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Reframing residual sugars as value: A review on selective fermentation for ethanol and fructose co-production

Mohammed A. Zeinelabdeen*, Adil A. Mohammed, Muzamul M. H. Siddig, Khalid M. O. Mohamad, Abubakr Hassan Kheiri

Department of Chemical Engineering, Karary University, Khartoum 12304, Sudan

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ABSTRACT

This review examines selective fermentation as an emerging strategy for the co-production of ethanol and fructose from mixed-sugar feedstocks. Conventional fermentation processes aim to maximize ethanol yield through complete sugar conversion, thereby treating residual sugars, particularly fructose as process inefficiencies. In contrast, selective fermentation exploits the intrinsic glucophilic behavior of *Saccharomyces cerevisiae*, enabling preferential conversion of glucose into ethanol while preserving fructose as a high-value co-product. Date-based substrates, including low-grade fruits and processing residues, are highlighted as abundant and underutilized resources rich in glucose–fructose mixtures. The review discusses the fundamental aspects of yeast metabolism, sugar transport mechanisms, and fermentation pathways that govern substrate selectivity. In addition, the role of fructose as a versatile platform molecule for the production of bio-based chemicals is emphasized within an integrated biorefinery framework. Key operational parameters affecting selective fermentation performance, such as temperature, pH, aeration, and substrate concentration, are critically analyzed. Existing studies reveal a persistent trade-off between ethanol yield and fructose retention, particularly under high-sugar and industrial-scale conditions. Furthermore, current limitations in kinetic modeling and process optimization are identified as major barriers to industrial implementation. Selective fermentation presents a promising approach to enhance process efficiency and economic value in biomass conversion systems. Future research should focus on developing robust kinetic models, optimizing operating conditions, and integrating downstream processing to enable scalable and economically viable ethanol–fructose biorefineries.

1. Introduction

The increasing demand for sustainable bio-based products has driven significant interest in the valorization of carbohydrate-rich feedstocks through fermentation processes. Conventional bioethanol production primarily focuses on maximizing ethanol yield from fermentable sugars, often neglecting the potential value of residual sugars present in the fermentation broth [1,2]. In particular, mixed-sugar systems containing glucose and fructose are widely available in nature, including substrates such as sugarcane molasses, fruit extracts, date syrup, and lignocellulosic hydrolysates. However, current fermentation strategies typically aim at complete sugar conversion, treating any remaining sugars especially fructose as undesirable residues rather than valuable co-products [3,4,5].

Interestingly, *Saccharomyces cerevisiae*, the most widely used microorganism in industrial fermentation, exhibits an inherent glucophilic behavior, where glucose is preferentially consumed over fructose. This phenomenon, often associated with glucose repression and transporter specificity, has been extensively studied in the context of incomplete fermentation, particularly in wine production where residual fructose is considered a defect [6,7]. Recent studies have therefore focused on overcoming this limitation through adaptive laboratory evolution, strain engineering, and transporter modification to enhance fructose utilization. While these approaches are beneficial for achieving complete fermentation, they overlook an alternative and potentially valuable strategy: leveraging this natural selectivity to produce ethanol from glucose while preserving fructose in the medium [8].

From a biorefinery perspective, fructose is not merely a residual sugar but a high-value platform molecule with broad industrial applications. Beyond its role as a sweetener in the food industry, fructose serves as a key precursor for the production of 5-hydroxymethylfurfural (HMF), which can be further converted

* Corresponding author.
Email: mazaaam@yahoo.com
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into bio-based chemicals such as 2,5-furandicarboxylic acid (FDCA), levulinic acid, and biofuels like 2,5-dimethylfuran (DMF) [9,10]. Therefore, a process capable of simultaneously producing ethanol and a fructose-rich stream could significantly enhance the economic viability of biomass conversion processes.

Despite its potential, studies explicitly addressing selective fermentation for ethanol-fructose co-production remain limited. Existing works are largely confined to specific substrates such as date extracts, where partial success has been achieved in retaining high fructose concentrations alongside ethanol production. However, these studies often report a trade-off between ethanol yield and fructose retention, particularly during scale-up or prolonged fermentation [11,12]. Moreover, systematic investigations on process control parameters such as fermentation time, aeration, pH, and stress conditions are still lacking, and kinetic models describing dual-product optimization remain underdeveloped.

Despite the growing interest in selective fermentation, the development of robust kinetic models for mixed-sugar systems remains limited. Existing studies have primarily employed conventional modeling approaches such as Monod-type kinetics, modified Gompertz models, and, to a lesser extent, cybernetic and structured frameworks to describe microbial growth and product formation. Monod-based models are widely applied to represent the relationship between microbial growth and substrate concentration; however, they are generally limited in capturing complex multi-substrate interactions and preferential sugar utilization in mixed-sugar systems [13]. Similarly, the modified Gompertz model has been extensively used to describe microbial growth and product formation kinetics, particularly for estimating lag phase duration and maximum production rates, yet its empirical nature restricts its ability to explain mechanistic interactions between glucose and fructose [14]. More advanced modeling developments highlight that conventional kinetic models often fail to fully capture complex fermentation behavior and multi-stage dynamics, indicating the need for improved modeling frameworks [15].

More importantly, most existing kinetic models are developed for single-objective optimization, typically focusing on maximizing a single product such as ethanol, without explicitly addressing the inherent trade-off between ethanol production and fructose retention. In selective fermentation systems, this trade-off represents a critical challenge, as prolonged fermentation conditions that enhance glucose conversion may simultaneously increase unintended fructose consumption. Therefore, there is a pressing need for a structured kinetic modeling framework that integrates substrate selectivity, regulatory effects, and process variables to enable simultaneous optimization of ethanol yield and fructose preservation.

In this context, the present study aims to develop a selective fermentation strategy that exploits the glucophilic nature of *S. cerevisiae* to achieve simultaneous ethanol production and fructose retention. The study focuses on optimizing key operating conditions and identifying the critical fermentation window that maximizes co-product generation. By reframing residual fructose as a target product rather than a process inefficiency, this work contributes to the development of an integrated biorefinery concept for sustainable and value-added biomass utilization. In addition to highlighting date-based substrates, this review also provides a comparative analysis with other widely used industrial feedstocks, including molasses, lignocellulosic hydrolysates, and high-fructose corn syrup (HFCS), in terms of sugar composition, availability, and process feasibility. This comparison aims to position date-derived substrates within a broader industrial context and to evaluate their suitability for selective fermentation strategies. The analysis reveals that the near-equimolar glucose–fructose composition of date-based substrates offers a unique advantage for dual-product generation, distinguishing them from other feedstocks that require extensive pretreatment or lack selective sugar utilization potential.

2. Date

Date palm (*Phoenix dactylifera* L.*)* is a fruit-bearing plant native to the Middle East and North Africa and has long been cultivated as a staple food source in these regions. The plant exhibits a high level of adaptability to arid and semi-arid environmental conditions, making it widely cultivated in regions with limited water availability. Global date production is primarily concentrated in countries such as Saudi Arabia, Iran, Egypt, Iraq, and Algeria, while cultivation has also expanded to other regions, including Pakistan, India, and the United States. To date, date palm continues to play a significant role in supporting economic development and food security, particularly in arid regions [16].

2.1. Uses of date

A portion of date fruits is consumed directly, either in fresh or dried form, particularly those of high quality. In contrast, lower-quality dates or those that do not meet market standards are typically utilized as raw materials for processed products such as syrup and paste, which can be further applied as natural sweeteners in various food applications. These include products such as jams, beverages, bakery items, and snack foods. Moreover, the processing of dates generates a range of by-products that can be further valorized as value-added materials within the food industry [17]. Date fruits have long been utilized in traditional medicine and are recognized for their therapeutic potential due to the presence of bioactive compounds [18].

A portion of dates that do not meet market standards, commonly referred to as date by-products, is generated during post-harvest handling and processing. These by-products are unfit for human consumption due to quality deterioration, including inadequate texture, spoilage, and contamination by microorganisms or insect infestation. Moreover, date waste, including Date Press Cake (DPC) and low-grade fruits, is produced in significant quantities and poses a challenge for post-harvest and processing management within the date industry [19]. A large proportion of date production results in low-grade fruits and processing residues that remain largely underutilized, despite containing important nutrients and bioactive compounds [20]. These date wastes, including low-grade fruits, Date Press Cake (DPC), and other processing residues, present promising opportunities for conversion into value-added products and sustainable applications in both food and non-food industries.

2.2. Production of date

As shown in Table 1, the total increase of world production from 1991 to 2001 was 43% while the world production in 2001 was about 5 million tons. On the other hand, the world production of dates increased from 2.3 million tons in 1974 to 4.6 million tons in 1994 and then to 6.9 million in 2004 [21]; even in 2010 the global production reached about 8 million [22]. It is reported [23] that Saudi Arabia is one of the largest date-producer, the largest production was in Egypt followed by Saudi Arabia, Iran, United Arab Emirates (UAE), and Pakistan. Furthermore, the five top date-exporting countries in 2004 were Iran, Pakistan, UAE, Saudi Arabia and Tunisia.

Saudi Arabia as one of the largest producer in the world has produced about 700 hundreds metric tons per year in 2000 and jumped to about 1 million tons in 2011 [24]. The country has over 8 million date palm trees which occupy 94 million hectares. About 400 various varieties of dates are grown in Saudi Arabia that spread in many regions, e.g., Riyadh, Qassim, Madina, Assir and Eastern region [25].

Table 1. Date producing country and world production (in thousands tones)*

Country	1991	1993	1995	1997	1999	2001	2003	2005	2007	2009	2011
Egypt	603	631	678	741	906	1113	1122	1160	1314	1270	1374
Iran	634	716	780	877	908	900	965	997	1054	984	1030
Saudi Arabia	528	563	589	649	712	712	884	970	983	992	1008
Pakistan	293	577	533	537	581	550	423	497	558	531	557
Iraq	566	613	881	625	438	400	868	404	431	507	619
Algeria	209	262	285	303	428	370	492	516	527	601	725
UAE	173	236	237	288	305	318	758	758	758	759	239
Oman	135	163	173	185	282	260	220	247	256	259	268
Tunisia	75	86	69	95	103	105	111	113	124	162	190
Morocco	107	111	98	110	73	32	54	48	74	85	103
Total	3323	3958	4323	4410	4736	4760	5897	5710	6079	6150	6113

Country	2013	2015	2017	2019	2021	2023	2025	% change 1991-2025
Egypt	1328	1685	1542	1604	1700	1900	1730	187
Iran	1014	1033	1202	1308	1200	1000	1030	62
Saudi Arabia	1095	1038	1224	1540	1600	1600	1610	205
Pakistan	527	468	441	483	838	504	733	150
Iraq	676	602	619	640	750	636	715	26
Algeria	848	990	1059	1136	1200	1300	1250	498
UAE	238	403	345	324	383	329	397	130
Oman	308	345	361	373	374	395	377	180
Tunisia	195	223	260	289	345	386	369	392
Morocco	112	100	130	102	150	107	160	50
Total	6341	6887	7183	7799	8540	8157	8371	1880

*The data are adapted from Food and Agricultural Organization (FAO).

2.3. Content of date

Date fruits consist of pits (seeds) and flesh, where the fleshy part constitutes approximately 85–90% of the fruit dry weight. The pulp contains carbohydrates ranging from 65.2% to 88.02% of dry weight and includes about 70% readily digestible sugars, mainly glucose (35%), fructose (26%), and sucrose (0.5%), along with small amounts of protein, fat, ash, and polyphenols [26]. Other researchers reported that date fruits contain 44-88% sugars, 0.20-0.5% fat, 2.3-5.6% protein, 15 salts and minerals, vitamins and 6.4-11.5% dietary fiber [27]. The detailed content range of date fruits is presented in Table 2. The sugars contain mainly the same amount of glucose and fructose, small amount of sucrose and other oligosaccharides. However, few varieties of dates

contain high sucrose as shown in Table 2. Various vitamins such as riboflavin, thiamine, biotin, folic and ascorbic acid are also available in dates [28]. Potassium, boron, calcium, cobalt, copper, fluorine, iron, magnesium, manganese, phosphorus, sodium and zinc are the main minerals in dates.

Table 2. Contents range of date at various varieties*

Composition (g/100 g)	Carbohydrates (g/100 g)	Minerals (mg/100 g)	Vitamins (µg/100 g)
Moisture (7.2-50.4)	Fructose (13.6-36.8)	Mg (31.0-150)	A Retinol (3.0-44.7)
Fat (0.1-1.4)	Glucose (17.6-41.4)	Na (1.0-261)	B1 Thiamin (50-120)
Ash (1.0-1.9)	Sucrose (0.5-33.9)	Ca (5.0-206)	B2 Riboflavin (60-160)
Protein (1.1-2.6)		P (35.0-74)	B3 Niacin (1274-1610)
Carbohydrate (52.6-88.6)		K (345-1287)	B6 Pyridoxal (165-249)
Amino acids (0.51-2.55)		Mn (0.01-0.4)	B9 Folate (39-65)
		Fe (0.1-1.5)	C Ascorbic acid (400-16000)
		Zn (0.02-0.6)	α-Carotenoids (3-3)
		Cu (0.01-0.8)	β-Carotenoids (2.5-146)
		Se (0.24-0.4)	Zeaxanthin (33-33)
			β-Zeaxanthin (9-9)
			Lutein (28-541)
			Neoxanthin (184-381)
			Phenolics (3.91-661 mg/100 g)
			Anthocyanins (200-1500)

* Data are adapted from [28]

3. Fructose

Sugars are generally classified into monosaccharides, disaccharides, and polysaccharides based on their structural complexity. Monosaccharides such as glucose and fructose are simple sugars, while disaccharides (e.g., sucrose and maltose) consist of two monosaccharide units, and polysaccharides (e.g., starch and cellulose) are composed of long chains of sugar units. Fructose is a six-carbon ketose and an isomer of glucose [29]. Fructose and glucose have same molecular formula ($C_6H_{12}O_6$); however, they have different structure as shown in Fig. 1. Fructose, together with glucose and sucrose, is one of the main soluble sugars present in fruit tissues, and sucrose serves as an important carbohydrate that contributes to sugar composition and sweetness in fruits [30].

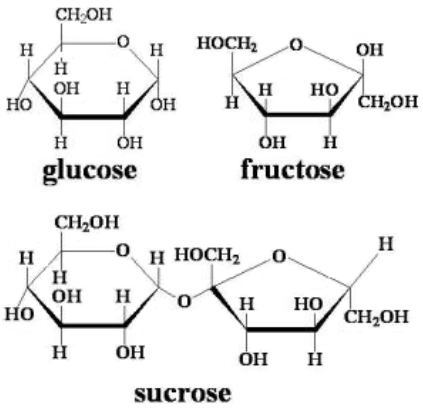

Fig. 1 Structures of glucose, fructose and sucrose

Fructose is naturally present in fruits and vegetables and is also found in honey as a naturally occurring monosaccharide. In addition, dietary fructose is commonly consumed as part of sucrose, which is composed of equal amounts of glucose and fructose, and is widely present in the human diet through natural and processed food sources [31]. Different sources will have variation levels of these three sugars. The content of fructose in apples and pears is twice that of glucose, while date has the same proportion. Though the world production of apple is ten times than that of date, half of date is still wasted while the apple production is completely consumed.

3.1. Uses of fructose

Fructose is consumed in the human diet primarily as part of fructose-containing sugars, including sucrose, and through various food and beverage sources. In dietary patterns, these sugars are commonly derived from both natural foods and processed products, contributing to overall fructose intake in the population [32].

Fructose has higher solubility than other sugars and thus difficult to crystallize from an aqueous solution [33]. Fructose exhibits distinct hydration behavior in aqueous systems, which is reflected in water activity and sugar–water interaction behavior [34]. Because of tremendous humectant and retain moistures for long time period, fructose might contribute to improved quality, better texture and longer shelf life to any food products [33]. Thus fructose, based on the described advantageous properties and texture, is prospectively used as a sweetener more than others such as refined sugar, dextrose and edible syrups as shown in

Table 3.

Various beverages and foods such as drinks, cupcakes, cookies, muffins, doughnuts, granola bars, *chocolate*, ice cream, *sweetened* yogurt, cereal, *candy use fructose commercially as sweetener* for palatability and taste enhancement, and for browning of some foods, such as baked goods.

Increased intake of dietary fructose, mainly from sucrose and sweetened beverages, has been associated with a higher prevalence of metabolic disorders such as type 2 diabetes mellitus, hypertension, fatty liver disease, dyslipidemia, and hyperuricemia [31]. However, the health effects of fructose remain debated, while the liver is recognized as the primary site of fructose metabolism. Fructose is absorbed in the small intestine and then transported to the liver, where it is mainly metabolized into intermediates that contribute to glycogen synthesis and de novo lipogenesis, including triglyceride formation [35].

Table 3. Relative sweetness of sugars and sweeteners*

Sweetener	Relative sweetness to sucrose, %
Lactose	16-20
Galactose	32-35
Maltose	30-50
Invert sugar	50-70
Glucose	70-80
Honey	97-102
HFCS-42%	100
Sucrose/Granulated sugar	100
HFCS-55%	110
Apple syrup	115
Pear syrup	120
Agave nectar syrup	120
HFCS-90%	130-160
Crystalline fructose	120-180
Fructose	140-173

* (adapted from [33,36])

3.2. Production of fructose

Commercial production of fructose is nowadays obtained from corn, sugar beets and sugar cane. Two types of fructose are commercially produced: crystalline fructose and high fructose corn syrup (HFCS) as mixture of glucose and fructose. The hydrolyzed corn starch is utilized for the production of HFCS as a raw material via the enzymatic process that converts glucose into fructose. HFCS-42 containing 42% fructose in the fructose-glucose mixture is produced via enzymatic process through three steps using enzymes: (i) alpha-amylase [37] that produces shorter chains of sugars namely oligosaccharides from raw corn starch; (ii) glucoamylase [33] that breaks down the oligosaccharides to yield the simple sugar glucose; and (iii) xylose isomerase [38] that converts glucose to fructose thereby yielding a mixture of 42% fructose, 50-52% glucose and the polysaccharides of the remaining. The production of HFCS is constrained by equilibrium limitations in the glucose isomerization process, which limits the extent of glucose conversion into fructose [39].

The production of 90% fructose syrup is industrially carried out via continuous multistage chromatography process [40]; this process suffers from high cost and separation difficulties. The blending of the 42% and 90% HFS produces 55% HFS as the final fructose product. The enzymatic production of fructose-rich syrups using glucose isomerase is generally limited by reaction equilibrium, which restricts the attainable fructose yield in a single-step process. Therefore, further downstream processing is commonly required to improve fructose concentration and product quality in industrial HFCS systems [41,42]. Recent studies report that high-fructose syrup production and purification are increasingly improved through membrane-based separation technologies such as ultrafiltration, which are effective in removing impurities and enhancing syrup clarity and quality during processing [43]. In addition, enzymatic conversion using glucose isomerase, including immobilized enzyme systems, remains the primary industrial method for producing fructose-rich syrups with improved efficiency and operational stability [39]. However, despite their advantages in efficiency and product quality, membrane materials and process solvents are relatively costly; therefore, preliminary economic assessments are required to determine the feasibility and scalability of these technologies for industrial applications.

To reduce the production cost of high fructose syrup, any processes using materials that are rich in fructan such as inulin, dahlia, chicory, Jerusalem artichoke and date, have been undertaken and developed. Inulin as a fructose polymer, is not sweet in solution. It thus has to be converted to D-fructose (monomeric form) before it is utilized as a sweetener [40]. Recent

studies show that inulin-rich substrates can be hydrolyzed into fructose-rich syrups using enzymatic processes involving inulinase under optimized reaction conditions. This enzymatic hydrolysis approach has been widely reported as an efficient and selective method for converting inulin into fermentable sugars, particularly fructose, in food and bioprocess applications [44,45]. However, the economic aspects of product separation and enzyme recovery should be carefully considered. The solid catalyst namely zeolite LZ-M-8 utilized in this process has been invented by [40] to reduce the cost of separation. About 96% fructose fraction could be obtained, while the inulin was utilized. They also applied the catalyst to the Jerusalem artichoke medium with about 75% fructose fraction achieved. Moreover, in term of the reusability of the catalyst, the three times repetition of the used catalyst showed similar conversion and yield of fructose to the fresh one.

3.3. Comparative analysis of industrial substrates

The selection of an appropriate substrate is a critical factor in determining the feasibility and scalability of integrated biorefinery systems, particularly for dual-product strategies involving ethanol and fructose. While various industrial feedstocks such as molasses, lignocellulosic hydrolysates, and High Fructose Corn Syrup have been extensively utilized in fermentation processes, their suitability for selective sugar utilization varies significantly depending on sugar composition, process requirements, and economic considerations. For instance, molasses is predominantly composed of sucrose (approximately 50–62%), along with glucose and fructose, requiring hydrolysis prior to fermentation and often leading to simultaneous sugar consumption [46]. In contrast, lignocellulosic hydrolysates mainly contain glucose and pentose sugars such as xylose, with negligible fructose content, thereby limiting their applicability for fructose co-production [47]. On the other hand, HFCS provides a relatively high and consistent fructose fraction (42–55%), but its high production cost and competition with the food industry reduce its attractiveness for large-scale biorefinery applications.

In comparison, date-based substrates exhibit a near-equimolar composition of glucose and fructose, making them particularly suitable for selective fermentation processes that exploit the glucophilic behavior of Saccharomyces cerevisiae. This characteristic enables preferential glucose consumption for ethanol production while preserving fructose as a value-added co-product. A comparative overview of these substrates in terms of sugar composition, availability, and process feasibility is presented in Table 4.

Table 4. Comparative Analysis of Industrial Substrates for Ethanol–Fructose Bioprocess

Substrate	Sugar Composition (wt% of total sugars)	Availability & Source	Limitations	Relevance for Dual-Product (Ethanol–Fructose)	Reference
Date-based substrates	Glucose: ~45–55% Fructose: ~45–55% (varies by cultivar)	Date fruit waste, processing residues	Seasonal availability – Compositi-on variability	Highly suitable: near-equimolar glucose–fructose enables selective glucose consumption by Saccharomyces cerevisiae while preserving fructose	[48]
Molasses (sugarcane/beet)	Sucrose: ~50–62% Glucose: ~19–21% Fructose: ~18–23%	By-product of sugar industry (highly abundant)	- Requires sucrose hydrolysis - High impurities (ash, salts)	Moderate: fructose is present but rapidly co-fermented after hydrolysis	[47]
Lignocel-lulosic hydrolysa-te	Glucose (C6): dominant Xylose (C5): significant Fructose: negligible	Agricultural residues, wood biomass	- Requires intensive pretreatment - Formation of inhibitors (furfural, HMF)	Not suitable: lacks fructose, limiting dual-product strategy	[46]
High Fructose Corn Syrup (HFCS)	HFCS-42: 42% fructose, 53% glucose HFCS-55: 55% fructose, 41% glucose	Industrial corn starch processing	- Expensive - Competes with food industry	Technically suitable but economically less attractive for waste-based biorefinery	[49]

While the comparison in Table 4 highlights the compositional and practical differences among substrates, it is important to note that process performance metrics such as ethanol yield, sugar utilization rate, and fermentation efficiency also vary significantly depending on substrate type and pretreatment requirements. These factors further reinforce the suitability of date-based substrates for selective fermentation due to their balanced sugar composition and minimal pretreatment needs.

3.4. Downstream processing of fructose-rich streams

Despite the promising potential of selective fermentation for

dual-product generation, the downstream processing of fructose-rich streams represents a major bottleneck that critically determines the industrial feasibility of the proposed concept. The separation of fructose from fermentation broth is inherently challenging due to the coexistence of glucose, ethanol, microbial biomass, and other soluble compounds with similar physicochemical properties [50]. In particular, the close structural similarity between glucose and fructose results in comparable molecular sizes and polarity, rendering conventional separation methods such as distillation ineffective for sugar fractionation [51].

Membrane-based processes, including nanofiltration and reverse osmosis, have been widely investigated due to their relatively low energy consumption and mild operating conditions [52]. However, their application in glucose–fructose separation is limited by low selectivity [53] and severe membrane fouling caused by organic compounds and microbial residues [50]. While these systems are attractive for pre-concentration, they are generally insufficient as standalone purification techniques [54]. Chromatographic separation, particularly simulated moving bed (SMB) technology, is currently the most established industrial method for glucose–fructose fractionation and is widely used in the production of high-purity fructose syrups [55]. This technique offers high separation efficiency and product purity; however, it is associated with high capital investment, complex operation, and significant water consumption, which may limit its integration into cost-sensitive biorefinery systems [56].

Emerging separation approaches, such as selective adsorption using functionalized materials and controlled crystallization, have shown potential to improve fructose recovery efficiency [54,55]. Nevertheless, these methods often require precise control of process conditions and remain limited in terms of scalability and industrial maturity [59]. In addition, fructose stability presents another critical challenge, as it is susceptible to thermal and acid-catalyzed degradation, leading to the formation of by-products such as 5-hydroxymethylfurfural (HMF), which can reduce product quality and process yield [60].

From an economic standpoint, downstream processing can account for up to 50–70% of the total production cost in biochemical processes, highlighting its dominant role in determining process viability [61]. Therefore, the success of fructose valorization strategies strongly depends on the development of cost-effective and scalable separation technologies. In this context, process intensification strategies, such as the integration of selective fermentation with in situ separation (e.g., membrane-assisted bioreactors or hybrid systems combining fermentation and chromatography), have emerged as promising approaches to reduce separation load and improve overall process efficiency [62]. Overall, while significant progress has been made in sugar separation technologies, further research is required to develop integrated and economically viable downstream processes that can support large-scale implementation of dual-product biorefineries.

4. Single Cell Protein

Single cell protein refers to a protein extracted from sources such as algae, yeasts, bacteria and used for animal feed or dietary supplements. Yeasts, such as *Saccharomyces cerevisiae*, are eukaryotes that belongs to kingdom Fungi, single-celled or unicellular [63] that can reproduce sexually or asexually [64]. Yeast and certain bacteria could ferment sugars to produce some products. The differences in characteristics of the two microorganisms are presented in Table 5.

Table 5. Differences of yeast and bacteria*

	Yeast	Bacteria
Domain	Eucariotic	Procaryotic
Kingdom	Fungi	Eubacteria
Type of cell	Mostly unicelluler	Unicelluler
Diameter size	3-4 μm	0.2-2 μm
Reproduction	Mostly asexual by mitosis	Asexual
Metabolism	Aerobic, facultatively anaerobic, limited to heterothropic	Aerobic, facultatively anaerobic, anaerobic, limited to autothropic
Cell wall	Glucans, mannans, chitin (no peptidoglycan)	Peptidoglycan
Product of fermentation	Ethanol, bread, beer, cider and wine	Ethanol, lactic acid, buthanol, hydrogen, acetic acid

*[65,66,67,68]

The products of the fermentation depend on the type of the yeast or bacteria used; however, most yeasts are used for the production of ethanol. The dried cells of microorganisms are referred to as single cell protein (SCP). 60-80% of the dried cells weight is protein; the remainder being carbohydrates, fats, nucleic acids, minerals and vitamins.

4.1. Uses of single cell protein

Increased world population and limited agricultural production make food supplements from yeasts or SCP extremely important [69,70]. Single cell protein has many uses: a biocatalyst in medical industry, animal and human fodder, aroma and vitamin carrier, etc [71,72]. Yeast propagation from cheap sources and ease of harvesting due to their flocculation abilities and their relatively bigger sizes make them excellent candidates as protein sources. As a food supplement, yeasts have many advantages, including: rapid growth rate, cheap raw materials, high protein content, no pathogenicity, fast digestibility and palatability [73]. *Saccharomyces cerevisiae* yeast has been used as a protein source for humans and animals to produce vaccines, growth hormone and renin [74].

To obtain higher yields of biomass, appropriate technologies that provide suitable growth conditions must be sought. Fed-batch systems are usually favored over batch systems as they provide adequate control of feeding rates of the carbon sources [77,78]. The aeration feed must also be controlled as demand for oxygen grows with biomass concentration [79]. On the other hand, it is believed that Chemostats can provide a better option at industrial level as they facilitate continuous carbon source feed and continuous harvesting of cells [80].

Table 6. Contents of dry weight cell for some microorganisms*

Nutrient	Fungi	Algae	Yeast	Bacteria
Protein	30-45	40-60	45-55	50-65
Fat	2-8	7-20	2-6	1.5-3.0
Ash	9-14	8-10	5-9.5	3-7
Nucleic Acid	7-10	3-8	6-12	8-12

*[75,76]

4.2. Production of single cell protein

Various raw materials such as paraffins hydrocarbon, methane, alcohol and carbohydrates can be utilized in the production of single cell protein. The production of single cell protein by fermenting waxy n-paraffins (a product that is produced by oil refineries) using yeast has been researched since 1960s at British Petroleum; they initially called "protein-from-oil process" [81]. Single cell protein can be also produced by extraction of wastes; however the method encountered drawbacks such as low concentration (less than 5%) and cost of process. In order to increase the concentrations, some strategies should be applied including centrifugation, flotation, precipitation, coagulation, and filtration, or the use of semi-permeable membranes [82].

Single cell protein is generally produced when microbes ferment waste materials such as wood, straw, cannery and food processing wastes, residues from the production of alcohols, hydrocarbons, or human and animal waste [83]. Microbes utilized include yeasts such as *Saccharomyces cerevisiae, Pichia pastoris, Canadida utilis* and *Geotrichum candidum*; other fungi such as *Aspergillus oryzae, Fusarium venenatum, Sclerotium rofsii, Polyporus* and *Trichoderma*; bacteria such as *Rhodopseudomonas capsulate*; and alga such as *Chlorella* and *Spirulina* [84,85]. A typical yield of 43 to 56% can be obtained with protein contents of 44 to 60% [86].

Gas and liquid hydrocarbons and chemicals including methane, purified n-alkanes, crude oil, and fractions obtained from crude oil, such as gas oil and kerosene, methanol, and ethanol has been used for the production of SCP [87]. Continuous production of bacterial SCP from methane resulted in high productivities and yield coefficients; however, the productivity was limited by the transfer of oxygen and methane from the gas phase to the bacterial cells [88]. Explosive hazards requiring operation below 12.1% volume of oxygen as well as high heat production at high productivities were also encountered [89]. The utilization of crude oil, fuel oil and kerosene as substrates for production of SCP has been operated in a pilot plant scale; the results showed a sufficiently promising process to justify further commercial development [90].

Methanol and ethanol as substrates for production of SCP have some advantages, including high solubility in water, lack of explosive hazards of methanol/ethanol-oxygen mixtures, free from traces of aromatic hydrocarbons and ease of removal from the microbial cell [91]. These substrates are prepared in extremely pure condition and leave no residues associated with the cell mass leaving the fermentor [92].

A common substrate for production of SCP is the carbohydrate source. This source can be available as cellulosicraw material or starch. Cellulose is the most abundant material found in agricultural waste. The conversion from cellulose to sugars is the most crucial step in this SCP production process. The process will be economically possible; however, the suitable scale up processes have not been proven [93]. Simply, starch that does not need the conversion process to sugars is directly ready to use than cellulose. For example, molasses as a by-product of the sugar manufacturing process that has high sugar content, minerals organic compounds and vitamins is a prospective material; though the process of biomass production requires the additional supplements molasses [94]. Starch can be also available in agricultural sector; however, the type of substrates will compete with food market. Thus, the waste materials are only possible substrate to be economically considered.

5. Bioethanol

Ethanol is one of the most potential products used in various markets such as solvent, fuel, chemical reagent, raw materials for many important chemicals, etc. The demand for ethanol is steadily increasing especially as an energy source [95]. The annual worldwide production of oil declined from 25 billion barrels in 2002 to approximately 5 billion barrels in 2050 [96]. Compared to the gasoline, ethanol is renewable, safe to store, easy to handle, not toxic and sulfur-free material, less contribution to the air pollution and global warming and also provides competitive price [97].

Plenty of researches in the production of ethanol has been carried out using various source materials such as starch, cellulose, algae, etc. To alleviate competition with food and from economic point of view, production of ethanol from agricultural waste material is more appealing. The cost of ethanol is relatively still high compared to fossil fuel [98]. The commercial ethanol production has been developed using corn starch and a big portion of the worldwide production of ethanol is derived from sugar cane [99]. However, such raw materials will compete with the food market due to the limited agricultural land. On the other hand, the prospective source for the production of ethanol with the low cost material is by utilizing lignocellulosic materials such as crop residues, grasses, sawdust, wood chips and solid animal waste [100]. The biochemical process of conversion of biomass into ethanol requires 4 steps, i.e., pretreatment, saccharification, fermentation and distillation. Thus, due to this complex process, the economic evaluation of the integrated system should be assessed.

The tolerance of yeast to the fermentation process on the effectiveness of the production of ethanol in industrial scale is an important matter [101]. A number of studies of temperature effect on various microorganism have been investigated [102,103,104]. Higher temperature led to the higher inhibitory effect of the ethanol. On the other hand, the optimum temperature for the production of ethanol was 5 to 10^{o}C higher than the optimum temperature for cell growth [105,106]. The effect of ethanol on the yeast is also complex [107,108]; however, the temperature effect is greater than ethanol effect on *S. cerevisiae* imposition [109]. The optimum range of temperature for *S. cerevisiae* is between 30-35^{o}C, while no growth of yeast was observed above

45.4°C [110]. The temperature above the optimum affected the cell membrane, it further led to an increase of its permeabilit to protons [111].

Many researchers have investigated the simultaneous production of ethanol and fructose. A very promising technique, still in its infancy, for the production of fructose from sugar mixtures is selective fermentation of glucose and other sugars (except fructose) to bioethanol [112,113,114]. Preliminary economic studies on the production of fructose and ethanol by selective fermentation proved its viability [115]. The ethanol purification to high value (>95%) is also complex and costly. Since, the ethanol-water mixture forms an azeotrope at 95% ethanol volume, expensive azeotropic distillation should be applied. Thus, from this concern, the simultaneous production of fructose and single cell protein (replacing ethanol) should be considered.

6. Fermentation Process

Biomass or yeast cells can be produced through the fermentation of a suitable carbohydrate, such as: glucose and/or fructose. Two techniques have been employed for cell multiplication: *aerobic* system (also called "oxidative pathway" as oxygen or air are continuously fed to the system) that leads to the production of more biomass as the main product and *anaerobic* system (also called "reductive pathway" where the system is deprived of oxygen) that leads to the production of, both, products (e.g., ethanol) and biomass as a by-product [116,117]. The oxidative pathway is the main technique for production of biomass as it converts all glucose source to biomass while ethanol production is suppressed. Increased respiration and carbohydrate breakdown, maximum growth of biomass in aerobic system is achieved [118]. The presence of oxygen in aerobic systems plays positive roles in: increasing respiration, providing mixing, inhibiting fermentation to ethanol and stimulating vegetative growth. The yeast fermentation metabolism pathway is described in Fig. 2 (adapted from [119]).

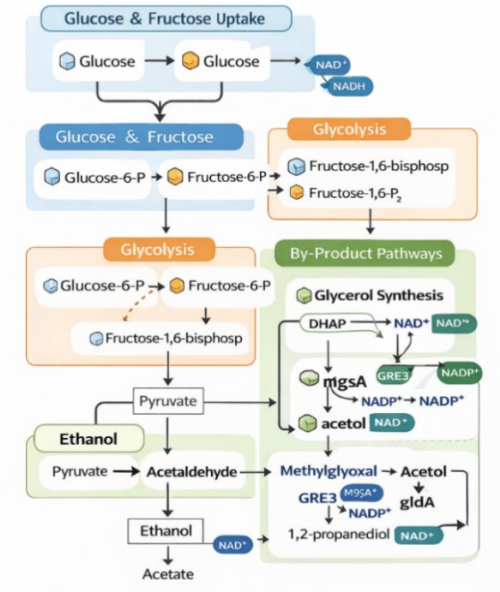

Fig. 2. Yeast fermentation metabolism for anaerobic and aerobic system

The pathway of anaerobic process is divided in 3 steps:

(i) glycolysis process: the conversion of glucose to pyruvate;
(ii) acetaldehyde formation along with CO_2 production;
(iii) production of ethanol from acetaldehyde.

On the other hand, in the aerobic process the production of acetaldehyde from pyruvate is suppressed and the presence of oxygen will lead to cell growth as well as the production of CO_2 and H_2O.

6.1. Anaerobic fermentation

The yeast *Saccharomyces cerevisiae* ATCC 36859 has been employed to convert glucose to ethanol and biomass in a synthetic medium of glucose-fructose mixture [120,121]. The results revealed yeast inhibition due ethanol production; also, small amounts of fructose were consumed during fermentation. Recent studies have shown that during mixed-sugar fermentation by Saccharomyces cerevisiae, glucose is preferentially consumed over fructose due to its inherent glucophilic nature. As a result, glucose is often rapidly depleted, while fructose remains partially unutilized at the end of fermentation, leading to substrate losses. This imbalance is particularly critical in processes targeting high fructose utilization, such as high-fructose syrup production. Additionally, high initial sugar concentrations can induce osmotic and metabolic stress, which inhibits yeast activity, reduces sugar uptake rates, and ultimately lowers ethanol productivity [122,123].

Other researchers have investigated the utilization of yeast *Saccharomyces cerevisiae* ATCC 36858. While the strain of ATCC 36859 could not hydrolyze sucrose due to lack of invertase (an enzyme that breaks sucrose to fructose and glucose), conversely, the strain of ATCC 36858 could do, thus sucrose could be converted to fructose and ethanol. However, the amount of sucrose is very less in dates' syrups, therefore, the presence of invertase is less significant compared to their work that used sucrose or molasses media. Atiyeh and Duvnjak, further reported that the fructose yield was above 93% of the theoretical value when using ATCC 36858 strain with total sugar concentration 9.49-31.24% (w/v). For sugar concentration below 27.62% (w/v), the ethanol yield was in the range of 59–76% of the theoretical value. Their results constituted a basis for potential industrial production of ethanol and high-fructose syrup from sugar beet molasses.

Atiyeh and Duvnjak reported that when using ATCC 36858, the fructose yield is similar and the ethanol yield is 13% lower than that obtained by Koren and Duvnjak who used ATCC 36859. However, the growth rate of the strain ATCC 36858 is slightly higher than ATCC 36859; moreover the medium for ATCC 36858 was only supplemented with one-third yeast extract.

Using conventional fermentation, date syrups have been utilized to produce ethanol; biomass; fructose and ethanol. Fructose fractions in remaining sugars in previous processes were less than 78% and the fructose loss was more than 40%. In order to improve fructose yield, selective fermentation has been employed using various substrates. *Tricholoma mudum* NRRL 2371, *Fusarium* sp F5, *Pullularia pullulans* ATCC 9348,

Zymomonas mobilis (ATCC 39676, ATCC 53432, ATCC 53431) and *Saccharomyces cerevisiae* ATCC 36858 have been used to ferment sucrose media. Mucor sp M105, *Zymomonas mobilis* (DSM 3126 and ATCC 53431) and *Saccharomyces cerevisiae* ATCC 36859 have been used to ferment glucose-fructose mixtures. However, the fermentation process using most of these strains showed significant consumption of fructose (up to 50% in some cases) and formation of undesired by-products (e.g., sorbitol, >4%), whereas the fermentation processes using yeast strain *S. cerevisiae* overcame these concerns as shown in Table 7.

Table 7. Some microorganisms used for the production of fructose*

Microorganism	Feedstock	Operation	Result	Reference
Saccharomyces cerevisiae	Date extract / date syrup	Scale-up was conducted across three fermenters with a working volume ratio of 1:40:400	The study modeled the simultaneous production of ethanol and fructose; the fructose fraction remained high during scale-up, but in larger fermenters, a portion of fructose began to be co-fermented.	[113]
S. cerevisiae	Date syrup	A kinetic study based on the modified Gompertz model, examining the effects of temperature and agitation.	The article emphasizes the prediction of product formation and fructose fraction for industrial applications.	[14]
S. cerevisiae ATCC 36858	Date extracts	Aeration at 0.1–1.5 vvm and pH 4.5–5.6.	An optimum biomass concentration of approximately 10 g/L was achieved at 1.25 vvm, with the highest fructose yield reported at around 91% under specific conditions.	[124]
Several strains of *S. cerevisiae*	Synthetic/ grape-must-like system	Analysis of sugar transporter expression during the late stage of fermentation.	Demonstrates that differences in glucose–fructose consumption are associated with transporter activity and regulatory mechanisms during the late stage of fermentation.	[122]
Four wine strains of *S. cerevisiae*	Synthetic must	Cell pretreatment at 45 °C for 1 hour and/or 14% (v/v) ethanol.	Pretreatment influences the patterns of glucose and fructose consumption as well as ethanol production performance.	[125]
S. cerevisiae	Grape must	Wine fermentation.	Confirms the classical stoichiometric basis: hexose sugars are fermented into ethanol and CO_2; this is relevant for calculating theoretical yields in selective fermentation.	[126]
S. cerevisiae AWRI 796 and an evolved isolate	Semillon juice/ CDGJM	EMS mutagenesis +directed evolution	Used to improve fructose utilization and enable more complete fermentation.	[127]
S. cerevisiae CFB and BLR strains	High-glucose fermentation broth	Adaptive laboratory evolution over 100–200 generations under high-ethanol selection pressure.	The evolved populations produced significantly higher ethanol levels and exhibited faster fermentation compared to the parental strains.	[128]
Mutant *S. cerevisiae*	Fuel ethanol medium	Omics mutant high-ethanol analysis.	The ethanol fermentation capacity increased compared to the original strain.	[129]
Thermotolerant *S. cerevisiae* DBKKUY-53	Sweet sorghum juice	37°C, with optimization of cell concentration, sugar concentration, and yeast extract.	Demonstrates that medium composition strongly influences sugar consumption rates and ethanol formation in sugar-rich substrates.	[130]
Populations of *S. cerevisiae* obtained through adaptive laboratory evolution (ALE)	Natural grape must	Oenological evaluation of evolved populations.	Some evolved populations were able to complete fermentation more rapidly due to improved fructose consumption.	[131]
S. cerevisiae	Grass press-juice	32°C, pH 5.3, 120 rpm, 72 jam; short-term adaptation	Fructose conversion increased from 79% to 90% after adaptation; ethanol reached approximately 18 g/L with a yield of around 0.50 g/g sugars.	[124]
S. cerevisiae GJ2008	Sucrose-rich medium	Benzoic acid stress of approximately 1.2 g/L.	Under control conditions, ethanol reached approximately 122.69 g/L; under stress conditions, ethanol decreased while residual sugar increased significantly.	[132]
S. cerevisiae TA2 + Wickerhamomyces anomalus HCJ2F-19	Sugarcane molasses	Co-fermentation	Demonstrates that mixed-culture approaches can alter sugar utilization in real industrial substrates.	[133]
Wickerhamomyces subpelliculosus ZE75	Glucose medium	Optimization of pH and salinity; up to 175 g/L glucose.	High ethanol production can be achieved using alternative yeast strains.	[134]

Table 7 (continued). Some microorganisms used for the production of fructose*

S. cerevisiae	Palm trunk sap + single sugars	Fermentation up to 144 hours.	Sucrose yields the highest ethanol production, followed by glucose and fructose, confirming that fructose is less favorable for *S. cerevisiae*.	[135]
S. cerevisiae CFB and BLR obtained from ALE	Fructose broth; then mixed sugars consisting of 100 g/L glucose and 100 g/L fructose.	100 generations of ALE.	The article emphasizes that the innate glucophilicity of *S. cerevisiae* causes a glucose–fructose consumption mismatch; evolution increases fructophilicity and ethanol tolerance.	[136]
Fructophilic yeasts, especially *Starmerella lactis-condensi*	Sun-dried Pedro Ximénez must/ fresh must	Screening on very high sugar media.	In fresh must, the selected strains showed faster and preferential fructose consumption compared to glucose; in concentrated must, they were able to produce base wine with approximately 11% v/v ethanol and high residual glucose.	[137]
Low-ethanol breeding-derived strains	Grape must	Pilot-scale fermentation.	Ethanol production can be reduced by approximately 10.7% in certain strains.	[138]
Engineered *S. cerevisiae* expressing the AtSWEET7 transporter	Renewable mixed-sugar feedstocks	Sugar transporter substitution.	Recent reports indicate that transporter substitution can reduce glucose repression and enable simultaneous sugar utilization.	[139]

* Data are adapted from. F, G, S and So refer to fructose, glucose, sucrose and sorbitol, respectively.

Date syrup as a medium has been used in production of ethanol using the commercial baker's yeast *S. cerevisiae* [140]. As expected, both glucose and fructose were equally consumed. Furthermore, the yield of ethanol was observed to depend on many parameters such as fermentation temperature, pH and agitation speed. The yeast strains ASN-3 and HA-4 were active in ethanol fermentation. However, a process using strain HA-4 resulted in higher biomass and the higher yield of ethanol was obtained at pH 4.5, 120 rpm, and 30°C. On the other hand, ethanol fermentation of juices of sweet sorghum stalks using the common S. *cerevisiae* was investigated [141]. The best conditions were found at pH 4.5, agitation rate of 150-200 rpm and 34°C. Thus, the selection of appropriate parameter's value is an extremely important factor as different yeasts and fermentation substrates (medium) require certain suitable conditions [142,143,144].

Recent studies on high-gravity and very-high-gravity fermentation systems have shown that increasing initial sugar concentration induces strong osmotic and metabolic stress in Saccharomyces cerevisiae, where inhibition of cell growth and biomass formation is more pronounced than the reduction in ethanol production. This indicates that yeast metabolic flux toward ethanol remains relatively robust even under stress conditions, while growth-related processes are more sensitive to high sugar and associated inhibitory environments [145]. Adaptive laboratory evolution (ALE) approaches have been widely applied to generate S. cerevisiae strains with improved tolerance to ethanol and high-sugar environments. These evolved strains typically show enhanced stress resistance and more efficient sugar utilization, supporting their potential application in high-gravity industrial fermentation processes [146].

The effect of adding various supplements in sugar cane media was investigated by using the common yeast *S. cerevisiae*. Both urea (2, 3, 4 g/L) and yeast hydrolysate (YH) dosage (0.5 g/L) supplements were used to increase the fermentation efficiency. Optimum condition was observed to result in significant improvements in ethanol yield and efficiency which were 7.8% (w/v) and 76.3%, respectively. Parrondo et al. has investigated the effect of supplements on ethanol fermentation. The Crabtree-negative yeast *Kluyveromyces marxianus* was employed using lactose media. Furthermore, the combination of two or more vitamins of the four vitamins Nicotinic acid, biotin, panthotenic acid and inositol was observed to diminish cell growth and lactose consumption thereby increasing ethanol production [147].

The addition of minerals in a yeast cultivation medium has been shown to play a positive role in yeast growth and subsequent fermentation. The presence of magnesium in the fermentation process prolonged the exponential growth phase and increased the yeast cell concentration. Iron as an enzyme cofactor contributed positively to the cellular metabolism [148,149,150]. Cobalt was an essential element for vitamin B12 formation. Both Fe and Co have been shown to enhance the fermentation yield [151]. Manganese was identified as an essential element for metabolism and growth and nickel was an important nutrient for organisms [152]. Zinc was essential for protein biosynthesis and a carbohydrate metabolism that contributed to higher ethanol production [153]. Urea, as an inexpensive source of nitrogen, was shown to increase ethanol production and fermentation efficiency [154].

6.2. Aerobic fermentation

Low-level aeration has been shown to significantly enhance yeast performance in ethanol fermentation. In continuous fermentation using Saccharomyces cerevisiae, microaeration (0–11 mL air/L/h) increased cell concentration from 2.3 to 8.2 g/L and ethanol productivity from 1.7 to 4.1 g/L/h, while ethanol yield improved from 0.37 to 0.45 g/g glucose. However, specific ethanol production rate decreased slightly from 0.75 to 0.5 g/g

cell/h, indicating a shift toward higher biomass formation under oxygen-limited conditions (Ryu-type microaeration studies; supported in recent continuous fermentation literature) [155]. Microaeration has also been reported to improve yeast viability and ethanol productivity in very-high-gravity (VHG) fermentation systems by enhancing membrane lipid synthesis and stress resistance. Optimized oxygen supply conditions result in higher ethanol output compared to strict anaerobic fermentation due to improved cell robustness and cofactor balance [156]. In VHG sweet sorghum fermentation, controlled aeration (0.5–2.5 vvm with optimized timing) increased ethanol production significantly compared to non-aerated conditions, demonstrating that small oxygen doses can improve fermentation efficiency without reducing ethanol yield [157].

Under very-high-gravity (VHG) fermentation conditions, controlled aeration strategies can significantly improve ethanol productivity by promoting the formation of a healthy and metabolically active yeast population. Optimized oxygen supply enhances cell propagation and viability, which subsequently leads to higher ethanol production rates compared to strictly anaerobic conditions [156]. However, excessive oxygen availability can redirect yeast metabolism from fermentative to respiratory pathways. In Kluyveromyces marxianus cultivated in lactose medium, an aeration rate of approximately 0.6 L/min in 250 mL Erlenmeyer flasks (50 mL working volume) resulted in a metabolic shift toward respiration, leading to a biomass concentration of ~17 g/L after 40 h cultivation with no ethanol production detected, indicating complete suppression of fermentative metabolism under oxygen-rich conditions [158].

Agitation plays an important role in maintaining medium homogeneity and, in aerobic or microaerobic systems, ensuring uniform oxygen and nutrient distribution. In very-high-gravity (VHG) fermentation using sweet sorghum juice with Saccharomyces cerevisiae NP01, increasing agitation speed from 100 to 200 rpm significantly improved mass transfer processes, including nutrient uptake into yeast cells and ethanol diffusion out of the cells. This enhancement led to improved sugar utilization and reduced ethanol inhibition effects on yeast cells [159]. However, further increasing agitation beyond 200 rpm did not result in higher ethanol concentration, indicating that fermentation became metabolically limited rather than mass-transfer limited. This suggests that yeast metabolic capacity, rather than mixing intensity, becomes the controlling factor at high agitation conditions in VHG systems [155].

7. Conclusion

This review demonstrates that selective fermentation offers a promising shift from conventional ethanol-focused processes toward value-oriented biorefinery systems. By exploiting the glucophilic behavior of *Saccharomyces cerevisiae*, glucose can be selectively converted into ethanol while preserving fructose as a high-value co-product, thereby redefining residual sugars as valuable streams rather than inefficiencies. Date-based substrates emerge as attractive feedstocks due to their high mixed-sugar content and availability, supporting both resource efficiency and waste valorization. However, a persistent trade-off between ethanol yield and fructose retention, along with limited kinetic modeling and process integration, remains a key challenge for industrial implementation. Future research should focus on optimizing operating conditions, developing predictive models, and integrating efficient downstream separation to enable scalable and economically viable ethanol–fructose biorefinery systems.

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