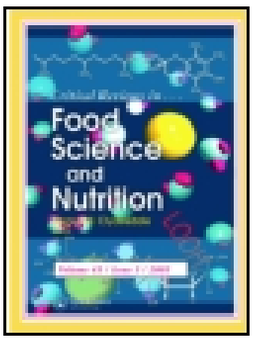

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REVIEW

Redefining methods for augmenting lactic acid bacteria robustness and phenyllactic acid biocatalysis: Integration valorizes simplicity

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ABSTRACT

The production of phenyllactic acid (PLA) has been reported by several researchers, but so far, no mention has been made of augmented PLA production using an orchestrated assembly of simple techniques integrated to improve lactic acid bacteria (LAB) metabolism for the same. This review summarizes sequentially tailoring LAB growth and metabolism for augmented PLA catalysis through several strategies like monitoring LAB sustenance by choosing appropriate starter PLA-producing LAB strains isolated from natural environments, with desirably fastidious growth rates, properties like acidification, proteolysis, bacteriophage-resistance, aromatic/texturing-features, etc.; entrapping chosen LAB strains in novel cryogels and/or co-cultivating two/more LAB strains to improve their biotransformation potential and promote growth dependency/sustainability; adopting adaptive evolution methods designed to improve LAB strains under selection pressure inducing desired phenotypes tolerant to stress factors like heat, salt, acid, and solvent; monitoring physico-chemical LAB fermentation factors like temperature, pH, dissolved oxygen content, enzymes, and cofactors for PLA biosynthesis; and modulating purification/downstream processes to extract substantial PLA yields. This review paper serves as a comprehensive preliminary guide that can evoke a strategic experimental plan to produce industrial-scale PLA yields using simple techniques orchestrated together in the pursuit of conserving time, effort, and resources.

KEYWORDS

Lactic acid bacteria; phenyllactic acid; metabolism; growth; fermentation; improve; yield

1. Introduction

Lactic acid bacteria (LAB) are efficient microbial biofactories fermenting carbohydrates using metabolic pathways to yield lactic acid (LA), and other bioactive molecules viz., acetic acid, phenyllactic acid (PLA), diacetyl, cyclic dipeptides, bacteriocins (Virdis et al. 2021). LAB are an amenable group of bacteria with simple energy demands, metabolisms, and small genomes, which makes them preferred candidates for devising metabolic engineering strategies during primary and secondary metabolism ensuring high and stable product yields (Luo et al. 2020). Common low-cost substrates for LAB fermentation include waste biomasses from agro-food industries like milk/cheese whey, pear processing residues, potato/tomato pomace, etc. (Costa et al. 2020); among them, cheese whey (remnant liquid stream derived after milk is transformed to cheese) is an inexpensive nitrogen-rich substrate which can be exploited holistically by LAB (Lappa et al. 2019; Catone et al. 2021). The biosynthesis of PLA makes LAB industrially useful as probiotic agents and food preservatives exhibiting antimicrobial activities (Mora-Villalobos et al. 2020).

PLA or 2-hydroxy-3-phenyl propionic acid or $C_9H_{10}O_3$ (previously known as 3-phenyllactic acid/β-phenyllactic acid), is a natural organic acid (molecular weight of 166.17 g/mol) derived from phenyl-alanine catabolism and metabolized by lactate dehydrogenase (glycolysis) (Jung, Hwang, and Lee 2019; Mu et al. 2012), occurring in foods like honey, milk, cheese, pickles, sourdough (Behera et al. 2020). Chemically it is a monomer of poly-phenyllactic acid (biodegradable), occurring in two enantiomeric forms D-PLA and L-PLA based upon the C_2 position chirality. D-PLA has better antimicrobial potential, efficiency at operational pH ranges, thermostability, high diffusibility and water solubility, safe antiseptic activity, with versatile applications in food and feed industries, and can be used for the biosynthesis of poly-phenyllactic acid and other pharmaceuticals (Luo et al. 2020). The current state-of-art research in PLA production, calls for the development of robust LAB strains with augmented metabolism/physiologies to achieve holistic exploitation of inexpensive agro-industrial substrates. High-throughput technologies of synthetic biology and metabolic engineering can be adopted to design LAB strains of desired attributes (Liu et al. 2019).

Comprehending LAB metabolism, refining their robustness, and adopting requisite optimization techniques can augment PLA biosynthesis. Common industrial bottlenecks occurring during LA fermentation like 'acid tolerance' caused by LA accumulation, 'withstanding environmental stress', and phage resistance issues, can be addressed by adopting strategies like adaptive metabolic engineering of LAB strains (Liu et al. 2019). Noted LAB genera producing PLA are

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Lactobacillus, *Leuconostoc,* and *Enterococcus*, but some non-LAB like *Bacillus coagulans, Brevibacterium lactofermentum, Escherichia coli* also produce high amounts of PLA (Valerio et al. 2004; Yang et al. 2019). Lactate dehydrogenases (LDH) and pyruvate reductases are key enzymes for PLA biosynthesis from phenylalanine and central carbon metabolism in LAB; several studies have reported gene cloning/expressing native/site-mutated LDHs and pyruvate reductases in some LAB (*Sporolactobacillus inulinus*, *Lactobacillus sp.*) and *E. coli* to increase PLA productivity (Chaudhari and Gokhale 2016; Rajanikar 2021; Xu, Zhang, and Ni 2016). Highly pure optically-active 3-PLA and 4-hydroxyl-PLA were produced using phenylpyruvate reductase and its coding-gene (Konishi and Takaya 2012). However, genetic techniques require tremendous effort and long periods, while adaptive metabolic engineering is less time-conserving and is budget friendly. Within the context of this review considering quintessentially favorable research factors (time, effort, resources), we discuss a strategy for the probable production of industrial-scale yields of PLA using inexpensive substrates and robust LAB with improved metabolism, and by optimizing fermentation and purification/characterization stages. Table 1 shows the various levels of PLA production from various LAB strains adopting various methodologies.

2. Tailoring LAB growth and metabolism for PLA catalysis

2.1. Monitoring LAB sustenance

Choosing appropriate starter LAB strains for PLA production is an essential step. Desired LAB strains can be chosen/selected based on properties like quick rates of growth and acidification in milk, proteolytic characteristics, resistance to bacteriophages, and potential to synthesize required levels of PLA and other aromatic/texturing compounds (Derkx et al. 2014; Meruvu and Harsa 2022). Isolation of LAB strains from their natural environments is worth considering while strain selection; for instance, 24 PLA-producing LAB strains could be isolated from the pig's cecum, large/small intestines (80–119 mg/L) and feces, while the highest production (233.0 mg/L) was reported from fecal-isolate *Lactobacillus plantarum* r16 (Liu Changjian 2012), other LAB strains reported with innate PLA metabolism include cheese-isolate *Geotrichum candidum* (600–1000 mg/L) (Dieuleveux et al. 1998), olive phylloplane-isolate *Leuconostoc mesenteroides* (10.0–101.1) (Valerio et al. 2004), sourdough bread-isolate *Lactobacillus plantarum* 21B (56.0 g/L) (Lavermicocca et al. 2000) pickle-isolate *Lactobacillus ssp.* SK007 (91.0 mg/L) (Li, Jiang, and Pan 2007). A preliminary

Table 1. Compendium showing LAB strain, its source and medium, and the subsequent PLA production levels.

S.n.	LAB strain	Source	Medium	PLA production	Ref.
1.	*Lactobacillus crustorum* NWAFU 1078	Naturally fermented vegetables	MRS broth, supplements: phenyl pyruvic acid (PPA), $CaCO_3$	45.2 mmol/L	(Xu et al. 2021)
2	*Lactobacillus delbrueckii* ŁOCK 0987	Human intestinal tract	MRS broth, supplement: galactosyl polyol	84.3 mg/L	(Lipinska-Zubrycka et al. 2020)
3	*Lactobacillus plantarum* KP3, KP4	Commercial fermented foods	*Porphyra* residues	4.58 mg	(Huang et al. 2021)
4	*Lactobacillus plantarum* CECT-221	–	Cheese whey hydrolyzates, supplement: PPA	45.4 ± 3.02 mM	(Rodríguez-Pazo et al. 2013)
5	*Lactiplantibacillus plantarum* CXG9	Fermented vegetable-stinky xiancaigeng	Fermented vegetable-stinky xiancaigeng	51.31 mg/kg	(Zhang, Zhang, et al. 2022)
6	*Lactobacillus paracasei* *Lactobacillus buchneri*	–	Phenylalanine	0.314 mg/mL	(Lou, Hou, et al. 2022)
7	*Lactobacillus paracasei* 16C3	–	–	202 mg/L	(Zhang, Zhao, et al. 2022)
8	*Lactobacillus paracasei* 16C3	Pickled vegetables	Glucose	73 mg/L	(Yun et al. 2018)
9	*Lactococcus lactis* F44 *Lactococcus lactis* F44/DLDH	–	Yeast extract, peptone, KH_2PO_4, sucrose, NaCl, $MgSO_4{\cdot}7H_2O$, corn steep liquor, cysteine supplement: PPA	1.344 g/L	(Liu et al. 2021)
10	*Lactobacillus plantarum* YM-4-3y	Chinese fermented soybeans or milk	MRS medium	400 mg/L	(Wu, Deng, et al. 2020)
11	*Lactobacillus reuteri* R29	Human intestine	MRS medium, supplement: phenylalanine	–	(Schmidt et al. 2018)
12	*Pediococcus pentosaceus* SK25	Traditional Chinese pickles	MRS broth	135.6 mg/L	(Yu et al. 2015)
13	*Lactobacillus plantarum* ZJ316	–	MRS broth	108.87 mg/mL	(Gu, Li, and Zhou 2018)
14	*Lactobacillus plantarum* CNQ7	Chinese homemade pickles	Pickled cabbage, mustard, cowpea	49.80 mg/kg	(Li et al. 2015)
15	*Lactobacillus plantarum* FST1.7	Wheat sourdough	Wheat sourdough	33.47 mg/kg	(Ryan et al. 2009)
16	*Lactobacillus plantarum* X5	Alfalfa silage	Alfalfa silages	0.054 mg/mL	(Wu, Xu, et al. 2019)
17	*Lactobacillus buchneri* GBS3	Traditional Chinese pickles	PPA	10.93 g/L	(Guan et al. 2019)
18	*Lactobacillus plantarum* IMAU10124	–	MRS medium, supplement: PPA	2.90 g/L	(Zhang et al. 2014)
19	*Lactobacillus* sp. SK007	–	PPA, supplement: glucose	17.38 g/L	(Mu et al. 2009)

step to be followed for PLA biocatalysis is orchestrating the growth needs of LAB by adding suitable supplements to the fermentation medium as it is the simplest way to improve PLA production. Research studies have been conducted to trigger PLA production from LAB (viz., *Lactobacillus plantarum* 21B, *Lactobacillus fermentum* 18B, *Lactobacillus brevis* 18F) by supplementing defined growth media with phenyl pyruvic acid (PPA) (PLA-precursor), which consequently increased antifungal activity and polyporic production alongside (Valerio et al. 2016). The most common defined growth medium widely used for culturing *Lactobacilli* in laboratory environments is the De Man Rogosa Sharpe (MRS) which is optimally fermented for 24 hours (Jung, Hwang, and Lee 2019; Nazareth et al. 2019); nevertheless the cost of MRS growth medium and the deficit of all prerequisite growth components demand finding cost-cutting alternatives like usage of supplements, and substrates like agro-byproducts or dairy whey for commercial/industrial production (Wu, Deng, et al. 2020). It was reported that PLA biosynthesis from *Lactiplantibacillus plantarum* ITM21B was not observed when the basal growth medium was devoid of phenylalanine, but its incorporation at 0.1–0.4 g/L concentration range showed a hike in the PLA production (0.17–0.33 mM) (Valerio et al. 2004). Several researchers have determined that supplementation of phenylalanine and phenyl pyruvic acid (PPA) in the growth medium positively triggered PLA production (Rodríguez et al. 2012; Schmidt et al. 2018; Zheng et al. 2011). Phenylalanine and PPA were also reported to be used as substrates for the fermentation of *Kodakella ohmeri* strain W5 resulting in high PLA yields of 2250 mg and 7490 mg (per liter of fermentation liquor) respectively. In another case, replacing phenylalanine with PPA curbed the phenylalanine to PLA transformation step, resulting in augmented PLA production from *Lactobacillus* spp. SK007 by 14-fold (Li, Jiang, and Pan 2007). The presence of galactosyl polyols in the growth medium of *Lactobacillus* spp. improved its antifungal activity, PLA production (84.3 mg/L), and hydroxy-PLA production (Lipinska-Zubrycka et al. 2020). *Lactobacillus crustorum* NWAFU 1078 was reported to produce 45.2 mmol/L 3-PLA using supplements like phenyl pyruvic acid (60 mmol/L) and 5.0% $CaCO_3$ (neutralizer) (Xu et al. 2021). There was a 30-fold PLA production by *P. pentosaceus* upon supplementation with NADH and NADH-regeneration catalysts which was triggered by the involvement of an auxiliary pathway (Yu et al. 2014). Using the technique of crystal glue chromatography, "*Lactobacillus paracasei* enzymes adsorbed/immobilised onto anion exchange semi-hydrophobic polyester resins" (biocatalyst) were added to a reaction solution (containing PPA and NADH coenzyme) for simple and large-scale bioconversion into PLA (Zhu et al. 2022). Two strains of *Lactobacillus plantarum* (KP3, KP4) were fermented using algal residues of *Porphyra* yielding 2.5 times higher PLA compared to fermentation of the duo with de Man, Rogosa and Sharpe broth (Huang et al. 2021). Fed-batch fermentation of *Lactobacillus plantarum* CECT-221 with cheese whey hydrolyzates and PPA supplements produced antimicrobial PLA and LA as the chief metabolites (Rodríguez-Pazo et al. 2013). *Lactobacillus delbrueckii* strains have been reported for the production of polylactic acid production from cheese whey (Cuervo Garces Laura 2021).

2.2. Lab co-cultivation and cryogel-entrapment

Improving the biotransformation potential of LAB could also be achieved by using co-cultivation of LAB strains and/or by using novel cryogels for cell-entrapment. Co-culturing and fermenting two/more LAB strains can be considered a more feasible approach that could promote good PLA yields without the need for any genetic biotransformation. A rational blending of two/more strains could promote growth dependency/sustainability and desired product profiles, particularly in the cheese/yogurt fermentation industry (Sieuwerts 2016). *Lactobacillus acidophilus*, *Lacticaseibacillus rhamnosus*, and *Pediococcus acidilactici* strains when fermented as co-cultures produced improved PLA yields compared to when fermented as monocultures, and found practical application in fermenting food 'okara' (Hadj Saadoun et al. 2021). In a recent study, PLA bioproduction from phenylalanine was reported by co-culturing *Lactobacillus paracasei* and *L. buchneri* strains by entrapping their cells within semi-hydrophobic matrices. Using cryogenic entrapment, the cell growth rate observed was 40.6 g/L, and the maximum PLA yield was 1.0 mg/mL which was 39.6% higher than *L. casei* and *L. paracasei* co-cultured without using cryogels (Lou, Hou, et al. 2022). *Lactobacillus* cell-loaded (semi-hydrophobic poly 2-hydroxyethyl methacrylate-butyl methacrylate) cryogels were also employed as biocatalysts in PLA production using budget-friendly precursors like phenylalanine. Co-cultures of *L. casei* and *L. paracasei* could be successfully grown with high cell concentrations of 32.7 g/L and 38.7 g/L (higher than singly cultured strains using cryogels), with PLA yields 5.4 and 4.2 times higher than single strain cultures using cell-loaded cryogels (Lou, Jiang, et al. 2022). 202 mg/L of PLA yield with 7.1 mg/L/h productivity was obtained with 8% *Lactobacillus paracasei* cell-loaded (poly2-hydroxyethyl methacrylate-based anion-exchange) cryogel-beads in 100 mM phosphate containing 1 mg/mL phenylalanine and 2 mg/mL glucose (with 80 rpm agitation at 35 °C) using stirred-tank bioreactors (Zhang, Zhao, et al. 2022). Lactate dehydrogenase (LDH) (entrapped in metal-organic framework ZIF-90) served as a novel, robust, reusable, cost-effective, and eco-friendly catalyst for the biosynthesis of D-PLA (Wang et al. 2022).

2.3. Adaptive evolution methods promoting LAB growth

Adaptive laboratory evolution methods promote strain improvement under selection pressure to induce desired phenotypes, growth, and metabolite production by mimicking the natural process of evolution, despite the lack of comprehensive understanding of host metabolism (Ko et al. 2020; Papadimitriou et al. 2016). The natural diversity of LAB can be harvested by adapting them to tolerate

high levels of stress (Boguta et al. 2014; Dijkstra et al. 2014), and tolerance to stress factors can be interrelated in LAB strains that can bear multi-stress resistance (caused by mediated-expression of chaperone proteins) (Papadimitriou et al. 2016; Rallu et al. 2000). Heat Tolerance in LAB is a vital factor as heat stress occurs during industrial fermentation processes. *Lactococcus lactis* subsp. *cremoris* MG1363 when mutated as TM29 with a maximal increase in growth temperature (Chen et al. 2015) and *Lactobacillus acidophilus* NCFM (Kulkarni et al. 2018) showed increased acidification rates by gradually increasing their thermotolerance whilst surviving critical temperatures for prolonged periods. Short-term exposures to sub-lethal high temperatures for a few days could also yield thermotolerant LAB strains like *Lactococcus lactis* subsp. *cremoris* MG1363 and *Lactobacillus helveticus* DSM 20075 (Smith et al. 2012; Spus et al. 2017). Various mutant sub-population strains of *Lactococcus lactis* subsp. *cremoris* SK11 were isolated by repeatedly exposing them to heat stress, and were found to bear resistance to both heat stress and spray-drying (preparation for long-term storage) as well (Dijkstra et al. 2018). *Lactococcus lactis* subsp. *cremoris* MG1363 showed improved heat and acid stress tolerance after small heat shock proteins (Lo18) from *Oenococcus oeni* ATCC BAA-1163 were expressed in it (Weidmann et al. 2017). Heterologous expression of 'chaperone proteins (DnaK) from *E. coli* JM109' (Abdullah et al. 2010) and 'DNA-repair proteins (RecO) from *Lactobacillus casei* Zhang' (Wu et al. 2013) when expressed in *Lactococcus lactis* subsp. *cremoris* NZ9000 promoted tolerant growth at 40 °C conferring tolerance to multiple stress factors like heat, salt, acid, solvent, etc. *Lactobacillus delbrueckii* subsp. *bulgaricus* CFL1 upon exposure to 30 cycles of freezing-thawing-growing in milk exhibited improved survival rates after freezing (Monnet, Béal, and Corrieu 2003), while *Lactobacillus rhamnosus* GG showed improved re-activation from frozen culture conditions when subjected to exposure to 150-times of freeze-thaw-growth cycles (Kwon et al. 2018). Tolerance to acids is a necessary requisite for LAB fermentation and metabolite production because at low levels of pH (desirably below 3.8), LA occurs in its free form to be harvested through electrodialysis or ultrafiltration (Hongo, Nomura, and Iwahara 1986; Othman et al. 2017). *Leuconostoc mesenteroides* subsp. *mesenteroides* KCTC 3718 when adapted to high concentrations of LA (at pH 6.5) for a year were found to bear high acidic stress (Ju, Kim, and Lee 2016). LAB are mostly anaerobic/facultative anaerobic bacteria, so exposure to oxygen/reactive oxygen species is detrimental. But oxygen tolerance can induce robustness in probiotic strains that must undergo oxidative damage during production/storage/ingestion in the gastrointestinal tract (Maresca, Zotta, and Mauriello 2018; Zotta et al. 2018). Spontaneous mutants of *Lactococcus lactis* subsp. *cremoris* MG1363 strains could be mutated spontaneously by selective exposure to hydrogen peroxide to survive long periods in aerated environments and whilst co-culturing with (hydrogen peroxide producing) *Lactobacillus delbrueckii* subsp. *delbrueckii* (Rochat et al. 2005). Probiotic LAB strains like *Lactobacillus johnsonii* and *Lactobacillus gasseri* showed tolerance to oxygen stress owing to their respiratory capacity triggered by catalase production (Maresca, Zotta, and Mauriello 2018).

2.4. Monitoring LAB fermentation factors for PLA biosynthesis

Owing to food safety concerns and the frantic search and/or want for natural food preservatives throughout the world, PLA is garnering much attention due to its antimicrobial and antibiofilm properties. Typically, PLA production can be done using precursors either through chemical synthesis (from benzaldehyde) (Deng, Chen, and Zhou 2001), extraction from plant materials like thistle honey (Tuberoso et al. 2011) and fruit/cereal vinegar (Yunan et al. 2021), and microbial synthesis (from several substrates) (Wu, Guang, et al. 2021). Microbial fermentation methods are widely practiced as eco-friendly means for PLA production instead of chemical methods which are disadvantageous due to high-energy requirements and the generation of complex toxins or pollutants (Wu, Guang, et al. 2021). PLA production has been reported from several LAB strains: *Lactobacillus* sp. SK007 (Mu et al. 2009), *Lactobacillus plantarum* (Lavermicocca et al. 2000; Li et al. 2015; Yang et al. 2019; Zhang et al. 2014), *Lactobacillus reuteri* (Schmidt et al. 2018), *Lactobacillus alimentarius* (Valerio et al. 2004), *Lactobacillus buchneri* (Guan et al. 2019), *P. acidilactici* DSM 20284 (Mu et al. 2012), *Pediococcus pentosaceus* SK25 (Yu et al. 2015), from a myriad of fermented foods like traditional pickles, koumiss, kimchi, sourdough (Wu, Guang, et al. 2021).

Monitoring physico-chemical fermentation factors (temperature, pH, dissolved oxygen content, enzymes, and cofactors) traditionally and/or statistically (Meruvu and Donthireddy 2014) can regulate LAB fermentation and PLA biosynthesis. Temperature and pH control can regulate secondary metabolism and PLA biosynthesis by influencing growth and intracellular activity. *Lactobacillus* sp. SK007 showed optimal growth and PLA yields at 30 °C rather than higher/lower temperatures under static cultivation mode (lower dissolved oxygen contents) (Li et al. 2007), while *Lactobacillus paracasei* W2 showed optimal PLA yields when cultured at 6.5–7.0 pH ranges instead of acidic/alkaline environment (Wu, Guang, et al. 2021). PLA production from *Lactobacillus* strains in fed-batch fermentation (1 to 10 L) was monitored by controlling pH values, glucose, phenyl pyruvic acid, sodium hydroxide, agitation, etc., thereby promoting better yields (20 g/L) (Bo et al. 2008). Enhanced production of PLA has also been reported by fermenting recombinant *Escherichia coli* under limited oxygen conditions because lower dissolved oxygen content could trigger l-phenylalanine production which is the precursor for PLA production oxygen limitation (Kawaguchi et al. 2019). *Lactococcus lactis*—aminotransferases (purified and characterized) could be used for catalyzing

phenylalanine substrate into phenyl pyruvic acid (direct PLA-precursor) (Yvon et al. 1997). Lactate dehydrogenases (LDH) of LAB can trigger PLA catalysis from phenylalanine substrates (due to their higher affinity/activity and substrate-specificity) at optimum temperature and pH ranges of 30–45 °C and 5.5–7.0, some of them reported include: L-LDH from *Lactobacillus plantarum* SK002 (Jia et al. 2010), D-LDH from *Pediococcus pentosaceus* (Yu et al. 2012), and *Pediococcus acidilactici* which exhibited a high substrate-specific catalytic efficiency—k_{cat}/K_m value of 105 m/M/S (Mu, Yu, Zhu, Zhang, et al. 2012). The activation of LDH can be triggered by the addition of cofactors like NADH/NADPH to improve the LAB metabolism and PLA catalysis, and the usage of NAD^+-dependent dehydrogenases is an economic option. NAD^+-dependent dehydrogenases that can be used for cofactor regeneration include formate dehydrogenases of engineered *Escherichia coli* (Zheng et al. 2015) and *Ancylobacter aquaticus* (Nanba, Takaoka, and Hasegawa 2003), glucose dehydrogenases of *Lactobacillus rossiae* (Luo et al. 2020), etc. PLA synthesis has been reported using a semi-hydrophobic crystal gum-based whole-cell-catalyst (*Lactobacillus paracasei*) within a stirring-type bioreactor with improved yields compared to the traditional free cell biosynthesis (Zhang, Li, et al. 2021).

Purification/separation techniques for extracting PLA yields include solvent extraction (Lavermicocca et al. 2000), chromatography (Magnusson et al. 2003), capillary electrophoresis (Li et al. 2004), etc. Several researchers have reported myriad methodologies to render high-purity extraction of PLA: 80.2–90.8% recovery from *Lactobacillus buchneri* (whole cells)—fermented crude bioconversion broths using deionized water (running buffer) and NaCl (eluent) even devoid of any pretreatment, further recovery up to 97.6% with the aid of poly(hydroxyethyl methacrylate)-based cryogels along with anion-exchange and hydrophobic-benzyl groups (Guan, Guan, et al. 2018); 97% (DeMan–Rogosa–Sharpe medium) and 88% (synthetic medium) recovery was reported by extraction with ethyl acetate and supernatant-treatment with formic acid after rotary evaporation (Valerio et al. 2004). Reverse phase High Performance Liquid Chromatography (RP-HPLC) could be employed for the simultaneous and rapid detection of PLA and 4-hydroxy PLA contents (Liu et al. 2020). HPLC could be used also for qualitatively and/or quantitatively analyzing DL-3-PLA content in MRS broth fermentation supernatant fluid (by adopting reversed-phase ion suppression technology and Agilent Zorbax SB-C18 chromatographic column), thereby facilitating the rapid screening of LAB strains that produce high DL-3-PLA yields (Chenjian et al. 2011; Liu et al. 2013). An HPLC mobile phase addition method could be adopted for determining the content of PLA isomer using the chromatograph Agilent 1200 system, it was found to be rapid, simple, sensitive, and convenient offering strong specificity at low costs (Hu et al. 2021). Enantiomeric separation of (±)-PLA from racemic mixtures was reported through surface-molecular-imprinting of nylon fibers (Bukhari, Monier, and Elsayed 2019), capillary electrophoresis using suitable chiral selective agents like mono-6^A-(3-methoxypropyl)-1-ammonium-β-cyclodextrin chloride (Wang et al. 2014) and 6^A-4-hydroxylethyl-1,2,3-triazole-6^C-3-methoxypropylamino-β-cyclodextrin (Zhou et al. 2015) that can form different stable-complexes with different PLA isomers; and chiral-ligand-exchange counter-current chromatography (Tong et al. 2017).

3. Conclusion

PLA is a benign green chemical produced through LAB metabolism with versatile applications owing to its broad-spectrum antimicrobial properties and immune-regulatory functions. It can be used as a food preservative (Chatterjee et al. 2017; Fang et al. 2022; Jiang, Yang, et al. 2022; Liu et al. 2021; Zhang, Wang, et al. 2021; Zheng et al. 2019) and additive agent for texturing/flavoring foods, as a cosmetic-additive for reducing wrinkles (Park 2020; Yu Ruey and Van Scott Eugene 1997) and decelerating the signs of aging (Park Yong 2021), for synthesizing poly-PLA (raw material for biodegradable plastics) (Guan, Yun, et al. 2018), and as an animal feed-additive for improving growth in pigs and hens (Wang, Yoo, Lee, Jang, et al. 2009; Wang, Yoo, Lee, Zhou, et al. 2009). The applications of PLA are detailed in Tables 2 and 3.

The current state-of-art research in PLA production calls for the development of robust LAB strains with augmented metabolism/physiologies and novel synthesis strategies for high PLA yields thereby bridging the demand-supply barrier of the industrial sectors. High-throughput technologies of synthetic biology, metabolic engineering, and microbial biochemistry that can be adopted to design LAB strains of desired attributes for boosting the biotechnological production of PLA have been presented comprehensively. It is recommended that a sequential application of myriad techniques (Figure 1) viz., "primarily tailoring robust LAB growth and metabolism for PLA catalysis through adaptive evolution, LAB co-cultivation and cryogel-entrapment, traditionally/statistically monitoring LAB fermentation factors for efficient PLA biosynthesis, and finally purification and characterization techniques apposite to extract high PLA yields," could promote achieving economic yields. Orchestrating LAB sustenance followed by adaptive evolution could trigger the growth and identification of robust strains with augmented PLA production, speeding up the process of choosing the starter strains. LAB co-cultivation and/or entrapment with cryogels, monitored fermentation, and choosing apposite purification/characterization techniques would contribute to the cost-cutting strategies by conserving resources. A schematic illustration of PLA production through subsequent stages and its applications has been depicted in Figure 2. This review paper serves as a comprehensive preliminary guide that can evoke strategic experimental plans to produce industrial-scale PLA yields using simple techniques orchestrated together.

Table 2. Compendium showing antimicrobial/antibiofilm applications of PLA.

S.n.	Property	PLA producing microorganism	Microorganisms susceptible to PLA	Application	References
1	Antimicrobial and antibiofilm activity	*Lactococcus lactis* *Lactobacillus casei* *Enterococcus faecium* *Enterococcus faecalis*	*Enterobacter cloacae*	Antibiotic	(Kenar et al. 2020)
2	Antibacterial and antibiofilm activity	*Lactiplantibacillus plantarum*	*Shigella flexneri*	Food preservation	(Jiang, Xin, et al. 2021)
3	Antibiofilm Effect	*Lactobacillus casei* *Lactobacillus reuteri*	*Proteus mirabilis*	Antibiotic to combat urinary tract infections	(Shaaban et al. 2020)
4	Antibacterial and antibiofilm activity	*Lactobacillus plantarum* KU200656	*Staphylococcus aureus* *Listeria monocytogenes* *Escherichia coli* *Salmonella typhimurium*	Probiotic in food industry	(Lee, Lee, and Paik 2021)
5	Antibacterial activity	*Lactococcus lactis*	*Staphylococcus xylosus* *Micrococcus luteus*	Food preservation (meat and dairy)	(Liu et al. 2021)
6	Antibiofilm activity	*Lactobacillus* species	*Pseudomonas aeruginosa*	Food preservation	(Chatterjee et al. 2017)
7	Antibiotic activity	*Lactobacillus acidophilus* *Lactobacillus rhamnosus* *Lactobacillus casei*	*Salmonella enterica* Javiana	Protective effect against intestinal epithelial infection	(Burkholder et al. 2019)
8	Antimicrobial activity	*Pediococcus pentasaceus*	*Bacillus subtilis* *Escherichia coli* *Salmonella typhimurium* *Staphylococcus aureus*	Food preservation	(Haziyamin et al. 2020)
9	Antimicrobial activity	*Lactobacillus fermentum*	*Escherichia coli* *Salmonella typhimurium* *Staphylococcus aureus*	Food preservation	(Haziyamin et al. 2020)
10	Antibiofilm activity	*Lactobacillus acidophilus* *Lactiplantibacillus plantarum* *Lacticaseibacillus rhamnosus*	*Listeria monocytogenes*	Food grade sanitizers	(Masebe and Thantsha 2022)
11	Antibiofilm, antiadhesive, and anti-invasive activity	*pediococcus acidilactici*	*Listeria monocytogenes*	Antibiotic uses	(Lee et al. 2022)
12	Antibacterial, antibiofilm activity	*Lactiplantibacillus plantarum* CCFM8724	*Streptococcus mutans* *Candida albicans*	Oral probiotic	(Li et al. 2022)
14	Antifungal activity	*Lactobacillus plantarum* 21B	*Eurotium repens* *Eurotium rubrum* *Penicillium corylophilum* *Penicillium roqueforti*	Bread preservation	(Lavermicocca et al. 2000)
15	Antibacterial activity	*Lactobacillus plantarum* CECT-221	*Salmonella enterica*	Preservative in poultry, eggs, milk, beef, pork	(Rodríguez et al. 2012)

Table 3. Miscellaneous applications of PLA and allied patents.

S.n.	Patent	Claim/Summary	Application	References
1	CN 113150941A	*Gluconacetobacter* FBFS 97 was used to synthesize PLA for adding to table vinegar in an increased content of 439.26 mg/L.	Production of healthy table vinegar production	(Wu, Chen, et al. 2021)
2	US 5643953A	Topical application of 3-phenyllactic acid to skin wrinkles or affected skin of face to reverse the effects of aging	Cosmetic: treating wrinkles	(Yu Ruey and Van Scott Eugene 1997)
3	CN 110870859A	*Lactobacillus plantarum* DR7 metabolite-2-hydroxyisocaproic acid and 3-PLA, used in cosmetic formulations	Cosmetic: delaying aging signs	(Park 2020)
4	CN 111135157A	The composition of 3-PLA and probiotics can be used to reduce growth of pathogenic bacteria to improve vaginal bacterial phase	Probiotics for improving bacterial phase (female vagina)	(Lin 2020)
5	CN 113412853A	A coating preservative was prepared by mixing components: chitosan, PLA, kojic acid, tea-polyphenol, plasticizer, acetic acid, and water.	Preservative for aquatic products at low temperatures	(Pan et al. 2021)
6	CN 108029751A	A film coating fresh-keeping agent for cherries was prepared from a combination of 20-30%wt of PLA concentrate, carboxy methyl chitosan, glacial acetic acid, edible glycerin and water	Fresh keeping film-coat agent for cherries' preservation	(Gong et al. 2018)
7	CN 114084497A	Manufacturing a fruit and vegetable fresh-keeping bag composed of polyethylene and phenyllactic acid.	Fruit and vegetable fresh-keeping bag to improve shelf-life	(Chen et al. 2022)
8	CN 101906392A	*Lactobacillus sp.* W2 was used to transform phenylpyruvic acid and extract PLA from ferment using ethyl acetate to produce high yields up to 1.038 g/L	Inhibition of putrefactive bacteria in food	(Limei et al. 2010)

(*Continued*)

Table 3. (Continued).

S.n.	Patent	Claim/Summary	Application	References
9	CN 106434483A	*Lactobacillus buchneri* was used to ferment phenylpyruvic acid and glucose to produce PLA (13 g/L) and lactic acid (1.8 g/L) synchronously	Industrial application: Synthesis of biochemicals	(Yun, Guan, and Guan 2017)
10	CN 114002363A	PLA can be used as a food-detector and typical marker of Xinjiang black bee honey.	Characteristic marker of Xinjiang black bee honey	(Sun et al. 2022)
11	CN 114527222A	DL-3-PLA, malic acid, and 3-hydroxy-3-methyl glutamic acid could be used for preparing reagents that are applied as markers for detecting prostate cancer	Biomarker is used for diagnosing prostate cancer	(He et al. 2022)
12	WO 2010/082846 A1	Phenolic compounds like PLA, methoxylated PLA, methoxylated benzoic acids, syringic acid, methyl syringate and isomers, etc, could be used in compositions for preparing medical formulations	Medical and Nutritional Formulations	(Schlothauer and Stephens Jonathan Mcdonald 2010)
13	CN 112168846A	*Lactobacillus plantarum* TCI378 and its metabolites selected from group including 3-PLA, can be used for preparing fat-reducing compositions/drugs	Preparation of a fat-reducing composition/drugs to combat obesity	(Lin et al. 2021)

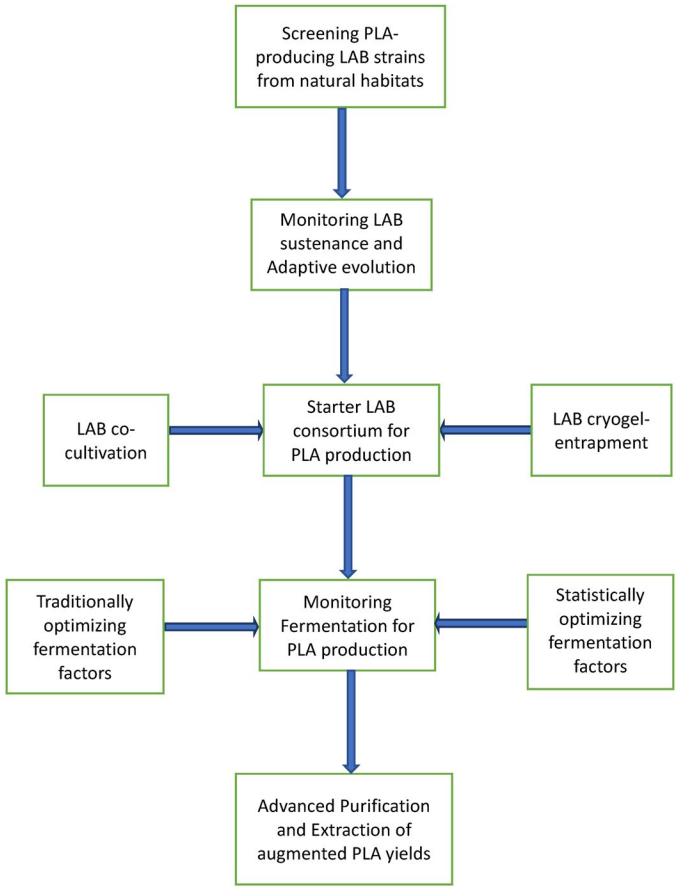

Figure 1. Schematic presentation that effectively explains the "Integration valorizes simplicity" concept for augmented PLA production yields (LAB: lactic acid bacteria, PLA: Phenyllactic acid).

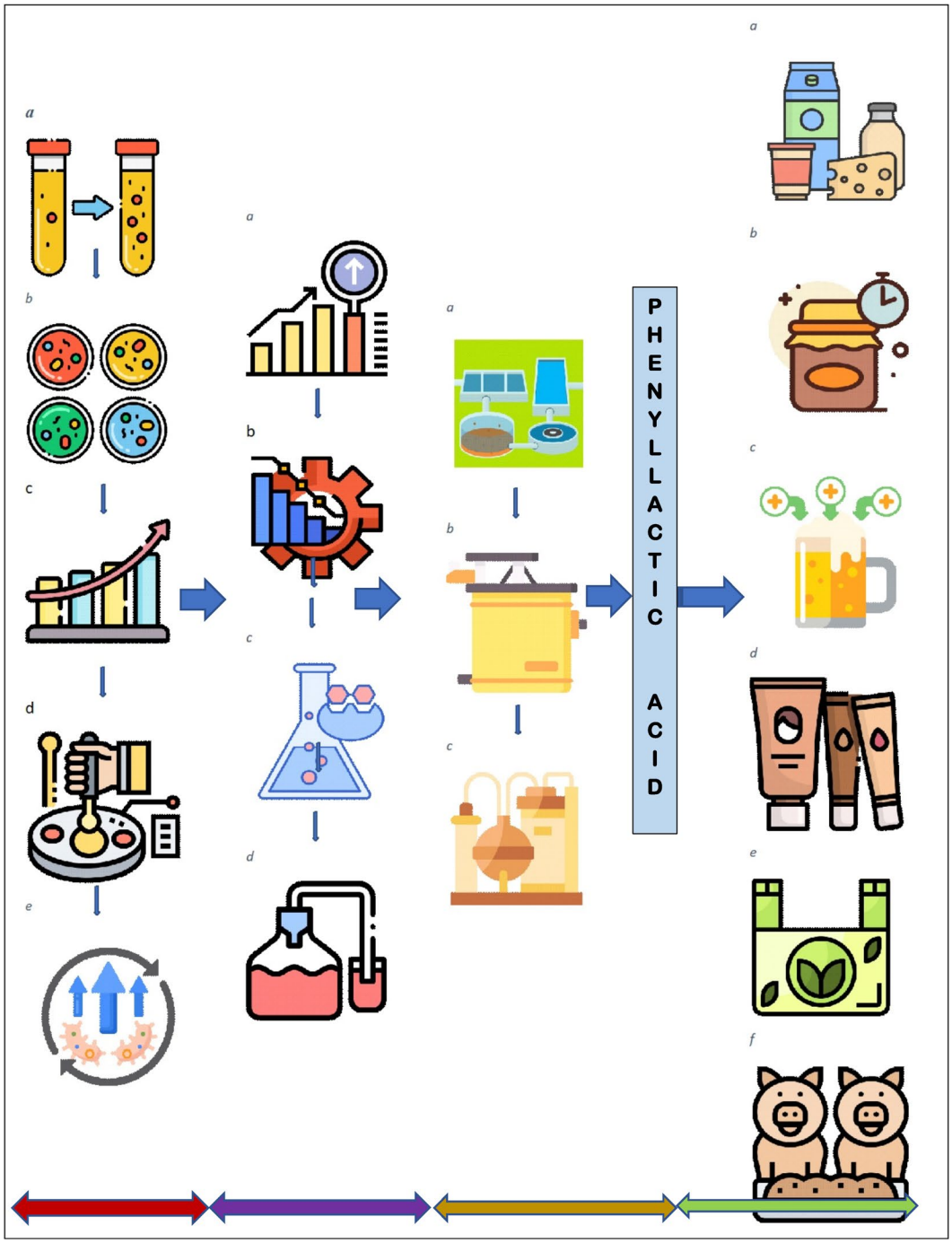

Figure 2. Schematic illustration of arraignment of steps in Phenyllactic acid production and its applications. Red arrow shows the steps in Lactic acid bacteria strains' screening and isolation: (a) isolation and culturing of indigenous LAB strains, (b) monitoring nutrition and growth requisites of LAB, (c) adaptive evolution of LAB strains, (d) co-cultivation of LAB strains, (e) LAB strain entrapment; violet arrow shows fermentation procedures for enhanced PLA production: (a) physico-chemical factors' optimization conventionally, (b) fermentation factors' optimization statistically, (c) fermentation process monitored at optimized conditions (d) using fed-batch, stirred tank bioreactors for pilot-scale production. Golden arrow shows the processes for purification and extraction (a–c). Green arrow depicts the various applications of the produced PLA in (a) food preservation, (b) improving shelf-life of food products, (c) food additive to improve the flavor/texture of foods, (d) cosmetic industry, (e) manufacture of bioplastics (poly-phenyllactic acid), (f) animal feed-additive.

Author contributions

Haritha Meruvu: Project Coordinator (Researcher), Conceptualization, Data curation, Investigation, Resources, Funding acquisition, Writing—original draft, review, editing.

Schematic Credits

Fig: 2 of the present manuscript has been designed using free icons resources from Flaticon.com (authors: Paul J., Eucalyp, Freepik, Pixelmeetup, ultimatearm, shmai, surang, Kanyanee Watanajitkasem, Darius Dan, Flat Icons, justicon).

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