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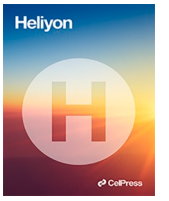

Review article

The outlooks and key challenges in renewable biomass feedstock utilization for value-added platform chemical via bioprocesses

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ABSTRACT

The conversion of renewable biomass feedstock into value-added products via bioprocessing platforms has become attractive because of environmental and health concerns. Process performance and cost competitiveness are major factors in the bioprocess design to produce desirable products from biomass feedstock. Proper pretreatment allows delignification and hemicellulose removal from the liquid fraction, allowing cellulose to be readily hydrolyzed to monomeric sugars. Several industrial products are produced via sugar fermentation using either naturally isolated or genetically modified microbes. Microbial platforms play an important role in the synthesis of several products, including drop-in chemicals, as-in products, and novel compounds. The key elements in developing a fermentation platform are medium formulation, sterilization, and active cells for inoculation. Downstream bioproduct recovery may seem like a straightforward chemical process, but is more complex, wherein cost competitiveness versus recovery performance becomes a challenge. This review summarizes the prospects for utilizing renewable biomass for bioprocessing.

1. Introduction

Currently, environmental sustainability and using renewable resources are significant concerns for human life. The conversion of biomass into value-added products and fuels has gained considerable attention for reducing the consumption of fossil-based resources and environmental pollution. Microorganisms play a crucial role in the industrial synthesis of various human-beneficial supplies and have had a tremendous impact on our lives and life expectancy. Beverages, dietary supplements, nutritional supplements, household supplies for humans and livestock, and biofuels are examples of these products. Compared to compounds from chemical synthesis,

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microbial metabolites are more affordable as they are produced from low-cost renewable feedstocks, including plant biomass, agricultural products and residues, and industrial waste. The metabolites produced via microbial platforms have a wide range of applications and are considered green and sustainable, whereas the compounds and materials derived from fossil-based feedstocks have negative impacts on climate change and cause environmental damage [1]. Microbial processes can generate a variety of platform chemicals, such as succinic acid, which can simply be placed into the existing polymerization processes for polybutylene succinate (PBS) [2]. Lactic acid is another microbial metabolite that has long been used in the food and pharmaceutical industries. Lactic acid can be used as a building block for the synthesis of compostable polylactic acid (PLA) [3,4]. Current trends in human wellness have driven strong demands for novel foods and feed production that also provides health benefits. Probiotics, vitamins, and supplements are examples of the functional foods produced using microbial platforms [5,6]. Consequently, the exploration and production of sustainable and renewable products from microbial platforms to substitute the traditional non-renewable fossil-based processes has become a developing target from research to industrial and government levels [7].

Process performance and cost competitiveness are major factors in bioprocess design for producing desirable products from biomass feedstock [8]. Biomass conversion involves three major steps. These processes include biomass pretreatment, fermentation, and downstream product recovery and purification. This review focuses on the major elements in the development of microbial platforms. Conversion technologies for bio-based feedstocks are also discussed. The development of a fermentation platform is emphasized and case studies on the fermentation process are provided. Downstream recovery and purification of the product from the fermentation broth are also reviewed and compared using chemical routes. This review presents the current status and future directions of microbial process development.

2. The pretreatment technologies for conversion of sustainable biomass resources

To increase the efficiency with limited use of harsh chemicals and decrease byproduct formation, novel pretreatment techniques have been developed using mechanical, thermal, chemical, and biological methods. This section provides an overview of the technical characteristics of pretreatment technologies ranging from conventional to novel protocols. Fig. 1 summarizes the major pretreatment techniques widely used in treatment of various biomass feedstocks for the hydrolysis step to obtain monosaccharides, oligosaccharides, and/or lignin derivatives. Thus, detailed principles are presented.

2.1. Physical pretreatment

The main purpose of physical pretreatment is to reduce the particle size of biomass feedstocks. The crystallinity and degree of polymerization of the cellulosic biomass decrease, thus increasing the surface area accessible for subsequent hydrolysis by chemicals or enzymes. No chemicals are used during physical pretreatment. Biomass chipping, milling, grinding, and extrusion are all categorized as physical pretreatments. Thermal, ultrasonic, and microwave technologies have also been included in this group [9].

To increase the surface area, mechanical pretreatment is applied to break down the solid feedstocks and release the interior cell components. Mechanical pretreatment is simple, with no chemical use and moderate energy consumption [10]. However, microbial pathogens contaminating feedstock are not eliminated by this process [11]. Thermal pretreatment entails the application of high temperatures to disrupt the chemical linkages in the cell walls of feedstocks, thereby enhancing the accessibility of the cell constituents

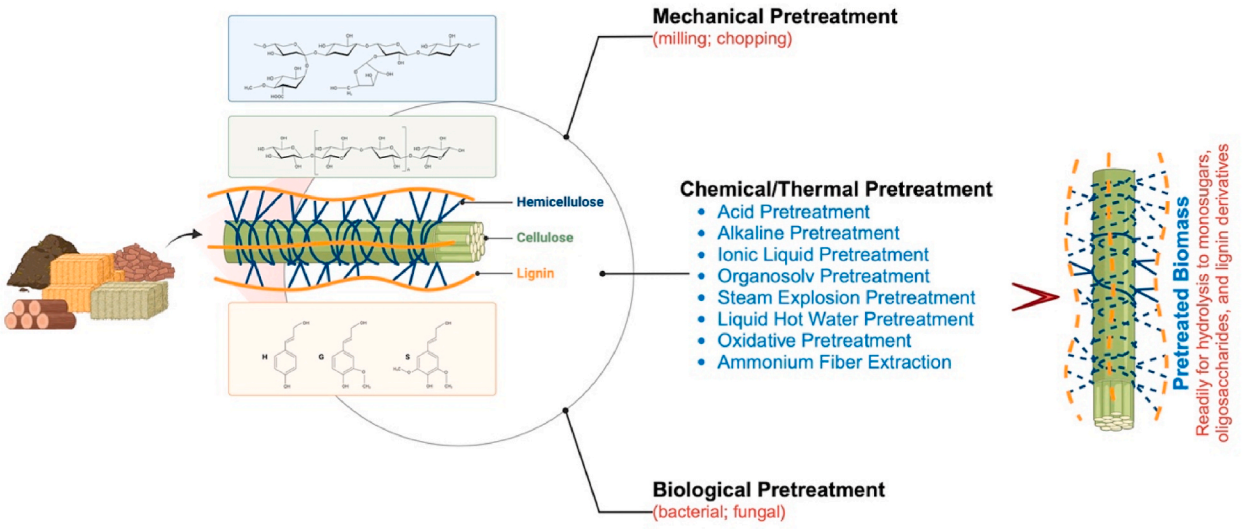

Fig. 1. The major pretreatment techniques widely used in the treatment of various biomass feedstocks for the hydrolysis step to obtain monosaccharides, oligosaccharides, and/or lignin derivatives.

[12]. The autoclave is an example of a thermal treatment process that is conducted at 121 °C, 15 psig [12–14]. During autoclaving, water molecules within the biomass matrices expand rapidly, resulting in a large shear force that destroys the biomass structure. Due to its short residence time and low pressure, autoclave pretreatment does not provide sufficient structural breakdown for further processes to recover cellulose and hemicellulose [15].

Steam explosion is a well-established pretreatment technique. Steam is introduced for fiber breakdown, allowing the accessibility of biomass for the following processes: hydrolysis, densification, and fermentation [16,17]. In the first step of stream explosion, biomass is pretreated with hot steam (160–260 °C) under pressure (0.69–4.83 MPa). The biomass is explosively compressed under these conditions, and the hard structure of the fibers is ruptured [18–20]. Cellulose is recovered, making it ready for hydrolysis. Biomass pretreatment by steam explosion can range from minor structural breakdown to complete defibrillation of biomass fibers, depending on the temperature and residence time [17,19]. Harsh conditions are required to increase cellulose digestibility; however, it partially degrades hemicellulose [21,22]. Lignin degradation during steam explosion often generates furfural, hydroxymethyl furfural, and weak acids (acetic and formic acids) [16]. Detoxification methods have been applied to minimize the inhibitory effects; nevertheless, they incur additional costs [22].

Microwave pretreatment applies an electromagnetic field, commonly at an irradiation frequency ranging from 0.3 to 300 GHz and an oscillation rate of approximately 4.9×10^9 times per second [23]. This leads to the vibration of the molecular structure, which generates heat for lignocellulosic pretreatment. Microwaves destroy the tenacious structures of biomass feedstocks by heating their polar components in an aqueous environment. Molecular vibrations due to microwaves generate heat directly within the substance, whereas conventional heating techniques distribute it through the surface, resulting in high heat loss [24]. Microwave pretreatment has gained interest because it meets eco-friendly requirements and is faster with lower energy intensity than conventional heat processes. Similar to steam explosion, there is no chemical or solvent consumption in microwave pretreatment; therefore, this technique does not generate chemical effluents, pollutants, or smoke [25]. Microwave pretreatment requires a residence time ten times shorter than that of conventional heating techniques. Therefore, this technique can conserve energy [26].

2.2. Chemical pretreatment

Chemical pretreatment typically disrupts the lignocellulosic matrix by dissolving the hemicellulose and lignin glycoside bonds. Both concentrated and diluted solutions can be used to pretreat biomass feedstocks. However, the use of concentrated solutions requires stringent safety precautions and corrosion-resistant equipment design.

Among other methods, acid pretreatment is frequently used to disrupt lignocellulosic matrices. The hydronium ions produced by the acid catalyst cleave the glycosidic linkages in the lignocellulosic matrix, converting the polysaccharides into oligomeric and monomeric sugars. The acidic catalysts contain organic and inorganic acids. Formic, oxalic, and levulinic acids are the organic acids employed in acid pretreatment, whereas hydrochloric, sulfuric, and phosphoric acids are the inorganic acids [27–29]. To acquire sufficient structural cleavage, a strong concentration of acid catalysts (30–70 %) was employed at a low temperature (below 100 °C) during pretreatment, whereas the low acid concentration (0.1–10 %) is sufficient to pretreat the lignocellulosic biomass at the high temperature (100–250 °C). Although acid pretreatment facilitates enzymatic digestibility of lignocellulosic biomass feedstocks, it has several drawbacks. The most important ones are the inhibitory compounds produced by the breakdown of sugars and decomposition of lignin during pretreatment. These compounds include aldehydes, ketones, and phenolic acids [29].

Alkaline pretreatment relies on the solubilization of lignin in alkaline solutions, such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, and hydrogen peroxide. Calcium hydroxide has a weaker pretreatment power than other alkaline solutions, but the process provides cost-effectiveness, proper practices, and straightforward recovery [30]. Alkaline pretreatment cleaves the glycosidic bonds between lignin and polysaccharides, lowers the degree of polymerization and crystallinity, causes the fibers to swells, and destroys the lignin structure [31]. Compared to acid or hydrothermal pretreatments, alkaline pretreatment is superior in terms of its ability to solubilize and remove lignin from lignocellulosic structures. Uronic acids are also discarded from hemicelluloses with a relatively little loss of polysaccharides in the biomass feedstock [32].

Organosolv solubilizes hemicellulose and extracts lignin using a combination of organic and aqueous organic solvents. The most frequently used organic solvents include methanol, ethanol, acetone, and ethylene glycol, whereas organic acids, such as oxalic acid and salicylic acid, act as catalysts [33]. The intracellular linkages between lignin and hemicellulose as well as the ether and ester interpolymer linkages are digested when lignocellulosic biomass is subjected to an organosolv pretreatment. In the liquid phase, lignin and hemicellulose are solubilized, yielding a solid fraction of cellulose with high purity [34]. The formation of hydrogen ions caused by the presence of organic acids during the organosolv process facilitates delignification. The advantages of organosolv pretreatment includes a high cellulose yield for further hydrolysis and fermentation, it is a non-corrosive process, produces low inhibitory byproducts, and has possible solvent recovery and regeneration [35]. Owing to the consumption of organic solvents, organosolv is a cost-intensive process with a high capital investment for additional solvent recovery and regeneration and a high operating cost [36].

2.3. Biological pretreatment

Utilizing oxidative and hydrolytic enzymes produced by bacteria and fungi facilitates the pretreatment of lignocellulosic biomass. The degree of cellulosic polymerization was significantly reduced, hemicellulose was hydrolyzed, and the delignification process was greatly accelerated by enzymatic pretreatment [37]. Enzymatic pretreatment requires low chemical usage and low energy consumption. This process does not harm the environment because the operating conditions are mild. However, poor hydrolytic rate and high enzyme cost are drawbacks of this technique [37,38].

The biological pretreatment of biomass using bacteria and fungi has been reported in many studies. For example, rice straw pretreatment with *Bacillus firmus* recovered 74 % yield of glucose after 48 h [39]. In other work, biological pretreatment of rice straw with *Myceliphthora thermophila* BJTLRMDU3 [40] and *Trametes hirsute* [41] enhanced the liberated reducing sugars by approximately 86.74 and 284.13 mg/g substrate, respectively. In addition, Mamudu and Olukanmi (2019) reported that bio-pretreatment of rice straw with *Aspergillus niger* resulted in 0.959 g glucose/g substrate [42].

Several methods have been introduced for pretreating lignocellulosic biomass prior to fermentation. The key characteristics, mechanisms, and limitations of these techniques are presented in Table 1 [29,43–48]. Examples of techniques employed for different types of biomass are presented in Table 2.

Table 1
Key characteristics of the pretreatment technologies.

Technique	Key characteristics	Mechanisms	Limitations
Mechanical pretreatment	Milling; chopping	Reduces the particle size and crystallinity of cellulose Increases surface area for hydrolysis	High-power input
Acid pretreatment	Use of diluted or concentrated acids (HCl, H_2SO_4, H_3PO_4, HNO_3)	Increases solubilization of hemicellulose Improves disintegration of lignin Promotes subsequent cellulose hydrolysis	Requires neutralization, chemical recovery, and effluent treatment Forms inhibitors High toxicity and corrosion
Alkaline pretreatment	Use of alkaline compounds (NaOH, KOH, $Ca(OH)_2$, and NH_4OH)	Reduces polymeric bonds and increases lignin degradation Lignin and hemicellulose solubilization at low cost	Salt formation; crystallization during lignin isolation High water consumption during washing
Ionic liquid pretreatment	Use of an ionic liquid composed of anionic and cationic salt solution at room temperature and very low pressure	Increases breakdown of oxygen bonding High dissolution capacity and high product stability Requires low energy No reagent required	High operating cost (solvent cost, solvent recovery, and regeneration)
Organosolv	Use of short-chain alcohol (methanol or ethanol mixed with an organic or inorganic acid)	Improves dissolution of lignin and disruption of lignin and hemicellulose High lignin purity Increases digestion of cellulose with high sugar yield Requires low boiling point solvent Low toxicity	High cost of solvent recovery and regeneration Economically unviable
Steam explosion pretreatment	Use of high pressure and temperature steam in a short duration; may use chemicals as a catalyst	Increases the solubility of hemicellulose Increases the porosity and surface area Low water consumption Low hazardous chemical use	High pressure and temperature Promotes the degradation of fermentable sugars Requires washing step for Detoxification High production cost
Liquid hot water pretreatment	Use of water at high temperature and pressure at a short time	Improves dissolution of hemicellulose as liquefied soluble oligosaccharides High pentose recovery and low product degradation Low equipment cost No catalyst required Process is cost saving	High pressure High energy input High water input
Oxidative pretreatment	Use of oxygen species as an oxidizer (O_2, H_2O_2, CH_3CO_3H, O_3) and gradient temperature (low to high) in suspended biomass	High cellulose content Low inhibitory products Increases solubility of hemicellulose and lignin removal	Loss of monosaccharide content
Ammonium fiber extraction	Use of NH_3 as a catalyst with the steam explosion at a mild temperature	Improves disruption of ester bond at the linkage of lignin and carbohydrates Increases exposure of cell wall surface Increases decrystallization of cellulosic structure	High energy consumption in NH_3 recycling and recovery
Biological pretreatment	Use of the enzymes from bacteria and fungi as a biocatalyst	Accelerates degradation of cellulose and hemicellulose as fermentable sugars Decreases crystallinity and degree of polymerization of cellulose Enhances lignin removal Low chemical consumption Eco-friendly process	Long operating time Requires control and management of enzyme production

3. Fundamental elements in the fermentation process development

Industrial process development relies on a remarkably high production efficiency and cost-effectiveness. The key elements that control the fermentation process performance are discussed herein.

3.1. Industrial strains

Robust strains are key elements of success in commercial bioprocess platforms. The common requirements for industrial strains are growth on a simple medium with high production performance of the desired product and low byproduct formation. With the developed platform, industrial strains should provide reproducible and repeatable production at any scale. The product obtained should meet the market specifications. Technically, the characteristics of industrial microbial strains also include genetic stability, ability to efficiently produce a targeted product in a short time, ability to utilize a wide range of low-cost substrates with low nutrient requirements, amenability to genetic engineering, and non-pathogenicity [54]. To date, bacteria, yeasts, and fungi have been used in large-scale fermentation for the production of food additives, beverages, organic acids, enzymes, antibiotics, vitamins, biofuels, and bioethanol [55]. Traditionally, wild-type strains screened from nature are used in commercial processes. Recently, genetically modified microbes have gained increasing interest, especially for the manufacture of high-value products, including drugs, chemicals, and fuels [56].

To isolate and select microbes for industrial purposes, the fundamental concepts mainly focus on the targeted screening of microorganisms from natural resources and proper characterization techniques, so that the isolates can be implemented in large-scale operations. The classic technique for microbial isolation and screening from natural resources involves collecting samples from well-chosen surroundings under specific conditions that allow for the presence of the desired microbial population [57]. The potential to isolate and select microorganisms with targeted uses and applications relies on the geographic conditions of the sample sources, the availability of resources, and the physiology and metabolic activities of the microorganisms. To discover robust living microbes with

Table 2
Examples of biomass pretreatment using different techniques.

Pretreatment	Biomass	Key results	Reference
Milling	Digested manure fibers	Improved digestion of fibers was up to 45 %	[10]
	Elephant grass (*Pennisetum purpureum*)	Decrease in digestion time increased methane yield up to 22 %	[11]
	Wild Mexican sunflower (*Tithonia diversifolia*)		
	Siam weed (*Chromolaena odorata*)		
Acid pretreatment (H_2SO_4)	Wheat straw	Glucose yield of approximately 92.9 % was obtained	[49]
Thermal-acid pretreatment (H_2SO_4)	Corncob	High recovery yield of lignocellulosic sugars was achieved which resulted in the recovery of 90.5 % cellulose, 8.0 % xylan, 4.4 % glucose; 78.9 % xylose; and 64.5 % lignocellulosic solids	[13]
Thermal-acid pretreatment (levulinic acid)	Poplar wood	Hemicellulose recovery percentage was approximately 82.05 % while repolymerization of lignin was effectively inhibited	[27]
Alkaline pretreatment (NaOH)	Sweet sorghum bagasse	Glucan and xylan recovery percentage were approximately 95 % and 70 %, respectively while 65 % lignin was removed	[30]
Thermal-alkali pretreatment ($Ca(OH)_2$)	Corn stover	Pretreatment enhanced enzymatic hydrolysis resulting in high glucan conversion (90 %) and ethanol titer (73.1 g/L)	[14]
Steam pretreatment (SO_2 catalyst)	Softwood chips	80 % recovery of hemicellulose-derived sugars with 28 % recovery of glucose in the liquid fraction	[17]
Steam explosion (0.5 % H_2SO_4 catalyst)	Sugarcane bagasse	92.4 % cellulose and 57.7 % xylan were obtained after pretreatment	[19]
Microwave-assisted alkali pretreatment (NaOH)	Rice straw	After pretreatment, 69.2 % cellulose and 10.2 % hemicellulose were obtained while 64 % lignin was removed	[50]
Microwave-assisted acid pretreatment (H_2SO_4)	Garden biomass	Recovery of 53.95 % cellulose and 11.62 % hemicellulose was achieved	[51]
Hot liquid water	Corn brittle stalk	Glucose yield of 96 % was obtained with a subsequent bioethanol yield of 19 %	[52]
Organosolv pretreatment (ethanol mixed with NaOH)	Sugarcane bagasse	Improved enzymatic hydrolysis yielded 91.6 % glucose after 72 h	[34]
Organosolv pretreatment (glycerol mixed with HCl)	Rice husk	After pretreatment, the recovery percentages of cellulose and hemicellulose were 88.2 % and 7.9 %, respectively	[53]
Biological pretreatment (*Myceliphthera thermophila* BJTLRMDU3)	Rice straw	86.74 mg reducing sugar per g rice straw was obtained	[40]
Biological pretreatment (*Bacillus firmus* K-1)	Rice straw	Recovery yield of 74 % glucose was obtained after pretreatment	[39]
Biological pretreatment (*Aspergillus niger*)	Sugarcane bagasse	0.959 g glucose per g substrate was obtained	[42]
Biological pretreatment (*Trametes hirsute*)	Rice straw	284.13 mg reducing sugar per g substrate was obtained	[41]

high productivity or attractive characteristics, the isolates should be screened from extremely harsh environments, including geographical poles, arid deserts, volcanoes, deep ocean trenches, upper atmosphere, outer space, and the environments of every planet in the solar system, except Earth [48,58]. An example of a microbe screened under harsh conditions is an uncultured electroactive microorganism (EAM) that possesses an extracellular electron transfer process for biosensing and bioelectronics applications and the valorization of liquid and gaseous wastes. It can be screened from extreme environments with high salinity, alkalinity, pressure, and temperature [59]. Compared with EAM screened from mild environments, extremophilic EAM can be used in broader microbial electrochemical technologies. Polyhydroxyalkanoate (PHA) producers are another example of microorganisms that have been screened from severe environments. Screening for PHA-accumulating thermophilic bacteria requires rapid, simple, efficient, and reliable techniques. The most widely used screening method involves agar-based assays [60]. To date, omics technology has been rigorously applied in the high-throughput screening of microbes with specific characteristics [61,62].

Several approaches for strain improvement have been developed for wild-type isolates to improve fermentation performance, including increasing metabolic yield, improving substrate utilization, and increasing tolerance to environmental stresses [63]. Conventional strain improvement techniques include high-throughput screening of mutants generated by random mutations, engineering of targeted gene sequences (gene overexpression, deletion, and knockout), targeted mutagenesis, and adaptive evolution [63–66]. Synthetic biology has become a crucial tool in strain improvement to optimize microbial metabolism and enhance production efficiency by balancing cellular resources for biocatalysts and desired metabolite formation [67]. Despite a systematic approach to the metabolic engineering of industrial strains for improved stability over long-term operation, only a few engineered microbes have been successful in commercial production. This has driven numerous attempts to develop novel approaches in synthetic and systems biology to access microbial platforms targeting the metabolic and physiological stages of the microbes of interest. Thus, a robust strain with specific functions can be designed for specific uses under industrially relevant conditions in a fermenter [68].

3.2. Seed train development

The population of microbes transferred into the fermentation medium is referred to as an "*inoculum*." Optimal physical and chemical conditions are required to prepare an effective inoculum. Typically, a pure culture isolated from natural resources or a modified strain can be appropriately preserved in several ways, such as storage in a freezing solution, storage on fresh agar medium, and lyophilization [69,70]. Before fermentation, the pure culture was activated and enumerated under appropriate cultivation conditions. This step is called preculturing or seed cultivation. A laboratory-scale seed cultivation protocol should be readily designed for translation to large-scale industrial fermentation. To achieve high fermentation productivity, the total cultivation time from preculture to fermentation and the number of seed stages should be minimized. This can be achieved by passaging the active cells to the next step. Specifically, the total number of cells must increase rapidly. This is typically observed in the optical density of the culture medium [71]. In addition, inoculum size, which is the volume of the preculture being transferred to the next cultivation step and cell cycle, plays a crucial role in seed train development. With the correct cell phase and proper inoculum size, the process performance in production fermentation is accelerated, resulting in a high product titer and yield. The correct cell phase and proper inoculum size directly affect microbial activity [72,73]. Using heavy inoculum size transfer, rapid substrate consumption with corresponding growth and product formation were observed. However, at very small inoculum sizes, growth is slow, resulting in delayed processing and low production performance [74]. Zheng et al. (2022) studied the effect of the inoculum size on α-linolenic acid by *Chlamydomonas reinhardtii* [75]. The results suggested that a 1.56-fold increase in the concentration of α-linolenic acid was obtained with an increase in the inoculum size to 25 %.

Microbial growth phase is another key criterion for large-scale seed culture preparation. Microorganisms can be categorized according to their product formation kinetics, and the fermentation platform should be designed according to the kinetic model. In the case of primary metabolites, preculturing in the exponential growth phase is preferable for transfer into the production fermentor. Transferring the improper growth phase of the preculture, either the lag or stationary phase, can reduce substrate consumption and product formation [76]. Transferring a heavy inoculum (50 % inoculum size) into the production fermentor during the exponential growth phase resulted in a very high production rate of l-lactic acid by *Bacillus* sp. BC-001. The seed culture steps and fermentation were repeatable and reproducible at the laboratory scale (5 L of stirred fermentor) up to the pilot scale (30 L, 300 L, and 3000 L fermentors) [4]. Secondary metabolites are usually produced during the late growth stages. Therefore, active growth is not necessary for fermentation of secondary metabolites; however, high cell concentrations can result in high productivity [77].

3.3. Medium formulation

During fermentation, the culture medium directly affects cellular metabolism. The medium composition should be optimized to achieve high production of the metabolite of interest. Medium optimization can be performed using modern mathematical techniques to obtain effective, efficient, economical, and robust results [78,79]. The chemical formula of a microbial cell is generally defined as $CH_xN_yO_z$ with different levels of x, y, and z, depending on the microbe type. Therefore, it is evident that the culture medium should contain carbon, nitrogen, and oxygen so that the cell can take up compounds containing these atoms [80]. The carbon source was found to be the energy source and backbone of the synthesized metabolites. Carbon can be derived from sugars, starch, oils, and complex carbohydrates [81]. Previous studies reported that various carbon sources, including maltose, sucrose, glucose, and fructose, affect curdlan production in *Alcaligenes faecalis*. Maltose resulted in the highest cell growth and curdlan production, whereas fructose was found to be a non-preferred carbon source [82]. Nitrogen sources, in the form of either inorganic salts or organic compounds, contribute to the intracellular biosynthesis of nucleic acids, proteins, enzymes, vitamins, and cellular energy [83]. The most commonly

used nitrogen sources in laboratory culture media are yeast extract and peptone. However, these compounds are expensive and therefore unsuitable for commercial-scale fermentation [84]. There has been a growing interest in the utilization of low-cost feedstocks such as starch, lignocellulosic sugars, and corn steep liquor as alternatives. Maddipati et al. (2011) conducted ethanol fermentation by *Clostridium* sp. P11 [85]. Higher ethanol production was observed during fermentation when corn steep liquor was used as the nitrogen source. A 32 % increase in ethanol yield was obtained compared to when fermentation contained yeast extract. Trace elements serve as enzyme cofactors that participate in many enzymatic reactions inside the cell, thereby contributing to metabolic functions. The common trace elements include zinc, manganese, copper, molybdenum, and cobalt. Most of these elements are required in trace amounts in the culture medium [86,87]. FitzGerald et al. (2019) reported on the role of trace elements in fermenting bacteria during the biogas monodigestion of grass silage. Compared with the control, the fermentation time decreased (from 120 h to 24 h) when supplementing $MnSO_4{\cdot}5H_2O$ into the fermentation medium of *Lactobacillus casei* [88].

3.4. Environmental process conditions

Several environmental factors significantly affect the fermentation performance, including metabolic rates, product yield, byproduct synthesis, medium composition, pH, temperature, dissolved oxygen, and operation mode [89,90]. Industrial bioprocesses require controlled operation under optimal fermentation conditions to achieve a high concentration of the target product at the desired specifications. The specific operating conditions that yield desirable fermentation specifications depend on the requirements and characteristics of the industrial strains used in the process [91,92]. Temperature and pH are the two major environmental factors that are commonly monitored and controlled during fermentation cultivation because these factors directly affect the enzymatic reactions in cells and, therefore, the metabolic rates. The optimal temperature and pH vary depending on the microbes used [93]. Roslan et al. (2023) investigated differences in the predominant lactic acid bacteria over a wide range of temperatures [94]. Different microbial communities were also investigated at different temperatures in the biohydrogen production unit using food waste as the substrate.

The molecular oxygen demand during microbial cultivation depends on the strain requirements and metabolic route of the desired product. An oxygen supply is typically required in aerobic fermentation, where microbes require molecular oxygen as the final electron acceptor in the energy and cofactor regeneration processes. During aerobic fermentation, oxygen is usually limited when the fermentation broth becomes viscous [95]. This evidence is more pronounced for large-scale fermentors [80]. The difference in the molecular oxygen requirements of each industrial strain leads to different fermentation process designs and controls. During aerobic fermentation, the dissolved oxygen (DO) level is usually maintained at 30 % saturation, whereas obligate anaerobic fermentation requires a very low DO level, near zero [96]. Oxygen can be supplied through agitation and aeration in a typical stirred-tank fermentor, whereas pressurized air is used to supply oxygen in an air-lift fermentor. In addition to agitation and aeration, oxygen transfer is typically affected by culture broth rheology. At the critical DO level, microbial activity can be dramatically reduced, resulting in decreased product formation. Song et al. (2022) reported on the role of oxygen in the optical purity and yield of lactic acid [97]. Excess oxygen supply lowered the lactic acid yield as acetic acid was produced as a by-product. Similarly, during PHA fermentation, DO levels influence the accumulation of PHAs and other byproducts. A sufficient DO level yields adequate energy regeneration for the conversion of the substrate into essential cellular components, including proteins, peptidoglycans, and glycogen. Therefore, the oxygen level should be maintained at an appropriate level to drive the correct metabolic routes towards the fermentation target.

3.5. Fermentation process operation and case studies

Fermentation can generally be performed in batch, fed-batch, or continuous mode. The batch process is a simple operation mode with a low risk of contamination and an acceptable production performance. In a batch process, microbes are grown in a fixed volume and composition of the medium is without the addition of supplements. The nutrients provided are gradually consumed by cellular metabolism, resulting in product synthesis. Thus, the chemical and physiological characteristics of the fermentation broth change as the fermentation proceeds. This operational mode is simple; therefore, it is convenient for laboratory-scale experiments conducted for optimization purposes, such as the determination of nutrient requirements and operating conditions. The major drawbacks of batch operation are the low yield and productivity of both biomass and product during fermentation in the case of substrate or product inhibition [98,99]. To overcome the limitations of batch operations owing to substrate inhibition, fed-batch fermentation is a useful alternative. The fed-batch process is widely accepted as a common approach for obtaining a high final product concentration with an acceptable yield. In fed-batch fermentation, a wide range of feeding programs has been proposed for specific operational purposes [100]. With a suitable substrate feeding program, essential nutrients (typically the carbon source) are maintained at an optimal concentration such that a high product yield and productivity are obtained [101]. Improved rhamnolipid production has been observed during fed-batch fermentation using various substrates including glucose, corn oil, and glycerol [102]. Hemansi and Saini (2023) used fed-batch cultivation for simultaneous saccharification and fermentation of ethanol by the tolerant yeast *Kluyveromyces marxianus* JKH5C60 from the high-gravity bagasse hydrolysate [103]. With the biomass feeding strategy developed in this study, the mass transfer limitation observed with high substrate loading during batch operation decreased. This increased the ethanol production yield. Fed-batch fermentation involves the accumulation of high product concentrations during cultivation. Cell immobilization is commonly introduced into fed-batch operations as a protective tool for cells or enzymes from harsh environments; for example, a high ionic strength and an inhibitory effect from high product concentration [104]. Immobilized *Clostridium acetobutylicum* cultivated under a combination of repeated batch and fed-batch operations resulted in an increase in the production rate of biobutanol [105]. Lu et al. (2012) also reported a 3.46-fold increase in butanol yield during fed-batch fermentation using immobilized *C. acetobutylicum* [106].

During continuous fermentation, the volumetric feed rate and broth removal rate were equal, resulting in a constant fermentation

broth level throughout the process. At a steady state, the growth rate and other environmental conditions remain constant [107,108]. Continuous fermentation reduces product inhibition. A high growth rate can be achieved when the feed rate is properly maintained, resulting in high-cell-density production [109,110]. The efflux of non-sterile broth with the remaining essential nutrients, the high risk of contamination during the long-term operation, cell loss, and decreasing product formation are the critical factors of concern during continuous operation [111,112]. Commercial-scale continuous fermentation has emerged mostly for bio-based platform chemicals [113]. Rahimi et al. (2019) reported an increased yield and productivity of recombinant hepatitis B surface antigen (rHBsAg) by *Pichia pastoris* in a continuous process when compared with fed-batch fermentation [114]. Continuous ethanol fermentation is another successful case study involving continuous operation. Crespo et al. (2012) reported enhanced production performance of continuous ethanol fermentation from sugarcane bagasse hydrolysate by the anaerobic bacterium *Caloramator boliviensis* [113]. Their experimental results were consistent with those of other studies reported in the literature. Dhandayuthapani et al. (2021) also reported that continuous ethanol fermentation improved the ethanol yield to 86.70 mg ethanol per gram of biomass hydrolysate when compared with the conventional batch process [115]. Cell immobilization has also been introduced into the continuous fermentation process to achieve high cell density, prevent cell loss, and, subsequently, high productivity. Zhang et al. (2023b) studied the effect of immobilized photosynthetic bacteria (I-PSB) with the addition of nano-SnO_2 on hydrogen production [116]. The results suggested that the immobilized I-PSB with 100 mL of nano-SnO_2 generated the highest cumulative hydrogen yield, which was 33.06 % higher than that obtained in free cell fermentation.

3.6. Current production of biobased product using renewable feedstocks

The recent development of bioproduct production from renewable resources is a promising solution for economically efficient industrial processes and ecosystem sustainability. Various renewable feedstocks, including bioplastics, renewable chemicals, and biofuels, have emerged as potential substrates for manufacturing multiple bio-based products. During the fermentation process, refined sugars (e.g., glucose, sucrose, and lactose) derived from food crops (e.g., starchy materials, sugarcane, and whey) are typically used as production substrates. These are recognized as first-generation biomass feedstocks [117]. However, there are concerns regarding the competition for land use for food and feed production. Therefore, the use of lignocellulosic biomass residues (such as corncob, rice straw, sugarcane bagasse, cassava bagasse, and wheat straw) has gained increasing attention because of their abundance, renewability, large availability, cost-effectiveness, and non-competitive substrate with food crops [118]. Most lignocellulosic biomass residues cannot be directly utilized in microbial fermentation without a pretreatment step to release fermentable sugars. Different pretreatment methods for sugar hydrolysis (physical, chemical, and biological processes) have been employed to develop efficient fermentation processes to obtain monomeric sugars (e.g., glucose, xylose, arabinose, mannose, and galactose) and to utilize them by potential microbes for bio-based product formation. Nevertheless, there are still many challenges in using lignocellulosic biomass as a fermentation substrate because inhibitor compounds (such as furfural and phenolic acid) are released, and mixed sugars (hexose and

Table 3
Bioproducts derived from multi-feedstocks by microbial fermentation process.

Feedstock	Biobased product	Microorganisms	Yield (g product per g substrate)	Reference
First generation feedstocks				
Corn starch	Bioethanol	*Saccharomyces cerevisiae*	0.45–0.51	[130]
	n-Butanol	*Clostridium* sp.	0.18–0.21	[123]
	Lactic acid	*Lactobacillus* sp.	0.90	[131]
	Succinic acid	Engineered *Escherichia coli*	~1.0	[132]
	Polyhydroxyalkanoates	*Ralstonia eutropha*	0.30–0.40	[133]
Sugarcane juice	Bioethanol	*S. cerevisiae*	0.45–0.51	[130]
	Lactic acid	*Lactobacillus* sp.	0.90	[134]
Molasses	Citric acid	*Aspergillus niger*	0.70–0.90	[135]
	L-Glutamic acid	*Corynebacterium glutamicum*	0.60	[136]
	Lysine	*E. coli*	0.40	[136]
Glucose	1,3-Propanediol	*Clostridium thermosaccharolyticum* HG-8	0.20	[137]
	2,3-Butanediol	*Klebsiella* sp. *Enterobacter* sp.	0.40–0.50	[138]
Glycerol	1,3-Propanediol	*Klebsiella* sp. *Clostridium* sp.	0.51	[139]
Second generation feedstocks				
Corn stover	Bioethanol	*S. cerevisiae*		[140]
Sugarcane bagasse	L-Lactic acid	*Bacillus coagulans*	0.87	[134]
Rice straw	Polyhydroxyalkanoates	*Bacillus cereus* VK92	0.59	[122]
Third generation feedstocks				
Microalgae	Bioethanol	*S. cerevisiae*	0.52	[141]
Green seaweed	Lactic acid	*Lactobacillus* sp.	0.51–0.68	[142]
Next generation feedstocks				
CO_2 H_2	Ethanol	*Clostridium ljugdahlii*	3 g/L·day	[143]
CH_4	Astraxanthin	*Methylomonas* sp.	2.4 mg per g dry cell weight	[144]
CH_4	L-Glutamate	*Bacillus methanolicus*	60 g/L	[145]
Acetate	Polyhydroxybutyrate	*E. coli*	0.29	[146]

pentose) derived from lignocellulose cannot be efficiently utilized by most microbes [119,120]. Thus, fermentation processes based on the use of alternative raw materials are mainly in the development phase, whereas most commercial production of bio-based chemical products is primarily achieved using first-generation sugar feedstocks [121]. As presented in Table 3, several bio-based compounds have been commercialized using biomass-derived sugars as fermentation substrates. In recent decades, industrial production of bio-based chemicals has mainly used sugarcane and corn starch for fermentation, depending on the substrate availability in the producing country. Short-chain alcohols, such as ethanol, *n*-butanol, and isobutanol, are the primary classes of compounds produced from biomass-derived sugars via microbial fermentation. Industrially, bioethanol is produced from corn starch, which is hydrolyzed by an enzymatic process to release glucose and subsequently converted to ethanol by a yeast strain [122]. In the production of a mixture of acetone, butanol, and ethanol (ABE), ABE production plants have been established using cornstarch, which can be hydrolyzed to glucose and then converted into products by anaerobic fermentation by *Clostridium* strains. Furthermore, the traditional commercial process of ABE fermentation is conducted under a CO_2 atmosphere using corn mash or molasses as a fermentation substrate [123]. However, recent limitations of biological ABE production at the industrial scale have been widely discussed owing to the financial crisis and feedstock availability [121]. The large-scale production of isobutanol has been demonstrated at a large production scale by developing fermentation technology from sugar feedstocks, such as corn-, sugar beet-, and sugar cane-derived feedstocks, in which fermentable sugars are released by enzymatic hydrolysis, and isobutanol is formed by yeast fermentation [121]. In addition to alcohol products, biotechnological processes for industrial production of short chain diols (e.g., 1,2-propanediol, 1,3-propanediol, 1,4-butanediol, and 2,3-butanediol), glycerol, organic acids (e.g., lactic acid, succinic acid, and citric acid), amines, amino acids, terpenes, fatty acids, and PHAs are mostly commercialized through the fermentation of bio-based feedstocks, including biomass-derived sugars, glycerol, and oil-based substrate. Other generations of biomass-derived feedstocks that can be applied in fermentation processes for the production of biobased products include microalgae and gasses (e.g., methane, a mixture of H_2 and CO, and CO_2) [124,125]. Microalgae are considered a third-generation feedstock and a potential renewable source of biomass for biofuel production, which is beneficial for converting CO_2 into lipids and polysaccharides with faster growth rates and high ability to survive harsh conditions [126]. Additionally, the residual microalgal biomass obtained at the end of ethanol fermentation, which contains organic compounds and minerals, can be utilized as a biofertilizer [127,128]. Another biomass-derived gas has been extensively developed as a fermentation substrate to produce value-added chemicals. Several efforts have been made to establish a fermentation process to convert C1 (CO_2, CO, methane, formate, and methanol) and C2 (acetate and ethanol) into short-chain alcohols and fatty acids using acetogenic bacteria [125]. In addition, the gas fermentation of biomass-derived waste gases is emerging as a feedstock for the commercial-scale production of PHAs [121]. Based on the aforementioned information, the fermentation process has significant advantages for the conversion of biomass-derived feedstocks to bulk chemicals that can be used as building blocks for the production of other bio-based products. More importantly, the production of various bio-based products (e.g., ethanol, lactic acid, and 1, 3-propanediol) has already been established at a commercial or demonstration scale using first-generation sugar feedstocks. However, there are challenges in using another generation of biomass-derived feedstocks that require strain improvement and bioprocess design technologies [125,129]. Once a suitable route for the production of bio-based products from biomass-derived feedstocks is developed, it will play a significant role in the future circular economy.

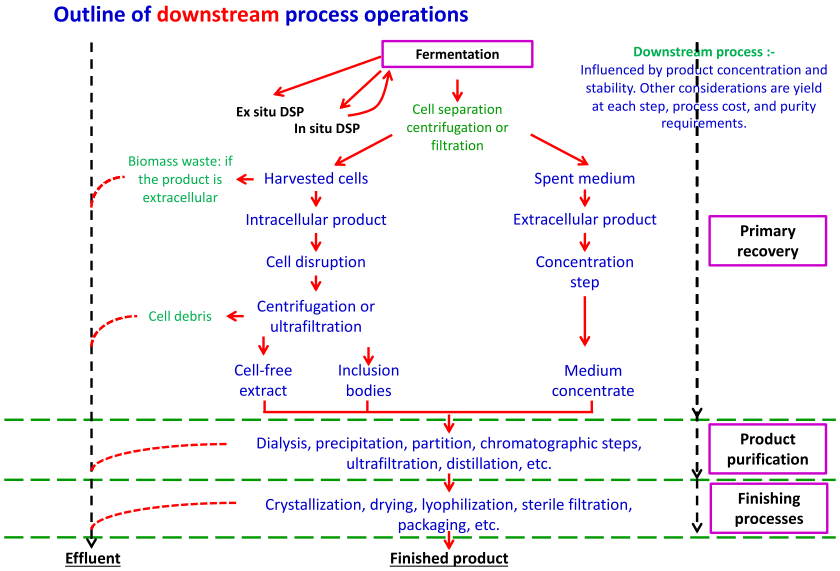

Fig. 2. The outline of downstream process operations.

4. Downstream process design and operation

Downstream processing is an important step in the fermentation industry. The cost of this process comprises almost 50 % of the overall operating expenditure [147]. Downstream processes mainly comprise product recovery, concentration, and purification (to different extents) based on specific requirements. Downstream processing usually involves a large volume of fermentation broth as the inlet stream, with low product concentrations and product sensitivity at high temperatures. This section covers the details of the major unit operations and their specific functions in product recovery and purification from upstream fermentation. Examples of downstream recovery and purification processes are briefly described herein.

4.1. Major unit operations in product recovery and purification

Large-scale product recovery, isolation, and purification from fermentation are mostly associated with similar processes in the chemical industry. These processes include sedimentation, filtration, extraction, distillation, evaporation, crystallization, and drying. Given the specific characteristics and properties of biological feed streams and products, sophisticated approaches for downstream processing are usually required. Several criteria must be set in the bioseparation process design. These include the type and characteristics of the starting materials, origin/location of the target product, volume and components in the inlet stream, stability and bioactivity of the target product after purification, final form of the product, product purity, effluent discharge, and overall process cost.

Typical downstream processes in the fermentation industry are shown in Fig. 2. The first step in the downstream product recovery and purification is primary recovery, in which cell separation occurs. In large-scale operations, cell biomass separation is typically performed using centrifugation and/or microfiltration. The addition of coagulants or flocculants aids the separation of cell biomass, which has a density not much different from that of the fermentation broth [148,149]. The aqueous two-phase system (ATPS) is another technique that enables biomass separation. ATPS spontaneously forms when two water-soluble polymers or salts are mixed in a solution at a certain concentration. ATPS provides low interfacial tension, low viscosity, rapid phase separation, high separation yield, high biocompatibility, and ease of scaling-up [150].

The two main process operations begin after cell separation. For the extracellular product, the cell biomass is discarded, and the spent cell-free medium is passed through the next process unit. In contrast, the cell biomass is collected for further product isolation in the case of intracellular or membrane-bound products. To isolate the extracellular product, the spent medium is concentrated before purification to remove the abundant impurities. Product concentration can be achieved through ultrafiltration, dialysis, evaporation, and precipitation, depending on the type of product and impurities to be removed. Product separation and purification can be performed using a multistep process to achieve the targeted purity with an acceptable recovery yield and process cost. Intracellular products require cell disintegration using thermal, mechanical, chemical, or enzymatic methods. An appropriate cell disruption technique is required for specific microorganisms owing to their internal osmotic pressure. The most practical cell disruption techniques are mechanical methods, such as bead grinding, high-pressure homogenization, and microfluidization [151–154]. Although ultrasound is well practiced on a laboratory scale, there are some drawbacks in large-scale operations, such as high cost, limited scaling ability, damage to heat-sensitive products, and chemical changes in the molecules of the desired product [151,155–159].

4.2. Examples of downstream product recovery and purification

Product purity, yield, and process costs are mandatory issues to address when designing the downstream product recovery from the fermentation broth. Ideally, the downstream recovery process should provide simple operation, high process performance, reasonably low cost, and little environmental impact [8]. Therefore, most downstream process designs involve multiple steps to obtain the targeted product specifications because each unit provides the specific function, operating conditions, cost, and drawbacks in the recovery. However, production costs increase with an increasing number of unit operations and process steps. Examples of downstream processes for the recovery and purification of extracellular and intracellular products are further described.

During extracellular lactic acid recovery from typical bacterial fermentation, lactate species, that is, free lactic acid and lactate salts, are generated in the fermentation broth. The ratio of the two species and the form of lactate salts depends on the operating pH and neutralizing agent used for pH control during fermentation. In addition, the lactic acid fermentation broth contains residual components in the culture medium. Therefore, a multi-step downstream process is employed to recover and purify lactic acid. The conventional steps in primary lactic acid recovery include centrifugation, microfiltration, and ultrafiltration, in which the cell biomass and large macromolecules, such as proteins, are removed [160–162]. The remaining lactic acid in the cell-free fermentation broth can be separated by extraction, esterification, distillation, ion exchange adsorption, and electrodialysis [163–167]. In the final purification step, the remaining trace components are removed by nanofiltration and adsorption by activated carbon before evaporation, where lactic acid is concentrated to the desired specification [168]. Downstream processes to purify lactic acid have been reported in the literature. This process improvement was conducted for either single-unit operation or combined units to achieve the targeted product purity and recovery [168,169].

Typically, high-quality lactic acid in the fermentation broth can be directly separated using a molecular distillation unit with a low recovery yield. The recovery yield can be improved by using a simplified calcium salt precipitation and wipe-film distillation. Introducing a solvent extraction step before centrifugal short-path distillation results in a high lactic acid purity of 91.3 % with a significantly increased recovery percentage [169]. In situ product removal (ISPR) by crystallization coupled with fermentation was developed to produce lactate salts. The final magnesium lactate concentration of 143 g/L with a yield of 0.94 g/g and a productivity of

2.41 g/L·h was obtained. In the in situ ISPR fermentation process, the fermentation medium is reused, thereby saving 40 % water, 41 % inorganic salts, and 43 % yeast extract compared with fed-batch fermentation [170]. In situ ISPR fermentation was also used to recover calcium lactate. This technique had 1.7 times higher average productivity with a 74.4 % higher lactic acid concentration compared with fed-batch fermentation [171].

Polyhydroxybutyrate (PHB) is one of the most well-known natural biosynthetic polymers. It belongs to the PHA group. PHB is synthesized intracellularly and accumulates during the unbalanced growth of various microorganisms [101,172]. Because PHB is stored as granules in the cellular cytoplasm, downstream recovery is a technological barrier to its use. High-cost processes account for 50 % of the final polymer price [173]. Several techniques have been developed for the extraction and purification of PHBs. Among these techniques, solvent-based extraction is extensively used for downstream recovery of PHB from microbial fermentation. The solvents used in PHB extraction include halogenated solvents such as chloroform, 1,2-dichloroethane, and methylene chloride; non-halogenated solvents such as cyclohexane and γ-butyrolactone; and green solvents such as ethylene carbonate and dimethyl carbon [174]. The conventional process is chloroform extraction because of its high extraction efficiency of approximately 95 % [175–177]. Hexane is used as an anti-solvent in the conventional chloroform extraction process to improve the purity and recovery of PHB [178]. The use of chloroform and hexane in PHB extraction and purification is concerning because of their negative impacts on human health and environmental protection. Dimethyl carbonate (DMC), an acyclic alkyl carbonate, has low toxicity in humans. Mongili et al. (2021) used DMC and ethanol as solvents and polishing as an alternative to the chloroform-hexane system for the recovery of PHB from PHB-rich biomass [173]. The extraction yield and purity were similar to the conventional chloroform-hexane process. Biomass pretreatments, such as heating, freeze-drying, sonication, and chemical oxidation, favor PHB extraction performance, but they can affect the characteristics of PHB. With increasing PHB yield, chemical oxidation pretreatment led to a decrease in the molecular weight of the polymer. Freeze-drying and heating rearrange the polymer chains, resulting in variations in crystallinity. In addition, biomass pretreatment before PHB extraction requires investments in additional equipment, materials, energy, and labor [179–181]. Montiel-Jarillo et al. (2022) pre-treated mixed microbial cultures (MMC) with NaClO before extracting PHB with DMC or chloroform [182]. To improve biopolymer recovery, NaClO pretreatment was not required in the DMC extraction process whereas pretreatment with MMC was mandatory in the chloroform extraction process. The supercritical CO_2 process was performed for PHB recovery at different pressures, temperatures, times, biomass loadings, and modifier volumes. The PHB extraction efficiency was approximately 80 %. The purity was also 80 % with a molecular weight of 0.37×10^6 [174].

4.3. Outlook of downstream recovery and purification

The unit operations employed in cell biomass separation are similar to those used for solid-liquid separation in chemical plants. The tools used in chemical engineering can be directly applied. Nonetheless, there are major differences, in addition to similar separation techniques and equipment, that affect the specificities of some biotechnological products. As a result, an approach based on the product characteristics, properties, and operating costs must be appropriately selected.

5. Current status, challenges, and perspectives

5.1. Problems associated with biomass resource assessment and the pretreatment process

Several biomass feedstocks have been investigated throughout the years. Their availability and characteristics have been thoroughly investigated for industrial applications. Over the past few years, many initiatives have been launched to advance technology and address the problems associated with chemical production via biorefinery platforms. To drive further progress, technological and economic problems relevant to the utilization of cellulosic biomass via biorefinery platforms need to be resolved. These are described here.

Inhibitory compounds in biomass hydrolysate: There is a chance that several inhibitory substances such as phenolic acids, pyrroles, and carboxylic acids could occur during the pretreatment of lignocellulosic biomass [183]. Hydrolysis and fermentation performance can be decreased by these inhibitors. The incorporation of a detoxification step after pretreatment is a simple and affordable way to eliminate inhibitors in a targeted manner [22,184].

Cost and environmental concerns: In manufacturing cost-effective biofuels, a simple and efficient pretreatment process with a low loss of carbohydrates and adequate lignin removal is mandatory. Pre-treatment sometimes requires chemicals that are difficult to recover or recycle. Therefore, this process is energy-intensive and not cost-efficient [183]. Additionally, some chemicals are harmful to human health and the environment. This makes conventional pretreatment of concern in terms of economic feasibility, carbon emissions, long residence time, and the occurrence of inhibitors [185,186]. Although several studies have been conducted in recent years, more affordable products should be developed to achieve a high production rate of purified monomeric sugars at a low cost [187].

5.2. Technical burden in fermentation process development

The four key elements in the successful development of a fermentation platform are medium formulation, medium sterilization, inoculum development, and active cells that produce a desirable product.

A robust fermentation microbe: Fermentation performance relies on a microbial cell factory. Mixed sugars, which are the major products of feedstock pretreatment and hydrolysis, contain both glucose and xylose. In general, microbes prefer to utilize glucose over

xylose because of glucose repression [188,189]. Therefore, microbes that simultaneously utilize glucose and xylose are preferred [190, 191]. Such microbes can be found either naturally as wild isolates or as adapted strains acquired through mutations and synthetic biology.

Substrate and product inhibition: Substrate inhibition limits the use of concentrated medium formulations, whereas process inhibition results in a low concentration of the product entering downstream processing. This intrinsically leads to high investment costs as large equipment is required to acquire a sufficient annual production amount, along with high operating costs when working with the diluted feed stream in the fermentation and downstream processes. Bioethanol production is an example of a substrate and product inhibition. When yeast is grown in a hypertonic solution with an excessive amount of substrate (glucose) in the culture medium, its viability and performance become limited, leading to a decrease in ethanol production. At high ethanol concentrations, glucose transport and metabolic systems are inhibited. This results in the limitation of subsequent metabolic pathways. According to the process limitation due to high sensitivity to high substrate and ethanol concentrations, it is necessary to maintain the ethanol concentration at the proper level so that fermentation can proceed at a sufficiently high production rate. Ethanol-tolerant mutants or genetically modified microbes are good process alternatives [192,193].

5.3. Cost competitiveness versus the recovery performance as a challenge in downstream processing

The downstream separation and purification of bioproducts are vital in bioprocessing. Downstream processing comprises 20–50 % of the overall operating cost of bioprocessing operations. Several bioprocessing facilities have experienced remarkable encounters in product recovery and purification in different aspects, with product inhibition during fermentation, which causes low feed concentration in downstream processing and subsequent low product yield [194]. To obtain a higher product concentration and yield, and to allow the use of a higher substrate concentration to improve fermentation performance, fermentation can be integrated with separation into a system so that the product can be removed simultaneously with fermentation. This can significantly reduce or eliminate product inhibition and therefore increase the final product yield and concentration [195]. Separation technologies for integrated product recovery include gas stripping, pervaporation, liquid-liquid extraction, adsorption, electrodialysis, and membrane-based processes. Examples of common fermentation-separation systems include extractive fermentation and membrane-integrated fermentation [196,197]. Although process integration improves product concentration and yield, the additional cost of equipment modification and installation and the sophisticated control system should have sufficient trade-offs with production performance.

5.4. Key challenges in developing the biotechnological platform adopted from chemical technology

Renewable bio-based feedstocks suitable for producing biofuels, platform chemicals, and bio-based products using bioprocessing include starchy biomass, sugar-rich plants, oily plants, lignocellulosic biomass, agricultural, household, municipal, and industrial residues. Unlike first-generation edible feedstocks, second-generation products are based on non-food crops and other lignocellulosic biomasses that can significantly reduce greenhouse gas emissions, while simultaneously reducing the consumption of fossil-based feedstocks. Third-generation bio-based products are made from genetically modified crops or microorganisms that may be carbon-neutral. Biofuels from algae and products directly produced by microorganisms using advanced biochemistry and molecular biology are examples of this group. Fourth-generation bio-based products consume more carbon than they generate during their entire life cycle; thus, they are considered carbon negative. Examples of fourth-generation feedstocks include carbon-fixing plants such as low-input, high-diversity perennial grasses [195].

The development of novel biotechnological products, such as monoclonal antibodies, plasmid DNA, recombinant RNA, and cultured meat, has led to the emergence of novel product recovery and purification techniques. Process integration has been introduced in both upstream and downstream process designs, and consists of multiple process steps. These include equilibrium-based, affinity-based, membrane, and solid-liquid separation [195]. Some techniques developed for this purpose include ATPS, affinity chromatography, size-exclusion chromatography, hydrophobic-interaction chromatography, ion-exchange chromatography, expanded bed adsorption, fiber-based adsorption, and convective flow systems. Table 4 summarizes and compares the key characteristics of the chemical processes and biotechnology [147].

Table 4
Comparison of chemical technology and biotechnology [147].

Key characteristics	Chemical technology	Biotechnology
Mode of operation	Multi-step technology, many processes of intermediate isolation; batch and continuous processes	The fermentation process is usually a single-stage process; mostly batch and fed-batch processes
Operating conditions	Drastic conditions; high temperatures and pressures; high equipment cost	Mild conditions; ambient temperatures and pressures; low equipment cost
Catalysts	Catalyst recovery is required; high cost and mostly toxic to the environment	Whole-cell biocatalyst produced during fermentation
Reaction selectivity	Low reaction selectivity; racemic mixtures produced	High selectivity; high optical purity
Production rate	Rapid reactions; short process time	Slow reactions; long process time
Sterilization	No sterilization required	Sterilization required
Product inhibition	Varied	Strong inhibition; low product concentration

5.5. Bioprocess comprehension

Recently, bioprocessing has been gaining popularity owing to several advantages compared to traditional oil-based manufacturing processes. Bioprocessing provides reduced dependence on fossil fuels, environmentally friendliness, high production yield, low production costs, improved quality of wide-range products, reduced energy consumption, and increased sustainability. The three key steps of bioprocess are upstream processing, fermentation, and downstream processing. The bioprocess can be a fully integrated process which involves every stage of the key steps starting from the original feedstock and ending at the final product. But a typical bioprocess exploration in a laboratory scale focuses on a selected stage. Bioprocess integration of an entirely new bioprocess remains challenging and requires refinement work.

Data availability

Data was included in the article and referenced in article. The related data are available from the corresponding authors upon request. No restriction were imposed on data security.

CRediT authorship contribution statement

Panwana Khunnonkwao: Writing – review & editing, Writing – original draft, Methodology. **Sitanan Thitiprasert:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Phetcharat Jaiaue:** Writing – original draft, Methodology, Formal analysis, Data curation. **Katsaya Khumrangsee:** Writing – original draft, Formal analysis, Data curation. **Benjamas Cheirsilp:** Supervision, Funding acquisition. **Nuttha Thongchul:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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