Lactose and Permeate Valorization in Non-food Applications: A Literature Review

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Introduction

Once considered "waste" or, at best "by-products" of the dairy industry, lactose, whey, and lactose-rich milk and whey permeate are now valuable co-products with a multitude of applications in the dairy, food, and non-food industries. Since the 1930s, when lactose was used as a filler (57) or placebo tablet in drug efficacy research (64), lactose has been used as a tableting excipient (bulking agent). The fact that lactose is sweet is only part of the reason-the functional properties of the three forms of lactose[1] have also made it a go-to compound for oral drug delivery for decades (55, 74).

As early as the 1960s (72), lactose, whey and whey permeate were being studied for applications in production of rigid polyurethane foams. Heating dried whey permeate (9.5% water), an oxidizing agent (propylene oxide) and a catalyst (potassium hydroxide), Viswanathan et al. (148) synthesized a polyether polyol liquid. Coupled with the phosphorus in permeate, incorporation of urea into the polyether polyol reduced the amount of flame retardants needed to make self-extinguishing low-density polyurethane foams from renewable dairy side-streams.

In the early 1990s, 94.4% of lactose was directed to human foods, 3.7% to animal feed, and 1.8% to non-food applications (107). Predominant non-food uses at the time included ethanol manufacture, microbial polysaccharides, polymer conversion, insulating foam and wood-binding adhesives. By 2003, the value of whey permeate and lactose derivatives was being realized in non-food applications (13). For instance, potassium acetate was used for airport runway deicer; lactulose in laxatives; lactitol in plasticizers; and lactobionic acid in organ transplant preservation solution. By 2018, lactose fatty acid esters were considered "high-value-added derivatives of lactose" for the food, cosmetic, detergent, and pharmaceutical industries (91).

Available at lower cost than many renewable options, lactose and permeates are among the dairy ingredients with expanding potential in numerous industries, with seemingly endless opportunities for valorization (Figure 1; Table 1). With limited fossil fuels, the role of these ingredients to serve as renewable substrates is growing. An objective of writing this literature review is to provide scientists from a variety of fields an overview of some applications where lactose and permeates have found use, with hopes to inspire further innovation. Expanding valorization of lactose and permeate contributes to the U.S. Dairy Industry's Net Zero Initiative (Dairy Management Inc. (DMI 2025)).

1 α-anhydrous, β-anhydrous, α-monohydrate

Figure 1. Example methods and resulting product categories demonstrating valorization of lactose and permeate (DLP: delactosed permeate; DWP: demineralized whey permeate; LML: lactose mother liquor).

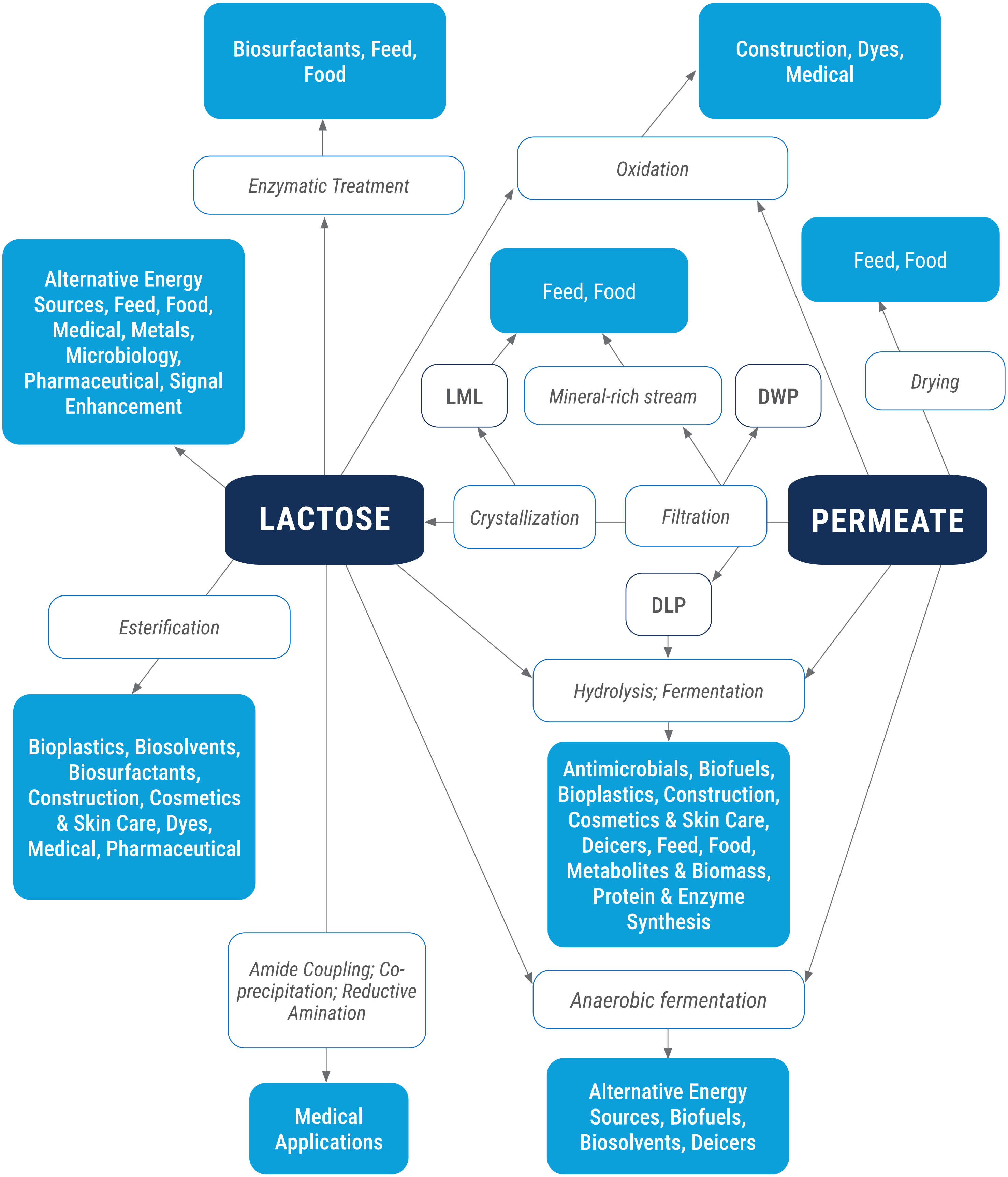

Table 1. Non-food applications for lactose and permeate.

Category	Applications(s)	Dairy Ingredient(s)	Reference(s)
PHARMACEUTICALS, COSMETICS & SKIN CARE	Tablets	Lactose	12, 57, 64, 74, 88, 107, 123, 133
	Hyaluronic acid	Whey protein hydrolysate, whey permeate	103
	Lactose octoacetate (antiviral, antifungal)	Lactose	10
	2-phenylethanol (rose-like fragrance)	Lactose	49
	Resveratrol (antioxidant, antibacterial, anti-inflammatory, anti-aging)	Lactose	37
	Cinnamic acid sugar ester derivatives (sunscreen)	Lactose	111, 112
MEDICAL	Lactose-modified chitosan (repair of articular cartilage, osteoarthritis therapeutic treatment)	Lactose	47, 99, 140
	Lactose-modified hyaluronic acid (therapeutic treatment of smoking-related diseases)	Lactose	48
	Lactobionic acid (drug delivery systems, tissue engineering, nanomedicine, organ preservation)	Lactose, whey (acid, sweet), ricotta cheese whey, whey permeate	5, 6, 7, 43, 66, 125, 129
	Phage-loaded calcium phosphate-based bioceramic powder (prevent hospital-acquired infections after joint surgery)	Lactose	41
BIOPLASTICS	Polyhydroxyalkanoates (PHAs)	Lactose, whey, whey permeate, HLP	39, 52, 85, 83, 84, 119, 120, 150, 155
	Polylactic acid (PLA)	Whey, whey permeate*	58, 76, 94, 121
	Edible films	Deproteinized whey, whey permeate*	4, 125
	Hydroxymethylfurfural (building block chemical)	Lactose, whey permeate, ultrafiltered whey permeate	114

Table 1. Non-food applications for lactose and permeate (cont.)

Category	Applications(s)	Dairy Ingredient(s)	Reference(s)
BIOFUELS	Bioethanol	Lactose, whey, whey permeate (acid, sweet), DLP	14, 28, 29, 59, 116, 117, 127, 128, 138, 149, 154, 161
	Biomethane	Milk permeate, whey permeate*	139
	Biodiesel	Lactose, whey, whey permeate, HLP, DLP	24, 45, 51, 137
	Biohydrogen	Lactose, whey, whey permeate*	35, 40, 115, 118
BIOSOLVENTS & BIOSURFACTANTS	Bio-butanol (also a biofuel)	Whey permeate	54, 56, 87, 122, 132
	Ethyl acetate (for cleaning, adhesives, paints, etc)	Whey permeate, DLP, partially demineralized whey permeate	69, 141, 142
	Sugar-based fatty acid esters (e.g., lactose palmitoleate)	Lactose	91, 97, 130, 131, 146
ALTERNATIVE ENERGY SOURCES	Microbial fuel cells	Lactose, whey, whey permeate, DLP*	9, 32, 33, 67, 152
	Rechargeable aqueous zinc metal batteries (ASMBs)	Lactose	93
	Microalgae farming	Whey permeate (acid, sweet)	16, 61, 109, 113, 136
CONSTRUCTION	Concrete (self-healing)	Lactose mother liquor, whey permeate	2, 62, 75, 82, 163
	Wood (esterification)	Whey permeate	25, 81
	Adhesives (for laminated composites)	Lactose	26, 27
	Polyurethanes	Lactose	31
	Rigid polyurethane foam	Lactose, whey, whey permeate	72, 148
DEICERS	Calcium magnesium acetate (CMA), calcium magnesium propionate (CMP), propylene glycol	Whey, whey permeate, lactose	102, 143, 144, 145, 160

* No peer reviewed research utilized the specific dairy ingredient, but it shows promise.
DLP: delactosed permeate; HLP: hydrolyzed whey permeate

Table 1. Non-food applications for lactose and permeate (cont.)

Category	Applications(s)	Dairy Ingredient(s)	Reference(s)
DYES	Glycol-azadyes (dying of wool, polyester, cotton, nylon, acetate)	Lactose	20, 21
	Indigo dyeing (blue denim jeans)	Lactose	126
	Naturalization of wood dyes	Lactose	147
METALS	Magnesium alloys (metal composite)	Lactose	50
	Carbon-bonded alumna foam filters (for steel filtration)	Lactose	23, 65, 68, 156
	Lactose xanthates (for heavy metal removal from wastewater)	Lactose	106
SIGNAL ENHANCEMENT	Molecular fingerprinting (Tetrahertz absorption spectroscopy magnification)	Lactose	90, 110, 151, 159
	Clinical diagnosis of liver cancer	Lactose	164
PROTEIN & ENZYME SYNTHESIS	β-galactosidase, a variety of proteins and lipases	Lactose, whey permeate, milk permeate	19, 42, 63
VALUABLE METABOLITES & BIOMASS	Lactulose, single-cell protein, organic acids, volatile aromatic compounds	Lactose, whey, whey permeate	46, 77, 78, 79

Pharmaceuticals, Cosmetics & Skin Care

For approximately 100 years, lactose has been one of the most widely used excipients in **tablets** (~70% of oral solid dosage formulations) because of its favorable compressibility, polymorphic forms, binding properties, sweetness, and solubility (88, 133). Whereas in the past, excipients were used as binders, disintegrants, fillers and lubricants, in recent years, they have also contributed to drug release modulation, prolonging tablet residence time, taste masking, and solubility enhancement (12). A few examples of how lactose has contributed to these functional benefits are included in the following paragraphs.

Drugs that have poor compressibility require a high amount of directly compressible excipient, which increases the weight and size of the tablet, which is unappealing to patients (123). The oral diabetes drug, Metformin HCl, shows very good water-solubility, but very poor flow and compressibility properties. In an effort to improve compressibility, Raval and colleagues (123) combined Metformin HCl and anhydrous lactose in various w/w% ratios in ethanol at room temperature then induced crystallization in a 4-5°C freezer. Various mechanical properties of pure Metformin HCl, lactose-Metformin HCl crystals and tablets with different formulation excipients were compared. In addition to demonstrating a stable nature (good shelf-life), novel lactose-Metformin HCl crystals and tablets had improved mechanical properties, solubility and compressibility over the pure drug, suggesting feasibility of the drug crystal engineering approach on a commercial scale.

Dissolution of active pharmaceutical ingredients for subsequent absorption is typically preceded by disintegration of tablets--an important consideration in oral drug development (74). Tablet disintegration involves swelling, strain recovery and wicking effects of the disintegrant (12). In an effort to better understand the impact of fillers on disintegration properties of drugs, Janssen and colleagues (74) compacted different forms of lactose[2] into tablets of different solid fractions. All six formulations were suitable for direct compression of tablets in a commercial setting, as well as to undergo subsequent stresses during distribution. Their linear models revealed that pore size distribution and polymorphic composition of lactose affected tablet disintegration most. Higher concentrations of α-lactose monohydrate led to faster tablet disintegration, and disintegration time increased when anhydrous and amorphous lactose composed the tablets. The findings are particularly useful for tablet formulation development.

Recently, Shi and collaborators (133) characterized the effects of moisture sorption and lactose type[3] on tablet quality. Powders and tablets were stored at three relative humidity levels (33, 55, 75%) before evaluating properties across one month of storage. Lactose grade largely determined hygroscopic and compression properties as well as tablet quality. Moisture sorption induced reductions in compressibility, compactability and tabletability. For instance, higher rates of isomerization (from β- to α-) were noted for spray dried and granulated lactose than for α-lactose monohydrate and anhydrous lactose. This was an important finding, helping to explain why tabletability is greater for β-lactose than α-lactose. The authors concluded that attention should be paid to the ambient humidity during production and storage of lactose powders intended for tablets to minimize adverse effects resulting from of moisture uptake.

In recent years, **hyaluronic acid** has gained popularity in the cosmetics industry, particularly with the help of advertisements featuring models carefully pronouncing the compound to provide familiarity with the term. Hyaluronic acid (HA) is a polysaccharide consisting of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine that is a natural component of skin and joints (73, 1). Several *Streptococcus* species produce HA, but many are pathogenic (73, 103). While *S. thermophilus* can produce HA, an abundant

2 spray dried, granulated, anhydrous, granulated anhydrous

3 sieved α-lactose monohydrate, granulated, anhydrous, and spray-dried lactose

carbon source is necessary for it to do so (11). Mohan et al. (103) demonstrated that both whey permeate (82% w/w lactose) and whey protein hydrolysate (20% degree of hydrolysis) can serve as suitable feedstocks for *S. thermophilus* to produce HA.

Arabadzhieva and colleagues (10) utilized microwave irradiation to esterify lactose with acetic anhydride for synthesis of lactose octaacetate. **Lactose octoacetate** has antiviral activity against herpes simplex virus type 1 and certain influenza viruses. Since solvents were not used, this is considered an environmentally-friendly method. Lactose octaacetate exhibited low cytotoxicity against three cell lines. While lactose octaacetate did not demonstrate antimicrobial activity at the tested levels, it displayed antifungal activity against *Aspergillis niger* ATCC 1015, *Penicillium* species, *Rizopus* species, and *Fusarium moniliforme* ATCC 38932. The authors concluded that lactose octoacetate can be successfully applied for cosmetics purposes.

Drężek et al. (49) demonstrated an environmentally friendly aerobic fermentation process to produce the natural rose-scented antimicrobial compound, **2-phenylethanol** (2-PE), from whey permeate using two GRAS yeast strains of *Kluyveromyces marxianus* and one of *K. lactis*. Approximately 2g/L 2-PE as well as useful yeast biomass could be produced through L-phenylalanine biotransformation in whey permeate-based media in a continuous system. In clean-label "naturally-scented" cosmetics and personal care products, fermentation-derived 2-PE may be used.

Costa and collaborators (37) described methodology to valorize "lactose-rich wastes" using a biologically engineered Saccharomyces cerevisiae strain for de novo production of **resveratrol** from lactose via aerobic fermentation. Resveratrol, a polyphenol naturally found in some plants, has antioxidant, antibacterial, anti-inflammatory, and anti-aging properties that make it appealing in cosmetics applications. A recombinant S. cerevisiae was engineered to utilize one pathway to produce phenylalanine from lactose, and another pathway to utilize phenylalanine to produce resveratrol through p-coumaric acid. Although whey powder with 71% lactose served as the feed in their study, pure lactose or whey permeate could serve as promising feed sources.

More recently, Olivieri et al. (111, 112) described synthesis, cytotoxicity and physicochemical properties of new **cinnamic acid sugar ester derivatives** (CASEDs), including one derived from lactose (i.e., lactose tetraacetal). These compounds consist of a cinnamate moiety, linked via ester bond through enzymatic esterifiction, to the non-anomeric carbon of a glycosyl backbone. Their preliminary results suggest that some of the CASEDs show potential for use as UVB filters in sunscreen products, as a potential replacement for ethylhexyl methoxycinnamate (EHMC), which can be harmful to marine ecosystems (111).

Medical Applications

In reconstructive surgery for bone and cartilage, synthetic polymers, ceramics and metals are often used (134). However, sometimes biodegradable, porous, polymeric scaffold matrices are needed to support, reinforce, or help organize regenerating tissue (101, 134). Natural compounds like fibrin, hyaluronan, collagen and calcium alginate gels have been shown to support tissue growth and repair, but until the early 2000s, production of long-lasting cartilage of optimal mechanical strength had not yet been realized (47, 101). Madihally and Matthew (99) were among the first to demonstrate the ability of chitosan-based materials to mimic the cartilage matrix and serve as a scaffold for tissue engineering. Considering the ability to modify biological activity of chitosan by exploiting the reactivity of amino groups (158), Donati and colleagues (47) conducted reductive amination reactions (N-alkylation[4]), to graft the aldehyde group of lactose to the

4 An amine nitrogen is bonded to an alkyl group derived from a carbonyl compound; the intermediate imine is

amino group of the glucosamine residues of chitosan to create a highly-soluble engineered polysaccharide. The **lactose-modified chitosan** (Chitlac) was non-toxic, acted as a bridging agent for neighboring cells, and induced cell aggregation of a primary culture of pig chondrocytes. The work demonstrated the potential for application of Chitlac in the repair of articular cartilage.

Building on these and other findings, Tarricone and colleagues (140) evaluated the effect of a combination of hyaluronic acid (HA) and Chitlac in an osteoarthritis model. Osteoarthritis, the most common form of arthritis, is a progressive inflammatory degenerative disease that affects joints (95). Although not fully understood, macrophage-mediated inflammation is a key player in cartilage deterioration (140). The extracelluar matrix, of which HA is a component, are primarily degraded by matrix metalloproteinases (MMPs), which are induced by inflammatory mediators (95, 100). Tarricone et al. (140) measured pro-inflammatory molecules and metalloproteinase expression using an in vitro model of macrophage-mediated inflammation. Results revealed that HA, Chitlac and their combination (HA-Chitlac) counteracted oxidative damage and restored gene transcription for pro-inflammatory cytokines and inflammation regulators[5] to near baseline levels. The authors concluded that HA-Chitlac can serve toward development of an early-stage osteoarthritis therapeutic treatment.

Similar to osteoarthritis, smoking-related lung diseases progress by way of macrophage-mediated inflammation, which leads to increased expression of proinflammatory cytokines and galectins, molecules that bind to β-glactosidase sugars[6] (48). Since some galectins act as regulators of inflammatory response in chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), galectins are good targets for drug design therapies (48, 71). Glycosylated molecules[7] can bind galectins, significantly reduce *in vitro* and *in vivo* galactin expression, and subsequently, reduce inflammation (101, 140). Considering these facts, Donato and colleagues (48) assessed the anti-inflammatory and antioxidant effects of **lactose-modified hyaluronic acids** (called HYLACH®[8]). Remarkably, the in vitro study with inflamed human bronchial fibroblasts revealed that HYLACH® with 10, 20 and 40% degree of lactosylation[9] counteracted oxidative damage and restored gene and protein expression for cytokines to near baseline levels. The findings are a promising step toward further development of lactose-modified HAs for therapeutic treatment of smoking-related diseases.

Switching gears, but staying in the medical field, lactose-derived **lactobionic acid** (LBA[10]) should be mentioned. LBA is comprised of one molecule of galactose attached to one molecule of gluconic acid via an ether-like linkage obtained from the oxidation of lactose (43, 66). It is used in drug delivery systems, tissue engineering, nanomedicine, and organ preservation because it is biocompatible, biodegradable, provides osmotic protection, chelates iron and other ions, has antioxidant activity, and stabilizes cell membranes (6, 43). Han et al. (66) engineered an *E. coli* strain to efficiently produce LBA from lactose, which shows promise industrially. Numerous studies have demonstrated the suitability of pre-treated (pasteurization or sterilization followed by filtration) sweet or acid whey as substrates for microorganisms to produce LBA (5, 6, 7, 128). De Giorgi et al. (43) utilized ricotta cheese whey (which has less protein than sweet whey or acid whey) and demonstrated that LBA could be produced at levels similar to pre-treated sweet cheese whey. Using whey permeate eliminates the need for pre-treatment (125).

5 IL-1β, TNF-α, Gal-1, MMP-3 and MMP-13

6 β-galactosidase sugars serve as substrates for the enzyme (e.g., lactose).

7 Sugar unit(s) attached to protein or lipid via glycosidic bonds.

8 Jointherapeutics, Como, Italy.

9 Lactosylation broadly means attaching lactose to a molecule (or "functionalizing with lactose"). Production of HYLACH® is technically amide coupling (combining carboxylic acid and amine).

10 The full chemical name for LBA is 4-O-β-(galactopyranosyl-D-gluconic acid.

In recent work, Decodts and collaborators (41) demonstrated that lactose was superior to sucrose in serving as a medium in the co-precipitation synthesis of **apatite biomaterials** (crystalline calcium phosphate). Specifically, they developed a phage-loaded calcium phosphate-based bioceramic powder to encapsulate bacteriophage[11] for sustained release over time. The objective was to create a material to combat hospital-acquired infections that are common (1 to 5%) after bone or joint surgery. The phage-loaded powder was effective against *S. aureus* and *E. coli* and was non-cytotoxic to human osteoblastic cells, showing promise for treatment of hospital-acquired infections.

Bioplastics

Prompted by high crude oil prices, commercialization of **polyhydroxyalkanoate (PHA) biopolyesters** began in the 1970s (85). PHAs are naturally produced by some bacteria, are non-toxic to humans and other life forms, are biodegradable, and have similar properties to polypropylene (8). Because of high prices a low availability, PHA commercialization dropped off after crude oil prices fell, but research continued (85). One example of early research using whey involved exploiting the recombinant *E. coli* strain GCSC 6576 to produce poly-(3-hydroxybutyrate) (also known as PHB or P(3HB)) from whey (155). PHB is the PHA biopolyester that is produced by the largest number of microbes in nature from simple feedstocks (e.g., lactose), and which has been studied the most (85). Wong and Lee (155) revealed for the first time that PHB can be produced efficiently from whey with a high polymer content, but pre-treatment of the whey powder was necessary. Of note is that they tested two forms of whey in the batch experiments. In fermentation A, whey powder (65% lactose) was sterilized in an oven, cooled, then added to the fermenter. In fermentation B, a whey solution (310 g whey powder and 0.36 g magnesium sulfate per L) was sterilized, cooled and centrifuged to remove precipitates [protein]. A salt solution[12] and trace metal solution[13] were then added to the supernatant prior to addition to the fermenter. At the time, mineral-rich permeate was not considered to replace centrifugation, salt solution and trace mineral solution, but in subsequent decades, several investigators demonstrated that whey permeate or hydrolyzed whey permeate can be good options for production of PHAs (39, 83, 84, 119, 120). While much of the research utilized hydrolyzed whey permeate, natural whey permeate is likely a more economically viable option, so it will be the focus in subsequent paragraphs.

Considering the large availability of whey in Italy, Povolo and Casella (119) set out to produce PHA (specifically, PHB) from lactose, whey and whey permeate using three lactose-utlilizing PHA-producing bacterial strains from soil. Results were promising, as the amounts of polymer produced in permeate were two-fold higher than those obtained in minimal medium using lactose as substrate. Later, investigators (120) effectively constructed a recombinant strain of *Cupriavidus necator* DSM 545 to grow on lactose[14]. The mutant performed better in whey permeate than in minimal medium containing lactose, which authors credited to the nutrients present in permeate.

Recently, Favaro and colleagues (53) investigated the potential of whey permeate to serve as a feedstock for sustainable production of PHAs by *Hydrogenophaga pseudoflava* DSM1034. *H. pseudoflava* DSM1034 utilizes lactose and galactose as carbon sources, but they recognized that optimization of fermentation parameters would be necessary for feasible large-scale industrial production of PHAs from whey permeate. The lag phase was shorter, and bacterial growth, cell densities and PHAs concentrations were better in whey perme-

11 Bacteriophage are bacteria strain-specific viruses, which are non-toxic to humans and other forms of life.

12 Salt solution contained potassium phosphate, ammonium hydrogen phosphate, citric acid.

13 Trace mineral solution contained ferrous sulfate, sodium tetraborate, calcium chloride, zinc sulfate, manganese sulfate, copper sulfate, ammonium heptamolybdate, sodium tetraborate.

14 *C. necator* is naturally able to produce PHAs, but unable to utilize lactose, so lacZ, lacI and lacO genes from E. coli were inserted to create the mutant C. necator DSM 545.

ate than in lactose. Similar to what was stated by (120) this improvement was credited to the nutrients in permeate. Going forward, using optimized conditions for a non-recombinant organism and non-hydrolyzed whey permeate for production of PHAs could create additional income for dairy processors and reduce the production costs of making PHAs to make it more competitive in the bioplastics market. Indeed, a techno-economic analysis of an industrial-scale production system of PHA from lactose powder, whey permeate, and delactosed permeate (DLP) by a halophilic (salt-loving) PHA-producing microorganism (*Haloferx mediterranei*) was conducted by Wang and colleagues (150). They concluded that using dairy-derived feedstocks has the potential to make PHA competitive in the bioplastics market.

Although the biodegradable thermoplastic **polylactic acid (PLA)** seems like a logical candidate for production from lactose or permeate, other substrates (e.g., corn starch, sugarcane, sugar beet, cassava, wheat) are much more commonly used (58, 98). Nevertheless, whey and whey permeate have shown potential for PLA production, including poly L-lactic acid (PLLA), Poly D-lactic acid (PDLA) and poly DL-lactic acid (PDLLA). PLLA has a low melting temperature (180°C), but a stereocomplex (1:1 ratio) of PLLA and PDLA has a higher melting point (230°C) and better mechanical performance, so the latter is more applicable to industrial applications (94). Sometimes the two are produced separately (by bacteria that preferentially make one or the other), then combined to make PDLLA materials. For instance, Prasad and colleagues (121) used whey permeate as a substrate for *Lactobacillus delbrueckii* subsp. *bulgaricus* LB-12 to produce pure L-lactic acid for PLLA. Juodeikiene et al. (76) pre-treated whey to make a hydrolyzed whey permeate, which subsequently served as a substrate for *Pediococcus acidilactici* KTU05-7 to produce a racemic (50:50 ratio) DL-lactic acid. Liu et al. (94) used hydrolyzed whey for production of D-lactic acid by L. bulgaricus CGMCC 1.6970 for PDLA.

More recently, Garavand et al. (58) pre-treated whey (90°C for 20 min, cooling, centrifugation), then used the supernatant [permeate] for a fermentation broth, which they supplemented[15]. *Lactobacillus paracasei* produced L-lactic acid, which was extracted and used to synthesize PLLA, with and without the addition of chitosan nanoparticles. Mechanical properties (e.g., tensile strength) and antimicrobial properties (i.e., inhibition of *Staphylococcus aureus*) of PLLA film without CNPs were similar to commercial PLA, but the properties were significantly improved by the addition of 2 to 3% (w/w) CNPs. Considering that supplements were added to the fermentation broth, whey permeate might serve as a cost-effective sustainable option for this methodology, requiring less pre-treatment than whey.

Mukherjee et al. (105) promoted implementing on-site industry-integrated bio-refineries at dairy production facilities to produce optically pure D-lactic acid from whey permeate, which would provide value to the operation and to contribute to the circular bioeconomy[16].

In an innovative application (125), whey permeate was used as the starting point for creation of **edible films** with probiotic *Lactobacillus plantarum* and prebiotic lactobionic acid (LBA). Deproteinized sweet whey [permeate] was fermented by *Pseudomonas taetrolens* LMG 2336 to produce LBA. Endotoxins produced by *P. taetrolens* were removed by microfiltration, then gelatin and L. plantarum CECT 9567 cells were added to the fermented permeate to create the films. More recently, Aleksandrovas et al. (4) evaluated the impact of conventional and ohmic heating[17] as pasteurization methods on the mechanical and rheological properties

15 Supplemented with yeast extract, potassium hydrogen phosphate, di-potassium hydrogen phosphate, manganese sulfate monohydrate, and magnesium sulfate.
16 A circular bioeconomy focuses on sustainable production and conversion of biomass into food, materials, energy or chemicals (using renewable biological resources).
17 Ohmic heating involves passing an alternating electrical current through a product, generating internal heat via resistance of the product itself (rather than external heat transfer).

of acid whey protein concentrate-based and acid whey permeate-based edible films.

Biofuels

Bioethanol is among the most extensively explored value-added products that can be obtained from lactose, whey, and whey permeate (28, 29, 117, 138). One of the first reports of the ability to produce alcohol from whey was published in 1928. The manuscript described a yeast[18] isolated from shelf-stable milk in India. Since whey was "at present wasted", the authors concluded that whey might be economically utilized in the production of alcohol (14). Mid-century efforts to produce alcoholic beverages from whey (to utilize the lactose-rich side-stream) were hampered by osmotic stress (high lactose and salts) to the yeast (154, 161). Thus, Gawel and Kosikowski (59) set out to adapt lactose-fermenting yeasts to higher lactose and mineral salt concentrations. One adapted strain of K. fragilis produced approximately 10% (v/v) ethanol from concentrated ultrafiltered cottage cheese whey [acid whey permeate] of high lactose levels (22.5%). Nearly four decades later, Saini and colleagues (127) adapted a strain of *K. marxianus* to improve its osmotolerance to lactose (up to 200 g/L) for bioethanol production. The adapted *K. marxianus* MTCC 1389 strain produced an ethanol titer that was nearly 17.5% higher than the parental strain, showing promise for use of lactose-rich whey permeates for bioethanol production.

Even delactosed whey permeate (DLP), with approximately 150-200 g lactose/L, can be used for ethanol production. Recognizing that DLP is a lower-value product than lactose and permeate, Wagner et al. (149) set out to valorize it. Since *K. marxianus* metabolism is inhibited by high salt concentrations (osmotic stress), the research team subjected DLP to desalination techniques[19] prior to fermentation. Dilution yielded 7% alcohol by volume (AbV), nanofiltration 7.5% AbV, and electrodialysis 11% AbV, but the latter two add expense. The authors concluded that upstream desalination of DLP will be a good option for production of ethanol by *K. marxianus*. Another currently-available option for this application is demineralized whey permeate.

Not only can the yeasts *K. marxianus, K. lactis*, and related *K. fragilis* ferment lactose directly to ethanol, but metabolic engineering techniques have enabled non-lactose-fermenting microorganisms (e.g., *Saccharomyces cerevisiae*) to efficiently produce bioethanol from lactose (28, 29, 128). For example, to evaluate if whey permeate could be incorporated into conventional grain-to-ethanol processing facilities, Parashar and colleagues (116) used whey permeate hydrolysates as partial process water replacement and co-substrate for an engineered *S. cerevisiae* in wheat-to-ethanol production. Since natural *S. cerevisiae* is unable to ferment lactose, whey permeate needed to first be hydrolyzed[20]—then glucose from wheat, and glucose and galactose from permeate hydrolysates, could serve as carbon sources for the yeast. A limitation to whey utilization in the ethanol industry has been the fact that lactic acid bacteria (LAB) may compete for carbon sources and produce acids that are toxic to yeast. To address this concern, they tested the impact of filtered (to remove LAB) and non-filtered permeate hydrolysates on yeast fermentation. Neither form of whey permeate hydrolysates negatively affected ethanol yield (~90%) when substituted by up to 10% of the process water. Higher levels (15 and 20% substitution) decreased ethanol yield (~85%), likely because of osmotic stress from higher fermentable sugars. This work demonstrated that hydrolyzed whey permeate can serve as a suitable co-substrate in wheat-to-ethanol fermentations without further treatment to remove LAB.

Sampaio et al. (128) investigated the ability of *K. lactis* to ferment whey permeate "as is" (38 g/L lactose) or concentrated (55 g/L or 75 g/L lactose, protein < 0.86% (w/v)) to produce bioethanol and yeast biomass with β-glactosidase activity. The use of 2x-concentrated permeate in static cultures maximized ethanol yield

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18 The yeast was referred to as *Torula lactis*--perhaps *Kluyveromyces* lactis under today's classification.

19 Desalination included dilution, nanofiltration and electrodialysis.

20 The authors used Lactozyme 3000L, a β-galactosidase from *K. lactis* (Sigma-Aldrich).

and β-galactosidase activity, while highest yeast biomass was obtained from permeate fermented in shake flasks. The authors promoted exploitation of whey permeate as a feedstock for industrial fermentations. Pendón and colleagues (117) evaluated the ability of 30 K. marxianus strains to produce fuel ethanol, whey protein, and probiotic yeast biomass from whey and whey permeate (100 g lactose/L). Cheese whey and whey permeate powders were resuspended (10% w/w) in distilled water and autoclaved to eliminate microorganisms. K. marxianus CIDCA 9121 fermented whey permeate with 90% ethanol yield, and, even after being used in the fermentation process to produce ethanol, retained viability and probiotic activity[21]. Although the research was conducted in a miniaturized industrial fermentation system, the investigators concluded that it provided evidence of feasibility to implement "food grade" probiotic yeast production into a bioethanol biorefinery.

Tarapata and colleagues (139) analyzed the possibility of using permeates to produce electricity and heat from **biomethane** generated in the process of anaerobic digestion. For analysis of physicochemical parameters and biogas efficiency, a fermentative inoculum[22] was combined in bioreactors with milk ultrafiltration permeate, milk diafiltration permeate, milk serum ultrafiltration permeate, milk serum diafiltration permeate or inoculum only (control). For economic analysis, they created a case study to represent a large-scale dairy plant in Poland solely dedicated to producing milk concentrates and using heat and electric power produced from biogas generated by anaerobic digestion of the permeates. Based upon the robust biogas production from permeates, implementation of an on-site anaerobic digestion facility at the dairy plant was shown to provide enough electricity and heat to exceed the amount necessary for running a large-scale facility. Although food-grade lactose production could exceed the profitability of biogas production, the authors pointed out that other aspects (e.g., renewable energy demand) should be considered when determining which by-product to produce at a given time (biogas or lactose).

Research publications about production of **biodiesel** from lactose and/or permeate are much more limited than other biofuels. Some investigators have utilized microalgae or yeast for bio-oil production. Microalgae can use carbon, light energy and nutrients to produce biomass that can be used for diverse applications, including lipids, dyes, enzymes, fertilizer, antibiotics, carbohydrates, vitamins, and biofuels (24). Espinosa-Gonzalez and colleagues (51) considered the fact that the lipid-producing algae, *Chlorella protothecoides*[23], prefers glucose as a carbon source; that pure glucose is expensive; and that whey permeate is a cheap alternative source of glucose. Whey permeate was used "as is" (182 g/L lactose in liquid form) or hydrolyzed[24] (to a final composition of 95 g/L glucose and 85 g/L galactose). The investigators conducted batch fermentations, small-scale, and scaled-up fed batch fermentations with *A. protothecoides* under conditions to promote bio-oil production (e.g., low nitrogen conditions). Since the fatty acid profile of the algal biomass grown using whey permeate feedstock was comparable to the more expensive pure glucose, authors concluded that whey permeate is a promising carbon source for biofuel production. Later, Borges and colleagues (24) evaluated the ability of *Scenedesmus* species to remove organic materials and produce bio-oil in growth media with a variety of sugars (including lactose), whey, or whey permeate. The microalgae effectively produced lipids when cultured in 2.5 g/L lactose. Although bio-oil production was not enhanced in media containing whey permeate, use of whey improved organic load removal, reducing chemical oxygen demand (COD) in the effluent.

Summers and collaborators (137) took advantage of the nutrient composition of DLP to feed a yeast known

21 Probiotic activity included but was not limited to modulation of inflammatory response in in vitro and in vivo models.

22 Anaerobic sludge was composed of methanogenic bacteria from a bioreactor.

23 Now classified as *Auxenochlorella protothecoides*.

24 With Lactozyme 3000.

to produce lipids, *Cryptococcus curvatus*. They conducted biological experimentation as well as techno-economic analysis and life-cycle analysis of producing renewable diesel from yeast fermentation of DLP in combination with hydrothermal liquefaction. The *C. curvatus* efficiently converted the available carbon (unrecovered lactose in DLP) into biomass, demonstrating a promising pathway for valorization of DLP. The team reported that biodiesel from DLP can be profitable when the biofuel is sold at greater than $4.78/gallon ($1.26/L). They went further to state that improvements in conversion efficiency, yeast biomass productivity and other modifications could dramatically improve economic feasibility.

More recently, Ding and colleagues (45) demonstrated the economically feasible opportunity to utilize whey permeate (90% lactose) as a substrate and inducer for the engineered *E. coli* strain (*E. coli* F13) to produce b-farnesene, a building block for biodiesel.

A less common fuel source, hydrogen (H_2), is a clean energy source because it does not contribute to greenhouse effects. Select anaerobic bacteria (e.g., *Clostridium, Bacillus, Enterobacter*) can consume organic material and produce H_2 gas and other compounds (e.g., CO_2, organic acids) (40). Several authors have investigated the potential of **biohydrogen** (bio-H_2) production from lactose or whey (35, 36, 40, 118). In their efforts to improve acetate production from lactose for use in calcium-magnesium acetate road deicer, Collet and colleagues (36) discovered that the mixed thermophilic anaerobic consortium containing *Clostridium themolacticum* efficiently produced high concentrations of lactate, CO_2, ethanol and H_2. This led them to focus their attention on H_2 production optimization in follow-up work. They showed that whey permeate could serve as a lactose source for *C. themolacticum* to produce both acetate and cheap bio-H_2 (35).

Davila-Vazquez et al. (40) incorporated whey powder (77% (w/v) lactose, 11% protein) into a continuous stirred tank reactor seeded with anaerobic granular sludge from an upflow anaerobic sludge blanket (UASB) reactor that treated wastewater from a confectionery factory. *Clostridium* species predominated the system, and predominantly produced H_2, butyrate and acetate. The fact that minerals[25] were added to the system along with whey powder suggests that use of whey permeate may reduce the need for mineral supplementation.

Pandey and collaborators (115) evaluated the ability of four food grade dairy cultures to produce bio-H_2 in in anaerobic batch experiments containing whey. *L. acidophilus* was the most efficient in bio-H2 production, followed by *Lactococcus lactis, L. paracasei*, and *L. casei*. Bio-H_2 production by *L. acidophilus* was in line with other research with non-food-grade bacteria and cheese whey. Furthermore, other valuable metabolites, including pyruvate, propionate, acetate, lactate, formate and butyrate were also formed. Although neither pure lactose nor permeate were used in the study, the methodology could likely be modified for their incorporation.

Although Polettini and colleagues (118) concluded their 2022 factor-based assessment of continuous bio-H_2 production from cheese whey manuscript by stating that full-scale implementation is "still a long way off," they evaluated whey, not permeate. Their critique centered around the high sensitivity of the H_2-producing biomass to the fluctuating fermentation environment. Nonetheless, they provided indicators that may form a basis for future full-scale applications.

While not a plastic in and of itself, **5-hydroxymethylfurfural (HMF)** is a building block chemical for a variety of valuable derivatives, including bioplastics, biofuels, green solvents, pharmaceuticals, etc. Whey perme-

25 Supplemental minerals included disodium hydrogen phosphate, ammonium dihydrogen phosphate, dipotassium, hydrogen phosphate, magnesium chloride, zinc chloride, ferrous sulfate, manganese sulfate, sodium molybdate, copper sulfate, and cobalt chloride.

ate, ultrafiltered whey permeate, and whey permeate powder have shown promise for valorization into HMF (115). The higher yield of HMF resulting from reactions in with permeate compared to pure lactose was attributed to the presence of amino groups in permeate.

Biosolvents & Biosurfactants

Bio-butanol is both a biosolvent and a biofuel. As a solvent, it has applications in varnishes, paints, dyes and adhesives; in cosmetics (e.g., eye makeup, nail care products); and as a building block for chemicals (e.g., methacrylate) (122). Bio-butanol is also considered an alternative to bioethanol because of its higher energy, density and boiling point, suitability for distribution through petrol pipelines (e.g., lower volatility and corrosivity) and mixability with gasoline (56). Since the 1980s, whey permeate (lactose) has been used as a substrate for butanol production by some *Clostridium species* (132). After hydrolysis, glucose is used by the bacteria to produce three parts acetone, six parts butanol, and one part ethanol, in a process named acetone-butanol-ethanol (ABE) fermentation (54). To date, bioethanol production using ABE fermentation has not been economically viable, because of high substrate costs, low yields (from end-product inhibition on the microorganisms), and high product recovery costs (122). Recognizing the low substrate cost of whey permeate, investigators are bioengineering microorganisms (87) and developing techniques to improve product recovery and removal (54) to validate the potential of ABE fermentation of whey permeate for production of value-added chemicals.

Currently produced from fossil resources, **ethyl acetate** is a versatile volatile organic solvent[26] (70). In addition to producing ethanol from lactose, the yeast *K. marxianus* is capable of producing environmentally-friendly ethyl acetate from whey permeate, DLP, or partially demineralized whey permeate under aerobic conditions (70, 141, 142).

Since the 1970s, lactose has been used as an inexpensive starting material for production of biodegradable **surfactants** (**surf**ace **act**ive age**nts**, or detergents) with emulsification, surface-active, permeability-enhancing and antimicrobial properties (91, 130, 131). Synthesis of sugar-based fatty acid esters/glycolipids commonly involves enzyme-catalyzed (e.g., with lipases) esterification or transesterification (91). Lucarini and colleagues (96, 97) enzymatically synthesized and characterized multiple lactose esters (e.g., lactose laurate, lactose palmitoleate). The compounds had profound antimicrobial activity against eight pathogenic Gram-positive and Gram-negative bacteria and fungi (e.g., *Listeria monocytogenes* ATCC 7644, *Escherichia coli* O157:H7 ATCC 35150) and showed no marked toxicity to intestinal Caco-2 colonic epithelium, while exhibiting desirable permeability-enhancing properties (across skin or mucous membranes), showing promise for use in drugs and biological compounds with biomedical applications. Coupled with these findings, and the fact that they are non-irritant, tasteless, odorless, biodegradable, and have antibiofilm properties, lactose-based esters have been proposed to replace synthetic parabens[27] in the pharmaceutical, cosmetic and food industries (146). Furthermore, because of their low toxicity to humans and low environmental impact, they have also been proposed for their potential to counteract the contamination of plants by larvae, fungi and insects (146).

Alternative Energy Sources

Microbial fuel cells (MFC) are used to convert chemicals (e.g., lactose) to electrical energy (32). Exoelectrogenic microorganisms, those that can release electrons, act as catalysts for the transfer of electrons from the substrate (e.g., lactose) to the anodic electrode where the microorganisms reside (9, 33). The anode and

26 Used for cleaning surfaces, production of adhesives and paints, etc.

27 Parabens are synthetic compounds commonly used as preservatives in cosmetics and skin care products.

cathode chambers are physically separated by a proton exchange membrane (PEM). Electrons flow through an external circuit (e.g., silver wires) to produce current; protons migrate to the cathode to balance the electronegative charge created by the electrons. Substantial work with MFC has centered around recuperating energy from wastewater with high chemical oxygen demand (COD[28]), including dairy farm and dairy plant effluents (9, 15, 32), but lactose and whey permeate have also shown promise for applications in biofuel cells for energy generation (32, 33, 152). The resulting effluents have substantially lower COD (9).

Antonopoulou and colleagues (9) evaluated generation of electricity using lactose or diluted cheese whey as an electrolytes solution/substrate in a two-chamber MFC. To seed the anode with electrochemically active bacteria, experimentation was initiated with anaerobic sludge and glucose as a substrate. Subsequently, lactose or whey, with added trace minerals[29], were used to replace the glucose. Both lactose and diluted cheese whey generated electricity, but lactose was more effective. The investigators concluded that power density and efficiency would be improved by pasteurizing cheese whey to eliminate non-electrogenic microorganisms since whey bacteria performed competitive reactions (e.g., production of methane, CO2) rather than electron production.

Choudhury and collaborators (33) selected *Escherichia coli* K12, the most potent of eight microorganisms, for application in MFCs to evaluate the impact of five process factors on growth and iron-reducing capabilitie[30] . Lactose concentration was determined to be one of the key factors influencing both growth and iron-reduction. Their optimized formulation was composed of 8 g/L lactose, 2 mL of a trace elements solution29, 4% (v/v) of inoculum, pH 7, and 35°C. Considering both of these works, mineral-rich permeate or DLP may be promising MFC substrate alternatives to reduce the supplemental trace element needs.

More recently, Han et al. (67) demonstrated the benefit of synergy among bacterial species in MFCs. They co-cultured *Shewanella oneidensis* MR-1 (exoelectrogen), *Pseudomonas aeruginosa* (exoelectrogen), and *Lactobacillus plantarum* in MFCs with lactate, glucose, and riboflavin as electrogenic substrate, electron donor, and electron shuttle, respectively. Since *L. plantarum* cannot directly utilize lactose, within the MFCs it used glucose to produce lactic acid, which served as an electrogenic substrate and electron donor for *S. oneidensis*. Simultaneously, *P. aeruginosa* used glucose to promote biofilm formation on the anode. The cocktail yielded profound synergistic improvement of substrate utilization, biofilm formation and power generation in MFCs compared to single-strain configurations. The investigators did not use lactose or whey permeate in their research. Future investigators may potentially capitalize on the natural presence of riboflavin in permeate and consider co-culturing *S. oneidensis* and *P. aeruginosa* with a lactose-fermenting culture that also produces riboflavin (e.g., L. acidophilus or S. thermophilus).

Rechargeable aqueous zinc metal batteries (AZMBs) are one of the most promising next-generation energy storage devices not only because of their storage capacity but because aqueous electrolyte solutions have lower cost, lower toxicity, and better environmental footprint than other options (93). They are non-flammable, which makes them a promising alternative to lithium-ion batteries in certain applications (e.g., not electric vehicles). Practical utilization of ASMBs has, in part, been limited by the formation of branch-like metallic protrusions from the Zn2+ anode, called zinc dendrites, that can lead to battery failure. Taking advantage of the high number of hydroxyl groups in lactose (with high electronegativity), Lin and colleagues

28 COD is the amount of oxygen needed to break down organic and some inorganic compounds in water using a strong chemical oxidant. Higher numbers represent greater pollution, or potential to harm aquatic life.
29 Supplement included zinc sulfate, manganese chloride, iron sulfate, cobalt chloride, copper sulfate, boric acid, and sodium molybdate.
30 Promotes electron transfer.

(93) incorporated lactose (0, 60, 100 or 140 mM[31]) into the 2M $ZnSO_4$ electrolyte solution. As an electrolyte additive, lactose improved the electrochemical performance, including reduced dendrite formation, stability during the cycling process, and enhanced charge efficiency, demonstrating promise of lactose for future applications in AZMBs.

In recent years, there has been an increasing need to recapture energy from waste streams, including dairy effluents. Dairy farming and dairy food processing contribute significantly to wastewater streams, necessitating efforts to apply circular economy[32] strategies to reduce environmental impacts (29, 113). Several reviews are available regarding advances in treatments of food waste effluent and dairy (farm and food) wastewater (29, 34, 135, 136). Recognizing that lactose-rich dairy side-streams contain a high nutrient load, numerous investigators have evaluated the potential of whey permeate for **microalgae farming** (108, 113). Algae are among the most efficient ways to economically recover nutrients (e.g., N, P and C) from wastewater for production of higher-value products (e.g., fertilizers and biofuels) (108, 136). Conveniently, the mineral requirements of microalgae are supported by the calcium (Ca_2^+), magnesium (Mg_2^+), sodium (Na^+), potassium (K^+) and phosphate (PO_4^{3-}) found in dairy side-streams (16, 113).

Girard and colleagues (61) demonstrated that *Tetradesmus obliquus* (a green microalga) growth was stimulated when sweet whey permeate was substituted at 40% (v/v) in standard (Bold's Basam medium (BBM[33]) media. Furthermore, the fatty acid profile revealed good suitability of oil from *T. obliquus* for biodiesel production. Later, Bentahar and colleagues (16) showed that acid whey permeate also served as a suitable a nutrient source for *T. obliquus*. They determined that substituting 20% (v/v) of BBM with acid whey permeate was ideal for biomass growth, production of β-galactosidase, and nutrient utilization. Not only does whey permeate serve as a source of carbon, but it also provides bioavailable phosphorous for cultivating monocultures and polycultures of freshwater and saltwater green algae (109).

Recently, Nham and colleagues (108) conducted studies in large-scale outdoor algal cultivation ponds in Sweden in the spring (high light) and autumn (low light). They compared a mixotrophic cultivation system (landfill leachate-whey permeate mixture) to a glucose control (leachate, chemical phosphate, glucose) and a photoautotrophic control (leachate, chemical phosphate). Since the landfill leachate had low concentrations of organic compounds, glucose and whey permeate served as carbon sources for algal metabolism (particularly during dark seasons). In photoautotrophic mode, the algal cultures (predominantly green algae) relied on sunlight and carbon dioxide for photosynthesis. When algal cultures were grown in whey permeate, their growth rate and productivity; N and P removal; and C, N and P recovery rates were high compared to glucose and photoautotrophic controls. The authors concluded that mixotrophic cultivation of mixed species has potential for producing algal biomass year-round in Nordic conditions.

Construction Applications

Concrete is the most-used construction material worldwide, which has major environmental consequences (30, 75, 163). Not only are resources depleted in the production, mining and transportation of cement and aggregate materials, but also in maintenance and repairs (62, 75). The tendency for concrete to crack limits it structural integrity and durability (30, 75, 82). Fortunately, not all microcracks develop into unstable

31 Molarity (M) is a measure of concentration. Specifically, it specifies how many moles of a solute (substance) are dissolved in one liter of solution. One mole is equal to 6.022 X 1023 particles.
32 A circular economy promotes sustainable practices, with emphasis on minimizing waste and making the most of resources by keeping products, materials and resources in use for as long as possible (e.g., recycling).
33 BBM contains micronutrients and macronutrients that freshwater green algae need (including but not limited to sodium nitrate, calcium chloride, magnesium sulfate, dipotassium sulfate, zinc sulfate, copper sulfate, cobalt nitrate and ferric chloride).

cracks, and in fact, may “self-heal” through a combination of chemical, physical and mechanical processes, often involving formation of calcium carbonate (153). When microcracks allow water into concrete matrix, bacteria can become active, produce calcium carbonate ($CaCO_3$), and seal the cracks. Self-healing is influenced by many factors, including but not limited to the type of bacteria, pH of concrete, dissolved inorganic carbon, and presence of calcium ions (82).

A variety of engineering strategies are used to promote self-healing and to increase durability of concrete (82). For instance, the fact that several bacteria can produce $CaCO_3$ (e.g., in caves, soils) has been exploited. By mixing bacteria into cement and aggregate, along with other fillers, natural “microbial concrete” has successfully filled microcracks and improved durability of concrete (30, 75, 104, 153). Achal et al. (2) demonstrated that lactose mother liquor (LML[34]) could be used as a source of nutrients for *Sporosarcina pasteurii*[35] to produce $CaCO_3$. The authors compared 10% w/w LML, 5 g/L NaCl, 20 g/L urea and 15 g/L $CaCl_2$ to other standard media. They concluded that LML could be used as less costly, environmentally-friendly and effective alternative for standard media in the production of microbial concrete. Using similar media as Archal et al. (2), Grabiec et al. (62) grew S. pasteurii in reconstituted whey permeate powder (10% w/w, 5 g/L NaCl, 20 g/L urea and 15 g/L agar). The culture media proved to be a suitable cost-effective, environmentally-friendly alternative in their process to recycle concrete aggregate.

Several authors have demonstrated the potential of certain microorganisms to produce $CaCO_3$ directly from calcium lactate for microbial cement. Jonkers et al. (75) incorporated vegetative cells and spores of alkali-resistant oxygen-tolerant (*Bacillus cohnii*) and calcium lactate into cement—copious amounts of $CaCO_3$ was produced. Khaliq and Ehsan (82) immobilized *Bacillus subtilis* in concrete aggregate along with calcium lactate (0.8%) and a variety of carrier compounds—enhancement of concrete compressive strength was exhibited. Zhang et al. (163) encapsulated *B. cohnii* in expanded perlite or expanded clay (along with calcium lactate and yeast extract) prior to immobilization in concrete—encapsulation enabled more significant enhancement of crack-haling capacity over free cells. Construction engineers may be able to capitalize on the fact that many cultures used in cheesemaking produce calcium lactate[36]. Perhaps co-culturing dairy cultures with $CaCO_3$-producing cultures (e.g., *Bacillus subtilis*) in whey permeate-based may serve as a next-generation media for microbial concrete.

Although **wood** is a common construction material, its applicability to non-residential construction is limited by its high flammability and vulnerability to bio-and photo-degradation, and tendency to swell and shrink due to fluctuations in humidity (25, 162). To make it more durable, give it new functionality, or improve its performance, wood is often modified (e.g., by acetylation, furfurylation) (162). Berube et al. (18) demonstrated improved dimensional stability in lodgepole pine and white pine after incorporation of novel citric acid-glycerol based polymers into the wood structure. Building on these findings, Cadieux-Lynch and colleagues (25) combined citric acid, water and whey permeate powder (WPP[37]) for wood esterification. A solution containing 12.5% w/w WPP and 25% w/w citric acid was heated to and maintained at 60°C until clear and homogeneous. Pre-conditioned trembling aspen and black spruce were immersed in the solution for impregnation under 50 mbar vacuum at ambient temperature for 1 h, followed by a rest time in the solution for 24 h at atmospheric pressure. The esterification reaction was performed at 160°C for 24 h. Controls were treated with distilled water. The low environmental impact treatment substantially increased the dimensional stability of both woods, which was attributed to generation of polymers filling the wood cell walls. The authors

34 LML is the co-product of lactose crystallization (this source contained 15.4% lactose).

35 Gram-positive urease-positive soil-dwelling rod-shaped bacteria.

36 Examples of cultures that produce calcium lactate include but are not limited to: *Lactobacillus delbrueckii* ssp. *bulgaricus, L. acidophilus, L. casei, L. lactis*.

37 This source of WPP contained 88% lactose, 5.8% ash, 2% non-protein nitrogen, 4% moisture.

concluded that the WPP solution treatment of wood shows potential for siding and paneling, where humidity is variable and coating adhesion is important. Recently, Keralta et al. (81) further optimized the method, further confirming the potential for whey permeate in wood polyesterification for furniture and construction applications.

Some of the common adhesives used to produce laminated composites like fiberboard, chipboard and plywood are potentially hazardous and consume petroleum resources (26, 27). Building on the work of Yang et al. (2023), who developed environmentally-friendly sucrose-based adhesives, Cao et al. (26) developed a novel lactose-based adhesive. To do so, they utilized an amino hyperbranched, water-soluble, cationic polymer called polyethylenimine[38] (PEI) to react with hydroxyl groups in lactose, by air oxidation methodology, to form dense networks of crosslinks they called L-PEI. The L-PEI exhibited excellent bonding properties and shear strength in dry, hot and boiling water. Authors concluded that the new high-performance biomass-based adhesive has development potential. Building on the success of L-PEI, Cao and colleagues (27) recently took advantage of the changes that lactose undergoes during the Maillard reaction. By constructing a triple-crosslinked network structure, based upon the Maillard reaction of oxidized lactose with biomass polyamines, they created an adhesive with improved water resistance and mechanical properties.

Polyurethanes are a class of diverse and rugged polymeric materials that can be incorporated into adhesives, coatings, paints, paper, insulators, fibers, foams, wood, etc. (3). Although most polymeric materials are manufactured from nonrenewable resources (e.g., petroleum), Cheng and colleagues (31) endeavored to use lactose to synthesize polyurethanes in a more environmentally friendly fashion. By combining lactose, toluene-2,4-diisocyanate (TDI) and anhydrous N,N-dimethylformamide, with either conventional heat or microwave, the successfully produced new polyurethanes from lactose. The ratio of TDI to lactose dictated whether the polymer was a liquid, a viscous liquid, a gel, or a solid. They further modified the polymer properties by incorporating poly(vinyl pyrrolidone) and polylactic acid (PLA) into the lactose polyurethanes. The authors concluded that the new polyurethanes could replace petroleum-based materials and add value to the dairy industry.

Other Value-added Applications for Lactose and Permeate

Deicers

In the early 1990s, it was demonstrated that whey permeate could be converted into **calcium magnesium acetate (CMA)** to replace salt as a non-corrosive, more environmentally benign road deicer (160). A co-culture of homolactic and homoacetic acid bacteria were used to convert lactose from whey permeate to lactate and then to acetate in continuous, anaerobic, immobilized cell bioreactors. The acetic acid produced from the fermentation was recovered with solvent extraction with a tertiary amine and reacted with dolomitic lime (Ca/MgO) to form a concentrated (>25%) CMA solution, which was dried to form granular CMA deicer. Furthermore, their techno-economic analysis revealed that about 40 tons (40,000 kg) of CMS can be produced from a plant processing 680,000 kg of whey permeate per day. At the time, the return on investment was estimated at 1.5 years (160).

Mathews (102) revealed that **calcium magnesium propionate (CMP**), made with the help of fermentation by *Propionibacteria* species, was also an effective road deicer. Considering these and other works, Vadlani et al. (144) used *Lactobacillus plantarum* for lactose fermentation (lactate production) and *P. acidipropionici* for lactate fermentation (propionate and acetate production) to produce an environmentally-friendly road deicer. Raw cheese whey, whey permeate derived from raw cheese whey, and commercial whey permeate powder

38 This liquid adhesive PEI is not to be confused with the rigid thermo-stable polymer PEI, polyetherimide.

were promising feedstocks in batch experiments. Later that year, the same investigators demonstrated the effectiveness of a continuous two-stage fermentation process to produce propionate and acetate salts from cheese whey (143). Ice-melting studies revealed that the cheese-whey-derived deicer was comparable to commercial salt.

Although the intentions of these investigators were good-to valorize "waste streams" to produce environmentally-friendly deicers to replace destructive salts-synthetic acetic acid and CMA production is less costly than the green approach. Thus, Veeravalli and Mathews (145) set out to develop a more affordable system. They took advantage of the ability of *Lactobacillus* species to ferment lactose at low pH along with the increased efficiency of acetic acid extraction at low pH. Their novel low pH (~4) anaerobic fermentation of lactose from whey permeate with *L. plantarum* and/or *L. buchner*i produced acetate and **propylene glycol** (PG) that is suitable for use in road and aircraft deicing applications.

Dyes

In an effort to "naturalize" synthetic dyes, to reduce the amount of harmful textile dyes entering the environment, Bianchini et al. (20) transferred chromophores onto lactose to create glycol-azadyes. The process enabled efficient dying of wool, polyester, cotton, nylon and acetate without the need for dispersing agents, surfactants or mordants. Building on their earlier work, Bianchini and colleagues (21) developed a double glycoconjugation process to naturalize high molecular weight disperse dyes to expand the process for even more applications.

Indigo dyeing of denim involves an oxidation-reduction reaction (126). In its original form, the oxidized pigment is insoluble (22). Addition of a reducing agent in alkaline conditions cleaves disulfide linkages to form a partially soluble "leuco" sulfur form of the dye, which enables adsorption and diffusion into cotton (22). Air-drying enables the leuco dye to oxidize back to the original form, resulting in denim blue jeans (126). Sodium dithionite ($Na_2S_2O_4$), the most common reducing agent, is environmentally unfavorable because sulfite and sulfate cause various problems when discharged into wastewater (22, 147). Numerous investigators have evaluated green options. Saikhao and colleagues (126) demonstrated that lactose could be used as a reducing agent, at elevated temperatures under alkaline conditions, to substantially reduce the amount of $Na_2S_2O_4$ needed (by about 50%) in the dyebath.

Naturalizing dyes with lactose for eco-friendly applications in wood has also been investigated. Vespignani and colleagues (147) naturalized both an anthraquinone-based dye and an azo dye with lactose. Beech and poplar wood were dyed by immersion in aqueous solutions or application of resin-based solutions by brush. Application was easy, color was vivid, and dyes exhibited good color fastness to washout with water. However, since color fading occurred when exposed to UV radiation (like other natural dyes), the authors concluded that the dyes were only suitable for indoor use.

Metals

Magnesium alloys are strong, lightweight, electrical-shielding metal composites, made primarily of Mg mixed with other elements (e.g., aluminum, zinc, rare earth metals). Although used in a variety of applications (e.g., automotive, aerospace, electronics) their use is limited by their susceptibility to corrosion (50). In an effort to use renewable resources to apply a protective oxide layer on the surface of magnesium alloys, (50) created coatings that included lactose, starch or dextrin (5, 10 and 15 g/L). They demonstrated that all three carbohydrate coatings improved performance (decreased surface roughness, inhibited spark discharge, and increased corrosion resistance).

Lactose has also been incorporated into **carbon-bonded alumina foam filters** used in the extremely high temperature (~1500°C) process of filtering impurities out of molten steel. Historically, the materials used to create steel melt filters have been environmentally unfriendly (23, 68, 156). Gueguen et al. (65) patented a high-temperature-resistant environmentally-friendly binder system that included lactose and tannin. Subsequently, multiple investigators have used techniques to improve the lactose-tannin binder system performance (e.g., filtration performance, compressive strength), demonstrating its potential in the steel industry (23, 68, 156).

Nath et al. (106) demonstrated the effectiveness of lactose xanthates for **removal of heavy metals from wastewater.** Synthesis of lactose xanthates involved a relatively simple process of combining lactose and sodium hydroxide or potassium hydroxide, dropwise addition of carbon disulfide, followed by extraction with diethyl ether and air drying. The lactose xanthates complexed with heavy metal ions of copper (Cu) and nickel (Ni), which were easily removed by filtration.

Signal Enhancement

Identification of molecular species uses spectroscopic analysis to capture **molecular fingerprints** based on ligand structures and spectral emission locations. Highly sensitive and non-destructive methods are used. Terahertz (THz) absorption spectroscopy is a method used to measure the interaction between an electromagnetic field and the electric and magnetic dipoles present in matter (89). Since material properties affect propagation of THz waves, unique spectral signatures shifts (fingerprints) permit identification of matter and understanding of its properties. This nanotechnology has applications in biomedical science, chemistry, biochemistry, materials science, etc. (90, 159). Although THz absorption spectroscopy enables rapid identification of biomolecules, the technology has been challenging for materials that are only available at trace levels. In a series of studies, investigators (90, 110, 151, 159) developed new methods for enhancing the detection of THz absorption spectra of trace analytes using lactose. The investigators effectively took advantage of the highly ordered crystalline structure of α-lactose monohydrate to alter surfaces to trap and localize electromagnetic waves and amplify broadband fingerprint spectrum signals. After coating a 0.2 μm layer film of α-lactose on a Teflon film substrate and studying the different reflection, absorption and transmission spectra of one-dimensional photonic crystal cavities, Wang et al. (151) saw an absorption enhancement factor of nearly 71 times. Nie et al. (110) reported an absorption enhancement factor of over 120 times using a 0.1 μm α-lactose film within coaxial photonic crystal sensors. After demonstrating a 270 times absorption enhancement factor from a 0.1 μm thick α-lactose film on gold-coated PDMS (polydimethylsiloxane) structures, Yan et al. (159) predicted many new future sensing applications.

Capitalizing on the fact that lactose has affinity for **liver cancer** cells, Zhang et al. (164) synthesized a macromolecular magnetic resonance imaging (MRI) contrast agent with lactose. The lactose-modified branched polymer enhanced the MRI signal intensity by 184% at liver cancer sites. The *in vitro* and *in vivo* toxicity and compatibility tests revealed that the compound shows great potential for clinical diagnosis of liver cancer.

Protein and Enzyme Synthesis

Certain lactic acid bacteria (e.g., *Lactococcus lactis* subsp. *lactis*) produce the antimicrobial peptide (bacteriocin against Gram-positive bacteria) **nisin**, which is colorless and odorless, has high thermal stability at low pH, and high water solubility (124). Low yields during production has led many scientists to innovate, and several have capitalized on the nutritive composition of whey permeate. For instance, investigators (17, 44) utilized a fermentation medium composed of whey permeate powder (6% w/w), yeast extract (1% w/v) and Tween 80 (0.1% w/v), to investigate the impact of various conditions (e.g., cell immobilization) on nisin production by *L. lactis* UL719. More recently, Rulence et al. (124) reported on their improved nisin purification methodology using a novel environmentally-friendly process[39]. Similar to previous work, L. lactis UL719 was grown in a whey permeate-based medium (8% w/v) containing yeast extract (4 g/L) and Tween 80 (1.5% v/v)).

Genetic modification of E. coli to express genes from another organism is one of the most common ways to efficiently produce **proteins and enzymes** for a variety of industries (38, 42, 63). In recombinant strains with plasmids containing the lactose operon (e.g., *E. coli* strain BL21(DE3)), lactose and/or isopropyl β-D-1-thiogalactopyranoside (IPTG) are commonly used to trigger gene expression. Lactose or IPTG bind to the repressor protein and prevent it from binding to the operator gene so that RNA polymerase can transcribe the structural gene and induce protein (or enzyme) expression (157). The efficacy of lactose and IPTG as carbon sources for recombinant *E. coli* is well documented. Nonetheless, to reduce production costs and improve efficiencies, some investigators have recently evaluated dairy permeates as alternative inducers. Griecius and collaborators (63) utilized different inducers (IPTG (1 mM), lactose (2, 4, and 6 mM) and milk permeate (2, 4 and 6 mM MPP85)) to induce *E. coli* BL2(DE3) to produce recombinant enzymes. Although it was only in a 2-L laboratory setting, four different recombinant lipolytic enzymes were efficiently produced, and the promising findings led authors to conclude that milk permeate can successfully be used as a cost-effective alternative to IPTG for industrial production of recombinant proteins.

In similar work, de Divitiis and colleagues (42) replaced lactose and IPTG with whey permeate (165 g lactose/L). The growth of *E. coli* BL21(DE3) cells in the presence of whey permeate was 1.3 times higher than that measured with IPTG or lactose. Whey permeate supported good induction levels of the two proteins of interest, similar to those obtained with lactose and IPTG. Additionally cell viability was promoted in the presence of whey permeate (~92% vs. ~80% after 48 hr) and superoxide dismutase activity remained below the basal level. The improved cell fitness and growth in the presence of whey permeate were attributed to its micronutrients, amino acids, organic acids, antioxidant properties, etc.

Using the same mutant as previous investigators (*E. coli* BL21(DE3)), Bianchi et al. (19) demonstrated the potential for sustainable production of **β-galactosidase** (lactase) in high-cell-density fed-batch cultures with crude glycerol and whey permeate. Using recombinant *E. coli* C41(DE3), Gennari et al. (60) demonstrated the feasibility of β-galactosidase to be produced for food and pharmaceutical applications from whey permeate or ricotta whey in a large-scale industrial bioprocess.

Valuable Metabolites and Biomass

In a series of studies, investigators subjected lactose, whey, and whey permeate solutions to electro-activation to produce *lactulose* (46, 77, 78, 79). Chemical isomerization and enzymatic synthesis of lactulose are expensive processes, so alternatives like electro-activation are appealing (46). In electro-isomerization, low-voltage direct current is applied to the cathodic compartment of the 3-compartment reactor (anodic, central and cathodic). Under alkaline conditions, isomerization of lactose yields a lactulose-enriched substrate. Not only does lactulose have prebiotic (bifidogenic) functionality, but it can also be used to produce other value-added derivatives, including lactitol, lactobionic acid, lactosyl urea, GOS (46, 79).

In subsequent work, investigators harnessed the advantages of electro-activation to ease assimilation of readily available monosaccharides and prebiotic lactulose for uptake by the yeast *K. marxianus* (80). Yeast-mold medium and a variety of substrates, formulated to 5% w/v) lactose equivalent, were used as is or were subjected to electro-activation prior to serving as media for K. marxianus ATCC 64884. When grown in electro-activated lactose, electro-activated whey, and electro-activated whey permeate, *K. marxianus* efficiently

39 Solvent-free and lower energy consumption than other methods.

generated valuable **single cell protein** (SCP[40]), as well as several **organic acids** (i.e., lactic, acetic, citric, butyric, propionic), and **volatile aromatic compounds** (i.e., bioethanol, 2-PE, isoamyl alcohol, isobutyl alcohol).

Conclusion

Although maligned by some, because of the discomfort it can cause upon consumption, lactose is arguably the dairy component with the most potential for value-addition. With diverse applications is construction, cosmetics, medicine, biofuels, bioplastics, and more, lactose and lactose-rich permeates are of value to all of us in one form or another. The relatively low cost of these dairy ingredients, their renewability, and the abundant research demonstrating their applicability, should serve as a springboard for future research and valorization opportunities.

40 SCP is protein-rich biomass produced by microorganisms, and can be used as a food or feed supplement.

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