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Advances in the optimized synthesis of biotechnologically valuable products from bio-engineered microbial cell factories

Eleftherios G. Halevas [1] Anastasia A. Pantazaki [1, *]

[1]Laboratory of Biochemistry, Dept. of Chemistry, Aristotle University, 54124 Thessaloniki, Greece

*corresponding author e-mail address:***natasa@chem.auth.gr**

ABSTRACT

The constantly arising solicitousness for the environmental impact and the potential limitation of petroleum and gas resources has focused the commercial interest on the development of industrially viable microbial strains with fine-tuned physiological capabilities. Synthetic biology, metabolic and protein engineering have become progressively important and valuable platforms in the development of microbial cellular networks for the generation of various pharmaceuticals, chemicals, food ingredients, and biofuels through the conversion of renewable resources. However, despite the comprehensive optimization of the biosynthetic pathways, the mass concentration and the low production rates represent the major obstacles in the exploration of new production hosts, the synthesis of novel enzymatic catalysts of natural and unnatural reactions, and the development of more effective tools for functional proteomics and genomics. Therefore, innovative synthetic biology research and diversified genome engineering approaches are anticipated to play the principal role in the achievement of engineered microbes with robust phenotypes, higher yields, and productivity. Herein, we thoroughly present the nascent technologies in the advancement of bio-engineered microbial cell factories for the optimized synthesis of biotechnologically valuable products.

Keywords: *Microbial cell factories, Biotechnological products, Metabolic bio-engineering, High added-value products, Synthetic biology.*

1. INTRODUCTION

The technologies of recombinant DNA, in combination with the approval of recombinant insulin [1], provoked the pursuit of convenient methods and sources for the controlled biological production of hardly reproducible molecules of high-added value, leading to the exploitation of microbial cell factories in the pharmaceutical, biotechnology and food industries as viable and cost-effective platforms of large-scale production [2]. *Escherichia coli* plain strains and *Saccharomyces cerevisiae* yeast were the first reported cell factories which were soon replaced by new strains. The novel engineered variants present enhanced performance as products of untargeted phenotypic selection and mutagenesis, metabolic engineering combined with synthetic biology and/or systems biology, and conventional genetic modification [3-18]. Additionally, the list of the newly utilized microbial cell factories is complemented by insect and mammalian cells of unusual physiological traits, such as fungi, algae, moss and psychrophilic bacteria [19-23], for the production of high purity and quality proteins [24, 25]. Research studies on the diversified microbial physiology and the variability of biosynthetic pathways have resulted in the development of innovative bio-products, such as micro- or nano-structured materials [26-28], and novel food-grade vectors in lactic acid bacteria (LAB) utilized in food microbiology and as new sources of proteins and metabolites [29-36]. Recently, the increasing medical and industrial demand for recombinant proteins with therapeutic potential, and the emerging environmental issues led to the development of systemic metabolic bio-engineering [37, 38], as a novel strategic and methodological approach for the optimization of biosynthetic and metabolic pathways [7, 14], and the design of gene and regulatory, signaling and metabolic networks for the sufficient production yields of bulk chemicals, pharmaceuticals, plastics, fuels, and high-added value materials [3-5, 39]. Moreover, the effective identification of pathways and target genes that are responsible for the enhancement of the microbial production under inexpensive processes and industrial requirements is achieved through *in silico* simulations of genome-scale metabolism, modeling, and profiling of proteome, transcriptome, fluxome, and/or metabolome [40]. The detailed analysis of all cellular characteristics and features that have emerged under specific environmental and/or genetic perturbations, in combination with the optimal design of microbial cell factories, contribute to the alternative cost-effective production of various industrially important materials and chemicals, already produced by the petrochemical industry, such as alcohols (ethanol, propanol, isobutanol, butanol), dicarboxylic acids (adipic acid, fumaric acid, malic acid, succinic acid), diols (1,3-propanediol, 1,2-propanediol, 1,4-butanediol, 2,3-butanediol), diamines (putrescine, cadaverine), and polymers such as polyhydroxyalkanoates (PHAs), spider silk filamentous protein, polylactic acid, poly-γ-glutamic acid, etc. [39]. Indicatively, the bacterial production of 1,3-propanediol from glucose required the bio-engineering of at least 70 genes, before the optimization process [41]. Polylactic acid is a representative specimen of a material produced by biobased products after the replacement of mineral oil as raw material, through the development of efficient technology, ecological and economic feasibility [42]. Nowadays, in an effort to expand industrial biotechnology, various groups of

academics, researchers and scientists, in cooperation with industry [39], share the mission to intensify the efforts on the development and exploitation of microbial cell factories for the synthesis of biotechnologically, industrially and commercially valuable products [43].

2. OPTIMIZATION OF BIOTECHNOLOGICALLY VALUABLE PRODUCTS

2.1. Production of biofuels.

The environmental impact, along with economic development, and the emerging energy security issues has grown the interest in the biofuel-based energy alternatives [44]. However, despite all efforts, alternative biofuels, such as the corn-based ethanol, have yet to become a profitable source of alternative fuels [45]. Thus, the adoption of cheaper, advanced, non-edible biofuel sources such as lignocellulosic biomass has become imperative [46].

2.1.1. Utilization of lignocellulosic biomass.

Lignocellulosic biomass is the non-edible portion of plants and constitutes an effective feedstock with a distinctive structure, ideal for the synthesis of biofuels because of its low requirements for energy, fertilizers, and pesticides [47]. However, the compact structures, in combination with the chemical complexity of the outer cellular membrane render the plants highly recalcitrant, thereby limiting the efficient and complete deconstruction and usage of lignocellulose-derived feedstocks. Lignocellulose-derived biomass is characterized by a distinctive structure with cellulose, its most abounding constituent, surrounded by a lignin and hemicellulose complex in order to be protected from hydrolytic enzymes [48]. Studies on the deconstruction of the cellulose crystalline structure proved the release of the fermentable monosaccharide glucose, a valuable compound in the synthetic procedure of biofuels. Consolidated bioprocessing (CBP) is a combinatorial microbial process that includes the: i) production of enzymes, ii) hydrolysis of cellulose and iii) fermentation of monosaccharides for biofuel production. CBP reduces the production cost of biofuels by eliminating the high production outputs of cellulases [49]. The development of a CBP microorganism relies heavily on the engineering of a naturally cellulolytic organism to produce ethanol [50]. An indicative procedure is the expression of GH12 and E1 cellulolytic enzymes from *Acidothermus cellulolyticus* in *Zymomonas mobilis*gram-negative bacterium because of its high ethanol productivity and tolerance. Moreover, the extracellular secretion of E1 and GH12 can be achieved through the inclusion of the secretion signals of native *Z. mobilis* [51]. *S. cerevisiae*, an effective ethanol producer, is another CBP organism [52]. The introduction of *Trichoderma reesei* endoglucanase and *Saccharomycopsis Wbuligera β*-glucosidase into *S. cerevisiae* results in a recombinant strain efficient at growing and multiplying on phosphoric acid-swollen cellulose (PASC) and attributes high ethanol yields [53]. The development of a recombinant yeast strain for the functional expression of *β*-glucosidases, cellobiohydrolases, and endoglucanases, through a trifunctional minicellulosome assembly via dockerin-cohesion interactions, has also been reported. The corresponding recombinant yeast strain exhibited high cellulolytic efficacy due to enzyme–substrate, andenzyme–enzyme synergistic effects [54]. Literature reports also describe the development of a synthetic yeast consortium of four dissimilar engineered recombinant yeasts. One yeast strain displayed a trifunctionalscaffolding. Subsequently, three strains expressed individually a dockerin-tagged cellulolytic enzyme for the surface assembly of its functional minicellulosome [55]. Lignocellulosic biomass consists mainly of hemicelluloses, lignin, and cellulose. Hemicellulose consists of pentoses (five-carbon sugars) including L-arabinose and D-xylose [56]. Inevitably, the inability of *S. cerevisiae* to utilize the corresponding pentoses for the sufficient production of ethanol, mainly due to “glucose repression” (repression of pentoses before the depletion of glucose) during the fermentation procedure of mixed sugars [57], increases the final production cost of bio-ethanol [58-60]. Optimization of bio-engineered pathways for the successful conversion of L-arabinose and D-xylose into D-xylulose-5-phosphate will eventually lead to ethanol production by *S. cerevisiae* [60, 61]. Studies on the development of novel approaches for the alleviation of glucose repression introduced the benefits of xylose and cellobiose co-fermentation utilizing recombinant *S. cerevisiae* strains for the co-expression of an intracellular *β*-glucosidase and a cellobiose transporter, thus eliminating the use of exogenous *β*-glucosidases and the intracellular glucose accumulation [62, 63].

2.1.2. Production of advanced biofuels.

Despite the success of bio-ethanol as a fuel alternative [64, 65], its low corrosiveness and energy content limitate its compatibility and applicability compared to other superior biofuels, including fatty acid derived fuels, hydrocarbons and higher alcohols [66]. In comparison to ethanol, *N*-butanol and isopropanol, synthesized by *Clostridium* species, are more commonly utilized fuel alternatives due to their lower aqueous solubility and higher octane number and energy content. However, the relatively slow life cycles in spore formation and growth rate of *Clostridium* species render the production yield of the corresponding alcohols difficult to control during fermentation [66]. Studies on novel bio-engineered synthetic methods of long-chain alcohols indicated the production of *n*-butanol from a *Clostridium* species [67], and isopropanol [68] through the CoA-dependent fermentation pathway via the introduction of various gene combinations from different *E. coli* and *Clostridium* species into *E. coli* [66, 67, 69-71]. However, the cytotoxicity provoked by the intermediate metabolite accumulation, and the redox imbalance caused by the heterologous pathway introduction result in low-production titers of long-chain alcohols [69, 72]. As a result, scientists focused their interest on the production of long-chain alcohols including 1-butanol, isobutanol, 2-phenyl ethanol, and 2-methyl-1-butanol via non-fermentative keto-acid bio-engineered pathways. Through these pathways, 2-keto-acids, as intermediate compounds in the biosynthetic pathways of amino acids, are decarboxylated into aldehydes by several 2-keto-acid decarboxylases (KDC).

Subsequently, they get interconverted to alcohols via reduction by alcohol dehydrogenases (ADH) [69, 70, 73]. Additionally, biofuel alternatives from fatty acids including fatty alcohols and fatty acid esters are also considered valuable alternative types of fuels. Moreover, studies on the bio-engineering and modification of recombinant *E. coli* strains [72], for either the mutation of fatty-acid degradation genes and the overproduction of free fatty acids via the overexpression of a cytosolic form of *E. coli* thioesterase or the direct production of fatty acid ethyl esters (FAEEs) through the utilization of *Z. mobilis* genes, suitable for ethanol production and the endogenously overexpressed wax-ester synthase. Moreover, hemicellulose of biomass is prominent for consolidated bioprocessing directly into biodiesels through the overexpression of hemicellulases via recombinant microbial systems of fatty acid derivatives and secretion into the growth medium. Alkanes and alkenes, as aliphatic hydrocarbons, are the most important components of jet fuels, gasoline, and diesel. Long-chain alkene synthesis can be achieved through the heterologous over-expression of *Micrococcus luteus* condensing genes and enzymes in an *E. coli* strain capable of overproducing fatty acids [74]. There are also literature reports on the biosynthetic pathway of cyanobacteria-derived alkanes [75]. This metabolic pathway includes an aldehyde decarbonylase and an acyl-acyl protein reductase carrier which synergistically convert long-chain fatty acids to alkenes and alkanes [75]. Cyanobacteria are photosynthetic prokaryotes that can regulate the CO_2 atmospheric concentrations and their bio-engineering can lead to the production of industrially valuable materials such as free fatty acids, alcohols, alkanes utilized in next-generation biofuels, and chemicals of commercial value such as farnesene or ethylene [76]. Cyanobacteria can be genetically modified, possess insignificant nutrient requirements, and are extremely tolerant to abiotic stresses rendering them effective biofuel-producing microorganisms [76].

2.2. Production of natural products.

2.2.1. Production of terpenoids (isoprenoids).

Terpenoids constitute a diverse group of naturally occurring molecules of industrial interest with variable medicinal properties. These molecules derive from modified assemblies of 5-carbon isoprene units. These lipids exist in all types of living organisms, and there are more than 25,000 terpenoids structurally characterized [77]. Dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) are the two main isoprene structural units of terpenoids, and they originate through the mevalonic acid or the non-mevalonic acid pathway according to the type of the produced species [78]. Their applications include electron transport and respiration (quinones), hormone signaling and membrane fluidity (steroids), antioxidant activity and photosynthesis (carotenoids). The isolated terpenoids from marine invertebrates and plants are used as bioactive materials in the cosmetic, food, and pharmaceutical industries [79]. The synthesis of terpenoids of high structural complexity through the IPP transformation has been an important research directive in metabolic engineering and synthetic biology [78]. An indicative example is the synthetic procedure of artemisinic acid, the precursor of artemisinin anti-malarial drug, from *S. cerevisiae* [80]. Artemisinic acid is also the product of a three-step oxidation reaction of amorphadiene, which is the main product of the farnesyl pyrophosphate (FPP) conversion by a) the amorpha-4,11-diene synthase gene (ADS), b) the cytochrome monooxygenase P450, and c) its redox copartner derived from *Artemisia annua* [81]. Cytochrome monooxygenases P450 are functional enzymes in the biosynthetic procedure of terpenoids. They are used as catalysts in the biosynthetic procedure of paclitaxel [82]. The effective bacterial expression and purification of plant P450s prevent the efficient biosynthesis of various compounds by recombinant bacteria because of the deficiency of either an endobacterial cytochrome reductase P450 (CPR) [83], and/or an endoplasmic reticulum, thus inducing the translational discordance of the transmembrane signaling modules [84]. Indicative examples are the production of functionalized terpenoids, such as 8-hydroxycadinene, from *Candida tropicalis* into *E. coli*, or the isoflavone synthesis into *E. coli*, by using heterologous plant P450s [85-87]. A successful combination of metabolic and protein engineering and synthetic biology of microbes was applied in the biosynthetic procedure of taxadiene, a valuable intermediate in the synthetic procedure of the anticancer taxol [88]. Taxol and its structural derivatives are originally directly extracted from the Pacific yew tree [89]. However, the low productivity yields [90, 91] of a) the direct extraction [92], b) the total chemical synthesis [93], and c) the semi-synthetic method [94] have led to the synthesis of Taxol into *S. cerevisiae* hosts, co-expression of *Taxus chinensis* cells in response to taxadiene synthases (TStc), and taxadiene biosynthesis through selection of geranylgeranyl pyrophosphate synthase (GGPPStc) [95]. Recently, researchers have also identified the cloning and characterization of sabinene synthases for the production of sabinene monoterpene from intermediate metabolites by microbial fermentation of *Escherichia coli* and *Saccharomyces cerevisiae* [96].

2.2.2. Production of alkaloids.

Alkaloids are a family of low molecular weight, naturally occurring, nitrogen-containing, basic organic chemical substances. They are synthesized by various organisms including bacteria, animals, plants, and fungi. This group derives from the process of decarboxylation of a variety of amino acids including tyrosine, tryptophan, histidine, lysine, and ornithine, and is characterized by significant pharmacological and medical activities [97]. More specifically, berberine, apart from its antimicrobial role, has been reported to decrease the bad cholesterol levels [98], sanguinarine possesses anticancer properties [99], tetrandrine, a bisbenzylisoquinoline alkaloid, regulates hypertension and is used against autoimmune disorders [100, 101], and a group of indolocarbazole alkaloids has been clinically tested as a promising remedy for Parkinson's disease, cancer, and diabetic retinopathy [102]. They are classified according to their diverse profile, structural complexity and number of amino acids from which they derive, into six major groups, including protoberberine-, morphinane-, pyrrolizidine-, ergot-, furanoquinoline-, and quinolizidine-alkaloids [103]. Additionally, more than 10,000 plant alkaloids have been structurally characterized. However,

despite their molecular complexities, structural diversities, and the development of carefully designed metabolic processes for the accomplishment of enhanced plant production rates, they have not been efficiently synthesized in satisfying yields [104-106]. The limited number of convenient and less complex biosynthetic pathways [107, 108], in combination with the interference from the intracellular transport of synthetic intermediates and metabolites in plant organelles [109], act as deterrents for the successful engineering and regulation of the alkaloid plant production. As a result, the biosynthesis of alkaloids in microbial cell factories ensures the: a) rapid accumulation and growth of biomass, b) optimization of the pathway expression through plentiful genetic tools, and c) convenience in the characterization and isolation conditions of the key intermediates and final products [110]. A representative example is the synthetic procedure of two benzylisoquinoline alkaloids, scoulerine, and magnoflorine, from *S. cerevisiae* and recombinant *E. coli* co-cultures [97], by using enzyme-derived dopamine as the main synthon of (*S*)-reticuline basic intermediate. Furthermore, an indicative procedure of balanced yeast engineering, through the expression of enzyme combinations generated by various sources, is the production of: a) downstream metabolites, b) reticuline intermediate, and c) reticuline derived sanguinarine/berberine and morphinan branches [110]. Various combinational strategies have been applied in order to expand the diversifiable profile of the existing alkaloids, aiming at the improvement of their therapeutic potential. More specifically, a combined expression of rebeccamycin and staurosporine partial clusters with biosynthetic genes of sugar in *Streptomyces albus*, led to the generation of a group of new indolocarbazole derivatives with substrate flexibility and enhanced selectivity as kinase inhibitors [111, 112].

2.2.3. Production of polyphenols.

Additionally to terpenoids and alkaloids, polyphenols are the 3rd group of plant-derived secondary metabolites [113]. They consist of at least two aromatic rings and phenolic hydroxyl groups, with some exceptions, as in the case of pyrogallol or gallic acid [114, 115]. Polyphenols do not involve in plant development and propagation, but they attract pollinators, provide coloration, confront infections induced by microbes or act protectively against herbivores [94, 116] and UV radiation through the neutralization of reactive oxygen species (ROS) in plant tissues exposed to light [117, 118]. The two important groups of plant-derived polyphenols are flavonoids and stilbenoids [119]. Stilbenes and flavonoids can be structurally modified with methyl, glycosyl, acetyl and other acyl moieties providing compounds with variable chemical properties including bioavailability, water solubility, and molecular stability [120-122]. The first plant-derived polyphenols, pinocembrin, and naringenin (2S)-flavanones, were synthesized within a microorganism through the utilization of phenylpropanoids p-coumaric acid and cinnamic acid as the main precursors of the synthetic procedure [119].

2.2.3.1. Production of flavonoids. Flavonoids constitute a category of fungus and plant-derived secondary metabolites, with a specific structure of a 15-carbon skeleton, abbreviated as linear C6-C3-C6 [123]. Their phenylpropanoid core can be modified by structural rearrangements, methoxylations, methylations, oxidations, alkylations, hydroxylations,and *C*- and *O*-glycosylations [124, 125], forming over 9,000 compounds with remarkable antioxidant, anti-cancer, antiviral, and antibacterial properties [126]. Following the phenylpropanoid biosynthetic pathway, the phenylalanine ammonia lyase enzyme (PAL) constitutes the catalyst of the phenylalanine deamination to cinnamic acid, which is further activated by the coenzymes 4-coumarate/cinnamate, hydroxylated by trans-cinnamate 4-monooxygenase (C4H), and condensed with three malonyl-CoA moieties, aiming at a chalcone formation, catalyzed by the mediation of chalcone synthase (CHS). The chalcone conversion in an intramolecular ring closing metathesis stage for the heterocyclic C-ring formation is applied by chalcone isomerases (CHI) [127]. An artificial biosynthetic pathway was used through the construction of a three-gene cluster encoding for enzymes of heterologous origin including gene encoding for *PAL* from the *Rhodotorula rubra* yeast, for *4CL* from the *Streptomyces coelicolor* A3(2) actinomycete, and for *CHS* from the *Glycyrrhiza echinata* plant in order to accumulate plant-specific flavanones, pinocembrin or naringenin, in *Escherichia coli* [128]. Flavonoids are classified according to their structural diversities into flavanones, flavonols, flavones, anthocyanins, catechins, and isoflavones [124]. *S. cerevisiae* and *E. coli* are also utilized as adequate systems for the production of flavonoids [129]. However, the limited biosynthetic potency has led to alternative biosynthetic methods including the over-expression of the acetyl-CoA carboxylase subunits (ACC) or the malonate utilization pathway, a biosynthetic procedure that improves the availability of UDP-glucose and malonyl-CoA. Efficient strains for the expression of plant 4-coumarate, such as CHI, CHS, CoA ligase (4CL), 3-*O*-glycosyltransferase (3-GT), and anthocyanin synthase (ANS) enhanced the production yields of flavanones and anthocyanins [124]. Generation of novel flavonoids can be achieved by exploiting the substrate-specific behavior of the flavonoid biosynthetic genes in combination with unconventional precursors. An indicative example is the whole-cell bio-transformational engineering of a reconstructed host for the efficient synthesis of glycosylated flavonoids [130].

2.2.3.2. Production of stilbenoids. Studies on the introduction of *Vitis vinifera STS* and *Nicotiana tabacum* cv. Samsun *4CL2* genes into an *E. coli* bacterial strain indicated the provoked resveratrol production from 4-coumaric acid [131]. A cluster of genes encoding for PAL, C4H, 4CL, and CHS from *Arabidopsis thaliana* was cloned and simultaneously co-expressed in *E.coli* leading in an inactive C4H enzyme. Exogenous supplementation of 4-coumaric acid resulted in resolution of the problem and in high production of flavanone naringenin [132]. In the case of stilbenoids, similar effects were observed after the co-expression of a STS encoding gene from *Arachis hypogaea* and *A. thaliana* 4CL1 into *E. coli* and the subsequent introduction of 4-coumaric acid [133]. Respectively, the corresponding addition of caffeic acid led to the production of piceatannol [134]. The synthetic procedure of several stilbenoids from phenylpropanoicacid analogs into *E. coli* initiated the production of resveratrol and pinosylvin [135].The incorporation of a rice *O*-methyltransferase

(OMT) gene (Os08g06100) in a bio-engineered *E. coli* cellular environment for the production of stilbenoids yielded pinosylvins, pterostilbene, and pinostilbene [136]. The incorporation of *P. crispum 4CL*, *R. glutinis TAL*, *R. trifolii matB* and *matC*, and *V. vinifera STS* into *E. coli* provoked the production of resveratrol through the utilization of L-tyrosine precursor [137]. Several research studies have proved the relatively low production yields of stilbenoids in yeasts compared to the corresponding values into *E. coli* [138]. Additionally, S*accharomyces cerevisiae* can act as a host system for the synthesis of resveratrol from 4-coumaric acid through the expression of a *N.tabacum 4cl gene* from *Populus sp.* combined with a *Vitis vinifera* derived *sts gene* [131, 139], and from L-phenylalanine through the incorporation of a) *Populus trichocharpa×deltoids* derived CPR and PAL, b) *Glycine max* derived 4CL and C4H, and c) *V. vinifera* 'Soultanina' derived STS [140]. *Lactococcus lactis*, *Streptomyces venezuelae*, and *Corynebacterium glutamicum* were also introduced as effective microbial hosts, adequate for the synthesis of polyphenols [141-143]. Currently, resveratrol is mainly extracted from *Polygonum cuspidatum* [144]. The codon optimization of *TAL* and the introduction of *E. coli area* transporter characterized by high-capacity and low-affinity enhanced the production of resveratrol [145]. Moreover, the construction of synthetic scaffolds for the utilization of STS and 4CL optimized the production of resveratrol within yeast cells [146].

2.2.3.3. Production of anthocyanins. As an important member of polyphenols, the family of anthocyanins has focused great attention mainly due to their commercial, industrial, pharmaceutical and neutraceutical value (Figure 1). Experimental studies on cloning and expression of i) flavanone 3-hydroxylase (F3H) and ANS genes from *Malus domestica*, ii) DFR genes from *Anthurium andraeanum*, and iii) flavonoid 3-O-glucosyltransferase (F3GT) genes from *Petunia hybrida* in a recombinant *E. coli* strain resulted in the enhanced production of cyanidin 3-O-glucoside and pelargonidin 3-O-glucoside using eriodictyol and naringenin as precursors [147]. Recent studies on anthocyanin biosynthetic pathways resulted in the bioengineering of an *E. coli* strain for the production of anthocyanin P3G using (+)-catechin flavonol as precursor [148]. Currently, all reported recombinant anthocyanin producing hosts are limited to *E. coli* derivatives [149,150].

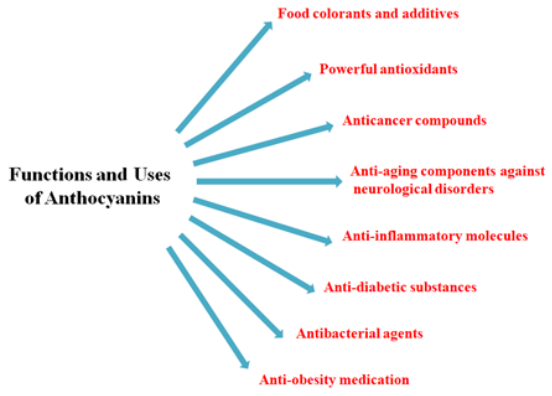

Fig. 1. Functions and uses of anthocyanins.

2.2.4. Production of polyketides and non-ribosomal peptides. Polyketides are valuable metabolites of medicinal importance that derive from filamentous fungi, plants, and bacteria, and are used clinically as antibiotics, antifungals, anticancer drugs, antiparasitics, cholesterol-reducing factors, and immunosuppressants [151]. Polyketides are produced by a group of functional polyketide synthases (PKSs). PKSs are classified according to their biochemical characteristics into types I, II and III. The products derived from the utilization of PKSs possess various chemical and/or structural transformations such as hydroxylation, oxygenation, methylation, cyclization, glycosylation, and acylation [152]. *S. cerevisiae*, *E. coli*, *P. putida*, *B. subtilis*, and many *Streptomyces* species have been used as the main bacterial strains for the redefining of PKS bio-engineered activity [153]. However, the lack of post-translational modifiable enzymes in *E. coli* and *S. cerevisiae* [154, 155], the inefficient translation and ineffective folding of mega synthases and the P450s in *E. coli*, in combination with the genetic modifications of *P. putida*, *B. subtilis*, and many *Streptomyces* species [115,116, 156] reduce the possibility for a satisfactory expansion of polyketide variety. An indicative *in vivo* reconstitution of PKS is the biosynthetic procedure of 6-deoxyerythronolide B (6-dEB) in *E. coli* [157]. Further improvement of the production of signaling molecules was achieved by the over-expression of the *S*-adenosylmethionine (AdoMet) synthetase MetK from *Streptomyces spectabilis* [158] or by muting the propionyl-CoA: succinate CoA transferase [159]. Various erythromycin and 6-dEB derivatives have been synthesized through module or domain insertions, replacements, and deletions [150,160, 161]. The largest modular type I PKSs consist by the epothilones and are reconstituted in *E. coli*. They are produced by a hybrid non-ribosomal peptide synthetase (NRPS)/polyketide synthase into the *Sorangium cellulosum* myxobacterium. On the contrary, type II PKSs derive from an actinomycete and are utilized in the production of pharmaceutically effective aromatic polyketides including anthracyclines and tetracyclines [162]. Utilization of bacterial type II PKSs enabled the expression of the ketosynthase-chain length factor (KS/CLF) heterodimer in a soluble form via targeting of fungal iterative Type I non-reducing PKSs, dissection, and extraction of the PKS4 minimal PKS parts of *Gibberella fujikuroi*, and reassembly of it within a synthetic PKS, thus synthesizing reactive to cyclization regioselectivity aromatic polyketides into *E. coli* [163]. There are three categories of the type III PKS products according to their distinct activities [154]. Flavanones, a basic precursor of various flavonoids, represent the product of the cyclization of intermediate polyketides by chalcone synthase [164]. Stilbenoids are produced through the formation of a stilbene backbone by stilbene synthase (STS) utilization as a catalyst of a corresponding intermediate polyketide cyclization [165]. Curcuminoids are the product of condensation reactions catalyzed by curcuminoid synthase (CUS) without the process of cyclization [166, 167]. Pinosylvin, resveratrol [135], and dicinnamoylmethane and bisdemethoxycurcumin [166] are the products of 4CL and phenylalanine ammonia lyase (PAL) co-expression with diverse type III PKSs. Precursor combinatorial co-

expression and biosynthesis [135,167] of post-PKS modifying enzymes [168, 169] generated various synthetic compounds. *Streptomyces* represent the most adequate host microorganisms for the polyketide production [6]. Actinomycetes, such as the *Streptomyces* genus, represent the major producer of the bioactive microbial metabolites [170]. Various literature reports summarize the recent synthetic approaches of bioactive compounds and their precursors by *Streptomyces* metabolic engineering [6,170,171, 172, 173]. In a similar way, the diverse and biologically effective non-ribosomal peptides (NRPs) are produced by large protein modularities, the non-ribosomal peptide synthetases (NRPSs). There are various pharmaceutical NRPs such as siderophores, bacitracin and vancomycin antibiotics and L-*α*-aminoadipate-L-Cys-D-Val (ACV) antibiotic precursor, and cyclosporine immunosuppressive natural drug [174]. The replacement of multiple or single modules in the DptBC subunit by A54145 and daptomycin NRPS modules led to the modification of the amino acid core of daptomycin. A54145A and daptomycin-related lipopeptide antibiotics were generated by *Streptomyces fradiae* and *Streptomyces roseosporus* after the combination of inactivated tailoring enzymes and exchanges of NRPS subunit [175-177]. The first literature reported successful production of NRPs in yeast was accomplished via the low temperature cluster integration inside the genome by using ACV as the model NRP. The ACV derived from the expression of ACV synthetase in *S. cerevisiae* through a combination of a high-copy plasmid and multi-source phosphopantetheinyl transferases (PPTase) [178].

2.3. Production of chemicals.

Nowadays, the majority of the industrial petroleum chemicals are gradually replaced by biobased industrial products and fuel alternatives of similar outputs [179, 180]. The development of cost-competitive synthetic, biochemical and fermentation procedures [181, 182], including either the direct extraction of petroleum from plants or the conversion of biomass to sugars or liquid fuel and other commodity chemicals [183, 184], have provoked progress in agricultural economics and process technology, enabling the exploitance of novel discoveries in chemical, genetic, and microbial engineering research [185, 186]. Biobased chemicals are highly desirable due to their high potential for the efficient sustainability of environmental quality, national security, and natural resources [187, 188].

2.3.1. Production of organic acids.

Organic acids, due to their applicability as basic synthons in chemistry along with their simple synthetic procedure from microbial cell factories, have been extensively investigated. More specifically, the commercial production of lactic acid is achieved through glucose fermentation by different *Lactobacillus* species or other renewable resources including cellobiose, cellulose, and glycerol [189-191]. Succinic acid (SA) and its esters are widely utilized surfactants and precursors of petroleum products such as 1,4-butanediol, and are biochemically synthesized by yeast/fungal strains including *Aspergillus fumigatus*, *Aspergillus niger*, *Candida tropicalis*, *Byssochlamys nivea*, *Paecilomyces varioti*, *Lentinus degener*, *Saccharomyces cerevisiae*, *Pichia kudriavzevii*, and *Penicillium viniferum*, or bacteria including recombinant *Anaerobiospirillum succiniciproducens*, *Actinobacillus succinogenes*, *Escherichia coli*, *Mannheimia succini-ciproducens*, *Basfia succiniciproducens*, and *Corynebacterium glutamicum* [192-194]. Recent scientific reports have proved the production of SA in recombinant *S. cerevisiae* through a quadruple gene deletion which further resulted in an interrupted TCA cycle [195]. Additional studies on innovative bio-engineering methodologies for the exploitation of combined synthetic procedures of succinate and biomass indicated the generation of a reconstructed *S. cerevisiae* bacterial strain which displays satisfactory both succinate titers and succinate yields on biomass and a negligible decrease in the biomass output in contrast to the reference strain [196]. 3-Hydroxypropionic acid (3-HPA), a functional organic acid of the polymer industry, is produced from either glucose or glycerol into recombinant *E. coli* through the simultaneous expression of aldehyde dehydrogenase and heterologous glycerol dehydratase [197, 198]. D-Glucaric acid constitutes a naturally derived organic acid found in mammals, vegetables, and fruits, with various therapeutic applications. It is the output of the mammalian pathway of D-glucuronic acid introduced by D-glucose or D-galactose. Additional literature reports on novel synthetic routes include the production of recombinant species of D-glucaric acid from *E. coli* strains by the heterologously expressed myoinositol-1-phosphate synthase (Ino1) from myoinositol oxygenase (MIOX) from *S. cerevisiae* [199]. Furthermore, a co-expression of a *Pseudomonas syringae* derived urinate dehydrogenase was reported, which enhances the production of D-glucaric acid through the converting procedure of D-glucuronic acid. Complimentary reports indicated the enhancement of the MIOX activity and the production yields of D-glucaric acid after the introduction of synthetic polypeptide scaffolds that increase the myo-inositol levels [199, 200].

2.3.1.1. Production of hyaluronic acid. Hyaluronic acid (HA), a glycosaminoglycan of great importance, is composed of repeating disaccharide units of *N*-acetylglucosamine and glucuronic acid, linked by glycosidic bonds. Bacteria *Streptococci* was the first host cell for the production of HA via microbial fermentation. Additionally, the bacterial pathogen *Pasteurella multocida*, the yeast *Cryptococcus neoformans* when catalyzed by glycosyltransferase (CPS1 gene), and the green algae *Chlorella* sp. when infected by the *Paramecium bursaria* chlorovirus (PBCV-1), are considered natural HA producing microorganisms [201]. Laboratory reports indicated the potential of *S. zooepidemicus* on HA production under various oxygen concentrations (anaerobic and aerobic conditions) and after exposure to *N*-methyl-*N*-nitro-*N*-nitrosoguanidinea and UV light [202]. HA is also produced from various heterologous hosts modified through metabolic engineering such as: *Enterococcus faecalis*, *Lactococcus lactis*, *Agrobacterium* sp, *Corynebacterium glutamicum*, *Streptomyces albulus*, *Escherichia coli*, *Pichia pastoris*, *Saccharomyces cerevisiae*, and *Bacillus subtilis* [201]. Gram-positive *Lactococcus lactis*, along with the co-expression of the *HasC* (UDP-glucose pyrophosphorylase) gene, is also considered an adequate fermentative microorganism for the production of HA [203, 204]. Unlike plasmid-based strains, integration of the bacterial genome

led to a two-fold increased production in the HA polymer MW. This difference in MW of HA may be explained by the different ratios of: i) the precursors UDP-GlcNAc/UDP-GlcUA and ii) the levels of *HasA*/*HasB* mRNA [201]. Respectively, the introduction of *HasA* gene in a capsular *Enterococcus faecalis* [205] and *Corynebacterium glutamicum* [206] enhanced the HA production yields. HA production from *Agrobacterium sp.* was observed only through the expression of the *pmHas* gene from *P.multocida* [207]. Recent studies on bioengineered and modified *E. coli* strains showed enhanced HA production yields through the expression of *P. multocida* subsp. *Multocida pmHas* gene or the simultaneous co-production of *E. coli* K5 UDP-glucose dehydrogenase and *P. multocida* HA synthase [208]. In the case of *Bacillus subtilis*, the combination of plasmid pAX01 utilization for the cloning of *P. multocida* HA synthase gene and the use of plasmid pHCMC05 for the generation of enzyme recombinant operons led to high HA production yields [209]. The introduction of *Xenopus HasA* gene DG42 into *S. cerevisiae* yeast, using the pYES2 episomal plasmid, resulted in high MW polymer [210].

2.3.1.2. Production of bioactive fatty acids. Punicic acid (PuA) is an 18-carbon fatty acid with three conjugated double bonds. It possesses anti-cancer, anti-diabetic, anti-inflammatory, anti-oxidant, and anti-obesity properties [211]. PuA and other fatty acids including conjugated linoleic acids (CLAs) can be produced by oleaginous microorganisms such as *Yarrowia lipolytica* oleaginous yeast [212]. Experiments on *Saccharomyces cerevisiae* yeast indicated a low detection and accumulation degree of PuA only after expression of FADX enzymes through the supplementation of the culture growth media with linoleic acid [213]. Metabolic bioengineering of *Schizosaccharomyces pombe* fission yeast, which contains high quantities of oleic acid, through the controlled by the *nmtl* promoter heterologous co-expression of codon optimized sequences *PgFAD2* and *PgFADX*, led to the production of high PuA and limited linoleic acid yields [214].

2.3.2. Production of sugar alcohols and rare sugars.

Xylitol is a low-calorie sugar substitute with favorable anti-cariogenic activity. It is produced by enzymatic or chemical hydrogenation of hemicellulose-derived hydrolysate and through subsequent purification of unusable reduction by-products, such as L-arabinitol, that increase the production cost. As a result, new synthetic routes from recombinant *E. coli* strains have emerged in order to ensure the limited existence of impurities during xylitol production. More specifically, a specific reduction of D-xylose to xylitol of 100% purity by a bio-engineered aldose reductase promiscuous enzyme, through *in vivo* selectivity methods, leads to increased production yields of D-xylose, mutation of the catalytic efficacy toward L-arabinose, and efficient maintenance of its activity [215, 216]. The rare L-Ribose sugar is an important synthon in the pharmaceutical, food, and agrochemical industries. Scientific reports indicate the development of a new bio-engineered synthetic route for the L-ribose synthesis from ribitol by a recombinant *E. coli* strain, through the utilization of an active and thermally stable NAD-dependent mannitol-1-dehydrogenase (MDH), which can act as a bio-catalyst for the interconverting procedure of various polyols and their L-sugar derivatives [217, 218].

2.3.3. Production of amino acids and vitamins.

Amino acids and vitamins represent a valuable group of nutritional supplements whose microbial bio-engineering has been thoroughly investigated [219, 220]. Recent progress in novel metabolic bio-engineering tools for the synthesis of these compounds includes the carbon storage regulator (Csr) of E. coli, a system designated for the improvement of phenylalanine biosynthesis [221]. Additional studies on the impact of csrB overexpression and csrA-csrD mutations on the production of phenylalanine from E. coli NST37 (NST) indicate that csrB overexpression, along with tktA overexpression, significantly increase the production of phenylalanine compared to csrA-csrD mutations [222].

2.3.4. Production of 1, 3-propanediol.

1, 3-Propanediol (1, 3-PD) constitutes a functional compound utilized in the synthesis of cosmetics, drugs, plastics, and lubricants. High 1, 3-PD production yields were attained in an engineered strain of *E. coli* by using either glycerol or glucose as substrates [223, 224]. The temperature-induced introduction of cloned *dhaB* and *yqhD* genes, that derived from *Citrobacter freundii* and *E. coli* respectively, into a recombinant strain of *E. coli*, followed by coenzyme vitamin B12 supplementation, enhanced the 1, 3-PD production rates [225]. Further studies indicated an increase in the 1, 3-PD production yields after utilization of glycerol as a substrate, *C. butyrium dhaB1* and *dhaB2* genes, and *yqhD* from *E. coli*, in combination with improved fermentation procedures [224]. Studies on the corresponding bio-engineering of *S. cerevisiae*, showed that the introduction of *yqhD* and *dhaB* genes, that derived from *E. coli* and *K. pneumonia* respectively, through the utilization of *Agrobacterium tumefaciens* gene transfer mechanism, stabilized the gene expression in the 1, 3-PD synthesis from glucose [226].

2.4. Production of biocatalysts in leather industry.

Depilation and unhairing, the conventional beamhouse operations, constitute the crucial procedures in leather processing [227-229]. Although the traditional treatment with lime sulfide for the reduction of the S-S bridge enhances hair solubility [230, 231], it eventually: a) deteriorates the quality of leather, b) causes generation of toxic and large solid waste, c) produces high yields of Cr(VI), S^{2-}, and d) increases wastewater alkalinity [232]. Enzymes, as biocatalysts, improve the beamhouse operations by shortening the liming time and increasing the expansion of the fibers [233], reduce the sulfide consumption, and produce leather of softer texture. Moreover, the proteolytic potency of biocatalysts decreases the BOD/COD values in wastewater [234, 235]. Recently, scientists have focused their interest on the emergence of new economical fermentation methodologies for the introduction of novel dehairing enzymes, such as proteases from microorganisms [236, 237], aiming at the expansion of the green depilation cycle [238]. An indicative example is the group of keratinolytic proteases because of their ability to hydrolyze disulfide-rich and highly hydrophobic proteins including hair and feather [239]. Keratinolytic proteases act more efficiently than

other available *Bacillus sp.* derived alkaline proteases in depilation processes maintaining the quality of leather [240, 241] by exhibiting exceptional stability and resistance to the alkaline profile of detergents [242] and high concentrations of NaCl [243, 244] and to various reducing compounds such as S^{2-}, β-mercaptoethanol, and dithiothreitol [245, 246].

2.5. Production of anti-inflammatory virulence factors.

Chronic inflammatory responses of the intestine are responsible for the inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD) [247]. Adherent-invasive *Escherichia coli* (AIEC) are invasive pathogens responsible for the colonization of the intestinal mucosa and adherence to the intestinal epithelial cellular milieu, being able to survive and also replicate intracellularly, and provoke the release of Tumor necrosis factor alpha (TNF-α) [248]. AIEC possess various virulence-associated factors that can contribute to the AIEC invasion and adhesion abilities such as long polar fimbriae (LPF) and type 1 fimbriae, flagella, outer membrane vesicles (OMVs) and outer membrane proteins (OMPs) [247]. OMPC affects the expression of type 1 fimbriae and flagella [249], and synergistically with flagellin can operate as antigens modulating the bacterial adhesion to provoke CD [250]. Type 1 fimbriae may induce AIEC adhesion to the enteric epithelial cells [248].

2.6. Production of biodegradation agents of cyanide waste.

Microbial biodegradation is a valuable methodology for the management of cyanide wastes. Combined with the addition of organic nutrients it can induce the microbial growth leading to the formation of environmentally friendly materials like CO_2, formate, CH_4, and formamide [251, 252]. Despite the toxic profile of cyanide, sodium and potassium cyanide have been utilized as nitrogen and carbon sources in the majority of the microorganisms [253]. The biodegradative procedure of bacteria is more favored than fungal degradation since bacterial substrates can be effectively modified both at genetic and biochemical levels [254]. Indicative bacterial strains, fungi, yeasts and algae-like microorganisms, implemented in the process of cyanide degradation, are presented in Table 1 [255].

Table 1. Bacterial strains, fungi, yeasts and algae-like microorganisms implemented in the process of cyanide degradation.

Species	Role	Reference
Bacteria		
Pseudomonas putida	Uses nitriles and cyanides as efficient nitrogen and carbon sources	[256, 257]
Arthrobacter spp., *Alcaligenes* spp., *Bacillus pumilus, Burkhoderia cepacia, P. flourescens, P. putida, P. aeruginosa, P. pseudoalcaligenes* CECT5344	Implemented in the cyanide degradative process	[258-260]
Alcaligenes xylosoxidans subsp., *Klebsiella pneumoniae, Moraxella,* and *Serratia*	Implemented in the cyanide degradative process	[261, 262]
Agrobacterium tumefaciens SUTS1	Grows under high cyanide concentrations and exhibits high removal efficiency	[263]
Escherichia coli strains such as *Acinetobacter, Alcaligenes, Bacillus, Stemphylium loti*	Exhibit high cyanide metabolism	[264]
Burkholderia cepacia strain C-3	Utilizes cyanide providing nitrogen for growth and producing NH_3 and CO_2 as end products	[265]
Klebsiella oxytoca	Degrades cyanide into NH_3 and CH_4	[266]
Azotobacter vinelandii	Degrades tetracyanonickelate (TCN)	[267]
Fungi		
Cerrena unicolor (D30), *Clavariadelphus truncatus* (T192), *Ganoderma applanatum* (M105), *Ganoderma lucidum* (D33), *Schizophyllum commune* (T701), *Polyporus arcularius* (T438), *Trametes versicolor* (D22), *Schizophyllum commune* (D35), *Pleurotus eryngii* (M102)	Implemented in the process of cyanide degradation	[268]
Fusarium solani, Gloeocercospora sorghi, F. lateritium	Implemented in the process of cyanide degradation	[269, 270]
F. oxysporum N-10, *Cryptococcus humicolus* MCN2	Degrade complexes of thiocyanate	[271, 272]
Yeast		
Cryptococcus cyanovorans sp.	Isolated from cyanide polluted soil	[273]
Algae		
Arthrospira maxima, Chlorella spp., *Scenedesmus obliquus*	Implemented in the decomposition of cyanide containing compounds	[274]

2.7. Production of bio-absorbents of hazardous metal ions.

Despite a large amount of research conducted in the scope of heavy metal contamination and its harmful impact on animals and humans health, little progress has been achieved in the emergence of inexpensive and effective methodologies for the decontamination of foodstuffs and polluted water [275]. The

applied methods of heavy metal decontamination are classified into biological and non-biological processes. The non-biological processes include coprecipitation and precipitation, adsorption, and ion exchange whereas biological processes concern the adsorption of hazardous metal ions by plants or microorganisms [275]. Several studies have indicated the relatively expensive utilization of inactivated algal, bacterial and fungal biomass for the adsorption of heavy metal ions [276-279]. Various microorganisms such as *Streptomyces*, *Staphylococcus*, and *Flavobacterium* sp. possess enhanced metal-binding ability for Cd, Pb, Cu, Au, and Hg. Recent studies have elucidated the metal-binding activity and the detoxifying mechanisms of various lactic acid bacteria (LAB) [280, 281]. The cell membranes of LAB contain high concentrations of teichoic acid and peptidoglycan, two strong metal ion chelators and facilitators of biosorption processes [282, 283]. Gram-negative bacteria are less effective compared to Gram-positive bacteria due to their low adsorptive effectiveness, owed to their narrow peptidoglycan layer and low concentrations of teichoic acid within the cell walls [284]. LAB are considered gastrointestinally safe and they possess immunomodulatory, antimicrobial, antiallergic antioxidant and anti-diarrheal properties [285].

2.8. Production of bacterial exopolysaccharides (EPSs).

Only a limited number of the numerous novel bacterial EPSs studied have been utilized as industrially and commercially valuable biopolymers [286]. Indicatively, bacterial cellulose is an important biomaterial [287, 288], and xanthan gum represents an effective aqueous rheology modifier [289]. Additionally, the emergence of bacterial EPSs with advanced physical properties such as gellan gum or xanthan gum can lead to the direct replacement of algae or plant-derived polysaccharides including pectin or guar gum and carrageenan or alginate [290, 291]. Levan and bacterial cellulose possess remarkable properties of commercial perspective [292]. GalactoPol, from *Pseudomonas oleovorans* [293], and FucoPol, from *Enterobacter* A47 [294], are two novel bacterial EPSs with numerous properties. Until today, several EPSs have been isolated from extreme ecosystems and environments and have been studied as potential biopolymers [295, 296]. The most extensively investigated and commercially available EPSs are presented in Table 2 [297, 298].

2.9. Production of β-lactam antibiotics.

The hydrolytic procedure of penicillin G by penicillin G acylase (PGA) enzyme, results in the generation of 6-amino penicillanic acid (6-APA), an important intermediate for various β-lactam antibiotics [308-310]. Additionally, PGA is a key synthon of valuable antibiotics including cefadroxil and amoxicillin [311-313], acting as a catalyst of the coupling reaction between the corresponding nuclei and the activated amide or ester moieties [314, 315]. Yet, uncontrollable intermediate reactions lead to relatively insufficient production yields and the formation of undesirable byproducts [316, 317]. Recently, the implementation of *Alcaligenes faecalis* (AfPGA), *Bacillus megaterium* (BmPGA), and *Escherichia coli* (EcPGA) bacterial strains improved the synthetic outcome [318-322]. Furthermore, the incorporation of diversified mutants reduced the hydrolysis rates and improved the production yields of various antibiotics including ampicillin, cefprozil, cefaclor, and cephalexin [319, 321, 322].

Table 2. The most extensively investigated and commercially available EPSs.

EPS	Applications	Components	Producer bacterial strains	References
Xanthan gum	Food, petrochemical pharmaceutical, agricultural, cosmetic industries	Glucose, Glucuronic acid, Mannose, Pyruvate, Acetate	*Xanthomonas*	[299, 300]
Sphingans (Diutan, Gellan, Rhamsan, Welan)	Food, pharmaceutical industries Utilized in gel electrophoresis and as agar substitutes	Rhamnose, Mannose, Glucuronic acid, Glucose, Glycerate, Acetate	*Sphingomonas*	[301]
Alginate	Food hydrocolloid Medicine	Guluronic acid, Mannuronic acid, Acetate	*Azotobater*, *Pseudomonas*	[291]
α-Glucans (Alternan, Dextran, Mutan, Reuteran)	Food, pharmaceutical industries Chromatographic media	Glucose	*Lactobacillus*, *Leuconostoc*, *Streptococcus*	[302, 303]
γ-glucans (Cellulose, Curdlan)	Cellulose	Glucose	*Achromobacter*, *Aerobacter*, *Agrobacterium*, *Azotobacter*, *Gluconacetobacter*,*Rhizobium*, *Salmonella*, *Sarcina*	[287, 304]
	Food industry (indigestible fiber) Biomedicine			
	Curdlan			
	Heavy metal bioabsorption Concrete additive Pharmaceutical industry			
Hyaluronan	Medicine Solid culture media	Glucuronic acid, Acetylglucosmine	*Pseudomonas aeruginosa*, *Streptococci* A and C group	[288, 305]
Succinoglycan	Food industry Oil recovery	Glucose, Acetate, Pyruvate, Succinate,	*Agrobacterium*, *Alcaligenes*,	[306]

EPS	Applications	Components	Producer bacterial strains	References
		Galactose	*Pseudomonas*, *Rhizobium*	
Levan	Food industry (prebiotic) Cosmetic industry Medicine	Fructose	*Aerobacter*, *Bacillus*, *Erwinia*, *Pseudomonas*, *Rahnella*, *Streptococcus*, *Zymomonas*	[288, 307]

2.10. Production of bio-surfactants.

Microorganisms can grow by using various organic substances as energy and carbon producing substrates. The potential insolubility of a hydrocarbon substrate urges microorganisms to facilitate their cell diffusion by generating specific compounds, the biosurfactants. Indicatively, some bacterial strains can excrete ionic surfactants for the emulsification of hydrocarbons inside the growth media such as rhamnolipids from *Pseudomonas* sp. and sophorolipids from *Torulopsis* sp [323]. Rhamnolipids are a group of bio-surfactants which mainly consist of a rhamnose sugar moiety combined with β-hydroxylated fatty acid chains. They have various applications in the fields of food, petrochemical, bioremediation and agricultural industries. *Pseudomonas aeruginosa*is the key producer of rhamnolipids. However, its pathogenic behavior can cause health and safety concerns during large-scale applicability and production. Three crucial enzymes (RhlA, RhlB, RhlC) are indispensable for the biosynthesis of rhamnolipids and are expressed exclusively in *Burkholderia* sp. and *Pseudomonas* sp. but have also been produced in various non-pathogenic host bacteria [324, 325]. Other types of microorganisms such as *Candida tropicalis*, *Candida lipolytica*, *Rhodococcus erythropolis*, and *Mycobacterium* sp. can change the structural characteristic of their cellular walls by producing non-ionic surfactants or lipopolysaccharides inside the cellular walls [323]. There are also lipopolysaccharides including emulsan from *Acinetobacter* sp. [323] or lipoproteins including subtilisin and surfactin from *Bacillus subtilis* [323]. Other useful biosurfactants are a) Ornithinlipides from *Gluconobacter cerinus*, *Thiobacillus ferroxidans*, and *Pseudomonas rubescens*, b) Mycolates Corynomycolates from *Corynebacteria* sp., *Mycobacteria* sp., *Nocardia* sp., and *Rhodococcus* sp. [323].

2.11. Production of bio-detergents.

Proteases are valuable enzymes responsible for the breakage of protein peptidic bonds through water addition across the peptidic bonds. There are four major categories of proteases: cysteine proteases, serine proteases, metalloproteases, and aspartic proteases. Their differences rely heavily on the structural and functional diversities of the moiety at the active site and the corresponding catalytic activity. They present neutral, acidic, or alkaline profile. Proteases derive from animals, microorganisms, and plants. However, proteases from fungi and bacteria possess improved characteristics adequate for industrial exploitation [326]. Lipases constitute a group of hydrolyzing enzymes that can cause the breakage of fatty acid esters or acyl glycerides at the oil-water interface. Lipases are the 3rd major category of the industrially derived enzymes and they also derive from microorganisms [327]. The enzyme-containing detergents ensure better detergency compared to the conventional products, reduce the required amounts of energy during the cleansing processes and prevent the stain redeposition onto a substrate due to the enhanced steric hindrance and electrostatic repulsion [328, 329]. The absence of enzymes results in limited stain removal, permanent oxidized residues, as well as denaturing provoked by drying and bleaching agents [330]. The corresponding proteases, utilized in the procedure of detergent formulation, can remove proteinaceous stains. Amylases remove food stains based on starch. Additionally, cellulase can remove encrusted soil from cellulose fibers, whereas lipases can remove lipidic stains [329]. Indicatively, the coproduced α-amylase and alkaline protease from *Bacillus* sp. SMIA-2 could remove egg yolk and tomato sauce stains from clothing with the simultaneous utilization of a commercial detergent [331]. Moreover, a mixture of protease and lipase from *Geobacillus* and *Bacillus licheniformis* removed protein and fat stains from clothes with and without the presence of a commercial detergent [332]. Research studies proved that the compatibility of the stable at alkaline pH proteases (eg. proteases from *Microbacterium luteolum* and *Bacillus* sp.) with a detergent and their proteolytic potency depend on the presence of specific components in the composition of the detergent, such as bleaches, oxidizers, and surfactants [333-335]. The proteases that are compatible with the majority of the detergents derive from microorganisms isolated from water, soil, mud, or mangrove depositions [329]. Sodium carbonate constitutes the basic source of natural alkalinity and also enhances the alkalophilic growth of the microorganisms [329]. The *Aspergillus* and *Bacillus* species are the most common producing bacterial strains of detergent-compatible proteases because of their fast, inexpensive and effectively bio-engineered growth procedures [336, 337]. The adequate method for the production of proteases and lipases is the submerged fed-batch and batch fermentation, as in the case of *Alcaligenes* sp. (MTCC 9730) [338]. Utilization of the resulting by-products reduces the cost of the fermentation procedure and prevents the disposal of environmental pollutants. Indicatively, agro-based and lignocellulosic by-products from agro-industries and dairies were utilized for the generation of proteases compatible with detergents, from *Aspergillus terreus* [339], *Aspergillus niger* [338] and *Bacillus circulans* MTCC7906 [340]. Correspondingly, the detergent-compatible lipases are produced from *Bacillus*, *Acinetobacter*, *Burkholderia*, *Rhodococcus*, *Streptomyces*, *Pseudomonas*, *Aspergillus*, *Staphylococcus*, *Cryptococcus*, *Talaromyces*, *Trichosporon* and *Fusarium* bacterial strains [337].

2.12. Production of bio-polyesters.

Polyhydroxyalkanoates (PHAs) constitute a group of structurally diverse biopolymeric macromolecules synthesized under growth conditions of restricted nutrient availability by several Gram-

positive and Gram-negative bacteria. PHAs are accumulated intracellularly as storage materials of energy and carbon [341, 342]. PHAs are the main products of several renewable resources via fermentation procedures and are considered eco-friendly biomaterials with various biotechnological applications (Figure 2) [343-346]. The first discovered PHA was the homopolymer poly(3-hydroxybutyric acid), P(3HB) from *Bacillus megaterium*. This discovery was later followed by the synthesis of 3-hydroxyoctanoic acid (3HO), 3-hydroxyhexanoic acid (3HHx), and 3-hydroxyvaleric acid (3HV) by axenic cultures of *Alcaligenes eutrophus*, *Pseudomonas oleovorans*, and *Bacillus sp.*, respectively [341]. Recent progress in the molecular biology and biochemistry of PHA bio-synthetic and bio-engineering procedures has provoked the emergence of novel PHA biosynthetic genes from various bacteria. Indicatively, research studies have shown that recombinant *Escherichia coli* harboring biosynthetic PHA genes from *Ralstonia eutropha* yielded the homopolymer P(3HB) [341]. PHA synthases constitute the most important enzymes for PHA biosynthesis. There are four classes (classes I- IV) of PHA synthases which are distinguished according to their subunit compositions and substrate specificities [341]. *Ralstonia eutropha* and *Alcaligenes latus* are indicative producing species of Class I PHA synthases. Representative examples of Class II PHA synthases are produced in *Pseudomonas sp.* 6-19 and *Pseudomonas sp.* 61-3. Some *Pseudomonas* species are characteristic types of PHA synthases Class III producers, whereas class IV PHA synthases are mostly found in *Bacillus* strains [341, 342]. The main body of P(3HB) polymer can be modified through the employment of naturally derived PHA synthases from *Alcaligenes latus*, *Allochromatium vinosum*, and *Ralstonia eutropha*. A distinct class of PHA synthases has been synthesized from *Thermus thermophilus* bacterial strain [347].

2.13. Production of quercitols.

Quercitols constitute the cyclitol family of deoxy analogs of inositols, including 16 possible quercitol stereoisomers. However, only 6 of them have been synthesized or identified in nature (Table 3). *Myo*-inositol is the most studied cyclitol and its biosynthetic pathways in microorganisms including *Bacillus subtilis* are well-established [348].

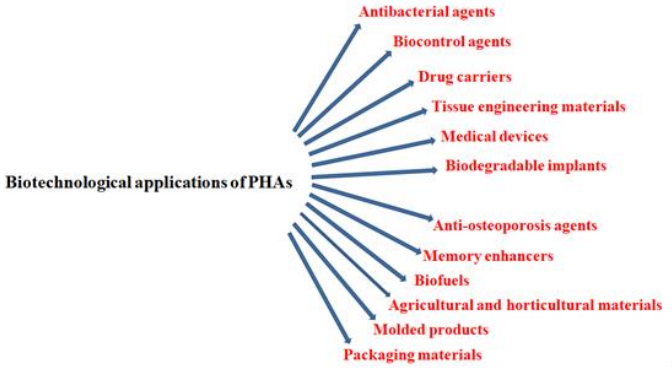

Fig. 2. Biotechnological applications of PHAs.

Studies on the biotransformation of *myo*-inositol by utilizing *Salmonella typhimurium* indicated a three-step procedure: i) an initial *myo*-inositol oxidation by inositol dehydrogenase to *scyllo*-inosose, ii) a subsequent dehydration by a dehydratase, and iii) a reduction by several reductases or dehydrogenases to three quercitols as the final products [348, 349]. It is reported that the main biosynthetic enzymes in the assimilation procedure of quercitols belong to the family of 2-deoxy-*scyllo*-inosose synthases (DOIS) and are isolated from microorganisms such as the genera *Arthrobacter*, *Pseudomonas*, and *Burkholderia* [350].

Table 3. Naturally-occuring and synthetic stereoisomers of quercitols [351].

Naturally occuring and synthetic stereoisomers of quercitols
(−)-*vibo*-quercitol(1L-1,2,4/3,5-cyclohexanepentol)
***scyllo*-quercitol (2-deoxy-*myo*-inositol:1,3,5/2,4-cyclohexanepentol)**
(+)-*proto*-quercitol (1L-1,3,4/2,5-cyclohexanepentol)
(−)-*proto*-quercitol (1D-1,3,4/2,5-cyclohexanepentol)
(+)-*epi*-quercitol (1D-1,2,3,5/4-cyclohexanepentol)

3. CONCLUSIONS

Until today, numerous outstanding achievements have been accomplished in the area of bio-engineered microbial cell factories for the manufacture of high-added value biomaterials. However, continuous efforts for the emergence of new ways and implements towards the exploration of new microbial host cells, the creation of novel or the improvement of already functional heterologous catalytic enzymes, and the evolution of novel utilitarian proteomics and genomics will expand the variety of products which are synthesized by microbial cell factories. Furthermore, the discovery of novel biosynthetic approaches for de novo genomic and bio-synthetic pathways will contribute to this effort rendering biology as effective as synthetic chemistry, expanding the renewable energy production standards of the emerging biomaterials. In the future, innovative metabolic bio-engineering implements are anticipated to produce a new evolutionary generation of microorganisms that will operate as bio-synthetic platforms of programmable and extremely robust bio-machines.

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