerance and product synthesis, but the additional production costs should be considered.

4. Concluding remarks

Plastic pollution caused by traditional plastics depending on fossil source has become a major global threat to the environment, human health and sustainable development. Yeast cell factories show promise for large-scale production of bioplastics or their monomers. Great progress has been made in the last 20 years in engineering yeast cell factories to produce biodegradable plastics and their monomers. The review includes (1) Biosynthesis of monomeric organic acid L-LA or D-LA of PLA, PHA, monomer SA and 1,4-BD of PBS, and monomer AA of PBA. (2) Performance improvement of yeast as cellular factory. (3) Improvement strategies of yeast acid stress tolerance. This review has discussed current developments and future trends in yeast biotechnology of biodegradable plastics. However, for economic bioproduction, it is important to achieve high titer, high yield and high productivity in yeast. Important aspects for further engineering yeast cell factories include:

4.1. Exploring regulatory mechanisms underlying the biosynthesis

Despite rich knowledge on metabolic pathways and regulatory network in laboratory yeast, much less is known on relevant aspects in industrial yeasts, which often have distinct regulatory mechanisms due to long-term strain development and adaptation to industrial fermentation conditions. Additionally, compared to bacteria, yeast strains have greater structural complexity in their cells, such as the separation of enzymes and substrates by organelles, and the functional genomes of yeast remain not quite mature, especially in non-conventional yeasts. Therefore, more research should be focused on the regulatory mechanisms of acid production in engineering yeast, and it is interesting to explore the common aspects and specific aspects for different products.

4.2. Utilization of renewable feedstocks and improvement of stress tolerance

Bioproduction from biomass, especially lignocellulosic biomass, is carbon-neutral and sustainable. To produce bioplastics and their monomers efficiently, yeast host strains that naturally utilize xylose in the hydrolysate are preferred. Alternatively, it's desired to have yeast strains that can be easily genetically engineered to utilize xylose. In addition, stress tolerance of the yeast is also an important trait for the bioproduction, and relevant stress factors including inhibitors present in the lignocellulosic hydrolysate, high temperature, osmotic stress, and so on. The challenge is how to achieve desirable production traits that are controlled by multiple genes and regulatory networks. This will require global regulation and rapid engineering technologies.

4.3. Establishment of database and developing machine learning tools

Machine learning can be used to predict phenotypes from genotypes, and thus can be used to synthesize organic acids efficiently. For example, a machine-learning model of the yeast *S. cerevisiae* has been constructed and used for D-LA productivity (Yamamoto et al., 2023) and bioethanol production (Konishi, 2020). Machine learning is increasingly being used in yeast metabolic engineering. To build a machine learning model, a large number of high-quality datasets are required. It will be nice to develop databases that focus on bioplastic production using yeast. In addition, in-depth collaboration between biotechnologists and computer scientists is highly desirable to develop perfect machine learning models.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

Not applicable.

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