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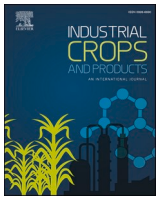

Recent progress on sugarcane-bagasse based lactic acid production: Technical advancements, potential and limitations

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ABSTRACT

India is the largest producer of sugarcane in Asia and its sugar industry represents the second largest agro-based industry. Sugarcane bagasse (SCB), a major waste from sugar industries, is indisputably lignocellulosic biomass (LCB) embedding ~60 % carbohydrates, making it a renewable source of fermentable sugars. Despite its unique chemical composition, SCB is primarily used for co-generation. The enormous potential of SCB can be unleashed, if sugar platform is created using biochemical route. Sugars serve as feedstock for fermentative production of several renewable fuels and chemicals, considered as key drivers for rapid industrialization. US Department of Energy has projected lactic acid (LA) as one of the top biomass-derived platform chemicals owing to its diverse applications and multi-billion-dollar market. Currently, the industrial production of LA is predominated by microbial fermentation (~90 %) which principally uses the starchy or sugar-rich edible feedstocks. If its low-cost manufacturing relying on LCB is enabled, it can be a boon for emerging economies like India, strategically strengthening their socio-economic status. The present review showcases the technical advances made in exploiting the biochemical route towards commercial realization of LA production with SCB as the feedstock. It comprehensively discusses strategies developed in the area of pretreatment, saccharification and fermentation, bridging the gap between lab-scale and industrial LA production. It gives a glimpse on downstream processing of SCB-derived LA, which is still in its nascent stage and briefly talks about our perspective on LA as preferred choice for scale-up in "sugar industry" over other bio-based fuels and chemicals.

1. Introduction

Indian sugar industry is one of the largest agro-based industries. It supports the livelihood of ~50 million farmers and 0.5 million workers associated with sugarcane processing and ancillary activities (Ministry of Consumer Affairs, Food and Public Distribution, Govt. of India, 2022). The global environmental challenges are pushing nations to make a transition from fossil-based economy towards establishment of modern bio-economy, also emphasized by International Energy Agency (Takkellapati et al., 2018). Recently, the Indian government revisited the Ethanol Blending Program (EBP) and set an aggressive target of mandatorily blending 20 % ethanol with gasoline by 2025–26 (Ministry of Petroleum and Natural Gas, Govt. of India 2022). The key motivation was to reduce import dependence on "crude oil", save foreign exchange, enhance the energy security of sectors that excessively rely on fossil fuels, and facilitate decarbonization with reduced greenhouse gas (GHG) emissions. In the light of this development and agriculture intensification, the Indian Sugar Mill Association (ISMA) anticipated sugarcane production to rise from an average of 362.07 to 419.25 million tonnes in the year 2021–22 (Chinimandi, 2021). Moreover, if we see the world scenario, India is 2nd largest producer of sugarcane after Brazil, constituting ~17 % of global cultivation. Sugarcane bagasse (SCB), a major waste from sugar industries, is obtained after extraction of juice from sugarcane. Crushing one tonne sugarcane invariably generates ~0.3 tonne SCB (Huang et al., 2020) and, hence in India alone > 100 million tonnes of SCB is generated. The Indian government had directed the sugar industries to restrict sugar production with intent to divert excess sugarcane juice and molasses for meeting the country's fuel ethanol requirements. However, there is no concrete roadmap to manage and leverage upon the inevitable surplus SCB generated.

The circular economy concept advocates the utilization of sustainable and renewable bioresources, mostly waste streams from agro-

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industrial sectors. SCB is a lignocellulosic biomass (LCB) with following composition; cellulose: 40–50 %; hemicellulose: 25–35 %; lignin: 20–30 % (Konde et al., 2020). Thus, SCB principally comprises ≥ 60 % structural carbohydrates embedded within the heterogeneous and complex aromatic polymer known as lignin (Torgbo et al., 2021). Being abundant, non-edible and renewable resource of organic and fermentable carbon, SCB possess all the characteristics of second generation (2 G) feedstocks and can be valorized into high value products. The current industrial practice involves use of SCB for co-generation, meeting the heat and electricity requirements of the sugar mill. However, the true potential of SCB can only be unleashed if its polysaccharides cellulose and hemicellulose are depolymerized to glucose and xylose respectively, using biochemical route. The sugar platform created thereafter can be transformed into an array of commercially important products including renewable fuels and chemicals.

"Bio-based" platform chemicals are one such remunerative and exceptional category of organic molecules with multiple & reactive functional groups at unique positions, whose labile nature transforms these molecules into new chemical entities with diverse industrial applications (Takkellapati et al., 2018; Gérardy et al., 2020). In 2004, the US Department of Energy (DoE) prepared potential list of platform chemicals obtainable from biomass, which was later revised in 2009. Interestingly, lactic acid (LA) represents one such platform chemical, which gained entry in the revised list of top ten biomass-derived value-added chemical building blocks (Bozell and Petersen, 2010). Chemically known as 2-hydroxypropanoic acid, LA is a chiral molecule and primarily exists as assimilative "L (+)" form (Rawoof et al., 2021). Fortunately, industrial LA production is dominated by microbial fermentation as it produces optically pure L (+) form and rarely D (-) enantiomer, while the chemical route invariably generates a racemic mixture of LA (Ahmad et al., 2020; Yankov, 2022). LA is a key intermediate for synthesizing biodegradable plastics like polylactic acid (PLA) and several other chemical entities such as acrylic acid, propylene oxide, and ethyl lactate (Yankov, 2022). LA and PLA find broad applications in the food, pharmaceutical, textile, cosmetic, polymer, electrical and electronics, biomedical, agriculture and packaging industry (Yankov, 2022; Naser et al., 2021).

In an emerging economy like India, LA and PLA imposed an import burden of 29.7 and 1.92 million USD in 2020–2021, respectively (Connect2India, 2021a and, 2021b). Owing to ban on single-use plastics in many countries including India is likely to boost the PLA market with a compound annual growth rate (CAGR) of 15.8 % surpassing 4.69 billion USD by 2031. Likewise, the revenue from LA is anticipated to cross 11.51 billion USD by 2031 (Transparency Market Research, 2021). Currently, 90 % of LA is manufactured through fermentative route and most global players like Corbion-Purac, Natureworks LLC, Musashino Chemical Laboratory Ltd, Galactic, Henan Jindan Lactic Acid Technology etc., thrive on edible sugar-rich or starchy feedstocks such as sugarcane juice, corn, tapioca, cassava, sugar beet etc. for industrial LA production (Ahmad et al., 2020). However, 2 G LA is looked upon as one of the most promising molecules with Technology Readiness Level (TRL) of 8 and its commercial manufacturing through the LCB route is underway (Biddy et al., 2016; Rosales-Calderon and Arantes, 2019).

The issue of sustainable supply chain management and logistics in the case of LCB pose one of the primary challenges for biorefinery development. In Indian context this challenge can be converted into an opportunity, if sugar industry proactively and consciously selects SCB as the starting feedstock (Quereshi et al., 2020) and target commercialization of bio-based product like LA. This bold step can set forth an example of waste minimization and create wealth by product diversification. SCB valorization to LA essentially includes four process modules: pretreatment, saccharification, fermentation and downstream processing. SCB-based biochemical platform can be easily annexed to any sugar industry, if its integrated modules are techno-economically competitive, environmentally benign and the overall process generates a profitable and sustainable business. The current review comprehensively discusses those innovational breakthroughs in each of these modules that used SCB as their starting feedstock and whose integration can pave a way towards commercial production of 2 G lactic acid.

2. Pretreatment of SCB

Biomass recalcitrance is the innate characteristic of any LCB which acts as the roadblock for enzymes to access cellulose, successfully extract fermentable sugars and subsequently valorize them to renewable fuels and chemicals (Baral, a et al., 2022). A desirable pretreatment strategy demands efficient reduction in biomass recalcitrance and recovering the maximum carbohydrate fraction either in hydrolyzed or un-hydrolyzed form. But industrial scale up also requires low capital and operational expenditure (CAPEX, OPEX) with minimal waste generation and optimum water usage. High-solids pretreatment and chemical recycling are two approaches which can enhance environmental and economic sustainability of any pretreatment strategy.

On the process front in past one decade, several high-solids pretreatment strategies have been evaluated with SCB as shown in Table 1. A special mention of DryPB process is necessary where LCB is mixed with 2–5 % (w/w) dilute sulfuric acid in the ratio of 2:1 and subjected to 175–190 °C for 3–5 min, followed by biological detoxification through *Amorphotheca resinae* ZN1 strain which selectively assimilates toxic oxidized sugar products including soluble and insoluble lignin inhibitors (Wu et al., 2021). With continuous process improvements, during pretreatment, solid loadings were increased from 30 % to 70 % and several LCB's including SCB have been tested, as mentioned in Table 1 (Wu et al., 2021; Liu et al., 2018). Optimization with especially designed high-solids pretreatment reactors which can process > 20 % solids with effective mass and heat transfer have also lately gaining huge popularity. A pertinent example is use of continuous single or twin-screw extrusion system where large volumes of biomass at high-solids can be pretreated in a short time with ultra-low loadings of chemicals such as deep eutectic solvents, alkali, ionic liquids etc. as reviewed extensively by Guiao et al. (2022). High shearing forces of the screws in extruders facilitate adequate defibrillation and promote efficient mixing of chemicals with biomass thereby enhancing biomass digestibility. The superiority of the extruder system in terms of bulk biomass processing in less time was demonstrated by Da Silva et al. (2013), where SCB was pretreated with 1-ethyl-3-methylimidazolium acetate. Comparable glucan conversion yields were obtained, when the batch study was conducted with 4.8 wt % solids at 140 °C for 4 h or when 25 % solids were pretreated in twin extruder system at 140 °C with residence time of 4 min and number of cycles repeated were two. The said experiment also brought "cellulose accessibility" in spotlight as specific surface area of the biomass played a decisive role in attaining high saccharification yields despite pretreated solids with high lignin content (Da Silva et al., 2013).

Biomass densification (BD) using pelletization technique is yet another trending technological development. The need and importance of BD in enhancing the industrial viability of 2 G biorefinery has lately been realized. It not only facilitates pretreatment at high-solids and overcomes issues like large space allocation during biomass transportation, storage but also reduces biomass vulnerability to microbial attack as well. Densifying lignocellulosic biomass with chemicals followed by autoclave (DLCA) and compacted biomass pretreatment with recycled ammonia (COBRA) are two such novel and proven strategies which have been successfully demonstrated with SCB (Shen et al., 2022; Morais et al., 2022). In the optimized DLCA approach, one kg SCB was charged with 50 g $H_2SO_4$and mixed with 500 g water followed by pelletization using flat die pelletizer with compression capacity of 70–120 kg h^{-1}. Pellets subjected to 120°C for one hour at 33.3 % solids, led to 84 % xylan hydrolysis post pretreatment and recovered biomass showed excellent (>95 %) glucan digestibility during high-solids enzymatic saccharification (Shen et al., 2022). COBRA is yet another next-generation NH_3 based pretreatment technique where in the 1st

Table 1
State of the art which demonstrates high-solids pretreatment with SCB as the feedstock.

Pretreatment strategy	SL (%)	Temp (°C)	Holding time	Chemical loading	(%) recovery in Residual Solids#			Process advantages	Process shortcomings	Reference
					Gln	Xln	KL			
1-ethyl-3-methyl-imidazolium acetate	25	140	4 min TSE- 2 passes	1:3 (S: L)				Biomass with ↑ specific surface area. 85 % sugar yields post saccharification	High cost of the IL	Da Silva et al. (2013)
Dilute Sulfuric acid	20	121	150 min	1 %	87.5	15.2	82.6	70 % xylan recovered as xylose in AH	Post saccharification low glucose yields	Da Silva Martin et al. 2015
Alkaline hydrogen peroxide (AHP)	20	90	60 min	7 % (v/v) H_2O_2in NaOH	94.0	30.9	32.18	Biomasses with ↑ water retention capacity. The glucan conversion yields from 10 % solids in 24 h were 76 % and 66.9 % respectively in	38 % xylan recovered in hydrolysate	
Ox-B	20	25	120 min	5 % Ox-B (10:1)	85.8	33.9	24.8	AHP and Ox-B process glucan conversion	Xylan lost in lignin-rich hydrolysate	
Sequential DA and NaOH	33.3	121: DA 100: Alk	0.5 h: DA 0.6 h: Alk	1 % (w/v) 3 % (w/v)	–	–	–	High delignification. 80.9 % glucan hydrolysis from 20 % solids	Incomplete xylan hydrolysis during DA pretreatment	da Conceição Gomes et al. (2018)
Alkali (NaOH)	16.67	110	1 h	1.8 %	94	76.6	23.56	Delignified biomass. FBH released > 200 g L^{-1} sugars from 33 % solids	> 20 % xylan lost in BL	Gao et al. (2014)
	15	121	0.5 h	2 %	93	65	35	FBH of 20 % solids yielded > 85 % sugars	35 % xylan lost in BL	Baral et al. (2021a)
	15	121	0.5 h	2 %	98	79	34.7		21 % xylan lost in BL	Baral et al. (2022b)
DA followed by glycerol	20	130-DA 170-Gly	0.25 h each	2.4 % - DA* 80 %- Gly	80.8	3.4	65.4	66.5 % xylose yields in AH; 99.2 % glucan digestibility reported	> 45 % carbohydrate fraction unrecovered	Hassanpour et al. (2020a)
Sequential DA-glycerol	23.8	130-DA 150-Gly	0.25 h each	3.33 %-DA*	84.9	7.9	69.8	70 % xylose yields in AH	Only 69 % glucan digestibility	Hassanpour et al. (2020b)
Glycerol	20	150	0.25 h	80 % Gly	88	18.7	72	92.5 % glucan digestibility claimed despite 72 % lignin	Xylose lost in pre-hydrolysate glycerol	
Sequential LHW wet disk milling	20	180	10 min WDM- 3 passes	Water	–	–	–	Delaminated biomass with ↓ inhibitors. 83.8 % glucose yields after EH	LHW solubilized < 40 % xylan with ↑ furfural, formic & acetic acid	Wang et al. (2018)
DryPB	50	175	5 min	20 mg acid/g biomass	–	–	–	78.5 % glucan hydrolysis yields from 30 % pretreated solids after EH	Bio-detoxification conducted for 60 h	Liu et al. (2018)

Note: Gln- Glucan; Xln- Xylan; KL-Klason lignin; # refers to Residual solids after pretreatment; TSE- Twin screw extruder; FBH- Fed-batch hydrolysis; AH- Acid hydrolysate; S:L-Solid: Liquid ratio; IL-Ionic liquid; DA –Dilute H2SO4; Alk- alkali; BL- black liquor; SL- Solid loading; * refers to wt % loading; LHW- Liquid hot water; WDM- wet disk milling; Gly- glycerol; Ox-B- pretreatment with hypochlorite–hydrogen peroxide; DryPB- Dry acid pretreatment and biodetoxification

stage SCB was densified to 560 kg/m^3 using a flat die pelletizer without any external binder. Further the biomass pellets were exposed to NH_3in 1:1 ratio and subjected to 100 °C for 3.5 h followed by draining of solubilized lignin and $NH_3$by purging N_2 leading to lignin extraction (LE). In this recent study, authors have claimed 65.7 ± 1.8 kg total sugars yields from 100 kg SCB using COBRA-LE approach and their higher fermentability to ethanol (Morais et al., 2022).

Though ultra high-solids (≥ 40 %) pretreatment strategies like phosphoric acid and H_2O_2 (PHP), ethylenediamine, acidified γ-valerolactone, alkali organsolv have been demonstrated with other LCB's as reviewed extensively by Baral et al. (2022a), their efficacy in reducing recalcitrance of SCB as feedstock is yet to be explored.

Chemical recycling is another attractive approach and more marketable where the chemicals used are either expensive such as deep eutectic solvents and ionic liquids (IL's) or impose environmental burden for example alkali. This strategy further aid in minimization waste generation and best suited only when the performance of the recycled chemical is comparable to the virgin/pure chemical during pretreatment. Table 2 depicts strategies adopted for recycling chemicals during SCB pretreatment and recycled chemical has shown a proven record of being equally effective during pretreatment and downstream. Recently, Nakasu et al. (2020) showed that during IL pretreatment, acid-base ratio (ABR) critically governed the performance of protic IL monoethanol-ammonium acetate (MEA) and its recycling. An in-depth analysis revealed that excessive MEA and acetic acid suppressed and elevated the inevitable acetamide formation respectively, which in turn displayed negative correlation with glucan conversion yields. Therefore, when the ABR was 0.5, IL acetamide formation was restricted to 30 % after three IL recycles and pretreated SCB showed high glucan and xylan conversion yields. However, when the ABR was 1.0, IL after every recycle, a high acetamide (86 % in 6th cycle) accumulation was observed, which steadily reduced the saccharification yields of both glucose and xylose (>75 % to <50 %) from IL pretreated SCB (Nakasu et al., 2020). Likewise, a recyclable novel solvent namely furoic acid (FA) was evaluated for production of xylooligosaccharides (XOS) from SCB and glucose after enzymatic hydrolysis (Dai et al., 2021). FA under optimized conditions (5 %; 175 °C; 15 min) not only produced 45.6 % XOS but it was easily recovered by concentrating the acid hydrolysate (AH) in rotavapor. Further freezing AH, also lead to FA precipitation and its use for next cycle. FA pretreated biomass liberated 83 g L^{-1} glucose from 15 % solids (Dai et al., 2021).

Despite different types of shortcomings associated with each of these pretreatment processes discussed above and researchers' targeting variegated bio-based products, most of the pretreated biomasses generated have shown high carbohydrate conversion yields during saccharification. Some of these strategies have been validated at pilot scale as well enhancing likelihood of their commercialization. However, there are very few pretreatment strategies which are qualified to be called as

Table 2
Chemical recycling strategies applied during SCB pretreatment.

Pretreatment reagent	Pretreatment Conditions	Recycling Strategy	Impact of recycling on process	Reference
1-ethyl-3-methylimidazolium acetate	Solid loading: 5 % Temperature: 120 °C Duration: 120 min	• Combinatorial use of ultra-filtration and electrodialysis • Recovered 94 % IL and reused four times	• The average delignification achieved from 4 recycles IL was 61.97 ± 0.68 % • Delignification efficiency of recycled IL was 97 % compared to fresh IL	Liang and Liu (2020)
$AlCl_3$-acidified aqueous glycerol	Solid loading: 10 % Temperature: 150 °C Duration: 60 min	• Organosolv lignin precipitated using ethanol: water (1:9 v/v) thrice • Vacuum at 50 °C used to remove ethanol and water • Acidified glycerol recycled for three consecutive pretreatment runs	• Recycled acidified glycerol showed a glucan recovery efficiency was 96–100 % compared to fresh pretreatment solvent • Delignification capacity reduced by 8 %, 14 % and 23 % in I, II and IIIrd recycling compared to fresh pretreatment solvent • Xylan removal efficiency reduced significantly	Zhu et al. (2021)
Alkali Sodium hydroxide	Solid loading: 10 % Temperature: 121 °C Duration: 60 min	• The BL obtained from Ist cycle reconstituted to 100 mL with deionized water and pH was readjusted to 13.7, representing the pH of fresh 2 % NaOH • Vacuum assisted black liquor recycling (VALBR) pretreatment repeated 7 times with fresh NaOH pretreatment in vacuum as + control	• 46 % and 20 % reduced water and alkali usage • The delignification achieved from 7 recycles was 78.52 ± 0.43 % compared to 79.94 % by fresh NaOH • Xylan recovery improved by 14 % (64.42 vs 56.12 %) by VALBR • Glucan recoveries were comparable (79.94 ± 0.96 % by VALBR vs 81.7 % by fresh NaOH) • Comparable glucose yields post-saccharification	Fan et al. (2020)
Alkali Sodium hydroxide	Solid loading: 10 % Temperature: 80 °C Duration: 120 min	• BL separated and solid residue is washed with 10 volumes of water in three stages. • BL is reconstituted with wash water from Stage I. • IIndbatch solid residue 1st time washed with wash water from Stage II of 1st Batch and 2nd time wash water from Stage III of 1stbatch	• 45.5 % reduced alkali usage and > 80 % saving of water and reducing waste water discharge by 15 % • Comparable hydrolytic efficiencies attained from biomasses obtained after BL and waste water recycling compared to fresh alkali pretreated SCB by doping 0.25 % Tween 80 in former case • Limitation of process is recycling of BL and wash water can be done just twice	Wang et al. (2016)
Tri-ethylbenzyl ammonium chloride/ lactic acid	Solid loading: 6.67 % Temperature: 120 °C Duration: 240 min	• Solids washed with EtOH and later the wash was mixed with DES- rich hydrolysate, which was later recovered as solid after rota-evaporation. • Recovered DES recycled five times	• Glucan digestibility reduced by 22 % (from 88 % to 68 %) after 5th DES recycling	Liu et al. (2021)

Note: BL-black liquor; EtOH- Ethanol; DES-deep eutectic solvent; IL-Ionic liquid

Table 3
High-solids enzymatic saccharification of pretreated sugarcane bagasse at cellulase loading ≤ 15 mg protein or FPU g^{-1} glucan content and attaining ≥ 80 % carbohydrate conversion yields.

Pretreatment Type	Enzyme Used	SL (%)	Enzyme loading (g^{-1} glucan)	Additives/ Enzymes used	Mode	Sugar titers (g/ L)	Sugar* / glucose productivity (g/L. h)	Carbohydrate conversion yields (%)	Reference
Formiline	Novozyme cellulase	30	11.6 FPU	None	FBH	Glucose: 247.3	1.26	86.1	Zhao et al. (2013)
NaOH	Cellic CTec3	22	11.54 mg protein	WP, CL, SPL, BG, HC, Tween 80	FBH	Glucose: 122	2.54	Glucan: 80	Xu et al. (2019)
Sequential SE NaOH& bleaching	Cellic CTec2	17.5	12.64 mg protein	None	BH	Glucose:125	1.74	Glucan: 80	Pereira and Arantes (2020)
al-AGO	LT4	20	3.45 mg protein	PEG 8000, Tween 80, BSA, BG &endoxylanase	FBH	Glucose: 107 G + X: 158	1.48 2.19 *	Glucan: 83	Nwamba et al. (2021a)
Sequential Alkali-ASE	Cellic CTec2	15	10 FPU	None	BH	Glucose: 75	1.56	Glucan: 84.4	Quintero et al. (2022)
NaOH	Cellic CTec2	20	15 mg protein	PEG 6000	FBH	Glucose: 126.8 G + X: 166.7	2.64 3.47 *	Glucan: 84.3 Xylan: 82.58	Baral et al. (2021a)
NaOH	Cellic CTec3	20	15 mg protein 12.5 mg protein	PEG 6000	FBH	Glucose: 122.5 G + X: 181.4 Glucose: 124.9 G + X: 183.5	2.55 3.77 * 2.60 3.82 *	Glucan: 86.3 Xylan: 93.2 Glucan: 82.7 Xylan: 93.3	Baral et al. (2022b)
COBRA COBRA-LE	Cellic CTec3	21	15 mg protein	Cellic HTec3 and Multifect pectinase	BH	Glucose: 57.8 G + X: 94.7 Glucose: 60.9 G + X: 97.1	0.62 0.98 * 0.63 1.01 *	Glucan: > 95 Xylan: > 95 Sugar: > 90	Morais et al. (2022)

Note: SL- Solid loading; $- glucan loading; SE- Steam explosion; al-AGO- alkali catalysed atmospheric glycerol; ASE- Alkaline sulfite with ethanol; COBRA- Compacted Biomass Pretreatment with recycled ammonia; LE- Lignin extraction; WP- Whey protein; CL- Calcium lignosulfonate; SPL- Sophorolipid; BSA- Bovine serum albumin; HC- hemicellulose; BG- β-glucosidase; PEG- polyethylene glycol; FBH- Fed-batch hydrolysis; BH-Batch Hydrolysis

"economically viable" and yields > 400 g total sugar from one kg biomass, a benchmark set by Mark et al. (2020), by conducting reaction network flux analysis (RNFA).

3. Enzymatic saccharification of pretreated SCB

For developing an industrially deployable sugar platform or generating concentrated second-generation sugar syrups, it is imperative to conduct enzymatic saccharification at high-solids (≥ 15 %). However, it should be noted that cost associated with cellulase production especially catering biorefinery segment, their consistent and bulk supply, process and enzyme related factors affecting efficient product output at high-solids are rate-limiting steps of the said module as reviewed extensively (Baral et al., 2022a; Reis et al., 2023). Rheological limitations during high-solids enzymatic saccharification (HSES) are often circumvented by preferring multi-step substrate feeding strategy over single step feeding regime and designing special enzyme reactors which facilitate efficient heat and mass transfer. However, the drawbacks of enzyme related factors are preferably met through use of auxiliary enzymes when the pretreated biomass has polysaccharides other than glucan and using lignin blocking additives which primarily belong to two groups namely surfactants and non-catalytic proteins as discussed comprehensively by Baral et al. (2022a). Despite extensive research on SCB valorization through biochemical route, there are very few reports where HSES was performed at cellulase loading ≤ 15 mg protein or FPU g^{-1} glucan content and ≥ 80 % carbohydrate conversion yields were attained (Table 3). In Table 3, only alkali and alkali catalyzed glycerol pretreated SCB yielded high sugar conversion yields and attained sugar productivity of > 2 g L^{-1} h^{-1}. High sugar productivity is extremely essential during industrial bioprocessing of LCB, as longer duration of HSES adversely impacts the overall OPEX of the process. Further, it reduces the chances of enzyme recycling, which can play a pivotal role in reducing the cost-economics of the said module. Those researchers who ignored this important aspect should focus on enhancing the sugar productivities. In their recent study, Baral et al. (2022b) conducted the HSES with alkali pretreated SCB and found that the sugar-rich hydrolysate retained 71 % enzyme as per Bradford assay. Since the duration of HSES was merely 48 h and PEG-6000 fortification aided in enzyme recovery, the likelihood of enzyme recycling and its re-use looks more feasible (Baral et al., 2022b). In the saccharification module there is an exceptional case which deserves attention. In the said study, 195 g L^{-1} monomeric sugars (Glucose: 139 ± 1.28 g L^{-1}; Xylose: 56 ± 0.64 g $L11^{-1}$) were produced in 72 h from 30 % SCB solids obtained after alkaline hydrogen peroxide pretreatment. This fed-batch hydrolysis resulted in 70 % carbohydrate conversion yields, when cellulase was dosed at ~10 FPU g^{-1} glucan with an additional doping of 100 U g^{-1}DM hemicellulase along with bio-additives comprising of sophorolipid and whey powder (Zhang et al., 2022a).

4. Synergism between pretreatment and saccharification to maximize sugar yields

Generally, "high sugars yields" during enzymatic saccharification overshadows the sugar recovery during pretreatment and is presumed to primarily influence the cost of lignocellulosic sugars. But the quality of the biomass generated after pretreatment governs the sugar yields during hydrolysis. Thus, simultaneous intensification in both the process modules namely pretreatment and saccharification is vital for maximizing sugar recovery from SCB, as they govern the overall cost of lignocellulosic sugars. Dedicated efforts especially in the past 2–3 years had led to evolving integrated processes which recovered ≥ 75 % sugar or ≥ 540 g principal (monomeric/fermentable/functional) sugars from one kg of raw SCB (Table 4), considering 725 g as the theoretical maximum (Morais et al., 2022). Only three high-solids pretreatment strategies cited in Table 4, namely alkali, DLCA and COBRA efficiently recovered the sugars from SCB during HSES at enzyme loadings between 12.5 and 20 mg protein/g glucan (Baral et al., 2022b; Shen et al., 2022; Morais et al., 2022). Earlier, the addition of sodium methoxide during

Table 4
State of art showing the recovery of > 540 g monomeric/fermentable sugars from one kg raw SCB post pretreatment and saccharification.

Pretreatment	Carbohydrate (g) in SCB		Sugars recovered (g) /kg SCB post-pretreatment[$] & saccharification		Loading during saccharification		Total sugars recovered in g from one kg raw SCB	Reference
	Before pretreatment	After pretreatment	Glucose	Xylose	Solid (%)	Cellulase (g^{-1} glucan)		
AH followed by mechanical refining	Glucan: 406 Xylan: 209	Glucan: 296.94 Xylan: 52.92	22[$] 331[ϵ]	151[$] 57	5	12.37 FPU	173[$]+ 388 (561)	Batalha et al. (2015)
CH_3ONa catalyzed glycerol pretreatment	Glucan: 391.5 Xylan: 272.52	Glucan: 347.35 Xylan: 201.58	–	–	2	11.10	(566.6)	Lv et al. (2018)
APPA	Glucan: 413 Xylan: 259	Glucan: 405.4 Xylan: 152.37	420	167	2.5	37.03 FPU	(587)	Han et al. (2020)
SC		Glucan: 380 Xylan: 236	372	175		39.47 FPU	(547)	
Acid catalysed LHW followed by FA-GOP	Glucan: 381.4 Xylan: 253.7	Glucan: 329.4 Xylan: 0.00	47.8[$] + 2.1[$] 285.9	171.5[$]+ 53.2[$]	5	15.78 FPU	274.6[$] + 285.9 (560.5)	Chotirotsukon et al. (2021)
$FeCl_3$-catalyzed EG/H_2O pretreatment	Glucan: 404 Xylan: 273	Glucan: 373 Xylan: 9.0	27[$] 369	230[£$] 8[£]	5	26.8 FPU	257[$] + 377 (634)	Wei et al. (2021)
LHW	Glucan: 414.4 Xylan: 260.1	Glucan: 420.6[γ] Xylan: 8.55	367.2	202.9	–	38.3 FPU	(570.1)	Zheng et al. 2021
NaOH	Glucan: 404.9 Xylan: 275.5	Glucan: 399.5 Xylan: 217.93	381.4 372.7	229 224.9	20	15 mg protein 12.5 mg protein	(610.4) (597.6)	Baral et al. (2022b)
COBRA	–	–	–	–	21	15 mg protein	(674)	Morais et al. (2022)
COBRA-LE	–	–	–	–			(657)	
AFEX	–	–	–	–		25 mg protein	(603)	
DLCA	Glucan: 353.5 Xylan: 258.6	Glucan: 303.9 Xylan: 41.4	12[$] 314	191.9[$] 45.5	20	20 mg protein	203.9[$] + 359.5 (563.4)	Shen et al. (2022)

Note: $- Refers to monomeric sugars in pre-hydrolysate; * refers cellobiose; # - total monomeric sugars; γ- higher glucan content than raw bagasse after LHW; ϵ- Glucose yields more than theoretical yield; £ - xylose equivalents; DLCA- Densifying lignocellulosic biomass with chemicals followed by autoclave; LHW- Liquid hot water; FA- GOP- Formic acid catalysed glycerol organosolv pretreatment; AH- Autohydrolysis; APPA-alkaline/peracetic acid; SC- sodium chlorite; data in brackets reveal total fermentable sugar recovered

glycerol pretreatment at high temperatures, not only preserved 88.7 % and 74 % glucan and xylan fractions respectively, but also led to 79.5 % delignification. The maximum combined yield of total fermentable sugars reported was 566.6 g/kg SCB (Lv et al., 2018). On the contrary, 41 % xylan loss was observed when the SCB was subjected to alkali-peracetic acid pretreatment (Han et al., 2020). This observation implies that there is sufficient scope of preserving xylan fraction by reducing the process severity and fine tuning it. In Table 4, one study in particular draws special attention, wherein introduction of ferric chloride as catalyst during ethylene glycol-water pretreatment led to 3.2-fold (28.3–91.5 %) enhanced glucose yields during saccharification step (Wei et al., 2021). Likewise, introduction of mechanical refining step after auto-hydrolysis resulted in 17 % improvements in glucan conversion yields of cellulolignin rich SCB when enzyme loading was 12.37 FPU g^{-1} glucan. However, auto-hydrolysis at 180∘C for 20 min had a serious drawback, as it led to 26.86 % glucan hydrolysis but only 18 % was recovered as glucose (Batalha et al., 2015). Among all the pretreatments cited in Table 4, there is only strategy where all the three components namely cellulose, hemicellulose and lignin were not only fractionated but recovered as well. Moreover, the second step which involved formic acid and glycerol, its spent liquor was recycled four times and there was no significant change in the efficacy in terms of product yield and selectivity (Chotirotsukon et al., 2021).

In their recent study, Baral et al. showed that during SCB bioprocessing process intensification in pretreatment and saccharification module reduced the overall cost of one kg monomeric fermentable sugars from 2.25 US$ to 1.32 US$ (2021a). Shifting from low solids (5 %) to high solid (15 %) pretreatment and reducing alkali usage from 0.4 to 0.12 g g^{-1} SCB along with optimized pretreatment conditions led to sharp decline of 3.18 fold (0.44 US$/kg to 0.14 US$/kg) alone in pretreatment. On the contrary, the impact of reducing enzyme dose at the cost of extending the duration of hydrolysis during HSES was less marked. Intensification in HSES led to cost reduction of this module from 1.64 to 1.0 US$/kg fermentable sugars. Cumulative intensification of these process modules lowered the environmental impact significantly and the contribution towards life cycle climate change reduced from 2.87 to 1.57 kg CO_2 equivalents (Baral et al., 2021a). Thus, it is very crucial to identify the process lacunas and environmental hotspots which deter the chances of creating an industrially viable sugar platform while exploiting biochemical route.

4.1. Fermentative production of lactic acid using SCB derived-2 G sugars

Numerous challenges hinder the techno-economic production of lactic acid using 2 G sugars despite of the fact that 90 % commercial LA is produced through microbial route. Several inherent metabolic issues are associated with bacterial systems including lack of necessary genes for xylose transport & its metabolism, carbon catabolite repression, production of side-products during hetero-fermentation, optical purity of the product (Cubas-Cano et al., 2018; Nwamba et al., 2021b). Genetic engineering approach addresses most of the innate drawbacks linked with LA fermenting microbes. Furthermore, substrate and end product inhibition, soluble and insoluble inhibitory compounds generated as a result of SCB degradation during pretreatment and saccharification are practical problems that evaluates the robustness of the fermenting strain and pose threat for industrial- scale up of 2 G lactic acid (Cubas-Cano et al., 2018; Nwamba et al., 2021b). Experimenting with different fermentation strategies, substituting multi-step or continuous feeding with single step substrate feeding, subjecting 2 G sugars to detoxification prior to fermentation, adaptive evolution of LA fermenting microbes, choosing microbes which thrive well in diverse metabolic environments are some potential ways to overcome these hurdles.

In a typical 2 G biorefinery, first a sugar platform is generated using enzymatic saccharification and then the sugar-rich hydrolysate is subjected to fermentation. This configuration is often referred to as separate hydrolysis and fermentation (SHF). Besides SHF, there are two other processes namely simultaneous saccharification and fermentation/ co-fermentation (SSF, SScF). These processes invariably begin with short duration pre-hydrolysis by enzymes to release sufficient sugars. Later, the fermenting microbe is inoculated, capable of assimilating single sugar (SSF) or multiple sugars (SScF) and biotransform them the LA. SSF and SScF relieve the cellulases from their inherent drawback of end-product inhibition and enhance their performance. Simultaneously, they also aid in reducing the CAPEX and OPEX of the entire process, leading to less waste generation and optimum water usage. However, for developing an SSF or SScF process requires microbe to be either thermophilic or thermo-tolerant, as most of the cellulase cocktails display a temperature optimum of 50 ± 5 °C and ability to work in acidic environment, as cellulases generally work in a pH range of 4.5–5.5.

In past 15 years, there are few reports where these fermentation configurations were exercised for LA production using 2 G sugars derived from SCB or pretreated SCB with final product titer reaching > 50 g L^{-1} (Table 5). The table also highlights the salient feature associated with each of these processes. However, for developing a commercially feasible 2 G LA process, it is essential that microbial strain exploited for fermentation should have a demonstrated ability for high sugar consumption rate and high metabolic yield of LA. Furthermore during fermentation, sterilization and maintaining sterility is an important step. It substantially contributes to overall process being an energy intensive unit operation. Many reports illustrated in Table 5 used moderately thermophilic *Bacillus* strains, where fermentation was performed under non-sterile conditions. Further, in Table 5, most of the processes displayed fairly good and promising TYP (titer, yield and productivity) metrics. The yield is high (>0.70 g g^{-1}) in all the reports. But very few processes produced LA with titer > 100 g L^{-1} (Peng et al., 2014; Zhou et al., 2016) and productivity > 2 g L^{-1} h^{-1} (Nalawade et al., 2020; Baral et al., 2020).

It is important to mention the report by Peng et al. (2014) who used SCB hydrolysate for LA production. For this, SCB was treated with acid (H_2SO_4) and alkali (NaOH) in sequential manner. After acid pretreatment, the solid fraction was treated with alkali followed by enzymatic hydrolysis using commercial cellulases. The hydrolysate obtained was concentrated and had following composition: 355 g L^{-1} glucose, 37.0 g L^{-1} xylose with 0.4 g L^{-1} acetic acid and 0.56 g L^{-1} lignin. The fed-batch fermentation was performed at 50°C using SCB hydrolysate and cottonseed meal as carbon and nitrogen source, respectively, under open non-sterile conditions with a high inoculum level of 30 % v/v to avoid any contamination. The *Bacillus sp*. strain P38 accumulated massive LA titer of 183 g L^{-1} with productivity of 1.93 g L^{-1} h^{-1}. The LA yield (0.99 g $g)^{-1}$) on total reducing sugars (glucose + xylose) was close to theoretical yield of 1g g^{-1}. Since no D-isomer was detected, the purity of L-isomer was 100 %. It was not mentioned what was done with xylose rich hydrolysate obtained after acid pretreatment. The diversion of xylose rich hydrolysate to LA or other high value product such as xylitol can further contribute to improvement in process economics. In another report Zhou et al. (2016) made use of bagasse sulfite pulp (BSP) for LA fermentation by *Bacillus coagulans* CC17. BSP is a byproduct from paper and pulp industries, obtained during traditional sulfite pulping of SCB. The BSP was enzymatically hydrolysed using cellulase and β-glucosidase from Novozymes. They found SSF more economical than SHF in terms of cellulase dosage as *B. coagulans* CC17 does not require additional β-glucosidase during SSF. The SSF was performed in a fed-batch mode with an initial cellulose loading of 30 g L^{-1} under non-sterile conditions. The sugars were assimilated as soon as they were released, as residual glucose and xylose during fermentation did not exceed 1.0 g L^{-1}. During fed-batch SSF period of 192 h, the strain amassed 110 g L^{-1} LA from total cellulose loading of 153.3 g L^{-1}. The LA yield on cellulose was 0.72 g g^{-1} while combined cellulose plus hemicellulose was 0.60 g g^{-1}.

Despite extensive work on SCB valorization to LA, there are very few reports which have conducted techno-economic analyslsis of their process. For instance, recently Munagala et al. (2021a) evaluated the process developed by Nalawade et al. (2020) assuming that LA plant was

Table 5
State of the art which used cellulosic and hemicellulosic fraction of sugarcane bagasse for producing > 50 g L^{-1} lactic acid.

Pretreatment type	Primary sugar valorized	Strain used	Fermentation strategy used	SCB-derived lactic acid			Salient feature of the process	Reference
				titer (g L^{-1})	yield (g g^{-1})	productivity (g L^{-1} h^{-1})		
Dilute H_2SO_4	Xylose	*Bacillus* sp. strain 17C5	B-SHF	55.56#	0.89	0.29	Thermo-tolerant & acidophilic bacterium assessed for LA production using lime treated AH rich in xylose	Patel et al. (2004)
Steam and alkali	Glucose and cellobiose	*Lactobacillus delbrueckii* Uc-3	B-SScF	67#	0.83	0.93	SSF performed using in-house cellulase cocktail derived from *Penicillium janthinellum* (EU1)	Adsul et al. (2007)
		L. lactis mutant RM2–24	B-SScF	73.31$	0.73	1.52	SSF performed using in-house cellulase cocktail derived from *P. janthinellum* (EU1)	Singhvi et al. (2010)
Sequential DA-NaOH	Glucose	*Bacillus* sp. P38	FB-SHF	185#	0.99	1.93	SCB-derived dilute sugar solution concentrated. Open high-cell density fermentation conducted with cottonseed as low cost N_2 source	Peng et al. (2014)
Sulphite pulping	Glucose	*B. coagulans* CC17	FB-SSF	110#	0.72	0.57	Compared to SHF, in FB-SSF enzyme dose reduced from 15 to 10 FPU/g DM	Zhou et al. (2016)
Dilute H_2SO_4	Xylose and glucose	*B. coagulans* DSM 2314	B-SScF	74.6#	0.92	0.92	SSF conducted with acid pre-hydrolysate rather than water addition	van der Pol et al. (2016)
Dilute H_2SO_4	Xylose	*Lactobacillus pentosus*	FB-SSF	72.75#	0.61	1.01	Strain adapted on acid-hydrolysate to enhance inhibitor tolerance &fermentation ability	Unrean (2018)
Sequential DA-NaOH	Xylose and glucose	*L. pentosus* ATCC 8041	B-SScF	64.8#	0.93	1.01	Non detoxified acid- hydrolysate mixed with glucose-rich hydrolysate.	Wischral et al. (2019)
Dilute HCl	Xylose	*B. coagulans* DSM ID 14–300 *	B-SHF	55.99#	0.87	1.7	*B. coagulans* assimilated furfural and HMF detoxifying xylose-rich pre-hydrolysate and fermented it to LA	de Oliveira et al. (2019a)
NaOH -DA	Glucose	*B. coagulans* NCIM 5648	B-SHF	71.8#	0.90	2.99	A comparative assessment of various pretreatment methods was done for recovery of maximum carbohydrate fraction from SCB and later for LA production	Nalawade et al. (2020)
NaOH				68.7#	0.92	2.86		
DA- NaOH				66.9#	0.88	2.79		
Cavitation with alkali				62.5#	0.92	2.6		
NaOH	Glucose	*B. coagulans* NCIM 5648	B-SHF	69.2#	0.76	2.88	Wash fraction of enzymatic hydrolysis used for preparing seed medium and conducted high-cell density fermentation	Baral et al. (2020)

Note: FB- Fed-batch; B- Batch; SHF- Separate hydrolysis and fermentation; SSF- Simultaneous saccharification and fermentation; SScF- simultaneous saccharification and co-fermentation; DA- dilute acid; AH-acid hydrolysate; $ refers to process which produced D(-)lactic acid; # refers to process which produced L(+)lactic acid

annexed to Indian sugar mill. They found that the cost of SCB-derived LA was 3.27 US$/kg with alkali as the choice of pretreatment but the total lifecycle climate change impact was relatively higher (4.62 CO_2 equivalents). However, they identified hotspots, which if addressed diligently could curtail down the cost of SCB-derived LA and alleviate the environmental burden. Based on proposition of Munagala et al. (2021a) when the upstream steps of pretreatment and saccharification were intensified, the cost of fermentable sugars reduced by 39 % (Baral et al., 2020, 2021a). This directly impacted the cost of SCB-derived LA, which reduced from 4.5 to 2.92 US$/kg and contributed to 3.58 CO_2 equivalents in terms of climate change impact. However, both the processes suffered a major drawback as the fermenting *Bacillus coagulans* NCIM 5648 failed to assimilate xylose and this valuable fraction remained un-utilized (Nalawade et al., 2020; Baral et al., 2020). These studies highlight the importance of choosing right LA fermenting microbe depending on sugars produced after saccharification.

Presently, one of the major drawbacks with LA fermentation is that, it demands pH-controlled environment for continuous LA production. However, most of the industrial strains belonging genus *Lactobacillus* require near neutral pH to constantly produce LA. Hence, acid tolerant microbes are being bio-prospected or genetically modified as they offer several advantages. One of the foreseen benefits is curtailed usage of alkali for pH restoration thereby minimizing environmental burden. In this regard, eukaryotic systems mainly yeasts are being explored. They are known to display high acid tolerance, high operational stability, and have proven credentials for being excellent host systems for expression of various genes. For instance, in the recent study, D-lactate dehydrogenase (D-LDH) gene from *Leuconostoc mesenteroides* was inserted in *Saccharomyces cerevisiae* and later to minimize the production of side product like glycerol two of its genes encoding for glycerol dehydrogenase (*gdh1* and *gdh2*) were knocked out. Further, the recombinant strain was cross-mated with weak acid-tolerant strain *S. cerevisiae* BCC39850. When the most promising hybrid strain was tested for D-lactic acid production under non-neutralized conditions using alkali pretreated SCB via SSF approach, the highest titers attained were 23.41 ± 1.6 g L^{-1} (Sornlek et al., 2022). In another study, *S. cerevisiae* BTCC3 was shortlisted for genetic recombination based on its robustness to grow in various biomass-derived inhibitors (acetic acid, formic acid, furfural and levulinic acid). Later, an exogenous LDH gene was introduced and two genes coding for pyruvate decarboxylase namely *pdc*1 and *pdc*5 were deleted to obtain LA2 strain. High cell-density fermentation was performed with the non-detoxified and non-neutralized glucose-rich hydrolysate generated after hot water pretreatment of SCB, without pH control. The recombinant strain produced a maximum of 25.34 ± 3.25 g L^{-1} L (+) LA, with yield and productivity being 0.51 and 1.69 g L^{-1} h^{-1}, respectively (Pangestu et al., 2022). The authors are of the view that in the near future use of acid tolerant microbes for industrial LA fermentation would be in great demand and this area needs a stimulus.

Attaining industrial titres of LA from SCB still seems to be a distant dream as there are only two isolated research investigations which proclaim LA titres of ≥ 90 g L^{-1} LA. However, there are few examples with other feedstocks where LA titer was ≥ 90 g L^{-1} and productivity being > 2 g L^{-1} h^{-1}, proving feasibility of industrial LA production via LCB route. For instance, in a recent study, SScF of oil palm empty fruit bunches (OPEB) employed a unique thermophilic *Bacillus coagulans* JI12 strain which tolerated 20 g L^{-1} acetate levels, detoxified furfural to furoic acid and simultaneously assimilated xylose and glucose. When the xylose-rich fraction after acid pretreatment of OPEB was mixed with cellulo-lignin, the strain produced 114 g L^{-1} LA with 5.7 g L^{-1} h^{-1} productivity. Yeast extract served as the primary nitrogen source, besides supplementing water soluble vitamins (Juturu and Wu, 2018). Earlier, Peng et al. (2013) isolated *Bacillus* sp. strain P38 which tolerated inhibitors like acetic acid, vanillin and furfural up to 6 g L^{-1} and displayed L(+) LA production from dilute HCl pretreated corn stover at

concentration of 180 g L^{-1} and 2.4 g L^{-1} h^{-1} productivity under FB-SHF mode. Likewise, Kuo et al. (2015) reported a novel *Lactobacillus paracasei* which was inhibitor tolerant and later modified the strain by knocking out *ldh* gene to produce optically pure L (+) LA. The strain produced 99.2 g L^{-1} LA from non-detoxified cellulosic hydrolysate of woodchips with 2.25 g L^{-1} h^{-1} productivity. Similarly, two independent studies were conducted with DryPB pretreated wheat straw using a genetically modified and thermotolerant strain of *Pediococcus acidilactici* ZY271, which efficiently assimilated both glucose and xylose to produce optically pure L (+) LA and was well adapted to biomass derived inhibitors. When the SScF was shifted from batch to continuous mode, LA productivity increased from 1.82 to 2.69 g L^{-1} h^{-1}, reducing its titers by 17.8 % to 107.5 g L^{-1} (Qiu et al., 2018; Zhang et al., 2022b). When a thermophilic and xylose assimilating *Bacillus coagulans* NBRC 12714 was used as LA fermentation from sugar-rich corn stover hydrolysates, a pronounced effect of membrane integrated continuous non-sterile fermentation over batch was observed. The former mode of fermentation yielded 92 g L^{-1} LA and 13.8 g L^{-1} h^{-1} productivity. However, under batch mode the LA productivity was 3.28 g L^{-1} h^{-1} while the LA titers reached 98.25 g L^{-1} (Ma et al., 2016). The examples cited in the preceding paragraph imply that some potential LA fermenting bacteria are yet to be evaluated with SCB or SCB derived sugars, besides exploring right fermentation configuration.

4.2. Advancements in downstream processing of SCB-derived 2 G Lactic acid

Downstream processing is an important step in predicting the commercial feasibility of bioprocess as it contributes to 30–70 % of total cost. Unlike the LA produced from whey and sugars derived from edible sugary or starchy feedstocks, the fermentation broth of 2 G lactic acid has several other soluble and insoluble biomass derived chemicals like residual sugars, phenolics, furfurals, acetic acid etc, which are likely to interfere during its downstream processing (DSP). Therefore, the obligation for obtaining high purity LA in an efficient, sustainable and cost-effective manner is a major bottleneck during the DSP of 2 G lactic acid, depending on the applications, the molecule is used for (Ahmad et al., 2020).

Alves De Oliveira et al. (2020) have comprehensively reviewed the merits and demerits of various DSP methods employed for purifying 2 G LA such as traditional method of neutralization and acid precipitation, membranes, solvent and reactive extraction, adsorption, ion exchange chromatography, electrodialysis, reactive separation, salting out extraction and short path evaporation. The review infers that the development of alternate industrial DSP of 2 G lactic acid is still in its nascent phase. Hence, this section specially discusses the research findings which used real time 2 G LA fermentation broth derived from SCB hydrolysates or pre-hydrolysates, for assessing different types of DSP methods. For instance, Oonkhanond et al. (2017) evaluated two different nanofiltration membranes (high flux and low flux) after purifying L (+) LA obtained after SHF of SCB hydrolysate using *Lactobacillus casei* TISTR 390. During nanofiltration, permeability coefficient decides the rejection or permeability of any molecule and is directly dependent on its molecular weight. Since LA and 2 G sugars (glucose and xylose) have a huge difference in molecular weight, their separation is easier. In the said study, when the cell free fermentation broth containing 21.3 g L^{-1} LA was passed through the two membranes at flow rate of 580 mL/min and 4 bar pressure, ~84.41 % glucose was rejected by the high flux membrane (M-N1812A5) retaining 84.7 % LA. However, low flux membrane (M-N1812A9) was more efficient in glucose rejection which touched 93.3 %. Simultaneously it retained only 65.7 % LA, resulting in its significant loss (Oonkhanond et al., 2017).

In yet another study Baral et al. (2021b) coupled salting out with liquid-liquid extraction (LLE) to intensify the phasing out SCB- derived L (+) LA from fermentation broth into the organic phase. The study involved screening the right combination of diluent and extractant besides inorganic salts that displayed high water solubility (>700 g L^{-1}). Owing to high ionization in water these salts reduced the solubility of LA in water and phase it out in organic phase, as LLE is primarily an equilibrium driven process. An efficient salting out LLE process was demonstrated where 60 % $(NH_4)_2SO_4$ addition to ethyl acetate: tri-butyl-phosphate system (1:1) extracted > 85 % L (+) LA in the organic phase under optimized conditions (Initial pH of fermentation broth: 1.6 ± 0.2; Extraction and settling temp: 25 °C & 4 °C; Time: 2 h). The extraction efficiency was independent of LA concentration in the fermentation broth. The salt recovery was illustrated by precipitation with chilled acetone and successful reuse of salt had no deleterious impact of LA extraction efficiency (Baral et al., 2021b). Moreover, the presence of residual glucose and xylose in the fermentation broth did not alter the extraction efficiency of optimized salting out solvent extraction system (data unpublished). Later, a back extraction strategy was devised using pH swing method using NaOH. The regenerated solvent system was used for three cycles and it demonstrated an LA extraction efficiency of not < 75 % and average back extraction efficiency being > 90 %. However, LA concentration in the organic phase was decisive for selecting optimum molarity of NaOH during back extraction, but at the end of back-extraction LA was concentrated 1.8–2.0 fold from its original concentration in fermentation broth (results unpublished).

Earlier, the 2 G lactic acid produced from the hemicellulosic fraction of SCB was attempted for separation using hybrid short path evaporation (HSPE) by de Oliveira et al. (2019b). The researchers deciphered the best operating conditions for HSPE using the fermentation broth comprising of 27.9 g L^{-1} LA and residual xylose was 36.8 g L^{-1} as feed. They could concentrate LA to 86.7 g L^{-1} in residual stream, but simultaneously the C5 stream also reached 120.0 g L^{-1}, when the evaporator and condenser temperature was 120 and 13 °C and the feed flow rate was 8.3 mL/min. Further, the presence of xylose and its concentration largely interfered making the separation of LA more difficult (de Oliveira et al., 2019a). The same group evaluated the process of molecular distillation (MD) for separation of LA, with feed containing 49.9 and 35.8 g L^{-1} residual xylose and LA respectively. They found that LA and xylose co-emerged in concentrated form, both residual (Xylose: 92.6 g L^{-1}; LA: 75.9 g L^{-1}) and distilled (Xylose: 75.9 g L^{-1}; LA: 65.8 g L^{-1}) stream (de Oliveira et al., 2020). In both the experiments it was concluded that the presence of residual sugar especially xylose in the fermentation broth adversely affected LA separation, while using processes like HSPE or MD. They other inferred that these processes are useful only when all the sugar is utilized during fermentation or need to be removed prior to use of such processes.

There are isolated reports where the hemicellulosic and the cellulosic hydrolysate from corn stover were fermented to LA and later purified. In the first case, the LA was extract using salting out (Tetrahydrofuran/NaCl) reactive extraction comprising trioctylamine-octanol system, with recovery being 83 % ((Lan et al., 2019). In the second study, three stage IL based sugaring out process was used, where the LA recovery was 89.5 % (Zhou et al., 2021). Unfortunately, in this area, the researchers preferably work with simulated fermentation broths and fail to anticipate the challenges associated while handling the real-time fermentation broths containing 2 G lactic acid during its DSP. Hence it is essential that the orientation of the future research should thrust upon using actual LA fermentation broths obtained via LCB-route.

5. Author's perspective and path forward

Soloman and Swapna (2022) in their recent review have suggested that diversification in Indian sugar industry can be a vital step towards self-reliance. Though they primarily focused on meeting the energy demands of India by targeting products such as steam, electricity, ethanol, biogas, bio-CNG, but have identified "sugarcane biorefinery" as most promising concept with huge investment potential. In this aspect production of 2 G lactic acid can be a lucrative option. Since LA is commercially produced via microbial fermentation, the process shift

from 1 G to 2 G may be more easy compared other bio-based platform chemicals for instance, 1,4 butanediol, 1,3 butanediol, 1,3 Butadiene, isoprene, farnesene, 2,5-furandicarboxylic acid, isobutanol etc. which are predominantly produced through chemical or petrochemical route. Moreover, even if we consider the popular fermentation product like "cellulosic ethanol", 180 g of glucose on theoretical basis yields only 92 g of ethanol and inevitably releases 88 g of carbon dioxide as the by-product. But, if the same cellulosic fraction is diverted to homo-lactic acid fermentation 180 g to glucose is theoretically biotransformed to 180 g lactic acid, giving a stoichiometric advantage of this molecule over ethanol. Furthermore, the minimum support price (MSP) of LA is relatively higher compared to ethanol. Nonetheless, the market potential of ethanol as energy product and platform chemical with variegated applications is undeniable, as this bulk energy-rich molecule dominates distinct and unique commercial segments, with predicted global demand reaching 117.5 billion USD by 2028 (Vantage Market Research, 2022).

Taking the example from India, if we consider the state of Maharashtra alone, which crushed 1320 lakh tonnes of sugarcane in the year 2021–22, the amount of SCB generated on dry weight basis would be 158.4–198 lakh tonnes (Huang et al., 2020; ET Bureau, 2022). In a hypothetical situation, if 50 % of this SCB (45 % glucan; 20 % xylan) is used for creating sugar platform where pretreatment and saccharification cumulatively displayed an efficiency of 70 %, 40–50 lakh tonnes of fermentable sugars can be generated where the share of glucose is likely to be 70 %. If only SCB-derived glucose is assumed to be valorized to LA via homo-fermentative route with 85 % efficiency, 24–30 lakh tonnes of LA can be produced from the cellulosic fraction of SCB alone. Considering the real-time process data (226 g LA/kg raw SCB) generated at Vasant Dada Institute, Pune, India from the same quantity of SCB, the estimated quantity of 2 G LA generated would be 36–45 lakh tonnes (Munagala et al., 2021b). These scenarios highlight the underlying potential of SCB-derived LA production in developing nations like Brazil, India, China, Thailand, Pakistan and Mexico which primarily produce sugar from sugarcane.

The technical breakthroughs discussed in the present review offer a platter of processes which have the potential of immediate pre-commercial scale up. Coupling the biomass densification with other promising pretreatment technologies and exploring the feasibility of chemical recycling can bring a radical change. It can lead to developing a pretreatment strategy which is not only minimizes waste generation and environmental friendly, but facilitates maximum sugar recovery in a cost effective manner. Creating a sugar platform by adopting green approach of using "cellulase cocktails" is the second most vital step. It should be noted that most of the research pursuits to attain concentrated sugar solutions have been conducted with commercial cellulase cocktails. Thrust on indigenous development of low cost and efficient cellulase cocktails and their onsite production seems a lucrative preposition in terms of self-reliance. These initiatives are necessary to break the monopoly of enzyme companies catering biorefining sector, promote microbial bio-prospecting (classical or metagenomic/ proteomic approach), identify new expression and host systems and develop designer enzyme blends as reviewed recently (Adsul et al., 2020; Siqueira et al., 2020). However, authors are of the view that in the next five years large scale production of newer enzyme cocktails to meet the demand of commercial SCB-bioprocessing is highly impractical. Partnering or getting into licensing agreement for on-site cellulase production with potential enzyme manufacturers are viable options to get a consistent enzyme supply and kick-start the functional realization of SCB-based biorefinery. A dedicated "enzyme development program" should be taken up as a long term strategic goal where academia and industry should collaboratively work to foster innovations in the said area. Further, they should validate the efficacies of the promising new blends at semi-pilot and pilot scale as a mandatory practice, to facilitate smooth transitioning.

Likewise in case of LA fermentation, there are limited industrial strains which can co-ferment xylose to LA with equal efficacy as glucose. In that case, in its preliminary stage, xylan should be selectively hydrolyzed as xylose during pretreatment. Hydrolyzed xylan can be further valorized to LA or any other bio-based products like xylitol, succinic acid or 2,3 butanediol as demonstrated by our group (Prabhu et al., 2020; Jokodola et al., 2022; Amraoui et al., 2021). In case xylose accompanies with glucose during fermentation and remains largely unutilized, after extracting LA, the xylose-rich fermentation broth may be used for anaerobic digestion to produce Bio-CNG. Thus, both the principal sugars recovered from biochemical route can be optimally valorized. Alongside, LA fermenting microbial strains which have repeatedly displayed their potential for pentose sugar utilization should be evaluated for pilot or demonstration scale operations. Furthermore, its high-time that academic-industrial collaboration should prioritize on developing a cost competitive and environmentally benign DSP protocol for 2 G lactic acid. The most desirable strategy would be the one, which not only purifies the product (>99 %) with minimum losses, but the process developed is reliable, foolproof and easy enough to be manifested for industrial scale-up. Generally the researchers tend to overlook the waste water streams generated during SCB bioprocessing, its valorization to LA, and later its DSP. In that case schemes for wastewater treatments versus its valorization (depending on assimilatory carbon load) should be carefully considered, evaluated and enforced to create a zero-liquid discharge (ZLD) biorefinery.

However, it is equally important that like "EBP program" a policy framework for bio-based chemicals should be launched in India. Special emphasis should be towards those chemicals, which can alternately produced through bio-based route and impose huge import burden, so that self-reliance can be attained. Implementation of such kind of policy framework would further strengthen the foundation of "Atmanirbhar Bharat" and expedite the concept of "Make in India", especially boosting the Indian biotechnology sector. The authors are optimistic that even if a demonstration scale SCB-based LA biorefinery is showcased by any sugarcane driven industry, a complete roadmap will be created at global level. This rationale is strongly supported by the fact that sugarcane rank first (1.9 billion tonnes in 2020) among the four crops accounting for half of the global primary crop production (FAO, 2021). If in the next 5 years, 2 G lactic acid production is up-scaled and integrated with sugarcane-based industry, it can contribute directly towards at least three sustainability development goals (SDG's) namely SDG 9 (Increase Industry, innovation and infrastructure), SDG 8 (Create decent work and economic growth), and SDG 13 (Climate Action), in all the major countries where sugarcane is predominantly grown as primary crop.

6. Conclusion

LA is a platform chemical, and its global market is increasing exponentially. Though LA is a bio-based product industrially produced through fermentative route, yet its commercial manufacturing using 2 G feedstocks is a distant reality. Further expanding its market base demands its low cost of production, which can be reduced using cheaper substrates. SCB is generated as an undeniable solid waste from sugarcane and associated industries, readily available for valorization. Being lignocellulosic in nature and displaying features like abundant availability, renewability, non-competition with food production, SCB is a promising and potential bioresource for production of bio-based chemicals. The current review sheds light on the technical processes that have provided impetus for the commercial realization of SCB-based biorefinery with 2 G LA as the targeted product. Though promising results have been achieved in upstream as well as downstream for LA accumulation from SCB, it is still in R & D stage. Crucial bottlenecks in the way of industrial 2 G-LA production like expensive saccharification, high TYP metrics matching industrial demand, economical downstream processing have been addressed to an extent through isolated efforts, but overall process integration still remains a challenge. It is high-time where academia should partner up with sugar and associated

industries to understand the real-time challenges in each of the process modules during scale-up operations troubleshoot the engineering and technical hurdles and offer sustainable solutions for biorefinery development. Enormously growing market demands for LA, advances in lignocellulosic sugar production and microbial strain engineering, have raised hopes for a viable SCB-based LA manufacturing with high profit margins. If a techno-economically feasible process for 2 G lactic acid production is showcased by sugar industries, they can minimize waste, enhance profitability and diversify their product portfolio. Further, it can offer indirect benefits like fostering bio-based rural economy, raising the socio-economic status of the stakeholders, creating new job opportunities and contributing towards environment sustainability.

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CRediT authorship contribution statement

DA: conceptualization, writing-original draft, reviewing & editing; VK: conceptualization, reviewing & editing and project management. Both the authors read and approved the final Manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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