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Review Article

Emerging Trends and Advancements in the Processing of Dairy Whey for Sustainable Biorefining

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Increased milk production has boosted the market of milk-driven products, and as a result, the by-product production has also increased, which is a challenge to dispose of. Whey, a cheese by-product, is also increasing yearly, and its disposal in water bodies is responsible for water pollution and thus is an issue for the dairy sector. In this context, extensive research has been going on to valorize this by-product and create alternative ways to remove the organic load in whey rather than disposing of it. Recently, exciting developments have been made to convert whey into value-added commodities such as biofuels (bioethanol, biodiesel, and biohydrogen), bioplastics, bacterial cellulose, food colors and flavors, bioprotective solutions, bioactive peptides, and single-cell proteins. In this review, we aim to comprehend the recent developments and challenges in producing a whole range of value-added ingredients with whey as feedstock through microbial fermentation. Particular focus was paid to the potential of novel genetically engineered or adapted microbial strains to valorize bovine whey economically and sustainably.

1. Introduction

The production and processing of milk are increasing by 10% every four years globally, which is further used in several dairy-based products [1]. With increased milk production, the cheese industry is also growing at a fast pace globally and so is the production of bovine whey. The production of bovine whey is estimated to be 160 million tons per year, as manufacturing 1 kg of cheese leads to producing around 10 L of whey [2, 3, 4]. Whey contains about 90% of the milk volume and carries 55% of milk nutrients in the form of 4.5-5% (*w*/*v*) lactose, 0.6-0.8% (*w*/*v*) protein, 0.4-0.5% (*w*/*v*) lipid, and 8-10% (*w*/*w* dried extract) mineral salts [5]. In addition, the ash content in whey is mainly composed of sodium chloride, potassium chloride, calcium salt, lactic and citric acids, urea, uric acid, and group B vitamins [4, 6]. Being the principal component of whey, lactose (5%) is responsible for high Biological Oxygen Demand (BOD) and Chemical Oxygen Demand (COD) values. Dairy industries manage whey mainly by membrane separation or fermentation [7]. Using membrane technology, whey protein concentrate, isolate, lactose, etc., are segregated with high economic inputs such as costly replacement and regeneration. On the contrary, microbial conversion of lactose and whey proteins allows the formation of promising bioproducts such as bioethanol, bioplastics, polylactic acid, bacterial cellulose, organic acids, antimicrobials, food colors, and flavors [7, 8, 9, 10].

The concept of a "Circular Economy or Zero Waste Economy" is picking pace by promoting environment-friendly, healthy, and sustainable technologies for value addition to waste, which may increase profit margins for

local markets [9]. As our world is progressing toward sustainable technologies and is mindful of man-created pollution reduction, these products are in high demand. The market scope of these products is excellent, and extensive efforts are made to achieve higher yields after fermentation. Still, there are some gaps in commercializing these technologies on a larger scale. This review focuses on the latest developments in the bioremediation of whey and innovative technologies for producing a wide range of valuable products. Special attention has been given to the development and role of robust microbial strains and compatible processing parameters in enhancing the yields of biomolecules of industrial importance. Moreover, the challenges and future perspectives have been discussed, providing insights into this field.

2. Health-Promoting Attributes of Whey

The health benefits of consuming whey were long recognized in the 17th century and have been used to heal wounds and treat sepsis and stomach ailments [11]. There are four major types of whey proteins: β-lactoglobulin (β-Lg), α-lactalbumin (α-La), immunoglobulins (IGs), and bovine serum albumin (BSA). The levels of immunoglobulins remain the highest in the colostrum as they provide passive immunity to the young mammal but are present at low levels in milk [12]. Whey proteins have a 15% greater biological value than egg albumin, contain branched-chain amino acids (BCAA), and show better absorption and digestibility. Therefore, whey proteins are mainly preferred as a dietary supplement [13]. In addition, lactoferrin, an essential protein that binds to iron and exhibits antimicrobial activity against pathogens, is also available in whey, although in low amounts. Rennet is an enzyme used to coagulate milk during cheese production. Rennet coagulated curds during cheese production release a peptide called glycomacropeptide (GMP) from k-casein [14]. Clinical studies evaluating GMP's effect on human physiology have shown positive effects on gastrointestinal, immune, and endocrine systems [15]. Noticeably, bioactive peptides such as IIAEK, INYW, and WLAHKALCSEKLDQ are produced by enzymatic hydrolysis of whey proteins [16, 17]. Microbial fermentation of whey also releases bioactive peptides. In addition, different microbial strains produce specific bioactive peptides with peculiar physiological effects [18]. Substantial scientific evidence indicates the health benefits of whey and its bioactive derivatives, including improved weight management, infant nutrition, physical strength, and heart function, and they show anti-cancerous and anti-infective effects [11, 16, 19, 20, 21]. Whey is also a source of growth factors that include insulin-like growth factors, transforming growth factors, fibroblast growth factors, and platelet-derived growth factors that can be used as a supplement to fetal bovine serum (FBS) during cell culturing. In addition, whey-derived growth factors and media are a cheaper and safe source compared to FBS obtained from animal blood [22, 23].

2.1. Different Ways to Valorize Whey. Microbial fermentation of whey can generate several value-added substances and thus solve not only the issue of its disposal but also be a suitable substrate for several industrially essential products. Recent studies discussing the potential of different microbial strains in yield and productivity to turn whey into various biomolecules (bioethanol, lipids, single-cell protein (SCP), bacterial cellulose, etc.) of industrial importance are included in Figure 1 [24]. Conventionally, raw whey has been utilized for manufacturing beverages, producing probiotic biomass, organic acids, and bioprotective solutions [25, 26]. The microbial groups and production efficiency have been reviewed over time; however, *Saccharomyces*, *Klyuveromyces*, *Cryptococcus*, *Lactobacillus*, *Mannheimia*, *Pseudomonas*, *Acetobacter*, *Gluconobacter*, and *Galactomyces* are widely used and well-studied bacterial and fungal genera. A few relatively newer and less studied genera include *Cystobasidium*, *Cellulosimicrobium*, *Monascus*, *Blakeslea*, *Wickerhamomyces*, *Cupriavidus*, and *Komagataeibacter* for their ability to utilize whey as a feedstock.

Recently, the demand for biofuels and bioplastics (cleaner alternatives to power generation and plastics, respectively) has increased as more stringent, environmentally safer guidelines and regulations are adopted worldwide, and we have started relying less on petrochemical resources [27, 28]. Bioplastics, biofuels, microbial colors, flavors, and bacterial cellulose have massive potential in food packaging, power generation, and biomedical applications [9, 29, 30, 31]. Moreover, efficient production of these products may provide sustainable solutions as they are biodegradable, biocompatible, and non-toxic. Here, we are discussing the possibilities of using whey as a substrate for these industrially important products one by one and the advancements that have happened so far.

2.2. Bioethanol. Several countries worldwide, including India, have started blending ethanol in different proportions with gasoline. Therefore, there is an intensified interest in finding better techno-economically feasible processes for ethanol production [32]. Bioethanol production from agro-industrial waste has gained momentum due to less greenhouse gas emissions and sustainability, which can be envisaged as a better step towards a circular economy and zero waste [9]. Whey has been a cheap feed source for reducing lactose into ethanol through microorganisms, generally yeasts, such as *Kluyveromyces marxianus*, *K. lactis*, and *Saccharomyces cerevisiae* (Table 1) [7]. The most critical constraint in bioethanol production is the selection of microbial strains. Lactose-fermenting yeasts *Kluyveromyces lactis* and *Kluyveromyces marxianus*, also known as dairy yeasts, possess the genes *LAC4* and *LAC12* encode for intracellular β-galactosidase and lactose permease, respectively [33]. Among the dairy yeasts, *K. marxianus* is usually preferred due to better fermentative performance at high temperatures (45–50°C) than *K. lactis* [34]. However, ethanol production with *K. marxianus* from cheese whey has a low yield due to its sensitivity toward ethanol concentration. Thus, the strains must tolerate ethanol concentration and temperature during fermentation to avert the catabolite repression and consequent growth inhibition of *K. marxianus*. Studies reported that a functional KmLac12 transport

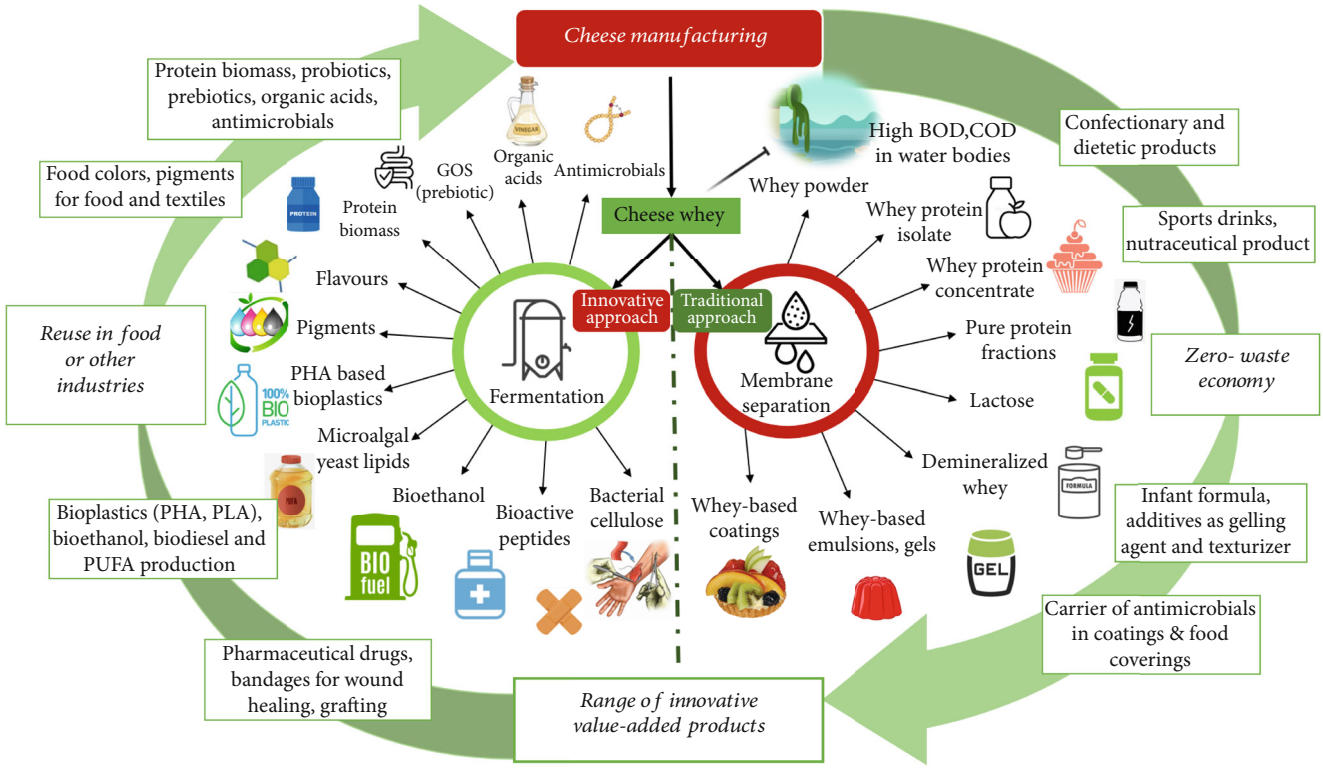

Figure 1: Emerging trends in sustainable biorefining of dairy whey.

system for lactose uptake is also essential for high-yielding strains, and thus strains can be engineered genetically to have this transport system.

Another important strain for alcohol production is *Saccharomyces cerevisiae*—the model organism; however, it has a few limitations regarding its use for ethanol production from cheese whey. *S. cerevisiae* does not produce β-galactosidase and cannot assimilate lactose in cheese whey [35]. However, if lactose in whey is pre-hydrolyzed into glucose and galactose, *S. cerevisiae* can be exploited to produce ethanol from whey in a two-step process. But it consumes glucose first and converts it to ethanol, while galactose is consumed later. Consequently, galactose uptake is hampered due to catabolite repression of enzymes required for galactose uptake. Thus, fermenting cheese whey with *S. cerevisiae* may lead to deviation from the primary product, *i.e.*, ethanol [35]. However, in the past decades, several researchers addressed this issue [27, 35, 36, 37]. Immobilization of *S. cerevisiae* cells and exogenous β-galactosidase enzyme from *K. lactis* in a suitable matrix has been observed to reduce the catabolite repression, wash out of cells, and improve the bioethanol production [36]. Another study showed that the co-immobilization of *Saccharomyces cerevisiae* and *Kluyveromyces marxianus* in silicon dioxide nanoparticles efficiently converted hydrolyzed whey into ethanol [35]. Using concentrated cheese whey (150 g/L of lactose), this system yielded an ethanol titer of 63.9 g/L with productivity of 1.925 g/L/h [38]. Similarly, direct contact membrane distillation of ethanol in bioreactors has also been proven an efficient method to avoid catabolite repression [39]. Bioethanol production has been increased by adding a mixture of *Eucalyptus globulus* wood and cheese whey powder in solid-state fermentation mode at high temperatures using the industrial *Saccharomyces cerevisiae* Ethanol Red® strain. A high ethanol titer (93 g/L) was achieved by using cellulase and β-galactosidase enzymes (24.2 filter paper unit/g and 20.0 unit/g, respectively) at 35°C from 37% of the solid mixture [27]. Stress adaptation and genetic intervention in the genome of model organisms have also been tested for increased production of ethanol from cheese whey. *K. marxianus* strain MTCC 1389 was made osmotolerant to a lactose concentration of 200 g/L for 65 days and then used to produce ethanol. The ethanol yield increased by 17.5% compared to the parental strain due to improved osmotolerance [37]. Recently, using the Clustered Regularly Interspaced Palindromic Repeats- (CRISPR-) Cas9 tool of genome editing, a wild-type *S. cerevisiae* strain was genetically engineered to flux more galactose from the concentrated whey medium, and increased ethanol titer (0.32 ± 0.007 g/g) was achieved [35]. A few studies have focused on producing other valuable substances and bioethanol from cheese whey. In a study, D-tagatose (an artificial sweetener) was produced along with bioethanol from lactose and cheese whey powder by fermenting with recombinant *Escherichia coli* with L-arabinose isomerase (L-AI) and then *Saccharomyces cerevisiae* NL22 [40]. In a recent study, Costa *et al.* [41] engineered a yeast *Saccharomyces cerevisiae* through heterologous expression of LAC12 and LAC4 from *Kluyveromyces lactis*. Two different promoter (TEF1p/PGK1p) combinations were used. The recombinant strain E2 (PGK1p → LAC4/TEF1p → LAC12) showed nearly 100%

Table 1: Yield and productivity obtained during the production of valuable biomolecules.

Whey-based medium/ supplementation/conditions	Microbial species	Yield	Productivity	References
Bioethanol				
Cheese whey permeate	*Kluyveromyces lactis* CBS2359	15.0 g/L	0.31 g/L/h	[34]
Cheese whey with lactose (200 g/L)	*K. marxianus* MTCC 1389 (adapted strain)	79.33 g/L	1.66 g/L/h	[37]
Deproteinized cheese whey with lactose (150 g/L) immobilized on silicon dioxide-based nanoparticles	*K. marxianus* and *S. cerevisiae* (3 : 1)	63.9 g/L	1.925 g/L/h	[35]
Cheese whey powder (CWP) and *Eucalyptus globulus* wood (EGW). Addition of cellulase and β-galactosidase enzymes (24.2 filter paper unit/g and 20.0 U/g, respectively) at 35 °C from 37% of the solid mixture	*Saccharomyces cerevisiae* Ethanol Red®	93 g/L	nd	[27]
Concentrated whey medium (CRISPR Cas9 system was used to genetically modify the *S. cerevisiae* strain to flux higher galactose)	*S. cerevisiae* MTCC 170	29.5 g/L	0.819 g/L/h	[35]
	S. cerevisiae MTCC 170 *ΔGal80*	31.6 g/L	0.929 g/L/h	
Mozzarella cheese whey with sugarcane molasses (15%)	*Candida tropicalis*, *Blastoschizomyces capitatus* (1 : 1)	0.849 g/L	nd	[115]
Cheese whey+lactose (200 g/L)	*Saccharomyces cerevisiae* E2 (heterologous expression of LAC12 and LAC4 from *Kluyveromyces lactis*)	92.2 g/L	nd	[41]
Lactic acid				
Cheese whey with steep corn liquor and ammonium sulfate	*Lactobacillus* sp. LMI8	52.37 g/L	nd	[90]
Cheese whey	*Pediococcus acidilactici* KTU05-7	47.0-51.2 g/L	nd	[89]
Cheese whey with 2% (*w*/*v*) of $CaCO_3$	*P. pentosaceus* KTU05-9			
Cheese whey ultrafiltrate	*Lactobacillus helveticus* strain Milano	nd	2.7 g/L/h	[91]
Cheese whey permeate	*L. casei* MT682513	44.87 g/L	nd	[85]
	Enterococcus camelliae MT682510	35.94 g/L	nd	
	Enterococcus faecalis MT682509	39.00 g/L	nd	
	Enterococcus lactis MT682511	41.15 g/L	nd	
	Weissella paramesenteroides MT682512	33.15 g/L	nd	
Whey permeate with initial lactose concentration was 30 g/L	*Lactobacillus delbrueckii* and *L. lactis*	0.48 g/g	nd	[86]
Succinic acid				
Whey with lactose	*Actinobacillus succinogenes*	nd	0.81 g/L/h	[93]
Whey permeate with $MgCO_3$	*Enterobacter aerogenes* LU2	0.54 g/g	0.33 g/L/h	[100]
Whey permeate	*Enterobacter aerogenes* LU2	57.7 g/L	nd	[101]
Cheese whey (initial lactose concentration 50 g/L)	*Actinobacillus succinogenes* 130 Z (inoculum size 5%)	0.57 g/g	0.44 g/L/h	[97]
Delactosed whey permeate (DLP)	*Actinobacillus succinogenes*	0.64 g/g	nd	[98]

Table 1: Continued.

Whey-based medium/ supplementation/conditions	Microbial species	Yield	Productivity	References
Lactobionic acid				
Cheese whey	*Pseudomonas taetrolens*	22.03 g/L	nd	[113]
Sweet whey	*Pseudomonas taetrolens* LMG 2336	42.4 g/L	nd	[107]
Acid whey	*Pseudomonas taetrolens* LMG 2336 (30% inoculum)	nd	1.12 g/L/h	[110]
Whey medium	*Pseudomonas* sp. LS13-1	175 g/L	1.12 g/L/h	[109]
Ricotta cheese whey	*Pseudomonas taetrolens*	34.25 ± 2.86 g/L	0.6-0.77 g/L/h	[105]
Deproteinized sweet cheese whey	*Pseudomonas taetrolens* LMG 2336	44.69 ± 5.84 g/L after 72 h	0.54-0.7 g/L/h	[112]
Cheese whey	*Pseudomonas fragi* NL20W		3.09 g/L/h	[111]
Butyric acid				
Untreated whey	*Clostridium butyricum*	9.9 g/L	nd	[121]
Proteolyzed whey	*Clostridium butyricum*	13.9 g/L	nd	
Cheese whey pH 5.5	*Clostridium beijerinckii*	nd	nd	[120]
Cheese whey USAB reactor purity > 90%	Activated sludge	2.5 g/L	nd	[122]
Acetic acid				
Sweet cheese whey supplemented with lactose	*Kluyveromyces fragilis*	5-6%	nd	[126]
Whey immobilized whey fermentation in cheesecloth showed	*Lactobacillus buchneri*	24 g/L	nd	[4]
Cheese whey	*Kluyveromyces marxianus* Y102, *Acetobacter aceti* DSM-G3508	nd	4.35 g/L/day	[130]
Cheese whey	*Zymomonas mobilis*, *Acetobacter pasteurianus*	4% (*v*/*v*) acetic acid	nd	[131]
Cheese whey	*Acetobacter pomorum* IWV-03	5.6%	nd	[127]
Polyhydroxyalkanoates				
Ricotta cheese whey	Mixed culture	0.74 ± 0.14 mg COD_{PHA}/mg $COD_{OA\text{-}in}$	nd	[135]
Cheese whey	1st stage: *Acetobacter pasteurianus* C1 2nd stage: *Bacillus* sp. CYR-1	240.6 mg/L	nd	[139]
Cheese whey permeate (genetically modified by insertion of *lacZ*, *lacI*, and *lacO* genes)	*Cupriavidus necator* DSM545	nd	nd	[140]
Cheese whey	*Paracoccus homiensis* (halophile)	1.1 g/L P-(3HB-co-3 HV) copolymer (29.0% of CDM) at 72 h	nd	[137]

Table 1: Continued.

Whey-based medium/ supplementation/conditions	Microbial species	Yield	Productivity	References
Single-cell protein				
Cheese whey with urea, batch culture	*Kluyveromyces marxianus*	nd	0.16 g/L/h	[73]
Cheese whey with urea, batch culture 86.8% COD removal efficiency	*Kluyveromyces marxianus+Candida krusei*	nd	0.20 g/L/h	[72]
Cheese whey, continuous culture 78.5% COD removal, productivity	*K. marxianus*	nd	0.26 g/L/h	[74]
Bacterial cellulose				
Cheese whey permeate	*Acetobacter xylinum* ATCC10821 and 23770	nd	nd	[144]
Whey-based media	*Acetobacter xylinus* ITz3 (GE-insertion of LacZ) 28-fold increase	1.82 g/L	nd	[145]
Cheese whey media	*Gluconacetobacter xylinus* PTCC1734	3.55 g/L	nd	[146]
Cheese whey	*Gluconobacter sucrofermentans*	5.45 g/L	nd	[147]
Cheese whey with residual liquid of grapes Corinthian currant finishing (CFS)	*Komagataeibacter sucrofermentans* DSM15973	18.9 ± 0.7 g/L	nd	[148]
Single-cell oil/biodiesel				
Cheese whey supplemented with 50% molasses 0.5 yeast extract, 4 KH_2PO4, 1 Na_2HPO_4, 0.75 $MgSO_4{\cdot}7H_2O$, and 0.002 $ZnSO_4{\cdot}H_2O$. pH 6.5	*Cryptococcus laurentii* 11	2.96 g/L	nd	[55]
Cheese whey+expired soft drinks	*Debaryomyces etchellsii* strain BM1	1.2 g/L	nd	[56]
Cheese whey	*Cryptococcus laurentii* UCD 68-201	9.9 g/L	0.165 g/L/h	[51]
1st step: cheese whey with urea 2nd step: addition of syrup from the candied fruit industry	*Cutaneotrichosporon oleaginosus*	38 g/L	0.57 g/L/h	[54]
Cheese whey supplemented with wine lees	*Mortierella ramanniana*	7.9 g/L	0.036 g/L/h	[52]
Cheese whey supplemented with free amino nitrogen (322.2 mg/L) and lactose (43.4 g/L) and wine lees (fed-batch bioreactor)	*Cryptococcus curvatus* ATCC 20509	33.1 g/L	0.494 g/L/h	[52]
1st stage: for biomass production in a preculture medium 2nd stage: deproteinized whey permeate (16% lactose) hydrolyzed with 0.25% of lactase solution (>2600 U/g)	*Mortierella isabelline* DSM1414	17.13 g/L	0.191 g/L/h	[47]
Hydrolyzed cheese whey 33.6°C and pH 4.5	*Mucor circinelloides*	2.20 g/L	0.013 g/L/h	[58]
Crude whey	*Rhodococcus opacus*	3.0 to 6.4 g/L	nd	[50]
Crude whey supplemented with ammonium sulfate and potassium dihydrogen phosphate, lactose	*Yarrowia lipolytica* B9	4.29 g/L	nd	[49]
Cheese whey untreated (UCW) Deproteinized cheese whey (DCW) 100%	*Cystobasidium oligophagum* JRC1	44.12 ± 0.84 g/L 21.79 ± 1.00 g/L	0.0335 g/L/h 0.0272 g/L/h	[59]

nd: not determined.

lactose metabolism in cheese whey and produced 92.2 g/L of ethanol from 200 g/L lactose, the highest titer of bioethanol from cheese whey till date (Table 1) [41]. This study indicates the role of different promoters in multi-enzymatic pathways; thus, selecting suitable microbial strains is vital for higher production. Several other components, like the type of bioreactor, microorganism chosen, aeration, immobilization, and substrate composition, play a critical role in competitive prices for bioethanol commercialization [42]. Considering these variables, researchers should optimize process parameters through mathematical models generated from surface response methodologies and improve the current technologies to increase bioethanol production from whey.

2.3. Single-Cell Oils or Biodiesel. Oleaginous yeasts accumulate lipids up to 70% on a dry weight basis, known as "single-cell oil" (SCO). Other microorganisms such as molds, microalgae, and thraustochytrids also accumulate lipids. However, yeast SCO has emerged as a promising candidate to meet the rising energy demand because of its higher growth rate, easy propagation in agro-waste, and scale-up process [43]. In addition, the fatty acid in yeast SCO is similar to vegetable oils, making it a suitable option for biodiesel production [44]. Food security has become a primary global problem, and the diversion of vegetable oil for biodiesel production raises the issue of "food versus fuel." Hence, microbial oil can be a potential alternative for obtaining cost-effective biodiesel apart from being a dietary supplement for animals and humans in pure form because of its high content of polyunsaturated fatty acids [45]. Currently, biodiesel production is not economically sound, and selecting a suitable feedstock, like cheese whey, is vital for minimizing production costs [46]. Oleaginous yeasts accumulate more lipids when the growth medium has more sugar and lacks nitrogenous compounds [47, 48]. The enzyme β-galactosidase, essential for utilizing lactose, is widely distributed among microbial species, especially yeasts. Hence, cheese whey represents a potential growth medium in biotechnological processes due to its nutritional profile [48]. Several researchers tried to optimize the bioprocess for producing microbial oil from cheese whey or its permeate [48, 49, 50, 51, 52, 53, 54]. Table 1 shows the yield of lipids produced by various microorganisms with cheese whey as feedstock. Cheese whey without any supplementation as a feedstock yielded lipids ranging from 2 to 7 g/L using species of *Cryptococcus*, *Mortierella*, *Rhodococcus*, and *Mucor* [55, 56, 57, 58, 59]. However, further scale-up in stirred tank reactors resulted in higher yields of up to 9.9 g/L using *Cryptococcus laurentii* UCD 68-201 on raw cheese whey [51]. Compared to untreated whey, deproteinized whey yielded more lipids when fermented with oleaginous yeast *Cystobasidium oligophagum* JRC1 [59]. The biomass lipid productivity of 0.0335 ± 0.0004 g/L/h and 0.0272 ± 0.0008 g/L/h and the lipid content of 44.12 ± 0.84 %and 21.79 ± 1.00% were achieved for 100% deproteinized cheese whey and untreated cheese whey, respectively [59]. Another way of increasing yield is to supplement deproteinized cheese whey with lactose and hydrolyze it. In one such study, hydrolysis of deproteinized whey permeate (16% lactose) with lactase increased the oil content from 3.65 g/L to 17.13 g/L. Moreover, 2.18–5.48% gamma-linolenic acid and 16.21–22.43% linoleic acid was achieved [47]. In addition to the methodologies mentioned above, hydrodynamic cavitation (HC) of cheese whey under an alkaline condition has increased lipid production [60]. The supplementation of cheese whey with other agro-waste positively affects the yield of microbial biomass and lipids. The highest productivity has been achieved by supplementing the cheese whey with accessible amino sources and other agro-wastes [52, 54]. For instance, wine lees were added to cheese whey to obtain lipids by fermenting it with *Mortierella ramanniana*. As a result, the total dry weight of lipids was 25.8 g/L, and 4.5% (w/w) was omega-6 fatty acid. Furthermore, lipid concentrations of 33.1 g/L and productivity of 0.49 g/L/h were reported in fed-batch bioreactor cultures with *Cryptococcus curvatus* using cheese whey and wine lees [52].

Lipid productivity also increases when a separate stage for biomass production is employed to have a prolific growth of oleaginous yeast with essential nutrients. Then, in the second stage, the agro-waste is used as feedstock for oil production. For example, a two-step process using liquid cheese whey permeate fermented with yeast *Cutaneotrichosporon oleaginosus* yielded higher lipids. In the first step, the yeast biomass increased due to the addition of urea as a nitrogen source. Then, in the second step, another agro-industrial waste syrup from candied fruit processing was added to trigger oil accumulation, resulting in 38 g/L of lipid and 0.57 g/L/h of productivity, the highest productivity of microbial oil to date [54]. The selection of strains is also important as certain yeast strains produce more lipids than others. Therefore, proper strain selection and supplementation of deproteinized whey with lactose or other agro-waste for readily available monosaccharides and accessible amino sources are crucial factors to ensure higher lipid yields from cheese whey.

2.4. Single-Cell Protein. SCP is the dried cells of certain microorganisms (yeast, mold, algae, and bacteria) commonly used as good-quality protein supplements. SCP contains substantial crude protein, ranging from 40 to 80% w/w of the dry cell weight of microorganisms apart from carbohydrates, vitamins, and minerals [61, 62]. SCP can be obtained rapidly and contains essential amino acids, limited in plant sources. Additionally, SCP production requires continuous culturing in the fermenter, and a wide range of carbon sources can be utilized. Therefore, a good quality protein is produced with less land requirement, cheaper media, and ecologically sustainable processes [63]. Among various microbial groups, yeasts are generally preferred due to their large size, easier isolation, less DNA than bacteria, and excellent propagation on cheaper carbon sources. The most commonly used Generally Regarded As Safe- (GRAS-) status yeast genera are *Saccharomyces*, *Candida*, *Kluyveromyces*, *Pichia*, and *Torulopsis* [64]. The feedstock for SCP production includes petroleum by-products, lignocelluloses, or other agro-industrial by-products. Molasses, a by-product of the sugar industry, which is considered a good source for SCP production, has been observed to have some

limitations in its use for SCP production, such as a high content of heavy metals and minerals that may retard the growth of the cells by inactivating enzymatic activity and not so easy availability of molasses from the sugar industry [65]. The use of whey for producing SCP has several advantages, such as being low-cost, readily available substrate, and easy to process. Hence, whey can be considered the best alternative source for biomass production [66, 67]. *Kluyveromyces* spp. is a lactose-utilizing species, often used to produce biomass and simultaneously reduce the COD of whey [68]. Being Crabtree-negative microorganism, *Kluyveromyces* spp. generally have ethanol at a higher initial lactose concentration at the expense of the biomass yield. But ethanol formation depends entirely on the oxygen supply concentration as *Kluyveromyces* spp. is a facultative fermentative microorganism. It cannot grow in severely anaerobic environments [69]. Therefore, a higher oxygen supply produces more biomass and less ethanol. Compared to a single culture, mixed culture of *K. marxianus* and *S. cerevisiae* (non-lactose utilizing) has achieved a better COD reduction of whey and biomass yield. The reason for this can be the consumption of extracellular intermediate metabolic products of *Kluyveromyces* spp. by *Saccharomyces* spp. [70]. Similar results were obtained by employing mixed cultures of *Torulopsis cremoris* and *Candida utilis*. The improvement in biomass yield may be because *C. utilis* consumed the metabolic by-products of *T. cremoris*, which resulted in increased biomass production with higher COD removal efficiency [71]. Yadav *et al.* [72] also reported a higher biomass yield and COD removal efficiency during mixed-culture cultivation of *K. marxianus* and *Candida krusei* (non-lactose consuming yeast). However, the main challenging issue during the cultivation of mixed cultures is the stability of the microbial consortium, which must be studied before implementing any mixed culture on an industrial scale [72, 73, 74]. SCP organisms can be genetically modified to improve their nutritional quality, such as producing omega-3 fatty acid by *Yarrowia lipolytica* [75]. In addition, genetic engineering technology can help eradicate the genes involved in toxin production and antibiotic resistance, leading to safer SCP products [62]. A strain of *Methylobacterium* spp., used for producing SCP-based meals using methanol as feedstock, was genetically engineered to produce carotenoids and taurine [76]. It has been patented by KnipBio (Lowell, MA) and marketed by KnipBio and String Bio (Bangalore, India). This strain is the first genetically engineered SCP approved by US FDA [77]. Further, efforts can be made to broaden the range of substrates utilized by microorganisms or increase their metabolizing efficiency to produce SCP, including cellulose, lignin, starch, and whey [78].

2.5. Organic Acids. Organic acids such as lactic, acetic, butyric, lactobionic, succinic, and propionic acid have been microbially produced using agro-industrial waste, including whey [79, 80, 81]. Table 1 shows the organic acid yields using cheese whey feedstock. Lactic acid, also known as α-hydroxy propionic acid, is often used as an acidulant in the food industry to improve shelf-life and flavor [82]. It has an increasing demand in the pharmaceutical, chemical, and food industries for its poly lactic acid polymers yield. The manufacture of this acid globally is estimated to be 45 million kg/year and is expected to grow annually by 8.6% [83]. About 80,000 tons of lactic acid are produced worldwide, of which 90% is by lactic acid bacterial fermentation. The remaining 10% are synthetically produced by the hydrolysis of lactonitrile [84]. Rod-shaped lactic acid bacteria (LAB), mainly *Lactobacillus helveticus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus acidophilus*, and *Lactobacillus casei*, have produced lactic acid from whey [85, 86]. A higher conversion rate than the other microbes makes *L. helveticus* the preferred strain, as it can produce almost twice the amount of lactic acid compared to typical LAB [87]. A large percentage of generated cheese whey is managed by membrane processes such as ultrafiltration. The permeate obtained contains a low protein content, a high lactose amount, and a high concentration of mineral salts. Both these conditions play an essential role in the microbial production of lactic acid [88, 89]. Several studies aimed at obtaining lactic acid after ultrafiltration of cheese whey have found that *L. helveticus*, cultivated in whey, is used along with steep corn liquor (CSL) being used as the nitrogen source [90]. Lactic acid production of 9.7 g/L/h using *L. helveticus* strain Milano was recorded through fermentation in a whey-yeast extract permeate medium [91]. Genetic modifications in microbial strains can help increase their acid tolerance, improving lactic acid yield and optical purity [92]. Genetic modification of *Corynebacterium glutamicum* and *E. coli* has increased lactic acid productivity [93].

Succinic acid (SA) is another crucial organic acid that finds its demand in the food, pharmaceutical, and chemical industries [93]. Succinic acid is the end product of anaerobic respiration in the Krebs cycle. Chemical technologies such as catalytic hydrogenation or electrolytic reduction of maleic anhydride are preferred for SA production. However, succinic acid's chemical production is costly and leads to the generation of greenhouse gases; that is why several studies have focused on producing SA by fermenting various carbon sources by microorganisms [80, 94]. Several microorganisms, including *Mannheimia succiniciproducens*, *Anaerobiospirillum succiniciproducens*, *Basfia succiniciproducens*, *Actinobacillus succinogenes*, and *E. coli*, are known to produce SA [95, 96]. Among these, *Actinobacillus succinogenes* has become a commercial choice for SA production due to its high acid tolerance and the ability to utilize various carbon sources [97, 98]. The highest yield and productivity from whey supplemented with $MgCO_3$ 0.54 g/g and 0.33 g/L/h were registered. *Enterobacter aerogenes* LU2, isolated from cow rumen, was utilized for producing SA using whey permeate. Under optimal conditions (10 g/L yeast extract, 100 g/L lactose, and 20% inoculum at 7.0 pH, incubated at 34 ˚C), the productivity of SA was 51.35 g/L with 53% yield [99, 100]. Interestingly, the productivity and output increased to 57.7 g/L and 62%, respectively, when whey permeate was used instead of lactose [101]. Genetic engineering technology can be utilized for improved yield and productivity of SA. Adaptive evolution has been used to obtain acid-tolerant mutants of SA-producing microorganisms [102]. In a study, *A. succinogenes* NJ113 was adapted, and four

mutants with stable and improved acid resistance were selected for SA production, which yielded higher than the parent strain [103]. Similarly, ammonium-tolerant *E. coli* has also been obtained by adaptive evolution for efficient SA production [104].

Lactobionic acid (4-*O*-β-galactopyranosyl-D-gluconic acid) is a polyhydroxy acid comprising glucose and a gluconic acid unit joined together by an ether-like linkage [105]. Lactobionic acid (LBA) has antioxidant, chelating, and humectant properties owing to multiple hydroxyl groups in its structure [106]. It is biodegradable, biocompatible, and extensively used in the pharmaceutical and cosmetic industries [107]. It is prepared by electrochemical and catalytic lactose oxidation involving expensive catalysts and the risk of forming undesirable side reaction products [108]. Biotechnological applications have recently increased interest in producing lactobionic acid from cheap lactose sources like a dairy waste. Bioconversion of lactose from whey to lactobionic acid is done in a bioreactor using bacteria of the species *Pseudomonas taetrolens* [109, 110, 111, 112]. The highest concentration of lactobionic acid (22.03 mg/cm^3) was obtained when whey was batch fed at 72 h intervals, pH was maintained at 6.25, and bacteria were enclosed in alginate microcapsules [113]. The first studies on the production of lactobionic acid were conducted using strains of *Zymomonas mobilis* and *Escherichia coli* [113, 114]. Oh *et al.* [115] utilized genetic modification of the *Pseudomonas taetrolens* strain by introducing quinoprotein glucose dehydrogenase (*gdh*) expression in the bacterial genome to improve lactobionic acid production. As a result, an LBA productivity of 16.7 g/L/h by whole cell biocatalyst (WCB) was obtained. The biocatalyst showed activity for at least seven rounds without a significant reduction in LBA productivity.

Butyric acid is widely used in the food, pharmaceutical, and cosmetic industries [116, 117, 118]. The majority of commercial butyric acid production is *via* chemical synthesis. However, environmentally friendly butyric acid production can be achieved by fermentation on cheap agricultural and dairy waste as substrate [118, 119]. A study on how variation in pH affects the butyric acid fermentation by *Clostridium beijerinckii* using cheese whey as a substrate was conducted, and pH 5.5 was concluded as best for the highest yield [120]. Butyric acid production by *Clostridium butyricum* increased in proteolyzed whey (13.9g/L) instead of untreated whey (9.9 g/L). Adding 5 g/L yeast extract or 50 μg/L biotin also increased the butyric acid production up to 19 g/L [121]. Dessì *et al.* [122] studied cheese whey fermentation in Upflow Anaerobic Sludge Blanked (UASB) reactors using activated sludge from an effluent treatment plant of a dairy industry for the production and in-line extraction of volatile fatty acids (VFA), including butyric acid. Butyric acid extraction was up to 2.5 g/L with a more than 90% purity. In an earlier study by Stevens *et al.* [123], the coculturing of *C. beijerinckii* and *Bacillus cereus* on cheese whey was investigated. With coculture, the butyric acid concentration reached 11.5 g/L. In another study, the coculture of a novel *Bacillus* sp. SGP1 strain with *Clostridium tyrobutyricum* ATCC 25755 led to an increased butyric acid production of 34.2 ± 1.8 g/L with a yield of 0.35 ± 0.03 $g_{butyrate}/g_{sucrose}$ with a significant parallel decrease in the production of other acids, such as acetic acid and lactic acid, thus showing a greater selectivity [124]. Genetic engineering of *C. tyrobutyricum* is primarily done to overexpress the genes involved in the butyrate biosynthesis pathway, eliminate the genes involved in the acetic acid biosynthesis pathway, and increase the range of substrate utilization [116].

Acetic acid, commonly known as vinegar, is a seasoning used in vinaigrette and mayonnaise and is employed in processing canned foods and cooking meat and fish. The concentration of acetic acid in marketable vinegar ranges from 5 to 6 g/100 mL (acetic degrees) [125]. Cheese whey has been used to produce acetic acid by several researchers. In one of these studies, cheese whey supplemented with lactose was first fermented with the yeast *Kluyveromyces fragilis* and then by *Acetobacter pasteurianus* to obtain 6% (*v*/*v*) acetic acid with a biotransformation efficiency of 84% [126, 127]. In another study, acetic acid and propylene glycol from whey lactose were produced by fermenting it with *Lactobacillus buchneri* at pH ~ 4.2, and concentrations up to 25-30 g/L were achieved [128]. In another study by Tamura [129], 3-fold whey concentrate was fermented with *K. marxianus*, and 8% ethanol containing whey liquor was obtained. Subsequently, this whey liquor was diluted two-fold and fermented with *A. pasteurianus* IFO 14814, resulting in whey vinegar containing 5.2% acetic acid [129]. Similarly, an ethanol yield of 6.7 g/L/day and an acetic acid yield of 4.35 g/L/day were obtained by sequential fermentation of cheese whey by *K. marxianus* and *A. aceti* [130]. Whey vinegar has also been used as an ingredient in cattle's diet. In a recent study, lacto-vinegar was developed utilizing a whey solution saccharified with a rapeseed meal [131]. First, sequential fermentation with *Zymomonas mobilis* and *Acetobacter pasteurianus* was employed to obtain 4% *v*/*v* acetic acid. Hence, two-stage fermentation, first with ethanol-producing yeast or bacteria and then with Acetic acid bacteria, plays a crucial role in getting higher vinegar yields.

2.6. Microbial Polyhydroxyalkanoates. Replacing plastics with bio-based, biodegradable plastics is one of the critical challenges of this century. Polyhydroxyalkanoates (PHA) are naturally occurring carbon polymers accumulated by different microorganisms in the form of granules in their cytoplasm when carbon is in excess and other nutrients are deficient (N, P, S, etc.). Therefore, PHA-based bioplastic can be a natural alternative to conventional plastics. PHAs can be of different types based on the length and capability of microorganisms to produce homo and/or heteropolymers. Microorganisms degrade PHA-based plastic into CO_2 and H_2O and methane under aerobic and anaerobic conditions [132]. PHA production cost is high due to the slow growth of microorganisms, increased energy for sterilization, intensive aeration, discontinuous fermentation, and tedious downstream processing. The production costs may be reduced using agro-industrial waste as substrate and novel microbial strains with high PHA accumulation rates [133]. Dairy whey is a suitable substrate for PHA production due to its relatively high organic load and has become a

research hotspot for weighing the possibility of PHAs production [133, 134, 135, 136, 137]. A recent study showed that *Paracoccus homiensis*, a halophile, was capable of converting organic material in cheese whey into scl-polyhydroxyalkanoates up to 3.3 ± 0.31 g/L of dry cell mass with 1.1 g/L of 3-hydroxybutyrate and 3-hydroxyvalerate copolymer (29.0% of dry cell mass) in 72 h [137]. In another study, deproteinized whey from ricotta cheese production was used as a substrate to produce biohydrogen via dark fermentation and PHA in a two-step bioprocess. During the first step, a volume of 3.47 liter/day of hydrogen and organic acid production up to 14.6 g/L/day from the second cheese whey was obtained. In the next step, the organic acids served as the substrate for a high yield of PHA up to 0.74 ± 0.14 mg $COD_{PHA}mg^{-1}$ $COD_{OA\text{-}in}$[135]. Coats *et al.* [138] tried PHA synthesis by mixed microbial consortia cultured on fermented dairy manure and could obtain an intracellular concentration ranging from 22.5 to 90.7% (mg PHA mg volatile suspended $solids^{-1}$). In another study, untreated cheese whey (CW) was used for PHA production *via* a two-stage process. The first stage involved acetic acid fermentation by *Acetobacter pasteurianus* C1, isolated from food waste. The resulting acetic acid containing CW was diluted to various concentrations of acetic acid. In the second stage, the acetic acid was converted into PHA by *Bacillus* sp. CYR-1. The 10-fold diluted CW (5.7 g/L acetic acid) showed higher PHA productivity (240.6 mg/L) as compared to the 4-fold diluted CW containing 12.3 g/L acetic acid (126 mg/L PHA). Furthermore, excess protein removal from CW increased PHA production by 3.26 times [139].

Besides using a low-cost substrate, genetically engineered robust microbial strains are another research hotspot in bioplastics. A few strains belonging to species of *E. coli*, *Pseudomonas*, and halophiles *Halomonas* have been genetically engineered for more PHA synthesis and accumulation. There can be four to five ways microorganisms can be genetically engineered to increase bioplastic competitiveness. For example, there can be a change in the biosynthetic pathway, altered the cell-growth pattern and morphology for more PHA accumulation and better separation, and engineering of extremophiles to produce PHA in extreme conditions of temperatures or salt. Any microbial cell uses fatty acids as precursors for forming short-chain-length (SCL) or medium-chain-length (MCL) PHAs. Because β-oxidation of fatty acids may hamper the conversion of fatty acids to PHAs, a weakened pathway for β-oxidation of fatty acids in a cell increases the efficiency of PHA biosynthesis [28]. The combined result of genetically engineered microorganisms and low-cost substrates like whey or dairy wastewater stream has gained much attention as a superior approach to manufacturing commercially compatible bioplastics. In a study, recombinant DNA technology was applied to *Cupriavidus necator* DSM 545, a well-known PHA producer, to make it capable of utilizing lactose as a carbon source for PHA production. An intracellular PHA depolymerase of *C. necator* was chosen for inserting *lac*Z, *lac*I, and *lac*O genes of *E. coli*. This enabled the organism to utilize lactose and simultaneously helped remove a part of the PHA intracellular degradation system [140].

2.7. Bacterial Cellulose. Bacterial cellulose (BC) is a nonfibrous, exopolysaccharide produced by acetic acid bacterial strains (AAB). Besides AAB, many species belonging to *Salmonella*, *Escherichia*, *Sarcina*, *Rhizobium*, *Agrobacterium*, and certain algal species also synthesize cellulose [125]. BC possesses superior physical and chemical attributes compared to plant cellulose. This is due to its unique ultrafine nanostructure, a higher degree of polymerization, and the absence of hemicellulose or lignin. As a result, BC exhibits greater stability at high temperatures, higher mechanical strength, crystallinity, and biodegradability [141]. Because of its unique properties, BC finds applications in the food, paper, and textile industries, biosensing materials, cosmetic and medical devices used for wound dressings, and burn treatments [142]. The Food and Drug Administration (FDA) has approved many BC-based scaffolds because of their low proteins and endotoxic unit content [143].

Though high in demand, industrial production of bacterial cellulose and commercialization are limited due to the low production yield. Therefore, a few researchers have investigated cheese or dairy whey's valorization for BC production. One of the studies showed that cellulose production by *Acetobacter xylinum* 10821 and *A. xylinum* 23700 using cheese whey was very low compared to standard Hestrin Schramm (HS) medium [144]. Therefore, selecting high-yielding strains can be the first solution to overcome this problem. Unfortunately, most strains used for BC production are non-lactose utilizing due to a lack of the *lacZ* gene. To avert this problem, a recombinant strain *Acetobacter xylinum* ITz3 was engineered by inserting the *lac*Z gene, thus allowing the hydrolysis of lactose [145]. As a result, *A. xylinum* ITz3 produced 1.82 g/L BC in the whey-based substrate, registering a 28-fold increase compared with the wild-type strain, but still, the yield was not high enough for BC production at the commercial scale. Pre-treatment of cheese whey with β-galactosidase enzyme has been another approach for increasing BC production by AAB. In addition, a few researchers have used enzymatic hydrolysis of cheese for BC production [146]. In this study, enzymatic hydrolysis of lactose in cheese whey resulted in higher BC production (3.55 g/L) by *G. xylinus* PTCC 1734 compared to untreated whey and standard HS medium (3.2 g/L). As expected, the crystallinity index of BC produced on whey (61.86%) was lower than the crystallinity index for BC produced on standard HS media (79.07%) [146]. Revin *et al.* [147] evaluated the possibilities of using cheese whey as an alternative source for BC production by fermenting it with *Gluconobacter sucrofermentans*. This strain yielded higher BC (5.45 g/L) using cheese whey compared to HS medium (2.14 g/L) as this strain can utilize lactose. However, the structure of microfibrils and attributes like crystallinity and strength changed when cheese whey was used as a growth medium and termed inferior compared to that obtained with HS media. However, cheese whey, combined with the residual liquid of grapes Corinthian currants finishing (CFS), has also been used for BC synthesis [148]. This study optimized an ideal process (50.4% whey percentage in the CFS, pH 6.36, and 1.7% yeast extract) for BC production by *Komagataeibacter sucrofermentans* DSM15973. The

average yield of BC obtained in this study was 18.9 ± 0.7 g/L [148]. In a recent study, an efficient scale-up process for BC production using *Acetobacter pasteurianus* RSV-4 (MTCC 25117) in whey medium with the addition of β-galactosidase (1.5 IU/mL) was investigated, and 5.6 g cellulose/L was obtained at 30°C after eight days of propagation [149].

Currently, reported BC productivity on cheese whey without supplementation remains relatively low (not higher than 5.6 g/L). Pre-treatment with β-galactosidase or supplementation with residues from grape processing along with nitrogen and vitamin supplementation has shown better BC production. However, changes in the crystallinity index and strengths of cellulose microfibrils were observed. Hence, further investigation should be aimed at high-yielding strains suitable for producing BC with superior physical properties with whey as a growth medium. Further, AAB strains with galactose utilization and high proteolytic activity should be searched to impact increased BC production significantly. Although whey is a cheaper feedstock for BC production, its use may result in an end product of inferior quality. Hence, supplemented whey with high-yielding strains can be considered promising for producing good-quality bacterial cellulose.

2.8. Food Colors. The increased health-conscious behaviour of people has encouraged food producers to shift their focus towards natural pigments, which are safer than artificial colors. The global market for natural food color pigments reached US$ 8.5 billion as of 2020 and is expected to double, reaching US$ 17 billion by 2031 (https://www.factmr.com). A wide variety of natural dyes, such as carotenoids, anthocyanins, chlorophyll, and betalains, offer a broad range of color spectrums. Natural colorants are conventionally sourced from agricultural produce, including fruits, vegetables, flowers, and seeds. However, their production requires a large agricultural area, time, labor, and specific seasonal requirements. Microbial pigments, on the other hand, can be produced under shorter periods, utilize cheaper raw materials, and are independent of seasonal changes [150]. Low-cost carbon sources such as dairy whey are used as media for culturing various pigment-producing microorganisms, as shown in Table 2. Several microbial species (Cellulosimicrobium sp., *Bacillus* sp., *Deitza* sp., *Kocuria* sp., and *Monascus* sp.) are reported to produce color pigments (Table 2) [150, 151, 152, 153, 154]. Several factors, including the type of substrate used, pH, water activity, incubation temperature, sugar concentration, inoculum ratio, oxygen availability, and light intensity, influence the yield of natural pigment production by microorganisms [155]. Enzymatic hydrolysis of dairy whey is required for enhanced fermentation. Bakhtiyari *et al.* [151] studied the production of carotenoid pigment from a strain of *Cellulosimicrobium* in whey in the presence of tricarboxylic acid cycle intermediates viz, citrate, malate, succinate, and glutamate. They noted that the intermediates increased the overall pigment production. Mehri *et al.* [150] reported that the production of red pigment from *Monascus purpureus* grown in demineralized whey was the highest compared to other agricultural waste (viz, soybean residue, coconut residue, bagasse, and cornmeal). Several species of *Penicillium* can thrive in medium with cheese whey (lactose) as the sole carbon source to produce yellow, orange, and red pigments [156]. Roukas *et al.* [157] used a bubble column reactor for cultivating *Blakeslea trispora* for carotene production in deproteinized hydrolyzed cheese whey supplemented with 30 g/L Tween 80, 30 g/L Span 80, and 0.2% (*v*/*v*) β-ionone, resulting in a considerably high carotene production of 405 mg/L/day. Production of carotenoids by yeast (*Rhodotorula mucilaginosa*) increases with increased sugar concentration, aeration, and supplementation with ammonium sulfate in dairy whey [158]. In addition, to optimize physical and chemical production parameters, other techniques like coculturing and genetic engineering are also being utilized to enhance pigment production [159]. Coculturing has been found effective in activating specific cryptic pathways through cell-cell interactions leading to the production of novel secondary metabolites, including certain pigments [160, 161]. Coculturing *Aspergillus chevalieri* with *Monascus* has shown increased effectiveness in pigment production [162]. Genetic engineering of microbial strains, including gene modification, gene cloning, and elimination of nonessential genes, has been investigated for enhancing pigment production and reducing toxins formation [163, 164]. A study has shown that the aurofusarin gene cluster was positively affected by transcription factor AurR1, enhancing the aurofusarin pigment production by *Fusarium graminearum* [165]. Further research may increase microbial pigment's efficiency, feasibility, and production yield.

2.9. Food Flavors. The flavor is a sensation produced by the complex interaction between volatile and nonvolatile components in food. Some of the flavoring compounds include amino acids, fatty acids, organic acids, aromatic hydrocarbons, aldehydes, ketones, alcohols, lactones, and esters. Commercially, flavors may be extracted from plants or obtained *via* chemical reactions. Almost all flavoring compounds can be produced synthetically. However, flavors' chemical production is not environmentally friendly [166].

Furthermore, people nowadays prefer natural and naturally sourced products. However, the extraction of flavors from plants is a costly process. Conversely, microorganisms can convert even cheaper substrates into flavoring compounds through fermentation (Table 2). In dairy products, lactic acid bacteria produce aromatic compounds such as diacetyl, acetaldehyde, hexanal, and butanal [167, 168]. Cheese whey has been utilized for flavor production after its electroactivation. Electroactivation of whey, i.e., electroisomerization of lactose into lactulose, could promote the growth of multiple cultures due to lactulose's prebiotic and antioxidant properties [169]. Electroactivated lactose whey can produce aroma volatiles by fermentation with *Kluyveromyces marxianus*, lactic acid bacteria, acetic acid bacteria, etc. [170, 171]. *Galactomyces geotrichum* has been reported to produce a flavor complex having a pleasant honey-rose aroma in dairy whey and buttermilk [172]. An attempt has been made to isolate several yeast strains and screen for 2-phenyl ethanol (2-PE) production using whey, glucose, and their combination as carbon sources. 2-PE is an alcohol

Table 2: Production of pigments, flavors, and antimicrobials using microbial fermentation, culture conditions, and yield obtained.

	Substrate	Microbial species	Remarks	Reference(s)
Pigments				
Carotenoid	60% (*w*/*v*) whey	*Cellulosimicrobium sp.*		[151]
	60% *w*/*v* whey+ citrate, malate, and succinate as carbon and nitrogen sources	*Cellulosimicrobium sp.*		[151]
Rubropunctamine and Monascorubramine	Raw whey powder, demineralized whey powder, and deproteinized whey powder	*Monascus purpureus* CMU 001	50 g/L lactose concentration; β-galactosidase (Saphera 2600L) enzyme for hydrolysis of lactose in whey; highest pigment concentration produced from demineralized whey	[150]
Melanin	5% whey powder and 0.25% L-tyrosine	*Dietziaschimae* NM3	L-tyrosine is critical for melanin production; 790 mg/L pigment productivity	[152]
Pulcherrimin	Whey lactose medium	*Bacillus licheniformis* DW2	The addition of Tween 80 improved pigment yield; the maximum yield obtained was 331.17 mg/L	[153]
β-Cryptoxanthin	Cheese whey	*Kocuria marina* DAGII	Maximum pigment, i.e., 17.14% productivity at 12% (*v*/*v*) of cheese whey; growth inhibition took place at substrate concentrations higher than 12% (*v*/*v*) of cheese whey	[154]
Flavors				
2-Phenylethanol (2-PE)	Whey-based media	28 different yeast strains, including *S. cerevisiae*, *Meyerozyma caribbica*, and *Metschnikowia chrysoperlae*	Maximum production was achieved by *S. cerevisiae* strains (3.3 g/L)	[173]
Flavor compound complex	Electroactivated whey, electroactivated whey permeate, and electroactivated lactose	*Lactobacillus strains*, *Lactococcus strains*, *Kazachstania exigua*, *Dekkera bruxellensis*, *Kluyveromyces marxianus*	Lyophilized Kefir grains were used as starter culture; electroactivated whey attained the maximum biomass production (6.04 g/L)	[170, 171]
Flavor compound complex	Sour whey and buttermilk	*Galactomyces geotrichum*	13 essential aroma compounds were identified; the highest odor activity values were found for phenylacetaldehyde (honey-like) in the buttermilk and 2-phenyl ethanol (rose-like) in the sour whey	[172]
Flavor compound complex	Glucose-added whey	*Wickerhamomyces pijperi*	12 aroma compounds were identified; major components were ethyl acetate, acetaldehyde, and isoamyl alcohol	[174]
2-Phenylethanol (2-PE)	Cheese whey	*K. marxianus* and *D. hansenii*	Coculturing of *K. marxianus* and *D. hansenii* increased flavor production by approximately twofolds (0.38 g 2PE/g L phe) compared to monocultures (0.16 ± 0.08 g 2PE/g L phe)	[175]
2,3-Butanediol	Cheese whey and whey permeate	*Escherichia coli* K12 MG1655	Genetically modified strain; various dilution ratios were used; undiluted effluents produced the highest 2,3-BD yield (0.43 g/g lactose)	[214]

Table 2: Continued.

	Substrate	Microbial species	Remarks	Reference(s)
Antimicrobials				
Antifungal activity	Whey	*L. plantarum*	Inhibitory effects against *Aspergillus*, *Fusarium*, and *Penicillium* in bread	[191]
Antifungal activity	Whey	*L. plantarum* N7	Whey beverage and yogurt, inhibitory effects against *Pichia pastoris* D3, *Aspergillus niger* D1, *Geotrichum candidum* N1, *Kluyveromyces marxianus* W1, and *Penicillium chrysogenum* B1	[193]
Antifungal activity	Freeze-dried whey	*Lactobacillus plantarum* (CECT 220, 221, 748)	*Fusarium moniliformis*, *F. graminearum*, and *F. verticillioid*es, fermented whey beverage, phenolic compounds	[190]
Nisin	M-17 media with whey permeate	*Lactococcus lactis* subsp. *lactis* ATCC 11454	Continuous nisin production using packed-bed bioreactor; maximum nisin titer was 2.6×10^4 activity unit/mL	[194]
Antifungal activity	Sweet whey	*L. plantarum* CECT 220, 221, 223, and 748	*Penicillium expansum* CECT 2278 and *Penicillium brevicompactum* CECT 2316, Pita Bread, 14 days shelf-life extension.	[192]
Antilisterial activity	Goat cheese whey	*L. lactis*	The maximum inhibitory effect after 18h at 31°C	[188]
Antibacterial activity	Curd whey	LAB and yeast strains	Tested against *Salmonella typhimurium* G 38 and *Bacillus subtilis* 17-89; synergistic effect of LABs and yeasts	[196]
Paenibacillin	Acid whey	*Paenibacillus polymyxa* OSY-EC	Potency against Gram-positive bacteria	[198]

having a characteristic, pleasant rosy aroma, chiefly used in the food, perfume, and cosmetics industries. Among the selected strains, only *Clavispora lusitaniae* WUT17 and WUT20 and *Meyerozyma guilliermondii* WUT22 could grow in whey. However, all strains grew well in whey and glucose-containing medium. *Saccharomyces cerevisiae* strains showed the highest production (3.3 g/L) [173]. Izawa *et al.* [174] investigated the production of aroma compounds by seven strains of yeast *Wickerhamomyces pijperi* in a whey medium with added glucose. Twelve different aroma compounds were identified in the fermentation mix. The significant proportions were ethyl acetate, acetaldehyde, and isoamyl alcohol. Although ethyl benzoate had a low concentration compared to other compounds, it produced a robust fruity flavor. The composition of the aroma complex varied with the fermentation media used. Notably, ethyl benzoate was only produced in fermented broth having whey-glucose. Castillo *et al.* [175] investigated the production of flavor compounds in cheese whey using *Kluyveromyces marxianus* and *Debaryomyces hansenii* as monocultures and cocultures. The main flavoring compounds included ethanol, glycerol, propionic acid, dihydroxyacetone, methanol, isopentanol, and 2-phenyl ethanol (2-PE). Owing to its commercial potential, 2-PE was selected as the target component. Both yeasts were able to produce 2-PE by metabolizing L-phenylalanine. It was observed that coculturing of *K. marxianus* and *D. hansenii* increased flavor production by approximately two folds (0.38 g 2-PE/gLphe) as compared to individual or monocultures (0.16 ± 0.08 g 2-PE/gLphe). Genetic modification of microorganisms can improve flavoring product yield, increase the range of utilised substrates, and reduce or eliminate toxin formation [176]. A wild strain of *Escherichia coli* K12 MG1655 was genetically modified by blocking biosynthetic pathways of various organic acid synthesis, such as acetic acid, succinic acid, and lactic acid. The resulting strain, *E. coli* JFR12, was studied to produce 2,3-butanediol using whey and whey permeate. The genetically modified strain could be commercialized for high 2,3-BD production (up to 0.41 g/g lactose) under mild operating conditions [177].

2.10. Antimicrobials. LAB are mainly used as selected agents for the fermentation of dairy products and are known to exhibit several technofunctional properties [178]. These attributes include the production of lactic acid, aroma, antimicrobials such as bacteriocins, bioactive peptides, phenolic compounds, and short-chain fatty acids [179]. LAB, especially adjunct starter cultures, are used to increase sensory quality and shelf life due to the production of acetate, ethanol, and carbon dioxide [180]. Apart from dairy products, LAB is also applied in manufacturing fermented fruits, vegetables, and meat products [181, 182]. Whey is an excellent medium to culture lactic acid bacteria to produce antimicrobials (Table 2). It has been observed that fermenting whey with lactic acid bacteria favors the proteolysis of whey proteins and the production of antimicrobial substances along with organic acids [183, 184]. Fermented whey shows antimicrobial activity attributed to bioactive peptides, bacteriocins, lactoferrin, and immunoglobulins. In fermented whey, lactoperoxidase, glycomacropeptide, and sphingolipids are also responsible for inhibitory activity against pathogens [185, 186, 187]. Generally, whey protein concentrates, or whey powder, is preferred over whey for its supplementation in the media to maximize antimicrobial production. Recent studies indicate that using whey-based media for antimicrobial production is cheaper than costly culture media [188].

Fermented products of dairy, cereal, fruits, and vegetables are usually spoiled by fungal contamination due to the inherent higher acidity in these products [189]. Several LAB has been found to excrete organic acid, bacteriocins, and phenolic compounds that inhibit the growth of spoilage fungi, help protect fermented products from being spoiled, and extend their shelf life. *Propionibacterium* sp., *Lactiplantibacillus plantarum*, *Lacticaseibacillus casei*, and *Lacticaseibacillus rhamnosus* have been associated with antifungal activity [189, 190, 191, 192]. In a study, Luz et al. [191] used whey-based media fermented with *L. plantarum* for dough preparation for loaf bread. They recorded a 0.5–0.6 log (Colony-Forming Unit) CFU/g reduction in *Penicillium expansum* growth with an extended shelf-life of 1–2 days compared to control bread. Xu et al. [193] prepared a whey beverage fermented with *L. plantarum* N7 with antifungal activity against many spoilage-causing fungal strains such as *Pichia pastoris* D3, *Aspergillus niger* D1, *Geotrichum candidum* N1, *Kluyveromyces marxianus* W1, and *Penicillium chrysogenum* B1. Several researchers optimized the process of producing nisin [194], enterocin [195], and other antilisterial substances [188] using whey as the base medium.

Interestingly, combined cultivation of specific LAB and yeast strains in supplemented curd whey has shown increased antimicrobial activity [196]. For example, the LAB and dairy yeast (*L. rhamnosus* 2012+*Kluyveromyces marxianus* 11) inhibited the growth of multidrug-resistant bacteria such as *Staphylococcus aureus* sp. and *Pseudomonas aeruginosa*. It was achieved due to the synergistic effect of their respective metabolites and by the interaction between lactic acid bacteria cells with the cell wall of yeasts. Some innovative way of using whey proteins and LAB is in the form of an edible coating or film with or without cell-free culture supernatant of a specific LAB to apply it as a wrapping or covering for shelf-life extension of food products [197]. In a recent study, ribosomal engineering was employed on a wild-type strain of *Paenibacillus polymyxa* to increase the productivity of Paenibacillin (a promising lantibiotic having potency against Gram-positive bacteria) in acid whey. The resulting strain, *Paenibacillus polymyxa* OSY-EC, showed improved productivity [198].

2.11. Biohydrogen. Biohydrogen is an emerging high-energy-density fuel that is clean and carbon-free. Biohydrogen is energy intensive with a calorific value of ~120-140 MJ/kg; only water is generated from combustion [199]. Biogases can replace carbon fuels for residential and industrial activities, thus reducing carbon emissions [200]. Biohydrogen is estimated to meet 8–10% of global energy requirements [201]. Hydrogen is obtained mainly from natural gas steam reformation, petroleum refining, and coal gasification. These energy-intensive hydrogen production methods emit large

Table 3: Production of biohydrogen through microbial fermentation using cheese whey as substrate.

Feed stock	Microbial species	Biohydrogen yield	Productivity	Reference(s)
Hydrolyzed cheese whey	Microbial consortium	1.93 mol H_2/mol of sugars	5.07 L H_2/L/day	[135]
Cheese whey (supplemented with buffalo manure)	Anaerobic sludge consortia	152.20 mL H_2/g of substrate	215.40 mL H_2/L/day	[211]
Acid cheese whey (mozzarella cheese)	Activated sludge consortia	371.00 L H_2/kg total organic $carbon_{whey}$	nd	[212]
Cheese whey (powder)	*Lactobacillus acidophilus*	1.00 mol H_2/mol of lactose	nd	[81]
Cheese whey (permeate)	Microbial consortium	3.60 mol H_2/mol of lactose	140.02 mmol H_2/L/day	[208]
Cheese whey (powder)	*Ethanoligenens* sp. and *Megasphaera* sp.	5.40 mol H_2/kg COD	129.00 mol H_2/L/day	[200]
Cheese whey (powder)	Microbial consortium	1.12 mol H_2/mol lactose	1080 mL H_2/L/day	[206]
Cheese whey (powder)	*Thermoanaerobacterium* and *Thermohydrogenium kirishiense*	3.67 mol H_2/mol lactose	nd	[207]
Fresh cheese whey	*Clostridium* sp. IODB-O3	6.35 mol H_2/mol lactose	139 mL/g/h	[204]
Cheese whey	*Lactobacillus* and *Bifidobacterium* spp.	178 mL/g COD	1.28 normal liter/L/day)	[210]
Cheese whey	*Lactobacillus acidophilus*	nd	1665 mL in 72 hours	[81]

nd: not determined.

amounts of greenhouse gases [202]. Water electrolyzation can be another method of producing hydrogen, which is much more energy-intensive. In the recent decade, a paradigm shift in biofuel production has been seen toward alternative ways of hydrogen production using biomass feedstock [203]. These cost-effective technologies are based on fermentation and photosynthesis, wherein agroindustrial waste and wastewater are used as feedstock for hydrogen production [204, 205]. Cheese whey is a frequently used substrate for biohydrogen production, and the utilization of cheese whey for gas production has the lateral advantage of reducing environmental carbon emissions (as shown in Table 3).

Biologically, hydrogen can be produced in three ways: through dark fermentation, biophotolysis, and bioelectrochemically by microbial fuel cells [30, 206, 207, 208, 209]. Dark fermentation of cheese whey with hydrogen-producing microorganisms such as *Enterobacter* sp. and *Clostridium* sp. has received attention due to higher yields of biohydrogen and organic acids [209]. The presence of methanogens in cheese whey decreases the hydrogen yields as it tweaks the biochemical activities toward methane production. Methanogens in cheese whey are thermally inactivated (85°C/30 min) [209, 210]. Critical parameters like pH and temperature should be maintained during dark fermentation as they affect the activity of the hydrogenase enzyme and, in turn, affect hydrogen productivity [30]. High organic load and concentration of volatile acids in the cheese whey present some problems with microbial anaerobic digestion. However, adding a cosubstrate with complementary characteristics or natural or inorganic buffering agents may subside these problems [211]. Researchers have used cheese whey to produce biohydrogen with wild and engineered microorganisms as a carbon source, as shown in Table 3. Nevertheless, several challenges, such as incomplete utilization of lactose, lesser productivity, lack of efficient bioreactors, scale-up, compression, and storage, need attention to produce biohydrogen at a large scale cost-effectively [212]. Also, the lack of distribution networks and platforms presents difficulties in adopting biohydrogen as a frequently used fuel [9]. An increase in biohydrogen production has been worked upon in many ways, such as multistage dark and phot-fermentation, genetically engineered strains, and other process parameters. For example, the strains of genetically engineered *Escherichia coli* WDHGFA have produced better biohydrogen yields [213]. For efficient removal of organic load from cheese whey, multistage fermentation is now focused most, which may lead to a circular economy and zero carbon emission [30, 31, 135, 214, 215]. Apart from the above, various simulation and statistical tools are essential in improving the biohydrogen yield using cheese whey as a feedstock.

2.12. Challenges and Future Perspective. Valorizing whey through microbial fermentation into value-added biomolecules has been challenging; however, exciting developments have been made to increase productivity. So far, the selection of wild strain and their adaptation for better utilization of cheese whey has played a critical role. Genetic engineering is the most effective strategy for higher productivity. Recombinant strain *Saccharomyces cerevisiae* E2 had the highest bioethanol productivity from raw cheese whey with added lactose. For efficient biodiesel production, a separate fermentation stage for the prolific growth of oleaginous yeast like *Cryptococcus curvatus* and *Cutaneotrichosporon* with essential nutrients (may be from another agrowaste such as wine lees) is a must. For the production of SCP-based meals, a mixed culture with *in situ* lactase activity is generally chosen for utilizing whey. It needs a constant oxygen supply; however, the stability of the composite culture is the main challenging issue here. Genetically modified SCP like *Yarrowia lipolytica* with more omega-3 fatty acid is an exciting research development. Specific strains (*Actinobacillus succinogenes* NJ113, *Pseudomonas taetrolens*, and *Lactobacillus helveticus* strain Milano) for particular organic acid production must be chosen, and accordingly, the feedstock must be

supplemented. For higher PHA, genetic modification of *Cupriavidus necator* DSM 545 has proven to increase yield. High-yielding AAB strains with galactose utilization and high proteolytic activity must be searched for superior-quality bacterial cellulose from cheese whey. Electroactivation of lactose whey has improved volatile aromatic compound yields with *Kluyveromyces marxianus*, *Wickerhamomyces pijperi*, lactic acid bacteria, acetic acid bacteria, etc. Commercial application of genetically engineered *E. coli* JFR12 for higher 2,3-BD production substantiates that microbial biotechnology is essential for a sustainable ecosystem. Multistage dark and photofermentation is an effective strategy for biohydrogen production. However, specialized fermenters must be sought for biorefining every biomolecule, and all other process parameters must be optimized. The entire process should be simulated on the pilot and an industrial trial scale to efficiently remove organic carbon from cheese whey so that laboratory concepts can be translated to the commercial platform faster.

3. Conclusions

Cheese whey and whey permeate are the primary wastes of the dairy industry and can be highly polluting if directly released into water bodies and landfills. The present work provides a comprehensive view of existing strategies and research developments regarding the biorefining of cheese whey. These strategies help reduce environmental pollution and provide ways to reap the economic benefit of dairy byproducts further. Still, there is a need to economize the process of reducing the organic carbon in the whey and producing higher amounts of value-added products.

In summary, cheese whey is an alternative feedstock for biotransformation into biofuels, bioplastics, natural colors and flavors, bacterial cellulose, and protein biomass. Specific microbial species such as yeasts, LAB, and AAB offer the opportunity to explore innovative bioconversion strategies. Selecting genetically modified or adapted new strains and optimizing process parameters is recommended. However, there is a need to integrate the existing technologies in a cascading manner to achieve zero carbon emissions. An integrated multistep biorefining strategy is needed, where at every step, the residual carbon from the previous bioprocessing step is utilized, allowing complete valorization of cheese whey.

Conflicts of Interest

The authors declare that they have no conflict of interest that could have appeared to influence the work reported in this paper.

Authors' Contributions

CG is responsible for funding acquisition, conceptualization, writing—original draft preparation, and editing. PD is assigned to writing—editing. ST is assigned to editing and review. SBD is responsible for the conceptualization, reviewing, and editing. PKS and JSD are responsible for visualization, reviewing, and editing. BSS is involved in conceptualization, writing—original draft preparation, reviewing, and editing.

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