Chapter 12
Microbial Engineering and Applications for the Development of Value-Added Products

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Abstract Downstream is a very affluent process for fermentation. It usually involves complicated equipment and processes to obtain desired chemicals or materials from intra- and/or extracellular spaces of microorganisms. Recently, it becomes possible to simplify the microbial cell separation processes by morphologically engineering the shapes of small microorganisms. Biologically engineered entities have enabled discoveries in the past decade and a half, spanning from novel routes for the syntheses of drugs and value-added products to carbon capture. The precise cellular reprogramming has extended to the production of nanomaterials owing to their ever-growing demand. Additionally, nutraceuticals are important natural bioactive compounds that confer health-promoting and medical benefits to humans. Globally, growing demands for value-added nutraceuticals for prevention and treatment of human diseases have rendered nutraceuticals a multi-billion dollar market. However, supply limitations and extraction difficulties from natural sources such as plants, animals, or fungi restrict the large-scale use of nutraceuticals. Metabolic engineering via microbial production platforms has been advanced as an eco-friendly alternative approach for production of value-added nutraceuticals from simple carbon sources. Microbial platforms like the most widely used

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Escherichia coli and *Saccharomyces cerevisiae* have been engineered as versatile cell factories for production of diverse and complex value-added chemicals such as phytochemicals, prebiotics, polysaccharides, and poly amino acids. This chapter highlights the recent progresses in biological production of value-added nutraceuticals via metabolic engineering approaches.

Keywords Microbial engineering · Microbes · Nutraceuticals · Phytochemicals

12.1 Introduction

Microbial engineering involves the use of biological, chemical, and engineering aspect of biotechnology that results in manipulations and development of microbes to get the desired products in different fields (Peralta-Yahya et al. 2012). The technology which is employed in microbiological systems and their derivatives to transform products used in daily need are highly beneficial for humankind (Okafor 2007). India is a country where more than half of the population is engaged in agricultural practices. India is also considered the second-largest producer of agricultural products worldwide (Gulati and Juneja 2018). Statics data reported that India produces approximately 81.285 million metric tonnes of fruits and 162.187 million tonnes of vegetables, respectively, in year 2013 (Negi 2014). Most of the production is consumed fresh; however, a larger quantity which accounts for approximately 25–40% gets rotten due to unavailability of proper postharvest facilities. This wastage causes a huge loss to crop yield and also exhibits great impact on economy. Henceforth, reducing the postharvest wastages requires utmost consideration for making a chain among consumption and supply. Microbial biotechnology has been used in handling food since ancient times such as in making bread or beverage. Though various metabolites are produced by microbes due to the introduction of modern biotechnology, microbial molecular structures possess strong potential that could be used in food industry particularly in fermentation of foods, enzymes, ingredients of food, testing of food, and postharvest administration of agricultural yields. However, microbial biotechnology in food processing division represents collection and advancement of microbes by ideas of refining regulated production, effectiveness, as well as the quality, safety, and consistency of bioprocessed foodstuffs. Microbes have a pivotal role in the production of fermented food. Microbial cultures could be genetically modified by traditional and molecular tactics.

A deliberate breakdown practice which is induced by microorganisms for the transformation of carbohydrates to alcohols or organic acids is generally referred to as fermentation (Battcock and Azam-Ali 1998). Fermentation is worldwide functional in the conservation of various raw agricultural products including vegetables, fruits, tubers and cereals, fish, milk, meat, etc. Some microorganisms accompanying the fermented foodstuffs such as *Lactobacillus* sp. are probiotic used as live microbial food complements or food constituents that help in improvement of the metabolic process of gastrointestinal tract's flora. Therefore, microbes are believed to be advantageous in maximum fermentations. Nowadays, nanotechnology is considered as innovative field of science which deals with the synthesis and use of material with nanoscale size in numerous aspect of life. However, the number of microbes is naturally proficient in generating nanoparticles either intracellularly or extracellularly while confronted with various metal salts. Accessibility of many biotechnological tools including synthetic biology, genetic, and protein engineering increases usage of microbial systems to up-skill synthesis of nanoparticles.

12.2 Nanoparticles Synthesis by Microbial Engineering

The idea of the natural synthesis of nanoparticles was first started in the 1960s and recently has seen an evolution in the last one and a half decade. Biological nanoparticle synthesis represents an extensive range of biological methods for generating nanoparticles through biotic hosts which are not restricted to bacteria, yeast, fungi, algae, and plants. Efficient synthesis of nanoparticle does require a compatible host that comprises molecular machinery to convert the raw material into the nanoparticle and can efficiently accommodate the end product, i.e. synthesized nanoparticle. Majorly few cellular proteins that have a protective role may interfere in the cellular metabolism and hinder the uptake of metallic ions and their conversion into nanoparticles with precise size and morphology. Therefore, the manipulation of such host and proteins should be achievable. The ultimate benefit of the biological synthesis of nanoparticles is their synthesis at ambient temperature and pressure, and no involvement of chemicals are required in the synthesis which could perhaps be hazardous.

Biosynthesis of nanoparticle through microbes occurs in two ways that further comprise two sub-modes, i.e. (a) intracellular in non-template or template mode and (b) extracellular in culture or membrane adherent mode. During intracellular synthesis, the cell culture is incubated with the metal salt solution where metal ions pass across the cell membrane and synthesis takes place inside the cells. Subsequently, the cells are lysed and nanoparticles are purified. On the other side, extracellular synthesis as the name suggests involves the synthesis of nanoparticle on the cell membrane or in the culture broth. Therefore, extracellularly synthesized nanoparticles are easier to retrieve and require lesser downstream processing phases. The very first report on biosynthesis of nanoparticle using genetically engineered bacteria was documented in 2006–2007 (Sambhy et al. 2006; Vigneshwaran et al. 2007). Later, Kang et al. (2008) genetically modified *E. coli* strain JM109 to express phytochelatin synthase of *Schizosaccharomyces pombe* along with improved g-glutamyl cysteine synthetase (GSHI) to synthesize cadmium sulfide (CdS) nanocrystals. The GSHI is responsible for catalysing the glutathione synthesis which is also a precursor of metal-binding peptide phytochelatin that in turn assists as capping agent for CdS nanocrystals. Phytochelatin synthesis of *S. pombe* is the best characterized natural defence mechanism towards cadmium toxicity. Further development in the above-mentioned approach was achieved in another strain, *E. coli* R189, where uniform CdS quantum dot (QDs) nanocrystals of 3–4 nm size were synthesized (Kang et al. 2008). Mi et al. (2011) expressed the transgene encoding CdS-binding histidine-rich peptide (CDS7) reported to bind with CdS (Peelle et al. 2005) to induce the formation of CdS QDs. Noble nanoparticles from silver and gold, alkali-earth (Cs, Sr), magnetic (Fe, Co, Ni, Mn), semiconducting (Cd, Se, Zn, Te) metals, as well as rare earth fluorides (Pr, Gd) were successfully synthesized using genetically engineered *E. coli*-expressing recombinant metallothionein from *Pseudomonas putida* and phytochelatin from *Arabidopsis thaliana* (Park et al. 2010; Ashraf et al. 2021). Some of the extremophiles including Antarctic bacteria have also been exploited to synthesize the fluorescent nanoparticle due to their natural resistant to cadmium and tellurides (Plaza et al. 2016). Several strains of *E. coli* have a CusCFBA silver/copper system that promotes the synthesis of silver nanoparticle in periplasmic space (Lok et al. 2008). Shi et al. (2007) also used a similar type of strain for the synthesis of silver nanoparticle in periplasmic space using anaerobic conditions. The procedure generates reduced metal nanoparticle using oxidized metal ions as electron acceptors with the assistance of cytochrome-c (Shi et al. 2007; Suresh et al. 2010).

12.3 Microbial Enzymes

Enzymes can be defined as the biotic catalyst which is involved in various biosynthetic reactions and metabolic processes (Li et al. 2021; Kumar et al. 2021). Microbes serve as a major source of enzymes. Microbes can replicate easily and rapidly and could be genetically engineered as per the desired requirement of the product (Bhandari et al. 2021; Verma et al. 2021). Microbial enzymes are relatively more active and stable compared to that of isolated from plants or animal sources (Gopinath et al. 2013; Anbu et al. 2017; Bhatt et al. 2021). Various extremophilic bacterial and fungal strains have been isolated from unfavourable pH and temperature as well as high salt and heavy metal conditions for the synthesis of different useful enzymes comprising properties of higher yield (Gopinat et al. 2003; Gopinath et al. 2005).

Microbial enzymes can be isolated from different microorganisms including thermophilic (requires a higher temperature for growth), acidophilic (optimally active in acidic pH range), and alkalophilic (activates at higher pH range) bacteria. The synthesis of these microbial enzymes can be carried out at extreme conditions that can decrease the possibility of contamination during large-scale production (Banat et al. 1992; Cadet et al. 2016). Revolution in enzymes acquired from microorganisms creates a great opportunity for the enhancement of low liveliness consuming improvements that could be applied for biotransformation of poultry waste into beneficial harvests. Enzymatic events may be accommodating to recycle waste rich in protein unconfined by the poultry industry, besides these lines protecting environment by declining waste (Atuanya and Aigbirior 2002). There are some enzymes that have various roles in industrial applications (Table 12.1).

Table 12.1 Various enzymes and their role in industries

Sr. no.	Enzyme	Role(s)
1.	Protease	Breaks proteins into their simple form
2.	Keratinase	Decomposes keratin found in hairs, nails, etc.
3.	Amylase	Breaks starch into sugars
4.	Xylanase	Converts polysaccharides into xylose
		Catalytic breakdown of hemicellulose
5.	Ligninase	Degrades lignin
6.	Cellulase	Breakdown of cellulose
7.	Lipase	Hydrolysis of fats, triglycerides
8.	Pectinase	Breakdown of pectin

12.4 Nutraceuticals

Nutraceutical, a fusion of nutrition and pharmaceuticals, is defined as 'a material which possesses the nutritional value of a diet and delivers pharmaceutical or health assistances such as preclusion and disease management' (DeFelice 1995). Further revision quoted nutraceuticals as 'a product isolated or purified from foods that are generally sold in medicinal forms not usually associated with food' (Pandey et al. 2010). Nutraceuticals have been obtained from various sources ranging from microbes (e.g. poly amino acids), plants (e.g. phytochemicals, vitamins), and animals (polysaccharides) as well as marine sources (glucosamine and chitosan) (Rasmussen and Morrissey 2007; Lordan et al. 2011; Wang et al. 2016). Nutraceuticals are potentially helpful in health up-gradation and disease prevention especially in avoiding age-related disorders such as depression, oxidative damages, inflammation, diabetes, gastrointestinal diseases, and even cancer (Jain and Ramawat 2013). The increasing demands and benefits of microbial supplements having health benefits have significantly stimulated advancement in the market of nutraceuticals. The global nutraceutical market has rapidly grown, and in 2014, it was valued at $171.8 billion. The market is expected to reach $722.49 billion in the next 6–7 years with a compound annual progress rate (CAGR) of 8.3% over the forecast period (NMSS&TA 2020). Though, the growing market of nutraceutical could barely be contented through the efficiency of straight nutraceutical industries. Direct extraction approaches are restricted with accessibility and price of raw ingredients, quality check of goods, and less content and pureness of nutraceuticals. While synthesis by chemicals could be another method, it is unsuitable to generate adequate quantity and quality of biochemicals and certainly not feasible for composite biochemicals (De Luca et al. 2012). To overcome the issue, metabolic engineering of microbes is considered a promising methodology that has recently attained prodigious improvement towards production of value-added nutraceuticals. We have further discussed the recent advances of microbial-based metabolic engineering and their role in nutraceutical production including phytochemicals, prebiotics, polysaccharides, as well as poly amino acids.

12.5 Phytochemicals

Phytochemicals are the broad spectrum of secondary bioactive metabolites obtained from different parts of the plants including stem, leaf, fruits, beans, and grains. Phytochemicals are often involved in plant defence mechanism against adverse biotic and abiotic conditions or may exert health-promoting or disease-resistant properties (Jain and Ramawat 2013). Some of the major types of phytochemicals are discussed further.

12.5.1 Alkaloids

Alkaloids are amino acid-derived nitrogenous complexes with various beneficial properties including antimalarial to anticancer effects (Marienhagen and Bott 2013). Due to long biosynthetic pathways and the complex structure, alkaloid production was limited to the plants for past few years. The most commonly used alkaloids are (a) monoterpene indole alkaloids (MIAs) derived from tryptophan and glucosinolates and (b) benzylisoquinoline alkaloids (BIAs) derived from tyrosine.

Due to the recent advancement and knowledge of the BIA biosynthetic pathway, the synthesis is now carried out in various microorganisms like *E. coli* and *S. cerevisiae* (Nakagawa et al. 2011, 2014; Fossati et al. 2014). The (*S*)-reticuline biologically synthesized from simple carbon sources is an intermediate of BIA pathway (Nakagawa et al. 2011). Apart from biosynthesis of (*S*)-reticuline in *E. coli*, *S. cerevisiae* also facilitate to synthesizes of (*R*, *S*)-reticuline that in turn engineered to produce salutaridine from (*R*)-reticuline and scoulerine, tetrahydroberberine, and tetrahydrocolumbamine from (*S*)-reticuline (Hawkins and Smolke 2008).

Metabolic engineering of MIA alkaloids in microbes is inadequate and not much diverse like that of BIA alkaloids. Strictosidine, a de novo MIA alkaloid, has been successfully produced in yeast by the deletion of three genes and the introduction of 21 new genes in yeast genome (Brown et al. 2015). Yeast has also been bioengineered by introducing eight genes of plants into its genome for the production of tryptophan-derived indolylglucosinolate (IG) (Mikkelsen et al. 2012). Tryptophan-derived IG is a sulphur-rich, amino acid-derived natural composites of glucosinolates. For metabolic engineering in microbes and large-scale alkaloid production, genes isolated from plant platforms are most stable and show promising potential for biosynthesis of plant-derived complexes (Brown et al. 2015; Mora-Pale et al. 2013).

12.5.2 *Terpenoids*

It serves as the largest class of phytonutrients with various beneficial properties like anti-infectious, anti-inflammatory, and anticancer properties (Jain and Ramawat 2013; Mora-Pale et al. 2013). It is generally present in cereals, soy plants, and green foods. Terpenoids are dimethylallyl pyrophosphate (DMAPP) or isopentenyl pyrophosphate (IPP) derived broad carbon skeleton compounds, like monoterpenes (e.g. menthol), diterpenes (e.g. paclitaxel), triterpenes (e.g. steroid saponins, oleanane, ursane), tetraterpenes (e.g. carotenoids), sesquiterpenes (e.g. artemisinin), and polyterpenes (Marienhagen and Bott 2013). Terpenoids production in microbes illustrates the success and advancement of metabolic engineering for the synthesis of terpenoid drugs. Most common terpenoids that are used in pharmaceuticals are (a) artemisinic acid which is a precursor of antimalarial drug known as artemisinin and (b) taxadiene which is an intermediate of anticancer drug known as paclitaxel (Besumbes et al. 2004; van Herpen et al. 2010).

In nutraceutical industries, carotenoids (a tetraterpene) including astaxanthin, α-carotene and β-carotene, and lycopene act as feed supplements and natural food colourants (Marienhagen and Bott 2013). For a long time, combinatorial carotenoid biosynthesis has been done in heterologous non-carotenogenic hosts including *E. coli* and *S. cerevisiae* due to large-scale production of carotenoid so the metabolically engineered efforts are generally focused on it only. Strain improvement through gene knockout technique generally increases the production of lycopene to a large extent in *E.coli* (Lin et al. 2014). Metabolic engineered *E. coli* have high supply of ATP and NADPH which help in the production of upgraded β-carotene up to 2.1 g/L β-carotene and increase the harvest up to 60 mg/g DCW (Zhao et al. 2013). A high amount of astaxanthin has been produced through harvest of 1.4 mg/g DCW when the biosynthetic genes of xanthophylls are chromosomally integrated with a plasmid-free *E. coli* (Lemuth et al. 2011). Lycopene *E. coli* has generally used for the production of carotenoids because it not only is involved in the production of novel carotenoid like 4-ketozeinoxanthin but also produces some rare carotenoids like decaprenoxanthin, sarcinaxanthin, and sarprenoxanthin (Netzer et al. 2010; Maoka et al. 2014).

12.6 Prebiotics

Prebiotics are nonviable components in food that encourage the growth or activity of useful microorganisms in the gastrointestinal (Pineiro et al. 2008). Prebiotics are polysaccharide with 3–10 monomeric units of sugar which will not further dissociate in the body; hence, it is nondigestible. Prebiotics show a beneficial effect on the metabolic activity and diversity of the gut microbiota, and this leads to major effect on the immune system of host. Prebiotics can also be used in treatment of diverse inflammation-induced diseases by improving the gut microbiota using probiotics such as *Bifidobacteria* or *Lactobacillus* sp. (Lin et al. 2014). A general example of prebiotics is soluble dietary fibres such as inulin, fructooligosaccharides (FOS), and lactose-based galactooligosaccharides (GOS). Inulin and fructooligosaccharides are produced by probiotic *Lactobacillus gasseri* strain (Anwar et al. 2010), whereas galactooligosaccharides (GOS) are short-chain and lactose-derived galactose polymer synthesized by *Kluyveromyces lactis* (Rodriguez-Colinas et al. 2011). Conversion of lactose to GOS is done when the codon-optimized β-galactosidase expresses from hyper-thermophile *Sulfolobus solfataricus* in *Lactococcus lactis*. In terms of infants and toddler, human milk has been accepted as a best nutritive substance due to the presence of most abundant oligosaccharide present in it, i.e. 2′-fucosyl lactose (2′-FL). 2′-FL can also be produced from lactose and glycerol with the help of *E. coli* by overexpressing the fucosyl transferase or by increasing the availability of GDP-L-fructose for the high yield (Lee et al. 2012; Baumgartner et al. 2013).

12.7 Polysaccharides

Polysaccharides are sugar polymers composed of the large number of small monomeric sugar units with highly versatile structure. Polysaccharides are produced by most of the microorganism, e.g. bacteria, fungi, and yeast, or may be extracted from plant and animal tissues. Due to their health beneficial properties, microbial polysaccharides including bacterial polysaccharides and fungal polysaccharides are referred to as the best source for nutraceuticals. Commercialization production of bacterial polysaccharides like gellan, dextran, xanthan, and alginate can be carried out through microbial engineering and refinement, respectively (Giavasis 2013). For dairy product usage, exopolysaccharides are produced through the metabolic engineering of *Streptococcus* and *Lactococcus* species (Jolly et al. 2002). Other than bacterial and fungal polysaccharide shows various extensive properties like immunostimulatory, antitumor, antimicrobial, antioxidant, hypocholesterolaemic, and hypoglycaemic benefits (Giavasis 2014).

Due to these properties, fungal polysaccharides show great potential in pharmaceutical and nutraceutical applications (Giavasis 2014). Scleroglucan excreted by mycelia of the fungus *Sclerotiumrol fsii* is a potent antiviral and antitumor glucan-based polysaccharide and the yield of the polysaccharide can easily be increased by the adding of L-lysine and uridine monophosphate (UMP) (Giavasis 2014). Hyaluronic acid (HA), chondroitin, and heparosan are animal-based polysaccharides which have been produced by microbial host instead of extracting it from the animal tissues. *E. coli*, *L. lactis*, and *Streptomyces albulus* are the major microorganisms used for the production of hyaluronic acid (Yu and Stephanopoulos 2008; Sheng et al. 2015; Yoshimura et al. 2015). Some therapeutically essential polysaccharides like heparosan and chondroitin could be synthesized from engineered *E. coli* at a relatively high titter (He et al. 2015; Zhang et al. 2012).

12.8 Poly Amino Acids

Poly amino acids comprising one or two amino acids are produced by microorganism through a ribosome-independent enzymatic reaction that differentiates them from polypeptides which are generally synthesized by translation. There are three poly amino acid found naturally, viz. poly-γ-glutamic acid (γ-PGA), multi-L-arginyl-poly (L-aspartic acid), and poly-ε-L-lysine (ε-PL). γ-PGA is a biodegradable polymer that is soluble in aqueous solutions and therefore used as drug carriers or hydrogels (Khalil et al. 2017). Few genetically engineered *Bacillus* species produced γ-PGA in high quantity ranging from 31.7 to 107.7 g/L, when it feeds on L-glutamic acid (Hsueh et al. 2017). An equimolar amount of arginine and aspartic acid is used to produce cyanophycin by cyanobacteria or some chemotrophic bacteria like *Acinetobacter calcoaceticus*, etc. Cyanophycin is used as a dipeptide precursor for therapeutic and nutritional applications (Watzer and Forchhammer 2018). Cyanophycin can be produced in *E. coli* by overexpressing the cyanophycin synthetase *cphA* gene isolated from *Synechocystis* sp. PCC 6803 with productivity of 120 mg/g CDW (Tseng et al. 2012). *Streptomyces* species like *Streptomyces albulus* are exclusively involved in the production of ε-PL and could reach up 35.14 g/L when glucose and glycerol are used as carbon source (Chen et al. 2012; Dodd et al. 2018). Poly-ε-L-lysine or ε-PL is a homo poly amino acid that is produced by the polymerization of lysine via ε-PL synthetase (PLS). ε-PL has been approved as food preservatives or dietary agents due to having antibacterial anticancer activities in developed countries like the United States and Japan (El-Sersy et al. 2012).

12.9 Conclusion

Nowadays, due to green manufacturing and sustainable development, microbial production of different substances is widely used, but this development is limited because of its high cost. For developing countries, it creates an opportunity for using microbes and their derivatives from small places like household and village-level production to large-scale industrial productions. These microbial processes need more exploration to be exploited with full intensity with their beneficiary effects. The last decades have recorded extraordinary advancements in production of nutraceuticals by metabolic engineering of microorganisms. Nutraceuticals own countless application including strengthening of immunity of human beings. Further studies are recommended for exploration of different microbial explorations in which microbes are directly involved in enhancing the productivity of processed food or food products. The use of metabolically engineered microbes opens a promising door not only in laboratory-based production but also for the industry-based production of intricate natural compounds from simple carbon sources. The emerging role of synthetic biology will promote the progression of this field in upcoming years, and hopefully, this will deliver requisite tools for tuneable synthesis and optimization of nutraceutical synthesis in biological hosts.

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