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Review

Lignocellulose-Derived Arabinose for Energy and Chemicals Synthesis through Microbial Cell Factories: A Review

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Abstract: The exploration of natural substrates for microbial conversion to synthesize industrial platform and fuel chemicals seems to be inevitable within a circular bioeconomy context. Hemicellulose is a natural carbohydrate polymer consisting of a variety of pentose (C5) sugar monomers such as arabinose, mannose, erythrose, and xylose. Among the C5 sugars, L-arabinose (L-Ara) is the second-most-abundant pentose sugar in the lignocellulosic biomass after xylose. L-Ara has been used as an industrial carbon source to produce several value-added chemicals such as putrescine, which is used to synthesize polymers in the textile industry; sugar alcohols that are used as sweeteners in diet foods; and amino acids such as L-lysine, L-glutamate, L-arginine, and L-ornithine, which are used in nutritional supplements, fertilizers, and other products in the food and beverage industries. L-Ara, a natural non-caloric sweetener, is used as a substitute in the food and beverage industry, when the risk of blood sugar and lipid levels could be reduced. Major use of L-Ara is also found in the medical and pharmaceutical sectors to treat several conditions, including mineral absorption disorder, constipation, and diabetes, among others. In recent years, there has been a rising interest in synthesizing various sugar alcohols and derivatives, including arabitol, xylitol, and 2,3-butanediol, through the modification of producer organisms either genetically or metabolically to produce value-added products. Understanding the current demand and the need to increase the diversified production of industrial green chemicals with the reduced waste of useful lignocellulosic resources, this review focuses on the background of L-Ara and its various sources, microbes that utilize L-Ara to produce high-value-added products, and the future prospects for strain improvements to increase the yield of high-value-added products.

Keywords: arabinose; hemicellulose; lignocellulosic biomass; metabolic engineering; value-added chemicals

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Citation: Jacob, S.; Dilshani, A.; Rishivanthi, S.; Khaitan, P.; Vamsidhar, A.; Rajeswari, G.; Kumar, V.; Rajak, R.C.; Din, M.F.M.; Zambare, V. Lignocellulose-Derived Arabinose for Energy and Chemicals Synthesis through Microbial Cell Factories: A Review. *Processes* **2023**, *11*, 1516. https://doi.org/10.3390/pr11051516

Academic Editor: Alok Kumar Patel

Received: 17 April 2023
Revised: 5 May 2023
Accepted: 11 May 2023
Published: 16 May 2023

1. Introduction

In recent times, the term 'Circular Bioeconomy' is one of the keystones of the new economical and societal era to reverse climate changes and produce sustainable green chemicals from renewable carbon sources [1]. Among the various renewable resource options, lignocellulosic biomass (LCB) seems to be the major contributor, with an annual production of 0.2 trillion metric tons [2]. LCB also circumvents the food vs. fuel debate that is prominent among developing countries that reserve the most-abundant non-edible carbon feedstock either as an agro-industrial residue or as dedicated bioenergy crops. The

plant biomass is mainly comprised of 65–85% of holocellulosic compounds (cellulose and hemicellulose) and 15–20% of lignin [3–5]. Over recent decades, substantial efforts have been taken for the conversion of cellulosic-derived glucose into biofuels and other value-added products. Hemicellulose is a natural carbohydrate polymer consisting of a variety of pentose (C5) sugar monomers such as arabinose, mannose, erythrose, and xylose. Among the C5 sugars, L-arabinose (L-Ara) is the second-most-abundant C5 sugar in LCB after xylose. L-Ara is used as an industrial carbon source to produce several value-added chemicals such as putrescine (a polymer used in the textile industry), ethanol/sugar alcohols (artificial sweeteners in diet foods, fuel additives, etc.), amino acids such as L-lysine, L-glutamate, L-arginine, and L-ornithine (nutritional supplements), fertilizers, and other products in the food and beverage industries [6–9]. Recent investigations revealed that the whole LCB could be an efficient resource for chemical and fuel production through a biorefinery framework, rather than only cellulose-based bio-renewables [10]. Therefore, a sustainable utilization of LCB prerequisites a completely integrated biorefinery framework that is analogous to a petroleum refinery. In a biorefinery, the holocellulosic fraction contributes a prime role in the production of bio-renewables, owing to its efficient hydrolysis into monomeric sugars that could be subsequently fermented into an array of high-value-added commodities. Table 1 represents a brief list of the value-added bioproducts that are produced. The global market value of food-grade L-Ara is expected to reach USD 33 million by 2028 [11]. In this regard, the valorization of L-Ara could be a promising alternative carbon source for industries that both economically and sustainably augment. There exists a bottleneck in the effective utilization of C5 sugars through microbial fermentation, wherein only a few industrially potent microbes are available for C5 sugar uptake through the specialized intramembrane transport mechanism and metabolic pathways, with a low product yield. However, the conventional metabolic pathway harbored by the microbial candidates possesses low-titer product yields. Hence, upgraded and adapted recent microbial technologies such as adaptive laboratory evolution (ALE) [12,13], metabolic engineering, and synthetic biology [14] have been recently emerging as a promising mitigation strategy to meet the industrial utilization of L-Ara for chemical synthesis and the purpose of establishing a sustainable greener technology [1]. To the best of the authors' knowledge, this is the first report to shed light on the significance of hemicellulose-derived L-Ara as a renewable carbon source and its valorization toward several value-added commodity chemicals. It also highlights the different metabolic pathways involved in the assimilation of L-Ara by various microbial candidates for industrially important chemicals. In addition, different research directions in terms of metabolic engineering, synthetic biology, and microbial strain improvement strategies are discussed.

Table 1. Value-added products and their corresponding yields.

ValueAdded Products	Yield	Microbe	'C' Source	Reference
Organic acids	Lactic Acid: 12.1 g/L Fumaric Acid: 7.4 g/L Acetic Acid: 4.5 g/L	*Lactobacillus sakei* WiKim31	Kimchi cabbage waste	[15]
Putrescine	19 g/L	*Clostridium glutamicum* PUT21	Glucose	[16]
Amino acids	L-Lysine: 9.9 g/L L-Ornithine: 25.8 g/L L-Arginine: 8.4 g/L	*C. glutamicum* ARG1	Glucose and L-Ara	[6]

2. Abundance and Significance of L-Ara as a Bioresource

Hemicellulose, a heterogenous polymer that contains C5 sugars such as α- L-Ara and β-D-xylose, could reach 20–30% of the total LCB [17,18]. Figure 1 represents the potential of LCB, its sugar composition, and its valuable application in industries through microbial metabolic processes. In addition, some other sugars such as α -fucose and α-L-rhamnose are also present to a small extent, albeit rarely [19]. Based on the composition, presence,

and side-chain ratio of the constituents, hemicellulose is distinguished as xyloglucan, glucuronoxylan, glucuronoarabinoxylan, galactoglucomanan, arabinoxylan, glucomannan, homoxylan, galactomannan, homomannan, arabinoxyloglucan, and arabinoglucuronoxylan. Among these, a considerable amount of L-Ara was found in arabinoglucuronoxylan, arabinoxyloglucan, glucuronoarabinoxylan, and arabinoxylan [20]. Rapid growth in the fresh juice industry has led to the abundance of fruit processing waste, which is not being efficiently utilized. Fruit processing waste such as pear peel, lime peel, orange peel, mandarin peel, and apple pomace is rich in pectin, i.e., 12–35% of the biomass dry weight has an insignificant amount of lignin (2%, w/w), compared to that of LCB [21–25]. Pectin is a complex heteropolysaccharide composed of α-1,4 linked D-galacturonic acid that contributes 70% of the total homogalacturonan polymer weight. When considering pectin, the presence of a limited amount of lignin merely enables the breakdown of polymers into monomers, where L-Ara becomes the most abundant of the C5 sugars. In addition to LCB, agro-industrial by-products such as wheat bran, corn fiber, sugar beet pulp, brewer's spent grain, and sugarcane bagasse contain around 10.6%, 12.0%, 18.0%, 8.7%, and 1.3% of L-Ara, respectively [26–31]. Table 2 represents the different feedstocks/sources of L-Ara and its potential industrial applications. These abundant waste resources could be sustainably tapped for the L-Ara waste production of chemicals through various microbial candidates, which is discussed in the subsequent sections.

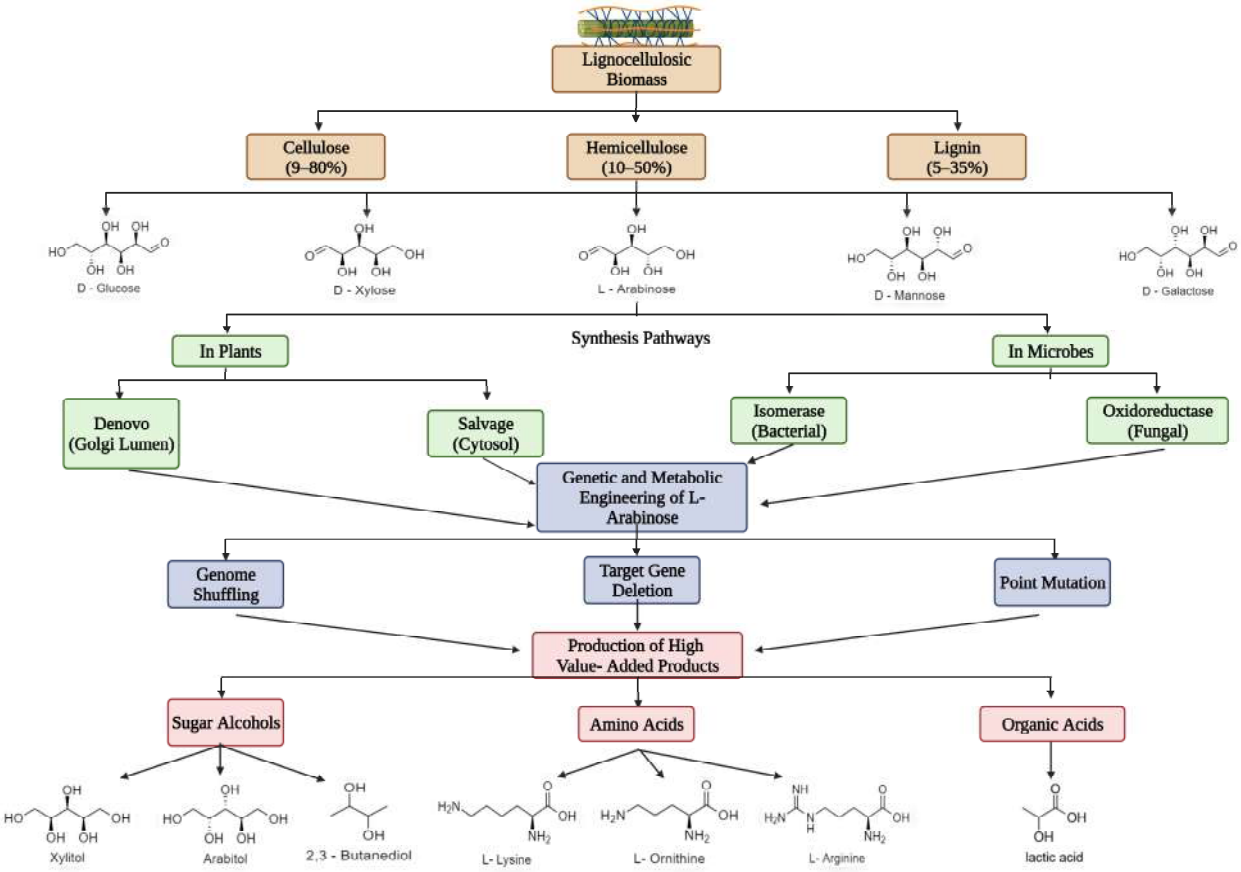

Figure 1. Production of value-added products from LCB-derived L-Ara.

Table 2. Different sources of L-Ara and its applications.

Feedstock	Lignin (%)	Hemicellulose (%)	Cellulose (%)	Pre-Treatment Method Used to Obtain L-Ara	Applications	References
Sugarcane bagasse	25–32	19–24	32–43	Acid hydrolysis resulted in 2.78 g/L of L-Ara	Food coatings, hydrogels, packaging films, cationic biopolymers, and other biomedical uses	[32–34]
Corn stover	19	22	36	Acid hydrolysis resulted in 38.2% L-Ara yield in 8 h reaction time	Advanced biofuels and livestock feed	[35–37]
Rice straw	15	18	35	Combined pre-treatment methods resulted in 2.7–4.5% of L-Arayield	Biofuel and ethanol production	[38–40]
Water hyacinth	10	35	25	Sulphuric acid treatment resulted in 33.3 g/L yield of L-Ara	Biothanol production using *Pichia stipitis*	[41,42]
Wheat straw	16–25	23–24	28–39	Hot water and NaOH treatment resulted in 2.37 ± 0.09% of L-Ara	Adsorbents, packing materials, bioplastic industry, and several other industries	[43–45]
Sugar beet molasses	6	30	22–24	Acid alkali pretreatment along with ultrafiltration resulted in 92% recovery of L-Ara	Food industry, as a bakery or confectionery product, apart from being utilized as a ruminant feed	[46,47]
Apple pomace	19	10	12	Sulphuric acid treatment resulted in 90% yield of L-Ara	Bioethanol, animal feed, citric acid, and several other applications	[48–50]
Orange peels	20	9	69	Acid alkali treatment to extract L-Ara	Bioethanol, essential oils, and biogas	[51,52]
Carrot pomace	17	7	28	Acid treatment to extract L-Ara	Fertilizer, feed for livestock, dietary fiber, and production of biofuels	[53,54]
Tomato pomace	7	31	38	Acid treatment to extract L-Ara	Fertilizer, feed for livestock, dietary fiber, and production of biofuels	[54–56]

2.1. 2,3-Butanediol

2,3-Butanediol (2,3-BD) or 2,3-butylene glycol has various applications, such as as a chemical feedstock, a solvent, a liquid fuel, and a raw material for several resins and synthetic polymers [57]. A microorganism, identified as *Enterobacter cloacae*, was found to produce meso-2,3-BD as its primary product during fermentation. There are reports that pathogenic bacteria and other microbes produced 2, 3-BD. *Klebsiella pneumoniae* had the most significant 2, 3-BD titer of any bacterium, measuring 150 g/L [58]. Another productive maker of 2,3-BD, classified as a class 2 bacteria, was *K. oxytoca,* and this strain produced 2, 3-BD concentrations up to 130 g/L. Three bacteria with the Generally Recognized as Safe (GRAS) designation are effective 2, 3-BD producers: *Bacillus amyloliquefaciens*, *B. licheniformis*, and *B. subtilis*. The discovery of new strains and the enhancement of optical clarity has received abundant interest. Industrially applicable hosts, such as *L. lactis*, *Saccharomyces cerevisiae*, and *Escherichia coli*, are better-suited for large-scale production than indigenous hosts due to their effective genetics and well-proven cultivation techniques [59].

In a study conducted by Saha and Bothast, the authors checked the production of 2,3-BD by *E. cloacae* NRRL B-23289 by utilizing each of the following carbon sources individually: xylose, glucose, and L-Ara. The study was conducted at a pH of 5.0, a temperature of 30 °C, and 200 rpm. It showed that *E. cloacae* NRRL B-23289 utilizes the above-mentioned carbon sources in the order: xylose < glucose < L-Ara. About 0.37 g of glucose and 0.38 g of xylose were consumed in 63 h, and 0.43 g of L-Ara was consumed in 39 h. The bacteria were cultivated on mixtures of A and B, made of sugar, in proportions of 1:1:1 and 1:2:1 for glucose, xylose, and L-Ara, respectively. The bacterium variety was

found to favor glucose over xylose and L-Ara over xylose. After a significant amount of L-Ara was consumed and only after all of the glucose was used up, the xylose started to vanish. Thus, the authors could use the *E. cloacae* NRRL B-23289 strain for the enhanced production of 2,3-BD using L-Ara as a carbon source [60].

For an array of sectors, including those in the chemical, cosmetics, agriculture, and medicine fields, 2,3-BD holds enormous potential. 2,3-BD has broad industrial applications, such as as a promising bulk chemical, which has plenty of further use. Its high heating value makes it an excellent drop-in fuel. It can also be converted to octane after adding the methyl ethyl ketone (MEK) and hydrogenation reaction, which is then used to produce superior aviation fuel. It is widely used to manufacture antifreeze agents, pharmaceuticals, synthetic rubber, fumigants, foodstuffs, perfumes, fuel additives, and printing inks [61].

2.2. Other Value-Added Products

For the past two decades, the market value for amino acids such as L-tryptophan, DL-methionine, L-lysine, L-aspartic acid, L-threonine, and L-glutamic acid has drastically increased owing to their wide range of applications in the food, cosmetics, agriculture, and pharmaceuticals sectors [62]. Recent studies reported the utilization of hemicellulose-derived L-Ara as the sole carbon source by engineering microbial strains for organic acids (lactic acid and succinic acid) and amino acids production [7,63,64]. Metabolic engineering of the *Corynebacterium glutamicum* ATCC 31831 strain resulted in the production of L-amino acids, namely, L-ornithine, L-lysine, L-threonine, L-methionine, L-glutamate, diamine putrescine (1,4-diaminobutane), and organic acids upon arabinose transporter gene (araE) expression [6,7,65]. On the other hand, overexpression of the ornithine decarboxylase gene (speC) from *E. coli* resulted in a high yield of putrescine by the *C. glutamicum* strain [16].

3. Overview of Distinct Natural Metabolic Pathways of L-Ara Assimilation by Microbes

Native microbes are able to grow on L-Ara derived from the hemicellulosic fraction of LCB via three distinct pathways, namely, the isomerase pathway, oxido-reductase pathway, and non-phosphorylative pathway (Figure 2). Firstly, the assimilation of L-Ara in eubacteria such as *Streptomyces* sp., *lactococcus*, *Corynebacterium*, and *E. coli* is initiated with the substrate uptake that is mediated by the active sugar transporters, followed by isomerization with L-arabinose isomerase to form L-ribulose. L-ribulose enters the central carbon metabolism (CCM) as D-xylulose-5-P through direct phosphorylation (catalyzed by L-ribulokinase) and epimerization (catalyzed by L-ribulose 5-P 4-epimerase) [1,66].

Secondly, in filamentous fungi, L-Ara metabolism is carried out by the oxido-reductive pathway. Similar to the isomerase pathway, L-Ara assimilation initiates with its uptake by relative sugar transporters. Concurrently, L-Ara reduces into L-arabitol by L-arabitol reductase (NADPH dependent) and then dehydrogenates into L and D-xylulose catalyzes by a series of enzymes such as L-arabitol dehydrogenase, L-xylulose reductase, and xylitol dehydrogenase. Finally, the phosphorylated D-xylulose enters the CCM pathway to recombine with glyceraldehyde-3-phosphate or its precursor molecule fructose-6-phosphate [26,67,68]. Though the overall pathway of L-Ara metabolism in filamentous fungi is redox-neutral, there exists a constraint in which a dissimilarity in the utilization of redox cofactors is observed. Thereby, making the C5 sugar, such as xylose, and L-Ara utilization as the sole carbon source possesses a major bottleneck for fermentative application. This is mitigated by employing a metabolic engineered yeast for fermentation [69]. Nevertheless, *Pichia stipitis* follows a distinct non-oxidative route, where D-xylulose is reduced into D-arabitol and then oxidized to D-ribulose by D-arabitol dehydrogenase and D-ribulose reductase, respectively [70]. This makes it a potent microbial candidate for C5 sugar fermentation.

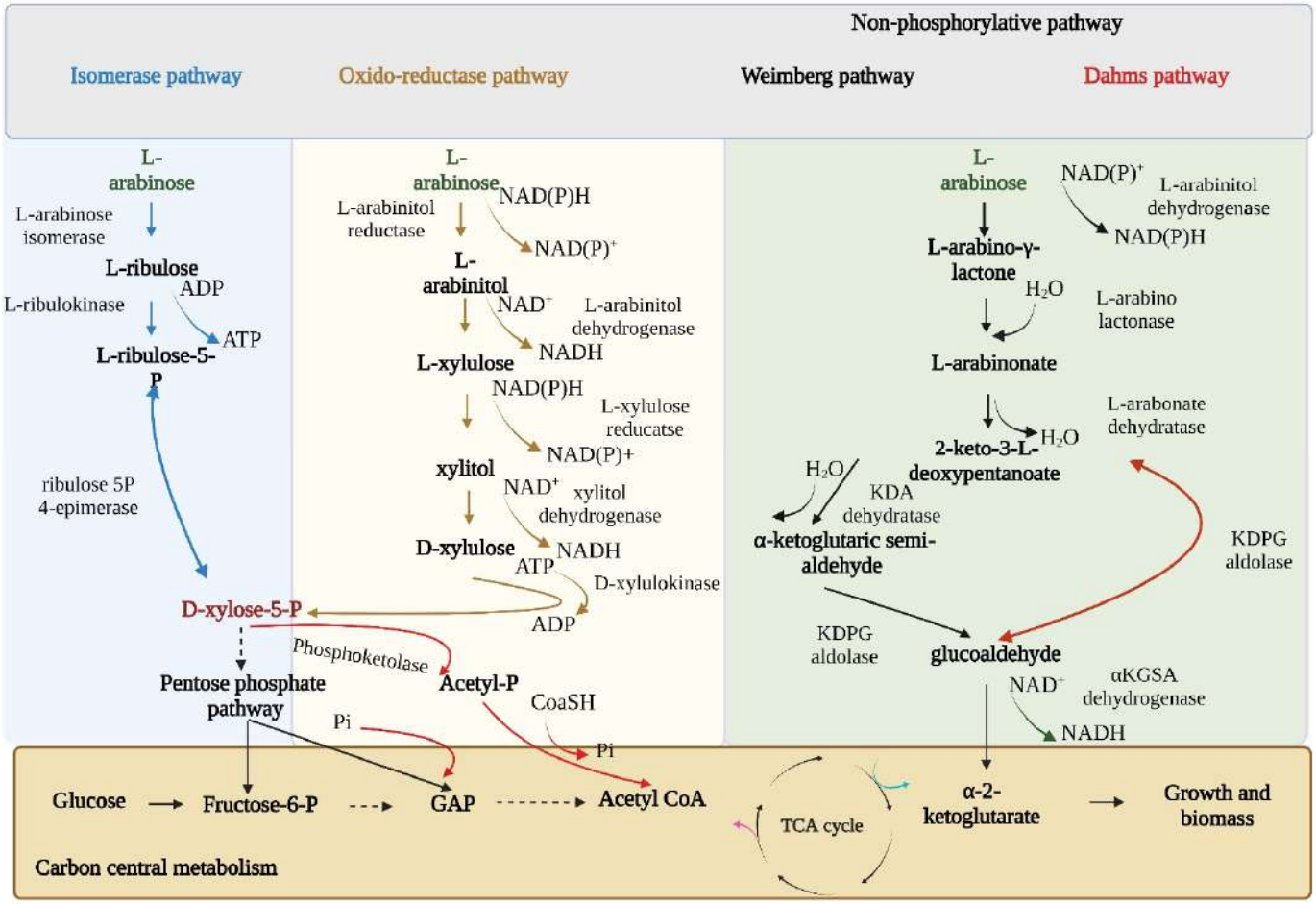

Figure 2. Native metabolic pathways for assimilation of L-Ara. ADP: Adenosine Diphosphate; ATP: Adenosine Triphosphate; L-ribulose-5-P: L-ribulose-5-Phosphate, D-xylose-5-P: D-xylose-5-Phosphate; NAD(P)H: Nicotinamide Adenine Dinucleotide Phosphate Hydrogen; $NAD(P)^+$: Nicotinamide Adenine Dinucleotide Phosphate; NADH: Nicotinamide Adenine Dinucleotide Hydrogen; NAD: Nicotinamide Adenine Dinucleotide, KDA dehydratase: 2-Keto-3-Deoxy-l-Arabinonate; KDPG aldolase: 2-Keto-3-Deoxy-6-Phospho Gluconate aldolase; αKGSA dehydrogenase: αKeto Glutarate Semialdehyde Dehydrogenase; Fructose-6-P: Fructuose-6-Phosphate; GAP: Glyceraldehylde-3-Phosphate; CoaSH: Coenzyme A; Pi: inorganic phosphate; TCA: tricarboxylic acid.

The third pathway, known as non-phosphorylating pentose, is prevalent in archae bacteria where L-Ara is converted into either glycolaldehyde (Dahms pathway) and α-2-ketoglutarate (αKG) (Weimberg pathway) converges with CCM during the tricarboxylic acid cycle [71,72]. Enzymes such as L-arabinose dehydrogenase, L-arabinose lactonase, L-arabonate dehydratase, 2-keto-3-deoxy-l-arabinonate (KDA) dehydratase, and ketoglutarate semialdehyde (αKGSA) dehydrogenase are prominently involved in catalyzing L-Ara assimilation by the Weimberg pathway, as shown in Figure 2. The end product 2-keto-3-L-deoxypentonate formed in the Weimberg pathway takes an alternate route to form glycolaldehyde, which is catalyzed by 2-keto-3-deoxy L-pentanoate (KDP) aldolase and followed by αKGSA dehydrogenase to enter the CCM pathway. The promiscuity of metabolic enzymes remains uncertain owing to their redox cofactors' dependence and also the co-existence of the Dahms and Weimberg biochemical routes in the same microbes, as represented in Figure 2 [1,73,74].

Kinetics of L-Ara Uptake by Different Microbes

In the near future, structural insights into highly conserved L-Ara catabolic enzymes and their substrate binding niche are likely to significantly progress. Herein, microbial genome data revealed that 30–40% of proteins belong to the paralogous/orthologous families, where the enzyme mechanism, the biochemical function, the oligomerization state, and protein–ligand interaction are uncovered by the protein structures [75,76]. In particular, Vermersch et al. [77] performed a mutation (Pro to Gly) in the L-Ara binding protein hinge, thereby enhancing and altering the binding and specificity. Thus, the structural and kinetic studies of the CAZymes in the L-Ara metabolic pathway provide an in-depth understanding of the enzyme mechanism for the entire pathway.

deGroot et al. [78] constructed a mathematical model based on the characterization of the kinetic parameters in various L-Ara catabolizing enzymes of *Aspergillus niger* such as L-arabitol dehydrogenase, D-xylose reductase, and L-arabinose reductase. The kinetic parameters of the relative enzymes such as L-arabinose reductase EW found to be V_{max} −70 U/mg and K_m −70 mM and V_{max} −96 U/mg and K_m −89 mM for L-arabitol dehydrogenase and V_{max}-57 U/mg and K_m-93 mM for D-xylose reductase in fungal L-Ara catabolism. Similarly, for *A. nidulans*, De Vries et al. [79] demonstrated that an increase in the production of L-Ara catabolizing enzymes enhances the accumulation of arabitol and, thus, reveals that sugar alcohol is a precise inducer of the system. Thus, the metabolic model could be used for analyzing the metabolite concentration and its flux in the L-Ara catabolic pathway, as indicated in Figure 2. Whereas, in the case of yeast, Fonseca et al. [80] investigated the L-Ara uptake kinetics for *P. guilliermondii* PYCC 3012 and *Candida arabinofermentans* PYCC 5603T, which showed a rapid and higher substrate-uptake rate. This study revealed that the aldopentose reductase of *C. arabinofermentans* PYCC 5603T such as aldose reductase or L-xylulose reductase (AR/LXR) showed a higher affinity toward the substrate, i.e., the L-Ara with 2.1 and 1.9 U/mg of Vmax, respectively, was higher than its counterpart. Recently, Lee et al. [81] intensified the thermophilic L-arabinose isomerase in the L-Ara catabolic pathway that is involved in catalyzing the L-Ara and L-ribulose interconversion. In detail, a comparative analysis of L-Ara catabolic protein structures such as *AraA*, *AraB*, *AraD*, and *AraF* was assessed to predict the L-Ara binding modules of *Geobacillus stearothermophilus*. In this study, the catalytic turnover rate (K_{cat}) of the mutant strains (11.9 to 27.8 s^{-1}) was found to be three-fold less than that of the parental strain (33.8 s^{-1}), which reveals that the mutation significantly reduced the K_{cat}. However, the K_m values of the mutant strains were observed to be two-fold higher, while L-Ara is used as the sole carbon source when compared to the wild type. Thereby, the catalytic efficiency (K_{cat}/K_m) of mutant strains such as E333, E261, and D195 was lowered as expected, which could play a vital role in the L-Ara binding affinity of *G. stearothermophilus* L-arabinose isomerase.

4. Native L-Ara Fermenting Strains and Its Metabolic Pathway

Among the C5 sugars predominant in hemicellulose hydrolysate, D-xylose is more often studied as a significant bioresource, whereas L-Ara utilization by any native industrial microbes remains unexplored. The catalytic pathways of the L-Ara in native fermenting strains are divided into the isomerase and oxidoreductase pathways for bacteria and fungi, respectively. The native fungal L-Ara pathway constitutes AR/LXR coupled with NAD(P)H oxidation to NADP+, whereas D-xylitol dehydrogenase (XDH) and L-arabitol-4-dehydrogenase (LAD) are coupled with the NAD+ cofactor followed by D-xylulose phosphorylation by D-xylulokinase (XK) [82,83]. The bacterial pathway for L-Ara catabolism is relatively simple when compared to the aforementioned fungal pathway, where *araA* encoding L-arabinose isomerase, *araB* encoding L-ribulose kinase, and *araD* genes encoding L-ribulose-5-phosphate-4-epimerase are the key enzymes involved [84]. In both pathways, D-xylulose-5-phosphate is formed from L-Ara, which is then either ideally metabolized by the phosphate ketolase pathway (as in *C. acetobutylicum*) or by the non-oxidative phase of the pentose phosphate pathway [85].

The native fungal pathway of C5 sugars such as L-Ara and xylose would share three enzymes in common: (NAD(P)H-specific AR/LXR and NAD^+-specific xylose dehydrogenase. Thus, the redox balance of the metabolic pathway in fungi under an aerobic condition leads to effective cell growth, whereas under an anaerobic condition L-arabitol is produced, owing to the NAD+ limitations that are lacking in the bacterial pathway of L-Ara. Among the 116 identified native arabinose fermenting microbes, three *Candida* sp. and one *Ambrosiozyma monospora* were able to catabolize L-Ara (80 g/L) as the sole carbon source, and the ethanol yield was found to be 0.18 g/g under an oxygen-limited condition [86]. Meanwhile, Millan and Boynton [87] screened and evaluated the efficiency of 15 native xylose-fermenting strains' ability to ferment L-Ara for ethanol production. In this study, L-Ara assimilated strains such as yeast (*C. tropicalis*, *C. shehatae*, *Pachysolen tannophilus* Y-2460, *P. tannophilus* Y-12891, *Scheffersomyces stipitis*, and *Torulopsis sonorensis*), mold (*A. oryzae*), and bacteria (*Erwinia chrysanthemi*) were identified as fermenting L-Ara combined with glucose and xylose as a co-substrate. During L-Ara metabolism, only *S. stipitis* produced 0.15 g/g of ethanol and yielded 0.24 g/g of arabitol compared to its other counterparts.

In general, the transport of sugar across the cell membrane is the foremost step in C5 sugar metabolism; nevertheless, only a meager amount of information is available on the yeast-based L-Ara transporters that could utilize L-Ara. In the case of *C. shehatae*, a native xylose-fermenting strain possesses a proton/L-Ara symporter [88]. Several types of yeast were identified as L-Ara assimilators, which produce cell biomass under aerobic and oxygen-limited conditions for L-arabitol production [80,89].

5. Metabolic Engineering of Microbial Cell Factories for Improved L-Ara Fermentation

The biosynthesis of biomass-based liquid biofuels and building block chemicals has been regarded as a renewable alternative to the conventional petroleum refinery. Over recent decades, extensive fundamental research on strain improvement has revealed that *S. cerevisiae*, *E. coli*, and *Zymomonas mobilis* possess innumerable desired characteristic features to be ideal candidates for the metabolic engineering and industrial production of the product spectrum such as sugar alcohols, biofuels, and value-added chemicals for a biomass-based biorefinery [90–93]. Different strategies for strain improvement such as mutagenesis, specific gene knockout, metabolic engineering, and ALE could aid a microbial candidate's amenability for the significant production of different value-added products [94–99].

5.1. Engineering Zymomonas Mobilis for L-Ara Fermentation

Z. mobilis, a promising ethanologenic candidate; the homologous recombination of genes such as xylose reductase-XR (which improves xylose utilization), lactate dehydrogenase-IdhA, alcohol dehydrogenase-adhB and pyruvate decarboxylase-pdc (which has a lower lactate and ethanol yield which improves the succinate from glucose, respectively), and glucose fructose oxidoreductase-gfo (which reduces in ethanol production under ethanol, heat, and osmotic stress), were selected as a target of specific gene knockout for improving the specific phenotype (Figure 3) [100,101]. ALE in a model organism emerged as a prevailing strategy, where adaptation and metabolic engineering were synergistically employed in *S. Cerevisiae* [94–97], *E. coli* [98,99], and *Z. mobilis* for strain improvement. In the case of *Z. mobilis,* certain features such as the simultaneous utilization of glucose and C5 sugars and inhibitor tolerance were developed by many researchers through ALE to substitute lignocellulosic hydrolysate as an alternate for a conventional biorefinery. Among them, *Z. mobilis* CP4 (pZB5) and *Z. mobilis* CP4 (pZB206) were the first recombinant strains developed, where operons encoding pentose phosphate, the xylose assimilation pathway, and five L-Ara metabolic genes were introduced from *E. coli*, which could ferment C5 sugars such as xylose and L-Ara into 86% and 98% theoretical ethanol yields, respectively [102,103]. Then, Zhang et al. [104] constructed a co-fermenting strain (*Z. mobilis* 206C (pZB301)) for glucose and C5 sugars' fermentation that resulted in 82%–84% of ethanol. However, the stability of

recombinant strains is highly undesirable in large-scale fermentation; thereby, the genetic stability of the *Zymomonas* genome was enhanced by integrating all the necessary genes of pentose utilization to obtain a stable co-fermenting strain, *Z. mobilis* AX101 [105]. Compared to *E. coli*, *Z. mobilis* was developed as an effective ethanologenic-engineered strain, owing to its distinct metabolic pathway with a higher restriction-modification system of enzyme activity that is not borne by bacteriophages [93]. In addition, its osmo-tolerant ability benefits in industrial fermentation, by tolerating a high sugar medium and the utilization of C5 sugars (xylose, L-Ara) in addition to glucose, makes it a novel candidate for future biomass-based biorefineries [106]. Functional genomics, omics-related approaches, clustered regularly interspaced short palindromic repeats (CRISPR)/Cas system, Zinc-finger nucleases, global transcription machinery engineering, genome shuffling, and site-specific recombinase provide a base to improve the robustness and fitness toward environmental stress in order to enhance cellular traits. Further implementation of these representative biotechnologies will pave the way for a promising future in optimizing the metabolic pathway of *Z. mobilis* for the production of biofuels and value-added commodity chemicals to establish a sustainable green chemistry, as represented in Figure 3 [107–112].

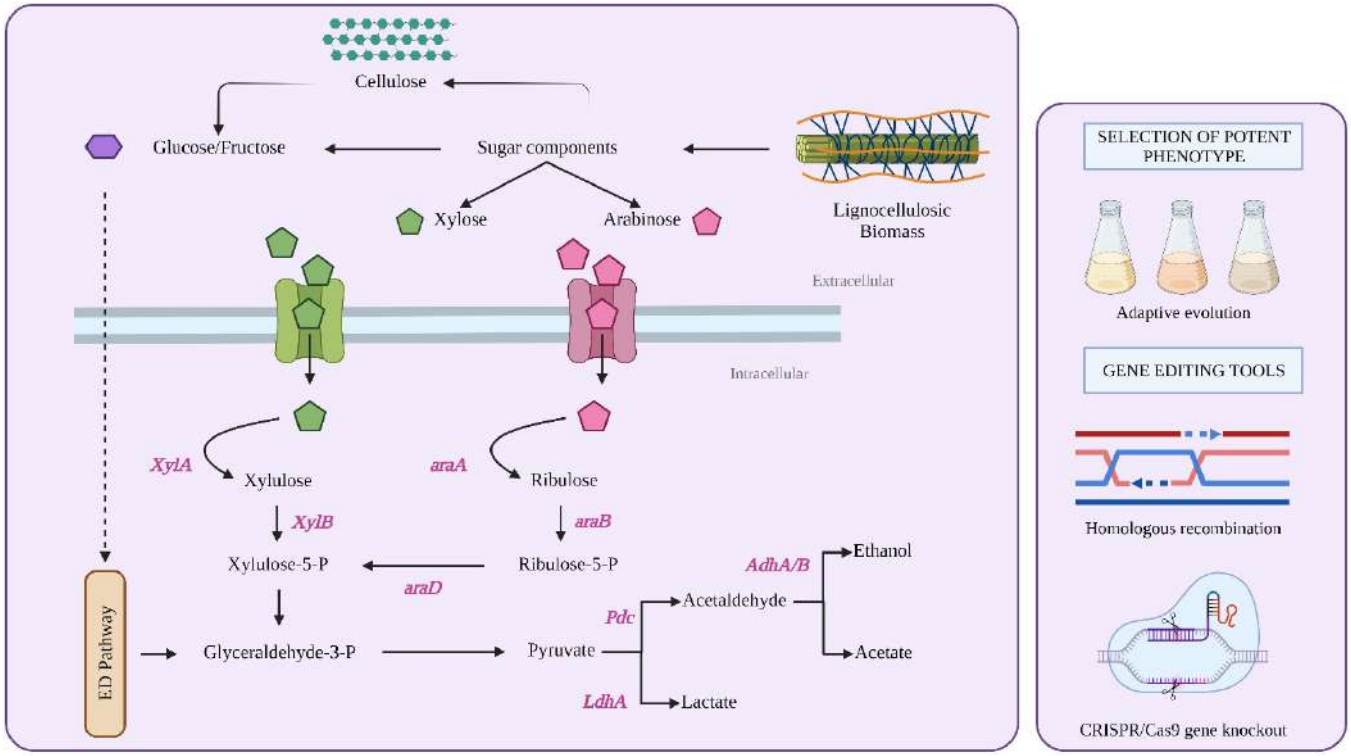

Figure 3. Schematic representation of L-Ara utilization pathway of *Z. mobilis* and its metabolic engineering strategies. *XylA*: Xylose isomerase; *XylB*: Xylulose-5-P kinase; *AraA*: Arabinose isomerase; *AraB*: Arabinose-5-P kinase; *AraD*: L-Arabinonate dehydratase; ED Pathway: Entner–Doudoroff pathway; Glyceraldehyde-3-P: Glyceraldehyde-3-Phosphate; *Pdc*: Pyruvate dehydrogenase complex; *AdhA/B*: Alcohol dehydrogenase genes; *LdhA*: Lactate dehydrogenase gene.

5.2. Engineering Saccharomyces Cerevisiae for L-Ara Fermentation

As reported in earlier studies, the L-Ara metabolic pathway in bacteria is cofactor-dependent, and lacks an effective enzymatic assay, and the pathway optimization was not straightforward in *S. cerevisiae*. Based on this study, the *E. coli* genes (*araA*, *araB*, and *araD*) expressed in *S. cerevisiae* were not able to assimilate L-Ara; however, only after the replacement of the isomerase gene, along with the *araA* from *B. subtilis* with an ALE, then ethanol was produced from L-Ara [113,114]. Further, improvement in L-Ara utilization was investigated by modifying the bacterial codon usage to be the ideal yeast

codon [115]. Thus, the *L. plantarum* metabolic genes for L-Ara were found to be more closely matched with the *S. cerevisiae* genes. Further, overexpression of this metabolic gene resulted in a high ethanol yield (0.43 g/g), with a 0.70 g/h/g dry cell weight (DCW) of the L-Ara consumption rate under an anaerobic condition [78]. Similarly, Wang et al. [116] modified the L-Ara metabolic pathway and transporter genes to investigate the metabolic ability of evolved *S. cerevisiae* with the overexpressed strain, where the recombinant strain resulted in a maximum ethanol yield of 0.43 g/g from L-Ara fermentation. Though many studies are focused on developing the D-xylose that assimilates *S. cerevisiae* strains, some [11–84,84–113,113–119] are focused on the heterologous expression of the fungal and bacterial pathways of the L-Ara metabolism. For instance, the heterologous expression of the *xyl1*, *xyl2*, and *xyl3* genes from the *Scheffersomyces stipitis* in *S. cerevisiae* possessed with NAD(P)H-dependent heterologous XDH, AR, and XDH genes showed a 50% higher L-Ara metabolism rate. Further, expressing LXR from *A. monospora* ALX1 and the LAD of *T. reesei* LAD1 in the parent recombinant strain assimilated 45 g/L of L-Ara into 10 g/L of ethanol [117,118,120]. In addition, the fungal metabolic pathway of L-Ara is considered to be non-redox-neutral, as it prefers dual cofactors (NAD(P)H and NADH), while the bacterial pathway is redox-neutral.

In order to enhance the D-xylose fermentation, ALE is proven to be an effective metabolic engineering strategy for both the bacterial and fungal pathways in an engineered strain of *S. cerevisiae.* Nevertheless, only engineered strains of *S. cerevisiae* with a bacterial L-Ara pathway were unveiled for ALE, as the optimization of multiple strategies is required to overcome the redox imbalance in *S. cerevisiae* during the heterologous expression of the fungal L-Ara pathway [82,121,122]. On the other hand, specific sugar transporters of L-Ara could be expressed to improve sugar fermentation; for example, *S. cerevisiae* could uptake L-Ara with some glucose sugar transporters (*Hxt5* and *Hxt7*). It was reported that *S. cerevisiae Gal2* had contributed to anaerobic fermentation with a high affinity toward L-Ara when used as the sole carbon source. The ability of some heterologous L-Ara-specific transporters in sugar uptake ranges from 116.7 mmol/h/g for DCW *N. crassa LAT-1* to 0.13 mmol/h/g DCW for *S. cerevisiae GAL2*. Similar to xylose, in L-Ara metabolism, catabolism is more limited than the non-specific uptake of L-Ara by the engineered *S. cerevisiae* strain [116,123–126].

Both types of metabolic pathways of L-Ara are well-established in a native ethanologenic *S. cerevisiae*, yet it lacks the ability to ferment L-Ara. The engineered *S. cerevisiae* strain expresses NADH-specific genes (AR and LXR) to reduce the redox imbalance associated with the fungal metabolic pathway, where the arabitol yield was high with 0.48 g/g of sugar consumption when co-fermented with L-Ara and xylose [127,128]. Thus, the sugar uptake rate is the foremost step in utilization and prerequisites an efficient sugar transporter in order to attain enhanced C5 fermentation. Some of the hexose (*Hxt5* and *Hxt7*) and galactose transporters (*Gal2*) show a high affinity toward C5 sugar assimilation [129,130]. Meanwhile, some of the C5 transporters such as *XAT-1* specifically differentiate and effectively transport L-Ara rather than D-xylose. As reported earlier, the L-Ara fermentation of the engineered *S. cerevisiae* using hemicellulosic hydrolysates remains as the major bottleneck, Li et al. [126] functionally characterized the two transporters, namely, *LAT-1* and *MtLAT-1* from *Neurospora crassa* (FGSC 2489) and *Myceliophthora thermophila* (ATCC 42464), respectively. Thus, heterologous expression of C5 sugar-specific transporters could alleviate the inhibition of sugar uptake as well as enhance the co-fermentation of C5 and C6 sugars by rewiring the pentose assimilation [131].

Though many studies highlighted the native organism involved in L-Ara assimilation, the commercial application has been limited owing to its inhibition by furfurals and low tolerance toward ethanol. As *S. cerevisiae* is an amenable industrial candidate for metabolic engineering, owing to it resistance in various stress environments, Ye et al. [132] recently performed the heterologous integration of the fungal L-Ara pathway by deleting a phosphatase gene (*PHO13*). Herein, this gene deletion enhanced the consumption rate of L-Ara and the specific productivity of ethanol, and further *TAL1* gene activation resulted in

the depletion of sedoheptulose. Thus, engineering the *PHO13* gene in a recombinant strain has ample potential as an industrial strain for L-Ara assimilation to ethanol. A schematic representation of the construction of a recombinant *S. cerevisiae* strain for the production of second-generation ethanol and arabitol using L-Ara is shown in Figure 4.

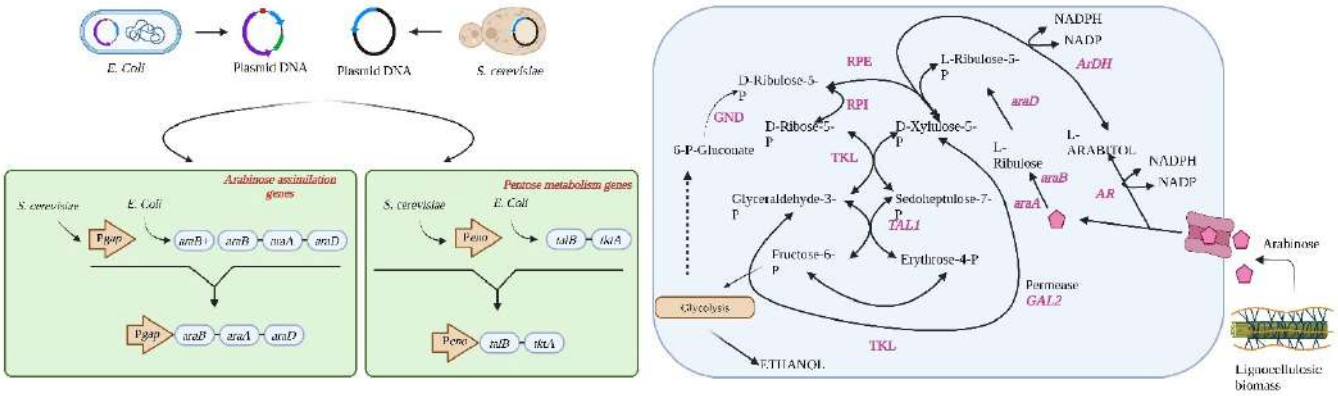

Figure 4. Construction of a recombinant *S. cerevisiae* strain for L-arabinose assimilation through metabolic engineering. *gap*: glyceraldehyde-3-phosphate promoter; *araA*: L-arabinose isomerase; *araB*: L-ribulokinase; *araD*: L-ribulose 5-phosphate 4-epimerase; *Peno*: enolase promoter; *tktA*: transketolase; *talB*: transaldolase; NAD(P)H: Nicotinamide Adenine Dinucleotide Phosphate Hydrogen; $NAD(P)^+$: Nicotinamide Adenine Dinucleotide Phosphate; *araA*: arabinose isomerase; *araB*: arabinose-5-P kinase; *araD*: L-arabinonate dehydratase; *AR*: Aldose Reductase; *ArDH*; D-Arabitol Dehydrogenase; permease Gal2: permease Galactose2; RPE: Ribulose-5-Phosphate Epimerase; RPI: Ribulose-5-Phosphate Isomerase; TKL: Transketolase; TAL1: Transaldolase 1; GND: 6-phosphogluconate dehydrogenase; Glyceraldehyde-3-P: Glyceraldehyde-3-Phosphate; D-Ribose-5-P: D-Ribose-5-Phosphate; D-Ribulose-5-P: D-Ribulose-5-Phosphate; Fructose-6-P: Fructose-6-Phosphate; Erythrose-4-P: Erythrose-4-Phosphate; Pseudoheptulose-7-P: Pseudoheptulose-7-Phosphate; D-Xylulose-5-P: D-Xylulose-5-Phosphate; L-Ribulose-5-P: L-Ribulose-5-Phosphate.

5.3. Fusants-A Distinct Hybrid Yeast

The genetic manipulation of microbes has opened new avenues in biomanufacturing. Among the different strategies, protoplast fusion technology (PFT) is a type of modification at the genomic level by the fusion of two protoplasts to form a hybrid cell, called a fusant. This PFT was proven to be a potential genetic manipulation, wherein the digestion of the cell wall by enzymes and the transfer of genetic material to the host strain enabled the combination of the superior traits of two different strains in a single producer strain. Some studies reported that yeast hybrids, known as fusant yeasts, attained through PFT are able to produce arabitol from fermentable sugars. Lin et al. [133] investigated the efficacy of a *Schizosaccharomyces pombe* and *Lentinula edodes* hybrid to produce L-arabitol with a yield of 0.76 g/g, using L-Ara as the sole carbon source. Karyoductants, obtained after a distinct fusion between the nuclei and protoplast of *P. stipitis* CCY 39501 and *S. cerevisiae*, respectively, would assimilate L-Ara; however, fusants named SP-K7 are identified by the ability to produce a high amount of L-arabitol (16.3 to 18.9 g/L) under the optimum condition [134].

5.4. Engineering Bacteria for L-Ara Fermentation

Recent studies are focused on improving the microbial capabilities for the overproduction of sugar alcohol such as sorbitol, xylitol, and mannitol by bacteria through various metabolic engineering strategies, for example, the co-expression of mannitol dehydrogenase, the facilitator protein of glucose, and formate dehydrogenase for mannitol production in *Corynebacterium glutamicum*; whereas, xylitol production is enhanced in *E. coli* through the heterologous expression of xylose reductase from yeast as well as achieving a higher sorbitol yield from glucose by overexpressing the sorbitol-6-phosphate dehydrogenase in

L. plantarum that is deficient in the lactate dehydrogenase gene [135]. In a native strain such as *E. coli*, the deletion of some genes such as pyruvate formate lyase (*pfl*) and lactate dehydrogenase (*Idh*) was required in order to enable ethanol fermentation using L-Ara [136]. Nevertheless, *K.oxytoca* lacks *adh* and *pdc* genes encoding alcohol dehydrogenase and pyruvate decarboxylase, respectively. Thus, Bothast et al. [137] studied the strain fermentabilities by introducing *Z. mobilis* genes to enable L-Ara-based ethanol fermentation. Recently, Xiong et al. [138] engineered metabolically versatile oleaginous *Rhodococcus jostii* RHA1 through the heterologous expression of *araBAD*, a catabolic operon from *E. coli*, and, thus, the recombinant strain could assimilate L-Ara as the sole carbon source. Further, the cell biomass and lipid yield were improved by the overexpression of the L-Ara transporter gene *araFGH* and the *atf1* gene (diglyceride acyltransferase) from *E. coli* and *R. opacus PD630*, respectively. Kawaguchi et al. [139] investigated the functional analysis of the gene cluster that encompassed the 6-cistron transcription unit that is involved in the utilization of L-Ara in *C. glutamicum ATCC* 31831. In this study, catabolic genes and operons such as *araE* and *araBDA* expression induced L-Ara and were negatively regulated by the *AraR* transcriptional regulator. Further, a unique L-Ara regulon (group of genes or operons) was found to be a distinct regulatory mechanism from the carbon catabolite repression of other bacterial strains. Table 3 represents the different organism types that were employed for L-arabitol production by utilizing L-Ara.

Table 3. L-Arabitol from L-Ara metabolizing yeast, fusants, and recombinants.

Type of Organism	Name of Organism/Strain	Product Produced	Product Yield (g g^{-1})	References
Yeast	*Debaryomyces nepalensis* NCYC 3413	L-Arabitol	0.48	[140]
	P. guilliermondii		0.54	[80]
	C. entomeae		0.77	[141]
Intergeneric fusant	*S. pombe* and *L. edodes* hybrid	L-Arabitol	0.80	[133]
Recombinant	*S. cerevisiae* AH22	L-Arabitol	0.62	[114]
	S. cerevisiae TMB 3664		0.48	[128]

6. Conclusions and Future Perspectives

The advent of lignocellulosic biomass-based biorefining strategies paves the way for the valorization of agro-industrial waste with abundant C5 sugars into various biofuels and high-value-added products. L-arabinose (L-Ara), a C5 sugar, is the second-most-predominant pentose sugar in LCB that has been utilized as an industrial carbon source for the production of various value-added chemicals such as ethanol, sugar alcohols, putrescine, fertilizers, and amino acids. There is a need for the exploration of non-conventional sugars (other than glucose) for microbial fermentation, which seems to be inevitable for an economic edge in bioproducts' development at an industrial scale. This review could provide a comprehensive aspect of arabinose, its natural availability, and an abundance of the lignocellulosic residue and microbial candidates suitable for arabinose valorization to chemicals and fuels. Though many industrial microbial candidates are able to naturally produce bio-compounds, genetic engineering strategies such as laboratory adaptive evolution have been widely explored for enhanced production. Whereas, non-native microbial candidates could be altered through metabolic engineering to facilitate the assimilation of hemicellulose-derived L-Ara. This would direct researchers and industry to explore the potential benefits of arabinose.

Author Contributions: Conceptualization, S.J. and V.K.; writing—original draft preparation (equal first author contribution), A.D., S.R., P.K., A.V. and G.R.; writing—review and editing, V.Z., M.F.M.D., V.K., R.C.R. and S.J.; visualization, G.R.; supervision, S.J., V.K. and V.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

Acknowledgments: R.G. and S.J. would like to acknowledge the Directorate of Research, SRM Institute of Science and Technology, Kattankulathur, for the financial support of their lignocellulosic research through the Selective Excellence Research Initiative scheme. A.D., S.R., P.K., A.V. and G.R. are grateful to the Department of Biotechnology, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, for the infrastructure support to carry out their research work.

Conflicts of Interest: The authors declare no conflict of interest.

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