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Conversion of whey and other dairy waste into antimicrobial and immunoregulatory compounds by fermentation

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Fermentation by lactic acid bacteria has been used for millennia to preserve food and make it more palatable. These microorganisms may also generate bioactive compounds with the potential to serve as components in active edible food packaging or as alternative therapeutics. Dairy waste products, especially whey, provide a substrate for growth of these bacteria, and can be incorporated into the formulations of edible food packaging. This minireview deals with the use of dairy waste to grow lactic acid bacteria to produce bioactive compounds, specifically antimicrobial peptides and immunoregulatory molecules, and their potential use in food and therapeutic applications.

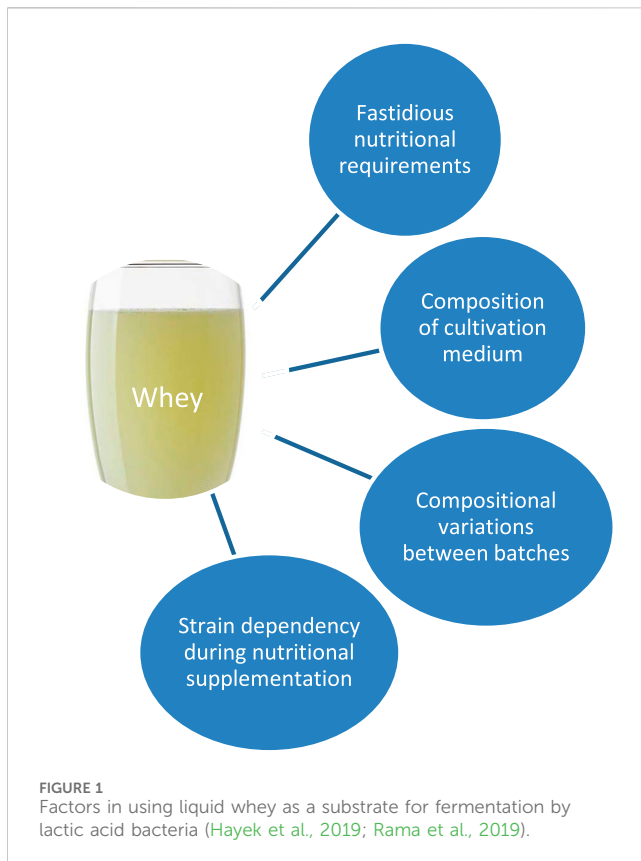
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1 Introduction

Around 18% of milk is wasted for various reasons, and these byproducts of dairy processing, including curd chunks, spilled and spoiled milk, waste ice cream, and whey, should be considered a serious problem for the environment due to their high chemical oxygen demand levels (Ahmad et al., 2019; Sar et al., 2022). Production of 1 kg of cheese generates at least 9 L of sweet whey (Tunick, 2009) and manufacture of 1 kg of Greek yogurt results in 2–3 kg of acid whey (Erickson, 2017). The major components of whey are water (around 94%), lactose (4%–5%), protein (0.8%–1%), and minerals (0.5%–0.7%) (Tsakali et al., 2010). Whey proteins constitute 20% of the protein in bovine milk and are comprised of approximately 50% β -lactoglobulin, 20% α -lactalbumin, 16% immunoglobulins, and 8% serum albumin, with the balance being designated as minor whey proteins, such as lactoferrin (Deeth and Bansal, 2019). Some whey is processed into more useful and valuable forms including whey protein concentrate (Senan et al., 2016), whey powder (Sabo et al., 2019), and whey permeate (Musatti et al., 2020), but much of the liquid whey generated in the manufacture of cheese and yogurt is discarded or fed to livestock (Tunick, 2009).

Upcycling dairy waste streams into valuable new products is clearly advantageous for the dairy industry and the environment. Fermentation with lactic acid bacteria (LAB) is one way to generate useful products from this waste (Patel and Shukula, 2017). LAB are Gram-positive non-spore formers that metabolize carbohydrates to lactic acid and other compounds. Fermented dairy products have been reported to possess numerous benefits such as anticarcinogenic, antimicrobial, antioxidant, hypocholesterolemic, hypotensive, and immunomodulatory properties due to microbial metabolites formed



during the fermentation process (García-Burgos et al., 2020; Ağagündüz et al., 2021; Raman et al., 2022; Dasriya et al., 2023).

Some of the most important bioactive compounds formed by LAB during the fermentation process are bacteriocins (antimicrobial peptides), exopolysaccharides, lactic acid, and peptides, along with amylase, lipase, and protease enzymes (Mathur et al., 2020; Ağagündüz et al., 2021). These compounds may be generated during routine manufacture of fermented dairy products (Akalin, 2014) but can be created from waste streams as well. Sweet whey from cheesemaking, acid whey from Greek yogurt production, and buttermilk from cultured butter preparation have all been cited as sources of bioactives and other useful compounds (Faria et al., 2023).

The valorization of whey and other dairy waste into useful products is a highly active research area. This minireview focuses on the advantages and challenges of fermentation by LAB of waste dairy streams to produce antimicrobial and immunoregulatory compounds, along with suggestions for future research.

2 Industrial production

Liquid whey and reconstituted whey powder have been used as fermentation substrates with various strains of LAB (Bandara et al., 2023; Vera-Santander et al., 2024). The steps involved usually include the addition of yeast extract, vitamins C and E, and Mg and Mn salts; incubation; and recovery of bioactives by centrifugation. The largest advantage in using this dairy byproduct is its availability and low cost – it is usually obtainable at no charge. Issues involving growth of LAB in whey are shown in

Figure 1. Lactose, the carbohydrate in whey, is often supplemented by glucose, which LAB hydrolyze faster (Hayek et al., 2019). Whey protein, peptides, and amino acids serve as nitrogen sources, which may be enhanced with peptone and yeast extract. Mg, Mn, and other minerals are added, as are buffering agents, which maintain the proper pH level, and surfactants, which improve nutrient uptake (Hayek et al., 2019).

3 Antimicrobials

LAB use a variety of proteases and peptidases to hydrolyze proteins, producing essential amino acids for their growth and potentially releasing bioactive peptides. The proteolytic activity of *Lactobacillus helveticus* strains has been extensively studied, with several novel antimicrobial peptides generated from the breakdown of casein (Fan, et al., 2019; Singh et al., 2023). In addition to antimicrobial peptides released during protein degradation, several LAB strains have been reported to naturally produce antimicrobial peptides called bacteriocins.

3.1 Bacteriocins

3.1.1 Properties

Whey and other waste from dairy processing have been investigated as inexpensive feedstocks for generating antimicrobial peptides, especially bacteriocins (Sar et al., 2022; Hameed et al., 2023; Miller et al., 2024). Bacteriocins, which are synthesized by ribosomes, are categorized into three or four classes and several subclasses based on their characteristics (Alvarez-Siero et al., 2016; Darbandi et al., 2022; Pujato et al., 2024). Bacteriocins are easily produced, sensitive to proteases, non-toxic to eukaryotic cells, and do not influence sensory properties of foods (Peng et al., 2020).

Bacteriocins produced by LAB exhibit antibacterial properties against Gram-positive bacteria, notably the foodborne pathogens including *Listeria monocytogenes*, *Staphylococcus aureus*, and species of *Clostridium* (Silva et al., 2023). Most LAB bacteriocins operate by forming pores within the cell membranes of susceptible bacteria leading to cell lysis, or by degrading bacterial cell walls (Pérez-Ramos et al., 2021). Interest in defining applications for LAB bacteriocins is high due to consumer demand for reducing the number of chemical preservatives within foods, and concern over the emergence of antibiotic-resistant microorganisms (Daba and Elkhateeb, 2023). Nisin remains the only LAB bacteriocin with “generally recognized as safe” status by the US Food and Drug Administration, while pediocin-producing *Pediococcus* spp. have been given “qualified presumption of safety” by the European Food and Safety Authority (Darbandi et al., 2022; Raman et al., 2022) status; thus, both bacteriocins have been used commercially as food preservatives (Radaic et al., 2020). Nisin is the most well studied Class I bacteriocin, or lantibiotic, which is characterized by presence of the amino acid lanthionine and undergoes post-translational modifications; while pediocin is a Class IIa bacteriocin, defined as a small, heat-stable peptide that does not undergo post-translational modification (Yi et al., 2022). Both nisin and pediocin are used to prevent the growth of *L. monocytogenes* (Grigore-Gurgu et al.,

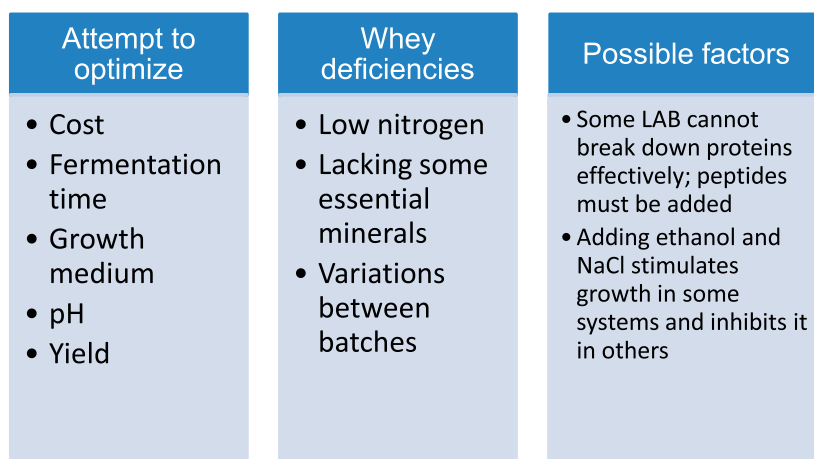


FIGURE 2
Factors involved in producing bacteriocins from fermentation of whey (Abbasiliasi et al., 2017; Ali et al., 2023).

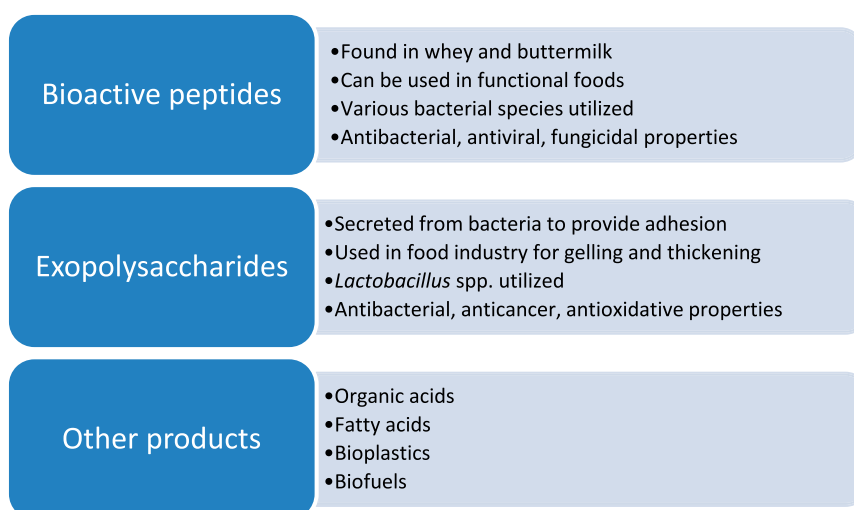


FIGURE 3
Other applications of dairy waste fermentation (Ahmad et al., 2019; Hameed et al., 2023; Sar et al., 2022).

2024), while other LAB bacteriocins, including lacticin 3,147 (Darbandi et al., 2022), durancin 41D (Renyé et al., 2009), and thermophilin 110 (Ceruso et al., 2021), are currently being investigated as alternative anti-listerials. Many other bacteriocins have been identified and are currently being studied for potential applications and approval by the Food and Drug Administration.

3.1.2 Production

Laboratory procedures for isolation and purification of bacteriocins have been established for years (Twomey et al., 2021), but such techniques are not cost-effective on an industrial scale (Kamal et al., 2023). These obstacles could be avoided by using bacteriocin-containing fermentates (Yi et al., 2022). Several companies market purified nisin and several others sell LAB as bioprotective cultures for generating bacteriocins directly in the food (Pujato et al., 2024). Use of dairy byproducts that are rich in

carbohydrates and protein would reduce the amount of waste while providing low-cost carbon and nitrogen sources for LAB. Whey is a good choice for this application due to the presence of lactose. Bacteriocins from whey are typically obtained by culturing LAB overnight, centrifuging, and adjusting the pH level. Protein is needed for normal metabolic processes but can also serve as a source of bioactive peptides via proteolysis. In one study, bacteriocin production was maximized in a bench-top fermenter when yeast extract was added to whey containing *Bifidobacterium animalis* subsp. *Lactis*, which acts against *L. monocytogenes* (Balciunas et al., 2016). In another study using goat cheese whey with prebiotic inulin and *Lactococcus lactis* added, bacteriocin was produced and found to be effective against *L. monocytogenes* (de Lima et al., 2017). Demineralized whey and deproteinized whey protein fermentation liquor have also been used to produce bacteriocins (Abbasiliasi et al., 2017). Bacteriocins have also been

isolated from waste ice cream. The ice cream was shaken and then strained to remove butter grains, and the aqueous phase was inoculated with strains of *Streptococcus thermophilus* or *Lactobacillus lactis*. Bacteriocins were produced in amounts comparable to concentrations detected in microbiological growth medium (Miller et al., 2024). The challenges in producing bacteriocins are shown in Figure 2.

3.2 Use of non-whey dairy waste as a substrate

The ice cream industry also generates a large amount of wasted material during production which cannot be sold commercially but is rich in valuable food grade components including sugar and proteins. Like other dairy waste streams, waste ice cream poses environmental hazards due to its chemical oxygen demand, thus it must be processed prior to disposal or used as animal feed. Disposal of this material can lead to a significant economic burden for ice cream producers, thus finding ways for upcycling this material is high priority for the industry. Recently it was shown that an aqueous product collected after the extraction of fat from melted vanilla ice cream could function as a fermentation substrate for bacteriocin production, specifically nisin and thermophilin 110 (Miller et al., 2024). More studies are needed to confirm that an aqueous stream from industrial, pooled waste ice cream would support the same level of bacterial growth and bacteriocin production.

In addition to bacteriocin production, caseins are known sources of antimicrobial peptides, such as casocidin, isracidin, kappacin, and lactenin. Casocidin and isracidin, for instance, are generated during fermentation of milk and can be used to ward off bacterial contamination (Somkuti and Paul, 2010). Any dairy waste stream containing caseins, including wasted cheese curd or ice cream, could be a source for generating milk-derived antimicrobial peptides via fermentation.

3.3 Therapeutic uses

Microbial fermentation of whey produces bioactive peptides that have been associated with antioxidant, antihypertensive, antidiabetic, anticancer, opioid, and immunomodulatory activity along with muscle protein synthesis (Minj and Anand, 2020). Bacteriocins are responsible for other Therapeutic use of health benefits. Macedocin, produced from *Streptococcus macedonicus*, kills oral pathogens and can be incorporated in toothpaste and mouthwash (Zoumpopoulou et al., 2013). PLNC8, a bacteriocin produced by *Lactiplantibacillus plantarum*, interacts with phospholipids in the cell membrane of *Helicobacter pylori*, which has been implicated in ulcers and other gastric diseases (Liang et al., 2022). More recently, it was reported that thermophilin 110, produced by the dairy starter culture *S. thermophilus*, can inhibit the growth of *Streptococcus mutans* and *Cutibacterium acnes*, suggesting potential applications for oral and skin care respectively (Renyé and Steinberg, 2021; Renyé et al., 2023). These bacteriocins could presumably be produced on an industrial scale using whey as a substrate.

Recombinant DNA technology may be employed to alter the genome of certain strains of LAB with the goal of increasing the yield

of bioactive compounds in milk and generating new ones. Developments in this area will allow amino acids to be inserted or removed, which could increase the efficiency and stability of the compounds produced (Kamal et al., 2023).

3.4 Incorporation in edible coatings

Edible coatings and films have been explored for preventing oxidation reactions that could negatively affect food quality and shelf life (Gamze, 2024). In addition, it has been shown that bioactive materials, such as bacteriocins, can be incorporated into these packaging materials resulting in active films and coatings which can be used to further prevent the growth of spoilage microorganisms and pathogens (Silva et al., 2023). The bacteriocins may be encapsulated as nanoparticles, nanofibers, or liposomes (Chandrakasan et al., 2019). Much of the research reported on biopreservation of dairy products has dealt with films based on whey protein and containing bacteriocins, especially nisin, or lysozymes (Esmer and Sahin, 2017; Kandasamy et al., 2021).

To take advantage of differing film properties, conventional materials may be used for outer packaging, with protein-based films containing bioactive compounds for inner packaging. Multilayer films containing antimicrobials usually have control, matrix, barrier, and outer layers. The bacteriocins are embedded in the matrix layer and the control layer regulates their release into the product (Rejeesh and Anto, 2023). Using protein-based films as inner packaging may lead to some shortcomings in technical properties in some cases but provides sustainable and so-called chemical-free food contact surfaces (Chen et al., 2019). Improvement of barrier properties, elongation at break, and tensile strength edible coatings based on whey protein will be helpful in the acceptance of this product (Chaudhary et al., 2022). Few studies have reported on the inclusion of fermentation-generated antimicrobials in edible packaging (Kandasamy et al., 2021), so further development in this area will help the dairy industry meet sustainability goals while enhancing food protection.

4 Fermentates

A fermentate is defined as a product of a microbial fermentation. Fermentation has been used for many centuries to preserve and enhance the flavor of food. By optimizing the types of microorganisms and fermentation conditions, the process can generate compounds such as bioactive peptides, enzymes, and vitamins (Hernandez-Figueroa et al., 2024). This section deals with fermentates containing bioactive molecules other than bacteriocins.

4.1 Antibacterial action

Fermentates contain LAB cells, either viable or inactivated, along with growth metabolites, and may be used as alternatives to antimicrobial agents such as benzoates, propionates, and sorbates (Hernandez-Figueroa et al., 2024). In addition to bacteriocins, fermentates may contain acetoin, antifungal peptides, diacetyl, ethanol, hydrogen peroxide, and organic acids, all of which act as

antimicrobials (Silva et al., 2018). Bovine lactoferrin, one of the minor whey proteins, acts as an antimicrobial agent by sequestering iron from bacterial pathogens, and two peptides produced by its digestion, lactoferrocin and lactoferrampin, exhibit antibacterial and antifungal properties (Superti, 2020). Novel antimicrobials have been identified from LAB species isolated from raw milk, including a strain of *Lactocaseibacillus paracasei* isolated from a popular acid curd cheese in the Baltic region. This strain exhibits antifungal activity and could be grown using the whey and waste cheese (Vasiliauskaite et al., 2023).

4.2 Immune response

Genetic factors, aging, lifestyle, and environmental factors can influence immune function (Kim et al., 2022). Some bioactive compounds in LAB fermentates have been shown to positively influence and play a crucial role in modulating the immune response (Mathur et al., 2020). Probiotics and LAB have been studied for their immunomodulatory properties, as they can stimulate immune cells and modulate the gut microbiota (Rocha-Ramírez et al., 2021; Saleena et al., 2023). The immunoregulatory properties of fermented dairy products are strain-dependent (Dasriya et al., 2023; Zou et al., 2024). Many studies have investigated the immunomodulatory properties of fermented dairy products like yogurt, kefir, milk, and cheese (Marco et al., 2017; Farag et al., 2020; Saleem et al., 2024). Research has shown that the consumption of specific functional foods can stimulate the activity of immune cells and provide protection against cancer, viruses, and bacteria (Hachimura et al., 2018; Kim et al., 2022).

4.3 Combating inflammatory bowel disease

An example of an illness where conventional medical management is supplemented with fermented dairy products is inflammatory bowel disease (IBD), which primarily consists of ulcerative colitis and Crohn's disease. The etiology of IBD is still unknown (El-Salhy, 2023). Ulcerative colitis is a type of IBD that manifests as non-specific chronic inflammation of the colonic mucosa with alternating cycles of remission and exacerbation (Huang et al., 2023). An estimated 0.4 percent of people in the US suffer from IBD (Gros and Kaplan, 2023). Colonic inflammation, remission, and relapse also afflict those with Crohn's disease, which affects 0.2 percent of people in the US (Gajendran et al., 2018). Research indicates that imbalance of intestinal flora, along with genetic and environmental factors, reduces the proper functioning of the intestinal epithelial barrier, leading to excessive immune responses and eventually to IBD (Jakubczyk et al., 2020). Current treatment of IBD relies on anti-inflammatory and immunosuppressive medications or surgery (Gros and Kaplan, 2023). The use of fermented foods containing probiotics may improve the composition and activity of the intestinal flora, which would regulate the intestinal immune response and inhibit adhesion of pathogenic bacteria to intestinal epithelial cells. Several genera of LAB have been investigated as potential probiotics for IBD treatment (Chlebicz-Wójcik and Śliżewska, 2021). Sweet whey supplemented with whey protein concentrate and fermented with a strain of *Limosilactobacillus fermentum* was found to reduce ulcerative colitis

in mice by increasing the production of anti-inflammatory cytokine while suppressing the secretion of inflammatory mediators (Kaur et al., 2022). In another mouse study, sweet whey fermented with a strain of *Lactocaseibacillus rhamnosus* also increased cytokine creation and stimulated the intestinal immune system (García et al., 2020). A recent meta-analysis showed that the remission effect induced by probiotics on ulcerative colitis was significantly higher than that induced by other drugs. These authors recommend that patients take probiotics as an adjunct to their usual treatment of IBD and that a personalized treatment plan should be employed (Chen et al., 2021).

4.4 Lowering blood pressure

Angiotensin-converting enzyme (ACE) is a component of the system that controls blood pressure in the body. ACE converts the hormone angiotensin to a vasoconstrictor, which increases blood pressure; ACE inhibitors are used to treat hypertension by suppressing this conversion and increasing the production of a vasodilator (Khurana and Goswami, 2022). Food-derived ACE inhibitors are safe and specific and have not been shown to result in side effects, which is an advantage over synthetic inhibitors (Li et al., 2023). An *in vitro* study of acid and sweet whey from cow, sheep, and goat milk indicated that the ACE inhibitory properties of fermentates was significantly higher than those of non-digested whey (Dalaka et al., 2024). A study of whey protein concentrate fermented by *Lactocaseibacillus paracasei* and *Saccharomyces cerevisiae* showed that peptides with antioxidant and ACE-inhibitory properties were generated (Chopada et al., 2023).

4.5 Production

Complex culture media that includes nutrient-rich mixtures such as brain heart infusion, glucose extract, and soy broth are often employed to generate high levels of bioactive compounds, but their cost and possible toxicity limits their use (Hernandez-Figueroa et al., 2024). Bioactive compounds produced using this media would require further purification, which would significantly increase production costs. The protein matrix in whey has been found to be a good substrate for generation of bioactive peptides (Venegas-Ortega et al., 2019) and would be a means for promoting a circular economy by upcycling a waste material.

5 Other applications

Whey and other dairy waste have been used as substrates for producing other useful materials. These are depicted in Figure 3.

6 Areas of future work

- More research is needed on reducing inefficiencies in scaling up the production of useful bioactive compounds from dairy waste. Whey is usually utilized as a substrate for this, and other dairy waste streams such as leftover milk, buttermilk, and ice cream should be targeted.

- Discovery of additional antimicrobial peptides in milk and how they affect humans is another area that requires investigation.
- Incorporation of bioactive compounds from milk into edible coatings is an area that should be explored.
- Antimicrobial resistance is a growing problem, and more work is needed to investigate the potential for antimicrobial peptides to act as alternate therapeutics to prevent resistance development to clinical antibiotics.
- Research should continue into identifying LAB capable of producing immunoregulatory metabolites, optimizing their production, and investigating applications for the prevention or treatment of disease.

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