**Yarrowia lipolytica** as an Oleaginous Platform for the Production of Value-Added Fatty Acid-Based Bioproducts

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The microbial fermentation process has been used as an alternative pathway to the production of value-added natural products. Of the microorganisms, *Yarrowia lipolytica*, as an oleaginous platform, is able to produce fatty acid-derived biofuels and biochemicals. Nowadays, there are growing progresses on the production of value-added fatty acid-based bioproducts in *Y. lipolytica*. However, there are fewer reviews performing the metabolic engineering strategies and summarizing the current production of fatty acid-based bioproducts in *Y. lipolytica*. To this end, we briefly provide the fatty acid metabolism, including fatty acid biosynthesis, transportation, and degradation. Then, we introduce the various metabolic engineering strategies for increasing bioproduct accumulation in *Y. lipolytica*. Further, the advanced progress in the production of fatty acid-based bioproducts by *Y. lipolytica*, including nutraceuticals, biofuels, and biochemicals, is summarized. This review will provide attractive thoughts for researchers working in the field of *Y. lipolytica*.

**Keywords:** *Yarrowia lipolytica*, cell factory, fatty acid metabolism, bioproducts, metabolic engineering

**INTRODUCTION**

With the growing crisis of oil energy, microbial production of biochemicals, as one potential alternative route, has received increasing attention (Levering et al., 2015; Ji and Huang, 2019; Ji and Ledesma-Amaro, 2020). Among these microorganisms, the oleaginous yeasts, such as *Rhodosporidium toruloides*, *Lipomyces starkeyi*, and *Yarrowia lipolytica*, are able to produce oleochemicals (Probst et al., 2016; McNeil and Stuart, 2018; Park et al., 2018b; Miller and Alper, 2019). *Y. lipolytica*, as Food and Drug Administration (FDA)-regarded Generally Recognized as Safe (GRAS) yeast with lipids over 20% of its biomass, performs many attractive characteristics and applications, including having mature genetic tools, secreting functional enzymes, and producing organic acids, lipids, and non-native chemicals (Xie, 2017; Darvishi et al., 2018; Larroude et al., 2018; Madzak, 2018; Ma et al., 2019). Currently, many researchers focus on the biotechnological application of *Y. lipolytica* (Xie et al., 2015; Markham et al., 2018; Robles-Rodriguez et al., 2018; Li et al., 2019). In particular, the different metabolic engineering strategies are applied in the lipid production for *Y. lipolytica* (Abdel-Mawgoud et al., 2018; Wang J. et al., 2020). In fact, *Y. lipolytica* is able to produce fatty acids in the form of lipids, either grown on hydrophobic materials (Spagnuolo et al., 2018; Ma et al., 2020). Generally, these fatty acid-based bioproducts from *Y. lipolytica* are divided into three different types, based on the chain length, the terminal
reductive state, and the modifications to the main chain of target product (Yan and Pfleger, 2020). With the development of metabolic engineering and synthetic biology, there are growing progresses on the production of value-added fatty acid-based bioproducts in Y. lipolytica. In the past 5 years, researchers have reviewed the production of fatty acid-derived products by Y. lipolytica, including fatty alkanes, fatty alcohols, and polyunsaturated fatty acids (PUFAs) (Ledesma-Amaro and Nicaud, 2016b; Ma et al., 2020). However, there is less review performing the metabolic engineering strategies for improving the production of fatty acid-based products and summarizing the current biosynthesis of fatty acid-based bioproducts in Y. lipolytica.

Herein, in this review, we describe a brief overview of the biochemistry metabolism of fatty acid in Y. lipolytica. Then, we focus on introducing the various metabolic strategies for increasing bioproduct accumulation, including constructing and engineering metabolic pathways, optimizing fermentation conditions, and engineering compartmentalization system. Moreover, we summarize the recent progress in the production of fatty acid-based bioproducts in Y. lipolytica, including nutraceuticals, biofuels, and biochemicals (Table 1). This article will provide attractive thoughts for researchers working in the field of Y. lipolytica.

**BIOCHEMISTRY OF FATTY ACID METABOLISM**

Currently, some articles have summarized the fatty acid metabolism of Y. lipolytica (Fickers et al., 2005; Abghari and Chen, 2014; Ledesma-Amaro and Nicaud, 2016a; Lazar et al., 2018). Previously, we reviewed in detail the characteristics of Y. lipolytica grown on various carbon substrates (Liu et al., 2015). Herein, the metabolism of fatty acid for producing its derived chemicals in Y. lipolytica is shown in Figure 1.

**Fatty Acid Biosynthesis**

With the development of metabolic engineering, it enables Y. lipolytica to utilize a wide range of carbon sources (Liu et al., 2015; Ledesma-Amaro and Nicaud, 2016b). Using hydrophilic substrates (such as glucose and glycerol) as carbon source, fatty acid is synthesized by de novo pathway in Y. lipolytica. With glucose as sole carbon source, it is converted into pyruvate via the glycolytic pathway in the cytosol. Then, pyruvate is transported to mitochondria and transformed into acetyl-CoA. Acetyl-CoA, a key precursor involved in fatty acid biosynthesis, can be produced by different metabolic routes, including citrate degradation catalyzed by ATP citrate lyase (ACL), fatty acid degradation from β-oxidation pathway, acetyl transformation by acetyl-CoA synthetase (ACS, YALI0F05962p), and pyruvate transformation by pyruvate dehydrogenase complex. Under nitrogen-limited conditions, citrate is secreted into cytosol from mitochondria in Y. lipolytica and acetyl-CoA is produced by ACL catalysis. In Y. lipolytica, ACL is encoded by ACL1 (YALI0E34793p) and ACL2 (YALI0D24431p). Further, acetyl-CoA is transformed into malonyl-CoA by acetyl-CoA carboxylase (ACC, YALI0C11407p).

Generally, acetyl-CoA and malonyl-CoA are used as substrates for fatty acid biosynthesis by fatty acid synthetases (FAS, YALI0B15059p, and YALI0B19382p) in Y. lipolytica. Naturally, Y. lipolytica can only produce C_{16} and C_{18} fatty acids (Beopoulos et al., 2009). Notably, the inherent long-chain PUFAs, including oleic acid (OA, C_{18:1}) or linoleic acid (LA, C_{18:2}), are synthesized by desaturase located in endoplasmic reticulum (ER).

Using hydrophobic materials (such as fats) as substrate, fatty acids are synthesized by ex novo pathway in Y. lipolytica. Generally, the extracellular fatty acids from the metabolism of hydrophobic materials are directly transported to cytosol in Y. lipolytica. Then, fatty acids are converted into derived chemicals by the corresponding oxidation process. Additionally, using alkane from oil refinery as carbon source, fatty acids are synthesized by the enzyme catalytic system located in ER, including cytochrome P450 reductase (EC 1.6.2.4), fatty alcohol oxidase (EC 1.1.3.20), and fatty aldehyde dehydrogenase (EC 1.2.1.3).

NADPH is an important reducing power involved in fatty acid biosynthesis in Y. lipolytica. Generally, there are two identified routes for providing NADPH pool in Y. lipolytica (Qiao et al., 2017). One route is from decarboxylation reaction catalyzed by malic enzyme (EC 1.1.1.40) that occurred in cytosol; the other metabolic route is from the pentose phosphate pathway in Y. lipolytica. Previously, it was reported that overexpression of malic enzyme has little impact on lipid accumulation in Y. lipolytica (Beopoulos et al., 2011; Zhang H. et al., 2013). Wasylenko et al. (2015) reported that the oxidative pentose phosphate pathway, harboring glucose 6-phosphate dehydrogenase (EC 1.1.1.49) and 6-phosphogluconolactonase (EC 3.1.1.31), is the primary source of lipogenic NADPH in Y. lipolytica.

**Fatty Acid Transportation**

To date, the mechanism of fatty acid transportation is unclear in Y. lipolytica. Generally, shorter carbon-chain fatty acids, such as C_{8:0} and C_{10:0}, are toxic for Y. lipolytica. Using primrose oil containing C_{18} fatty acids as substrate, Y. lipolytica performs a higher assimilation rate for unsaturated fatty acids (C_{18:3}, C_{18:2}, and C_{18:1}) than that for saturated fatty acid (C_{18:0}) (Aggelis et al., 1997). In this research, it was deduced that the fatty acids with different saturated levels are assimilated and transported via a selective uptake mechanism in Y. lipolytica. Recently, Duleermo et al. (2015) proposed a model of fatty acid transportation with chain length preferences in Y. lipolytica. According to this model, the extracellular fatty acids are transported into Y. lipolytica via unidentified transporters. Then, the internal fatty acids are activated to acyl-CoA by Ylfaa1p (YALI0D17864p) or transported into peroxisome by unknown transporters. Notably, the activated fatty acids can be sorted in the form of triacylglycerols or enter peroxisome via transporters YlPxa1p (YALI0A06655p) and YlPxa2p (YALI0D04246p). Importantly, fatty acids from lipid remobilization can enter the peroxisome via transporter Ylfat1p (YALI0E16016p).

In particular, the intracellular medium-chain fatty acids (C_{12}-C_{14}) are converted into fatty acyl-CoAs by fatty acyl-CoA synthetase II in the peroxisome for further degradation, whereas...
### TABLE 1 | Summary of the production of fatty acid-based bioproducts from the *Y. lipolytica* platform.

| Type                  | Target    | Strain                        | Genetic manipulation                                                                 | Production level                          | References                  |
|-----------------------|-----------|-------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------|
| Nutraceuticals        | DHA       | *Y. lipolytica* Po1h-A4       | Expression of artificial *pfa*-BGC version C1_{V2}.                                  | 350 mg/L (after 300 h)                    | Gemperlein et al., 2019     |
|                       | EPA       | *Y. lipolytica* Y4305         | Expression of C16 elongase, Δ12-desaturase gene, Δ9-elongase gene, Δ8-desaturase gene, Δ5-desaturase gene, Δ17-desaturase gene. Deletion of PEX10 gene. | 56.6% of total fatty acid                | Xue et al., 2013            |
|                       | EPA       | *Y. lipolytica* Y4184         | Deletion of Ylaf1.                                                                    | 7.6% of the DCW                          | Seip et al., 2013           |
|                       | EPA       | *Y. lipolytica* Z7344         | Expression of desaturases and elongases genes. Two-stage continuous fermentation.    | 48% of total lipids                      | Xie et al., 2017            |
|                       | Trans-10, cis-12 CLA | *Y. lipolytica* Polh-1292oPAI-5 | Expression of *pAI* gene.                                                            | 5.9% of total fatty acid                  | Zhang B. X. et al., 2012    |
|                       | Trans-10, cis-12 CLA | *Y. lipolytica* Polh-1292-spoppai-d12-16 | Expression of FADS12, d12 from Mortierella alpina and opai gene.                 | 16% of DCW                               | Zhang B. X. et al., 2013    |
|                       | CLA       | *Y. lipolytica* JMY3479, CLIB3039 | Overexpression of *pPAI* and Δ12-desaturase from Mortierella alpina                  | 302 mg/L                                 | Imatoukene et al., 2017     |
|                       | Trans-10, cis-12 CLA | *Y. lipolytica* WXYL037       | Overexpression of inherent diacylglycerol transferase gene, Δ12-desaturase from Mortierella alpina and isomerase gene from Propionibacterium acnes. | 132.6 mg/L                               | Wang et al., 2019           |
|                       | GLA       | *Y. lipolytica* pYLD6d12      | Co-expression of fungal Δ6-desaturase and Δ12-desaturase genes                      | 20% of GLA from endogenous LA and OA     | Chuang et al., 2010         |
|                       | GLA       | *Y. lipolytica* Po1f-6-D      | Expression of Δ6-desaturase gene from Mortierella alpina                            | 71.6 mg/L                                | Sun et al., 2017            |
|                       | ARA       | *Y. lipolytica* YL 6-1       | Expression of Δ6-desaturase, Δ6-elongase and Δ5-desaturase from Mortierella alpina. | 0.4% of total lipids                     | Liu et al., 2017a           |
|                       | ARA       | *Y. lipolytica* YL 6-1       | Transfer extracellular organic acids to the synthesis of intracellular ARA.          | 0.42% of total lipids                    | Liu et al., 2017b           |
|                       | ARA       | *Y. lipolytica* RH-4         | Enzyme fusion of Δ9-elongase and Δ8-desaturase with the rigid linker (GGLGG)      | 118.1 mg/L                               | Liu H. H. et al., 2019      |
|                       | RA        | *Y. lipolytica* JMY2556      | Expression of *CpFAH12* from C. purpureus. Overexpressing the native *LRO1*.        | 43% of total lipids                      | Beopoulos et al., 2014      |
|                       | RA        | *Y. lipolytica* CYLxR        | Overexpression of *SCD1, DGA1, LIP2* and *CpFAH12*.                                 | 2.2 g/L                                  | Guo et al., 2018            |
| Odd-chain FAs (C_{17,1}) | Odd-chain FAs (mainly C_{15,0}, C_{17,0} and C_{17,1}) | *Y. lipolytica* CCY 29-26-36 | Utilization propionate as substrate.                                                | 38% of total lipids                     | Kolouchová et al., 2015    |
| Odd-chain FAs         | Odd-chain FAs | *Y. lipolytica* JMY3776      | Overexpression of *ADH5*. Deletion of *ADH6*.                                       | 0.57 g/L, 0.75 g/L (Fed-batch)           | Park et al., 2018a          |
| Biofuels              | Fatty alcohols (C_{10}) | *Y. lipolytica* JMY7412      | Overexpression of the aspartate-ketobutyrate pathway                                | 0.36 g/L                                 | Park et al., 2020           |
|                       | Fatty alcohols (C_{12}) | *Y. lipolytica* Tafar1-5copy-Adga1 fao1 strain | Overexpression of FAR from Acidobacter thaliana and FAT from C. palustris. Deletion of the major peroxisome assembly factor Pex10. | Over 500 mg/L                      | Rutter and Rao, 2016       |
|                       | Fatty alcohols (C_{16}) | *Y. lipolytica* Maqu2220-EcfsdD | Expression of fatty acyl-CoA reductase Maqu2220 from Marinobacter aquaeolei and *faoD* from E. coli. Componentalization | 636.89 mg/L (intracellular), 53.32 mg/L (extracellular) | Wang et al., 2016          |
|                       | Fatty alcohols | *Y. lipolytica* Maqu2220-EcfsdD | Expression of fatty acyl-CoA reductase Maqu2220 from Marinobacter aquaeolei and *faoD* from E. coli. Componentalization | 2.15 g/L (in a 3-L bioreactor)           | Xu et al., 2016             |

(Continued)
| Type              | Target                  | Strain                      | Genetic manipulation                                                                 | Production level | References         |
|-------------------|-------------------------|-----------------------------|--------------------------------------------------------------------------------------|------------------|--------------------|
| FAEE              | Y. lipolytica AD strain | Expression of Acinetobacter baylyi ADP1 wax-ester synthase AbAtfA. Overexpression of a peroxisomal/mitochondrial carnitine acyltransferase, perCat2. Mixtures of dextrose and canola oil. Compartimentalization | 142.5 mg/L       | Xu et al., 2016    |
| FAEE              | Y. lipolytica GQY20    | Expression of WS gene from Marinobacter sp. Deletion of PEX10 gene.       | 1.18 g/L (containing 5 vol% ethanol)                                                 | Gao et al., 2018 |
| FAEE              | Y. lipolytica YL6      | Expression of pdc and adhB from Z. mobilis and maqu_0168 from Marinobacter sp. Deletion of mfe1, gut2, pex10. With vegetable cooking oils (VCOs). | 82 mg/L           | Ng et al., 2019    |
| FAEE              | Y. lipolytica Po1gp:pYLP1A1GAMh and S288C | Expression of PDC1, ADH1, GAPDH and MhAtfA. Co-culture. | 4.8 mg/L           | Yu et al., 2020    |
| C19 cyclopropanated fatty acids | Y. lipolytica ENGR-HHPHycoCFA-NAT-ycoCFA | Expression of CFA synthase from E. coli. | 3.03 g/L           | Markham and Alper, 2018 |
| FFAs              | Y. lipolytica JMY5743  | Overexpression of DGA2, TGL4, KITGL3. Deletion of faa1, mfe1.             | 10.4 g/L           | Ledesma-Amaro et al., 2016 |
| FFAs              | Y. lipolytica AD strain | Overexpression of hybrid hFAS-Ec TesA.                                     | 9.67 g/L (in a 3-L bioreactor)                                                     | Xu et al., 2016   |
| FFAs              | Y. lipolytica Y-4311   | Overexpression of ACC1. Deletion of gpd1, gut2, pex10.                     | 2033.8 mg/L         | Yuzbashieva et al., 2018 |
| Alkanes (C13)     | Y. lipolytica PO1f-1mfe1 | Deletion of mfe1.                                                          | 4.98 mg/L           | Blazek et al., 2013 |
| Alkenes (mainly C15 and C17) | Y. lipolytica S07004 | Expression of CvFAP (S121F) from Chlorella variabilis. Utilization half-light intensity. | 58.7 mg/L (Fed-batch) | Bruder et al., 2019 |
| Biochemicals      | γ-decalactone          | Y. lipolytica PO1fd strain | Expression of acyl-CoA oxidase gene.                                                | 16.3 mg/g·h       | Pagot et al., 1997 |
|                   | γ-decalactone          | Y. lipolytica Δpox2Δpox3 | Deletion of POX1 and POX5 genes.                                                    | 170 mg/L (2 L bioreactor) | Waché et al., 2001 |
|                   | γ-decalactone          | Y. lipolytica JMY185 | Possession of multiple copies of POX2 gene. Deletion of POX3 and POX5 genes.       | 150 mg/L           | Waché et al., 2002 |
|                   | γ-decalactone          | Y. lipolytica W29 | Increase O2 solubility                                                             | 300 mg/L (2 L bioreactor) | Aguedo et al., 2005 |
|                   | γ-decalactone          | Y. lipolytica W29 | Oxygen mass transfer in a biphasic medium.                                           | 141 mg/L (2 L bioreactor) | Gomes et al., 2007 |
|                   | γ-decalactone          | Y. lipolytica W29 | Optimization operating conditions of substrate concentration, biotransformation start-up procedure and oxygen transfer. | 87 mg/g·h         | Gomes et al., 2010 |
|                   | γ-decalactone          | Y. lipolytica W29 | Strategies of fed-batch culture.                                                    | 73 mg/g (Intermittent fed-batch) | Gomes et al., 2012 |
|                   | γ-decalactone          | Y. lipolytica ATCC20460      | Cell Immobilization.                                                                | 1597 mg/L         | Braga and Belo, 2013 |
|                   | γ-decalactone          | Y. lipolytica DSM 3286       | Supply of oxygen                                                                    | 220 mg/L (Fed-batch) | Moradi et al., 2013 |
|                   | γ-decalactone          | Y. lipolytica G3-2.21        | Genome shuffling of the haploid cells and the parent strains CQMCC 2.1405.         | 3.75 g/L           | Zhao et al., 2014  |
|                   | γ-decalactone          | Y. lipolytica W29 | The direct influence of oxygen transfer rate.                                        | 215 g/L (Fed-batch) | Braga and Belo, 2014 |

(Continued)
long-chain fatty acids (C₁₆–C₁₈) are converted into fatty acyl-CoA by fatty acyl-CoA synthetase I in the cytosol (Dulermo et al., 2015). Then, long-chain fatty acyl-CoA is either transported into peroxisome from cytosol or used as substrate for triacylglyceride biosynthesis in *Y. lipolytica*.

### Fatty Acid Degradation

Generally, fatty acids, either from intracellular triacylglyceride hydrolysis or from extracellular fatty acid transportation, can be transformed into fatty acid-based chemicals by oxidation in *Y. lipolytica*. Notably, the intracellular fatty acids are mainly degraded by peroxisomal β-oxidation or ω-oxidation pathway. In fact, the intracellular fatty acids from lipid remobilization are mainly converted into acetyl-CoA, via peroxisomal β-oxidation pathway. In particular, each cycle of ω-oxidation pathway in *Y. lipolytica* biosynthesis can produce the novel fatty acid-based bioproducts and lactones, whereas the ω-oxidation pathway can be engineered to produce ω-HFA and α,ω-dicarboxylic acids (DCAs) in *Y. lipolytica*.

**ENGINEERING STRATEGIES TO INCREASE OLEOCHEMICAL PRODUCTION**

Nowadays, different metabolic strategies have been used to *de novo* produce the novel fatty acid-based bioproducts and accumulate the production of these derived biochemicals in *Y. lipolytica* (Table 2).

| Type | Target | Strain | Genetic manipulation | Production level | References |
|------|--------|--------|----------------------|------------------|------------|
| γ-decalactone | *Y. lipolytica* w-YLG | Cell immobilization in attapulgite along with the use of ionic liquid as a cosolvent. | 8.05 g/L (Fed-batch) | Zhao et al., 2015 |
| γ-decalactone | *Y. lipolytica* CCMA 0242 | Optimization of cultivation conditions. | 0.128 g/L | Pereira de Andrade et al., 2017 |
| γ-decalactone | *Y. lipolytica* CCMA 0357 | Optimization of cultivation conditions. | 3.5 g/L | Soares et al., 2017 |
| γ-decalactone | *Y. lipolytica* CGMCC 2.2087 | Cell immobilization with BC-ALG carriers. | 8.37 g/L | Zhang et al., 2020 |
| δ-decalactone | *Y. lipolytica* KCTC 17170 | Expression of linoleate 13-hydrolase from *L. acidophilus*. | 16.3 mg/(L·h) | Kang et al., 2016 |
| HFAs (ω-HDDA) | *Y. lipolytica* H222Δpaαaf | Deletion of POX1-6, all relevant ADH genes and FAO1. | 7.9 g/L | Gatter et al., 2014 |
| DCAs (C₁₂) | *Y. lipolytica* iYLI847 | Deletion of POX1-6. | 11 g/L | Gatter et al., 2014 |
| DCAs (C₁₂) | *Y. lipolytica* MTLY 37 | ND | ND | Mishra et al., 2018 |
| Hexanal | *Y. lipolytica* PO1d-HPL | Expression of HPL gene. | 350 mg/L (Reaction medium) | Bourel et al., 2004 |
| Hexanal | *Y. lipolytica* JMY 861 | Expression the hydroperoxide lyase (HPL) gene from green bell pepper fruit. Under oxido-reducing conditions. | 600 mg/L | Santiago-Gómez et al., 2009 |
| Hexanal | *Y. lipolytica* JMY 861 | Overexpression of ADH from *S. cerevisiae*. | Increased by 84.1% | Aziz et al., 2016 |
| CFA (C₁₇ and C₁₉) | *Y. lipolytica* JMY 6068 | Expression of CFA from *E. coli*. | 2319 mg/L | Czerwiec et al., 2019 |

ND, not determine.
FIGURE 1 | Overview of fatty acid metabolism for the production of its based chemicals in *Y. lipolytica*. Different colored arrows are used to represent different metabolic pathways; black, de novo fatty acid metabolic pathway; green, acetate metabolic pathway; red, glycerol metabolic pathway; dark red, heterologous lipid metabolic pathway; purple, ex novo fatty acid metabolic pathway; blue, heterologous alkane metabolic pathway. Pathway localization with respect to specific subcellular organelles are also depicted. ER, endoplasmic reticulum; PER, peroxisome; MIT, mitochondria; TCA cycle, tricarboxylic acid cycle; DHAP, dihydroxyacetone phosphate; GA3P, glycerol-3-phosphate; iCit, isocitrate; α-KG, α-ketoglutarate; Suc, succinate; Fum, fumarate; Mal, malate; OAA, oxaloacetate; FAS, fatty acid synthase; EFA, essential fatty acid; FFA, free fatty acid; FAEEs, fatty acid ethyl esters.

TABLE 2 | Engineering strategies to improve fatty acid-based bioproducts accumulation in *Y. lipolytica*.

| Engineering strategies | Bioproducts | Strategy details | References |
|------------------------|-------------|------------------|------------|
| Constructing and engineering metabolic pathways | EPA | Constructing synthetic pathways | Xue et al., 2013 |
| Lipids | Improving acetyl-CoA supplement | Xu et al., 2016 |
| Lipids | Increasing NADPH availability | Qiao et al., 2017 |
| Trans-10, cis-12 CLA | Overexpressing the endogenous enzymes | Wang et al., 2019 |
| Fatty alcohols | Eliminating downstream degradation | Rutter and Rao, 2016 |
| Optimizing fermentation conditions | γ-decalactone | Improving oxygen transfer | Moradi et al., 2013 |
| GLA | A temperature-shift strategy of cultivation | Sun et al., 2017 |
| CLA | Changing the medium components | Wang et al., 2019 |
| EPA | Two-stage continuous fermentation | Xie et al., 2017 |
| Engineering compartmentalization system | FAEE | Endoplasmic reticulum or peroxisome localization | Xu et al., 2016 |
| Alkane | Endoplasmic reticulum or peroxisome localization | |
| Fatty alcohol | Peroxisome localization | |
| γ-decalactone | Cell immobilization | Zhang et al., 2020 |

*Yarrowia lipolytica*. For example, to *de novo* produce EPA in *Y. lipolytica*, the selected and optimized multiple copies of different chimeric genes from different microorganisms were integrated into yeast genome (Δ9-elongase, Δ8-desaturase, and Δ5-desaturase from *E. gracilis*, C16/18-elongase from *M. alpina*, Δ12-desaturase gene from *F. moniliforme*, Δ17-desaturase from *P. aphani dermatum*, and CPT), which led to the first engineered commercial strain Y4305 under strong promoters, containing 30 copies of nine
different genes, which can produce EPA at 56.6% of the total fatty acids (TFA), without γ-linolenic acid (GLA, C_{18:3}) accumulation (Xue et al., 2013).

Through overexpressing and eliminating the endogenous enzymes involved in the lipid degradation, the accumulation of fatty acid and its derivatives has been greatly enhanced in Y. lipolytica (Dulermo and Nicaud, 2011). Generally, the availability of precursors, including acetyl-CoA and NADPH, limits the lipid biosynthesis. Previously, by harnessing the carnitine shuttle mechanism, the lipid titer was enhanced 1.75-fold via increasing acetyl-CoA supplement (Xu et al., 2016). Qiao et al. (2017) performed a specific strategy of converting NADH to NADPH in 13 engineered strains of Y. lipolytica for improving lipid synthesis. Recently, Wang et al. (2019) showed that the increased conjugated linoleic acid (CLA, C_{18:2}) accumulation is reached by overexpressing the endogenous diacylglycerol transferase gene. Additionally, in order to block the lipid degradation in Y. lipolytica, Rutter and Rao (2016) showed that the peroxisome assembly factor Pex10 is the major enzyme involved in the peroxisomal β-oxidation or ω-oxidation pathway.

Optimizing Fermentation Conditions

The optimization of fermentation process, based on the microbial physiology, plays a key role in achieving the high titer, yield, and productivity of value-added products. Naturally, pH, temperature, and medium components are the common optimized approaches during the fermentation process of Y. lipolytica. Previously, the temperature-shift strategy of cultivation was successfully exhibited to increase GLA accumulation in Y. lipolytica (Sun et al., 2017). Recently, the production of CLA was increased by changing carbon and nitrogen source, carbon-t-nitrogen mass ratio, and CaCl₂ concentrations (Wang et al., 2019). In addition, the fed-batch fermentation approach has been used to increase the production of drop-in biochemicals (Park et al., 2018a; Bruder et al., 2019). Compared with the continuous fermentation processes, the batch and fed-batch processes perform lower volumetric productivities (Li et al., 2011). In fact, the productivities utilizing continuous fermentation processes were improved, typically at the cost of product concentration, conversion yield, or both (Ethier et al., 2011). Previously, the novel two-stage continuous process for EPA accumulation in Y. lipolytica was developed (Xie et al., 2017). In this research, compared with the single-stage continuous and fed-batch fermentation, the novel continuous process, equipped with a small growth tank (Stage 1) and a large production tank (Stage 2), successfully improved the volumetric lipid productivities by 80%.

Generally, Y. lipolytica requires a high oxygen supply in the large-scale bioprocess. Previously, researchers have showed that the heterologous expression of gene encoding the bacterial hemoglobin from Vitreoscilla stercoraria (VHb) can improve the oxygen utilization efficiency and further increase the productivity (Suen et al., 2014; Zhang et al., 2017). Recently, Mirończuk et al. (2019) performed that the improved erythritol synthesis is obtained in Y. lipolytica, by overexpressing the codon-optimized bacterial hemoglobin (VHb). Through improving oxygen transfer rate using higher agitation rates or pure oxygen for aeration, the production of γ-decalactone was successfully enhanced (Moradi et al., 2013).

Engineering Compartmentalization System

Naturally, each subcellular compartment in Y. lipolytica provides a unique microenvironment, including enzyme, precursor, and cofactor composition. Due to the distinct organelle characteristics, the separation of organelles in the cytosol performs the potential to eliminate metabolic crosstalk and enhance compartmentalized pathway efficiency (Hammer and Avalos, 2017). Previously, Xu et al. (2016) reported that the titer of drop-in product performs a 10–15-fold improvement, by targeting the fatty acid ethyl ester (FAEE) pathway to either ER or peroxisome of Y. lipolytica. Compared to free cell systems, the immobilized cells could tolerate unsuitable conditions (Li et al., 2009; Macario et al., 2009). For example, using cell immobilization systems with bacterial cellulose-alginate (BC-ALG) carriers, γ-decalactone production was successfully reached with 8.37 g/L in the repeated experiments in Y. lipolytica, an approximately 3.7-fold improvement over with an ALG carrier alone (Zhang et al., 2020).

Modular co-culture metabolic engineering combines the strains carrying each pathway module in the engineered strains to form a synthetic complex, which can accommodate different modules expressing functional genes in different hosts to produce drop-in bioproducts (Jawed et al., 2019). Recently, by coculturing and engineered Y. lipolytica and S. cerevisiae strain, a synthetic microbial consortium was constructed to increase the titer of FAEE. In this research, the titer of FAEE biodiesel at 4.8 mg/L was reached by the synthetic microbial consortium under the optimum coculture conditions (Yu et al., 2020).

PRODUCTION OF FATTY ACID-BASED BIOPRODUCTS

Nutraceuticals

Due to the potential applications of microbial lipids in the field of food supplements, the microbial production of PUFAs is becoming an industrial reality (Bellou et al., 2016). Of these oleaginous yeasts, Y. lipolytica can synthesize OA and LA.

Omega-3 PUFAs with special function, particularly α-linolenic acid (ALA, C_{18:3}), EPA, and docosahexaenoic acid (DHA, C_{22:6}), are gaining importance. Previously, using inherent LA as carbon substrate, Xue et al. (2013) constructed an engineered Y. lipolytica strain Y4305 capable of de novo producing EPA at 56.6% of TFA, by the combined metabolic engineering strategies. With Y. lipolytica as a host, the highest titer of ALA at 1.4 g/L was produced in the engineered strain containing a bifunctional Δ12–Δ15 desaturase from Rhodospiridium kratochvilovae, under the optimized fermentation conditions (Cordova and Alper, 2018). Recently, an artificial PUFA biosynthetic gene clusters, encoding DPA/DHA-type PUFA synthases, was expressed in Y. lipolytica. In this research,
under the optimized fermentation process, the DHA level over 350 mg/L was reached (Gumperlein et al., 2019).

Omega-6 PUFAs, including conjugated CLA, GLA, and ARA, are a major family of PUFAs with diverse bioactivities (Xu and Qian, 2014). In 2017, the combined elimination of \( \beta \)-oxidation pathway and overexpression of \( \Delta 12 \)-desaturase was conducted in \( Y. \) lipolytica, which leads to CLA production at 302 mg/L (Imatoukene et al., 2017). Recently, Wang et al. (2019) showed that the maximum content of trans-10, cis-12 CLA at 132.6 mg/L is reached by the engineered \( Y. \) lipolytica under the optimized fermentation conditions, by the overexpression of inherent diacylglycerol transferase from \( Y. \) lipolytica, \( \Delta 12 \) desaturase from \( Mortierella alpina \), and \( Propionibacterium acnes \) isomerase. With LA as substrate, the GLA biosynthetic pathway was constructed in \( Y. \) lipolytica harboring \( \Delta 6 \)-desaturase from \( M. \) alpina. Under the optimized fermentation process, the titer of GLA at 71.6 mg/L was achieved (Sun et al., 2017).

Ricinoleic acid (ARA, \( C_{18}:1 \)) and its derivatives perform oleochemical applications, due to the special characteristics. Meesapyodsuk and Qiu (2008) first identified an oleic acid-like hydroxylase (\( CpFAH12 \)) from \( Claviceps purpurea \). Previously, with LA as substrate, an engineered \( Schizosaccharomyces pombe \) strain capable of producing RA, harboring heterologous \( CpFAH12 \) from \( C. \) purpurea, was constructed (Holic et al., 2012). Using \( Y. \) lipolytica as a host, Beopoulos et al. (2014) reported that RA accumulation at 42% of total lipids is achieved, by overexpressing \( C. \) purpurea \( \Delta 12 \)-hydroxylase and native \( Y. \) lipolytica \( Lro1p \) acyltransferase. Recently, by the combined overexpression of \( SCD1 \) gene encoding stearoyl-CoA desaturase, \( DGA1 \) gene encoding acyl-CoA:diacylglycerol acyltransferase, \( LIP2 \) gene encoding lipase, and \( CpFAH12 \) gene encoding hydroxylase, the production level of RA at 2.2 g/L was obtained by the engineered \( Y. \) lipolytica using cellulose as substrate (Gao et al., 2018).

Odd-chain fatty acids with special biochemical and biological activities are receiving growing attention on potential applications (\( \text{Rezanka and Sigler, 2009} \)). Previously, Kolouchová et al. (2015) performed that \( Y. \) lipolytica is capable of producing heptadecanoic acid (\( C_{17}:1 \)) using propionate as substrate. Recently, the deletion of the \( \text{PHDI} \) gene and optimization of the fermentation process were applied to produce odd-chain fatty acids (mainly \( C_{15}:0 \), \( C_{17}:0 \), and \( C_{17}:1 \)) by \( Y. \) lipolytica grown on propionate (Park et al., 2018a). Additionally, Park et al. (2020) constructed an engineered \( Y. \) lipolytica capable of de novo producing odd-chain fatty acids, using glucose as sole substrate without any propionate supplementation.

**Biofuels**

The microbial production of fatty alcohols is becoming an alternative method to meet the increasing demand. Presently, various microorganisms, such as \( \text{Escherichia coli} \) and \( \text{Saccharomyces cerevisiae} \), have been engineered for fatty alcohol production (Zhang et al., 2011; Zhou et al., 2016). Using \( Y. \) lipolytica as a host, Wang et al. (2016) constructed a novel fatty alcohol-producing workhorse, harboring \( Tafar1 \) gene coding fatty acyl-CoA reductase. Under the optimized tri-module condition, the intracellular hexadecanol at 636.89 mg/L and extracellular hexadecanol at 53.32 mg/L was produced, respectively. Meanwhile, through the overexpression of fatty acyl-ACP-thioesterases and fatty acyl-CoA reductase, and deletion of the major peroxisome assembly factor Pex10, the medium-chain alcohol, especially 1-decanol over 500 mg/L, was produced in the engineered \( Y. \) lipolytica (Rutter and Rao, 2016).

Researchers have performed that FAEEs or fatty acid methyl esters (FAMEs) can be produced \( \text{via} \) the microbial fermentation, using \( E. \) coli and \( S. \) cerevisiae (Steen et al., 2010; Nawabi et al., 2011; Yu et al., 2012). Fortunately, Xu et al. (2016) reported that the highest titer of FAEEs at 142.5 mg/L is produced in the engineered \( Y. \) lipolytica, using the compartmentalized metabolic engineering. Recently, an engineered \( Y. \) lipolytica strain, harboring the heterogenous pyruvate decarboxylase (\( pdc \)), alcohol dehydrogenase II (\( addh \)) from \( Zygomonas mobilis \), and wax ester synthases from \( \text{Marinobacter sp.} \), was constructed for producing FAEE. In this research, the titer of FAEE up to 82 mg/L was achieved by the supplementation of vegetable cooking oil (Ng et al., 2019). Meanwhile, Yu et al. (2020) developed the synthetic co-culture system comprising the engineered \( S. \) cerevisiae and \( Y. \) lipolytica strain, which was able to produce FAEE at 4.8 mg/L. To overcome the limitation of oxidative stability in the traditional FAMEs, Markham and Alper (2018) first performed the production of \( C_{19} \) cyclopropanated fatty acids in the engineered \( Y. \) lipolytica strain, harboring the heterologous cyclopropane fatty acid synthase from \( E. \) coli. In this research, the titer of \( C_{19} \) cyclopropanated fatty acids over 3.0 mg/L was produced under the bioreactor fermentation.

Free fatty acids (FFAs) are special oleochemicals with wide applications in the field of agricultural chemicals, soaps, and surfactants. Previously, Zhou et al. (2016) engineered \( S. \) cerevisiae capable of producing FFAs. Using \( Y. \) lipolytica as a workhorse, FFAs up to 9.67 g/L were produced by the engineered strain under the bioreactor scale with pH control (Xu et al., 2016). With the mixture of glucose and glycerol as carbon source, Yuzbasha et al. (2018) showed that the engineered \( Y. \) lipolytica \( Y-4311 \) strain can produce FFAs (2033.8 mg/L) by the addition of dodecane.

Alkane(s) are the major components of gasoline, diesel, and jet fuel. Presently, many studies have explored that the microbial production of alkanes is a conceivable method (Choi and Lee, 2013; Zhou et al., 2016). Using \( Y. \) lipolytica as a host expressing soybean lipoygenase enzyme, Blazeck et al. (2013) first developed a microbial platform capable of producing pentane. In particular, in this research, using LA as substrate,
the high titer of pentane at 4.98 g/L was produced. Recently, Bruder et al. (2019) revealed that the engineered *Y. lipolytica* is able to produce odd-numbered alkanes and alkenes (mainly C15 and C17), by the expression of light-driven oxidase. Interestingly, using the lighting bioreactors, the titer of alkenes at 58.7 mg/L was first reached in this research.

**Biochemicals**

γ-decalactone, a well-known aroma compound, is mainly synthesized via β-oxidation. Previously, we have summarized in detail the γ-decalactone production by *Y. lipolytica* (Liu et al., 2015). Recently, using the immobilized culture technology, the maximum production of γ-decalactone reached 8.37 g/L by *Y. lipolytica* strain on bacterial cellulose-alginate carriers (Zhang et al., 2020). Additionally, using a one-pot biotransformation process containing whole *Y. lipolytica* cells, the highest production of δ-decalactone at 58.7 mg/L was first performed (Kang et al., 2016).

HFAs, as valuable building blocks, can be synthesized by the biotransformation of fatty acids via the terminal carbon oxygenation (Seo et al., 2015). To date, the microbial production of ω-HFAs by the engineered *E. coli* has received specific progress (Kim and Park, 2019). Using *Y. lipolytica* as a promising workhorse, an engineered strain capable of synthesizing ω-hydroxy dodecanoic acid was constructed, through the deletion of acyl-CoA oxidase-coding genes (POX 1–6), fatty alcohol oxidase gene (FAO1), and alcohol dehydrogenase genes (ADH 1–8) (Gatter et al., 2014). Recently, Rigouin et al. (2019) showed that the engineered *Y. lipolytica* is able to produce polyhydroxyalkanoates composed of 3-HFAs, using methyl myristate as precursor.

DCAs are also important intermediates in the industrial field. At present, the microbial production of DCAs, as an alternative method, are gaining interests (Huf et al., 2011; Ledesma-Amaro and Nicaud, 2016b; Werner and Zibek, 2017). *Y. lipolytica* can produce DCAs via alkane degradation (Nicaud et al., 2006). Previously, researchers have shown that the engineered *Y. lipolytica* can produce dioic acids (Smit et al., 2005; Nicaud et al., 2006). In particular, Gatter et al. (2014) showed that the overexpression of *FAO1* leads to an improved production of dodecane dioic acid at 11 g/L. Recently, using the in silico model-based metabolic engineering strategies, the metabolic flux toward DCAs production was obviously increased in *Y. lipolytica* (Mishra et al., 2018).

Hexanal, one of C-6 aldehydes with green odor, can be synthesized via the degradation from LA using lipoxygenase and hydroperoxide lyase. Previously, using *Y. lipolytica* as a host, Bourel et al. (2004) showed that hexanal is produced by expressing fatty acid hydroperoxide lyase. Further, Santiago-Gómez et al. (2009) reported the effect of oxido-reduction environment on hexanal production. Interestingly, in this research, under the optimized conditions, the highest titer of hexanal at 600 mg/L was produced by the engineered *Y. lipolytica*.

In addition, cyclopropane fatty acids (CFAs), as good unusual fatty acid candidates, were produced by the engineered *Y. lipolytica* (Czerwiec et al., 2019). In this research, by expressing genes from various organisms and optimizing the expression level of CFAs synthase and fed-batch fermentation, it was shown that CFAs at 2319 mg/L (mainly C17:0 and C19:0 cyclopropanated form) are finally synthesized in the strain JMY 6068. Compared with *E. coli* and *S. cerevisiae*, the fatty acid derivatives produced by *Y. lipolytica* are more abundant (Table 3).

**CONCLUSION AND FUTURE PERSPECTIVES**

*Y. lipolytica* is a promising workhorse gaining great attention. Currently, the advance of metabolic engineering and synthetic biology enables *Y. lipolytica* to produce various value-added chemicals with different substrates and metabolic engineering strategies, including the design and construction of synthetic pathways, regulation of endogenous genes, and optimization of the fermentation process. However, several challenges remain in limiting the wide applications of *Y. lipolytica*.

### TABLE 3 | Comparison of the productivity of fatty acid-derived biofuels between *E. coli*, *S. cerevisiae*, and *Y. lipolytica*.

|   | *E. coli* | *S. cerevisiae* | *Y. lipolytica* |
|---|-----------|-----------------|----------------|
| Titer | References | Titer | References | Titer | References |
| Fatty alcohols | 1.8 g/L | Mehrer et al., 2018 | 6.0 g/L (Fed-batch) | d'Espaux et al., 2017 | 2.15 g/L (in a 3-L bioreactor) | Xu et al., 2016 |
| FAEE | 1.5 g/L (minimal medium) | Zhang F. et al., 2012 | 0.005 g/L | Runguphan and Keesing, 2014 | 1.18 g/L (containing 5 vol% ethanol) | Gao et al., 2018 |
| FFAs | 2.1 g/L (modified MOPS minimal medium) | Kim and Gonzalez, 2018 | 33.4 g/L (Fed-batch) | Yu et al., 2018 | 9.67 g/L (in a 3-L bioreactor) | Xu et al., 2016 |
| Alkanes | 0.426 g/L | Fatma et al., 2018 | 0.003 g/L (Delphi minimal medium) | Zhu et al., 2017 | 58.7 mg/L (Fed-batch) | Bruder et al., 2019 |
| γ-decalactone | ND | ND | Increase by 11% | Rong et al., 2017 | 8.37 g/L | Zhang et al., 2020 |
| HFAs | 275 mg/L | He et al., 2019 | 347 mg/L (Fed-batch) | Liu J. J. et al., 2019 | 7.9 g/L | Gatter et al., 2014 |
| DCAs | ND | Wang F. et al., 2020 | 92.5 g/L (Fed-batch) | Lee et al., 2018 | 11 g/L | Gatter et al., 2014 |
| Hexanal | ND | ND | Increased by 84.1% | Aziz et al., 2016 | 2319 mg/L | Czerwiec et al., 2019 |
| CFA | ND | Guangji et al., 2010 | ND | Kochan et al., 2019 |

ND, not determine.
When developing and optimizing *Y. lipolytica* for improving the production of value-added chemicals, the whole bioprocess, including the upstream of strain development and bioproducts production, the midstream of scale-up fermentation, and the downstream of recovery and purification, is needed to be considered first. Ko et al. (2020) showed that systems metabolic engineering, integrating systems biology, synthetic biology, and evolutionary engineering can enable microbial strains to efficiently produce chemicals. Therefore, systems metabolic engineering can be further applied to better manipulate the engineered *Y. lipolytica* to synthesize the desired bioproducts. Meanwhile, to optimize cell metabolism, such as reducing the negative effects of intermediate accumulation and metabolic perturbations, the dynamic metabolic engineering capable of tuning the cell growth and bioproducts formation is becoming a promising approach to better engineer the host strain (Xu, 2018). Moreover, due to the limits of dimorphic nature, cellular engineering and bioprocess engineering can be used to improve the yield of products at the industrial scale (Soong et al., 2019). Additionally, to reduce the cost of bioprocess, other low-value carbon sources, especially single-carbon substrates, will be utilized and converted to valuable fatty acid-based bioproducts by metabolic engineering *Y. lipolytica*. Conclusively, the application of *Y. lipolytica* for fatty acid-based chemicals production shows a great promise for researchers working in this field.

**AUTHOR CONTRIBUTIONS**

HL conceived the outline and revised the manuscript. YT finalized the topic of this review, and all authors wrote the manuscript. All authors read and approved the final manuscript for publication.

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