Recent advances in lactic acid production

Maham Aslam*, Ansa Khalid and Sikander Ali

Institute of Industrial Biotechnology (IIB), GC University Lahore, Pakistan

**Correspondence:* mahamaslam2018@gmail.com

Abstract:

Lactic acid (LA) is an organic acid that has several uses in cosmetic, food, pharmaceutical, leather, and textile industries. LA is synthesized chemically or by fermentation method. The fermentation method for LA production is more favourable because both isomers of LA (L and D) can be obtained separately. Microorganisms that produce LA are bacteria, fungi, yeast, algae, and cyanobacteria. Lactic acid can be produced by submerged and solid-state fermentation. Lactic acid production is improved by using recent technologies i.e. co-culture, genetic and metabolic engineering, immobilized bioreactor, cell recycle fermentation and simultaneous scarification and fermentation procedures. Moreover, renewable materials are also being used to reduce environmental problems. This review summarizes the information about lactic production by chemical and microbial fermentation methods and also discusses the recent technologies involved in its production and purification.

Index Terms: Lactic acid; Optical isomers; Fermentation; Microorganisms; Substrate; Recent advances; Purification

Introduction

The quest for commercially valuable products has been increasing day by day. As the world population is increasing gradually, the demand for valuable products by microbial fermentation has been increased. Green methods are being employed for the synthesis of valuable products. With the utilization of microbial fermentation techniques, we can reduce the global energy problems and other environmental concerns. Lactic acid (2- hydroxypropionic acid) is an organic acid that was discovered in 1780 by a Swedish chemist Scheele from sour milk [1].

Lactic acid is the most substantial product and has marvellous uses in many fields of life. Figure 1 represents the lactic acid-based possible products and their applications. About 35% of produced LA is being utilized in the food industry. It has a significant character in the production of cheese and yogurt [2]. LA has a slight acidic taste that's why it is being utilized as acidulant in food items. It is also being utilized as a preservative, flavour enhancer, pH maintainer and as an inhibitor of microorganisms in different processed food items. It is an active ingredient in the preparation of fermented food items such as canned vegetables and butter

[3]. It also has numerous applications in the chemical industry, where it is utilized for the manufacturing of acetaldehyde, acrylic polymers, ethanol, poly-lactic acid, and propylene glycol. The derivatives and salts of lactic acid are also being utilized as solvents and plasticizers. In the leather industry, LA is being utilized for the removal of hairs and scales and in the textile industry it is utilized as a mordant to fix dyes on clothes.

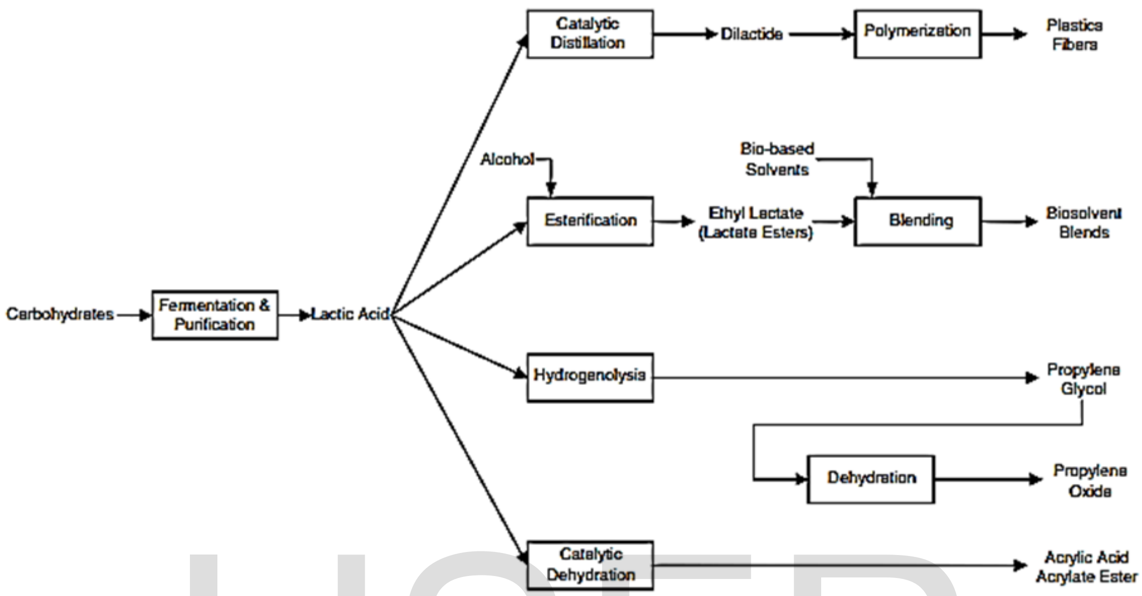

Figure 1: Lactic acid-based possible products and their applications.

Lactic acid also plays a significant role in controlled delivery of drug within the body. That's why in therapeutics it is utilized in dialysis, pills, and surgical structures formations. Lactic acid provides moisturizing, antibacterial and refreshing properties to the skin. Due to these marvellous properties, it is used in cosmetic industry for the production of sanitary compounds [2]. Advanced uses of LA have been established, where it has been utilized for the manufacturing of biodegradable poly-lactic acid polymers. About 39% of LA has been utilized for the production of biopolymers having high molecular weight and high tensile strength. With the removal of water from lactic acid as shown in Eq. 1, the lactides are formed which further utilized to form decomposable thermoplastic polymers [4].

$$2CH_3CHOHCOOH \rightarrow C_6H_8O_4 + 2H_2O \quad (1)$$

LA can be considered as alcohol and acid. There are two optically active stereoisomeric forms of LA, that are L (+) and the D (-) as shown in Figure 2. These two enantiomers have same physical properties such as melting point, density, and solubility. In humans, high level of D (-) lactic acid is dangerous. L- Lactate dehydrogenase enzyme is present in humans which can metabolize L (+) lactic acid that's why L (+) lactic acid is being utilized in the food and pharmaceutical industries [5].

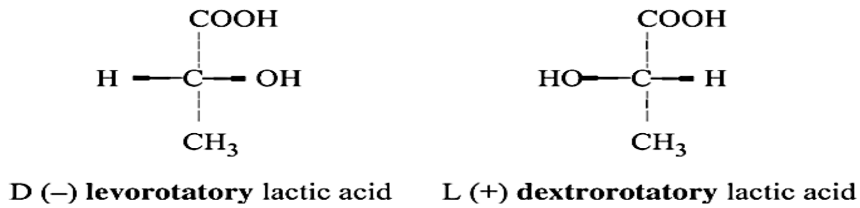

Figure 2: Optical isomers of lactic acid L (+) and the D (-)

LA can be synthesized either by microbial fermentation or chemical synthesis method. By microbial fermentation, pure form of L (+) and the D (-) lactic acid is produced. But in chemical synthesis, a mixture of both L (+) and the D (-) form of lactic acid is produced in equal proportion. Microbial fermentation has extra advantages than the chemical production methods e.g. cheap raw materials (e.g. cane sugar, beet, starch waste, molasses, and whey, etc.) can be used in microbial fermentation method. LA production can be obtained from bacteria such as *Bacillus* species, *Escherichia coli*, *Corynebacterium glutamicum*, and lactic acid bacteria (LAB). In fungi, *Rhizopus oryzae* is involved in the formation of L-lactic acid. Yeast and photosynthetic bacteria (such as cyanobacteria and algae) are also involved in the production of LA. Moreover, engineered microorganisms are now being used for the cost-effective and high quantity production of LA [4]. In the present review, new developments in LA production by using wild type, co-culture, and genetically modified organisms have been discussed.

Microorganism Responsible For Lactic Acid Production

Several microorganisms are responsible for the synthesis of LA such as bacteria, fungi, yeast, algae, and cyanobacteria. Figure 3 represents the microorganisms involved in lactic acid production. In bacteria, there are four important producers of lactic acid i.e. *Bacillus* strains, LAB, *E. coli* and *Corynebacterium glutamicum*. Lactic acid bacteria (LAB) give high productivity and high yield of lactic acid. LAB is Gram-positive bacteria that can be cultivated in a broader pH range i.e. 3.5 to 10.0 and also grows at a low temperature of almost 5^oC. The LAB can be grouped as homo-fermentative and hetro-fermentative on the basis of ending products of fermentation. In homo-fermentative LAB, lactic acid is produced as the main ending product but in hetro-fermentative LAB, many by-products are also produced in addition to LA. Mostly LA production is given by following genera having LAB species; *Aerococcus, Carnobacterium, Lactobacillus, Lactococcus, Leuconostoc, Streptococcus,* and *Enterococcus* [6].

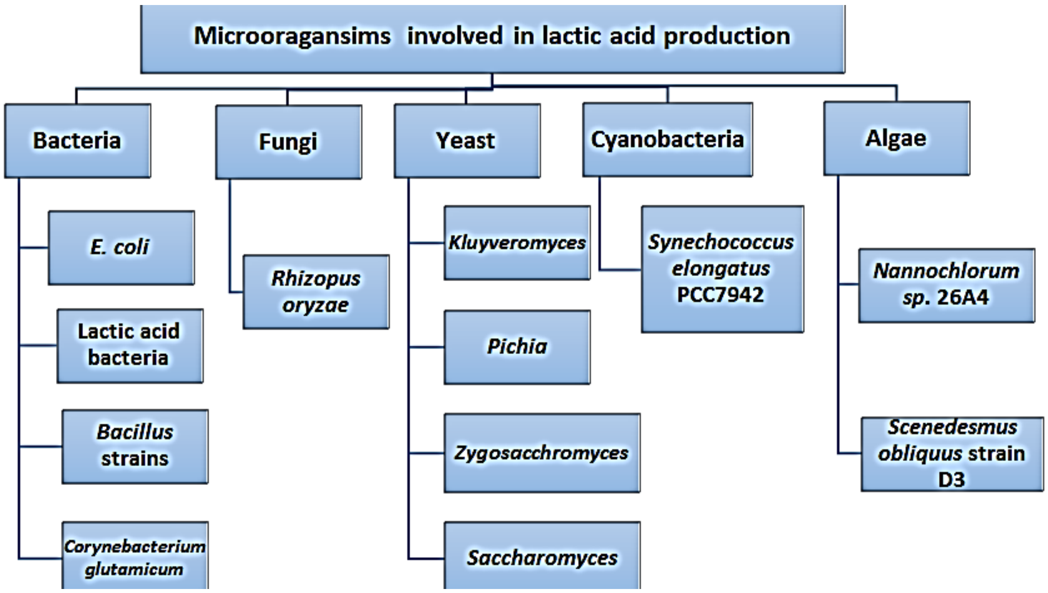

Figure 3: Microorganism involved in the production of lactic acid

Various species of Bacillus are also involved in the synthesis of LA, such as; *Bacillus subtilis*, *B. stearothermophilus*, *B. cheniformis* and *B. coagulans*. Bacillus species have some advantages over the LAB in lactic acid production i.e. can grow in less expensive and less complex medium having limited nitrogen sources [7]. Also, *Bacillus* species can tolerate the temperature of about ≥50 °C and pH of 9.0, which lessen the possibility of contamination during lactic acid production. Bacillus species can metabolize the hexose and pentose in lignocellulosic raw material and produce lactic acid.

The wild type of *E. coli* can synthesize many organic acids (lactic acid, formic acid, and acetic acid). Modified strains of *E. coli* can be utilized to obtain maximum yield of LA. Also, *C. glutamicum* produces many organic acids but in minute quantities. LA production can be enhanced by using modified strains of *C. glutamicum*, by using various sugars under oxygen-deprived conditions. For example modified strain of *C. glutamicum* synthesized 17.9g/L of D-LA afterward 16 hours of incubation which was 32.3% greater than the LA synthesized by wild type strain of *C. glutamicum* [8]. Table 1 shows various bacteria and their substrate utilization for the production of lactic acid.

The prominent fungal specie for LA synthesis is *Rhizopus oryzae*. This specie requires fewer nutrients and its mycelia development and oxygen requirements affect the synthesis of LA. The *Rhizopus* strain has various benefits over LAB i.e. it produces LA by a low-cost down-streaming process because the mycelia or pellet growth of fungi allows its easy separation from fermentation medium [9]. A major problem in the LA production is the cost-effective separation and purification from the fermentation medium. Yeast has the potential to grow in mineral medium that assists in easy recovery of LA from fermentation medium [10]. Yeast can grow at low pH of about 1.5, which helps in the establishment of non- lactate fermentation. The wild type of yeast is replacing engineered yeast, which produces high yield of LA.

Global warming is a major concern in the world shifting attention towards environmental friendly process. Photosynthetic microorganisms are being utilized for the production of LA. The photosynthetic bacteria has an alternative method for the synthesis of LA. Microalgae can utilize starch which they stored in the presence of light and oxygen and convert it into organic acid in the absence of oxygen and dark conditions [11]. Cyanobacteria need simple nutrient requirements. With the introduction of the lactic acid-producing gene in cyanobacteria, LA production can be attained. An L-LDH gene tfrom *B. subtilis* was introduced into the genome of *Synechocystis enlongatus* PCC6803 and that engineered strain produced 3.2mM of LA [12]. By using co-culture of microorganisms, the LA production can be enhanced. Moreover, genetically engineered microorganisms are also utilized in order to meet the commercial demands of LA. Genetically engineered microorganisms can enhance the production of LA and can also reduce the nutrients supply.

Table 1: Microorganisms involved in the production of lactic acid

Substrate	Microorganism	Fermentation process
Alfalfa fibers	*Lactobacillus plantarum*	Batch
Apple pomade	*Lb. rhamnosus ATCC 9595* (CECT288*)*	Batch
Cellulose	*B. coagulans* 36D1	Fed batch
Cheese whey	*Lb. casei* NRRL B-441	Batch
Corncob molasses	*Bacillus sp. strain*	Fed batch
Glycerol	*E. coli* AC-521	Batch
Lignocellulosic hydrolyzates	*Bacillus sp.* NL01	Fed batch
Date juice	*L. rhamnosus*	Batch
Wheat straw	*L. pentosus*	Fed Batch
Whey	*L. acidophilus*	Batch
Rice	*L. delbrueckii*	Fed Batch

Production Techniques of Lactic Acid

Naturally, LA is present in animals, plants, and microorganisms. It can also be produced artificially by the fermentation of carbohydrates or chemically from coal, natural gas, and petroleum. As the universal demand for lactic acid is increasing day by day due to its marvellous advantages, so its production on industrial level should be increased. On industrial level, there are two main procedures for the production of lactic acid i.e. chemical and fermentation method. Figure 4 represents two techniques of LA production; chemical synthesis and fermentation technology.

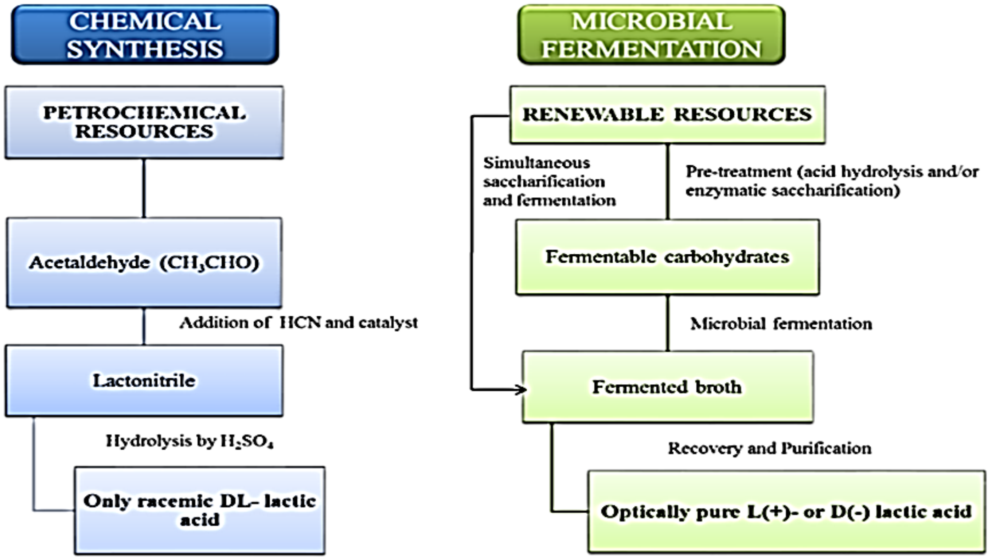

Figure 4: Overview of two production techniques of LA; chemical synthesis and fermentation technology

Chemical Synthesis of Lactic Acid

Monsanto (Texas, USA) was the first company that synthesized LA chemically in 1963. In chemical synthesis of LA, under high-pressure, acetaldehyde reacts with hydrogen cyanide, in a liquid phase and forms lactonitrile. After the separation and purification of lactonitrile, HCl or H_2SO_4 is added to convert lactonitrile into LA. Then, esterification of LA occurs by using methanol and methyl lactate is formed. Distillation method is further utilized for the separation and refining of methyl lactate. In the end, methyl lactate is hydrolyzed into LA in the presence of an acidic solution. Methanol is also produced in this reaction, which is utilized again in chemical synthesis [13]. There are many other chemical ways for the synthesis of lactic acid i.e. base-catalyzed metabolism of carbohydrates, oxidation of water and carbon monoxide at high temperature and pressure [14]. Figure 5 shows conventional method for the LA production from carbohydrates. Except the consumption of lactonitrile for LA synthesis procedures, other procedures are very complex and costly. Chemical synthesis of LA is not a desirable process because of following disadvantages; it is an expensive procedure because of utilization of fossil fuels, a racemic mixture of LA isomers synthesized and product impurity.

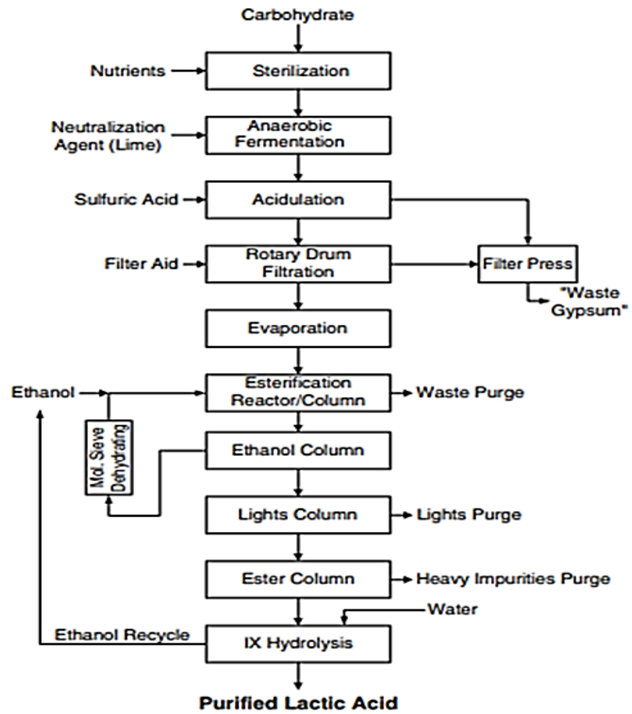

Figure 5: Conventional procedure for LA production from carbohydrate.

Fermentation Technology for the Production of Lactic Acid

Fermentation is a fast and less expensive procedure, which gives a high yield and productivity of desired product. By using this method, one of the two isomers or their mixture can be obtained. In this method, a medium containing nutrients and sugar are inoculated with a specific microorganism, and fermentation occurs. Aeration, agitation, temperature, pH, and nutrients are optimized depending upon microorganism used for fermentation. The search for the cost-effective substrates has led to the development of advanced methods to synthesize LA. Commonly the substrates utilized for the LA formation by microbial fermentation are following; whey, molasses date juices, starch, and lignocellulosic biomass.

Whey, molasses and date juice

Any substrate containing pentose or hexose can be exploited for the production of LA. The by-product of food industries can be used for this purpose. For-example, whey is produced from dairy industry. It is a by-product which is released in the wastewater effluent from these dairy industries and is a foremost pollution problem for them. Whey is an efficient substrate for microorganisms because it contains lactose sugar, fats, proteins, vitamins, and minerals. In theory, one mol of lactic is produced from four moles of lactose by a homo-fermentative pathway [4]. Molasses formed in sugar industries is also a large and cheap source for the synthesis of LA [15]. Date juices are also a good source for the synthesis of LA [16].

ISSN 2229-5518

Starchy and lignocellulosic materials

Starchy materials consisted of starch, which is a biopolymer of glucose linked by α (1→4) linkage. Starchy materials give an easy and cheap way to produce lactic acid in huge amounts. Various microbes can utilize starch easily because they have extracellular amylases, so there is no need to give them extra preliminary treatment to hydrolyze starch. Another substrate for LA production by microorganisms is lignocellulosic biomass. It is composed of 90% dry mass of cellulose, hemi-cellulose, and lignin. It is first depolymerized and then enzymatic hydrolysis occurs to convert it into simple sugars. Then sugar fermentation occurs by LAB and produce lactic acid. Currently, saccharification and fermentation procedures are performed collectively to prevent the degradation of enzymes by the products of fermentation [17].

Lactic acid production by submerged fermentation

The submerged fermentation method is environmentally friendly and can be easily operated. In submerged fermentation, soluble substrate are utilized for the synthesis of LA. Corn starch and soluble starch were consumed for the synthesis of LA in 1992 and 1995, respectively [18][19]. At the low concentration of soluble starch, about 90% LA production was obtained as compared to high concentration of soluble starch at which low yield of LA was obtained.

Lactic acid production by solid-state fermentation

Solid-state fermentation is a procedure in which microorganisms cultivate on a moist solid substrate with devoid of extra water. It is a difficult and lengthy process as compared to submerged fermentation but more valuable for the synthesis of LA. In this method, solid substrate provides nutrients and also supports the culturing cells. Different solid substrates can be utilized for the synthesis of LA in SSF i.e. wheat bran, corn fibre, black gram bran, and pigeon pea brans, etc. Mostly wheat bran is utilized for the synthesis of LA because it gives high yield of lactic acid. *L. amylophilus* GV6 gave high amount of LA about 90.111% by utilizing wheat bran as a solid substrate [20].

Lactic Acid Production; Recent Advances

Lactic acid has significant important roles ranging from life sciences to the food industry. Even though its production has been achieved by old fermentation methods but those conventional methods are not capable of achieving good quality and quantity; the basic needs of a consumer. This issue has ultimately shifted the focus towards the development of such technologies which not only make the resulting product economic but also enhance its yield [21]. Figure 6 represents the recent advancements in lactic acid production.

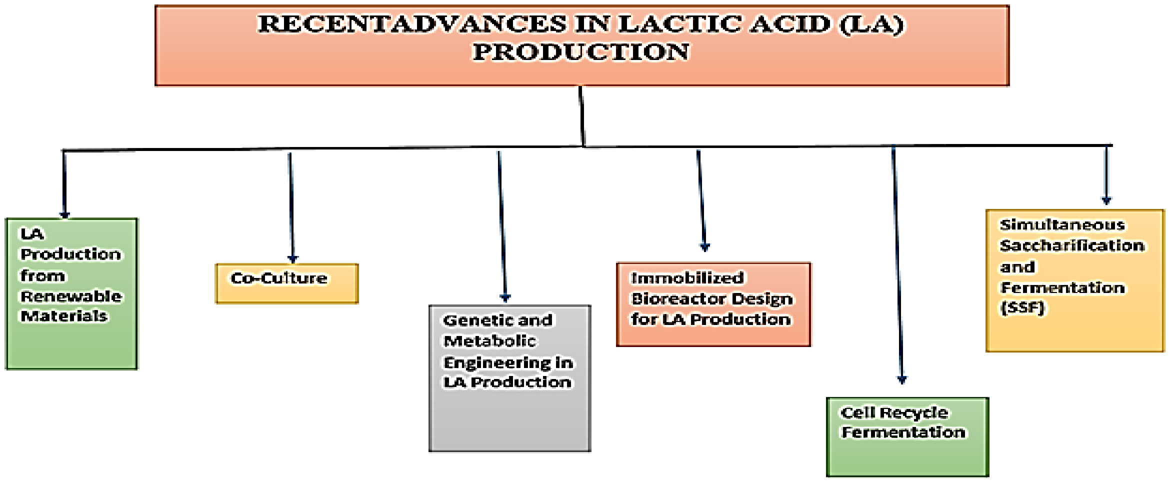

Figure 6: Recent advances in lactic acid production

Lactic Acid Production from Renewable Materials

Usage of renewable materials for the production of various chemicals has gained attention as it provides an eco-friendly alternative to the problems induced by fossil fuel depletion and petroleum industry. That's why for production of such chemicals, the usage of industrial and agriculture waste has gained attention. Mostly, glucose is used as raw material for LA production, but now focus is being shifted towards such renewable alternatives such as lignocellulose and starch which are not only economically stable but are quite efficient [22]. Thus, agricultural waste is one of the best modes of renewable resources for production of valuable chemicals and biofuels [23]. The process of LA production is briefly described below.

Pre-treatment of raw renewable materials

Enzymatic breakdown of raw material converts complex raw material into simple form and resulting hydrolyte can be used in fermentation. Renewable material is pre-treated to achieve several goals such as, to remove lignin, to increase the surface area for reaction to occur, to increase the porosity of the material and to partially depolymerize hemicellulose renewable material is pre-treated. Pre-treatment methods are described by Taherzadeh and Karimi, [24]. This step is advantageous as complex structure becomes simple as its size is reduced and its structure is opened for enzymes to make action [25].

Enzymatic hydrolysis

Enzymatic hydrolysis is required to breakdown complex sugars into simpler form, even in "water-insoluble solid fraction that remains after pre-treatment". Such hydrolysis is carried out by 3 types of cellulases i.e., endoglucanase (on attacking cellulose, creates "reducing and non-reducing" ends), exoglucanase (cleaves cellobiose from free chains) and β-glucosidase (catalyses cellobiose into 2 glucose molecules) [26]. Figure 7 shows the action of different types of cellulases.

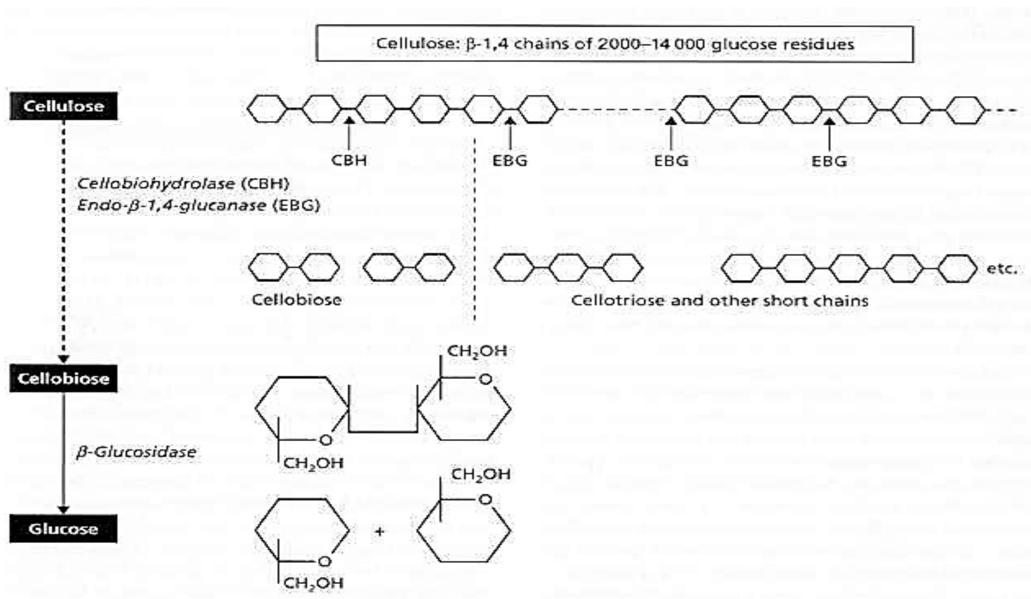

Figure 7: Schematic representation of activity of Cellulases

Fermentation modes and methods

Different fermentation methodologies such as "batch, semi-continuous, fed-batch, repeated batch, separate hydrolysis and fermentation and continuous", have been investigated for the production of LA from renewable materials. Batch fermentation gives higher yield as compared to continuous fermentation process [27]. During process of continuous fermentation, diluting media can result in reduction of end product inhibition. Higher cellular biomass can be achieved by employing continuous fermentation along with cell recycle system [28].

Separation and purification of lactic acid

The final quality and cost of a product depends upon separation and purification technologies being employed. The conventional purification method is described by [29]. Many other alternatives such as membrane bioreactor, adsorption, electro-dialysis, and liquid surfactant membrane extraction have been employed which perform not only separation but also concentration of LA [6].

Co-Culture

Fermentation technique which consists of "two or more cell populations" for the production of a specific product is known as co-culture. The need for co-culture occurs when one culture is not capable of growing alone, thus, a second culture is added to boost its growth. Some LAB are hetero-fermentative and produce significant amounts of by-products (ethanol and acetic acid) causing the overall yield of product to be low and making it economically unfeasible as additional separation and purification techniques would be required to get the pure product [21]. To solve the problem, homo-fermentative strains are used which can make other strains to utilize other metabolic pathways for conversion of xylose into lactic acid, eventually reducing the accumulation of various by-products [30]. Saho and Jayaraman, [13] reported enhanced yield of D-lactic acid through "co-culture of *L. delbrueckii* and engineered *L. lactis*".

Genetic and Metabolic Engineering

This technique results in LA production with lowest by-product formation, enhanced yield and low cost [32]. Metabolic engineering has helped in achieving three goals related to the product which are productivity, titre and yield [33]. Conventional LA production faces many problems such as strains used are low acid-tolerant and are capable of using only a limited amount of a substrate. The optical and chemical purity of LA varies due to ability of LAB to utilize substrates through inefficient metabolic pathway. To solve the problem, this technology helps in getting purer LA, increasing the acid tolerance of strains and making the strains to consume the substrate via metabolically efficient pathways. Metabolic engineering mainly focuses on heterologous gene expression. Different genetic and metabolic engineering techniques for enhanced LA production are shown below in Table 2 [34].

Table 2: Enhanced properties of lactic acid production via different engineering approaches.

Strain	Enhanced Properties	Engineering Approach
Synechocystis sp. PCC 6803	Optically pure D-lactic acid	Codon optimization and by balancing the cofactor (NADH) availability through the heterologous expression of a soluble transhydrogenase
Candida sonorensis ldhL strain	Increased productivity	Integration of two copies of the ldhL gene
S. cerevisiae strain CEN.PK2-1D	Improved LA titer	Redox balance engineering and heterologous L-lactate dehydrogenase (LDH) gene replacement
Pediococcus acidilactici TY112 and *P. acidilactici* ZP26	High titer L- and D-lactic acid production	ldhD or ldh gene disruption

Immobilized Bioreactor Design for LA Production

Conventional bio-catalytic methods have been used for decades for LA production. But with time consumer has been demanding for food products which have enhanced quality and in great portion [35]. LA has inborn property of enhancing the quality of foods, making researchers develop such techniques that enhance quality and quantity of different foods. Immobilized bio-catalytic processes have helped in this regard. Immobilization is a process that restricts the movement of a biocatalyst (cell or enzyme) but doesn't affect its catalytic activity. In case of enzymes, immobilization helps in its repeated use. For LA production, biocatalysts are metabolically engineered for production. To maintain a low cost of any product, biocatalysts need to be recovered [21]. Various immobilization techniques for LA production have been studied, i.e., encapsulation, adsorption, covalent binding, entrapment and cross-linking. Productivity of reaction is also greatly influenced by choice of the support material and immobilization technique used [2]. Based on immobilization techniques and support medium used, different types of bioreactors are discussed below.

Continuous stirred tank reactors (CSTR)

CSTR has been extensively used for LA production due to several advantages such as controllable production parameters and its high capacity. The first study on LA production in CSTR as a non-immobilised technique dates back to 1980s. Initially, optimum CSTR reaction parameters were not well understood [36].

Greater viability of "*L.bulgaricus*" in not only production but also in storage was obtained by encapsulating bacteria in beads of "κ-carrageenan-locust bean gum gel" in a CSTR using "whey permeate supplemented medium" as a substrate. As compared to free cells, acid production and lactose utilization were higher in the immobilization case [37]. This very first observation led to several investigations focusing on using new support medium to be used in CSTR. When "*L. casei* and *L. lactis*" were immobilized in other support materials (calcium alginate, polyacrylamide, and agar) using "deproteinized whey" as a substrate, no significant productivities were observed but such immobilization showed significant effect in terms of final lactic acid concentration and bacterial activity [38]. Vigorous mechanical stress during the fermentation process in CSTR results in burst of support material. Transgenic filamentous fungi are also being used for LA production [39]. But the problem with filamentous fungi is that they form micelle like structures that hinder proper mixing resulting in low productivity. Self-immobilization of the filamentous fungi can solve this problem [21].

Fibrous-bed bioreactor (FBB)

FBB is quite efficient in getting long term stability of the final product leading to enhanced production of LA. FBB systems are easy to be designed but support material for immobilization must be chosen with great care as it greatly affects the diffusion between fermentation broth and cells, and if not chosen wisely, may affect the process efficiency. According to Shi *et al.*, [40] FBB when operated in batch fermentation can give productivity up to two times more when compared to free cell system. The initial substrate concentration must be chosen with great care during repeated batch system as it ultimately affects the final productivity. Mass transfer limitations between immobilized microorganism and broth are frequently observed in fungi and are influenced by the type of material utilised to fill FBB [41].

Packed bed bioreactor (PBR)

For immobilizing biocatalyst into the column of a bioreactor in pellet or bead form, PBR system is used. As biocatalyst is immobilized, to feed biocatalyst along support material, fermentation broth is added into bioreactor through an inlet. These systems are suitable for working of such LABs which don't need oxygen. Length of packed column can affect the overall productivity as this may cause decrease in viable cell population due to starving of cells [42].

Cell Recycle Fermentation

Systems with cell recycling improve the overall productivity of LA production by allowing the production at high cell density. The insertion of "microfiltration membrane modules" enhance cell recycling. Following completion of production, production medium containing cells and permeate is introduced into "cross-flow microfiltration module", permeate is collected in a different chamber and cells are sent back to system for process to continue. Despite many advantages of this system, some unfavourable scenarios may occur as shown in Figure 8 [4].

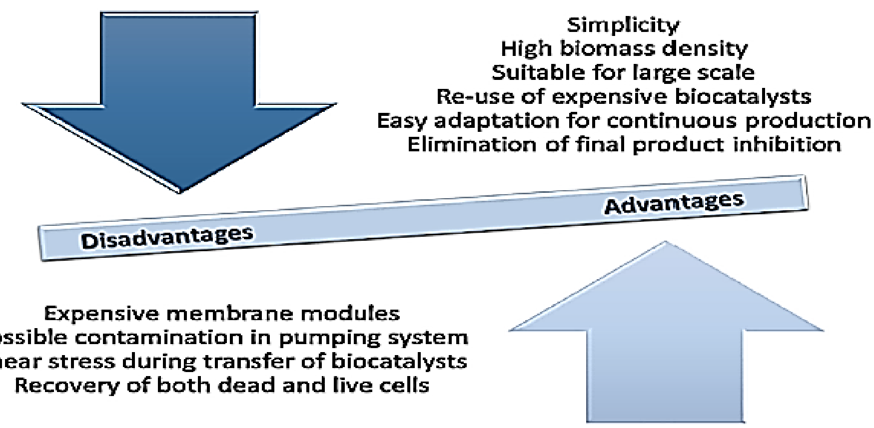

Figure 8: Advantages and disadvantages of cell recycling systems.

For continuous transfer of cells and permeate, a pumping system is required which will connect the whole system, but such a situation makes the sterilization more frequent, making it costly. LAB can suffer from loss of activity due to decrease flow and fouling in pumping system when a large scale LA production is required. Thus, in such case, process optimization is essential. Frequently, in such systems genetically modified strains are used for LA production which decreases the cost of process. End product inhibition (caused by LA when pH is low) can also be reduced here. Besides pH, microorganisms used, initial concentration of substrate and substrate type greatly influence the overall productivity of process. This system makes the by-product formation minimum, leading to few product purification steps and making the process cost-effective [21].

Simultaneous Saccharification and Fermentation (SSF)

Hydrolysing polysaccharides into simple saccharides so that the substrate can be used efficiently during LA production is known as saccharification. As compared to old process, SSF provides a “single-step enzymatic hydrolysis and fermentation”. This single-step reaction decreases the overall processing time [30]. The catalytic reaction of cellulase can be inhibited by high concentration of glucose. So, simultaneous use of glucose can not only avoid biocatalyst inhibition but can also prevent glucose elimination [6]. Reaction kinetics of a microorganism must be well understood as different strains result in different productivities due to their ability to consume glucose differently. In SSF, to achieve an ideal production value, glucose must be consumed more rapidly so that it won’t be accumulated in the fermentation medium. If not, the substrate (e.g. xylose) won’t be consumed ideally by microorganisms [43]. To decrease overall cost and to get high yield and concentrations of LA, SSF is a promising approach [44].

Conclusion

Lactic acid having various applications had always been the focus of researchers and industrialists. To meet the need of the consumer, conventional production methods are not enough, thus, technological advancements to enhance the overall yield and making a product economically stable is the main goal. The advancements discussed above can surely help in achieving the above-mentioned goals.

References

[1] U.A. Lima, E. Aquarone, W. Borzani, and W. Schmidell, “*Biotecnologia Industrial Processos Fermentativos e Enzimaticos,”* Blucher, Sao Paulo, Brazil, 2001.

[2] F.A.C. Martinez, E.M. Balciunas, J.M. Salgado, J.M. D. González, A. Converti, and R.P.S. Oliveira, “ Lactic acid properties, applications and production: A review,” *Trends Food Sci. Tech.*, vol. 30(1), pp. 70-83, 2013, https://doi.org/10.1016/j.tifs.2012.11.007.

[3] B.J. Naveena, “Amylolytic bacterial L (+) lactic acid production in solid state fermentation and molecular identification of the strain,” Ph.D. Thesis, Osmania Univ., Hyderabad, India, 2004.

[4] M.A. Abdel-Rahman, Y. Tashiro and K. Sonomoto, "Recent advances in lactic acid production by microbial fermentation processes," *Biotechnol. Adv.*, vol. 31(6), pp. 877-902, 2013, https://doi.org/10.1016/j.biotechadv.2013.04.002.

[5] K. Hofvendahl and B. Hahn-Hagerdal, "Factors affecting the fermentative lactic acid production from renewable resources," *Enzyme Microb. Technol.*, vol. 26, pp. 87-107, 2000, https://doi.org/10.1016/S0141-0229(99)00155-6.

[6] Y. Wang, Y. Tashiro and K. Sonomoto, "Fermentative production of lactic acid from renewable materials : Recent achievements , prospects , and limits," *J. Biosci. Bioeng.*, vol. 119, pp. 10-18, 2015, https://doi.org/10.1016/j.jbiosc.2014.06.003.

[7] Q. Wang, X. Zhao, J. Chamu and K.T. Shanmugam, "Isolation, characterization and evolution of a new thermophilic *Bacillus licheniformis* for lactic acid production in mineral salts medium," *Bioresour. Technol.*, vol. 102, pp. 8152-8158, 2011, https://doi.org/10.1016/j.biortech.2011.06.003.

[8] X. Jia, P. Liu, S. Li, S. Li and J. Wen, "D-Lactic acid production by a genetically engineered strain *Corynebacterium glutamicum*," *World J. Microbiol. Biotechnol.*, vol. 27, pp. 2117-2124, 2011, DOI: 10.1007/s11274-011-0675-9.

[9] C. Ruengruglikit and Y.D. Hang, "L (þ)-Lactic acid production from corncobs by *Rhizopus oryzae* NRRL-395," *Lebensm. Wiss. Technol*., vol. 36, pp. 573-575. 2003, https://doi.org/10.1016/S0023-6438(03)00062-8.

[10] S. Dequin, and P. Barre, "Mixed lactic acid-alcoholic fermentation by Saccharomyces cerevisiae expressing the Lactobacillus casei L-(+)-LDH," *J. Biotechnol.*, vol. 12, pp. 173-7, 1994, https://doi.org/10.1038/nbt0294-173.

[11] S. Hirayama and R. Ueda, "Production of optically pure D-lactic acid by Nannochlorum sp.," 26A4. *Appl. Biochem. Biotechnol*, vol. 119, pp. 71-77. 2004, https://doi.org/10.1385/ABAB:119:1:71.

[12] S.A. Angermayr, M. Paszota and K.J. Hellingwerf, "Engineering a cyanobacterial cell factory for the production of lactic acid," *Appl. Environ. Microbiol.*, vol.78, 7098-106, 2012, DOI: 10.1128/AEM.01587-12.

[13] P. Dey and P. Pal, "Direct production of L(þ) lactic acid in a continuous and fully membrane-integrated hybrid reactor system under non-neutralizing conditions," *J. Membr. Sci.*, vol. 389, pp. 355-362, 2012, https://doi.org/10.1016/j.memsci.2011.10.051.

[14] R.P. John, R. Sukumaran, K.M. Nampoothiri and A. Pandey, "Lactic acid fermentation from cassava bagasse using mixed culture Statistical optimization of simultaneous saccharification and L(þ)- of lactobacilli

by response surface methodology," *Biochem. Eng. J.*, 36(3), pp. 262-267, 2007, https://doi.org/10.1016/j.bej.2007.02.028.

[15] C. Kotzamanidis, T. Roukas and G. Skaracis, "Optimization of lactic acid production from beet molasses by Lactobacillus delbrueckii NCIMB 8130," *World J. Microbiol. Biotechnol.*, vol. 18, pp. 441-448, 2002, https://doi.org/10.1023/A:101552312.

[16] A. Nancib, N. Nancib and J. Boudrant, "Production of lactic acid from date juice extract with free cells of single and mixed cultures of Lactobacillus casei and Lactococcus lactis," *World J. Microbiol. Biotechnol.*, vol. 25, pp. 1423-1429, 2009, https://doi.org/10.1007/s11274-009-0029-z.

[17] F. Andres, C. Martinez, E. Marcos, M. Dom and R.P. De Souza, "Lactic acid properties, applications and production : A review," *Trends Food Sci. Technol.*, vol. 30, pp. 70-83. 2013, http://dx.doi.org/10.1016/j.tifs.2012.11.007.

[18] I. Yumoto and K. Ikeda, "Direct fermentation of starch to L(+)-lactic acid using *Lactobacillus amylophilus*," *Biotechnol. Lett.*, vol. 17, pp. 543–546, 1995, https://doi.org/10.1007/BF00132025.

[19] P. Mercier, L. Yerushalami, D. Rouleau and D. Dochania, "Kinetics of lactic acid fermentations on glucose and corn by Lactobacillus amylophilus," *J. Chem. Technol. Biotechnol.*, vol. 55, pp. 111-121, 1992, https://doi.org/10.1002/jctb.280550204.

[20] B.J. Naveena, C. Vishnu, Md. Altaf and G. Reddy, "Wheat bran an inexpensive substrate for production of lactic acid in solid state fermentation by *Lactobacillus amylophilus* GV6-optimization of fermentation conditions," *J. Sci. Ind. Res., vol.* 62, pp. 453-456, 2003.

[21] I. Es, A.M. Khaneghahb, F.J. Barbac, J.A. Saraivad, A.S.SantAnab and S.M.B. Hashemi, "Recent advancements in lactic acid production- a review," *Food Res. Int.*, vol. 107, pp. 763-770, 2018, https://doi.org/10.1016/j.foodres.2018.01.001.

[22] M. Neureiter, H. Danner, L. Madzingaidzo, H. Miyafuji, C. Thomasser, J. Bvochora, S. Bamusi and R. Braun, "Lignocellulose feedstocks for the production of lactic acid," *Chem. Biochem. Eng. Q.*, vol. 18, pp. 55-63, 2004.

[23] J. Grewal and S.K. Khare, "One-pot bioprocess for lactic acid production from lignocellulosic agro-wastes by using ionic liquid stable Lactobacillus brevis," *Bioresour. Technol.*, vol. 251, pp. 268-273, 2018, https://doi.org/10.1016/j.biortech.2017.12.056.

[24] M.J. Taherzadeh, and K. Karimi, " Pretreatment of lignocellulosic wastes to improve ethanol and biogas production: a review," *Int. J. Mol. Sci., vol.* 9, pp. 1621-1651, 2008, https://doi.org/10.3390/ijms9091621.

[25] M. Idrees, A. Adnan and F.A. Qureshi, "Optimization of sulfide/sulphite pretreatment of lignocellulosic biomass for lactic acid production," *Biomed. Res. Int.*, 934171, 2013, http://dx.doi.org/10.1155/2013/934171.

[26] M. Dashtban, H. Schraft and W. Qin, "Fungal bioconversion of lignocellulosic residues; opportunities and perspectives," *Int. J. Biol. Sci.*, vol. 5(6), pp. 578-595, 2009, doi: 10.7150/ijbs.5.578.

[27] K. Shibata, D.M. Flores, G. Kobayashi and K. Sonomoto, "Direct L-lactic acid fermentation with sago starch by a novel amylolytic lactic acid bacterium, *Enterococcus faecium*," *Enzyme Microb. Technol.*, vol. 41, pp. 149-155, 2007, https://doi.org/10.1016/j.enzmictec.2006.12.020.

[28] Y. Tashiro, W. Kaneko, Y.Q. Sun, K. Shibata, K. Inokuma, T. Zendo and K. Sonomoto, "Continuous D-lactic acid production by a novel thermotolerant *Lactobacillus delbrueckii* subsp. lactis QU 41," Appl. *Microbiol. Biotechnol.*, vol. 89, pp. 1741-1750, 2011, https://doi.org/10.1007/s00253-010-3011-7.

[29] J. Vijayakumar, R. Aravindan and T. Viruthagiric, "Recent trends in the production, purification and application of lactic acid," *Chem. Biochem. Eng. Q.*, vol. 22, pp. 245-264, 2008, https://hrcak.srce.hr/24811.

[30] L. Zhang, X. Li, Q. Yong, S.T. Yang, J. Ouyang and S. Yu,. "Simultaneous saccharification and fermentation of xylo-oligosaccharides manufacturing waste residue for L-lactic acid production by *Rhizopus oryzae*," *Biochem. Eng. J.*, vol. 94, pp. 92-99, 2015, https://doi.org/10.1016/j.bej.2014.11.020.

[31] K. T. Saho and G. Jayaraman, "Co-culture of *Lactobacillus delbrueckii* and engineered *Lactococcus lactis* enhances stoichiometric yield of d-lactic acid from whey permeate," *Appl. Microbiol. Biotechnol.*, vol. 103, pp. 5653-5662, 2019, https://doi.org/10.1007/s00253-019-09819-7.

[32] B. P. Upadhyaya, L.C. DeVeaux and L.P. Christopher, "Metabolic engineering as a tool for enhanced lactic acid production," *Trends Biotechnol.*, vol. 32(12), pp. 637-644, 2014, https://doi.org/10.1016/j.tibtech.2014.10.005.

[33] T. Un-Chae, , S.Y. Choi, J.W. Kim, Y.S. Ko and S.Y. Lee, "Recent Advances in systems metabolic engineering tools and strategies," *Curr. Opin. Biotechnol.*, vol. 47, pp. 67-82, 2017, https://doi.org/10.1016/j.copbio.2017.06.007.

[34] S.H. Baek, , E.Y. Kwon, Y.H. Kim and J.S. Hahn, "Metabolic engineering and adaptive evolution for efficient production of D-lactic acid in Saccharomyces cerevisiae," *App. Microbiol. Biotechnol.*, vol. 100(6), pp. 2737-2748, 2016, https://doi.org/10.1007/s00253-015-7174-0.

[35] N. N. Misra, M. Koubaa, S. Roohinejad, P. Juliano, H. Alpas, R.S. Inacio, J.A. Saravia and F.J. Barba, "Landmarks in the historical development of twenty first century food processing technologies," *Food Res. Int.*, vol. 97, pp. 318-339, 2017, https://doi.org/10.1016/j.foodres.2017.05.001.

[36] T.P. Hanson and G.T. Tsao, "Kinetic studies of lactic acid fermentation in batch and continuous cultures" *Biotechnol. Bioeng.*, vol. 14,pp. 233-252, 1972, https://doi.org/10.1002/bit.260140207.

[37] P. Audet, C.Paquin and C. Lacroix, "Immobilized growing lactic acid bacteria with x-carrageenan – locust bean gum gel," *Appl. Microbiol. Biotechnol.*, vol. 29, 11-18, 1988, https://doi.org/10.1007/BF00258344.

[38] T. Roukas, and P. Kotzekidou, "Production of lactic acid from deproteinized whey by coimmobilized *Lactobacillus casei* and *Lactococcus lactis* cells," *Enzyme Microb. Technol.*, 13(1). Pp. 33-38, 1991, https://doi.org/10.1016/0141-0229(91)90185-D.

[39] T. Mori, , H. Kako, T. Sumiya, H. Kawagishi and H. Hira, "Direct lactic acid production from beech wood by transgenic white-rot fungus *Phanerochaete sordida* YK-624," *J. Biotechnol.*, vol. 239, pp. 83-89, 2016, https://doi.org/10.1016/j.jbiotec.2016.10.014.

[40] Z. Shi, P. Wei, X. Zhu, J. Cai, L. Huang and Z. Xu, "Efficient production of L-lactic acid from hydrolysate of Jerusalem artichoke with immobilized cells of *Lactococcus lactis* in fibrous bed bioreactors," *Enzyme Microb. Technol.*, vol. 51(5), pp. 263-268, 2012, https://doi.org/10.1016/j.enzmictec.2012.07.007.

[41] N.C. Anandha, S. Thitiprasert, V. Tolieng and N. Thongchul, "Improved oxygen transfer and increased L-lactic acid production by morphology control of *Rhizopus oryzae* in a static bed bioreactor,". *Bioprocess Biosyst. Eng.*, vol. 34(2), pp. 163-172, 2011, https://doi.org/10.1007/s00449-010-0457-z.

[42] M.R. Kosseva, P.S. Panesar, G. Kaur and J.F. Kennedy. "Use of immobilised biocatalysts in the processing of cheese whey," *Int. J. Biol. Macromol.*, 45(5), pp. 437-447, 2009, https://doi.org/10.1016/j.ijbiomac.2009.09.005.

[43] Y. Zhang, and P.V. Vadlani. "Lactic acid production from biomass-derived sugars via co-fermentation of *Lactobacillus brevis* and *Lactobacillus plantarum,". J. BioSci. Bioeng.*, vol. 119(6), pp. 694-699, 2015, https://doi.org/10.1016/j.jbiosc.2014.10.027.

[44] H. Chen, W. Huo, B. Wang, Y. Wang, H. Wen, D. Cai, C. Zhang, Y. Wu and P, Qin, "L-lactic acid production by simultaneous saccharification and fermentation of dilute ethylediamine pre-treated rice straw," *Ind. Crops Prod.*, vol. 141, pp. 1-9, 2019, https://doi.org/10.1016/j.indcrop.2019.111749.