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Review

Industrial Biotechnology Today: Overview of Main Products

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Abstract: Industrial microbiological biotechnology is one of the key areas of modern economy, which is actively developing globally and also in Russia. It focuses on the application of biological processes and various organisms, including bacteria, fungi, microalgae and their metabolites, to solve significant economic and environmental problems. Microbiological biotechnology encompasses the production of a variety of products that have wide applications in the medical, agricultural, food, biofuels, and biomaterials industries. The present review focuses on the analysis of the main products of industrial microbial biotechnology. Particular attention is paid to modern advances in the production of biopolymers, enzymes, lipids, antibiotics, amino acids and other products using microorganisms.

Keywords: industrial biotechnology; microbiology; lipid; biopolymer; enzyme; amino acid; organic acid; antibiotic; vitamin; hormone

Contents

Introduction

Industrial biotechnology is one of the key areas of modern science and economics that develop at the intersection of biology, chemistry and engineering technologies. It is based on the use of biological processes and organisms, such as bacteria, fungi, microalgae and their metabolites, to solve urgent economic and environmental problems.

The global industrial biotechnology market was valued at over USD 400 billion in 2020 and is further expected to grow at an average of 7-10% in the coming years [1]. The main segments of the global industrial biotechnology market include such areas as biopharmaceuticals (production of drugs using microorganisms and cells), biopolymers (use of natural sources to create environmentally friendly packaging materials), biofuels (production of bioethanol and biodiesel to replace fossil fuels), and industrial enzymes used in the food and cosmetic industries [2]. The biotechnology market in Russia lags far behind the global indicators, but it has demonstrated positive dynamics in recent years. According to some estimates, the Russian biotechnology market is about 35-40 billion rubles, and is expected to grow by 19-22% in the next five years [3]. Despite the growth, the Russian biotechnology industry faces a number of challenges, namely: lack of investments, high barriers to market entry, and insufficient cooperation between research institutions and industry [4]. The main challenges is also the need to create an effective regulatory framework and to develop strategies to attract investment.

Industrial biotechnology processes can be divided into two main groups: production of biomass and production of metabolic products. But this classification does not take into account the key technological features of industrial biotechnology. It is important to analyze the stages and specificity of biotechnological production taking into account the final goal of the process. Figure 1 demonstrates a biotechnological production scheme.

The first step in any industrial process is to select an efficient producer by screening strains from various environments. It is also possible to use modern technologies such as CRISPR/Cas9 and genetic engineering, which allow modifying the metabolism of microorganisms to increase their ability to synthesize specific compounds (e.g., antibiotics or biopolymers) [5]. The next step is fermentation, which involves the use of microorganisms to convert carbon sources into various products such as enzymes, acids, alcohols and polymers. An example is the use of Saccharomyces cerevisiae to produce ethanol from sugars. In this case, it is necessary to ensure optimal conditions for the cultivation of yeast cells (temperature, pH and substrate ratio), which are critical for obtaining the desired yield of the target product [6]. One of the important economic components of the industrial fermentation process is the use of inexpensive and renewable carbon sources, such as agricultural waste or industrial by-products. Khan, M. I et al. demonstrated that bacteria of the genera Rhodococcus and Pseudomonas can utilize plant wastes to produce bioplastics and biofuels, which reduces the cost of production and improves the environmental conditions [7]. In addition, modern bioreactors are always equipped with sensors to monitor various cultivation parameters, which also contributes to maximizing the yield of target products and ensures high efficiency of the processes. López N. I. et al. were able to increase the yield of polyhydroxyalkanoates during continuous cultivation by optimizing the culture growth parameters [8]. At the final stage of industrial production, efficient extraction and purification of the target products must be carried out, which often involves such methods as centrifugation, precipitation, and chromatography [9].

Industrial biotechnology has great potential to address global challenges such as food security, development of clean energy sources and creation of new materials with improved properties. However, to fully unlock such its potential, further research and development, as well as favorable conditions for the introduction of biotechnological solutions into practice are needed. The advances in molecular biology, genetic engineering and microbiology open up new horizons for the creation of innovative products that can be applied in medicine, agriculture, ecology, food and energy industries. This review discusses the main types of industrial biotechnology products that have applications in various human endeavors. Special attention is paid to biopolymers, enzymes, biologically active substances and other products of biotechnological proesses.

Industrial biotechnology products can be segmented in different ways, for example, according to their type, source, or application area. The following types of industrial biotechnology products will be presented in this section: biopolymers, enzymes, amino acids, organic acids, lipids, antibiotics, vitamins, and hormones.

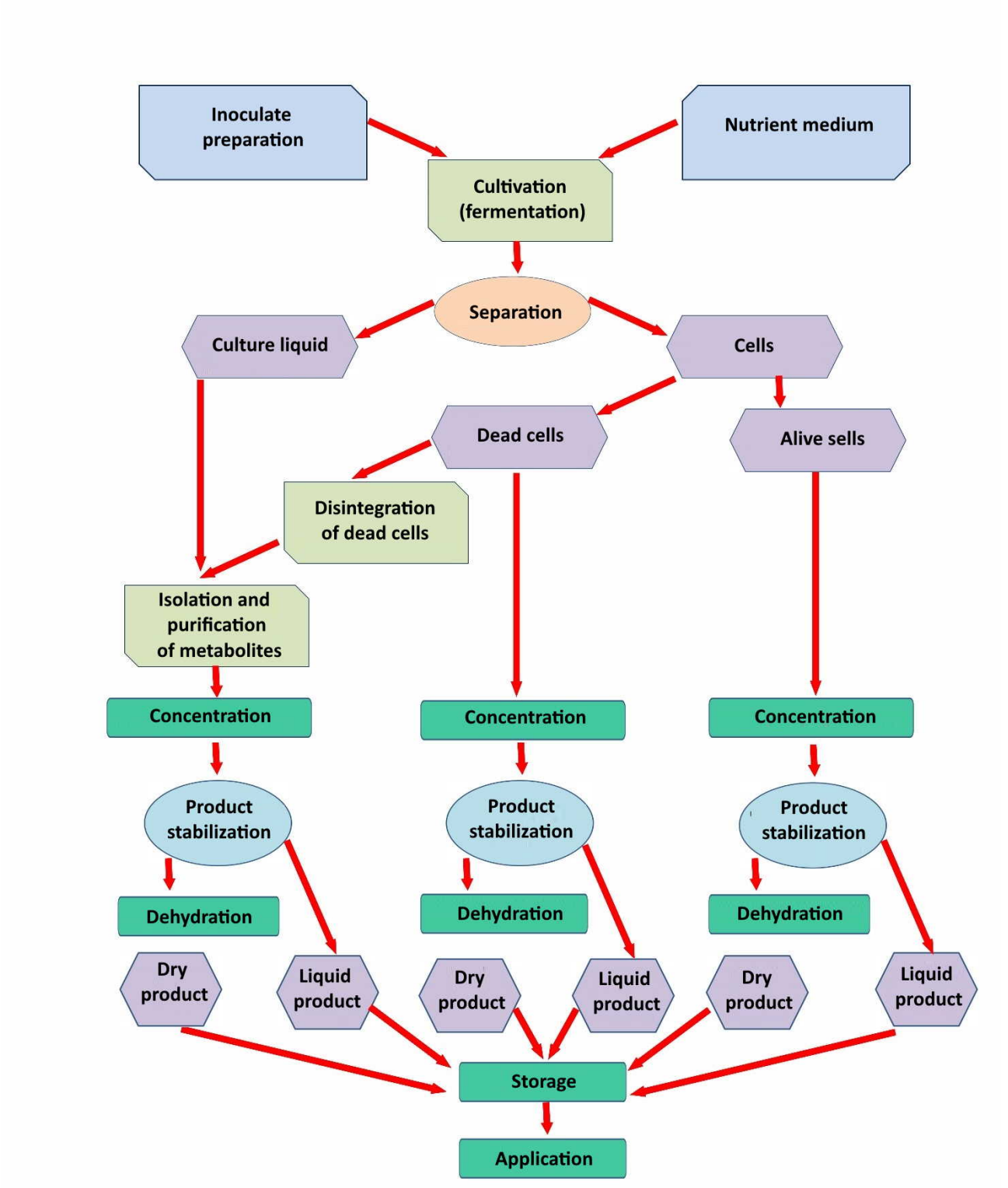

Figure 1. Biotechnological production scheme.

1. Biopolymers and their applications

Biopolymers synthesised by microorganisms represent an important class of materials that are widely applied in various industries, including medicine, food, agriculture and biotechnology. Polyhydroxyalkanoates, exopolysaccharides, chitosan, alginates and other polymers have unique properties including biocompatibility, biodegradability and the ability to be produced from renewable resources.

1.1. Biopolymers produced by bacteria

Bacteria are one of the most studied sources of biopolymers due to their ability for high levels of biosynthesis under strictly controlled conditions.

Polyhydroxyalkanoates have more than 150 varieties and are one of the most studied classes of biopolymers synthesised by the bacteria *Cupriavidus necator*, *Schelegelella thermodepolymerans*, *Pseudomonas* spp., *Ralstonia eutropha* and *Bacillus* spp. Polyhydroxyalkanoates accumulate in microbial cells as storage materials at the deficiency of nutrients, such as nitrogen or phosphorus, and in the presence of excess carbon [10]. These polymers can be used in the production of packaging materials, medical implants, biodegradable films, and in agriculture [11, 12]. Polyhydroxyalkanoates are produced inductrially in Brazil, Austria, and China where various organic substrates are used including agricultural waste.

Exopolysaccharides such as xanthan and hyaluronic acid are produced by bacteria of the genera *Xanthomonas*, *Leuconostoc* and *Streptococcus*. Xanthan, produced by aerobic fermentation of sugars, is widely used in the food industry as a thickener and stabilizer, while hyaluronic acid, due to its moisturizing and regenerating properties, is applied in cosmetics and medicine [13]. Dextran and levan synthesized by bacteria of the genera *Leuconostoc*, *Lactobacillus*, *Streptococcus*, *Aerobacter* and *Weissella* [14] are used in the pharmaceutical industry, including the production of plasma substitutes and delayed drug release systems [15]. Exopolysaccharide curdlan is obtained by deep fermentation of bacteria of the genera *Rhizobium*, *Agrobacterium*, *Alcaligenes*, *Cellulomonas*, and *Bacillus* [16]. Due to its gelling ability, curdlan is used in food industry and biomedical research.

1.2. Biopolymers produced by fungi and yeasts

Yeasts are widely used in the production of polysaccharides such as β-glucans and mannans.

Chitosan, a chitin derivative, is synthesized by fungi *Aspergillus niger* and *Mucor rouxii*. This biopolymer demonstrates antimicrobial, antioxidant and biocompatible properties, which makes it promising for use in medicine, e.g. as wound coatings and for drug delivery [17].

β-glucans produced by the yeasts *Saccharomyces cerevisiae*, *Candida albicans* and *Kluyveromyces lactis*, and by the fungi *Pleurotus ostreatus* have immunomodulatory properties and are used in production of food supplements and in medicine as pharmaceuticals imporving the work of immune system [18].

Mannan-oligosaccharides synthesized by yeast *S. cerevisiae* are used as prebiotics in animal feeds to improve intestinal health and immune response [19].

Fucin is a biopolymer synthesized by some species of fungi, including those of the genera *Fusarium* and *Aspergillus*. This biopolymer is formed during metabolism in fungi and is released into the environment as exopolysaccharide. Fucin production depends on cultivation conditions such as nutrient medium composition, pH, temperature, and aeration [20]. Optimization of these parameters can increase the yield of the biopolymer and make its inductrial production economically viable [21]. Fucin is biodegradable and therefore attractive for use in various areas including medicine (e.g., development of biodegradable films and drug delivery systems) and agriculture (e.g., production of biodegradable packaging materials) [22].

Pullulan is mainly obtained as water-soluble polysaccharide from the yeast-like fungus *Aureobasidium pullulans*. Other known fungi producing pullulan are *Tremella mesenterica*, *Cryphonectria parasitica*, *Teloschistes flavicans*, *Rhodotorula bacarum*, *Cytaria harioti* and *C. darwinii* [23]. Pullulan is widely used in various industries including pharmaceuticals, cosmetics, biomedicine, and food production. Due to its high adhesive properties, it is in demand in paper production.

1.3. Biopolymers produced by algae

Alginates synthesized by brown algae (e.g., *Laminaria* spp.) are widely used in the food industry as thickeners and stabilizers, and in pharmaceutical industry to create hydrogels and wound coatings [24].

Carrageenans derived from red algae (e.g., *Chondrus crispus*) are used in food industry to improve the texture of products and in pharmaceuticals to create dosage forms and microcapsules [25]. Industrial production of alginates and carrageenans is actively developing in countries with rich aquaculture, such as Indonesia and Norway.

Due to their unique properties and ability to be produced from renewable resources, biopolymers help to reduce dependence on fossil resources and thereby reduce the negative impact on the environment. In general, industrial production of biopolymers requires optimization of microbial cultivation conditions, including strain selection, nutrient medium composition, pH, temperature, and aeration. Modern biotechnological approaches such as metabolic engineering and CRISPR/Cas9 can improve microbial productivity and reduce production costs [26]. In addition, further research in metabolic engineering and optimization of production processes will expand the applications of biopolymers and make them more accessible for industrial use.

2. Classification of enzymes and their application in various branches of industrial biotechnology

Environmental safety requirements for most industrial areas are constantly growing. That is why in various industrial areas chemical catalysts are replaced by enzymes, and primarily of a microbiological origin. The latter is due to the economic component of the fermentation process. In addition, microbial enzymes have some advantages compared to enzymes of plant and animal origin, amomg them a wide variety of microbial producers, easy production of enzyme in fermenters, the possibility of continuous cycles (daily), easy controllability of the process, etc.

Despite the long history of enzyme technology applications, large-scale production of enzymes in the form of purified and well-characterized preparations became possible only with the development of recombinant DNA technology. They have become widely used in a variety of industrial products and processes, including chemical, detergent, textile, food, feed, tanning and pulp and paper industries.

The development of techniques such as protein engineering and site-directed mutagenesis provides an opportunity to design enzymes with novel properties [27].

Industrial technologies of enzyme production using microorganisms differ depending on the type of the used producer and production conditions.

2.1. Bacterial enzymes

The bacteria *Bacillus subtilis*, *Bacillus licheniformis* and *Escherichia coli* are often used to obtain enzymes such as amylases, proteases and lipases [28] mostly by submerged fermentation method, where the cell mass is cultured in a liquid nutrient medium under high aeration. This method provides rapid bacterial growth and high enzyme yield [29]. The enzymes are isolated most often by centrifugation and protein precipitation.

2.2. Fungal enzymes

Half of the commercially produced enzymes are of fungal origin due to the easy cultivation of fungi in bioreactors and high yields [30]. The fungi *Aspergillus. niger*, *Trichoderma reesei*, and *Penicillium* spp. are the major producers of cellulase, pectinase, and amylopectinase [31]. The enzymes are most commonly obtained by surface fermentation of fungal cells on solid nutrient media such as wheat bran or rice hulls. This method is effective for production of exoenzymes [32]. The submerged fermentation method is also used to cultivate fungi in liquid media with high carbohydrate content [33].

2.3. Microalgae enzymes

Microalgae such as *Chlorella vulgaris* and *Spirulina platensis* are used to produce lipases and phosphatases [34]. Microalgae synthesize enzymes in open or closed photobioreactors where they grow in liquid cultures under optimal light and in the presence of carbon dioxide. Since some algae act as autotrophs, their enzymatic productivity depends on light intensity and CO_2 availability, which requires the use of specific bioreactors [35].

The emergence of new applications of enzymes is leading to an increased demand for industrial enzymes, and the industry is responding with a steady stream of innovative products. Among the industrial enzymes currently in use, hydrolases such as proteases and lipases are the most common and are widely used in various industries e.g. in production of detergents, dairy products, and chemicals. Carbohydrases, especially amylases and cellulases, represent a significant group of enzymes [36-37].

Enzymes can be classified according to the main directions of their application: technical enzymes (used in the production of synthetic detergents; in the textile, leather, pulp and paper industries; in the production of biofuels); enzymes for the food and beverage industry; feed enzymes [38]. Table 1 summarizes the enzymes most frequently used in various industries.

2.4. Proteases

Proteases (proteinases, proteolytic enzymes) are a group of enzymes capable of hydrolyzing peptide bonds in proteins. They are divided into exopeptidases (cleaving end peptide bonds) and endopeptidases (acting within proteins). Proteases are classified according to substrate specificity, catalytic mechanism, pH optimum, and other properties.

Subtilisins are serine proteases actively used in detergents due to their stability and low substrate specificity [40]. These ptoteases are produced by *Bacillus* spp. bacteria; they are active in the pH range of 6-11, with an optimum of 9-11. In 1985, the first genetically modified subtilisin, less sensitive to oxidation by hydrogen peroxide, was created [41]. Subsequent studies improved such subtilisin properties as thermostability, activity in organic solvents and at extreme pH [42].

Proteases are applied in the food industry to hydrolyze proteins and produce nutritious protein hydrolysates [43]. Acidic proteases used in the dairy industry replace rennet enzyme in cheese production [44]. Alkaline proteases are used to process waste materials such as keratinous materials and in production of feed [45]. In the leather industry, they replace chemicals for soaking hides and removing hair, which reduces contamination and energy costs [46].

Research on proteases is mainly focused on the development of new enzymes with improved characteristics and new applications. These works represent a significant potential for the improvement of industrial processes [47-48].

2.5. Lipases

Lipases catalyze the hydrolysis of triglycerides to glycerol and fatty acids; they are widely distributed in nature. Lipases possess a catalytic triad (serine, histidine, and aspartate) and interfacial activation, which makes them highly efficient in applications with hydrophobic surfaces [49]. Lipases also perform esterification and transesterification, and are therefore actively employed in the food industry, production of biofuels and detergents, and in organic chemistry [50-51].

In the food industry, lipases are used to transesterify palm oil to create cocoa butter substitutes, synthesize flavor compounds, remove phospholipids, and create low-calorie products. Immobilized lipases are economically advantageous due to the possibility of their multiple uses [52]. In production of detergents used to remove grease stains, the best choice are enzymes resistant to alkaline environments such as lipases produced by *Thermomyces lanuginosus* and *Pseudomonas mendocina* [53]. In the leather industry, lipases used to degrease skins help to reduce the environmental pollution [54].

Table 1. Enzyme preparations and scope of their application [39].

Enzyme, class (EU)	Source of production	Scope of application
Glucose oxidase (EC 1.1.3.4)	*Aspergillus* spp.	Detergents, bakery industry
Laccase (EC 1.10.3.2)	*Myceliophthora spp., Trametes* spp., *Thielavia* spp.	Detergents, textile industry
Catalase (EC 1.11.1.6)	*Aspergillus spp., Scytalidium* spp., *Thermoascus* spp.	Textile industry
Lipase (EC 3.1.1.3)	*Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Humicola* spp., *Rhizomucor* spp., *Thermomyces* spp.	Detergents, leather industry, pulp and paper industry, biocatalysis, bakery industry, dairy and oil and fat industries
Pectinase (EC 3.1.1.11; EC EC 3.2.1.15; EC 4.2.2.10)	*Aspergillus* spp.	Juice and wine production
Phospholipase (EC 3.1.1.32; EC 3.1.4.1)	*Aspergillus spp., Fusarium* spp., *Thermomyces* spp.	Modification of fats
Hemicellulase (EC 3.1.1.73)	*Aspergillus* spp.	Juice and wine production
Phytase (EC 3.1.3.8; EC 3.1.3.26)	*Aspergillus* spp., *Peniophora* spp.	Feed production
α-amylase (EC 3.2.1.1)	*Aspergillus* spp., *Thermoactinomyces* spp.	Pulp and paper industry, bakery industry, brewing industry, juice and wine production
Amyloglucosidase, glucoamylase (EC 3.2.1.3)	*Aspergillus* spp., *Talaromyces* spp., *Trichoderma* spp.	Detergents, biofuel production, sweetener production, juice and wine production
Cellulase (EC 3.2.1.4; EC 3.2.1.91)	*Humicola* spp., *Myceliopthora* spp., *Thielavia* spp.	Detergents, textiles, biofuels, pulp and paper industry
β-glucanase (EC 3.2.1.6)	*Thermoascus* spp., *Trichoderma* spp.	Feed production, biofuel production, brewing industry
Xylanase (EC 3.2.1.8)	*Actinomadura* spp., *Aspergillus* spp., *Thermomyces* spp., *Trichoderma* spp.	Pulp and paper industry, bakery industry, brewing industry, fodder production
Lactase	*Aspergillus* spp., *Kluyveromyces* spp.	Dairy industry
Pullullanase	*Hormoconis* spp.	Biofuel production, alcohol production
Protease	*Aspergillus* spp., *Cryphonectria* spp., *Fusarium* spp., *Rhizomucor* spp., *Trichoderma* spp.	Meat and dairy industry, leather industry, detergents, dishwashing detergents, food industry, animal feed additives, leather processing, pharmacology and drug production

In biodiesel production, lipases act as an environmentally friendly alternative to chemical catalysts, providing high product purity and efficient glycerol separation. Their high cost is partially decreased due to immobilization, the use of recombinant DNA and protein engineering [54-55]. Lipases are also in demand in organic chemistry for the synthesis of chiral compounds inpharmaceuticals and agrochemicals.

2.6. Amylases

Amylases (glycoside hydrolases) hydrolyze α-1,4-glycoside bonds in starch, breaking it down to sugars. Microbial amylases are divided into exo- (glucoamylases and β-amylases) and endoamylases (α-amylases). Glucoamylases hydrolyze α-1,4 and α-1,6 bonds, releasing glucose, while β-amylases release maltose [56]. Endoamylases break internal bonds in starch to form oligosaccharides. Alpha-amylases, thermostable enzymes derived from fungi and bacteria, are used in food, textile, paper and fermentation industries [57-58]. Amylases are in demand due to their stability and activity under extreme conditions. For example, *Bacillus* sp. strains (*B. subtilis*, *B. licheniformis*) produce enzymes active in the pH range of 1.0-11.5 and temperatures of 25-90 °C, which is suitable for industrial processes.

Amylases are used to enzymatically liquefy and saccharify starch, replacing the less efficient acid hydrolysis. Amylases are also used in ethanol production: α-amylases break down starch into sugars, which are then fermented into ethanol by *S. cerevisiae*. In detergents, α-amylases help to remove starch even at low temperatures [58].

In the paper industry, α-amylases such as Amizyme® and Thermamyl® reduce the viscosity of starch for paper gluing, which improves paper stiffness and quality. In baking, enzymes break down starch into dextrins, which increases volume, improves texture, flavor, and color and extends the shelf life of bread [59].

2.7. Pullulanases

Polysaccharides such as starches are polymers of D-glucopyranose with α-1,4 bonds and α-1,6 branching bonds. Complete hydrolysis of starch requires enzymes capable of cleaving both types of bonds. Pullulanases, widely distributed in nature, hydrolyze α-1,6 bonds by breaking the branching bonds in starch, amylopectin, and glycogen. Type I pullulanases (branching removal enzymes) act only on α-1,6 bonds, while type II pullulanases (amylopullulanases) can hydrolyze both α-1,6 and α-1,4 bonds [60]. For example, in the food industry, pullulanases are used to form maltotriose syrup, which has mild sweetness, low freezing point and moisture retention properties. Such syrup is used in the production of desserts, baked goods, beer and pharmaceutical products, including solutions for intravenous administration.

2.8. Pectinases

Pectinases (pectinolytic enzymes) hydrolyze pectin substances - plant polysaccharides with a framework of α-D-galacturonate links linked to α-1,4. They are divided into three groups: protopectinases (convert insoluble protopectin into soluble pectin), esterases (remove methoxy esters), and depolymerases (break α-1,4-linkages in pectin) [61]. The most common application of pectinases is in the extraction and clarification of fruit juices, where they degrade pectins, facilitating pressing, clear juice production and removal of turbidity. Cellulases and xylanases are also used to improve the efficiency of this process [62].

Pectinases are actively used in the textile industry, where together with other enzymes (amylases, lipases) they remove adhesives before dyeing fabrics, thus reducing the use of aggressive chemicals [63]. In addition, these enzymes are used to treat cotton, replacing alkaline treatment with the more environmentally friendly biopecanation, which improves water absorption and preserves fibers. In bast fibers, pectinases in combination with xylanases effectively remove gum thus reducing the adverse effect on the environment.

Pectinases are also used for the enzymatic treatment of wastewater from the plant food industry, promoting its decomposition [64]. In feed additives, enzymes increase nutrient digestibility in animals and reduce waste. Further studies on their stability, specificity and properties are needed to optimize the use of pectinases.

2.9. Xylanase

Plant biomass contains about 23% lignin, 40% cellulose and 33% hemicellulose, including xylan. Xylan is a heteropolymer with D-xylose in the backbone, branched L-arabinose and glucuronic acid. Its hydrolysis requires a complex of enzymes such as endoxylanases, β-xylosidases, esterases, etc. Endoxylanases cleave the main chain of xylan and β-xylosidases convert xylooligosaccharides into xylose. Xylanases are actively produced by *Aspergillus* and *Trichoderma* fungi [65].

The main application of xylanases is in the pulp and paper industry to remove lignin from kraft pulp, which reduces the use of chlorine bleaches and improves pulp quality. Enzymes are also used to improve dough properties in baking, increase bread volume and prolong its freshness [66]. In animal feed production, xylanases hydrolyze arabinoxylans in cereals, reducing their viscosity in the intestine and promoting weight gain [67].

In agriculture and the food industry, xylanases help to process wastes, converting xylan to xylose, which can be used in wastewater or to produce oligosaccharides. These enzymes also contribute to the synthesis of phytosterols, phytoalexins and alkylglycosides applied as surfactants [68].

2.10. Laccases

Laccases also known as benzenediol oxygen oxidoreductase enzymes are able to oxidize a variety of organic substrates including ortho- and para-diphenols, aminophenols, polyphenols, polyamines, lignins and aryldiamines, as well as some inorganic ions. The laccase molecule is a glycoprotein, usually dimeric or tetrameric, with four copper atoms on each monomer distributed in three redox reaction centers. Laccases are widely used in biobleaching, delignification of cellulose, removal of dyes and pollutants, creation of biosensors, biofuel cells, and in food and textile industries [69].

In the pulp and paper industry, they provide environmentally friendly delignification and clarification without the use of chlorine. In the textile industry, laccases are used to degrade synthetic dyes and bleach fabrics. In bioremediation, they degrade xenobiotics including polycyclic hydrocarbons [69].

In the food industry, laccase are used to remove phenols from beverages (juices, beer, wine), improving their transparency. They also affect the properties of dough, increasing its stability by crosslinking biopolymers [69].

2.11. Transglutaminases

Transglutaminases are a class of enzymes that participate in the catalytic formation of a covalent bond between the free amino group of lysine (acyl acceptor) and the gamma-carboxamide group of glutamine (acyl donor) in proteins and peptides. This leads to modification of proteins by cross-linking intra- or intermolecularly, which in turn improves the end use of the protein [70]. In addition to cross-linking, transglutaminases are also capable of catalyzing the deamination of glutamine residues, which are acceptors of amino groups. In the absence of substrates with amino groups, water molecules can act as acceptors for the deamination of glutamine residues. Transglutaminases are found in animals, plants, and microorganisms and differ in size and calcium dependence: mammalian enzymes require calcium, while microbial enzymes do not [70].

In the food industry, transglutaminases improve the properties of proteins (dairy, soy, meat, and fish), increasing their nutritional value, elasticity, and moisture content. These enzymes are also used to create heat resistant films and increase the shelf life of products by protecting lysine residues [71]. In addition, transglutaminases find application in the textile industry to improve the quality of wool [72].

2.12. Phytases

Phytases (phosphatases) play an important role in phytate hydrolysis and make phosphate available to organisms [73]. Phytases have been found in various organisms and can be divided into several groups depending on the carbon content of the phytate myo-inositol ring [73]. Some of them may also be called histidic acid phytases, α-propeller phytases, cysteine phytases or purple acid phytases based on their catalytic mechanism [73]. Phytases are widely used in animal feeds (pigs, poultry, and fish), increasing phytate-phosphorus uptake by 20-45% and reducing inorganic phosphorus requirements [73]. This reduces phosphate pollution of the environment and lowers costs for feed producers [74-75].

Phytases can be used in baking, plant protein production, corn milling and food additives. They are also promising for the development of functional foods.

2.13. Xylose isomerase

Xylose isomerase is an enzyme that catalyzes the reversible isomerization of D-glucose to D-fructose and of D-xylose to D-xylulose. This enzyme belongs to the isomerase family, it has been found in nearly one hundred species of bacteria. The production of glucose syrups began in Russia in 1811, when the German chemist Konstantin Kirchhoff from the Imperial Academy of Sciences in St. Petersburg obtained glucose syrup by heating starch with sulfuric acid [76]. Already in the middle of the 20th century, the discovery of the enzyme xylose isomerase, which converts glucose into fructose, played a key role. Takasaki from the Japanese Fermentation Institute identified a thermostable xylose isomerase from Streptomyces, which became the basis for the commercial production of high fructose syrups [77]. In 1967, Clinton Corn Processing (USA) adopted the Japanese technology to produce glucose-fructose syrups (GFS) and then improved the process using immobilization of the enzyme to produce syrup with 42% fructose [77]. Chromatographic separation was used to further increase the fructose concentration. GFSs with high fructose content have found applications as sugar substitutes in foods [78-79]. Technology development continues, aiming to reduce production costs [80].

Currently, enzymes operating under mild conditions are actively used in industry and various processes due to their efficient catalytic properties. However, thanks to new advances in protein engineering and directed evolution, we can expect the development of new enzymes with improved characteristics that will be used in both established technical fields and in completely new areas where the use of enzymes was previously impossible.

3. Amino acids and their production by industrial biotechnology

Since the beginning of the 20th century, the demand for amino acids has continued to grow due to their role in protein synthesis and participation in metabolism. These compounds are widely used in food, pharmaceutical, cosmetic industry and agriculture to improve enzymatic activity, immunity and muscle metabolism [81-83]. The importance of amino acids is emphasized by their deficiency, which can cause serious diseases [84-85].

Recent advances in genetic engineering have made it possible to obtain high-quality products with the desired properties [86]. Discoveries in this field have led to the development of innovative techniques for the isolation of amino acids, including fermentation using microbial cultures, extraction from protein hydrolysates, and chemical synthesis. Such techniques enable the development of sustainable products for food and agriculture [86]. The growing interest to amino acids has stimulated the development of innovative technologies, especially with an emphasis on sustainability.

Kikunae Ikeda, who researched monosodium glutamate in 1907, paved the way for the commercial production of flavor enhancers and initiated research in this field. Today, amino acids are used in various areas including food and feed additives, cosmetics, polymers and chemicals. The main challenge remains the optimization of methods for their industrial synthesis to improve efficiency and sustainability [87].

3.1. Production of amino acids

There are three main approaches to obtaining amino acids: extraction from protein hydrolysates, chemical synthesis, and microbiological techniques.

Extraction from protein hydrolysates is based on the unique characteristics of amino acids, such as pH, and is used to extract, for example, L-cysteine from keratin-containing materials (hair, feathers). This method is efficient and economical because it utilizes industrial waste [88]. Extraction using alkali generates environmental problems due to the formation of wastewater with toxic compounds [89]. The development of methods using supercritical water has improved the results while minimizing the negative environmental impact [90-91]. However, resource limitations of protein materials remain a problem.

Chemical synthesis involves reactions such as the Strecker method, but it requires expensive catalysts, is characterized by the use of toxic compounds (e.g., cyanide) and lack of enantioselectivity [92-93]. The well-known Bucherer-Bergs method is used for the synthesis of racemic amino acids, but it requires biochemical methods to separate isomers and is energy-consuming [94].

The microbiological process involves fermentation using microorganisms such as *E. coli* or *S. cerevisiae*. This method allows the production of optically pure amino acids with high efficiency and low amount of by-products [86]. Enzyme immobilization has been shown to increase process stability and product yield [95]. Fermentation is considered the most economical and environmentally friendly method despite the high costs of aeration, sterilization and equipment [96]. This approach prevails in the production of L-amino acids for the food industry and pharmaceuticals because it ensures high purity of the products.

3.2. Amino acids produced by bacteria

The most commonly used microorganisms for amino acid fermentation are *Corynebacterium glutamicum* and *E. coli* [86]. Genetically modified *C. glutamicum* efficiently produces amino acids such as L-lysine and glutamic acid with high yields reaching 50% [97-98]. This glucose-preferring strain is used to produce L-glutamate, L-lysine, L-phenylalanine, L-tryptophan and other amino acids [99-100]. However, its growth is inhibited at high substrate or product concentrations, such as glucose above 50 g/L or L-glutamic acid above 12 g/L [101].

E. coli is used for the synthesis of such amino acids as L-methionine, L-lysine, and L-threonine [86]. Site-specific mutagenesis and modification of metabolic pathways make it possible to create strains for the production of branched-chain amino acids such as L-valine, L-leucine, and L-isoleucine, which makes them promising for feed, cosmetics, and pharmaceuticals [102].

Genetic engineering has made it possible to use waste as a raw material for fermentation, making the process economical and environmentally friendly. Innovative technologies such as nanofiltration membranes for integrating purification and production, as well as reactor modeling, are contributing to increased efficiency and lower costs. Looking forward, the use of bacteria and microalgae to convert waste into amino acid-rich proteins opens up new opportunities for protein supplementation and sustainable production [86].

4. Organic acids and their applications

Organic acids are low molecular weight organic compounds containing one or more acidic functional groups such as carboxyl, sulfonic, hydroxyl or thiol groups. Because of these functional groups, organic acids serve as important building blocks for the production of chemical compounds that have a wide range of applications in global markets. In the past, such acids were often derived from petroleum, but given the unsustainability of this resource and associated significant greenhouse gas emissions, a shift to biotechnological production methods is becoming necessary [103].

4.1. Bacteria — producers of organic acids

Bacteria are important producers of various organic acids. Among the most well studied compounds are lactic, succinic and acetic acids.

Lactic acid is produced by various strains of *Lactobacillus casei*, as well as *Rhisopus oryzae* and *Endomycopsis fibuligera* [104]. It is widely used in the production of biodegradable plastics (e.g., polylactide) and in the food industry as a preservative and acidity regulator.

Acetic acid is synthesized by the bacteria *Acetobacterium woodi* and *Clostridium aceticum* by microbiological conversion of hydrogen and carbon dioxide [105].

Succinic acid (butanoic acid) is an important chemical compound that is widely used in various industries [106]. The main bacteria involved in the synthesis of succinic acid are: *E. coli*, *Basfia succiniproducens*, *C. glutamicum*. This acid has gained commercial importance as a fuel additive and raw material for the chemical industry [107].

4.2. Fungi — producers of organic acids

Fungi also play a significant role in the biosynthesis of organic acids. Of particular interest are strains of the genera *Aspergillus* and *Penicillium*, which are used to produce citric and oxalic acids.

Citric acid (2-hydroxy-propane-1,2,3-tricarboxylic acid) is a widely demanded compound in the food and pharmaceutical industries due to its safety, high water solubility, and pronounced chelating and buffering properties. In addition, citric acid is widely used in the production of detergents, cosmetic products, and a number of other industrial applications [108]. Modern industrial production of citric acid is based on the use of *A. niger* and various *Rhizopus* species in the process of deep fermentation in media supplied with starch or sucrose [109]. To increase the competitiveness of this production, researchers are trying to reduce costs by switching to cheaper substrates such as agro-industrial waste [110]. However, such substrates require pre-treatment to ensure nutrient digestibility, which can increase the complexity and cost of the process, especially if high product purity is required.

Another example is gluconic acid synthesized by *Aspergillus* spp. which is used in the textile and paper industries and is also applied as a rust remover [111]. Synthesis of this acid is carried out by microbial fermentation using various carbon sources containing glucose hydrolysates.

Itaconic acid is an α,β-unsaturated biaxonic carboxylic acid produced by the fungi *Aspergillus itaconicus* and *Aspergillus terreus* [112]. This compound finds wide application in the chemical industry, mainly in the production of various polymers including carboxylate rubbers, styrene butadiene polymers and nitrile latexes [113]. In addition, itaconic acid serves as a feedstock for the synthesis of pyrrolidones, butyrolactone, methylbutanediol, and is also used in the production of detergents, herbicides, and solvents [114].

Fumaric acid is a trans-isomer of butenedioic acid, which is produced by various representatives of mucor fungi, including the genera *Mucor*, *Rhizopus* and *Cunninghamella* [115]. This biotechnological process is based on the ability of these microorganisms to convert carbohydrates to fumaric acid through tricarboxylic acid metabolic pathways. The resulting fumaric acid is widely used in various industries: food industry (food additives, flavorings), pharmaceuticals (synthesis intermediates), cosmetics (acidity regulators), and chemical industry (polymer production). Fumaric acid is used to obtain maleic acid, which is applied in the production of: resins, paints and varnishes [115].

4.3. Yeast — producers of organic acids

There are various yeast species capable of producing organic acids. One of the most studied is *Yarrowia lipolytica*, as well as a number of other non-fermenting yeasts such as *Candida* sp., *Pichia* sp. and *Kluyveromyces* sp. These microorganisms have high enzymatic activity and are able to efficiently convert simple and complex substrates into target products - organic acids. The mechanism of organic acid biosynthesis in yeast is due to the conversion of carbon sources such as glucose, xylose or hydrocarbons into

metabolites of the intermediate and terminal Krebs cycle as well as other anabolic pathways. A peculiarity of the yeast *Y. lipolytica* is their ability to process hydrophobic substrates (e.g., fatty acids and oils), which makes them extremely promising for processing plant and animal wastes [116]. For example, this yeast can produce citric and dicarboxylic acids by decomposition of alkanes.

In addition to citric acid, yeast shows high efficiency in the production of succinic acid. This metabolite is considered as "platform chemistry" with diverse applications ranging from biomaterials to pharmaceutical ingredients. The strains of *Candida utilis* and partially modified *S. cerevisiae* were used in the large-scale production of succinic acid, and application of genetic techniques for strain improvement increased the yield of this acid in industrial processes [117].

Another important area is lactic acid biosynthesis. The cells of the yeast *Kluyveromyces lactis* produce lactic acid under favorable conditions of anaerobic fermentation [118]. This process is used to produce biodegradable plastics, which is relevant in the context of the global environmental program aimed at reducing plastic waste.

4.4. Microalgae — producers of organic acids

Microalgae are promising organisms for the synthesis of organic acids on an industrial scale due to their ability for rapid fermentation and high carbon dioxide assimilation efficiency [119]. They can produce a variety of organic acids such as myristic, palmitic, and lanolic acids, as well as other metabolites including lipids and carbohydrates [120]. The main advantages of their use are their ability to absorb CO2 in a highly efficient manner, which helps to reduce greenhouse gas emissions [121], and their growth rate, which allows more production in a shorter time. [122]. Microalgae are attractive for application in various ecosystems as they are able to survive in both fresh and salt water [123]. Currently, there are difficulties in the development of bioproducts using microalgae on an industrial scale, which are related to the optimization of cultivation conditions and extraction of metabolites [124].

Despite the obvious advances, the production of organic acids faces a number of limitations. For example, the use of expensive pure substrates, low yields in some cases, and difficulty in scaling up processes require the development of more efficient synthesis methods. Ongoing research in this area is aimed at reducing production costs, increasing productivity and expanding the functionality of organic acids to address a range of challenges related to environmental safety.

5. Lipids for industrial biotechnology

Lipids are important components of cell membranes, they provide the structural integrity of cells and transport of substances [125.]. In industry, lipids are widely used for the production of biodiesel, food additives, creams, lotions, and pharmaceuticals [126]. In recent years, microbial lipids have become a promising alternative to traditional lipids due to their rapid production, environmental friendliness, and ability to be grown on various substrates, including agricultural waste.

The application of microbial lipids in the food industry, such as the production of omega-3 and other fatty acids, has received special attention [127]. Polyunsaturated fatty acids such as n-3 (ω-3) and n-6 (ω-6) are healthy and are intensively used in fortified foods [128]. Microorganisms are also used to produce high-value cocoa butter, the cost of which is increasing due to growing demand [129].

Modern technologies, including CRISPR/Cas9 gene editing, have significantly increased the efficiency of microbial lipid production and improved fermentation processes [130].

5.1. Bacterial and yeast lipids

The production of bacterial biomass to obtain lipids is becoming promising due to their potential use in biofuels and production of sustainable energy. Many bacteria such as *Rhodococcus opacus*, *Acinetobacter calcoaceticus* and *Acinetobacter* spp. accumulate up to 87% of their mass as triacylglycerides, which are

converted into biodiesel [131-132]. Compared to oilseed crops, bacteria grow faster, produce higher lipid yields, and efficiently utilize various carbon substrates, including industrial wastes [133].

The accumulation of triacylglycerides is associated with cellular stress and consists of two stages: active growth in a carbon-rich medium and the "oil" phase, which is triggered by nitrogen deficiency [134]. The choice of substrate (glucose, sucrose or cheap waste) affects the efficiency of the process. For example, *R. opacus* accumulated up to 64.47% of lipids using sugarcane cake hydrolysate as cheap substrate [135].

Modern enzymatic methods, such as additional supplies of essential nutrients, have improved lipid yield by prolonging the growth phase and controlling the resource limitation [136]. For example, addition of glycerol to the culture medium enhanced lipid accumulation in *R. opacus* [137]. Thus, methods for optimizing substrates and culture conditions are the key to increasing the profitability of microbial lipid production.

The major yeast genera used for lipid production include *Yarrowia*, *Candida*, *Rhodotorula*, *Rhodosporidium*, *Cryptococcus*, *Trichosporon* and *Lipomyces*, but only about 30 species are able to accumulate more than 20% of their biomass as lipids [138-139]. The most studied are *Yarrowia lipolytica*, *Rhodotorula glutinis*, *Rhodosporidium toruloides*, *Cryptococcus curvatus* and *Lipomyces starkeyi*; *Trichosporon fermentans* also produce high amounts of lipids [140]. Lipid production is stimulated by excess carbon from glucose, glycerol or fatty acids under nitrogen limitation, leading to the synthesis of triacylglycerides (TAGs), the main lipid stores, accounting for up to 90% of the total lipid content [141-142].

High carbon to nitrogen (C/N) ratio and the activity of enzymes such as glycerol-3-phosphatacyltransferase enhance lipogenesis [143-144]. Oxygen saturation stimulates the synthesis of unsaturated fatty acids, and oxygen is also important for the Krebs cycle [145]. Environmental factors such as temperature, pH, and phosphorus for membrane phospholipids significantly affect the process [146-147].

5.2. Fungal lipids

Lipids accumulated by fungi include triglycerides, fatty acids, and polar lipids that serve as energy reserves and components of cell membranes. The fungi *A. niger* can produce biomass with up to 52% protein and 1% to 10% lipid content [148-149], while *Mucor circinelloides* and *A. terreus* are highly lipid-producing, with accumulation levels up to 38% of dry biomass. For example, *A. terreus* is rich in oleic and stearic acids, making it promising for biodiesel production [150-151].

Lipid accumulation occurs in two stages: active biomass growth and transition to lipogenesis, when nitrogen sources are depleted but carbon remains abundant [152-153]. The process is based on carbohydrate metabolism and synthesis of acetyl-CoA converted into lipids [154].

Fungal fermentation can be carried out by two methods: deep and solid state cultivation. Deep fermentation allows better control of environmental parameters and reduces the risk of contamination, which makes it preferable for industrialized production [155-156]. It is widely used for the production of fungal lipids and biomass, especially due to its efficiency and technological sophistication.

5.3. Lipids of microalgae

The composition of microalgae biomass varies greatly depending on species and growth conditions. The protein content ranges from 18 to 56%, lipids from 7 to 48%, and carbohydrates from 15 to 46% [157]. For example, the protein content of *Spirulina maxima* reaches 71% protein, microalgae contain essential amino acids, polyunsaturated fatty acids, carotenoids and chlorophyll [158-159]. *C. vulgaris* and *Scenedesmus* spp. are characterized by high protein (56.1% and 49%) and lipid content (12.5% and 12.1%) [160]. They exhibit diverse fatty acid profiles: *C. vulgaris* is rich in polyunsaturated fatty acids, while *S. platensis* is rich in saturated fatty acids, including palmitic acid.

Fungi and yeast are superior to microalgae and bacteria in lipid production due to their ability to metabolize a wide range of substrates, which contributes to the yield of fatty acids such as palmitic (C16:0), oleic (C18:1), linoleic (C18:2) and α-linoleic (C18:3) [161-162]. These compounds are in demand in food, cosmetic and pharmaceutical industries due to their properties and nutritional value. Linoleic acid and γ-

linoleic acid are used in nutrition and in the treatment of inflammation, while saturated fatty acids such as myristic acid (C14:0) are applied in personal care products [163]. Lipid production by fungi and yeast shows commercial potential due to high yields and a wide range of lipid applications, including biofuels.

5.4. Lipid extraction

Lipids produced by microorganisms include fatty acids with chain lengths ranging from 6 to 36 carbon atoms and are classified as saturated, monounsaturated or polyunsaturated ones [164-165]. These fatty acids are widely used in biofuels, and monounsaturated or polyunsaturated fatty acids produced by microalgae and traustochytrids find applications in nutraceuticals [164].

Lipid extraction remains a key challenge for industrial production due to their diverse polarity and location (intracellular and extracellular). Extracellular lipids are extracted more easily using filtration or centrifugation, whereas intracellular lipids require disruption of the cell wall [166]. This is accomplished by wet or dry biomass methods. The wet solvent extraction method is preferred due to low energy consumption, but it depends on lipid availability and mass transfer process [131, 166].

Chemical solvent extraction methods are efficient but pose environmental and financial risks [167]. Mechanical methods, such as bead milling and homogenization, are safer but require significant energy input [168]. Physical methods, including pulsed electric field technology and ultrasonic processing, are environmentally friendly and scalable, demonstrating high lipid yields and low energy consumption [169-170].

Overall, it is noteworthy that microbial lipids are a promising source for the production of sustainable bioproducts such as biosurfactants, carotenoids, dietary supplements, biofuels, pharmaceutical and cosmetic products [171-172], highlighting their versatile industrial potential [173-174]. Their versatility covers energy, nutrition, cosmetics and biodegradable materials. The production of lipids from agro-industrial wastes increases the efficiency of synthesis, reduces land use and competition with food crops, making them a sustainable feedstock for biofuels and reinforcing their importance in the bioeconomy [171, 175].

6. Antibiotics as products of industrial biotechnology

Antibiotics are a heterogeneous group of biologically active molecules that inhibit the viability of microorganisms. Initially, they included only compounds of natural origin produced by microorganisms, but later the definition included synthetic drugs [176-177]. The first anti-infectious drug, salvarsan, was synthesized by Paul Ehrlich in 1907 and was used to treat syphilis [178-179]. The discovery of penicillin by Alexander Fleming in 1928 ushered in the era of antibiotics, but its commercial production started only in the 1940s thanks to *Penicillium chrysogenum* [180-181].

The golden age of antibiotics is considered to be the 40s-60s of the 20th century, when many natural and synthetic compounds were discovered [182-183]. The classical producers are fungi and bacteria, in particular actinobacteria, which synthesize about 90% of commercial preparations [184]. In recent years, microalgae and cyanobacteria have been investigated for their potential to develop new antimicrobial drugs [185-186]. Current developments are focused on chemical modification of known microbial metabolites, allowing the development of semi-synthetic antibiotics with improved characteristics including broad spectrum of action and resistance [176]. Current research shows the high potential of entomopathogenic fungi [187] and microalgae [188] as sources of new antibiotics.

6.1. Classification of antibiotics

There are several classifications of antibiotics: by type of pharmacological effects (bactericidal and bacteriostatic), by activity (broad and narrow spectrum of action), but the most common types of classifications are based on the molecular structure and mode of action of antibiotics [189-190]. According to the mode of action, antibiotics are divided into inhibiting cell wall synthesis, disrupting the structure or function of the cell membrane and protein synthesis, affecting the structure and function of nucleic acids, or

blocking key metabolic pathways [191]. Based on the molecular (chemical) structure, antibiotics are classified into β-lactams, macrolides, tetracyclines, quinolones, aminoglycosides, sulfonylamides, peptide antibiotics, and oxazolidines [192]. It should be noted that β-lactams, aminoglycosides, glycopeptides, quinolones, and lipopeptides acr as bactericides, while sulfonamides, tetracyclines, and oxazolidinones exert a bacteriostatic effect [193-194]. Among macrolides there are preparations of both bactericidal and bacteriostatic character. Since one of the ways to obtain new antibiotics is to modify the chemical structure of already known antibiotics, some classes of antibiotics differing in chemical structure and including natural and semi-synthetic compounds will be discussed in more detail below.

6.1.1. β-lactam antibiotics

Antibiotics of the β-lactam class contain a β-lactam ring in their chemical structure, which inhibits peptidoglycan synthesis by binding to penicillin-binding proteins of bacteria. This disrupts the cell wall, causing cell lysis and cell death [195-196]. The β-lactams include penicillins, cephalosporins, monobactams, and carbapenems, which differ in side chains and structure [197].

Penicillins contain a β-lactam ring connected to a thiazolidine ring. They are enzymatically produced on the basis of 6-aminopenicillanic acid [198], the synthesis of which depends on the nutrient medium and genetic modification of strains [199]. The production of semi-synthetic penicillins involves chemical addition of side chains to 6-aminopenicillanic acid to produce compounds such as ampicillin and amoxicillin [200-201].

Cephalosporins produced by *A. chrysogenum* are characterized by stability and spectrum of activity. The production of semi-synthetic cephalosporins is based on the modification of 7-aminocephalosporanic acid [202]. Genetic engineering is used to increase titers and develop new compounds [203-204].

Monobactams, such as aztreonam, have a monocyclic structure and are entirely synthetic in origin [205].

Carbapenems, such as thienamycin, were first isolated in 1976 from *Streptomyces cattleya* [206-207]. However, due to their low yield and instability, their commercial production is based on chemical synthesis.

6.1.2. Macrolides

Macrolides are antibiotics containing 14-, 15-, 16-, or 18-membered lactone rings with attached aminosugars [208-209]. The first macrolide, erythromycin A, was isolated from *Saccharopolyspora erythreus* (formerly *Streptomyces erythreus*) in 1952. It became the prototype for the creation of semi-synthetic analogs such as azithromycin and clarithromycin [210-211].

14-membered oleandomycin is synthesized by *Streptomyces antibioticus*, and 18-membered fidaxomicin by *Dactylosporangium aurantiacum* [212-213]. The composition of the nutrient medium strongly affects the biosynthesis of macrolides: for example, propyl alcohol is added to the medium for erythromycin production and ammonium nitrogen, instead of nitrate nitrogen, is added for nystatin production (by *S. noursei*) [214].

6.1.3. Tetracyclines

Tetracyclines are broad-spectrum antibiotics based on the tetracyclic nucleus (A, B, C, D) [215]. The first tetracycline, chlortetracycline (aureomycin), was isolated in 1945 from *Streptomyces* by Benjamin Duggar, and in 1949 oxytetracycline (terramycin) was discovered by Alexander Finlay [216]. Their study made it possible to create synthetic and semi-synthetic analogs, as well as to modify the cultivation medium to obtain compounds with altered structure, for example, tetracycline instead of chlortetracycline in the absence of chlorine [217]. Semi-synthetic doxycycline is obtained from oxytetracycline, for example, by dehydration at C6 using a catalyst (rhodium on carbon) [218].

Tetracyclines are divided into generations: natural (1st), semi-synthetic (2nd) and synthetic (3rd) [219-220]. Their production was for a long time based on the fermentation by strains of the genus *Streptomyces* or semi-synthetic processes, later the third generation clinical preparations were approved [221].

6.1.4. Aminoglycosides

Aminoglycosides contain two or more aminosaccharides linked by glycosidic bonds to an aminocyclic ring and are among the oldest antibiotics along with β-lactamases, macrolides, and tetracyclines [222-223]. Streptomycin was the first compound of this class to be discovered in 1943, derived from *Streptomyces griseus*; the second was kanamycin in the culture fluid of *Streptomyces kanamyceticus* [224]. The high toxicity of streptomycin necessitated the search for new less toxic representatives of aminoglycosides, which led to the discovery of such antibiotics as gentamicin (isolated during fermentation from *Micromonospora purpurea*), neomycin (isolated from *Streptomyces fradiae*), tobramycin (isolated from *Streptomyces tenebrarius*), and amikacin (a semi-synthetic derivative of kanamycin), among others. [225]..

6.1.5. Peptide antibiotics

Antimicrobial peptides are natural compounds with a broad spectrum of action against bacteria, viruses, fungi, and even cancer cells. They are synthesized to compete with microorganisms [226-228]. The first peptide antibiotic, gramicidin, was discovered in 1939 by René Dubo from bacteria of the genus *Bacillus* [229]. The classification of antimicrobial peptides varies and includes classes such as polypeptide, lipopeptide and glycopeptide antibiotics.

Polypeptides, such as polymyxins, are cationic cyclic decapeptides synthesized by *Bacillus polymyxa*. Polymyxins B and E (colistin) are used in clinical practice [230-231].

Lipopeptides such as daptomycin are produced by *Streptomyces roseosporus* and are used to treat various infections due to their antimicrobial and surface action [232-233].

Glycopeptides like vancomycin and teicoplanin contain a peptide framework with aromatic amino acids and sugars. *Amycolatopsis orientalis* and *Actinoplanes teichomyceticus* are the producers. Modern semi-synthetic analogs, such as telavancin and oritavancin, have improved properties, including efficient binding to the target and an extended half-life [234-235].

Thus, the development of industrial antibiotic production has not only focused on improving the performance of strain-producing strains, but also on the development of new nutrient media formulations and various methods of catalyzing the antibiotic molecule to remove unwanted side chains and/or attach new ones [236-237].

6.2. Main steps in biotechnological production of antibiotics

Industrial production of antibiotics involves many steps aimed at increasing product yield and reducing production costs, using modern technologies such as computerized control of fermentation parameters [238-241]. For example, the technology of penicillin production has evolved significantly: instead of a batch process using lactose, semi-continuous cultivation on substrates such as mixtures of glucose and sucrose with computer-controlled parameters has been used [200].

Industrial production includes the following main steps: obtaining the producer strains, development of cultivation conditions, isolation and purification of the antibiotic, scale-up and production fermentation [242]. Genetic and metabolic engineering enables the development of highly efficient producer strains [243-245]. Cultivation conditions include the selection of media with sources of carbon, nitrogen, and phosphorus, as well as factors such as trace elements and amino acids, which can enhance biosynthesis [198, 242]. For example, for *A. chrysogenum*, the addition of methionine stimulates the synthesis of cephalosporins [200].

Antibiotics, being secondary metabolites, are synthesized in the stress phase of the growth of microbial cells following the exponential phase. This phenomenon is used in two-stage cultivation: first, the

biomass is increased, and then the active synthesis of antibiotic is started in a special medium [246-247]. The obtained preparations can be chemically modified to produce semi-synthetic antibiotics.

After fermentation, the culture liquid is treated; the product is isolated and purified. Methods include organic solvent extraction, adsorption, ion exchange and chemical precipitation, the choice of approach depending on the characteristics of the antibiotic [239, 242]. For example, penicillins G and V are extracted with organic solvents, whereas aminoglycosides require other methods due to their polarity [240]. In the final step, the drug is treated to remove water, often using lyophilic drying to preserve biological activity [248-249].

Thus, modern fermentation and downstream processing technologies, accompanied by genetic engineering tools and process optimization, allow the successful production of antibiotics on an industrial scale.

7. Vitamins obtained through microbial synthesis

In recent decades, there has been considerable interest in environmentally friendly and sustainable methods of vitamin production. Vitamins essential for the maintenance of human health have traditionally been obtained from plant sources or synthetically. However, the use of microorganisms such as bacteria, fungi and microalgae opens new horizons for biotechnological production of vitamins on an industrial scale [250-251].

7.1. Bacteria as sources of vitamins

Bacteria are key players in vitamin biosynthesis, e.g., species of the genera *Corynebacterium* and *Bacillus* are used for the production of vitamins B - B12, B2 and B6. For example, BASF (Germany) is engaged in the production of riboflavin using a genetically modified strain of *B. subtilis* [252]. *C. glutamicum* is widely used in industry for vitamin B12 biosynthesis due to its ability to assimilate various carbon and nitrogen sources [253]. *Propionibacterium shermanii*, *Propionibacterium freudenreichii* and *Pseudomonas denitrificans* are highly productive when fermentation conditions (pH, temperature) and nutrient medium composition are optimized; therefore, they are used for industrial synthesis of cyanocobalamin (vitamin B12) [254]. One of the most significant examples is the production of ascorbic acid (vitamin C) based on the combined Reichstein-Grüssner technology, which includes sequential stages of chemical synthesis and biotechnological conversion. The process involves the bacterium *Gluconobacter oxydans*, which transforms glucose into sorbitol with its subsequent oxidation to sorbose [255]. The cells of *Brevibacterium* spp. efficiently uptake carbohydrates and produce pantothenic acid (vitamin B5) during their life cycle, which plays a key role in cell metabolism and coenzyme A synthesis [256]. Photosynthetic bacteria such as *Rhodobacter sphaeroides* and *Corynebacterium* play a significant role in the biosynthesis of vitamin A through its precursor β-carotene [257].

7.2. Role of fungi in vitamin production

Fungi are also extensively used in the biotechnology industry due to their ability to produce vitamins, especially ergosterol, the precursor of vitamin D2. For example, the yeast *S. cerevisiae* is able to accumulate large amounts of ergosterol, which is converted to vitamin D2 when exposed to ultraviolet radiation [258]. *A. oryzae* and *A. niger* are employed in vitamin B2 production due to their high fermentation activity and easy adaptation to industrial conditions [259]. *Eremothecium ashbyi* is also one of the microorganisms used for the production of vitamin B2 (riboflavin) [260]. The fungi *C. maltosa* are used in the industrial production of ergosterol and ubiquinones by extraction from microbial lipids, which are by-products in the production of protein-vitamin concentrates [261].

Various mold fungi are capable of synthesizing vitamin A (in the form of β-carotene), and their content of the provitamin is many times higher than its amount in plant sources. For example, when cultivating *Blakeslea trispora*, its biomass accumulates 3-8 thousand μg of β-carotene per 1 g of mycelium,

while in carrots it only makes up 60 μg. *B. trispora* is one of the most efficient carotenoid producers, demonstrating stable productivity under controlled fermentation conditions lasting 6-7 days [262]. For industrial production of β-carotene, a special fermentation process is used, where female and male mycelial strains are grown separately and then mixed in a bioreactor at a ratio of 1:15, which allows achieving a concentration of β-carotene up to 2 000 mg/L [263].

7.3. Vitamin production by microalgae

Microalgae represent one of the most promising platforms for industrial vitamin production [264]. Microalgae capable of producing carotenoids, including β-carotene, have received special attention. Microalgae such as *Chlorella* and *Spirulina* are capable of synthesizing vitamins A, E and D [265]. These algae can be used both as food and as a source of vitamins for dietary supplements. In addition, they contain many other nutrients such as proteins, minerals and antioxidants [266]. Of particular importance is that the content of some vitamins in microalgae far exceeds their concentration in terrestrial plants [267].

Vitamins and carotenoids obtained from microalgae are widely used in the food industry (food fortification), pharmaceuticals (production of vitamin supplements), and cosmetology (creation of cosmetics). However, despite significant prospects, the development of industrial microalgae biotechnology is limited by high production costs [263]. The solution to this problem requires optimization of all production stages - from strain selection to extraction and purification methods.

Thus, microbial synthesis of vitamins demonstrates high efficiency and environmental safety, which makes it a priority in the modern vitamin industry.

8. Hormones produced by microbial synthesis

Hormones and steroids play an important role in medicine, agriculture and biotechnology [268]. Current methods for the production of these biomolecules include not only chemical synthesis but also biosynthesis using bacteria, fungi and algae [269]. These methods provide the possibility of producing complex molecules with high efficiency, lower costs and less environmental impact compared to traditional approaches [270]. In recent years, microorganisms have been considered as promising biocatalytic platforms that can produce both natural and modified analogs of steroidal compounds and hormones.

8.1. Synthesis of hormones and steroids using bacteria

Synthesis of hormones using bacteria can be cost-effective and allows the production of hormones without the need to extract them from organic sources. The bacteria *E. coli* and *B. subtilis* are model organisms for heterologous expression of various peptide hormones [271]. A significant achievement of biotechnology was the development of a method of insulin production using recombinant DNA technologies [272]. This method involves the introduction of genes encoding the production of preproinsulin into the genome of bacterial cells, which provides them with the ability to produce this hormone on a large scale [273]. Bacteria can also synthesize other hormones, such as somatotropin, which is used to stimulate growth of farm animals [274].

One of the important areas of research is the study of the use of actinomycetes and other bacteria for biotransformation of complex steroid compounds. Studies have shown that bacterial strains *Rhodococcus ruber*, *Mycobacterium* sp. and others possess key enzymes that can selectively change the structure of steroids at given positions. For example, the process of steroid hydroxylation at positions C-9 and C-11, which is an important step in the production of drugs such as cortisone and prednisolone, has been described [275]. Donova with co-authors, in their study of steroid catabolism by bacteria of the genus *Mycobacterium*, which can degrade the steroid molecule with the removal of the side chain, demonstrated a process important for the production of such intermediates as androstenone and androstadienedione [276].

8.2. Biotechnological synthesis of hormones by fungi

Fungi of the genera *Aspergillus*, *Penicillium* and *Rhizopus*, are key biotechnological agents in the transformation of steroids [277]. Their unique ability to specifically hydroxylate steroid compounds makes it possible to obtain important pharmaceuticals including cortisone and prednisolone [278]. For example, *Rhizopus nigricans* has traditionally been used for the hydroxylation of progesterone to produce pharmaceuticals with anti-inflammatory and immunosuppressive properties. The mechanism of progesterone hydroxylation by the fungus *Rh. nigricans*, involves the conversion of progesterone to the less toxic 11α-hydroxyprogesterone, which is then excreted from the mycelium. The hydroxylation process is inducible and involves specific progesterone receptors [279]..

The production of sterols by fungi occupies a special place in modern biotechnology [280], among which ergosterol is an important precursor for the synthesis of vitamin D [281]. The unique enzymatic systems of fungi provide highly selective modification of steroid molecules [282], which greatly simplifies the production of the required compounds. With an improved understanding of fungal metabolic pathways [283] and advances in genetic engineering [284], it has become possible to create specialized strains with improved production characteristics. These “super strains” demonstrate the ability to synthesize complex hormonal compounds on a large scale [285], which opens up new perspectives for their industrial applications.

Despite the prospects of hormone synthesis by fungi, scaling up the process is difficult. The key limitations are the relatively low growth rate of fungal cultures and insufficient concentration of target metabolites, which requires careful optimization of fermentation conditions [286].

8.3. Algae as a source of hormones and steroids

Algae are a unique natural source of steroidal compounds and phytohormones with potential biological activity [287]. Of particular interest are representatives of *Sargassum* and *Chlorella*, characterized by the presence of specific steroidal components, which makes them promising raw materials for the production of biologically active additives [288]. The phytohormonal complex of algae includes important plant growth regulators: auxins, cytokinins and gibberellins. These compounds are not only involved in the regulation of growth and development of algae themselves, but can also have a stimulating effect on higher plants when used as biostimulants [289]. Thus, biotechnological processes based on the use of algae can be employed in production of new sources of phytohormones for agriculture, as well as functional additives to human diet and animal feed.

Conclusion

The products of industrial biotechnology play an important role in various fields of human activity. Despite the active use of plants and animals in medical, cosmetic, agricultural and food industries, it is the microbiological area that is the key player in industrial biotechnology. It is connected with obtaining various biotechnological products using microbiological approaches: antibiotics, enzymes, biopreparations based on microbial biomass, amino acids, feed proteins, bioethanol, biogases, vitamins, organic acids, polysaccharides, as well as bioproducts obtained on the basis of recombinant DNA technology (hormones, biologically active substances, etc.). Industrial biotechnology is actively developing; it contributes to the identification of new microorganisms-producers, improvement of technological processes and creation of innovative products. At the same time, the tasks of increasing the resistance of microorganisms, optimizing fermentation processes and reducing production costs remain relevant. Industrial microbial biotechnology has a significant potential to stimulate economic growth, improve public health and environmental protection. Continued scientific research in this area is of fundamental importance.

Conflict of interest

The authors declare no conflict of interest.

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