Chapter

Value-Added Compounds with Health Benefits Produced from Cheese Whey Lactose

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Abstract

Cheese whey (CW) is the yellow-green liquid main by-product from cheese manufacturing. Historically, it has been recognized as a major environmental pollutant. Nowadays, it represents a source of high-quality nutrients, such as lactose. Enzymatic bioprocesses, chemical synthetic reactions and microbial bioprocesses use lactose as substrate to obtain relevant derivatives such as lactitol, lactulose, lactosucrose, sialyllactose, kefiran and galacto-oligosaccharides. These lactose derivatives stimulate the growth of indigenous bifidobacteria and lactobacilli improving the intestinal motility, enhancing immunity and promoting the synthesis of vitamins. Also, they have versatile applications in pharmaceutical, biotechnological and food industries. Therefore, this book chapter shows the state of the art focusing on recent uses of CW lactose to produce value-added functional compounds and discusses new insights associated with their human health-promoting effects and well-being.

Keywords: cheese whey, bioprocesses, value-added functional compounds, lactose, kefiran

1. Introduction

Cheese whey (CW) is the yellow-green liquid main by-product from the manufacture of cheese [1]. "Serum milk" remaining after the precipitation and removal of milk proteins by proteolytic enzymes or acid may also be defined as CW [2]. Industrial cheese manufacturing processes produce sweet or acid whey (**Figure 1**). Normally, the production of 1 kg of cheese requires 10 kg of milk originating 9 kg of CW [3, 4]. Worldwide cheese production was estimated by FAO (Food and Agricultural Organization) at 22.65 M tons in 2014 [5]. Therefore, CW is estimated at 203.9 M tons. Besides, the global growth rate of it is parallel to the cheese production and it has been calculated about 2% per annum [6]. This amount represents a challenge difficult to deal with.

Previous studies have reported high quantity of organic matter in CW [7]. The chemical composition of it is shown in **Table 1**. This by-product has 50, 000–102, 000 mg/L Chemical Oxygen Demand (COD) and 27, 000–60, 000 mg/L Biological

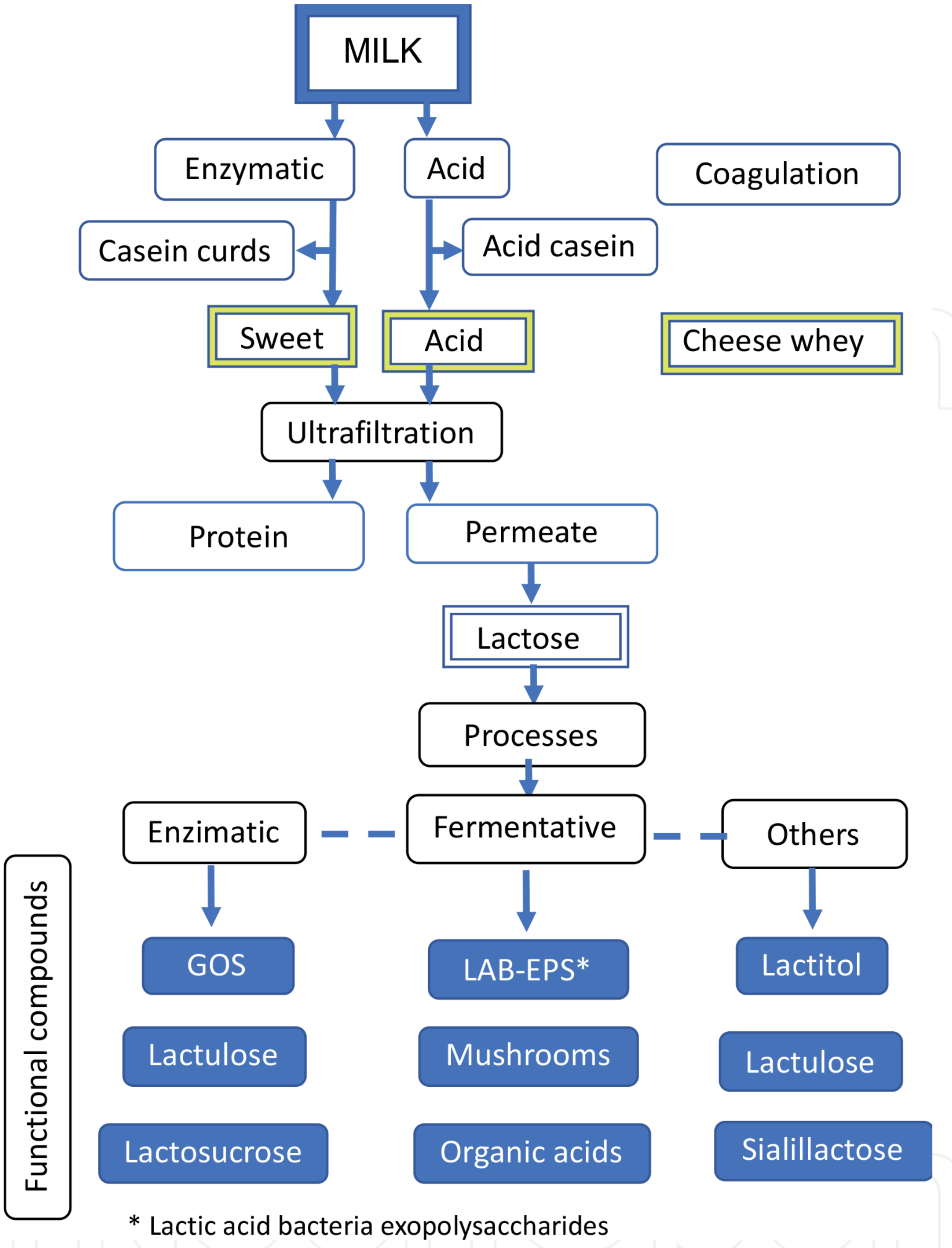

Figure 1.
Overview of value-added functional compounds using lactose from cheese whey as substrate.

	Chemical composition (g/100 g)				
Cheese whey type	**Total solids**	**Lactose**	**Protein**	**Fat**	**Ash**
Sweet cheese whey	6.7	4.8	0.6	0.25	0.54
Sweet cheese whey permeate	5.5	4.7	0.05	<0.01	0.51
Acid cheese whey	5.1	4.4	0.73	0.05	0.6
Acid cheese whey pemeate	5.8	4.3	0.06	<0.01	0.56

Table 1.
Chemical composition of different types of cheese whey.

Oxygen Demand (BOD) [7]. Due to its high BOD, CW presents 175-fold higher organic load than typical sewage effluents [6]. Lactose (4-*O*-ß-D-galactopyranosyl-D-glucose) is one of the main CW components. It causes about 90% of COD and BOD [8]. Moreover, CW represents about 85–95% of the milk volume. This amount has been partially land spreading, disposal to natural water bodies or municipal sewer systems [2–4]. Consequently, it is considered a major pollutant to the environment.

On the other hand, CW is a liquid with high nutritional content [9]. It retains about 55% of the milk nutrients such as lactose, whey proteins, lipids, vitamins and minerals (**Table 1**). The chemical make-up of it can vary depending on the animal species from which milk was obtained [1]. It has been reported that about 50% of the total CW worldwide production is used it [10]. Animal feeding or as an ingredient in therapeutic formulations and food applications are common CW uses [11, 12]. Several technological approaches have been developed to transform it into value-added compounds reducing the environmental impact. CW processing is carried out directly by physical or thermal treatments to obtain protein isolate (WPI), whey protein concentrate (WPC), whey protein hydrolysates, whey permeate, lactose and other fractions. Indirectly, CW is used as substrate for enzymatic/microbial bioprocesses to produce biogas, bioethanol, bioprotein, biopolymers, flavors and organic acids among others [11, 13]. Thus, it is an excellent substrate for physical treatments, enzymatic catalysis and metabolic microbial reactions that could be exploited by the medical, agri-food and biotechnology industries [6].

CW is a source of functional proteins, peptides, lipids and carbohydrates. This by-product is the main source of lactose manufactured on an industrial scale, as well as a low-cost substrate able to reduce high production costs. This disaccharide ($C_{12}H_{22}O_{11}$) is the most abundant in CW representing around 70–72% (w/w) of the total solids [14]. The manufacture of edible lactose includes physical treatments such as ultrafiltration, nanofiltration, concentration, crystallization, washed and dried [15]. Lactose is a valuable ingredient used in a wide variety of products, such as bread, supplement in baby milk formulae, confectionaries and excipients for pharmaceutical products [16].

The use of lactose as raw material is a key point to several industrial and laboratory transformation processes. This disaccharide represents an ideal substrate to obtain relevant lactose derivatives associated with health-promoting benefits. For example, lactulose ($C_{12}H_{22}O_{11}$; 4-*O*-ß-D-galactopyranosyl-ß- D-fructofuranose), which is synthetized by chemical isomerization, is a typical prebiotic as bifidus factor added to infant formulae [16].

Enzymatic catalytic and fermentation bioprocesses also use CW lactose as substrate to produce important value-added functional compounds [16, 17]. Kefiran, organic acids, lactosucrose and galacto-oligosaccharides (GOS) are some of the most representative compounds able to improve human health and well-being (**Figure 1**). For instance, GOS [Gal-(Gal)n-Glu] that are produced by enzymatic polymerization using ß-galactosidase, improve gut health. Besides, exopolysaccharides such as kefiran are synthetized by the fermenting bioprocesses of lactic acid bacteria [16, 18]. Therefore, this chapter discusses recent uses of lactose from CW to produce value-added functional compounds. New insights associated with human health benefits of these compounds are explored.

2. Lactose derivatives with health benefits

2.1 Lactitol

Lactitol is a lactose-derived compound defined as synthetic sugar alcohol ($C_{12}H_{24}O_{11}$; 4-O-ß-D-galactopyranosyl-D-glucitol; molecular weight (MW), 344.31 g/mol) comprising galactose (D-Gal) and D-sorbitol. This compound is synthetized by catalytic hydrogenation reactions using lactose as substrate. Industrially, this chemical process is based on the addition of molecular hydrogen to the carbonyl group of the glucose molecules. This chemical reaction needs 110°-150°C temperature, 20–70 bars of hydrogen gas pressure, as well as 1.5–10% Ni, Pd or Ru transition metals in either carbon or alumina. Lactitol is the primary reaction product with reaction yields of >90%. This polyol has been used in the food industry as a relevant ingredient in desserts, bakery products, chewing gums, chocolate and confectionary products. One of the advantages of lactitol used as sweetener is that it can be metabolized by saccharolytic bacteria providing only 2 kcal/g. It also exerts properties such as cryoprotectant, dryoprotectant, stabilizer agent, hydrogel delivering bioactive compounds and additive for the development of biosensors [19].

Several human health benefits have been associated to lactitol intake. Clinical trials have demonstrated positive gastrointestinal health benefits of this polyol [20]. A random-effect meta-analysis of lactitol supplementation on adult constipation demonstrated favorable efficacy and tolerance when it was compared to stimulant laxatives and placebo. Lactitol was able to induce increased fecal volume by stimulating peristalsis [21]. In fact, lactitol is one of the most frequently prescribed osmotic laxative agents to treat constipation [22]. Investigations performed on the effectiveness of lactitol for treatment of several types of hepatic encephalopathy in infants, children and elderly subjects have demonstrated positive results. Actually, lactitol is recommended as a first-line treatment for hepatic encephalopathy as a result of decreasing the absorption and production of ammonia and reducing the intestinal pH [23, 24]. Indeed, in the last years advances in the field of nanomedicine had led to the development of polylactitol as a multifunctional carrier for liver cancer therapy [24].

Lactitol is a non-digestible carbohydrate with prebiotic effect. Prebiotic is a substrate that is selectively utilized by host microorganisms conferring a health benefit [25]. Previous studies have reported relevant lactitol symbiotic effects. Medical practitioners frequently recommend them as therapeutics. Recently, it was demonstrated that the consumption of the symbiotic combination with this lactose-derived prebiotic, *Bifidobacterium bifidum* and *Lactobacillus acidophilus* was able to eradicate OXA-48-producing *Enterobacteriaceae*. The measure of this metabolite is used as prophylaxis to prevent intestinal translocations in neutropenic patients and for the prevention of pneumonia [26]. Also, the symbiotic supplementation on the gut microbiota of healthy elderly volunteers with *Lactobacillus acidophilus* NCFM and lactitol improved their health status modifying the intestinal environment and the microbiota composition. It was observed an increasing lactobacilli and bifidobacteria and a possible stabilizing effect on *Blautia coccoides-Eubacterium rectale* and *Clostridium cluster* XIV levels [27]. Even though the Federal and Drug Administration (FDA) agency categorized lactose-derived prebiotic as "GRAS" (Generally Recognized as Safe), the excess consumption has adverse effects such as osmotic diarrhea, abdominal pain and vomiting [20]. It has been reported that the maximum permissive dosage of lactitol for Japanese adults not to induce transitory diarrhea was 0.36 g/kg of body weight [28]. It was also found that the dose of this lactose-derived prebiotic treatment is age- and case-dependent [20].

2.2 Lactulose

Lactulose is a semi-synthetic disaccharide ($C_{12}H_{22}O_{11}$; 4-O-ß-D-galactopyranosyl-ß-D-fructofuranose; MW, 342.30 g/mol) comprising D-galactose (D-Gal) and D-fructose (D-Fru) linked by ß-1-4 glycosidic bond [16, 29].

Commercially, this artificial disaccharide is synthetized by alkaline isomerization of lactose via the Lobry de Bruyn e Alberda van Ekenstein rearrangement in which the D-glucose unit at the reducing end of the lactose molecule is converted to D-fructose. The maximum yield of lactulose relative to initial lactose concentration adding complexing agents may reach up to 88% [30]. Electro-activation is a novel eco-friendly technology able to synthetize lactulose from CW-lactose at maximum yield of 35% [31]. In the last decade lactulose has been synthetized at lab scale using lactose as substrate by the transgalactosylation activity of ß-glucosidase [29]. This disaccharide is formed in milk during heat treatments also, so pasteurized milk usually has <100 mg/L lactulose content, meanwhile ultra-high temperature (UHT) milk generally has a lactulose content over 500 mg/L [32]. Actually, this polyol has demonstrated versatile applications in pharmaceutical and food industries. Lactulose can be found as relevant functional ingredient of infant food formulae, fermented dairy products, bakery products, confectionary products and soy milk [33, 34].

Previous studies have reported remarkable health benefits associated to lactulose consumption. In fact, this disaccharide is used in clinical practice since 1957. This disaccharide is lactose-derived prebiotic able to prevent and to treat diseases [35]. Lactulose is only metabolized by specific species of colonic microbiota through ß-glucosidase activity altering the microbial balance by increasing the probiotic growth and reducing putrefactive bacteria. Consequently, lowering intestinal pH, enhanced colonic motility, reduced concentration of ammonia and improved absorption of minerals are also benefits of the physiological action of lactulose upon bacterial metabolism in the large intestine [30].

In silico, *in vitro* and *in vivo* studies have demonstrated the efficacy of lactulose in the treatment of several diseases [35]. Since the 1960s, patients of all ages have been prescribed with lactulose to treat constipation, even if it is chronic. This lactose-derived prebiotic is an osmotic laxative [33]. The effect of lactulose was studied in healthy volunteers. A significant increase of *Bifidocaterium*, *Lactobacillus* and *Streptococcus* was reached, meanwhile the population of coliforms, *Bacteroides*, *Clostridium* and *Eubacterium* was significantly decreased. These changes in the microbiota reduced activity of pro-carcinogenic enzymes, increased short-chain fatty acids in feces and pH decreased [36]. Clinical trials also have reported favorable results using lactulose to treat hepatic encephalopathy and chronic kidney disease [30]. Recently, the prebiotic effect of lactitol, raffinose, oligofructose and lactulose was evaluated on *Lactobacillus* spp. and bacterial vaginosis-associated organisms (BV) and *Candida albicans*. Results showed that lactulose had the most broadly and specifically growth stimulation on vaginal lactobacilli and did not to stimulate BV or *Candida albicans* [37]. On the other side, *in vitro* and *in vivo* studies have confirmed that lactulose possesses patient- and dose-dependent prebiotic properties [35].

2.3 Sialyllactose

Sialyllactose ($C_{23}H_{39}NO_{19}$; NeuAcα2-xD-galactopyranosyl-α-D-glucopyranoside; MW, 633.6 g/mol) is essentially sialic acid (N-acetylneuraminic acid, NeuAc) bound to a lactose molecule. This lactose-derived compound is naturally found in high concentrations at the beginning of lactation in colostrum and decreases towards the end of lactation [16]. The predominant forms of sialyllactose are 6′-sialyllactose and 3′-sialyllactose. The concentrations of 6′-sialyllactose in human colostrum is 250–1300 mg/L, meanwhile the concentration of 3′-sialyllactose in bovine colostrum is 354–1250 mg/L [38]. These lactose-derived compounds are extracted from CW using ultra and nanofiltration processes on a tangential flow type laboratory scale membrane filtration system [39]. Even though this still an expensive procedure to extract sialyllactose, some infant formulae use it as functional ingredient [16, 40].

In vivo studies have demonstrated the ability of sialyllactose to improve positively in health. Pathogenic microorganisms have been effectively inhibited using it [16, 40]. It was reported that the consumption of dietary sialyllactose modified the colonic microbiota, e.g. Bacteroidetes were significantly increased, meanwhile Firmicutes and Cyanobacteria were significantly decreased. Moreover, this lactose-derived prebiotic was able to diminish stressor-induced alterations in colonic mucosa and anxiety-like behavior [41]. One of the major causes of morbidity and mortality in premature infants is necrotizing enterocolitis (NEC). Recently, it was found that human milk oligosaccharides 2′-fucosyllactose and 6′-sialyllactose can reduce NEC and attenuate NEC inflammation [42]. In addition, intact sialylated oligosaccharides can be absorbed in concentrations high enough to modulate the immunological system and facilitate proper brain development during infancy [43].

3. Functional compounds bio-produced using lactose as substrate

3.1 Biocatalytic processes

3.1.1 Galacto-oligosaccharides

Galacto-oligosaccharides [Gal-(Gal)n-Glu] are lactose-derived non-digestable oligosaccharides (GOS) recognized as relevant functional compounds. Industrially, GOS are produced using CW lactose as substrate through biocatalytic reaction. Lactose is transgalactosylated by ß-galactosidases enzymes (E.C. 3.2.1.23) from several microbial strains [44]. GOS are the best substitute for human oligosaccharides, have a sweet taste, low energy value (2 kcal/g), as well as tolerate high temperatures and low pHs. So, they are widely used in the food industry as functional ingredient in the manufacturing of infant formula, confectionary, chewing gum, yogurt, ice cream and bakery products [45].

Previous studies have demonstrated the impact of GOS promoting gut health and well-being. These lactose-derived prebiotics serve as substrates for the microbiota, improve saccharolytic metabolic activities and stimulate the growth of indigenous bifidobacteria and lactobacilli. In consequence, the formation of volatile fatty acids, lowering of the luminal pH and decreased formation of toxic secondary bile acids are microbial metabolic associated effects. Also, they inhibit the formation of toxic bacterial metabolites, such as ammonia, hydrogen disulphide, phenolic compounds and biogenic amines [44]. Moreover, GOS have a bifidus factor similar to the effect of human milk oligosaccharides stimulating the growth of specific intestinal microbiota, improving the intestinal motility, enhancing immunity, promoting the synthesis of vitamins, reducing the high levels of cholesterol and triglycerides and decreasing the risk of colon cancer development [45, 46].

3.1.2 Lactosucrose

Lactosucrose is an oligosaccharide comprising Gal, Fru and Glu. This carbohydrate molecule ($C_{18}H_{38}O_{16}$; MW, 510.4 g/mol) is a ß-D-fructofuranosyl-4-O- ß-D-galactopyranosyl-α-D-glucopyranoside [16]. Lactosucrose can be regarded as a condensate of sucrose and galactose molecules or lactose and fructose molecules. Production protocols include transferring the ß -galactosyl group produced by the decomposition of lactose to the C4 hydroxyl group of glucosyl in sucrose by the enzymatic activity of ß-galactosidase (E.C. 3.2.1.23). Also, it can be produced by the catalysis of ß-fructofuranosidase (E.C. 3.2.1.26) or levansurase (E.C. 2.4.1.10) transferring the fructose group generated by the decomposition of sucrose to the C1 hydroxyl group at the reducing end of the lactose. Industrially, ß-fructofuranosidase is one of the most common enzymes used to the production of lactosucrose due to its availability and low cost [47]. This non-reducing trisaccharide is an ingredient of cosmetic and pharmaceutical products. Moreover, it is widely used in a large number of functional foods. In fact, in Japan, lactosucrose has the status of FOSHU ingredient. So, it has been used in a large number of healthy foods and drinks, such as bakery products, yogurt, ice creams, infant formula, chocolates, juice and mineral water [48].

In the last decades, the demand for lactosucrose has significantly increased. This can be explained by the widely uses of it in the preparation of functional foods. Lactosucrose is well known by its prebiotic effect. *In vivo* studies in animals, as well as in humans have demonstrated the association between lactosucrose consumption and health-promoting effects. Their review includes enhancement of beneficial bacteria and or inhibition of pathogenic microorganisms, decrease of fecal pH, production of short chain fatty acids and gases, reduction of putrefactive products, enhancement of intestinal absorption of minerals, treatment of chronic inflammatory bowel diseases, normalization of intestinal microflora and prevention of abdominal symptoms of lactose intolerance [48].

3.2 Microbial bioprocesses

3.2.1 Lactic acid bacteria exopolysaccharides (LAB-EPS)

Lactic acid bacteria (LAB) play a key role in the fermentation processes of food worldwide. These group of microorganisms improve the preservation, enhance sensory characteristics, increase nutritional values of a large variety of food and beverages products and have been recognized by their health-promoting attributes [49]. Several LAB have the ability to produce exopolysaccharides (EPS) as cell wall constituents named peptidoglycan located in the extracellular medium without covalent bounds with bacterial membrane [49, 50]. EPS are a diverse group of high-molecular-mass polysaccharides in terms of chemical composition, quantity, molecular size, charge, presence of side chains rigidity of the molecules, including mechanisms of synthesis [49, 51].

LAB-EPS are classified depending on the composition of the main chain and their mechanisms of synthesis. They can be divided into homopolysaccharides (HoPs) or heteropolysaccharides (HePs) In general, HoPs contain only one type of monosaccharide (glucose or fructose) through linear or branched α or β links, with more than 10^6 Da molecular mass. These EPS are produced in grams per liter by *Lactobacillus*, *Leuconosctoc*, *Oenococcus* and *Weissella* extracellularly from sucrose or starch without noncarbohydrate groups. On the other side, HePs contain more than one type of monosaccharide, mainly glucose, galactose and rhamnose together through α and β links, typically branched with 10^4–10^6 Da molecular mass. Most of them are produced in milligrams per liter by *Lactobacillus*, *Lactococcus*, *Bifidobacterium* and *Streptococcus* from intracellular intermediates with the presence of noncarbohydrates groups [51].

Kefiran is the main HePs synthetized by kefir grains microorganisms. Kefir grains are a consortium of symbiotic LAB, acetic acid bacteria, bifidobacteria and yeast microorganisms embedded in a matrix of proteins, lipids, polysaccharides and water [52] . These microorganisms are able to synthetize kefiran from CW lactose even if it is deproteinized [53]. In fact, using CW lactose as a fermentation medium presents the opportunity to create value-added products [54]. *Lactobacillus kefiranofaciens* has been identified as the most important kefiran producer. Previous study demonstrated this extracellular polysaccharide is water soluble and it has the same amounts of D-glucose and D-galactose, approximately. Kefiran has several relevant applications within the biotechnology, food and pharmaceutical industries [52]. Therefore, increasing attention has been paid to these EPS.

Kefiran is a natural EPS that offers relevant food and pharmaceutical industrial advantages. It could be added to a formulation or it could be produced i*n situ* through fermentation processes. As a polymer, kefiran exert versatile functionality. In food industry, for example it has widely applications such as stabilizer, additive, film-forming agent and gelling agent. In recent years, it has been discovered novel nano applications of this HePs, e.g. kefiran-based bio-nanocomposites and kefiran based nanofibers. Moreover, this bio-molecule also has shown biological activity properties. Several *in vitro* and *in vivo* studies have demonstrated the ability of kefiran to increase peritoneal IgA, reduce blood pressure induced hypertension, wound healing, antioxidant activity, antitumoral activity, favor the activity of peritoneal macrophages, modulation of the intestinal immune system and protection of epithelial cells against, prevent several cancer, anti-inflammatory and prebiotic effect [55, 56].

HoPs have also potential uses in the food and pharmaceutical industries. Fructans (levan and inulin-like), α -glucans (dextran, reuteran, alternan and mutan) and β -glucans are the most important HoPs [49, 51]. HoPs such as dextran have been using in bakery products improving softness or in confectionary, ice cream, frozen and dried-food and non-alcoholic wort-based beverages as stabilser. Levan and inulin-like HoPs can be used as fat substitute and sugar replacer, respectively. Besides, these HoPs may influence human host health. For example, β-glucans have demonstrated a cholesterol-lowering effect increasing cardiovascular health. Moreover, *Lactobacillus delbrueckii* subsp. *bulgaricus* strains HoPs removed cholesterol from *in vitro* culture media. Indeed, HoPs have been recognized by their benefits on the microbial gut modulation acting as prebiotics [51].

3.2.2 Mushrooms

In recent years, the use of CW for mycelial growth has been explored. CW as substrate offers a wide diversity of nutrients such as proteins, carbohydrates, lipids, vitamins and minerals. On the other side, the metabolism of mycelia of fungi produced edible mushrooms utilizes the nutrients from the medium to bioaccumulate microelements such as Se, Fe and Zn. Therefore, the use of CW for mycelial growth may be a valuable nutritional supplement, reducing the impact of discharging CW to the environment and biofortifies mushrooms composition.

The nutritional, culinary and nutraceutical properties of mushrooms have attracted the researchers, pharmacists and nutritionists attention. The chemical composition of mushrooms includes bioactive molecules such as polysaccharides, terpenoids, low molecular weight proteins, glycoproteins among others that play a key role in boosting immune strength, lowering risks of cancers, inhibiting of tumoral growth, maintaining of blood sugar, etc. [57].

Information on mushrooms chemical composition, nutritional value and therapeutic properties has expanded during the last few years. *Pleurotus* spp. (oyster mushrooms) are one of the most cultivated mushrooms worldwide [58]. Recently, it was demonstrated that the mycelial growth of *Pleurotus djamor* in a liquid culture medium containing CW was able to produce bioactive compounds such as ergosterol and β-glucans. The addition of selenium to the medium decreased the concentration of lactose. Moreover, it was observed that the mycelium showed potential in absorbing and accumulating elements e.g. Ca, Fe, Mg, K and Zn from the CW [59].

3.2.3 Organic acids

Several organic acids are produced during the metabolic pathways of the fermentation processes. Some organic acids e. g. lactic acid, propionic acid, butyric acid, isobutyric acid, acetic acid, capric acid, caproic acid, caprylic acid, lactobionic acid, etc., are responsible for characteristic flavors [60, 61]. However, they play a key role as functional compounds enhancing health-promoting effects and well-being. It has been demonstrated that conjugated linoleic acid (CLA, 9,11-Octadecadienoic acid, MW, 280.4 g/mol) modulate the fatty acid composition of the liver and adipose tissue of the host [62]. Indeed, succinic acid ($C_4H_6O_4$, MW, 118.09 g/mol) has shown its ability to stabilize the hypoxia and cellular stress conditions focusing on the maintenance of homeostasis in aging hypothalamus. Therefore, it is hypothesized that succinate has the potential to restore the loss in functions associated with cellular senescence and systematic aging [63]. Most of the commercial succinic acid production is done by chemical technologies like catalytic hydrogenation or electrolytic reduction of maleic anhydride. In the last years, it was found that it can be produced using CW and lactose as substrates by *Actinobacillus succinogenes* 130Z in a batch fermentation [64].

According to the international market demands, lactobionic acid, fumaric acid and glucaric acid are classified as high value-added compounds [61]. These organic acids have demonstrated potential uses in food, medicine, pharmaceutical, cosmetic and chemical industries [61, 65, 66]. Glucaric acid ($C_6H_{10}O_8$, MW, 210.14 g/mol) is found in vegetables and fruits, mainly grapefruits, apples, oranges and cruciferous vegetables. Commercially, it is synthetized by chemical oxidation of glucose releasing toxic byproducts. Thus, microbial fermentation of glucose by *Saccharomyces cerevisiae* and *Escherichia coli* has been proposed as alternative. This organic acid and its derivatives increases detoxification of carcinogens compounds and tumor promoters [67, 68]. Fumaric acid (trans-1,2-ethylenedicarboxylic acid, MW, 116.07 g/mol) is traditionally synthetized from maleic anhydride, which in turn is produced from butane. Nowadays, the production of this organic acid may be done by fermenting glucose through the metabolic pathways of *Rhizopus* species, also fixing CO_2. Fumaric acid is widely used as starting material for polymerization and esterification reactions to produce paper and unsaturated polyester resins. In medicine field, it can be used to treat psoriasis, meanwhile it is also used as food and beverage additive. Moreover, Fumaric acid supplements have the ability to reduce methane emissions of cattle [66].

Lactobionic acid (4-O-ß -galactopyranosyl-D-gluconic acid, MW, 358.3 g/mol) is a high value-added lactose derivative. This organic acid has received growing attention due to its multiple applications in cosmetics, chemical, pharmaceutical, biomedicine, and food industries [61]. Lactobionic acid production is based on chemical synthesis requiring high amounts of energy and costly metal catalysts [69]. Nowadays, lactobionic acid is able to be bio-produced either through enzymatic or microbial biosynthesis at cost-effective and environmentally friendly using cheese whey lactose. In fact, high-level production of it has been recently reported controlling pH and temperature during the fermentation of lactose with *Pseudomonas taetrolens* [70]. Lactobionic acid offers wide versatile uses in nanotechnology, tissue engineering and drug-delivery systems, antibiotics, preservative solutions for organ transplantation, anti-aging, regenerative skin-care, sugar-based surfactant. Also, this value-added compound functions as food additive, gelling agent, solubilizing agent, sweetener, water holding capacity agent and bioactive ingredient enhancing calcium absorption, antioxidant activity and exerting prebiotic effects [61].

Lactic acid (2-hydroxipropionic acid, MW 90.08 g/mol) is an organic acid with a prime position due to its versatile applications in textile, leather, chemical, pharmaceutical and food industries. Lactic acid applications associated to food and food-related represent 85% of total production, approximately. This organic acid has been recognized as GRAS by the FDA [71]. It is used as flavoring, buffering agent, inhibitor of bacterial spoilage, acidulant, dough conditioner and emulsifier [72]. Most of lactic acid is produced through microbial fermentation, mainly *Lactobacillus delbrueckii or Lactobacillus amylophilus* strains, using beet extracts, molasses, starchy and cellulosic materials and cheese whey [71].

Polylactic acid is a biocompatible polymer with unique properties. Lactic acid and lactide are the building blocks to obtain it through a polycondensation reaction. This biodegradable and renewable biopolymer is a relevant alternative to plastics derived from petrochemicals, so its demand has been increasing considerably. In fact, the global polylactic acid market was expected to grow over 1.2 million tons in 2020. Nowadays, most polylactic acid is manufactured for single-use applications in packaging, including food packaging supplies [73]. However, it has important biomedical uses, due to its GRAS status recognized by the FDA. This biomaterial has been transformed into sutures, scaffolds, cell carriers and drug delivery systems such as liposomes, polymeric nanoparticles, dendrimers and micelles [74, 75].

4. Conclusions

Cheese whey production is increasing worldwide every year. Even though CW is considered a major environmental pollutant, due to its quantity and quality of chemical components, there is a huge opportunity to use it as raw material to produce value-added functional compounds. CW lactose is an excellent substrate to obtain high quality products able to improve human health and well-being, e.g. lactitol, lactosucrose, GOS, lactulose, sialyllactose and organic acids. For example, GOS and sialyllactose have a bifidus factor similar to the effect of human milk oligosaccharides stimulating the growth of specific intestinal microbiota, enhancing immunity, promoting the synthesis of vitamins and decreasing the risk of colon cancer. Moreover, microbial bioprocesses use CW lactose to produce relevant health-promoting metabolites such as kefiran and organic acids. Future perspectives are focusing on the sustainable transformation of CW lactose as by product into value-added functional compounds to be used as novel ingredients in a diverse formulation of food, pharmaceutical, and cosmetic new products. Therefore, additional research concentrated on the development of innovative technological processes, more efficient and able to discover new bioactive compounds are essential.

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