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LACTIC ACID: INDUSTRIAL SYNTHESIS, MICROORGANISMS-PRODUCERS AND SUBSTRATES: A REVIEW

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Abstract. The article contains comprehensive information on groups of bacteria producing lactic acid, which have high metabolic activity and can be used in industrial production. In addition, an overview of the most common fermentation methods (batch, continuous, multiple), as well as cheap carbon sources: starch and cellulose-containing, industrial and food waste is provided.

Keywords: lactic acid; biotechnology; production; lactic acid producers; substrates for the synthesis of lactic acid.

1. Introduction

The growing level of interest in organic acids can be seen globally due to the increasing demand and market volume. According to the transnational consulting company "Future Market Insights" (FMI) forecasts, the market of organic acids is expected to grow by 7.5 billion US dollars and reach a value of 18.8 billion dollars by 2032[1]. This trend is due to a combination of various factors, among which we can highlight: change in consumer preferences from synthetic additives to natural ones; focus on the production of "eco-friendly" goods and products; ban on the use of food antibiotics in animal feed.

Among carboxylic acids, the leading place belongs to lactic (2-hydroxypropanoic) acid. The global market for lactic acid was valued at USD 3.37 billion in 2023, with an expected compound annual growth rate (CAGR) of 8.0 % from 2024 to 2030, due to its unique structure and properties[2]. Lactic acid (LA) has antimicrobial, antiviral, and antiseptic effects and is actively used as a preservative and acidity regulator of food products and animal feed. According to a study by the research and consulting company "Grand View Research", the main industries where lactic acid is actively used are chemical, food, light, pharmaceutical, and cosmetic, as shown in Fig. 1[2].

The largest lactic acid application segment according to Fig. 1 is the chemical industry, namely the polylactide production – ecological and safe bioplastic (polylactic acid, PLA). Polylactide is actively used in 3D printing technology due to its low melting point, high strength, and low thermal expansion. In addition, according to some experts, polylactide can effectively replace most of the known non-ecological polymers (polypropylene and polyethylene) in the future, which pollute the environment due to improper disposal[2–5].

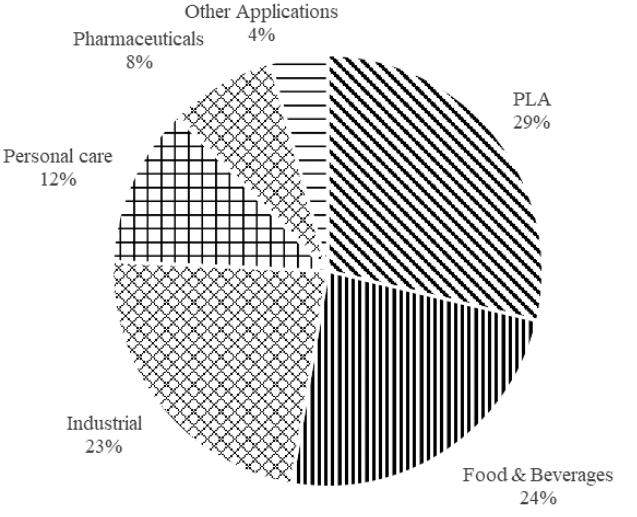

Fig. 1. Areas of lactic acid application [compiled on the basis of [2]

Lactic acid is widely used in the food industry, namely in the production of beverages and food products. In particular, lactic acid is known as a food additive under the standard code E270, which has an antioxidant effect. Lactic acid is a preservative used in milk processing, confectionery, bakery, and fermented foods (beer, kvass, and others). In addition, it is used in the technology of cheese, sauces, mayonnaise, and other wares of the oil-fat complex. Lactic acid also serves as an acidity regulator in the production of meat production, fruit and vegetable preserves, as well as carbonated soft drinks[6].

Besides chemicals and food, LA is also used in other industries. In particular, it is known as an active and auxiliary compound in the pharmaceutical industry. Lactic acid serves as an active pharmaceutical ingredient (API) in preparations for the treatment of gastroesophageal

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reflux and stomach ulcers, and as an auxiliary compound – to give the shape and structure of tablets, adjust pH, and stabilize API[7]. Lactic acid and its salts are widely used in the production of detergents and cosmetics, including hygienic products for skin care and home peeling. Due to its strong biological action, LA penetrates the epidermal barrier and actively affects physiological processes in all skin layers by stimulating reparative processes in response to damage. In the textile industry, it is part of fungicidal antifungal drugs that are used to treat various fabrics. Technical lactic acid is used to extract lime from skins (decalcification). In veterinary medicine and poultry farming, lactic acid is used as a caustic agent, as well as in the form of an aerosol for air disinfection in incubators of poultry farms and calf pens[8]. Oral solution of LA (40 %) inhibits the reproduction and development of putrefactive intestinal microflora of domestic animals. Also, it has a detrimental effect on Eimeria (a genus of apicomplexan parasites) parasitizing in the body of chickens, rabbits, and other animals. Moreover, it reduces the formation of toxic products from the decomposition of organic substances in the body, improves metabolic processes, and helps increase productivity[9].

The purpose of this article is to review the current level of development of industrial production of lactic acid which includes microorganisms-producers, cultivation methods, and cheap components of the nutrient medium.

2. Methods of Industrial Lactic Acid Production

2.1. Chemical Synthesis of Lactic Acid

Industrial production of lactic acid by chemical synthesis using the lactonitrile method began in 1960. The obtained lactic acid was used in bread baking. Wastes from the petrochemical industry and acrylonitrile production were usually used as raw materials[10]. The production of LA by the lactonitrile method consists of the following stages:

- Oxidation of ethylene with the formation of acetaldehyde (Wacker process).
- Conversion of acetaldehyde to lactonitrile.
- Hydrolysis of lactonitrile to obtain a racemic mixture of DL-lactic acid.

The resulting acetaldehyde in the first stage is converted to lactonitrile by adding hydrogen cyanide in the presence of a catalyst. The process is carried out under high pressure. The resulting lactonitrile is recovered, purified by distillation, and hydrolyzed with sulfuric acid to obtain LA and an ammonium salt. To obtain lactic acid with a high degree of purity, it is esterified with methanol. The resulting methyl lactate is recovered, purified by distillation, and hydrolyzed with acidified water to obtain lactic acid and methanol. The scheme for obtaining lactic acid by chemical synthesis is shown in Fig. 2[11].

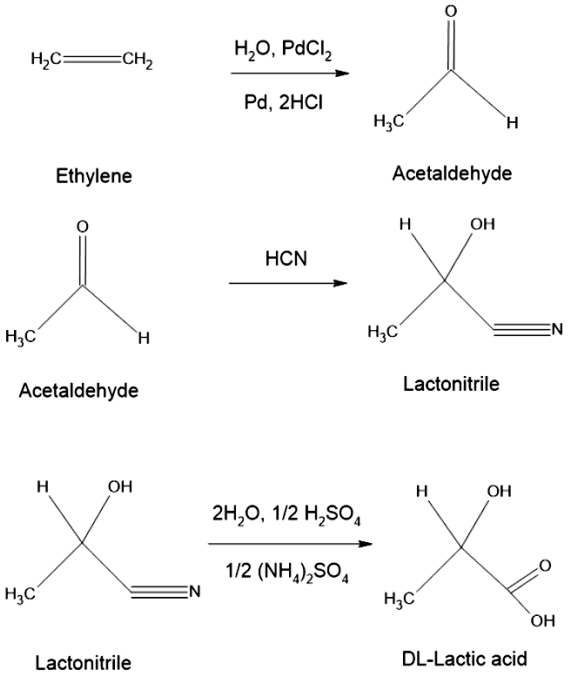

Fig. 2. Chemical synthesis of lactic acid by the lactonitrile method

Lactic acid was also obtained in industrial conditions by propene nitration in the presence of oxygen to obtain α-nitropropionic acid, which is subsequently hydrolyzed. The detailed conditions for the synthesis of LA are a commercial secret and are not known for sure. The general synthesis scheme is shown in Fig. 3[12].

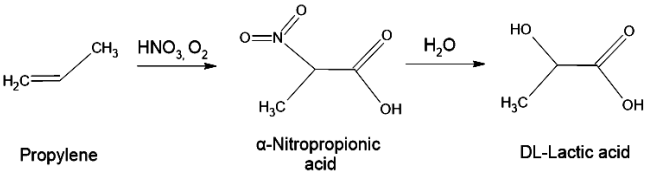

Fig. 3. Scheme of lactic acid synthesis from propene

Besides the hydrolysis of lactic acid derivatives (nitriles and esters), LA can also be obtained by the following chemical reactions:

- hydrolysis of other 2-substituted propionic acids;
- decarboxylation of certain derivatives of 2-methylmalonic acid;
- reduction;

- oxidation;
- rearrangement and disproportionation.

However, the methods described above have not been used in industry due to the low yield of lactic acid and high production costs[12].

There were significant changes in the production of lactic acid in 1990, almost all large enterprises changed the production technology from chemical synthesis to biotechnological cultivation, which was associated with the following factors:

- dependence of production on raw materials;
- use of limited and expensive fossil resources as raw materials;
- obtaining a racemic mixture of DL-lactic acid;
- high cost of final product purification.

2.2. Biotechnological Production of Lactic Acid

In general, the essence of lactic acid biotechnological production is based on the ability of microorganisms to convert carbohydrates into LA under the influence of the lactate dehydrogenase enzyme. The general scheme of obtaining lactic acid by enzymatic process is shown in Fig. 4, and a detailed description of the metabolism of lactic acid producers will be considered in the next section.

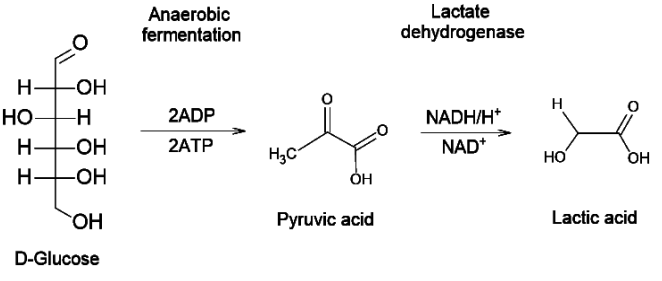

Fig. 4. Scheme of conversion of glucose into lactic acid by the biotechnological method

The biotechnological production of LA can be carried out in various ways, which largely depend on the producer himself, the components of the nutrient medium, the regulated time of cultivation, the availability of appropriate equipment, technological support, and the scale of the process. In general, there are four strategies for the production of lactic acid: batch, fed-batch, continuous and repeated fermentation[13].

2.2.1. Batch Fermentation

Batch fermentation is a classic cultivation method for most biotechnological processes of obtaining biomass, primary and secondary metabolites. The batch cultivation method is quite simple in terms of technological equipment, as it does not require special equipment (such as additional satellites, dosing pumps, or flow meters), and the development of the producer microorganism is subject to the classical model of the growth curve for batch cultures. With batch cultivation, the risk of contamination is minimal due to the closed system. However, conditions are created for culture inhibition by the substrate and the end product, which on an industrial scale can reach sufficiently high values (from 100 to 200 g/L).

2.2.2. Fed-Batch Fermentation

During fed-batch fermentation, the components of the nutrient medium are gradually introduced into the culture liquid to reduce the phenomenon of inhibition by the substrate. In addition, the microorganism culture in this way remains in the stationary phase for quite a long time, when the synthesis of LA stays at its peak. In lactic acid production, only a source of carbon is usually used as a feed, which is associated with its high concentrations in the fermentation medium. Other components of the nutrient medium − nitrogen source, mineral salts, and vitamins are usually introduced immediately. The main disadvantages of this process are the high concentration of the final product in the fermenter, the possible risk of contamination when feeding, complex equipment and technical support (capacitive reactors, special dosing pumps or flow meters), constant monitoring and the need for personnel who will carry it out.

2.2.3. Repeated Fermentation

In repeated fermentation, the cell mass of the microorganism culture is reused for a long time until the complete loss of metabolic activity and lysis. In the production of lactic acid, this method is extremely effective because the biosynthesis process is quite often limited by the low density of the microbial population. The design feature of reactors used for re-fermentation is the presence of special modules on which the producer's culture is immobilized. Special substrates are used to immobilize microorganisms, including Ca^{2+}-alginate gels, poly(ethyleneimine), and plastic composite substrates. The advantages of this process are high values of productivity, high yield of the resulting product, reduction of the total fermentation time, and resources required for the preparation of seed material. On the other hand, the disadvantages are complex hardware and technical support, as well as a high risk of contamination during repeated fermentation.

2.2.4. Continuous Fermentation

During continuous fermentation, portions of a fresh nutrient medium are brought into the fermenter at a constant flow rate and portions of culture liquid are removed. The correct organization of such cultivation

mode ensures constant concentration of the nutrient medium components, metabolic products and the final product, which allows to avoid the phenomenon of inhibition of the synthesis process by the substrate and the final product. In addition, the producer microorganism is constantly in the stationary phase, during which the synthesis of LA is maximal. The continuous mode of cultivation is more economically profitable due to the shorter time of additional operations, the reduction of which significantly reduces the costs of human resources and energy carriers for equipment preparation. The main disadvantages of continuous cultivation are the low degree of conversion of the carbon source into lactic acid, complex equipment and technical support, the need for the constant presence of experienced personnel and a high risk of contamination[14–17].

3. Characteristics of Lactic Acid Producers

In the environment, various groups of organisms can synthesize lactic acid, including bacteria, fungi, cyanobacteria, and even algae. However, they must have stable and high metabolic activity for their effective use in industry. To be used as lactic acid industrial producers, the organisms must synthesize lactic acid in a concentration of more than 100 g/L with a conversion value of more than 90 %.

When choosing a lactic acid-producing organism, the synthesis of a certain enantiomer (L-(+)– or D-(-)-lactic acid) and optical purity, which depends on the stereospecificity of lactate dehydrogenases that reduce pyruvate, are also quite important. Some species contain only D-lactate dehydrogenase and therefore form the D-isomer of LA, others contain only L-lactate dehydrogenase and form the L-isomer. Certain species have lactate dehydrogenases of different stereospecificity, which leads to the formation of a racemic mixture (Table 1)[18].

For industrial purposes, a lactic acid producer must possess only L-lactate dehydrogenase activity and synthesize L-lactic acid, the natural enantiomer in humans and other higher life forms. Unlike L-lactic acid, D-lactic acid has a neurotoxic effect on the human body, causing encephalopathy, acidosis, and ataxia. Although D-lactic acid has negative effects on human and animal health, it is not a highly toxic compound because the expected average lethal doses are quite high. The LD_{50} value for rats after oral administration is approximately 4.5 g/kg[19].

In industry, lactic acid bacteria are the classic producers of lactic acid, but research articles describe the application of other taxonomic groups of bacteria. In particular, the use of *Bacillus bacteria*[20–22], *E. coli*[23, 24], and *Corynebacterium glutamicum*[25] has been described.

Table 1. Comparative characteristics of microorganisms according to their ability to synthesize L(+) and D(–) isomers of lactic acid[18]

Producer	Percentage content of LA stereoisomers, %	
	L(+)	**D(-)**
Streptococcus cremoris	About 100	–
Streptococcus lactis	About 100	–
Streptococcus faecalis	About 100	–
Lactobacillus helveticus	70	30
Lactobacillus lactis	–	100
Lactobacillus acidophilus	60	40
Lactobacillus bulgaricus	0	100
Lactobacillus casei	About 100	–
Leuconostoc cremoris	–	About 100

3.1. Lactic Acid Bacteria

Lactic acid bacteria (LAB) are a heterogeneous group of phylogenetically related microorganisms that are capable of synthesizing lactic acid as the only or main product. Bacteria of this group are gram-positive, immobile, facultative anaerobes, do not form spores (except for the genus *Sporolactobacillus*), catalase-negative, and resistant to low pH values. The typical shape of an LAB cell is rods (long and short) and cocci (Fig. 5).

According to taxonomy, all LAB belong to the division *Firmicutes*, class *Bacilli*, order *Lactobacillales*, which includes the following families (the number of species in the family is given in brackets): *Aerococcus* (7); *Alloiococcus* (1); *Carnobacterium* (12); *Dolosigranulum* (1); *Enterococcus* (49); *Globicatella* (2); *Lactobacillus* (189); *Lactococcus* (7); *Leuconostoc* (23); *Pediococcus* (15); *Oenococcus* (2); *Streptococcus* (101); *Tetragenococcus* (5); *Vagococcus* (8) and *Weisella* (18)[26,27].

Lactic acid bacteria are divided into homofermentative and heterofermentative based on the metabolic pathway of carbohydrate conversion and accumulation of final fermentation products.

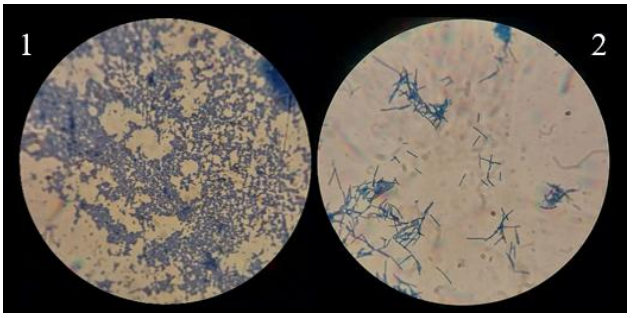

Fig. 5. Typical shape of LAB cells under microscopy (×100):
1 – *Enterococcus faecium*,
2 – *Lactobacillus lactis* [own image]

Carbohydrate catabolism by homofermentative bacteria is carried out by glycolytic and pentose phosphate pathways. Hexoses in the glycolytic pathway are transformed with the help of specific kinases (hexo- and fructokinase) into fructose-1,6-diphosphate, which is cleaved by aldolase to phosphorus-glyceraldehyde (PGA). Pentoses under the influence of specific kinases are transformed into xylulose-5-phosphate, which in a series of metabolic transformations gradually degrades to fructose-6-phosphate and PGA. As a result, pyruvate is formed. With the participation of lactate dehydrogenase, it is transformed into lactic acid. The end product of the metabolism of this type of LAB is only LA.

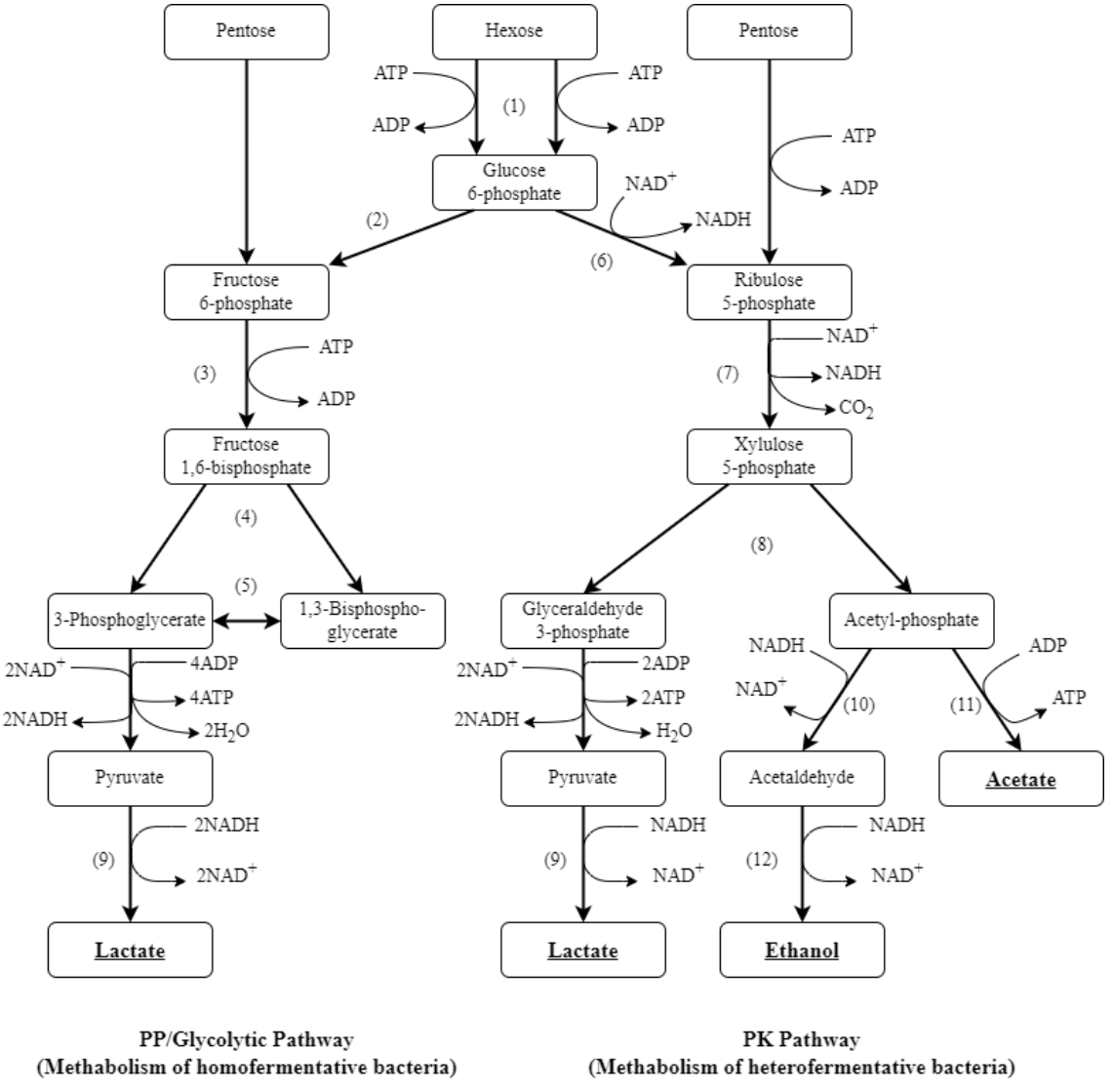

Fig. 6. The general scheme of the LAB metabolism
1 – Hexokinase; 2 – Glucose-6-phosphate isomerase; 3 – Phosphofructokinase-1;
4 – Fructose-bisphosphate aldolase; 5 – Triosephosphate isomerase; 6 – Glucose 6-phosphate dehydrogenase and 6-Phosphogluconolactonase; 7 – Ribulose 5-Phosphate 3-epimerase; 8 – Transketolase; 9 – Lactate dehydrogenase, 10 – Acetaldehyde dehydrogenases; 11 – Acetate kinase; 12 – Alcohol dehydrogenase [compiled on the basis of 13, 28].

On the other hand, the conversion of carbohydrates in heterofermentative bacteria is carried out by the phosphogluconate or phosphoketolase pathway, which is explained by the absence of fructose-1,6-aldolase, which breaks down fructose-1,6-diphosphate. The final products of heterofermentative fermentation can be a whole range of compounds: lactic acid, ethanol, carbon dioxide, diacetyl, acetoin, or acetic acid[13,14,28,29].

Bacteria strains that perform only homofermentative lactic acid fermentation (homofermentative LAB) are used for the production of LA on an industrial scale, due to the absence of by-products of synthesis, a high value of yield (more than 90 %), productivity and optical purity (>99 %). Bacteria of the genera *Streptococcus, Lactococcus, Enterococcus, Pediococcus,* and some species of *Lactobacillus* belong to the homofermentative LAB. Among them, *Lactobacillus delbruckii, L. acidophilus, L. helveticus, L. casei, Lactococcus lactis,* and *Streptococcus salivarius* are mainly used for the synthesis of lactic acid[16,29].

The main disadvantages of LAB strains when used in industry are the complex need for expensive nutrient medium components – animal and bacterial sources of nitrogen (mainly yeast extract, peptone, and some amino acids). In addition, lactic acid bacteria lack enzyme systems capable of breaking down complex carbon sources. Therefore, during the industrial production of lactic acid by LAB strains fermentation, the raw material must be hydrolyzed to simple carbohydrates (glucose).

3.2. Bacillus Strains

Bacillus is a genus of Gram-positive rod-shaped (Fig. 7) aerobic or facultatively anaerobic bacteria, catalase-positive. They can form spores under the influence of negative environmental factors. The genus *Bacillus* is widespread in nature and is found in water, soil, sand, and even in the bodies of plants and animals.

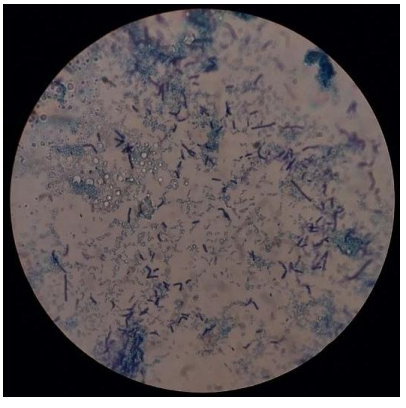

Fig. 7. Cells and spores of the genus *Bacillus* on the example of *Bacillus subtilis* (×100) [own image]

Traditionally, the genus *Bacillus* is divided into three main groups based on morphological features:

1. Gram-positive, produce central or terminal, ellipsoidal or cylindrical spores that do not distend the sporangium. It comprises two subgroups:
   - Large cell subgroup includes *Bacillus anthracis, Bacillus cereus, Bacillus mycoides, Bacillus thuringiensis,* and *Bacillus megaterium*.
   - Small cell subgroup includes *Bacillus pumilus, Bacillus subtilis,* and *Bacillus licheniformis*.
2. Group 2 – Gram variable with central or ellipsoidal spores and swollen sporangia: *Bacillus circulans* and *Bacillus coagulans. Bacillus alvei, Bacillus brevis,* and *Bacillus macerans* belonged to this group but have been reclassified to other genera.
3. Group 3 – Gram variable, sporangia swollen with terminal or subterminal spores: *Bacillus sphaericus*[30].

The transformation of carbohydrates into lactic acid in cells of the genus *Bacillus* occurs in the same way as in homofermentative LAB: hexoses by the glycolytic pathway, and pentose by the pentose phosphate pathway.

The genus *Bacillus*, which can be used in industry as producers of lactic acid, includes*: B. coagulans, B. stearothermophilus, B. licheniformis*, thermophilic strains of *B. licheniformis, B. subtilis*, alkaliphilic strains of *B. circulans var. alkalophilus, B. alkalophilus sp. halodurans, and B. alcalophilus*[29].

The main advantage of using bacteria of the genus *Bacillus* in industry is the simple requirements for the components of the nutrient medium. They grow and synthesize lactic acid on inexpensive media with mineral salts and synthetic or plant sources of nitrogen (particularly, $(NH_4)_2SO_4$ or steep corn liquor). The use of thermophilic strains with a growth optimum greater than 45 °C is quite attractive from an industrial perspective, which allows the process of LA synthesis to be carried out in non-sterile conditions on a non-sterile nutrient medium simultaneously with the process of hydrolysis of complex hydrocarbon substrates. In addition, bacteria of this genus can metabolize a wide range of hydrocarbon substrates, synthesize only the L-isomer of lactic acid (they lack D-lactate dehydrogenase) and are more resistant to adverse environmental conditions[16,29].

3.3. *Escherichia coli*

Escherichia coli, a gram-negative, non-sporulating, rod-shaped facultative anaerobe, is an inhabitant of the intestines and feces of warm-blooded animals and reptiles. *Escherichia coli* is the most studied microorganism and is quite often used in genetic engineering to construct supersynthetic strains of primary and secondary metabolites[31]. Unlike strains of LAB and bacteria of the

genus *Bacillus*, strains of *Escherichia coli* synthesize an extremely small amount of lactic acid. However, by constructing genetically modified microorganisms, strains of *Escherichia coli* can also be used as producers of LA.

The synthesis of lactic acid in *Escherichia coli* occurs under anaerobic conditions in the process of mixed acid fermentation, during which a mixture of acids is formed: succinate, formate, acetate, and ethanol to maintain the redox balance of the cell. As shown in Fig. 8, the synthesis of acetate, ethanol and formate is related to enzyme activity pyruvate-formate lyase, and succinate – phosphoenolpyruvate carboxylase. To construct a strain-producing lactic acid using genetic engineering methods, the genes responsible for the synthesis of these enzymes are removed[32,33].

Compared to strains of lactic acid bacteria, the bacterium *Escherichia coli* has simple needs in the components of the nutrient medium and is easily amenable to genetic manipulation. However, the use of *Escherichia coli* also has significant disadvantages, namely: low values of process productivity (≤1.04 g/L/h) and lack of resistance to low pH values of the environment[16].

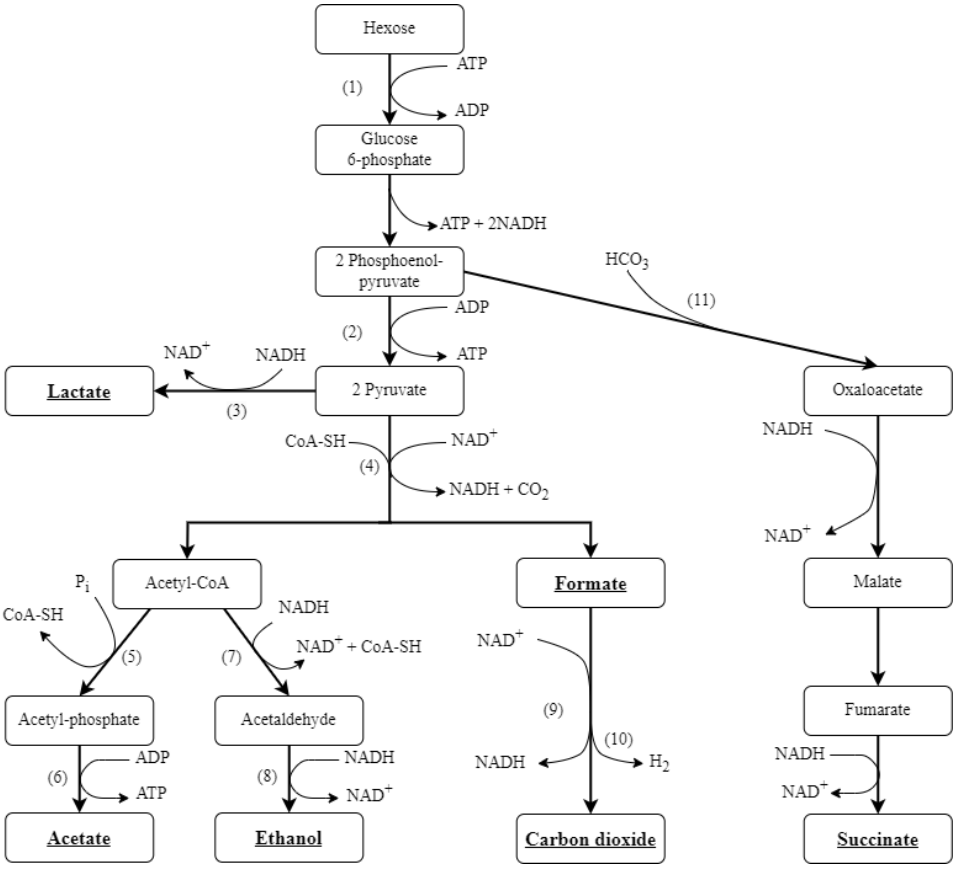

Fig. 8. General scheme of mixed acid fermentation of *E.coli:*
1 – Hexokinase; 2 – Pyruvate kinase; 3 – Lactate dehydrogenase; 4 – Pyruvate-formate lyase; 5 – Phosphotransacetylase; 6 – Acetate kinase; 7 – Acetaldehyde dehydrogenases; 8 – Alcohol dehydrogenase; 9 – Aerobic formate dehydrogenase; 10 – Formate-hydrogen lyase; 11 – Phosphoenolpyruvate carboxylase [compiled on the basis of 32, 33].

3.4. *Corynebacterium glutamicum*

Corynebacterium glutamicum is a well-known industrial strain used for large-scale production of various amino acids, namely L-glutamate, L-lysine, L-arginine, L-histidine, L-valine, and so forth. Morphological signs of Corynebacterium glutamicum: gram-positive; nonsporulating; nonmotile; not acid-fast; and straight or slightly curved rods, ovals, or clubs; a "coryneform" (club shape) is often observed and generally exhibits a typical V-shaped arrangement of cells; facultatively anaerobic to aerobic; catalase-positive[34]. Genetically unmodified strains of this bacteria synthesize a very small amount of lactic acid mixed with other acids under anaerobic conditions. Similarly to *Escherichia coli*, strains of *C. glutamicum* can be used in industry after genetic modifications involving the deletion of genes responsible for the by-product synthesis.

The synthesis of LA is carried out from pyruvate, which is formed by the Embden-Meyerhoff-Parnas (EMP) pathway, under the action of lactate dehydrogenase. Acetyl-CoA is also formed from pyruvate, which can be converted into acetate under the action of enzymes phosphotransacetylase and acetate kinases or to succinate in the tricarboxylic acid cycle (TCA). Metabolic pathways have already been described above[35,36].

The advantages of using *Corynebacterium glutamicum* for industrial LA production are the absence of specific requirements for the nutrient medium components, a high value of output, and optical purity. The disadvantages are low resistance to acidic pH values and the selection of specific cultivation conditions due to the relationship between the amount of biomass and synthesized lactic acid[29].

Comparative characteristics of possible industrial bacterial producers with a LA concentration of more than 90 g/L, output value, carbon source in the nutrient medium, and fermentation mode are given in Table 2.

Table 2. Comparative characteristics of possible industrial bacterial producers with a concentration of more than 90 g/l of lactic acid

Bacteria	Strain	Fermentation mode	Source of carbon	Lactic acid		Reference
				C, g/L	*Y*, %	
Lactic acid bacteria						
Lb. delbrueckii ssp delbrueckii	CECT 286	Fed-batch	Hydrolyzate of orange waste	99.8	83.2	[37]
Lb. delbruckii	NCIMB 8130	Batch	Molasses	90.0	96.7	[38]
Lb. paracasei	NCBIO01-M2-ldhL1-HT	Batch	Glucose	221.0	96.0	[39]
Lb. rhamnosus	LA-04-1	Fed-batch	Glucose	170.0	–	[40]
Lb. rhamnosus	HG09F5-27	Batch	Starch from yam tubers	157.22	–	[41]
Lb. bulgaricus	CGMCC 1.6970	Fed-batch	Dry cheese whey	113.2	–	[42]
Lb. species	RKY2	Repeated batch	Cheese whey	95.11	99.0	[43]
Lb. casei	NRRL B-441	Batch	Lactose	96.0	93.0	[44]
Lb. pentosus	NRRL B-227	Batch	Potato processing waste	150.0	93.7	[45]
Lc. lactis	ATCC19435	Repeated batch	Artichoke hydrolyzate	92.5	68.0	[46]
Lc. lactis sp. lactis	AS211	Batch	Wheat flour hydrolyzate	107.0	91.0	[29]
Enterococcus faecalis	RKY1	Repeated batch	Glucose	94.0	–	[47]
		Batch	Molasses	95.7	94.9	[48]
Bacillus strain						
B. coagulans	DSM1	Fed-batch	Bread waste	155.4	85.0	[49]
B. coagulans	H-1	Fed-batch	Glucose	165.7	92.0	[50]
B. coagulans	36D1	Batch	Paper	92.0	77.0	[51]
B. coagulans	C106	Fed-batch	Xylose	215.7	95.0	[52]
Bacillus sp.	WL-S20	Fed-batch	Food with peanuts and glucose	225.0	99.0	[53]
B. subtilis	MUR1	Fed-batch	Glucose	183.2	98.5	[20]
Escherichia coli						
E. coli	CICIM B0013-070 (pUC-ldhA)	Batch	Glycerol	111.5	78.0	[54]
E. coli	WYZ-L	Batch	Saccharose	97.0	90.0	[55]
E. coli	HBUT-D	Batch	Glucose	127.0	93.0	[56]
Corynebacterium glutamicum						
C. glutamicum	-	Fed-batch	Glucose	120.0	86.5	[25]

Note: *C* – concentration; *Y* – yield; *Lb.* – *Lactobacillus*; *Lc.* – *Lactococcus*.

As can be seen in Table 2, a high amount of lactic acid is synthesized by natural and genetically modified strains of lactic acid bacteria. As a substrate, monosaccharides or hydrolyzate monosaccharides of starch-containing materials are used, which significantly increases the cost of production. On the other hand, strains of the genus Bacillus give a smaller amount of lactic acid from non-hydrolyzed substrates, food or industrial waste,

which is quite attractive from an economic point of view. The use of other genera of bacteria is rarely found in the literature and is almost of no interest to the scientific community. Therefore, the most optimal industrial producers of lactic acid are lactic acid bacteria and bacteria of the genus Bacillus. When developing a technology for obtaining lactic acid using these strains, it is necessary to take into account the type of available carbohydrate substrates, which directly affects the profitability of the future enterprise.

4. Substrates for the Synthesis of Lactic Acid

The basic substrate required for the synthesis of lactic acid by microorganisms is a source of carbon, namely carbohydrates. From 1 gram of pentose or hexose, 1 gram of LA can theoretically be formed, which corresponds to 100 % product yield, but in practice, this is almost impossible. Highly productive sources of carbon are mono– and disaccharides, namely glucose, sucrose, and lactose, but their use as nutrient medium components is economically unjustified. In addition, the main producers of lactic acid – LAB have rather complex requirements for the nutrient medium components, which play a significant role in the functioning of the metabolic pathways of converting carbohydrates into lactic acid. They need complex protein sources and a large number of amino acids, vitamins (mainly group B), and metal ions. For other types of lactic acid producers (bacteria of the genus *Bacillus*, strains of *E. coli,* and *C. glutamicum*), simple sources of nitrogen and some metal ions are usually required, which are involved in the development and reproduction of the microbial population.

When choosing the nutrient medium components, it is necessary to take into account not only the needs of the producer, but also the cost of raw materials. The main obstacle in the industrial synthesis of lactic acid is the selection of cheap and productive substrates, which often account for 50–60 % of the final product price and affect production profitability. Raw materials for the production of LA by fermentation should have the following characteristics: cheap; with a low level of toxic and polluting substances and by-products; when using this raw material, the producer microorganism must have high values of productivity and output; the ability to ferment with little or no pretreatment; accessible and renewable[16].

Based on literature sources[11,13–17], the substrates that can be used for the synthesis of lactic acid in industry can be divided into two main groups:

- Agricultural products and waste.
- Waste of light and food industry.

4.1. Starch− and Cellulose-Containing Materials

4.1.1. Starchy Materials

Starchy materials that can be used for the industrial production of lactic acid by fermentation include crops (potatoes, rice, corn, wheat), industrial processing products (flour and starch), and waste.

Starchy materials undergo the process of hydrolysis to be used as a substrate. Classical hydrolysis is a two-phase process using alpha (EC 3.2.1.1) and glucoamylase (EC 3.2.1.3). In the first stage, alpha-amylase converts starch molecules into oligosaccharides of different lengths, and in the second stage, glucoamylase converts these oligosaccharides into glucose. According to Yong Wang, approximately 90 % of LA on the market is produced by fermentation using corn as a substrate. The disadvantage of using products with a high starch content is their high cost, which is almost 70 % of the production total cost[57]. Therefore, the use of waste with a high starch content is promising and profitable. For example, research articles describe the use of potato processing waste[45,58,59].

Some natural and genetically modified strains of LAB can convert starch into lactic acid without prior hydrolysis due to the presence of an amylolytic enzyme complex. Such LABs include *L. amylophilus; L. amylovorus; L. plantarum A6;* strains *of Lactobacillus* LEM220, 207 and 202; *Leuconostoc strains; L. acidophilus; L. cellobiosus; L. plantarum;* strains of *L. fermentum* Ogi E1 and MW2; *Lactobacillus amylolyticus* and *Lactica-seibacillus manihotivorans* strains[60–62].

4.1.2. Cellulosic and Lignocellulosic Waste

Cellulosic and lignocellulosic substrates that can be used as substrates include lignocellulosic biomass (straw, corn cobs, sunflower husks, green parts of plants)[63–66], wood industry waste, wood[67,68], paper[51] and other household wastes.

These substrates must be hydrolyzed for the production of lactic acid. Cellulosic waste can be converted to glucose by acid or enzymatic hydrolysis. Enzymatic hydrolysis is more profitable and safer. The splitting of cellulose into glucose occurs by the sequential action of the cellulolytic complex enzymes, which include three stages. Initially, endocellulases (EC 3.2.1.4) randomly cleave internal bonds in the cellulose molecule, resulting in the formation of short chains. Subsequently, exocellulases (EC 3.2.1.91) cleave short chains to tetra– or disaccharides, which are converted into glucose under the action of cellobiase (EC 3.2.1.21).

Compared to cellulosic substrates, enzymatic hydrolysis of lignocellulosic biomass without pretreatment is

inefficient due to the high stability of the material structure, which is caused by the association of cellulose and hemicellulose with lignin. Therefore, before the hydrolysis process, preliminary treatment is carried out, the purpose of which is to remove lignin, separate cellulose and hemicellulose, partially depolymerize cellulose, and increase the porosity of the material to facilitate the subsequent access of hydrolytic enzymes. Pretreatment methods include physical (mechanical), physicochemical (steam pretreatment, hydrothermolysis, wet oxidation), and chemical (action of acids, alkalis, and other compounds). Unlike starchy materials, lignocellulosic biomass is much cheaper and available in large quantities, but the process of preparing it for fermentation is quite complex and expensive. In addition, the process of LA synthesis from lignocellulosic hydrolyzate by microorganisms is usually inhibited by inhibitors, namely: furfural, 5-hydroxymethylfurfural, and acetic acid[11,14].

4.2. Industrial Waste

4.2.1. Cheese Whey

Whey is a major byproduct of the dairy industry, containing approximately (w/v) 5 % lactose, 1 % protein, 0.4 % fat, and some minerals. It has a high content of BOD (biological oxygen demand) and COD (chemical oxygen demand) (40,000–60,000 ppm), which is a serious hazard when released into the environment[44]. Cheese whey as a substrate for the production of lactic acid is often mentioned in research articles[42–44,69].

The advantages of using cheese whey as a substrate for the synthesis of lactic acid are low price and widespread use. The main disadvantage is the presence of complex proteins that are unavailable to LA producers without prior hydrolysis. Therefore, it is necessary to add other sources of nitrogen (amino acids and peptides), vitamins, and trace elements to whey before the fermentation process. In addition, during the production of lactic acid from cheese whey, it is also worth paying attention to the inhibitory effect of lactic acid, which is present in the whey before fermentation. To reduce the initial content of lactic acid in cheese whey, it must first be passed through ionic membranes[29].

4.2.2. Molasses

Molasses is the main product of sugar production in the industry, containing approximately 50 % sugars (sucrose, glucose, fructose, raffinose), nitrogen-containing compounds, organic acids, amino acids, heavy metals, and others. Molasses is often used as a classic substrate for the cultivation of various taxonomic groups of bacteria, yeasts, and microscopic fungi. In research articles, it is used in the synthesis of LA by lactic acid bacteria strains[38,48,70,71].

4.3. Food Waste

Food waste is a promising substrate for use in the production of lactic acid, which contains large amounts of carbohydrates. In addition, the use of waste is an effective way to reduce it.

Food waste that can be used for LA production includes: damaged and expired yogurt[72], unfit bread[49], leftover food with a high carbohydrate content (vegetables, fruits, cooked cereals)[73], and even vegetable and fruit peels[37].

5. Conclusions

The rate of production of lactic acid during the last decade has increased significantly, which is connected with its wide application in industry. The biotechnological method of lactic acid production is a promising way, by which more than 90 % of lactic acid in the world is obtained. The main aspects of the biotechnological production of lactic acid are the selection of the producer strain, cultivation mode, and substrate. The work described in detail the metabolic pathways of carbohydrate conversion into lactic acid, which is necessary for a general understanding of the biosynthesis process; microbial cultivation regimes with their advantages and disadvantages; cheap and common sources of carbon. These three aspects are considered in detail in this work, which is the valuable information in the development of the technology for obtaining lactic acid in industry.

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МОЛОЧНА КИСЛОТА: ПРОМИСЛОВИЙ СИНТЕЗ, МІКРООРГАНІЗМИ-ПРОДУЦЕНТИ ТА СУБСТРАТИ: ОГЛЯД

Анотація. *Ця стаття містить вичерпну інформацію про групи бактеріальних продуцентів молочної кислоти, що мають високу метаболічну активність і можуть застосовуватись у промисловому виробництві. Крім цього, здійснено огляд найпоширеніших методів ферментації, а саме: періодична, періодична з підживленням, безперервна і повторна, та дешевих джерел карбону: крохмале– та целюлозовмісні промислові та харчові відходи.*

Ключові слова: *молочна кислота, біотехнологія, виробництво, продуценти молочної кислоти, субстрати для синтезу молочної кислоти.*