Applied Microbiology and Biotechnology
https://doi.org/10.1007/s00253-020-10917-0

MINI-REVIEW

Current advance in biological production of short-chain organic acid

Li Sun[1,2] · Mengyue Gong[3] · Xueqin Lv[1,2] · Ziyang Huang[1,2] · Yang Gu[1,2] · Jianghua Li[1,2] · Guocheng Du[1,2] · Long Liu[1,2]

Received: 18 July 2020 / Revised: 14 September 2020 / Accepted: 17 September 2020

Abstract

As natural metabolites, organic acids have been widely applied in food, pharmaceutical, and bio-based materials industries. Particularly, the short-chain organic acids, including C2, C3, C4, C5, and C6 organic acids, are necessary intermediate metabolites in cells and are also alternatives to some commercial chemical products. As the necessary metabolites in cells, most major short-chain organic acids can be produced through microbial fermentation. Specifically, with the development of synthetic biology, metabolic engineering could endow cells with the ability to produce more short-chain organic acid products including propionic acid, pyruvate, lactic acid, 3-hydroxypropionic acid, malic acid, succinic acid, fumaric acid, butyric acid, itaconic acid, α-ketoglutaric acid, glutaric acid, citric acid, gluconic acid, muconic acid, adipic acid, xylonic acid, and so on. The recent advances in the biological production of short-chain organic acids, as well as the challenges and perspectives, are summarized in this review to promote the generation of microbial cell factories for the production of short-chain organic acids.

Key points

- *Outlines the production strategy of short-chain organic acids*
- *Provide guidance for efficient synthesis of short-chain organic acids*
- *Impacts the necessary factor of acid resistance on the successful production of host cells*

Keywords Short-chain organic acids · Biosynthetic pathways · Metabolic engineering · Organic acid biosensor · Acid tolerance

Introduction

Short-chain organic acids are low molecular weight organic compounds with one or more acidic groups, of which typically include carboxylic, sulfonic, and thiocarboxylic (Yin et al. 2015). According to the number of carbon atoms, short-chain organic acids can be divided into carbon two (C2), carbon three (C3), carbon four (C4), carbon five (C5), and carbon six (C6) organic acids (Wittmann et al. 2015). Commonly, C3 organic acids include propionic acid (PA), pyruvate, lactic acid (LA), and 3-hydroxypropionic acid (3-HP). C4 organic acids include malic acid (MA), fumaric acid (FA), succinic acid (SA), and butyric acid (BA). C5 organic acids include itaconic acid (IA), α-ketoglutaric acid (α-KG), glutaric acid, and xylonic acid (XA), while C6 organic acids include citric acid (CA), muconic acid (mainly *cis*, *cis*-muconic acid, CCM), gluconic acid (GA), and adipic acid (AA).

Short-chain organic acids have many industrial applications in food, pharmaceuticals, cosmetics, detergents, polymers, and textiles industries (Alonso et al. 2015; Garcia et al. 1999; Goldberg et al. 2006); for example, the calcium, sodium, and ammonium salts of PA are relatively good choices for preservatives in animal feed and human food owing to the preservative effect (Guan et al. 2016; Liu et al. 2016). IA can be used to prepare synthetic fibers, synthetic resins, and plastics, and its ester derivatives can also be used for the copolymerization of styrene or as plasticizers of polyvinyl chloride (Zhao et al. 2018c). MA and CA have the huge market prospect as food acid seasoning (Dai et al. 2018; Dhillon et al. 2011). These acids occupy a major position in the industrial production of the short-chain organic acids due to their wide range of applications.

✉ Xueqin Lv
lvxueqin@jiangnan.edu.cn

✉ Long Liu
longliu@jiangnan.edu.cn

[1] Science Center for Future Foods, Jiangnan University, Wuxi 214122, China

[2] Key Laboratory of Carbohydrate Chemistry and Biotechnology, Ministry of Education, Jiangnan University, Wuxi 214122, China

[3] School of Food Science and Technology, Jiangnan University, Wuxi 214122, China

Published online: 25 September 2020

Over the past century, short-chain organic acid-related products have established a tight relationship between grocery needs and the petrochemical industry. Short-chain organic acids such as CA, MA, α-KG, IA, and GA were synthesized by traditional industrial chemistry using a variety of simple chemical units (mostly derived from fossil resources) (Becker and Wittmann 2015). However, the production processes of traditional industrial chemicals have caused environmental pollution, climate change, and shortage of raw materials to a certain extent, which promoted people to seek new sustainable resources for synthetic short-chain organic acids. Considering these unavoidable consequences in industrial chemical production, researchers are searching for a new available method, microbial production, which is environmentally friendly and sustainable (Becker and Wittmann 2015; Chae et al. 2020; Wang et al. 2016b).

In this review, we summarized sixteen short-chain organic acids, including PA, pyruvate, LA, 3-HP, MA, SA, FA, BA, IA, α-KG, XA, glutaric acid, CA, GA, CCM, and AA. From the perspective of metabolic engineering, we discussed the latest research techniques for the production of short-chain organic acids in microorganisms. We also focused on the development and utilization of acid-resistant industrial chassis cells for the production of short-chain organic acid.

Current advance in biological production of short-chain organic acid

Host microbes for the production of short-chain organic acids

Till now, strategies on biology and synthetic biology have been developed by choosing new biotechnologies to produce organic acids. As the intermediates of microorganisms, more and more short-chain organic acids are produced in microorganisms via metabolic engineering (Fig. 1). Specifically, *Escherichia coli*, a model strain in industry, is usually used to produce various short-chain organic acids (Alonso et al. 2015; Liu et al. 2017). Considering the renewability and cheapness raw materials, glucose, and glycerol were added as a substrate during the fermentation process (Becker et al. 2015). Additionally, *Propionibacterium acidipropionici*, *Propionibacterium jensenii*, *Aspergillus oryzae*, *Aspergillus terreus*, *Aspergillus niger*, *Yarrowia lipolytica*, and *Saccharomyces cerevisiae* can also be used as host microbes for the production of short-chain organic acid (Table 1).

Strategies and tools for the production of short-chain organic acids

To meet the current industrial production needs, researchers begun to design and construct an efficient screening system for selecting high-yield strains of short-chain organic acids. High-throughput screening methods based on biosensor responses were developed in many reports. The key component of biosensor is the transcription regulator of the target organic acid (Snoek et al. 2020). A biosensor responding to *cis, cis*-muconic acid (CCM) was designed in *S. cerevisiae* based on small molecules binding transcriptional activators BenM, which was a native CCM-inducible transcriptional activator, from *Acinetobacter* sp. ADP1 superfamily of LysR-type (Bian et al. 2016). Moreover, CCM-biosensors were coupled to GFP (Green fluorescent protein) expression to screen high-yield CCM-producing yeasts via high-throughput screening (Wang et al. 2020). Engineering of biosensor system in search of a general biosensor design can help host microbes to produce target short-chain organic acids more efficiently (Snoek et al. 2020).

However, almost all short-chain organic acids shared common characteristics: with the accumulation of concentration, the acids were highly toxic to the growth of host cells. The research of acid-resistant chassis cells for the production of organic acids became a hot area in recent years. According to the available expression and transcription factor binding data, researchers have designed and identified a powerful set of synthetic promoters for the production of LA in *S. cerevisiae* under acidic conditions (pH ≤ 3). The literature on transcription regulation and known rules for promoter architecture had improved the low pH performance of *ygp1* promoter by modifying the transcription factor binding sites in accordance with their upstream activation order (Rajkumar et al. 2016). In *E. coli*, researchers designed a pH-sensitive genetic device based on a riboswitch to control gene expression based on different environmental pH (Pham et al. 2017). The application of the digital pH-sensitive system was proved a success in a genetic program that can autonomously regulate the evolutionary engineering of DNA. Therefore, in this case, the resistance is to a variety of organic acids and have a valuable phenotype for metabolic engineering and bioremediation applications (Pham et al. 2017). Researchers also used error-prone PCR methods to engineer the global regulator cAMP receptor protein (CRP) of *E. coli* to improve its performance at low pH from the transcription level (Basak et al. 2014). Based on its mutagenic performance, the best mutant AcM1 was identified from a random mutagenesis library. Compared with the control, the growth rate of AcM1 increased from 0.062 h^{-1} to 0.113 h^{-1} at pH 4.24 (Basak et al. 2014). The evolved strain in Archaeon *Sulfolobus solfataricus*, which was called the super acid-resistant *Crenarchaeota* (SARC), and its additional thermophilic and eosinophilic abilities were tested through adaptive evolution and acquired a line of resistance and genomic stability relative to the wild-type parents. One more interesting thing is that acid resistance was heritable (Payne et al. 2018). While the acidity of the culture solution was gradually increasing, the change of pH value of the culture resulted in a

Table 1 Overview of the development of fermentative and enzymatic production of main organic acids in recent years

Number of carbon atom	Production	Strains	Genotype	Titer (g/L)	Yield (g/g)
C3	Propionic acid	*P. acidipropionici* (Jiang et al. 2014)	Trehalose synthesis mutant (overexpression of *otsA* gene)	135	0.67
		P. acidipropionici (Zhang and Yang 2009)	Δ*ack*, H^+-ATPase mutation	100	0.53
		P. jensenii (Liu et al. 2015b)	Overexpression of *gdh* and *mdh*from *K. pneumoniae*	39.43	0.65
		P. jensenii (Liu et al. 2016)	The overexpression of *ppc* from Klebsiella pneumoniae and deletion of *ldh*	34.93	N/D
	Pyruvate	*S. cerevisiae* (van Maris et al. 2004)	Pdc^- *S. cerevisiae* mutant (TAM)	135	0.54
		T. glabrata (Liu et al. 2007)	Osmotic-tolerant mutant of *T. glabrata* CCTCC M202019	94.3	0.64
		E. coli (Zhu et al. 2008)	YYC202 *ldhA*::*Kan*, arcA726::*FRT*, *atpFH*::*Cam*	90	0.68
	Lactic acid	*R. oryzae* (Yamane and Tanaka 2013)	From glucose, batch and fed-batch cultures of *Rhizopus oryzae*	231	0.93
		C. glutamicum (Tsuge et al. 2015)	Overexpressing the genes coding for GLK, GAPDH, TPI, and FBA.	195	0.9
		B. coagulans (Xu and Xu 2014)	Using a co-feeding strategy	168.3	0.88
		S. cerevisiae (Baek et al. 2016)	Overexpressing *ldhA*, Δ*dld1*, Δ*jen1*, Δ*pdc1*, Δ*adh1*, Δ*gpd1*, and Δ*gpd2*.	112	0.80
	3-Hydroxypro-pionic acid	*E. coli* (Chu et al. 2015)	GabD4 (Aldehyde dehydrogenase), mutant GabD4_ E209Q/E269Q	71.9	N/D
		E. coli (Kim et al. 2014)	Δ*glpk*, Δ*yqhD*, overexpressing *PSALDH*	57.3	0.88
		K. pneumoniae (Huang et al. 2013)	Expressing *aldH*	48.9	0.66
C4	Malic acid	*A. oryzae* (Brown et al. 2013)	Overexpressing *C4T318*, *PYC*, and *MDH*	154	1.03
		A. oryzae (Liu et al. 2018a)	Overexpressing *pyc*, citrate synthase RNAi, overexpressing NADH oxidase	117.2	0.9
		U. trichophora (Zambanini et al. 2017)	Overexpression of *PYC*, *MDH*, and two malic acid transporters	134	0.56
		E. coli (Gao et al. 2018)	Using multiplexed CRISPRi	36	0.85
	Fumaric acid	*R. oryzae* (Zhang et al. 2012)	Overexpressing *pyc* and *pepc*	78	0.78
		E. coli (Li et al. 2014)	Overexpression gene *ppc*or the glyoxylate shunt operon *aceBA*	41.5	0.44
		E. coli (Song et al. 2013)	Overexpressing *PPC*, *sdhCDAB*, and *CS*, Δ*aspA*	35.1	0.49
		A. oryzae (Papadaki et al. 2018)	Using renewable resources soybean cake via a two-stage bioprocess	40	0.86
		S. cerevisiae (Xu et al. 2013)	*RoPYC*, *RoMDH*, and *RoFUM1* from *Rhizopus oryzae* were overexpressed	5.64	0.11
	Succinic acid	*E. coli* (Liang et al. 2013)	Δ*pflB*, Δ*ldhA*, Δ*ppc*, ΔptsG, overexpressing *pepck*	83	0.87
		S. latissima (Marinho et al. 2016)	The macroalga *Saccharina latissima* as feedstock	36.8	0.92
		E. coli (Olajuyin et al. 2016)	Δ*ldhA*, Δ*pta-ackA*, Δ*poxB*, Δ*pfl*, overexpressing *pck*	22.4	0.73
	Butyric acid	*C. tyrobutyricum* (He et al. 2020)	Overexpressing *galK*, *galE*, *galT* and *galP*	34.3	0.37
		C. tyrobutyricum (Huang et al. 2011)	In a fibrous-bed bioreactor using *Jerusalem artichoke* as the substrate	60.4	0.38
		C. tyrobutyricum (Luo et al. 2018)	Overexpressing *xylT*, *xylA*, and *xylB*	36.4	0.43
		C. tyrobutyricum (Suo et al. 2017)	Overexpressing *groESL*	52.2	N/D
C5	Itaconic acid	*A. terreus* (Hevekerl et al. 2014)	By a single pH shift ranging from pH 4 to 6 or by a pH control to pH 3	146.1	0.59
		A. terreus (Kuenz et al. 2012)	A systematic process optimization	86.2	0.62
		A. terreus (Huang et al. 2014)	Overexpressing *cadA*	78.5	0.57
		A. terreus (Krull et al. 2017)	Controlling the pH value to pH 3.4 in the production	160	0.46
	α-Ketoglutaric acid	*E. coli* (Niu et al. 2014)	From l-glutamic acid vial-glutamateoxidase	104.7	0.95
		Y. lipolytica (Yu et al. 2012)	Using a two-stage pH control strategy	66.2	0.51
	Xylonic acid	*P. kudriavzevii* (Toivari et al. 2013)	Expressing a D-xylose dehydrogenase coding gene	171	1.0
		S. cerevisiae (Toivari et al. 2012)	Expressing D-xylonolactone lactonase *xylC*	43	0.8

Table 1 (continued)

Number of carbon atom	Production	Strains	Genotype	Titer (g/L)	Yield (g/g)
		E. coli (Liu et al. 2012a)	Disrupting two genes *yagE* and *yjhG*	39.2	0.98
	Glutaric acid	*C. glutamicum* (Rohles et al. 2018)	Overexpressing *gabT*, *gabD*, and *cgl0841*	90	0.7
		E. coli (Wang et al. 2018)	Xylose catabolic pathways (isomerase, Weimberg, and Dahms pathways)	0.6	N/D
		E. coli (Zhao et al. 2018b)	Expressing the enzymes of RADP, Δ*arcA*, Δ*ldhA*, Δ*atoB*, and Δ*pflB*	4.8	0.82
C6	Citric acid	*Y. lipolytica* (Förstерr et al. 2007)	Overexpression of the invertase-encoding *suc2* gene	140	0.82
		Y. lipolytica (Liu et al. 2013b)	Δ*acl1*, overexpression of *icl1*	84	0.84
		Y. lipolytica (Liu et al. 2010)	Expression of inulinase from *K. marxianus*	77.9	0.92
	Gluconic acid	*A. niger* (Singh and Singh 2006)	By pseudo-immobilization of *A. niger* ORS-4.410	96.52	0.7
		A. niger (Zhang et al. 2016)	Using dry dilute acid pretreated corn stover (DDAP) hydrolysate	76.67	0.949
		K. pneumoniae (Wang et al. 2016a)	Deletion of *gad*, with accumulation observed at pH 5.5 or lower	422	1.0
	Muconic acid	*S. cerevisiae* (Wang et al. 2020)	Biosensor-aided genome engineering	20.8	0.066
		E. coli (Choi et al. 2019)	System for the conversion DHS into MA, and expression of *asbF*, *aroY*, and *catA*.	64.5	N/D
		C. glutamicum (Becker et al. 2018)	Elimination of *catB*, overexpression of *catA*, with lignin hydrolysate as substrate	85	0.81
		P. putida (Kohlstedt et al. 2018)	Deletion of the *catBC* genes, expression of *catA* and *catA2*	64.2	1.0
	Adipic acid	*E. coli* (Cheong et al. 2016)	MG1655 Δ*ldhA*, Δ*poxB*, Δ*pta*, Δ*adhE*, and Δ*sucD*	2.5	0.05
		C. tropicalis (Ju et al. 2020)	*C. tropicalis* KCTC 7212 Δ*AOX4*::*AOX5* mutant	12.1	N/D
		E. coli (Zhao et al. 2018a)	Through the reverse adipate-degradation pathway	68	0.38
		E. coli (Zhou et al. 2020)	Expressing the enzymes of RADP, Δ*arcA*, Δ*sucD*, Δ*atoB*, Δ*ldhA*, Δ*adhE*, and Δ*pflB*,	57.6	N/D

N/D not detected

178-fold increase after the strains of adaptive laboratory evolution growth at pH 0.8 and 80 °C (McCarthy et al. 2016).

In addition, researchers found that the acid resistance reaction (ATR) system was required for *E. coli* to grow in pH 4.2 (Xu et al. 2020a). Among the two-component system CpxRA, which consisted of histidine kinase CpxA and cytoplasmic response regulator CpxR, directly sensed acidification through the protonation of periplasmic histidine residues of CpxA and maintained intracellular pH homeostasis (Xu et al. 2020a). The ATR system was important for the production of higher levels of 3-HP during fermentation, and the ATR system appeared to be conserved among other Gram-negative bacteria (Xu et al. 2020a).

C3 organic acids:propionic acid, pyruvate, lactic acid, and 3-hydroxypropionic acid

Propionic acid

PA, a 3-carbon short-chain organic acid, is a valuable chemical intermediate with a variety of applications in food, pharmaceutical, and manufacturing industries (Liu et al. 2012b). Other applications can also perform as an intermediate for the synthesis of perfumes, cellulose fibers, and feedstuffs (Guan et al. 2016).

Microbial synthesis of PA was mainly based on glucose and glycerin, which were cheap renewable raw materials. Using glucose or glycerol as substrate, PA was eventually produced in the Wood-Werkman cycle with the catalysis of succinyl-CoA, which was produced by the TCA cycle, and methylmalonyl-CoA (Fig. 1). Currently, a variety of metabolic synthesis methods have been developed for the production of PA. For example, gene *gldA* (encoding glycerol dehydrogenase) from *Klebsiellan pneumoniae* was expressed by using a *P. jensenii-Escherichia coli* constructed shuttle vector, and then increased the PA production by 26.07% (Zhuge et al. 2013). Furthermore, the additional enzyme malate dehydrogenase (MDH) had been found to produce PA. Engineered strains, in which *gldA* and *mdh* were simultaneously overexpressed, can improve the titer of PA (Liu et al. 2015b). In the metabolic pathway of PA, *ppc* (encoding phosphoenolpyruvate carboxylase) and *ldh* (encoding lactic acid

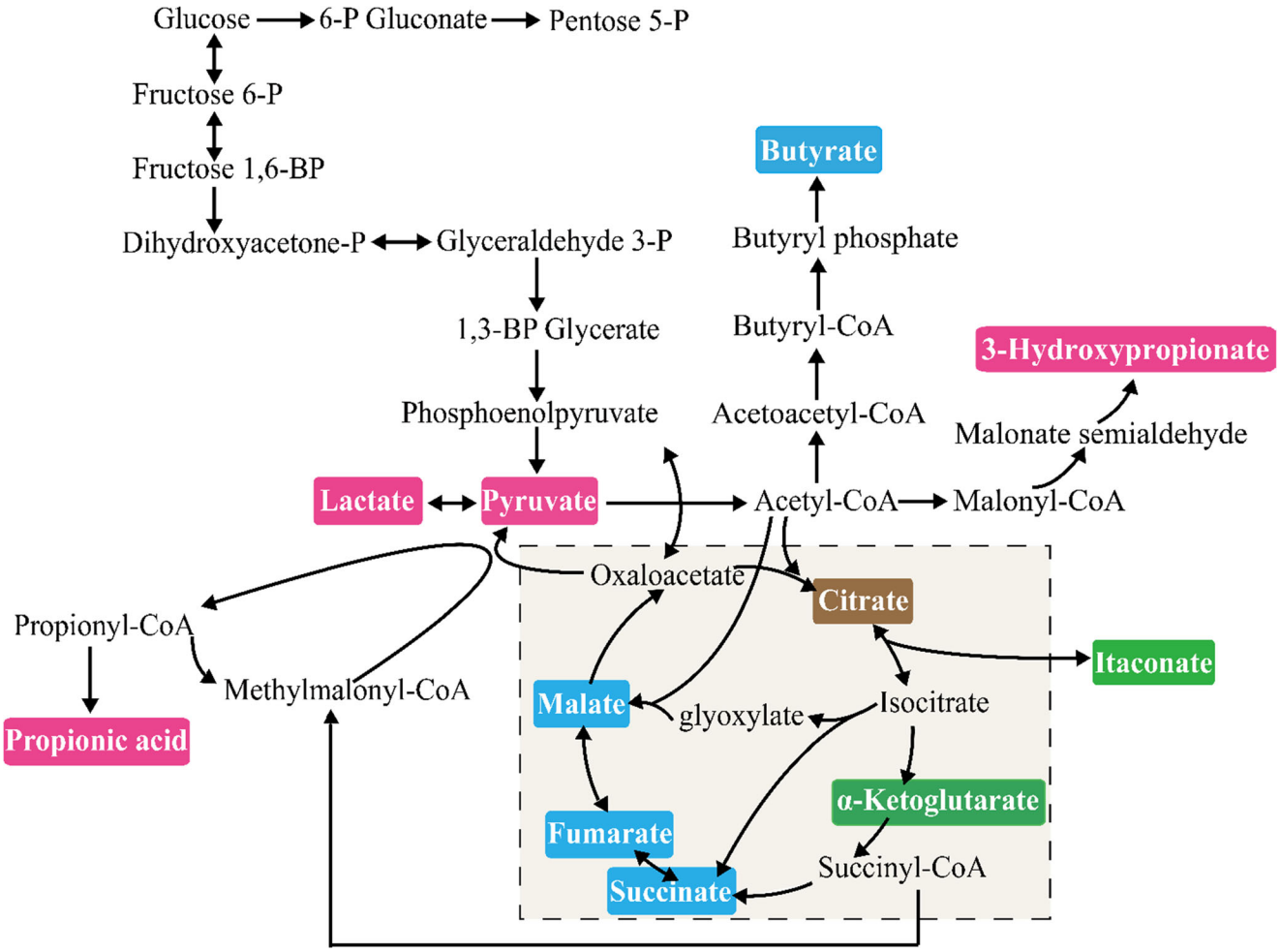

Fig. 1 Metabolic pathways of short-chain organic acids starch in microorganisms. The dotted line is the tricarboxylic acid cycle (TCA). Rose red: carbon three, including propionic acid, pyruvate, lactic acid, and 3-hydroxypropionic acid. Blue: carbon four, including malic acid, fumaric acid, succinic acid, and butyric acid. Green: carbon five, including itaconic acid and α-ketoglutarate. Brown: carbon six, citrate

dehydrogenase) were key genes that affect synthesis. The overexpression of *ppc* from *Klebsiella pneumoniae* and deletion of *ldh* increased the PA titer to 34.93 ± 2.99 g/L (Liu et al. 2016). In addition, higher titers PA of 100 g/L and 135 g/L were obtained in *P. acidipropionici* by construction of H^+-ATPase mutation (Zhang and Yang 2009) or overexpression of *otsA* (encoding as a homolog of trehalose 6-phosphate synthase) (Jiang et al. 2014). Also, the arginine deaminase and glutamate decarboxylase (GAD) systems contributed significantly to the acid resistance of *Propionibacteria* at the microenvironmental level (Guan et al. 2013), proteomics level (Guan et al. 2014), and metabolomics level (Guan et al. 2015).

PA was a strong inhibitor to cell growth even at a relatively low concentration (10 g/L) (Goswami and Srivastava 2001; Zhang and Yang 2009). To improve the tolerance of cells to PA in many fermentation processes, researchers have constructed PA-tolerant chassis cells before producing PA. For example, knockout gene *ack* (encoding acetate kinase) for acetic acid synthesis and adaptively spontaneous evolution of cells with high concentration of PA can improve tolerance to PA (Zhang and Yang 2009). Furthermore, the overexpression of gene *gadB* (encoding glutamate decarboxylase) increased PA-tolerant and yield most effectively, which was over 10-fold higher than that of the wild-type (Guan et al. 2016).

Pyruvate

With the properties of carboxylic acids and ketones, pyruvate is an important small molecule organic acid and also a C3 keto acid produced by microorganisms (Wieschalka et al. 2013). Pyruvate can be converted to acetyl-CoA by pyruvate dehydrogenase, and further, acetyl-CoA can be completely oxidized to carbon dioxide and water through TCA cycle, which supplies energy for cell growth and maintenance. Therefore, pyruvate is a key intermediate in sugar metabolism. In addition, pyruvate can be converted into sugars, fats, and amino acids in the body through the cycle of acetyl-CoA and tricarboxylic acids (Zhu et al. 2008).

Glycolysis pathway was the major pathway for microorganisms to synthesize pyruvate (Fig. 1). *E. coli* and *S. cerevisiae* have been engineered to produce pyruvate. During the process of synthesizing pyruvate with glucose as a substrate, the most immediate obstacle is the degradation of pyruvate by pyruvate decarboxylase (Pdc) (van Maris et al. 2003). However, the *pdc*$^{-}$ mutant also blocked acetyl-CoA synthesis and two issues present in the fermentation process: (I) cultures required small amounts of ethanol or acetate to sustain aerobic and (II) strains of *pdc*$^{-}$ mutant cannot grew in batch cultures on synthetic medium with glucose (van Maris et al. 2004). In order to solve the glucose-limited growth problem in *pdc*$^{-}$ mutant, researchers overexpressed the gene *glY1* (encoding threonine aldolase) in *S. cerevisiae*, which can catalyze threonine into glycine and acetaldehyde. The acetaldehyde produced by threonine aldolase, which was the precursor of acetyl-CoA, successfully solved the problem of acetyl-CoA supplication in the cytoplasm (van Maris et al. 2003). In the other direction, through directed evolution of the Pdc^{-} strains, the mutant strain TAM obtained tolerance of glucose, and the highest titer of pyruvate in *S. cerevisiae* reached 135 g/L (van Maris et al. 2004). In *E. coli*, the glycolytic rate and pyruvate productivity were related to four nutrient limitation conditions, including glucose, acetate, nitrogen, or phosphorus at the logarithmic growth phase. Among these conditions, acetate resulted in the highest glycolytic flux, with mutations in genes involved in pyruvate metabolism including *aceEF* (encoding pyruvate dehydrogenase complex), *pfl* (encoding pyruvate formate lyase), *poxB* (encoding pyruvate oxidase), *pps* (encoding phosphoenolpyruvate synthase), and *ldhA* (encoding lactate dehydrogenase), while pyruvate productivity reached 90 g/L (Zhu et al. 2008). Also, in an NaCl-tolerant mutant of *Torulopsis glabrata*, the titer of pyruvate reached 94.3 g/L by enhancing the osmotic stress resistance (Liu et al. 2007). Of course, besides using glucose as the substrate, researchers have also investigated the use of other substrates to produce pyruvates, such as lactic acid (Gao et al. 2010), alginate (Kawai et al. 2014), mannitol (Yoshida et al. 2015), and D/L-alanine (Hossain et al. 2016).

Lactic acid

LA, which has both hydroxyl and carboxyl groups, is the most widespread hydroxycarboxylic acid in nature and can participate in a variety of reactions, such as oxidation reactions, reduction reactions, condensation reactions, and hydroxyl substitution, to prepare various lactic acid derivatives (Joshi et al. 2010). LA also has a mild and moderate acidity, which can increase the taste of food in the food industry (Zhang et al. 2018). Moreover, adding a certain amount of LA to seasoning can refrain microorganisms and maintain the stability and safety in products. In the fermentation industry, LA can be used to control the pH value and improve the purity of fermentation products as well (Yamane and Tanaka 2013).

Recent reports have shown that many strategies play an important role in the microbial production of LA, including both metabolic transformations and traditional fermentation optimization processes. In terms of metabolism, LA was a direct product of D/L-lactate dehydrogenase, which reduced the pyruvate to D/L-enantiomer of LA (Fig. 1). Glycolysis was the fundamental pathway for metabolizing glucose to pyruvate, which was an important precursor for LA synthesis. In an experiment where ten genes were overexpressed, five genes encoding glucokinase (GLK), glyceraldehyde phosphate dehydrogenase (GAPDH), triosephosphate isomerase (TPI), phosphofructokinase (PFK), and bisphosphate aldolase (FBA) have shown an effect to increase the production of LA in *Corynebacterium glutamicum* (Tsuge et al. 2013). Shortly afterwards, the five glycolytic genes were simultaneously overexpressed, and the optimal combination of glycolytic genes was obtained, clarifying that the PFK encoding gene was essential for achieving high production (195 g/L) of D-lactate (Tsuge et al. 2015). In traditional fermentation optimization processes, *Rhizopus oryzae* NBRC 5384 was cultured by glucose fed-batch fermentation to make the production of LA achieved 231 g/L (Yamane and Tanaka 2013), and a co-feeding strategy based on the utilization of cane molasses/glucose carbon sources was used to efficiently produce LA in *C. glutamicum* (Xu and Xu 2014).

However, host cells of LA producers had low acid tolerance, which were unfavorable for the industrial production. Therefore, acid-resistant cell engineering was used to synthesize LA. In *S. cerevisiae*, *CCW14* was a cell wall glycoprotein reportedly activated by the CWI pathway under citric acid stress at pH 3.5 (Lawrence et al. 2004). Compared with the native *TEF1* promoter, the best-effect engineered *CCW14V5* promoter, which was the modified inducible *CCW14* promoter, was used to improve the cell tolerance (pH ≤ 3) and tenfold increase in the titer of LA (Rajkumar et al. 2016). Likewise, to obtain cost-effective non-neutralizing fermentation host strains, both rational pathway engineering and adaptive evolution were investigated in *S. cerevisiae*. Among the adaptive evolution strains, *S. cerevisiae* JHY5330 showed the higher gene *haa1*(encoding a transcription activator) mRNA levels, and *haa1* mainly contributed to enhancing acid tolerance and LA production ability (Baek et al. 2016).

3-Hydroxypropionic acid

3-HP is an isomer of lactic acid. Due to the different hydroxyl positions, chemical properties of 3-HP are more active in the synthesis of many industrially valuable chemicals, including malonic acid, 1,3-propandiol, acrylic acid, propiolactone, 3-hydroxymethyl-propionate, and several polymers (Chu et al. 2015). The chemical industry has recently focused on

emerging high-value organic acids with broader industrial applications (Alonso et al. 2015; Wieschalka et al. 2013).

The synthesis methods of 3-HP included chemical and microbiological methods. Chemical methods used non-renewable resources that have many by-products which were difficult to be separated, and may easily cause environmental pollution. In recent years, attentions have been paid to the microbial conversion of 3-HP with glycerol as a substrate. The main hosts to produce 3-HP through microbial fermentation included *E. coli* (Chu et al. 2015; Kim et al. 2014) and *Klebsiella pneumoniae* (Huang et al. 2013). In *E. coli*, rapid iterative CRISPR EnAbled Traceable genomic Engineering (iCREATE) method was used to determine the construction and productivity of combinatorially modified genomes. With central carbon metabolism, the ability of engineered strains to produce 3-HP and the tolerance to 3-HP were improved, and then the titer, yield, and productivity increased approximately 60 times compared to the wild-type strains (Liu et al. 2018b).

The accumulation of the intermediate product 3-hydroxypropanal (3-HPA) was essential to increase the productivity of 3-HP, while 3-HPA was toxic. Therefore, researchers identified GabD4, a new aldehyde dehydrogenase that possesses high enzyme activity towards 3-HPA from *Cupriavidus necator* (Chu et al. 2015). In order to enhance the activity of GabD4, site-directed and saturated mutagenesis were performed based on homology modeling; thus, the mutant GabD4_E209Q/E269Q showed the highest enzyme activity and increased the production of 3-HP to 71.9 g/L, which should be the highest reported in *E. coli* (Chu et al. 2015). On the other hand, there are other studies on how to reduce the toxicity of 3-hydroxypropionaldehyde for cell growth. In recombinant *E. coli*, gene *glpK* (encoding glycerol kinase) and *yqhD* (encoding an endogenous propanediol oxidoreductase) were double knocked, and *Pseudomonas aeruginosa* gene *psaldh* (encoding semialdehyde dehydrogenase) and *Lactobacillus brevis* gene *DhaB-DhaR* ($DhaB_1B_2B_3$ encoding glycerol dehydratase complex and $DhaR_1R_2$ encoding DhaB reactivase) were overexpressed; as a result, the 3-HP titer reached 57.3 g/L (Kim et al. 2014). To achieve economically viable 3-HP production targets and improve 3-HP tolerance, the latest research reported that via an acid-tolerance response (ATR) system in *E. coli* that can grow exponentially at pH 4.2 with high productivity of 3-HP (Xu et al. 2020a).

C4 organic acid:malic acid, fumaric acid, succinic acid, and butyric acid

Malic acid

MA, a cyclic intermediate of tricarboxylic acid, is an important ingredient in natural fruit juice. MA is also a necessary organic acid for the human body and the favored food additive with low calories (Dai et al. 2018). At present, it shares the largest amount of food additives and possesses a good development prospect in the world food industry (Liu et al. 2017). Due to the oxidation capacity, which will reduce the sensory properties of foods, reduce nutritional value, and shorten shelf life, adding food antioxidants can delay oxidation, extend shelf life, and maintain the color of food (Cheng et al. 2017; Wei et al. 2017). Exactly, MA has favorable antioxidant properties that are widely used in food, agricultural, pharmaceutical, and chemical (Cheng et al. 2017; Liu et al. 2015a; Wang et al. 2016b).

Recently, a variety of hosts have been developed for MA production, including bacteria, yeast, and filamentous fungi, such as *E. coli*, *A. flavus*, *Rhizopus delemar*, *R. oryzae*, *S. cerevisiae*, *Zygosaccharomyces rouxii*, *Aspergillus oryzae*, *Aureobasidium pullulans*, *Ustilago trichophora*, and so on. There are four pathways to synthesize MA: (I) intracytoplasmic reduction TCA cycle (rTCA), (II) TCA cycle, (III) cyclic-glyoxylate cycle, and (IV) noncyclic-glyoxylate cycle (Brown et al. 2013). Among them, the highest rate of MA synthesis pathway was rTCA cycle. In this pathway, there are two key enzymes that contribute significantly in the synthesis of MA: MDH and pyruvate carboxylase (PYC). These two key enzymes have been overexpressed in *S. cerevisiae* and *A. oryzae* to increase the production of MA and had obvious effects (Brown et al. 2013; Zelle et al. 2008). On the other hand, the production of MA in *A. oryzae* was through the carbon metabolism and redox metabolism in the cytosol and mitochondria, finally reached 117.2 g/L (Liu et al. 2018a). In *U. trichophora*, two malate dehydrogenases (*mdh1*, *mdh2*) and two malate transporters (*ssu1*, *ssu2*) were overexpressed, and the titer of MA increased to 134 g/L (Zambanini et al. 2017). The development of using inorganic nitrogen sources has also made contribution to in the production of MA in *A. oryzae* (Ding et al. 2018).

In addition, researchers also investigated the glyoxylate pathway for reallocating metabolic flux. In *E. coli*, the multiple regulation of the five-enzyme cascade in the glyoxylate pathway by combining in vitro and module engineering with CRISPRi technology in vivo had led to the conversion of MA from pyruvate. CRISPRi technology can minimize the metabolic burden caused by heterologous expression of multiple genes in the operon (Kim et al. 2016). The introduction of CRISPRi can solve imbalances between different modules, such as the accumulation of citric acid and α-ketoglutarate, resulting in a final MA titer of 36 g/L (Gao et al. 2018).

At present, the highest yield of MA is 201.24 g/L in fed-batch fermentation (with 28 g/L by-product CA), via knocking out the gene *oahA* (encoding oxaloacetate acetylhydrolase) and overexpressing *mdh3*, *pyc*, and *c4t318* (encoding C4-dicarboxylate transporter) using a Cre-loxP-based system for gene editing in *A. niger* (Xu et al. 2019). To eliminate the accumulation of by-product CA, researchers

continued to disrupt gene *cexA* (encoding citric acid transporter located on the cell membrane) and enhanced glucose transportation and glycolytic pathway, including gene *mstC* (encoding glucose transporter), *hxkA* (hexokinase), *pfkA* (6-phosphofructo-2-kinase), and *pkiA* (encoding pyruvate kinase) on the basis of the former strains; finally. the titer of MA reached 201.13 g/L without by-product CA (Xu et al. 2020b).

Fumaric acid

FA, a metabolic intermediate of the TCA cycle, is an important raw material of organic chemical, an intermediate for chemical products, and an important derivative of maleic anhydride. In the food industry, FA is used as a sour agent in refreshing beverages, wine, cold drinks, concentrated fruit juices, canned fruits, pickles, and ice cream (Sebastian et al. 2019). FA derivatives, especially fumarate (FAE), have been found to be important chemicals with wide biomedical applications (Sebastian et al. 2019).

The metabolic pathway of FA production by microorganisms was roughly the same as that of MA (Fig. 1). Therefore, the key enzymes PYC involved in the production and transformation of FA. For example, overexpressing endogenous PYC and exogenous phosphoenolpyruvate carboxylase (PEPC) could increase the FA production in *R. oryzae* (Zhang et al. 2012). In *S. cerevisiae*, co-expressing of *ropyc* (encoding pyruvate carboxylase of *R. oryzae*) and *sfc1* (encoding a succinate-fumarate transporter) (Xu et al. 2012) or overexpressing *romdh* (encoding malate dehydrogenases of *R. oryzae*), rofum1 (encoding fumarase of *R. oryzae*) and *ropyc* can also increase the titer of FA (Xu et al. 2013). Besides, FA can also be produced in *E. coli* by overexpressing the phosphoenolpyruvate carboxylase gene *ppc* (Li et al. 2014) or the glyoxylate shunt operon *aceBA* effectively or overexpressing *PPC*, *sdhCDAB*, and *CS* (Song and Lee 2015).

Recently, for the sustainable use of renewable resources, soybean cake was used to produce FA by a two-stage bioprocess. This involved bioprocess crude enzyme production via solid-state fermentations (SSF) cultivated on soybean cake, and enzymatic hydrolysis of soybean cake, which increased the FA production to 40 g/L (Papadaki et al. 2018).

Succinic acid

SA is also an intermediate of TCA cycle like MA and FA. SA has raised great interest in the development of bio-based production processes because of its great potential in the biological production of daily necessities, including food, pharmaceutical, detergents, lubricants, and cosmetics (Jiang et al. 2017).

Microorganisms produced SA with a widely host microbes. Natural SA-producing strains such as *Anaerobiospirillum succiniciproducens*, *Mannheimia succiniciproducens*, *Saccharina latissima*, and engineered strains like *E. coli* and *C. glutamicum* have been specifically used as microorganisms for producing succinic acid (Chen et al. 2014b; Cheng et al. 2013; Liang et al. 2013; Litsanov et al. 2012; Marinho et al. 2016). Several key enzymes were reported in the metabolic pathway of SA, such as phosphoenolpyruvate (PEP) carboxylase, phosphotransferase system (PTS), and malic enzyme (Tang et al. 2013; Wang et al. 2015). Meanwhile, evolutionary adaptation has successfully increased the yield of SA and the host's tolerance to SA. For example, overexpressed the *pyc* gene and disrupted the gene *ldhA* (encoding L-lactate dehydrogenase) in *C. glutamicum*, the titer of SA reached 146 g/L (Cheng et al. 2013; Okino et al. 2008). With high-density fermentation at 40 °C in *E. coli*, researchers used starch instead of glucose to produce succinic acid, and the titer of SA increased to 127 g/L (Chen et al. 2014a).

To reduce the cost of feedstock, the utilization of corn stalk (Zheng et al. 2010), cotton stalk (Li et al. 2013), sugarcane bagasse (Salvachúa et al. 2017), xylose (Salvachúa et al. 2017), and glycerol (Li et al. 2017) from biodiesel production have become a hot spot to produce SA. By now, the first attempt to use ferrous iron/α-ketoglutarate-dependent dioxygenases for producing SA via the most effective whole-cell catalysis system (WCSS) has been proved feasible (Sun et al. 2019).

Butyric acid

BA can be used to make butyric acid esters, cellulose butyrate, food, and medicine and can be used as an emulsifier, varnishes, cosmetic, bactericide, and extractant (Luo et al. 2018). Additionally, derivatives synthesized from BA have great potential to serve as solvents, such as ethyl butyrate (Paludo et al. 2015). BA is also an important precursor of biobutanol clostridium fermentation as an advanced liquid biofuel production solvent in Acetone-Butanol-Ethanol (ABE) (Luo et al. 2018).

At present, host bacteria for BA production mainly included *Clostridium tyrobutyricum*, *Butyrivibrio*, and *Propionibacterium freudenreichii* (Huang et al. 2011; Jha et al. 2014; Luo et al. 2018). Usually, glucose and xylose are used as carbon sources for BA synthesis in clostridia (Figs. 1 and 2a). However, when using xylose as a carbon source, the xylose utilization by *C. tyrobutyricum* was strongly inhibited by the presence of glucose. To eliminate this phenomenon, *xylT*, *xylA*, and *xylB* genes were overexpressed in *C. tyrobutyricum* to simultaneously co-utilize glucose and xylose for the production of BA (Fu et al. 2017b). Additionally,

C. tyrobutyricum Ct-pTBA also was excellent to co-utilize glucose and xylose (Fu et al. 2017a).

However, high concentration of BA exerted strong pressure on cells. The response to BA stress involved various stress-related genes. Therefore, overexpression of stress-related genes can improve BA tolerance. *C. tyrobutyricum* class I heat shock proteins (HSPs), protein gene such as *grpE*, *dnaK*, *dnaJ*, *groEL*, *groES*, and *htpG* play important roles in protecting bacteria from sudden changes of extracellular stress. Overexpression of *groESL* and *htpG* could greatly improve the resistance to BA, and the titer of BA reached a higher level of 52.2 g/L (Suo et al. 2017). The latest report in *C. tyrobutyricum* ATCC 25755/*ketp* showed 78.6% of BA production increase compared with the wild-type strain, which was up to 34.3 g/L (He et al. 2020).

C5 organic acid:itaconic acid, α-ketoglutaric acid, xylonic acid, and glutaric acid

Itaconic acid

IA contains two active carboxyl groups and a double bond inside the molecule (Krull et al. 2017). The double bond and carboxyl group are conjugated, which makes IA easily polymerized at various numbers and thus widely used in chemical synthesis industries (Nick et al. 2020).

The metabolic pathway of IA begun with glycolysis in the cytoplasm. Glucose was metabolized to pyruvate by the EMP pathway. Then pyruvate was transported to the mitochondria and converted to acetyl-CoA. In the mitochondria, acetyl-CoA and oxaloacetate were condensed into CA by citrate synthase and finally decarboxylated into itaconate by cis-aconitate decarboxylase (CAD) (Huang et al. 2014) (Fig. 1). IA microbial production host bacteria mainly included *A. niger* (Krull et al. 2017), *A. terreus* (Table 1), and *S. cerevisiae* (Becker and Wittmann 2015). Key genetic modification in *A. niger* shown that the relocation of specific steps of the biosynthetic pathway, either by modified subcellular targeting of aconitase and *CadA* or by introducing a cytosolic citrate synthase pathway (Blumhoff et al. 2013; Huang et al. 2014). Immediately, a systematic process optimization was performed with an isolated strain *A. terreus*, and IA production reached 86.2 g/L (Kuenz et al. 2012). In addition, the pH during the growth and production phase had a significant influence on the final IA concentration; thus, the pH control has become an increasingly effective means in the production of itaconic acid, which increased the highest titer to 160 g/L (Hevekerl et al. 2014; Krull et al. 2017).

α-Ketoglutaric acid

α-KG is an important organic acid that plays an important role in the metabolism of microbial cells. α-KG, which is also a precursor substance for the synthesis of a variety of amino acids and proteins, has a wide range of applications in food, pharmaceutical, and cosmetics industries.

As an important bond in the TCA cycle, α-KG was located after isocitrate and before succinyl-CoA (Fig. 1). α-KG connected the intracellular with carbon-nitrogen metabolism, which not only directly participated in the oxidative energy supply, but also participated in the chemical synthesis of various substances, and plays an important role in maintaining normal physiological functions of the cells (Christopher et al. 2011).

There are two different approaches to synthesize α-KG in microorganism, including bio-transformed and modification of metabolic pathway. In general, the microbial production of α-KG was bio-transformed. Recently, some strategies on α-KG synthesis by enzymatic reactions were reported (Hossain et al. 2014; Liu et al. 2013a). In *E. coli* BL21 (DE3), which heterologously expressed the L-glutamate oxidase (LGOX) gene, the maximum α-KG concentration reached 104.7 g/L from 110 g/L L-glutamic acid (Niu et al. 2014). In addition, using a two-stage pH control strategy, where the pH was buffered by $CaCO_3$ in the growth phase and then maintained at 3.0 in the α-KG production phase, the yield of α-KG increased to 66.2 g/L with the glycerol fed in the overall fed-batch mode (Yu et al. 2012).

Xylonic acid

XA or its conjugate base xylonate has potential applications as chelator, dispersant, clarifying agent, antibiotic, health enhancer, polyamide, or hydrogel modifier or 1,2,4-butanetriol precursor (Toivari et al. 2017). Actually, D-xylonic acid was mainly produced by decomposition of D-xylose during microbial production. The native D-xylose catabolic pathway was blocked by disrupting the D-xylose isomerase and D-xylulose kinase genes (Fig. 2a). In *S. cerevisiae*, the NAD^+-dependent D-xylose dehydrogenase (*xylB*) from *C. crescentus* and D-xylonolactone lactonase (*xylC*) were used to produce D-xylonic acid. Expression of gene *xylB* and gene *xylC* can produce D-xylonic acid at both pH 5.5 and pH 3.0, while the yield was higher at pH 3.0 (43 g/L) (Toivari et al. 2017). Through the introduction of a D-xylose dehydrogenase from *C. crescentus*, a D-xylonic acid-producing *E. coli* was constructed, and the recombinant *E. coli* produced up to 39.2 g/L D-xylonic acid from 40 g/L D-xylose (Liu et al. 2012a). In *Pichia kudriavzevii*, the production of D-xylonic acid was up to 171 g/L with D-xylose as substrate at pH 5.5, which should be the highest yield of D-xylonic acid by a microbe in current reports, but the titer of D-xylonic acid only 146 g/L at pH 3.0 (Toivari et al. 2013). D-xylonic acid production at low pH was the same as or even higher than that at neutral pH. Moreover, without neutralizers ($CaCO_3$, NaOH, etc.) low pH processes would reduce costs during both production and product separation (Sauer et al. 2013).

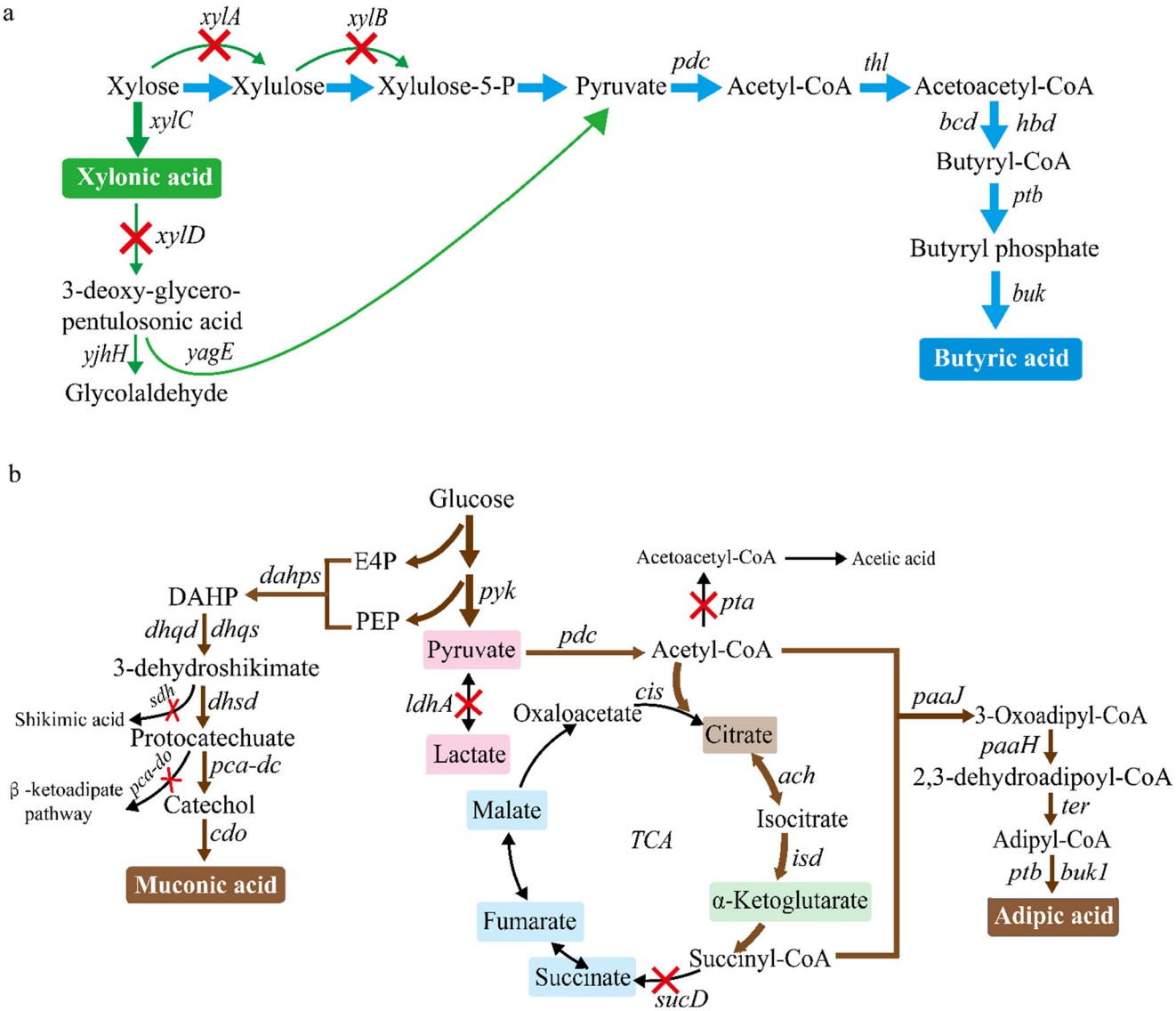

Fig. 2 Transformation process of organic acids in microorganisms. **a** Metabolic pathways of xylonic acid and butyric acid in microorganism from xylose. Blue: carbon four, butyric acid; green: carbon five, xylonic acid. The green line is in the xylonic acid synthesis pathway. During xylonic acid synthesis pathway, the red cross is the blocking pathway. The blue line is in the butyric acid synthesis pathway. *xylA*, xylose isomerase; *xylB*, xylulokinase; *xylC*, xylonolactonase; *xylD*, xylonate dehydratase; *yjhH* or *yagE*, aldolase; *pdc*, pyruvate decarboxylase; *thl*, acetyl-CoA acetyltransferase; *bcd*, butyryl-CoA dehydrogenase; *hbd*, beta-hydroxybutyryl-CoA dehydrogenase; *ptb*, phosphotransbutyrylase; *buk*, butyrate kinas. **b** Metabolic pathways of adipic acid and muconic acid in microorganism from glucose. Brown: carbon six, adipic acid, and muconic acid. During adipic acid or muconic acid synthesis pathways, the red cross is the blocking pathway. *pyk*, pyruvate kinase; DAHP, 3-deoxy-D-arabinoheptulosonate-7-phosphate; *dahps*, DAHP synthase; DHQ, 3-dehydroquinate; *dhqd*, DHQ dehydratase; *dhqs*, DHQ synthase; *sdh*, shikimate dehydrogenase; DHS, 3-dehydroshikimate; *dhsd*, DHS dehydratase; *pca-dc*, protocatechuate decarboxylase; *pca-do*, protocatechuate 3,4-dioxygenase; *cdo*, catechol 1,2-dioxygenase; *pdc*, pyruvate decarboxylase; *ptb*, phosphatebutyryltransferase; *ter*, 2,3-dehydroadipoyl-CoA reductase; *paaJ*, b-ketoadipyl-CoA thiolase; *paaH*, 3-hydroxy-acyl-CoAreductase; *buk*, butyrate kinas; *ldhA*, D-lactate dehydrogenase; *pta*, phosphotransacetylase; *sucD*, succinyl-CoA synthetase alpha subunit; *cis*, citrate synthase; *ach*, aconitic acid hydratase; *isd*, isocitrate dehydrogenase

Glutaric acid

Glutaric acid, a dicarboxylic acid, is mainly used to prepare glutaric anhydride, synthetic rubbers, and as an initiator for the polymerization of synthetic resins (Park et al. 2013). The microbial metabolic pathways of glutaric acid mainly included aminovalerate pathway, α-keto acid carbon chain extension pathway, α-keto acid reduction pathway, and reverse adipate degradation pathway (Chae et al. 2020). In 5-aminovalerate pathway, gene *gabD* (encoding glutarate semialdehyde dehydrogenase), gene *gabT* (encoding 5-aminovalerate transaminase), and gene *cgl0841* (encoding 5-aminovalerate importer) were overexpressed in *C. glutamicum* AVA-2, and the titer of glutaric acid reached 90 g/L in a fed-batch process (Rohles

et al. 2018). In α-ketoacid reduction pathway, researchers developed an aerobic-anaerobic two-stage strategy and expressed *hgdABC* (encoding 2-hydroxyglutaryl-CoA dehydratase), yielding 11.6 mg/L glutaric acid (Yu et al. 2017). Similar to the α-keto acid reduction pathway, five-step reverse adipate degradation pathway (RADP) from *Thermobifida fusca* was identified. In this pathway, researches constructed the *T. fusca* RADP in *E. coli* by expressing five genes *Tfu_0875* (encoding β-ketothiolase), *Tfu_2399* (encoding 3-hydroxyacyl-CoA dehydrogenase), *Tfu_0067* (encoding 3-hydroxyadipyl-CoA dehydrogenase), *Tfu_1647* (encoding 5-carboxy-2-pentenoyl-CoA reductase), and *Tfu_2576-7* (encoding adipyl-CoA synthetase) for glutaric acid production and knocked out four genes *arcA* (aerobic respiration control protein), *ldhA*, *atoB* (encoding acetyl-CoA acetyltransferase), and *pflB* (encoding formate C-acetyltransferase I), with the production of glutaric acid increased to 4.8 g/L (Zhao et al. 2018b). In addition, glutaric acid was synthesized by xylose metabolic pathway. Three xylose catabolism pathways (isomerase pathway, Weimberg pathway, and Dahms pathway) were researched, of which isomerase pathway and Weimberg pathway illustrated the synergetic effect to produce glutaric acid with a titer of 602 mg/L (Wang et al. 2018). Obviously, the aminovalerate pathway is more effective of the above pathways.

C6 organic acid:citric acid, gluconic acid, muconic acid, and adipic acid

Citric acid

CA, as a metabolic intermediate, can be used in other industries like pharmaceuticals, detergents, cosmetics, and various foods (Liu et al. 2017). In the beverage and brewed wine industry, CA is recognized as a safe food additive by the FAO/WHO expert committee and is called the first edible sour agent with a strongly acidic flavor. As a tricarboxylic acid widely existing in nature, CA can be used as an intermediate in chemical synthesis and a very important platform compound.

CA was mainly produced via the glycolysis pathway of the cytoplasm and the subsequent polymerization of mitochondria C4 and C2 (Yin et al. 2015). During glycolysis, glucose was decomposed into two molecules of pyruvate, one entered the mitochondria and converts to acetyl-CoA, and the other converted to oxaloacetate (Yin et al. 2015). Oxaloacetate was subsequently reduced to MA and transported to the mitochondria via the MA-CA anti-transport protein. The MA in the mitochondria entered the TCA cycle to form CA (Fig. 1). In current reports, the ATP-citrate lyase genes (*acl1*) from the recombinant yeast strain 87 and the transformant 30 were deleted, and the copy number of the iso-citrate lyase gene (*icl1*) was increased in the marine-derived yeast *Y. lipolytica* SWJ-1b (Liu et al. 2013b). However, the accumulation of glucose and fructose at high invertase expression level indicated a limitation of CA production by sugar uptake. Production of CA from sucrose or inulin successfully overcame the limitations in *Y. lipolytica* (Försterr et al. 2007; Liu et al. 2010). Additionally, CA could cause the pH to drop during fermentation. *A. niger* had the ability to ferment various crude materials for high CA productivity at low pH (with an optimal range of 3.8–6.0) and remained the best choice for commercial production (Dhillon et al. 2011).

Gluconic acid

GA is structurally similar to glucose, while the aldehyde group at the 1-position is replaced by a carboxyl group, and is an important intermediate for chemical productions, pharmaceutical, and food products (Singh and Kumar 2007). GA has potential in the production of gluconic acid derivatives or directly as a finished product. The biological fermentation method utilized the oxidation of microorganisms to synthesize gluconic acid from glucose, which can be divided into fungal fermentation, bacterial fermentation, immobilized cells, and immobilized enzyme fermentation. According to the existing reports, the most promising strain in fungal fermentation was *A. niger*. In the mutant *A. niger* ORS-4.410 (pH range 2.5–7.5), the utilization of solid surface fermentation (SSF) was used instead of conventional fermentation conditions for GA production (96.52 g/L) with grape juice as a cheap carbohydrate source (Singh and Singh 2006). Using dry dilute acid pretreated corn stover (DDAP) hydrolysate, researchers optimized the parameters of gluconic acid fermentation in flasks by *A. niger* and achieved 76.67 g/L GA in fermenters (Zhang et al. 2016). In *K. pneumoniae*, the gene *gad* (encoding gluconate dehydrogenase) was deleted, with the optimization of fermentation parameters, the titer of GA reached 422 g/L in fed-batch fermentation, and this should be the highest titer currently reported (Wang et al. 2016a).

Muconic acid

Muconic acid, a dicarboxylic acid, used as a raw material for the manufacture of various valuable polymers and drugs (Choi et al. 2020). *Cis*, *cis*-muconic acid (CCM), as the mainly bio-based muconic acid production, has progressed in several microorganisms, such as *S. cerevisiae*, *E. coli*, *C. glutamicum*, and *P. putida* (Table 1). In *C. glutamicum*, the gene *catB* (encoding muconate cycloisomerase) was deleted and the gene *catA* (encoding catechol-1,2-dixoygenase) was overexpressed; finally, the titer of CCM reached 85 g/L from catechol in a fed-batch process (Becker et al. 2018). However, catechol is highly toxic, which posed a challenge for the bioproduction of CCM by the β-ketoadipate pathway (Kohlstedt et al. 2018). In *Pseudomonas putida*, expression of genes *catA*

and *catA2* and deletion of genes *catBC* can increase catechol tolerance and catechol conversion rates (Kohlstedt et al. 2018). In *E. coli*, researchers found 3-dehydroshikimate was a useful precursor for the biosynthesis of muconic acid. First, the genes showing negative effects on 3-dehydroshikimate accumulation were disrupted, including *tyrR* (encoding tyrosine dependent transcriptional regulator), *ptsG* (encoding phosphoenolpyruvate phosphotransferase), and *pykA* (encoding pyruvate kinase 2). Next, the genes showing positive effects on 3-dehydroshikimate accumulation were overexpressed, including *aroB* (3-dehydroquinate synthase), *aroD* (3-de-hydroquinate dehydratase), *ppsA* (phosphoenolpyruvate synthase), *galP* (D-galactose transporter), and *aroGF* (3-deoxy-D-arabinoheptulosonate-7-phosphate synthase). Finally, overexpression the genes showing positive effects on 3-dehydroshikimate to CCM, including *asbF* (encoding 3-dehydroshikimate), *aroY* (encoding codon-optimized protocatechuate decarboxylase), and *catA*; the CCM production reached 64.5 g/L in 7-L fed-batch fermentation (Choi et al. 2019).

Adipic acid

AA, which has a green "bio" plastic label, is a dicarboxylic acid that has showed applications in engineering plastics, lubricants, nylon 6-6 fibers, and resin to produce chemical industries (Deng and Mao 2015). For the AA production route, the biological conversion of aromatic compounds was synthesized from glucose by de novo pathway. And several microorganisms have been reported in Cis-AA production with hydroquinone and toluene. The synthetic pathway of AA needed to block the diversion of pyruvate to lactic acid, TCA cycle to succinic acid, and acetyl-CoA to acetic acid (Zhao et al. 2018a) (Fig. 2b). The choice of microorganism for fermentation was also important for the determination of economic feasibility, as the composition of media and the environmental conditions during fermentation were dependent on the microorganism. Both *E. coli* and *Candida tropicalis* had the potential to produce AA (Cheong et al. 2016; Ju et al. 2020; Zhao et al. 2018a). A five-step reverse adipate-degradation pathway (RADP) identified in *T. fusca* was reconstructed in *E. coli*, and the AA production reached 68 g/L by fed-batch fermentation, which was the highest reported adipic acid titer in *E. coli* to the best of our knowledge (Zhao et al. 2018a). However, IPTG was used in the previous study, which was not feasible in the fermentation industry. Recently, researchers selected strong promoter-5′-UTR complexes (PUTR) for the production of AA (Zhou et al. 2020). In *Candida tropicalis*, *AOX* gene (encoding acyl-CoA oxidases)-deficient strains were constructed to inhibit the expression of acyl-CoA oxidase 4, and then AA was produced by short- or long-chain fatty acid acyl-CoA (Ju et al. 2020). Using genetic engineering to modify acyl-CoA oxidase mutants could efficiently increase the production of adipic acid in *C. tropicalis* (Ju et al. 2020).

Conclusions

In this review, the microbial production of organic acids was systematically described. Nowadays, synthetic biology is dedicated to genome editing, and the focus is on the interaction of all molecular elements. Meanwhile, the biosensors can respond to metabolite levels in biological cells by characterization of fluorescence intensity. Therefore, these biosensors are highly efficient and necessary to select high-yield host strains of organic acids through high-throughput screening.

Stress response is essential for the survival of all microorganisms, and cells depend on a homeostatic mechanism to cope with varieties of ambient stresses. However, it is well known that organic acids have a carboxyl group that makes them highly acidic and toxic to the growth of host cells. The tendency of host microorganisms to produce organic acids is to develop acid-resistant elements or to develop adaptive evolution strategy acid-resistant host cells. The interrelationship between organic acids and the acid resistance of host cells can help develop advanced industrial chassis cells, which will enable the host to produce a variety of organic acids. It is also desired to analyze the acid resistance mechanism and then apply technological innovation to build an organic acid response system to improve the acid resistance of cells in the future.

Authors' contributions Long Liu, Xueqin Lv, Jianghua Li and Guocheng Du conceived and designed the manuscript. Li Sun and Ziyang Huang provided and analyzed literature. LS wrote and revised the manuscript. Li Sun, Xueqin Lv, Yang Gu and Mengyue Gong revised the manuscript. All authors read and approved the manuscript.

Funding This work was financially supported by the National Natural Science Foundation of China (21676119, 31671845, 31871784, 31870069, 31930085) and the Key Research and Development Program of China (2018YFA0900300, 2018YFA0900504).

Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Alonso S, Rendueles M, Díaz M (2015) Microbial production of specialty organic acids from renewable and waste materials. Crit Rev Biotechnol 35:497–513

Baek SH, Kwon EY, Kim YH, Hahn JS (2016) Metabolic engineering and adaptive evolution for efficient production of D-lactic acid in *Saccharomyces cerevisiae*. Appl Microbiol Biotechnol 100:2737–2748

Basak S, Geng H, Jiang R (2014) Rewiring global regulator cAMP receptor protein (CRP) to improve *E. coli* tolerance towards low pH. J Biotechnol 173:68–75

Becker J, Wittmann C (2015) Advanced biotechnology: metabolically engineered cells for the bio-based production of chemicals and fuels, materials, and health-care products. Angew Chem Int Edit 54:3328–3350

Becker J, Lange A, Fabarius J, Wittmann C (2015) Top value platform chemicals: bio-based production of organic acids. Curr Opin Biotechnol 36:168–175

Becker J, Kuhl M, Kohlstedt M, Starck S, Wittmann C (2018) Metabolic engineering of *Corynebacterium glutamicum* for the production of *cis, cis*-muconic acid from lignin. Microb Cell Factories 17:115

Bian Y, Li L, Dong M, Liu X, Kaneko T, Cheng K, Liu H, Voss C, Cao X, Wang Y, Litchfield D, Ye M, Li SSC, Zou H (2016) Ultra-deep tyrosine phosphoproteomics enabled by a phosphotyrosine superbinder. Nat Chem Biol 12:959–966

Blumhoff M, Steiger MG, Mattanovich D, Sauer M (2013) Targeting enzymes to the right compartment: metabolic engineering for itaconic acid production by *Aspergillus niger*. Metab Eng 19:26–32

Brown SH, Bashkirova L, Berka R, Chandler T, Doty T, McCall K, McCulloch M, McFarland S, Thompson S, Yaver D (2013) Metabolic engineering of *Aspergillus oryzae* NRRL 3488 for increased production of l-malic acid. Appl Microbiol Biotechnol 97:8903–8912

Chae TU, Ahn JH, Ko YS, Kim JW, Lee JA, Lee EH, Lee SY (2020) Metabolic engineering for the production of dicarboxylic acids and diamines. Metab Eng 58:2–16

Chen C, Ding S, Wang D, Li Z, Ye Q (2014a) Simultaneous saccharification and fermentation of cassava to succinic acid by *Escherichia coli* NZN111. Bioresour Technol 163:100–105

Chen T, Zhu N, Xia H (2014b) Aerobic production of succinate from arabinose by metabolically engineered *Corynebacterium glutamicum*. Bioresour Technol 151:411–414

Cheng KK, Wang GY, Zeng J, Zhang JA (2013) Improved succinate production by metabolic engineering. Biomed Res Int 2013:12

Cheng C, Zhou Y, Lin M, Wei P, Yang S (2017) Polymalic acid fermentation by *Aureobasidium pullulans* for malic acid production from soybean hull and soy molasses: fermentation kinetics and economic analysis. Bioresour Technol 223:166–174

Cheong S, Clomburg JM, Gonzalez R (2016) Energy- and carbon-efficient synthesis of functionalized small molecules in bacteria using non-decarboxylative Claisen condensation reactions. Nat Biotechnol 34:556–561

Choi SS, Seo SY, Park SO, Lee HN, Song JS, Kim JY, Park JH, Kim S, Lee SJ, Chun GT, Kim ES (2019) Cell factory design and culture process optimization for dehydroshikimate biosynthesis in *Escherichia coli*. Front Bioeng Biotechnol 7:241

Choi S, Lee HN, Park E, Lee SJ, Kim ES (2020) Recent advances in microbial production of *cis,cis*-muconic acid. Biomolecules 10:1238

Christopher DD, David JS, Ned SW, Joshua DR (2011) α-ketoglutarate coordinates carbon and nitrogen utilization via enzyme I inhibition. Nat Chem Biol 7:894–901

Chu HS, Kim YS, Lee CM, Lee JH, Jung WS, Ahn JH, Song SH, Choi IS, Cho KM (2015) Metabolic engineering of 3-hydroxypropionic acid biosynthesis in *Escherichia coli*. Biotechnol Bioeng 112:356–364

Dai Z, Zhou H, Zhang S, Gu H, Yang Q, Zhang W, Dong W, Ma J, Fang Y, Jiang M, Xin F (2018) Current advance in biological production of malic acid using wild type and metabolic engineered strains. Bioresour Technol 258:345–353

Deng Y, Mao Y (2015) Biological production of adipic acid from renewable substrates: current and future methods. Biochem Eng J 105:16–26

Dhillon GS, Brar SK, Verma M, Tyagi RD (2011) Recent advances in citric acid bio-production and recovery. Food Bioprocess Technol 4:505–529

Ding Q, Luo Q, Zhou J, Chen X, Liu L (2018) Enhancing L-malate production of *Aspergillus oryzae* FMME218-37 by improving inorganic nitrogen utilization. Appl Microbiol Biotechnol 102:8739–8751

Försterr A, Aurich A, Mauersberger S, Barth G (2007) Citric acid production from sucrose using a recombinant strain of the yeast *Yarrowia lipolytica*. Appl Microbiol Biotechnol 75:1409–1417

Fu H, Yang S, Wang M, Wang J, Tang I (2017a) Butyric acid production from lignocellulosic biomass hydrolysates by engineered *Clostridium tyrobutyricum* overexpressing xylose catabolism genes for glucose and xylose co-utilization. Bioresour Technol 234:389–396

Fu H, Yu L, Lin M, Wang J, Xiu Z, Yang ST (2017b) Metabolic engineering of *Clostridium tyrobutyricum* for enhanced butyric acid production from glucose and xylose. Metab Eng 40:50–58

Gao C, Xu X, Hu C, Zhang W, Zhang Y, Ma C, Xu P (2010) Pyruvate producing biocatalyst with constitutive NAD-independent lactate dehydrogenases. Process Biochem 45:1912–1915

Gao C, Wang S, Hu G, Guo L, Chen X, Xu P, Liu L (2018) Engineering *Escherichia coli* for malate production by integrating modular pathway characterization with CRISPRi-guided multiplexed metabolic tuning. Biotechnol Bioeng 115:661–672

Garcia B, Olivera ER, Minambres B, Fernandez-Valverde M, Canedo LM, Prieto MA, Garcia JL, Martinez M, Luengo JM (1999) Novel biodegradable aromatic plastics from a bacterial source. Genetic and biochemical studies on a route of the phenylacetyl-coa catabolon. J Biol Chem 274:29228–29241

Goldberg I, Rokem J, Pines O (2006) Organic acids: old metabolites, new themes. J Chem Technol Biotechnol 81:1601–1611

Goswami V, Srivastava AK (2001) Propionic acid production in an in situ cell retention bioreactor. Appl Microbiol Biotechnol 56:676–680

Guan N, Liu L, Shin HD, Chen RR, Zhang J, Li J, Du G, Shi Z, Chen J (2013) Systems-level understanding of how *Propionibacterium acidipropionici* respond to propionic acid stress at the microenvironment levels: mechanism and application. J Biotechnol 167:56–63

Guan N, Shin HD, Chen R, Li J, Liu L, Du G, Chen J (2014) Understanding of how *Propionibacterium acidipropionici* respond to propionic acid stress at the level of proteomics. Sci Rep 4:6951

Guan N, Li J, Shin HD, Wu J, Du G, Shi Z, Liu L, Chen J (2015) Comparative metabolomics analysis of the key metabolic nodes in propionic acid synthesis in *Propionibacterium acidipropionici*. Metabolomics 11:1106–1116

Guan N, Li J, Shin HD, Du G, Chen J, Liu L (2016) Metabolic engineering of acid resistance elements to improve acid resistance and propionic acid production of *Propionibacterium jensenii*. Biotechnol Bioeng 113:1294–1304

He F, Qin S, Yang Z, Bai X, Suo Y, Wang J (2020) Butyric acid production from spent coffee grounds by engineered *Clostridium tyrobutyricum* overexpressing galactose catabolism genes. Bioresour Technol 304:122977

Hevekerl A, Kuenz A, Vorlop KD (2014) Influence of the pH on the itaconic acid production with *Aspergillus terreus*. Appl Microbiol Biotechnol 98:10005–10012

Hossain GS, Li J, Shin HD, Chen RR, Du G, Liu L, Chen J (2014) Bioconversion of L-glutamic acid to α-ketoglutaric acid by an immobilized whole-cell biocatalyst expressing L-amino acid deaminase from *Proteus mirabilis*. J Biotechnol 169:112–120

Hossain GS, Shin HD, Li J, Du G, Chen J, Liu L (2016) Transporter engineering and enzyme evolution for pyruvate production from

D/L-alanine with a whole-cell biocatalyst expressing L-amino acid deaminase from *Proteus mirabilis*. RSC Adv 6:82676–82684

Huang J, Cai J, Wang J, Zhu X, Huang L, Yang ST, Xu Z (2011) Efficient production of butyric acid from Jerusalem artichoke by immobilized *Clostridium tyrobutyricum* in a fibrous-bed bioreactor. Bioresour Technol 102:3923–3926

Huang Y, Li Z, Shimizu K, Ye Q (2013) Co-production of 3-hydroxypropionic acid and 1,3-propanediol by *Klebseilla pneumoniae* expressing *aldH* under microaerobic conditions. Bioresour Technol 128:505–512

Huang X, Lu X, Li Y, Li X, Li J (2014) Improving itaconic acid production through genetic engineering of an industrial *Aspergillus terreus* strain. Microb Cell Factories 13:119

Jha AK, Li J, Yuan Y, Baral N, Ai B (2014) A review on bio-butyric acid production and its optimization. Int J Agric Biol 16:1019–1024

Jiang L, Cui H, Zhu L, Hu Y, Xu X, Li S, Huang H (2014) Enhanced propionic acid production from whey lactose with immobilized *Propionibacterium acidipropionici* and role of trehalose synthesis in acid toleranc. Green Chem 17:250–259

Jiang M, Ma J, Wu M, Liu R, Liang L, Xin F, Zhang W, Jia H, Dong W (2017) Progress of succinic acid production from renewable resources: metabolic and fermentative strategies. Bioresour Technol 245:1710–1717

Joshi DS, Singhvi MS, Khire JM, Gokhale DV (2010) Strain improvement of *Lactobacillus lactis* for D-lactic acid production. Biotechnol Lett 32:517–520

Ju JH, Oh BR, Heo SY, Lee YU, Shon JH, Kim CH, Kim YM, Seo JW, Hong WK (2020) Production of adipic acid by short- and long-chain fatty acid acyl-CoA oxidase engineered in yeast *Candida tropicalis*. Bioprocess Biosyst Eng 43:33–43

Kawai S, Ohashi K, Yoshida S, Fujii M, Mikami S, Sato N, Murata K (2014) Bacterial pyruvate production from alginate, a promising carbon source from marine brown macroalgae. J Biosci Bioeng 117:269–274

Kim K, Kim SK, Park YC, Seo JH (2014) Enhanced production of 3-hydroxypropionic acid from glycerol by modulation of glycerol metabolism in recombinant *Escherichia coli*. Bioresour Technol 156: 170–175

Kim SK, Gui HH, Seong W, Kim H, Lee SG (2016) CRISPR interference-guided balancing of a biosynthetic mevalonate pathway increases terpenoid production. Metab Eng 38:228–240

Kohlstedt M, Starck S, Barton N, Stolzenberger J, Selzer M, Mehlmann K, Schneider R, Pleissner D, Rinkel J, Dickschat JS, Venus J, van Duuren JBJH, Wittmann C (2018) From lignin to nylon: cascaded chemical and biochemical conversion using metabolically engineered *Pseudomonas putida*. Metab Eng 47:279–293

Krull S, Hevekerl A, Kuenz A, Prusse U (2017) Process development of itaconic acid production by a natural wild type strain of *Aspergillus terreus* to reach industrially relevant final titers. Appl Microbiol Biotechnol 101:4063–4072

Kuenz A, Gallenmüller Y, Willke T, Vorlop KD (2012) Microbial production of itaconic acid: developing a stable platform for high product concentrations. Appl Microbiol Biotechnol 96:1209–1216

Lawrence CL, Botting CH, Antrobus R, Coote PJ (2004) Evidence of a new role for the high-osmolarity glycerol mitogen-activated protein kinase pathway in yeast: regulating adaptation to citric acid stress. Mol Cell Biol 24:3307–3323

Li Y, Li M, Zhang X, Yang P, Liang Q, Qi Q (2013) A novel whole-phase succinate fermentation strategy with high volumetric productivity in engineered *Escherichia coli*. Bioresour Technol 149:333–340

Li N, Zhang B, Wang Z, Tang Y, Chen T, Zhao X (2014) Engineering *Escherichia coli* for fumaric acid production from glycerol. Bioresour Technol 174:81–87

Li C, Yang X, Gao S, Wang H, Lin CSK (2017) High efficiency succinic acid production from glycerol via in situ fibrous bed bioreactor with an engineered *Yarrowia lipolytica*. Bioresour Technol 225:9–16

Liang L, Liu R, Li F, Wu M, Chen K, Ma J, Jiang M, Wei P, Ouyang P (2013) Repetitive succinic acid production from lignocellulose hydrolysates by enhancement of ATP supply in metabolically engineered *Escherichia coli*. Bioresour Technol 143:405–412

Litsanov B, Brocker M, Bott M (2012) Toward homosuccinate fermentation: metabolic engineering of *Corynebacterium glutamicum* for anaerobic production of succinate from glucose and formate. Appl Microbiol Biotechnol 78:3325–3337

Liu L, Xu Q, Li Y, Shi Z, Zhu Y, Du G, Chen J (2007) Enhancement of pyruvate production by osmotic-tolerant mutant of *Torulopsis glabrata*. Biotechnol Bioeng 97:825–832

Liu X, Chi Z, Liu G, Wang F, Chi Z (2010) Inulin hydrolysis and citric acid production from inulin using the surface-engineered *Yarrowia lipolytica* displaying inulinase. Metab Eng 12:469–476

Liu H, Valdehuesa KN, Nisola GM, Ramos KR, Chung WJ (2012a) High yield production of D-xylonic acid from D-xylose using engineered *Escherichia coli*. Bioresour Technol 115:244–248

Liu L, Zhu Y, Li J, Wang M, Lee P, Du G, Chen J (2012b) Microbial production of propionic acid from propionibacteria: current state, challenges and perspectives. Crit Rev Biotechnol 32:374–381

Liu L, Hossain GS, Shin HD, Li J, Du G, Chen J (2013a) One-step production of α-ketoglutaric acid from glutamic acid with an engineered l-amino acid deaminase from *Proteus mirabilis*. J Biotechnol 164:97–104

Liu X, Chi Z, Liu G, Madzak C, Chi Z (2013b) Both decrease in ACL1 gene expression and increase in ICL1 gene expression in marine-derived yeast *Yarrowia lipolytica* expressing INU1 gene enhance citric acid production from inulin. Mar Biotechnol 15:26–36

Liu G, Zhou Y, Luo H, Cheng X, Zhang R, Teng W (2015a) A comparative evaluation of different types of microbial electrolysis desalination cells for malic acid production. Bioresour Technol 198:87–93

Liu L, Zhuge X, Shin HD, Chen RR, Li J, Du G, Chen J, Schottel JL (2015b) Improved production of propionic acid in *Propionibacterium jensenii* via combinational overexpression of glycerol dehydrogenase and malate dehydrogenase from *Klebsiella pneumoniae*. Appl Environ Microbiol 81:2256–2264

Liu L, Guan N, Zhu G, Li J, Shin HD, Du G, Chen J (2016) Pathway engineering of *Propionibacterium jensenii* for improved production of propionic acid. Sci Rep 6:19963

Liu J, Li J, Shin HD, Liu L, Du G, Chen J (2017) Protein and metabolic engineering for the production of organic acids. Bioresour Technol 239:412–421

Liu J, Li J, Liu Y, Shin HD, Ledesma-Amaro R, Du G, Chen J, Liu L (2018a) Synergistic rewiring of carbon metabolism and redox metabolism in cytoplasm and mitochondria of *Aspergillus oryzae* for increased l-malate production. ACS Synth Biol 7:2139–2147

Liu R, Liang L, Choudhury A, Bassalo MC, Gill RT (2018b) Iterative genome editing of *Escherichia coli* for 3-hydroxypropionic acid production. Metab Eng 47:303–313

Luo H, Yang R, Zhao Y, Wang Z, Liu Z, Huang M, Zeng Q (2018) Recent advances and strategies in process and strain engineering for the production of butyric acid by microbial fermentation. Bioresour Technol 253:343–354

Marinho GAS, Alvarado-Morales, Merlin Angelidaki I (2016) Valorization of macroalga *Saccharina latissima* as novel feedstock for fermentation-based succinic acid production in a biorefinery approach and economic aspects. Algal Res 16:102–109

McCarthy S, Johnson T, Pavlik BJ, Payne S, Schackwitz W, Martin J, Lipzen A, Keffeler E, Blum P (2016) Expanding the limits of thermoacidophily in the archaeon *Sulfolobus solfataricus* by adaptive evolution. Appl Environ Microbiol 82:857–867

Nick W, Gennaro A, Peter SL, Matthias GS, Nuno PM, Punt PJ (2020) Metabolic specialization in itaconic acid production: a tale of two fungi. Curr Opin Biotechnol 62:153–159

Niu P, Dong X, Wang Y, Liu L (2014) Enzymatic production of α-ketoglutaric acid from L-glutamic acid via L-glutamate oxidase. J Biotechnol 179:56–62

Okino S, Noburyu R, Suda M, Jojima T, Inui M, Yukawa H (2008) An efficient succinic acid production process in a metabolically engineered *Corynebacterium glutamicum* strain. Appl Environ Microbiol 81:459–464

Olajuyin AM, Yang M, Liu Y, Mu T, Tian J, Adaramoye OA, Xing J (2016) Efficient production of succinic acid from Palmaria palmata hydrolysate by metabolically engineered *Escherichia coli*. Bioresour Technol 214:653–659

Paludo N, Alves JS, Altmann C, Ayub MAZ, Fernandez-Lafuente R, Rodrigues RC (2015) The combined use of ultrasound and molecular sieves improves the synthesis of ethyl butyrate catalyzed by immobilized *Thermomyces lanuginosus* lipase. Ultrason Sonochem 22:89–94

Papadaki A, Papapostolou H, Alexandri M, Kopsahelis N, Papanikolaou S, De Castro AM, Freire DMG, Koutinas A (2018) Fumaric acid production using renewable resources from biodiesel and cane sugar production processes. Environ Sci Pollut Res 25:35960–35970

Park SJ, Kim EY, Noh W, Park HM, Oh YH, Lee SH, Song BK, Jegal J, Lee SY (2013) Metabolic engineering of *Escherichia coli* for the production of 5-aminovalerate and glutarate as C5 platform chemicals. Metab Eng 16:42–47

Payne S, McCarthy S, Johnson T, North E, Blum P (2018) Nonmutational mechanism of inheritance in the Archaeon *Sulfolobus solfataricus*. Proc Natl Acad Sci 115:12271–12276

Pham HL, Wong A, Chua N, Teo WS, Yew WS, Chang MW (2017) Engineering a riboswitch-based genetic platform for the self-directed evolution of acid-tolerant phenotypes. Nat Commun 8:411

Rajkumar AS, Liu G, Bergenholm D, Arsovska D, Kristensen M, Nielsen J, Jensen MK, Keasling JD (2016) Engineering of synthetic, stress-responsive yeast promoters. Nucleic Acids Res 44:e136

Rohles CM, Gläser L, Kohlstedt M, Gießelmann G, Pearson S, del Campo A, Becker J, Wittmann C (2018) A bio-based route to the carbon-5 chemical glutaric acid and to bionylon-6,5 using metabolically engineered *Corynebacterium glutamicum*. Green Chem 20: 4662–4674

Salvachúa D, Mohagheghi A, Smith H, Bradfield MFA, Nicol W, Black BAB, Biddy MJ, Dowe N, Beckham GT (2017) Succinic acid production on xylose-enriched biorefinery streams by *Actinobacillus succinogenes* in batch fermentation. Biotechnol Biofuels 9:28

Sauer M, Porro D, Mattanovich D, Branduardi P (2013) Microbial production of organic acids: expanding the markets. Trends Biotechnol 26:100–108

Sebastian J, Hegde K, Kumar P, Rouissi T, Brar SK (2019) Bioproduction of fumaric acid: an insight into microbial strain improvement strategies. Crit Rev Biotechnol 39:817–834

Singh OV, Kumar R (2007) Biotechnological production of gluconic acid: future implications. Appl Environ Microbiol 75:713–722

Singh OV, Singh RP (2006) Bioconversion of grape must into modulated gluconic acid production by *Aspergillus niger* ORS-4.410. J Appl Microbiol 100:1114–1122

Snoek T, Chaberski EK, Ambri F, Kol S, Bjorn SP, Pang B, Barajas JF, Welner DH, Jensen MK, Keasling JD (2020) Evolution-guided engineering of small-molecule biosensors. Nucleic Acids Res 48:e3

Song C, Lee S (2015) Combining rational metabolic engineering and flux optimization strategies for efficient production of fumaric acid. Appl Microbiol Biotechnol 99:8455–8464

Song CW, Kim DI, Choi S, Jang JW, Lee SY (2013) Metabolic engineering of *Escherichia coli* for the production of fumaric acid. Biotechnol Bioeng 110:2025–2034

Sun D, Liu X, Zhu M, Chen Y, Li C, Cheng X, Zhu Z, Lu F, Qin HM (2019) Efficient biosynthesis of high-value succinic acid and 5-hydroxyleucine using a multienzyme cascade and whole-cell catalysis. J Agric Food Chem 67:12502–12510

Suo Y, Luo S, Zhang Y, Liao Z, Wang J (2017) Enhanced butyric acid tolerance and production by Class I heat shock protein-overproducing *Clostridium tyrobutyricum* ATCC 25755. J Ind Microbiol Biotechnol 44:1145–1156

Tang J, Zhu X, Lu J, Liu P, Xu H, Tan Z, Zhang X (2013) Recruiting alternative glucose utilization pathways for improving succinate production. Appl Microbiol Biotechnol 97:2513–2520

Toivari M, Vehkomaki ML, Nygard Y, Penttila M, Ruohonen L, Wiebe MG (2013) Low pH D-xylonate production with *Pichia kudriavzevii*. Bioresour Technol 133:555–562

Toivari M, Nygård Y, Kumpula EP, Vehkomäki ML, Benˇina M, Valkonen M, Maaheimo H, Andberg M, Koivula A, Ruohonen L, Penttilä M, Wiebe MG (2012) Metabolic engineering of *Saccharomyces cerevisiae* for bioconversion of D-xylose to D-xylonate. Metab Eng 14:427–436

Tsuge Y, Yamamoto S, Suda M, Inui M, Yukawa H (2013) Reactions upstream of glycerate-1,3-bisphosphate drive *Corynebacterium glutamicum* D-lactate productivity under oxygen deprivation. Appl Microbiol Biotechnol 97:6693–6703

Tsuge Y, Yamamoto S, Kato N, Suda M, Vertès AA, Yukawa H, Inui M (2015) Overexpression of the phosphofructokinase encoding gene is crucial for achieving high production of D-lactate in *Corynebacterium glutamicum* under oxygen deprivation. Appl Microbiol Biotechnol 99:4679–4689

van Maris AJ, Luttik MA, Winkler AA, van Dijken JP, Pronk JT (2003) Overproduction of threonine aldolase circumvents the biosynthetic role of pyruvate decarboxylase in glucose-limited chemostat cultures of *Saccharomyces cerevisiae*. Appl Environ Microbiol 69: 2094–2099

van Maris A, Geertman JM, Vermeulen A, Groothuizen MK, Winkler AA, Piper MD, van Dijken JP, Pronk JT (2004) Directed evolution of pyruvate decarboxylase-negative *Saccharomyces cerevisiae*, yielding a C2-independent, glucose-tolerant, and pyruvate-hyperproducing yeast. Appl Environ Microbiol 70:159–166

Wang D, Thakker C, Liu P, Bennett GN, San KY (2015) Efficient production of free fatty acids from soybean meal carbohydrates. Biotechnol Bioeng 112:2324–2333

Wang D, Wang C, Wei D, Shi J, Kim CH, Jiang B, Han Z, Hao J (2016a) Gluconic acid production by gad mutant of *Klebsiella pneumoniae*. World J Microbiol Biotechnol 32:132

Wang J, Lin M, Xu M, Yang ST (2016b) Anaerobic fermentation for production of carboxylic acids as bulk chemicals from renewable biomass. Adv Biochem Eng Biotechnol 156:323–361

Wang J, Shen X, Lin Y, Chen Z, Yang Y, Yuan Q, Yan Y (2018) Investigation of the synergetic effect of xylose metabolic pathways on the production of glutaric acid. ACS Synth Biol 7:24–29

Wang G, Ozmerih S, Guerreiro R, Meireles AC, Carolas A, Milne N, Jensen MK, Ferreira BS, Borodina I (2020) Improvement of *cis*,*cis*-muconic acid production in *Saccharomyces cerevisiae* through biosensor-aided genome engineering. ACS Synth Biol 9:634–646

Wei P, Cheng C, Lin M, Zhou Y, Yang S (2017) Production of poly(malic acid) from sugarcane juice in fermentation by *Aureobasidium pullulans*: kinetics and process economics. Bioresour Technol 224:581–589

Wieschalka S, Blombach B, Bott M, Eikmanns BJ (2013) Bio-based production of organic acids with *Corynebacterium glutamicum*. Microb Biotechnol 6:87–102

Wittmann C, Becker J, Lange A, Fabarius J (2015) Top value platform chemicals: bio-based production of organic acids. Curr Opin Biotechnol 36:168–175

Xu K, Xu P (2014) Efficient production of L-lactic acid using co-feeding strategy based on cane molasses/glucose carbon sources. Bioresour Technol 153:23–29

Xu G, Zou W, Chen X, Xu N, Liu L, Chen J (2012) Fumaric acid production in *Saccharomyces cerevisiae* by in silico aided metabolic engineering. PLoS One 7:e52086

Xu G, Chen X, Liu L, Jiang L (2013) Fumaric acid production in *Saccharomyces cerevisiae* by simultaneous use of oxidative and reductive routes. Bioresour Technol 148:91–96

Xu Y, Shan L, Zhou Y, Xie Z, Ball AS, Cao W, Liu H (2019) Development of a Cre-loxP-based genetic system in *Aspergillus niger* ATCC1015 and its application to construction of efficient organic acid-producing cell factories. Appl Microbiol Biotechnol 103:8105–8114

Xu Y, Zhao Z, Tong W, Ding Y, Liu B, Shi Y, Wang J, Sun S, Liu M, Wang Y, Qi Q, Xian M, Zhao G (2020a) An acid-tolerance response system protecting exponentially growing *Escherichia coli*. Nat Commun 11:1496

Xu Y, Zhou Y, Cao W, Liu H (2020b) Improved production of malic acid in *Aspergillus niger* by abolishing citric acid accumulation and enhancing glycolytic flux. ACS Synth Biol 9:1418–1425

Yamane T, Tanaka R (2013) Highly accumulative production of L(+)-lactate from glucose by crystallization fermentation with immobilized *Rhizopus oryzae*. J Biosci Bioeng 115:90–95

Yin X, Li J, Shin HD, Du G, Liu L, Chen J (2015) Metabolic engineering in the biotechnological production of organic acids in the tricarboxylic acid cycle of microorganisms: advances and prospects. Biotechnol Adv 33:830–841

Yoshida S, Tanaka H, Hirayama M, Murata K, Kawai S (2015) Production of pyruvate from mannitol by mannitol-assimilating pyruvate decarboxylase-negative *Saccharomyces cerevisiae*. Bioengineered 6:347–350

Yu Z, Du G, Zhou J, Chen J (2012) Enhanced α-ketoglutaric acid production in *Yarrowia lipolytica* WSH-Z06 by an improved integrated fed-batch strategy. Bioresour Technol 114:597–602

Yu JL, Xia XX, Zhong JJ, Qian ZG (2017) Enhanced production of C5 dicarboxylic acids by aerobic-anaerobic shift in fermentation of engineered *Escherichia coli*. Process Biochem 62:53–58

Zambanini T, Hosseinpour Tehrani H, Geiser E, Sonntag CK, Buescher JM, Meurer G, Wierckx N, Blank LM (2017) Metabolic engineering of *Ustilago trichophora* TZ1 for improved malic acid production. Metab Eng Commun 4:12–21

Zelle RM, de Hulster E, van Winden WA, de Waard P, Dijkema C, Winkler AA, Geertman JMA, van Dijken JP, Pronk JT, van Maris AJA (2008) Malic acid production by *Saccharomyces cerevisiae*: engineering of pyruvate carboxylation, oxaloacetate reduction, and malate export. Appl Environ Microbiol 74:2766–2777

Zhang A, Yang ST (2009) Engineering *Propionibacterium acidipropionici* for enhanced propionic acid tolerance and fermentation. Biotechnol Bioeng 104:766–773

Zhang B, Skory CD, Yang ST (2012) Metabolic engineering of *Rhizopus oryzae* : Effects of overexpressing pyc and pepc genes on fumaric acid biosynthesis from glucose. Metab Eng 14:512–520

Zhang H, Zhang J, Bao J (2016) High titer gluconic acid fermentation by *Aspergillus niger* from dry dilute acid pretreated corn stover without detoxification. Bioresour Technol 203:211–219

Zhang Y, Yoshida M, Vadlani PV (2018) Biosynthesis of D-lactic acid from lignocellulosic biomass. Biotechnol Lett 40:1167–1179

Zhao M, Huang D, Zhang X, Koffas MAG, Deng Y (2018a) Metabolic engineering of *Escherichia coli* for producing adipic acid through the reverse adipate-degradation pathway. Metab Eng 47:254–262

Zhao M, Li G, Deng Y (2018b) Engineering *Escherichia coli* for glutarate production as the C_5 platform backbone. Appl Environ Microbiol 84:e00814–e00818

Zhao M, Lu X, Zong H, Li J, Zhuge B (2018c) Itaconic acid production in microorganisms. Biotechnol Lett 40:455–464

Zheng P, Fang L, Xu Y, Dong J, Ni Y, Sun H (2010) Succinic acid production from corn stover by simultaneous saccharification and fermentation using *Actinobacillus succinogenes*. Bioresour Technol 101:7889–7894

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

Zhu Y, Eiteman MA, Altman R, Altman E (2008) High glycolytic flux improves pyruvate production by a metabolically engineered *Escherichia coli* strain. Appl Environ Microbiol 74:6649–6655

Zhuge X, Liu L, Shin H-D, Chen RR, Li J, Du G, Chen J (2013) Development of a Propionibacterium-Escherichia coli shuttle vector for metabolic engineering of *Propionibacterium jensenii*, an efficient producer of propionic acid. Appl Environ Microbiol 79: 4595–4602