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Review

Valorization of Spent Brewer's Yeast for the Production of High-Value Products, Materials, and Biofuels and Environmental Application

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Abstract: Spent brewer's yeast (SBY) is a byproduct of the brewing industry traditionally used as a feed additive, although it could have much broader applications. In this paper, a comprehensive review of valorization of SBY for the production of high-value products, new materials, and biofuels, as well as environmental application, is presented. An economic perspective is given by mirroring marketing of conventional SBY with innovative high-value products. Cascading utilization of fine chemicals, biofuels, and nutrients such as proteins, carbohydrates, and lipids released by various SBY treatments has been proposed as a means to maximize the sustainable and circular economy.

Keywords: spent brewer's yeast; high-value products; β-glucans; circular bioeconomy; process sustainability

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1. Introduction

Spent brewer's yeast (SBY) accounts for about 15% of total byproducts generated during beer production [1]. According to available data from Statista [2], 1.86 billion hectoliters of beer were produced worldwide in 2021. It is estimated that 0.00015–0.0003 kg of SBY is produced per hectoliter of beer, resulting in a production of 279,000 to 558,000 kg of SBY in 2021. The Global SBY market was estimated at USD 1289.33 million in 2021, with the average compound annual growth rate (CAGR) of 6.12% from 2021 to 2027 reaching USD 1841.92 million [3]. Considering this, SBY holds a significant economic potential. The trend of increasing valorization of SBY is confirmed by the growing number of reviews on this topic [4–9].

From the chemical point of view, SBY has high protein content, which can be between 45 and 60%. It is also packed with a high content of essential amino acids. SBY contains cca. 32% carbohydrates and 6% fat and is a good source of B vitamins and minerals such as phosphorus, calcium, magnesium, and iron [5,10]. Cell walls of SBY make up 15–30% of the dry matter and are composed of high-molecular-weight molecules (β-glucan, mannoprotein, chitin, and glycogen).

Reintroduction of production residues and byproducts in the production cycle through new and innovative high-value-added products is the backbone of the transition from a linear to a circular bioeconomy [11].

This review presents new scientific data on the valorization of SBY in the production of high-value products, materials, and energy, as well as for environmental protection. Considering that β-glucan is the most promising product that can be obtained from SBY and following requirements of the zero-waste concept, an evaluation of the possibility of

producing β-glucans from SBY in the first cascade, with residues used for biogas production in the second cascade, is suggested. An economic evaluation of the proposed cascade process is carried out as well.

2. Systematic Review Strategy

The strategy for the literature search presented in this paper was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) model of Moher [12].

Literature searches were conducted in academic bibliographic databases and relevant websites (Science Direct, Scopus, Web of Science, and Google Scholar). A combination of search criteria was used to identify literature applicable to this work, with the goal of ensuring consistency, research integrity, and transparency of the completed work. The search criteria were based on keywords, the title and abstract of the paper, the reference list, and the year the paper was published. The protocol of this systematic search is divided into three parts. In Section 1, a systematic review of the literature was conducted to collect all relevant data on yeast species, their characteristics, the chemical composition of SBY, and most common use. In Section 2, a systematic literature review was conducted to collect information on the potential use of SBY in the production of high-value products and environmental protection: (a) production of β-glucan, proteins, acids, and nucleotides; (b) SBY as an agent for encapsulation; and (c) production of biofuels and wastewater treatment. Section 3 provides an overview of the market and prices for high-value SBY products relative to SBY feeds.

3. Brewer's Yeast: Types and Characteristics

During beer production, yeast is used to transform simple sugars derived from malt into alcohol. In brewing, yeasts are conventionally classified into two groups: (a) ale, i.e., top-fermenting (*Saccharomyces cerevisiae*), and (b) lager, i.e., bottom-fermenting (*Saccharomyces pastorianus* var. *carlsbergensis*) yeasts [13].

The use of yeasts other than *Saccharomyces* opens the possibility of developing a wide range of beer aromas and flavors, which affects the organoleptic profile of the beer and allows for a variety of beer styles on the market. However, the limitations of using alternative yeasts are evident in the different fermentation characteristics and the impact on the quality and consistency of the beer in the form of beer cloudiness, problems with viscosity, filtration, and possible off-flavors [13]. It is well known that the type of yeast strain used in beer production significantly affects the process itself, including fermentation time and, ultimately, the chemical composition of the produced beer. In this regard, special attention is paid to craft beers, which can have various colors and flavors, for which the type of fermentation and the selected yeast are of great importance [14]. At the end of fermentation, yeast is separated from the rest of the contents by flocculation, during which the yeast cells form flocs, which then rise to the surface (top fermenting) or settle to the bottom of the vessel (bottom fermenting). It is very important for yeast to have good flocculation properties so that it can be used multiple times during fermentation. At the industrial scale, this ensures certain economical saving. A small amount of yeast from the previous fermentation is used to start the next fermentation in a process known as re-fermentation. Although the recycling of brewer's yeast in the new fermentation cycle is a common practice, the number of reuses is limited to maintain the quality of the beer. SBY that can no longer be used for beer production therefore ends up as waste, and the amount of this waste depends on the brewery's practice, i.e., the number of times it is reused [5,15–17].

The demand for different craft beers in terms of sensory and aromatic characteristics can be satisfied by using different yeasts and fermentation temperatures [18]. Table 1 shows the use of different commercial yeast types for the production of craft beers, the origin of the yeast, the degree (attenuation) and temperature interval of fermentation, and the ability to flocculate.

Table 1. Various types of yeast, their important properties for brewing beer, and the type of beer *.

Type of Beer	Species	Attenuation	Fermentation Temperature	Flocculation
American Ales (Pale Ale, IPA, NEIPA, Porter, and Stout)	*Saccharomyces cerevisiae*	73–77%	16–22 °C	Low to Medium
United Kingdom Ales (Bitter, Pale Ale, IPA, Porter, and Stout)	*Saccharomyces cerevisiae*	67–71%	18–22 °C	High
German Kölsch	*Saccharomyces pastorianus*	73–77%	13–21 °C	Low
German Wheat	*Saccharomyces cerevisiae*	70–76%	18–24 °C	Low
German Alt	*Saccharomyces cerevisiae*	73–77%	13–20 °C	Low
Bohemian Lager	*Saccharomyces pastorianus*	70–74%	10–14 °C	Medium to High
German Lager	*Saccharomyces pastorianus*	73–77%	7–20 °C	Low to Medium
Belgian Abbey Ale	*Saccharomyces cerevisiae*	74–78%	18–26 °C	Medium
Belgian Sour (Lambic, Gueze, and Flanders Red)	*Brettanomyces bruxellensis*	78–84%	16–24 °C	Medium
Belgian Wit	*Saccharomyces cerevisiae*	72–76%	17–24 °C	Medium

* The data in the table were collected from the website of Wyeast Laboratories (2022) [19].

Chemical Composition of Spent Brewer's Yeast

The chemical composition of SBY depends on many factors: the used strain itself, process conditions during fermentation and overall brewing process, the number of yeast reuses, and the process of separating the yeast from the mass [5,17].

SBY is a high-protein product, with an average protein content of 40–45% [4,20–22], but it can also reach 74% [23]. The high protein content is followed by a rich amino acid composition, especially glutamic acid and aspartic acid, known as flavor-enhancing amino acids [5]. Total carbohydrate content in SBY varies from 12.9 to 59% [4,24]. Lipids are present in lower amounts of 0.67–1.45% [20,23]. Of the fatty acids, palmitic and oleic acids are the most abundant [25]. The share of ash ranges from 1.74 to 14.53% [20,26], resulting in a rich composition of macro- and microminerals, of which phosphorus, potassium, and sodium are the most abundant, followed by magnesium, calcium, and zin [23–25]. SBY is rich in vitamins, especially those of the B group, of which B7 is the most abundant, followed by B3, B6, and B5 [23,24]. Of the polyphenolic compounds, naringin is present in the highest concentration, as well as catechin and gallic acid [24,27]. SBY also contains RNA at levels ranging from 1.90 to 12% [17,25].

The chemical composition of SBY is given in Table 2, presented as minimum and maximum value of the results exported from the literature.

Table 2. Chemical composition of SBY expressed as the minimum (min) and maximum (max) of the results taken from the literature.

Compound ($\%_{DW}$ *)	Min–Max Values	References
Crude protein	40.00–74.30	[4,20–26,28]
Total sugars	37.80–43.50	[21,28]
Ash	1.74–14.53	[20–26,28]
Total carbohydrates	12.90–59.00	[4,20,23–25]
Lipids	0.67–4.64	[4,20,23–26]
Fibers	4.31–6.60	[21,26]
RNA	1.90–8.12	[21,23–25]

Table 2. *Cont.*

Compound ($\%_{DW}$ *)	Min–Max Values	References
Amino acids (g/100 g protein)		
Lysine	2.93–6.73	[24–26]
Leucine	3.51–8.75	[24–26]
Isoleucine	3.23–5.37	[24–26]
Threonine	2.60–6.09	[24–26]
Tryptophan	0.00–0.96	[24–26]
Valine	4.94–6.07	[24–26]
Histidine	2.78–11.9	[24–26]
Methionine	2.28–3.12	[24–26]
Cysteine	1.24–2.19	[24–26]
Tyrosine	2.15–4.12	[24–26]
Glutamic acid	8.56–15.00	[24–26]
Aspartic acid	5.98–11.98	[24–26]
Serine	4.60–5.75	[24–26]
Proline	2.65–5.11	[24–26]
Alanine	6.89–9.29	[24–26]
Glycine	3.69–5.23	[24–26]
Arginine	4.02–6.00	[24–26]
Asparagin	2.00	[24]
Glutamine	3.13	[24]
Phenylalanine	3.01–5.57	[24–26]
Fatty acids (%biomass lipid fraction)		
Caprylic	0.29	
Capric	6.26	
Lauric	1.26	
Myristic	0.78	
Myristoleic	0.39	
Palmitic	34.33	[25]
Palmitoleic	2.99	
Stearic	9.56	
Oleic	11.02	
Linoleic	4.37	
Linolenic	0.63	
Polyphenols (mg/g_{DW})		
Gallic acid	0.23–0.55	[24,27]
p-coumaric acid	0.03–0.34	[24,27]
Rutin	0.06–0.10	[24,27]
Ferulic acid	0.05–0.09	[24,27]
Naringin	0.66	[24,27]
Quercetin	0.01	[24,27]
Kaempferol	0.03	[24,27]
Protocatechuic acid	0.13	[24]
Catechin	0.59	[24]
Cinnamic acid	0.01	[24]
Elements ($mg/100\ g_{DW}$)		
Phosphorus	17.31–3213.60	[23,25]
Potassium	14.21–9148.00	[23–25]
Sodium	9.13–1228.00	[23–25]
Magnesium	9.13–1228.00	[23–25]
Aluminum	3.02–695.50	[23,25]
Calcium	0.75–1.12	[23–25]
Iron	0.87–27.10	[23–25]
Selenium	0.03–25.12	[24,25]

Table 2. *Cont.*

Compound ($\%_{DW}$ *)	Min–Max Values	References
Elements (mg/100 g_{DW})		
Manganese	0.56–14.98	[23–25]
Lead	10.11	[25]
Chromium	0.02–9.05	[24,25]
Nickel	8.23	[25]
Lithium	6.13	[25]
Zinc	4.89–22.59	[23–25]
Copper	0.36–7.84	[23–25]
Vanadium	0.56	[25]
Cadmium	0.45	[25]
Cobalt	0.03–0.07	[24,25]
Molybdenum	0.003	[24]
Boron	0.64	[23]
Barium	0.35	[23]
Strontium	1.07	[23]
Vitamins (mg/100g_{DW})		
Nicotinic acid (B3)	77.20–94.19	[23,24]
Pyridoxine (B6)	4.86–55.10	[23,24]
Folic acid (B9)	3.01–4.52	[23,24]
Riboflavin (B2)	0.33–2.16	[23,24]
Cyanocobalamin (B12)	0.18–0.26	[23,24]
Thiamine (B1)	6.88	[23]
Pantothenic acid (B5)	20.36	[23]
Biotin (B7)	113.92	[23]

* dw—dry weight.

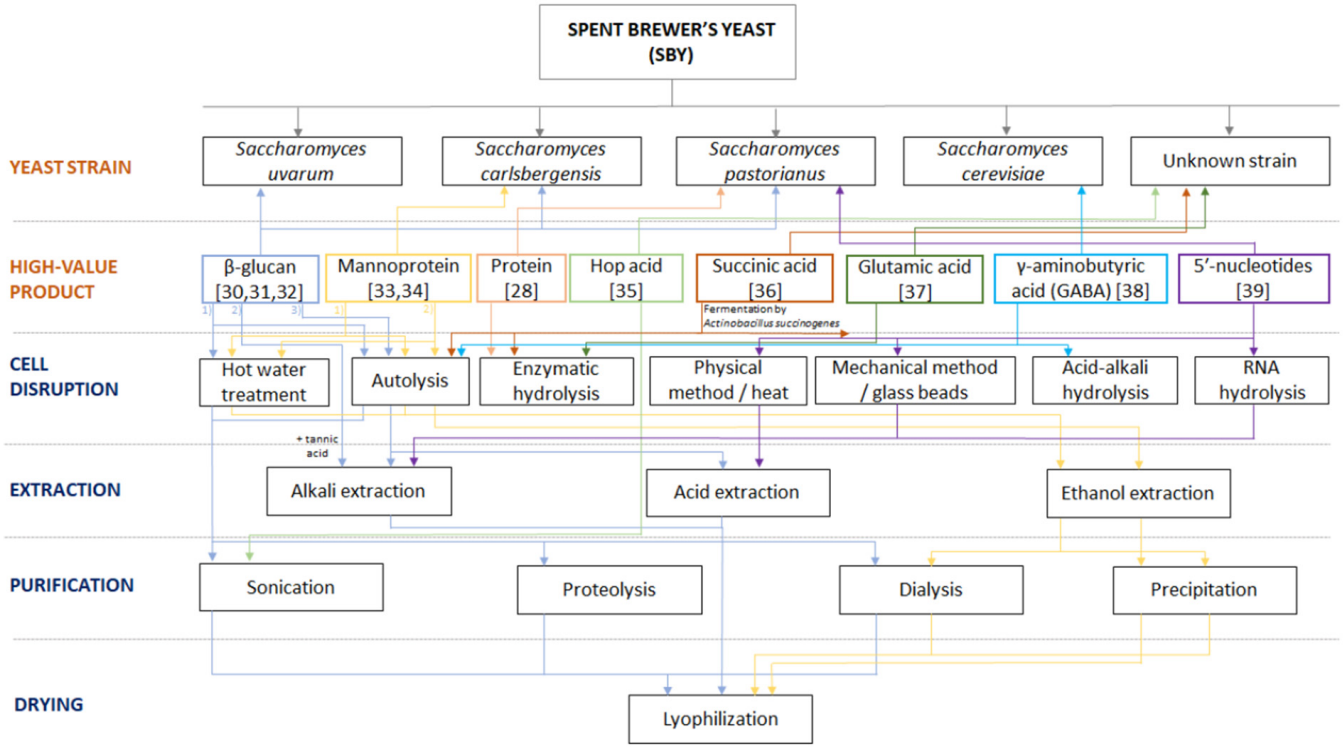
4. Valorization of Spent Brewer's Yeast

SBY is traditionally sold to farmers as a feed supplement and serves as a good source of protein, vitamins, and minerals. It can be applied in fresh, liquid, or dried form. Prior to being used in feed preparation, yeast should be inactivated by heat with the addition of organic acids to prevent serious gastrointestinal problems in pigs. In combination with brewer's spent grain, it has a positive effect on increasing egg production and quality, as well as fertilization efficiency and hatchability, when used as feed for turkeys and chickens [1]. A drawback for wider application of SBY as feed is its microbioactivity, which alters the feed composition during storage over time [29].

In addition, SBY can be used for the production of functional nutrients for human nutrition. As a good source of protein and essential amino acids, it is used in the development of new foods and dietary supplements rich in B vitamins, minerals, and polyphenolic compounds with antioxidant activity. Some examples of such products and supplements containing SBY are cooked ham, low-calorie mayonnaise, meat substitutes, yogurt, vegetable juices, toast spreads, soups, and ready-to-eat meals [5,10]. Nucleic acids limit the use of SBY in human nutrition, as their content can be up to 12% of dry weight, which is above the safety limits of 1–3% of dry weight [17].

4.1. Emerging Trends in the Use of Spent Brewer's Yeast

Emerging trends in the use of SBY involve (a) isolation of polysaccharides (especially β-glucans), proteins, and nucleic acids; (b) use in the development of encapsulation processes; (c) energy production (biogas and bioethanol production); and (d) environmental application (wastewater treatment). High-value compounds obtained from SBY and the associated production processes are shown in Scheme 1 and supported by a detailed description in the Supplementary Material in Table S1 [28,30–39].



Scheme 1. Production of high-value products from SBY [28,30–39].

To extract high-value products, SBY needs to be pretreated. The yeast cell wall can be broken down by physical, chemical, and enzymatic methods. Physical processes include mixing with glass beads, high-pressure or ultrasonic cavitation, and thermolysis. Chemical processes are carried out by alkalis, acids, surfactants, detergents, and various organic solvents. Chemical methods make the cell wall semipermeable, which allows the passage of intracellular products. These methods are complex and provide low efficiency and low economical cost effectiveness. They often affect the biologically active compounds as well. Yeast autolysis, which is commonly induced by adding chemicals or subjecting the cell to a radical change in temperature, is classified as an enzymatic method. Solvents (e.g., ethyl acetate) and salts (NaCl) are often added to increase the efficiency. In autolysis, endogenous yeast enzymes such as glucanases are activated and help to break down the cell wall, causing rupture. The addition of exogenous enzymes (proteases) is also possible because their catalytic action causes the release of components from the cell wall in a more controlled and efficient manner [17,40]. The SBY cell disruption method generally depends on the target substances that need to be extracted/isolated from the yeast cell and partly on the efficiency of the method itself, which depends on the working parameters of the implementation [41].

4.1.1. β-Glucans

The majority of research in the field of utilization of SBY is related to the isolation of β-glucans.

Yeast-isolated β-glucans are safe for oral use and designated as GRAS (generally recognized as safe). There are two types of β-glucans in the yeast cell wall: β-1,3 glucan and β-1,6 glucan. β-1,3 glucan comprises about 50% of the cell wall, while β-1,6 glucan makes up the remaining 10%. β-1,3 glucan is responsible for the mechanical and structural properties of the yeast cell wall. β-1,6 glucan enhances the macromolecular structure of the yeast cell wall because it binds β-1,3 glucan to chitin and mannoproteins, making the yeast cell wall insoluble [42].

β-glucans have been associated with many human health benefits, including prebiotic, anti-inflammatory, antidiabetic, anticancer, and immunomodulatory effects [5,43].

β-glucans are used in the food industry as thickeners, water-retention or oil-binding agents, and emulsion stabilization agents. Yeast β-glucans can be used to partially replace fat in mayonnaise, resulting in increased moisture content with a significant reduction in caloric value. However, they can cause negative sensory properties in mayonnaise [44]. Enrichment of yogurt with β-glucan can greatly affect the gel formation, which significantly reduces the fermentation time and allows for the potential use of β-glucan as a thickener [45]. Techniques such as homogenization and spray drying after autolysis and extraction of SBY increase the β-glucan yield. It is possible to achieve higher viscosity, water retention capacity, and emulsion stabilization ability compared to commercial products [46]. The commercial or industrial production of β-glucan is based on the use of edible cereal crops such as wheat, rye, and oats and relies on chemical methods that simultaneously threaten the environment and global food consumption. For this reason, the production of β-glucan from microbial sources is considered an excellent alternative due to its seasonality, efficiency, and sustainability. The biological properties of β-glucan depend on the source (fungi, bacteria, algae, or cereals), structure, degree of solubility, formation of conformation in solution, molecular weight, and polymer charge [47]. The immune activity of β-glucans can be increased by simple chemical (phosphorylation or carboxylation) and physical (purification and drying) modifications. The combination of carboxylation and air drying is known to result in high-quality extraction and increased immune activity of β-glucans from SBY [48]. In animal species, the consumption of β-glucan plays an important role in the adsorption of mycotoxins that accumulate in animal feed. The structures of β-glucan and mycotoxin complement each other, as the hydroxyl group on the intermolecular hydrogen bond of β-(1→3)-glucan forms a chemical complex with the hydroxyl group of the mycotoxin, the ketone group, or the lactone group, thereby reducing toxicity [49].

4.1.2. Proteins, Peptides, and Amino Acids

SBY contains 45–60% protein, including the essential amino acids [28]. SBY extracts contain a high proportion of amino acids known as flavor enhancers (glutamic acid, aspartic acid, glycine, and alanine). The concentration of free amino acids in the extract makes an important contribution to the aroma of beer. Leucine, isoleucine, valine, histidine, proline, cysteine, and glutamine are known to greatly affect the flavor of food products as well. The amino acid composition indicates whether the protein fraction of SBY extract can be potentially suitable for use in the food industry as an ingredient in protein-rich dietary supplements [17,24]. Additionally, yeast proteins have hydrophobic properties that correlate with potential antihypertensive and antioxidant effects; therefore, such extracts can be considered a source of IACE peptides (angiotensin-converting enzyme (ACE) inhibitory peptides). The correlation between the structure and activity of different IACE peptides indicates that enzyme binding is affected by the C-terminal tripeptide sequence of the substrate. Tripeptides and tetrapeptides identified in SBY extract, which contains a high proportion of hydrophobic amino acids (tyrosine, proline, and tryptophan) as C-terminals, can contribute to the binding affinity of peptides to angiotensin-converting enzymes (ACEs). IACE peptides have a low molecular weight and contain 2–12 amino acids. They are commonly produced by enzymatic hydrolysis of SBY and can be added to the diet for hypertension prevention. The antioxidant activity of peptides is closely related to several factors: their amino acid constituents, the sequence of amino acids, hydrophobicity, and the presence of amino acids with an aromatic ring (tyrosine, tryptophan, phenylalanine, and the imidazole group of histidines) [50]. Proteins and peptides from SBY can be used as emulsifiers and carriers in the microencapsulation of sunflower oil, and their concentration can be increased by applying ultrafiltration [51]. Protein and amino acid production using autolysis improves yeast extract production, and two-step autolysis increases amino acid yield by 25% [40].

4.1.3. 5′-Nucleotides

Spent brewer's yeast is known to be a good source of nucleotides due to its high content of RNA, which makes up 8–12% of dry matter. Moreover, certain nucleotides, especially 5′-monophosphates, are recognized as flavor enhancers. During autolysis, endogenous enzymes break down nucleic acids into nucleotides, producing 5′-nucleotides (71–88% RNA). They can be partially hydrolyzed by the addition of enzymes, usually with 5′-phosphodiesterase. Different processing methods can result in a wide range of flavor compounds in SBY as a result of interactions between amino acids, nucleotides, carbohydrates, and peptides. Yeast extracts rich in 5′-nucleotides are widely used in the food industry, mimicking meat or "umami" flavors. These flavors are created by the synergistic action of 5′-nucleotides, glutamic acid, and cysteine. The capacity of glutamate to improve taste increases by 10–15 times if 5′-nucleotides are added [5,39].

4.1.4. Acids

SBY hydrolysate has been proven to be a good source of nitrogen for the production of succinic, GABA, and lactic acids. Succinic acid is a four-carbon dicarboxylic acid used as a building block in the synthesis of valuable products and special chemicals. It is used as a raw material for the production of 1,4-butanediol, tetrahydrofuran, *N*-methyl pyrrolidinone, 2-pyrrolidinone, and gamma-butyrolactone and for the preparation of biodegradable polymers such as polybutylene succinate and polyamide. Currently, succinic acid is mainly chemically produced from *N*-butane via maleic anhydride, a petroleum-based material. The production of succinic acid from fossil sources is expensive and causes serious environmental pollution problems. Current research is focused on its production from renewable sources such as SBY. Enzymatic hydrolysate of SBY with the addition of biotin is used as a source of nitrogen for the production of succinic acid by the bacterium *Actinobacillus succinogenes*. This process has proven to be more cost-effective than the oil-based production process [52,53]. Furthermore, during autolysis, with the addition of glucose and monosodium glutamate, large amounts of glutamic acid and vitamin B6 can be produced from SBY and further used for the synthesis of GABA [38]. This neuroactive non-protein amino acid has a strong bioactive effect; regulates blood pressure; and protects against cardiovascular disease, hormonal disorders, and diabetes [54]. Lactic acid can be produced via chemical synthesis and fermentation from renewable sources, whereby the extract of SBY can be used as a source of nitrogen. In recent years, lactic acid has become an important raw material for biopolymer production and is also used in the pharmaceutical, food, textile, leather, and chemical industries [55].

4.1.5. Material Production

Yeast cells are considered an ideal applicable material for encapsulating bioactive compounds due to their protective barrier properties, especially the cell wall and plasma membrane [56]. Encapsulation is a process in which a bioactive compound is wrapped in a shell to form capsules. It is used to preserve bioactive substances and reduce their evaporation, avoid incompatibilities between the components of the packed mixture, and change the physical properties of the original substances. There are various types of encapsulations, such as spray drying, freeze drying, extrusion, emulsification, coacervation, molecular inclusion, and ionic gelation. Their selection depends on the substance to be encapsulated and the wall material that can be used, as well as the desired properties of the capsules [57].

SBY cells are used for microencapsulation of sunflower oil and the encapsulation of probiotic bacteria and ascorbic acid. Sunflower oil is considered unstable due to its high content of polyunsaturated fatty acids. Protein hydrolysate of SBY is used as a carrier material in oil microencapsulation for the purpose of protection against oxidation [51]. Heat treatment of SBY results in Maillard reactions, i.e., reactions between reducing sugars and amino acids, with the formation of Maillard reactions products. They can improve the functional properties of proteins, such as solubility. After Maillard reactions, SBY

hydrolysates can be used for encapsulation of ascorbic acid by spray drying, which ensures their stability and the possibility of wide use in the food industry [5,21].

Furthermore, SBY in combination with an aqueous extract of Damascus rose (*Rosa damascena*) can be used to synthesize silver nanoparticles. This process is based on the reduction of metal cations by natural reducing agents, such as microorganisms, plant extracts, and waste materials [58]. Silver nanoparticles have unique optical and antibacterial properties, which are the basis for obtaining improved biosensors, catalysts, and antimicrobials [59].

4.1.6. Biofuel Production and Environmental Application

SBY can be used in the production of biofuels (biogas and bioethanol) and in wastewater treatment processes. The production of biogas from SBY as an energy substrate in a batch reactor for anaerobic digestion sequencing is an effective way to replace natural gas. This technology can replace up to 50% of natural gas and significantly reduce costs and required energy resources in the process of gas production [60]. Furthermore, SBY can be used as a source of nutrients for bacteria in ethanol production. Supplementation of corn slurry with SBY positively affects the rate of ethanol production and shortens the time required for full utilization of sugar [61].

Significant concentrations of platinum metals accumulate in wastewater over the years, but their removal and recovery are very complex and limited due to physicochemical characteristics. The adsorption method has proven to be very efficient and economical since platinum-group metals interact with the nitrogen or amine ligands of the adsorbent. The use of SBY as a functionalized zeolite for the recovery of Pd (II), Ir (III), and Rh (III) from industrial wastewater has proven to be very effective, owing to the nitrogen groups of yeast, as well as its non-toxic, hydrophilic, and biocompatible characteristics [62].

5. Potential Processing Flow of the Main Components of Spent Brewer's Yeast Cells

The yeast cell wall consists of 50–60% β-glucans, 35–40% mannoproteins, 1–3% chitin, and 1–23% glycogen. Glycogen is composed of glucose molecules interconnected with α-(1→4) glycosidic bonds, and the chains are interconnected with α-(1→4,6)–glycosidic bonds. Glycogen can bind to β-glucan's covalent bonds, forming α- and β-glucan complexes. Mannoproteins mainly consist of mannose residues (89–96%), which form a branched, short-chain structure linked by 1,2,-1,3-, 1,4-, and 1,6-α-linkages [63,64]. Chitin is a linear reinforcing polymer of the yeast cell wall consisting of β(1→4)-linked *N*-acetylglucosamine residues [4]. The molecular organization of the yeast cell wall consists of several interconnected layers: on the outside of the wall are 1,6-β-glucans, to which mannoproteins are bound, and inside the network of 1,3-β-glucans are chitin chains [64]. In the cell, β-glucan synthesis takes place in the plasma membrane and is enzymatically catalyzed by glucan synthase (uracil diphosphate glucose (UDP-glucose); 1,3-β-D-glucan 3-β-D-glucosyltransferase; EC 2.4.1.34). The degree of polymerization of β-1,3-glucan depends largely on extrinsic factors and is achieved via two synthetic pathways associated with the growth phase and carbon source [4]. A series of mannoproteins in the yeast cell wall forms mannan, the fibrous outer layer of the wall. Oligosaccharide proteins undergo two types of modifications, with O-mannosylated proteins acquiring α-mannosyl bonds and *N*-glycosylated proteins acquiring *N*-glycosidic bonds. Chitin synthesis occurs through the action of three chitin synthases (EC 2.4.1.16, Chs1, Chs2, and Chs3) that deposit chitin at different sites at a particular time in the cell cycle [65]. Glycogen synthesis occurs through the activity of the enzyme glycogenin, a glycogen synthase (EC 2.4.1.11) that catalyzes mass synthesis, and a branching enzyme [66].

Effective removal and utilization of intracellular compounds require effective cell wall treatment methods. Different methods to destroy yeast cells have different effects on product content. Each method used during destruction and extraction has an impact on the efficiency of purification of isolated products from SBY [67]. At the beginning of SBY processing, it is necessary to destroy the cells and extract products by various chemical, physical, and enzymatic methods.

5.1. β-Glucan Production

The isolation and production of β-glucan begins with the destruction of the yeast cell wall by physical, chemical, and enzymatic methods. The use of a ball mill is one of the most effective methods for physical destruction of the yeast cell wall. Destruction of yeast cells in a ball mill is caused by compaction or shear stress, whereby energy is transferred from the balls to the cells. Cell destruction in a high-pressure homogenizer occurs when the suspension is forced through a homogenizing nozzle or valve under high pressure. When the suspension is processed in a high-pressure homogenizer, it is subjected to a high shear force, resulting in the formation of a fine homogenate [68,69]. The problem of low solubility of β-glucan has led to the development of chemical modifications to improve the solubility of the cell wall. The outer wall of yeast cells can be permeabilized by a number of chemical compounds, such as potassium hydroxide, sodium hydroxide, ethanol, petroleum ether, *N*-lauryl sarcosine, etc. Autolysis is one of the most commonly used methods, which can cause the destruction of yeast cells by their own enzymatic mechanisms at a temperature of 50–55 °C for several hours. External enzymes such as hydrolases, β-1,3-glucanases (lytic and non-lytic, EC 3.2.1.6), proteases (EC 3.4.21.112), β-1,6-glucanases (EC 3.2.1.75), mannanase (EC 3.2.1.78), or chitinase (EC 3.2.1.14), can also be used to destroy yeast cells. During destruction, the enzymes act synergistically. Enzyme methods have the advantage over other methods, as enzymes are specific and selective and enzymatically catalyzed reactions occur under mild process conditions (temperature and pH). However, the high cost of commercial enzymes remains a major barrier to the use of this process on a larger scale [4,69].

Extraction of β-glucan is carried out after the cell wall destruction process. Solvent selection is a key factor in successful extraction [70], and alkalis and acids are mostly used. Alkaline extraction is performed in several steps, usually using NaOH at high temperatures (90 °C). Alkaline extraction removes proteins, lipids, and nucleic acids. To obtain the highest yield and purity of β-glucan while dissolving mannoprotein and glycogen, acid–alkali extraction with a combination of NaOH, HCl, CH_3COOH, NaClO, and DMSO is used. High-pressure homogenization is used in the extraction of β-glucans for the purpose of separating the homogenized liquid phase (extract) from insoluble polysaccharide fragments (solid phase). The emergence of new green trends in β-glucan extraction suggests the use of ionic liquids and supercritical fluid extraction. The mutual combination of the abovementioned methods improves extraction efficiency and increases the purity of β-glucan [4].

After extraction, insoluble β-glucans from yeast are subjected to various purification methods [4]. The degree of purity of β-glucan isolated from SBY must be above 80%, with the following specifications: ash <2%, moisture <6%, protein <4%, and total fat <3%. The maximum permissible limits of heavy metals are lead <0.2 mg/kg, arsenic <0.2 mg/kg, mercury <0.1 mg/kg, and cadmium <0.1 mg/kg [71]. The aim of β-glucan purification is to remove mannoproteins and achieve β-glucan solubility at a neutral pH. Purified β-glucans are obtained by sterilization, enzymatic treatment with proteases, high-pressure homogenization, ultrasonic methods, or continued alkaline extraction. Most often, purification takes place with a combination of several methods. By combining alkaline treatment with high pressure, it is possible to achieve a final purity of β-glucan of 78.11% [4].

The choice of drying method is very important for the particle size of the final product, as well as its structure and biological activity. The most commonly used drying methods are air drying, spray drying, and lyophilization [4]. Spray drying is carried out at high temperatures, resulting in low water activity in β-glucans. The physicochemical properties of β-glucans mainly depend on the flow rate, particle size, viscosity, inlet and outlet spray-drying temperature, pressure, and type of nebulizer. By applying a combination of ultrasonic methods and spray drying, the original microstructure of β-glucan can be conserved [72]. Spray drying retains the biological activity of β-glucans to a greater extent and has an advantage over air drying and lyophilization, which cause agglomeration and changes in microtexture. During the lyophilization process, water is frozen and removed as a solid by sublimation, and the particles of lyophilized β-glucans are irregular in structure

and compressed into layers like sheets with a porous surface. Drying in air takes place at room temperature and results in larger, granular β-glucan particles [73].

5.2. Mannoprotein Production

The heterogeneity of the mannoprotein structure is a major challenge for its isolation. Therefore, isolation is usually performed by a combination of various methods of cell disruption and extraction with the aim of separating mannan and mannoprotein from glucan and other components of the yeast cell wall. Chemical methods using alkaline solutions (NaOH); buffers such as Tris, citrate, and phosphate buffers; and detergents (sodium dodecyl sulfate) are mostly used. Biological methods include autolysis and enzymatic hydrolysis of SBY with proteases, glucanases, and carbohydrases. Physical and mechanical methods include treatment with glass beads, temperature, and pressure. Successful isolation under mild conditions is necessary to preserve the proteins and prevent their denaturation. This can be achieved by biological methods, which are often very expensive due to the use of commercial enzymes, the cost of which can be reduced by immobilizing enzymes. Thermal hydrolysis has also led to successful isolation results, although careful choice of mass and volume ratios is required due to energy and water consumption [74–76].

The most common conventional form of purification of mannoproteins is precipitation with solvents such as ethanol, methanol and acetone, Fehling's solution, and Benedict's solution. Purification can be performed immediately after extraction by adding a solvent, and the precipitate is separated after centrifugation. To improve the success of the process, precipitation is carried out in two phases. Other purification methods include ultrafiltration, dialysis, and size- and affinity-based chromatographic methods. Freeze drying is most commonly used to dry products [75,76].

5.3. Chitin Production

The presence of intramolecular and intermolecular hydrogen bonds contributes to the crystalline structure of chitin and its low solubility, which limits its use [77]. Isolation of chitin begins with destruction of yeast cells by chemical methods using a buffer (Tris-HCl buffer) and mechanical methods in a homogenizer with glass beads. It is important to ensure that endogenous glucanases and proteases released during cell destruction are inhibited by phenylmethylsulfonyl fluoride under specific pH and temperature conditions. The most common methods are alkaline extraction with NaOH for solubilization/deproteinization of cell wall components and acid extraction with acetic acid. Extraction is followed by centrifugation, whereby the precipitate is separated and resuspended in HCl, neutralized with NaOH, dialyzed, and then lyophilized [78]. Phosphate buffer solution can be used to remove residual proteins, while acetone is used to remove lipids. A deionized water rinse is performed to wash away residual chemicals from the yeast cell wall treatment. Improvement in solubility and isolation of chitin can be achieved by its deacetylation to chitosan using enzymatic methods with chitin deacetylases (EC 3.5.1.41), chitinases (EC 3.2.1.14), and chitosanases (EC 3.2.1.132) [79].

5.4. Glycogen Production

The cell wall of yeast contains two forms of glycogen: soluble intracellular glycogen and insoluble glycogen bound to the cell wall. This fact must be taken into account when isolating the desired form of glycogen as a product. Glycogen forms multibranched, large granules, which makes extraction difficult. To achieve complete isolation and recovery of the final product, a combination of isolation methods is required. Most often, this involves alkaline extraction at high temperatures (100 °C) with KOH and NaOH, separating the soluble and insoluble fractions after centrifugation. The insoluble fraction is treated enzymatically with amyloglucosidase to isolate insoluble glycogen and remove sugars. The soluble fraction is subjected to acid hydrolysis with H_2SO_4 or CH_3COOH to separate

carbohydrates and isolate soluble glycogen. The soluble fraction can also be treated enzymatically after acid hydrolysis [80,81].

6. Economic Perspective of Cascade Use of Spent Brewer's Yeast

The economic perspective of circulating SBY as biobased product(s) in the economy depends on whether knowledge to reach the peak of the bioeconomy product pyramid is available and whether the investment is offset by the quantity and price ratio of the product on the market. While conventional valorization of SBY as feed allows for marketing of close to the total quantity of the input material dry matter, extraction of high-value products allows for the marketing of only a minor portion of the starting volume (labeled as green in Figure 1). Considering cascading use of remaining biomass reduces the novel biobased product price for landfilling cost.

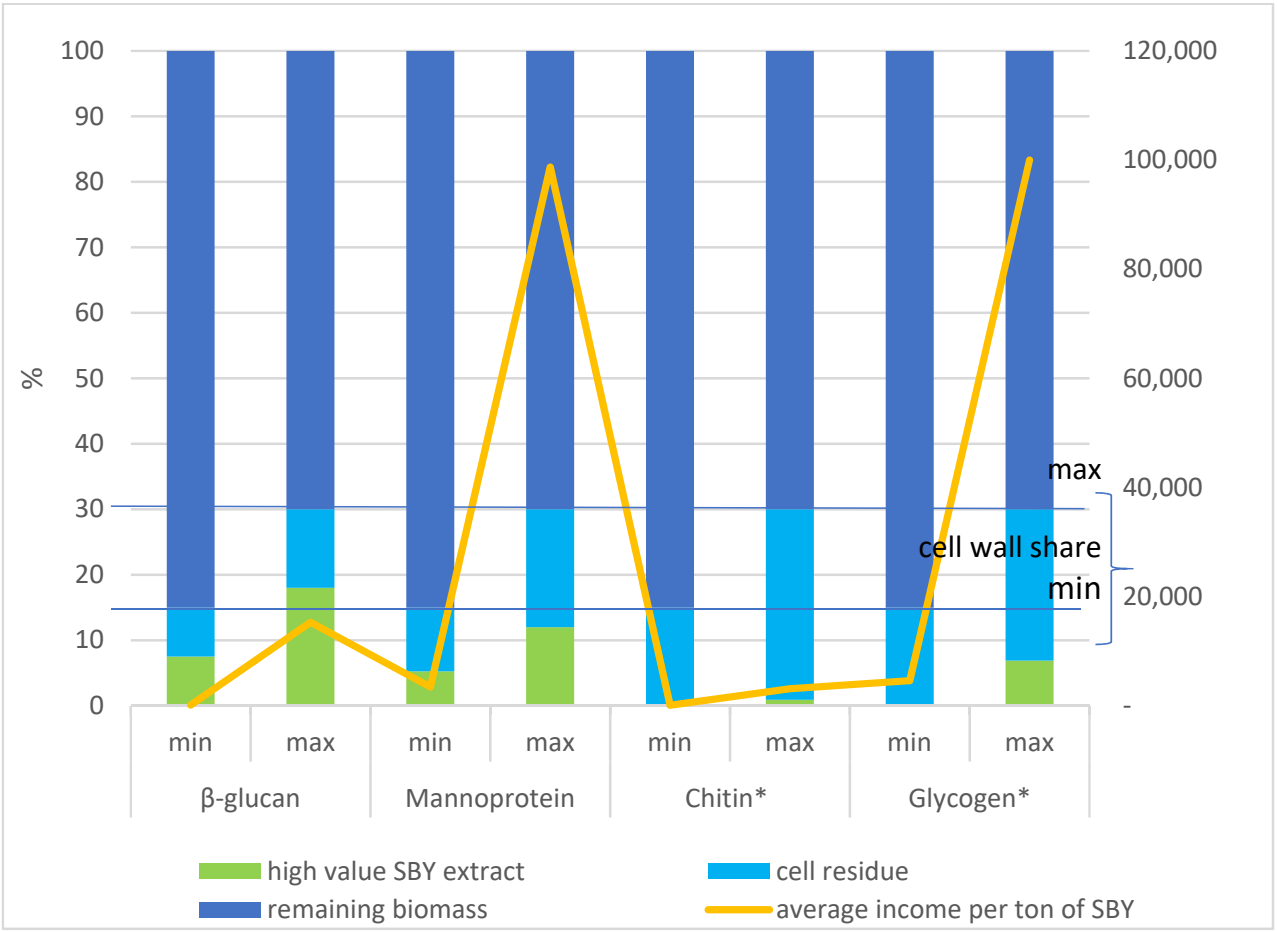


Figure 1. Overview of the marketable share of the total SBY as high-value bioproducts. * SBY chitin and glycogen have not been detected on the market; prices are based on those available on the market and are not discriminated by source.

To position the price difference between conventional (feed) and innovative (high-value extracts) products, wholesale Internet markets were screened (Table S2, [82–93]) to determine the average income per dry-matter ton of SBY (Figure 2), assuming equal production costs. While acknowledging that market prices follow dynamics of demand and supply, constrained by the availability of resources and the next best alternative, Figure 2 provides information about differences in indicative incomes from different SBY products per unit of SBY, with the upper limit (assuming the full extraction rate of the high-value compound). This information can be used to create a shortlist of innovative high-value products to be assessed in a more detailed technoeconomic analysis.

Figure 2. Indicative income ratios of high-value products per dry-matter ton of SBY in comparison to feed. * Glycogen from SBY was not detected in the market search.

Notably, economies of scale are the first handicap in the extraction of high-value bioactive compounds from SBY. The trading unit on the feed market is tons; β-glucan and mannoprotein are traded in kilograms, while chitin and glycogen are traded in grams. Cascading use was investigated, with β-glucan as illustrative example, as the most commercially advanced high-value biocompound among those considered (Table S1).

Research suggests [94–96] degradation of the cell walls of biomass by various thermochemical processes allows for more access to nutrients for methanogenic bacteria and could be used as a pretreatment for enhanced biogas production. In order to test the feasibility of cascading extraction residues, a 377 Nm3 t-1 of methane yield [97] or 13,500 MJ is assumed. Each of the extraction treatments for β-glucan (Table S1) are related to heat consumption that could be supplied internally from anaerobic digestion of the remaining part as the next cascade. Heat demand for extraction processes accounts for 1–3% of the total primary energy supplied from biogas (Table S3), which allows for the assumption of the feasibility of combining renewable energy production from remaining biomass with fine chemical production. Anaerobic digestion could serve as a cascade to ensure energy demand, not only for the heating process but also for electricity supply if an economy of scale is achieved. Micro- and macrominerals originally present in SBY are still available in the fermented mass or digestate. Depending on the pretreatment and final chemical composition of the digested SBY, the digestate could be used either as a soil enhancer or compost, closing the circle of nutrients as the last cascade. The suggested business model illustrated for β-glucan, including the valorization of SBY, represents a circular and sustainable business case, with maximum valorization of biomass through three cascades and achieving full circularity with zero waste. Innovative valorization of SBY for extraction of high-value compounds could find its market competitiveness faster in cascading use than through production in a linear business model. Further research is needed to optimize the high-value product extraction process, considering desirable properties for anaerobic digestion of the remaining biomass to achieve higher biogas yields.

7. Conclusions

SBY is a byproduct of the brewing industry with a valuable chemical composition for the sustainable production of a variety of products. It has great potential for the production of high-value products, new materials, and biofuels. It can also be used in environmental applications. High-value products from SBY form the basis for new global trends but require further research for industrial applications. Various mechanical, chemical, and/or biological methods of SBY processing need to be applied to provide high-quality products of global market interest, of which β-glucans are the most interesting.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/fermentation9030208/s1, Table S1: Production of high-value products from spent brewer's yeast; Table S2: Price ranges of various SBY products; Table S3: Heat energy demand for extraction processes in relation to biogas primary energy supply per ton of SBY dry matter.

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