Valoriz~~s~~ation of cheese whey ~~to improve human health and environmental sustainability by~~using microbial ~~bioprocesses~~ fermentations

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Abstract

~~Dairy industry produces considerable amounts of liquid discharges, with high organic load.~~ Cheese whey (CW), the liquid resulting from the precipitation and removal of milk casein during cheese-making, and the second cheese whey (SCW) derived from the production of cottage and ricotta cheeses, are the main by-products of dairy industry. The major constituent of CW and SCW is lactose, contributing to the high BOD and COD content. Because of this, CW and SCW are high-polluting agents and their disposal is still a problem in dairy sector. CW and SCW, however, also consist of lipids, proteins and minerals, making them useful for production of various compounds.

In this paper, microbial processes useful to promote the bioremediation of CW and SCW are discussed, and an overview on the main whey-derived products is provided. Special focus was paid to the production of health-promoting whey-drinks, vinegar and biopolymers which may be exploited as value-added products in different segments of food and pharmaceutical industries.

~~with a special focus on value-added products such as health-promoting whey drinks from lactic and acetic fermentations, vinegar and biopolymers (poly-hydroxyalkanoates and bacterial cellulose).~~

Introduction

~~Dairy industry produces considerable amounts of liquid discharges, with high organic load.~~ Cheese whey (CW), the liquid resulting from the precipitation and removal of milk casein during cheese-making, and the second cheese whey (SCW) derived from the production of cottage and ricotta cheeses, are the main by-products of dairy industry.

Currently, the income from the Market of CW and its derivates has a small impact on dairy sector. In fact, according to data obtained from private dairy industries/factories the average Market prices in North-Italy are as follows: CW is 25-30 €/ton; CW powder for both animal husbandry and human nutrition is 1000-1200 €/ton; food-grade lactose is 1600-1700 €/ton; whey permeate (WP) is 700-800 €/ton; whey protein concentrate (WPC) 35 powder is 3200 €/ton; WPC60 powder is 4900-5200 €/ton; WPC80 powder is 8500-12000 €/ton; CW DEMI50 is 1500-1700 €/ton; CW DEMI70 is 1800-1900 €/ton; CW DEMI90 is 2300-2600 €/ton ~~(Siso 1996).~~

Properties of CW are affected by the type of milk used in ~~The milk used in~~ cheese production. Therefore, c~~(cow, goat, sheep, buffalo and other mammals) influences the characteristics of the produced CW. Furthermore, c~~asein precipitation leads to the formation of two CW types: acidic whey (pH 5) ~~having a pH around 5 is~~ obtained ~~after~~ with fermentation or addition of organic or mineral acids, and sweet whey (pH 6.0-7.0) ~~is~~ obtained by addition of proteolytic enzymes (Panesar et al. 2006)~~like chymosin (Panesar et al. 2007)~~. Generally, CW exhibits high chemical oxygen demand (COD) (50-70 g/L) and biological oxygen demand (BOC) (27-60 g/L) because it retains about 55% of its total milk nutrients. The most abundant components are lactose (45-50 -g/L~~to 50 g/L~~), soluble proteins (6-8 g/L~~to 8 g/L~~), lipids (4-~~g/L to~~ 5 g/L) and mineral salts (8-10% of dried extract). The mineral salts include NaCl and KCl (more than 50%), calcium salts (primarily phosphate) and others. CW also contains lactic (0.5 g/L) and citric acids, non-protein nitrogen compounds (urea and uric acid) and group B vitamins (Carvalho et al. 2013)~~((Carvalho et al. 2013Siso 1996; Panesar et al. 2007)~~.

~~At large milk processing plants,~~ CW is usually used as feedstock for animal feeding or to produce ricotta cheese, generating another by-product, that is SCW. However, at small-scale, milk farm or cheese producers, which are common in isolated rural areas, CW is not recovered and has to be treated along with the other generated wastewaters from the installation. The mixing of the whey wastewater with the washing waters, results into a diluted polluting effluent (2-4 g/L COD). Due to strict legislative requirements for effluent quality (Regulation (EC) No 1069/2009), CW and washing waters should be treated before being discharged into receiving waters.

SCW results from the production of cottage or ricotta cheeses, and, similarly to CW, it is also a highly polluting effluent. Like CW, SCW maintains significant BOD and COD values (up to 50 and 80 g/L of O_2, respectively), high lactose content (around 50 g/L) and high salinity (7-23 mS/cm). SCW exhibits acidic pH values within the range 3-6, possesses low level of fat (0.5-8 g/L), total suspended solids (≈8.0 g L^{-1}) and protein (≈0.5-8 g/L) than CW. Moreover, it is normally free of amino acids and vitamins (Carvalho et al. 2013)~~(Carvalho et al. 2013)~~. It has been estimated that 15-20 L CW are needed to obtain 1 kg of ricotta cheese and producing 14-19 L of ricotta SCW (Mills 1986)~~(Mills 1986)~~.

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Currently, the treatment of SCW is considered more essential than that of CW, as CW is mainly used in ricotta and cottage cheese production. SCW is partially used as supplement feed for livestock, while most are not used by dairy. The disposal of this strong organic and saline polluting effluent remains a significant problem for the dairy industry. If SCW is incorporated into the wastewater, it increases the organic content, so the wastewater treatment becomes too expensive, particularly for small cheese plants. Considering that lactose is the major SCW constituent, the search for alternatives to minimize its environmental impact could be promising.

In this light fermentative processes converting it into value-added products will allow both to reduce the pollution potential and to valoriz~~s~~e SCW. However, only few studies were focused on SCW treatment to obtain value-added products (Sansonetti et al. 2009)~~(Sansonetti et al. 2009)~~.

~~The existing techniques for~~The management and valorization of CW and SCW are mainly based on physicochemical and biological treatments. Physicochemical processes (i.e. protein precipitation and membrane separation) are useful to produce whey powder, whey protein concentrate (WPC), whey protein isolate (WPI), whey permeate (WP), lactose and minerals. Biological treatments, instead, involve the microbial conversion of lactose, present in CW, SCW or cheese whey permeate, into organic acids, bioalcohols~~bioethanol~~, greenhouse gases (e.g. hydrogen, methane), and bioplastics (Prazeres et al. 2012; Yadav et al. 2015; Lappa et al. 2019)~~(Prazeres et al. 2012; Yadav et al. 2015; Lappa et al. 2019)~~.

In this paper, the microbial processes useful to promote the bioremediation of CW and SCW are discussed, and an overview on the main whey-derived products (Table 1) is provided. Special focus was paid to the production of ~~with a special focus on value-added products such as~~ health-promoting whey~~-~~drinks (from lactic and acetic fermentations), vinegar and ~~,~~ biopolymers (i.e. poly-hydroxyalkanoates, PHAs; bacterial cellulose, BC) (Fig. 1), which may be exploited as value-added products in different segments of food and pharmaceutical industries (*e.g.* functional beverages, bio-packaging).

~~Other compounds, not considered in this paper, are of industrial interest, however this review will contemplate microbial transformations that combine food production with valorisation of waste and by-product streams.~~

Main value-added compounds obtained by microbial fermentations of whey

The main products obtained by microbial fermentations of whey-based media and the involved microbial ~~groups~~ groups are ~~briefly~~ reported in Table 1. Many of these products (e.g. lactic acid, bioalcohols, biogases) have been extensively studied and reviewed overtime as possible solution for whey valorization because of their high industrial interest. Others received lesser attention, but their production could provide sustainability and economical boost for several food-related applications.

The bioconversion of whey into functional beverages and biopolymers rank in the objectives of current European policies driven to promote human-health and environmental sustainability. The market of functional beverages is recently gain interest because of increasing consumer demand for foods that enhance health and wellbeing. The synthesis of biopolymers for production of bioplastics may have great potential in food, biomedical and agricultural applications because of biodegradability, thermo-plasticity, biocompatibility and non-toxicity features.

Bio-valorization of whey and whey-derivatives in fermented lactic and acetic beverages as well as in poly-hydroxyalkanoates and bacterial cellulose will be addressed in this review.

Whey-based beverages

The use of CW and WP for the production of beverages, with or without microbial conversion, is one of the most attractive possibilities for the valorization and utilization of whey for human consumption.

The industrial production of whey-based drinks dates back to 1970s and different products (e.g. unfermented and fermented beverages, alcoholic beverages, diet beverages, high-protein sport drinks) have been developed and are currently available on the market (Chavan et al. 2015)(Chavan et al. 2015; Skryplonek and Jasińska, 2017). Whey proteins are today the best protein source for the Ready-To-Drink (RTD) protein beverages, an expanding market that is expected to reach $ 17.67 billion by 2025 (www.globenewswire.com). On the other hand, “Rivella”, a sparkling and flavored whey-based beverage, is the second soft drink in Switzerland, after Coca~~o~~-Cola. ~~One of the oldest and best-known whey-based beverages is “Rivella” (Anonymous 1960), a refreshing and thirst-quenching drink produced in Switzerland. Today, unfermented thirst-quenching beverages and whey-powder instant drinks cover a prominent position in the commercial whey-beverage segment.~~

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Whey drinks ~~gained attraction among dairy- and functional-beverages because~~ are produced with simple technologies and are characterized by a high nutritional value for the presence of proteins and peptides with several biological and health-promoting functions (e.g. antioxidant, anti-inflammatory, anticancer, immunomodulatory, cardioprotective and hypotensive activities~~; Patel 2015~~) (Patel 2015).

Despite this, whey beverages ~~Most of the whey proteins, in fact, have several health-promoting effects, and their fractionation by enzymatic and/or microbial activity may results in peptides with important biological functions, such as antioxidant, anti-inflammatory, anticancer, immunomodulatory, cardioprotective and hypotensive activities (Patel 2015). However, although the interest in whey-based drinks is rising, their production suffers from several limitations and these beverages~~ are sometimes perceived as unattractive products with poor ~~. The~~ sensory quality. ~~, in fact, is impaired by the~~The high lactose-glucose ratio, acidity level and mineral content, in fact, may ~~that~~ result in sweet, dairy/sour and salty/sour flavors, with ~~poor~~ reduced palatability. The high lactose concentration, additionally, makes these products highly perishable. To ~~counteract~~ overcome these drawbacks, several technological solutions ~~have been developed~~, ~~such~~ including ~~as ultrafiltration,~~ pH adjustment, ~~and~~ flavor supplementation and microbial fermentation, have been developed.

Lactic fermented whey beverages

Fermentation is one of the cheapest ways for preserving foods, improving nutritional value, and enhancing sensory properties. CW or milk enriched with CW, WPC or WPI are suitable substrates for the production of fermented beverages by using yeasts and lactic acid bacteria (LAB).

As for other dairy fermented drinks ~~(e.g. drinking yogurts, fermented milks)~~, LAB may improve the shelf-life (e.g. prevention of spoilage microorganisms through the lowering of pH), nutritional (e.g. protein degradation, production of bioactive peptides) and sensory (e.g. production lactic acid and aroma compounds) properties of whey-based beverages. Some ~~LAB~~ strains, moreover, are ~~also~~ able to degrade β-lactoglobulin, the main allergenic protein in milk and whey-based products (Pescuma et al. 2012)~~(Bertrand-Harb et al. 2003; Pescuma et al. 2012)~~. ~~The use of probiotic strains, moreover, may enhance healthy features~~

~~in fermented whey drinks (Turkmen et al. 2019).~~ LAB mostly used for the production of whey-based beverages belong to the *Lactobacillus* and *Streptococcus* genera. Combinations of yoghurt-derived *L. delbrueckii* subsp. *bulgaricus* and *S. thermophilus* cultures were extensively tested for their capability to reduce the lactose content, and for the acidifying and proteolytic activities (Gallardo-Escamilla et al. 2007; Pescuma et al. 2008; Almeida et al. 2009; Pescuma et al. 2012; Saeed et al. 2013; Schirabi et al. 2016; Skryplonek 2018)~~(Almeida et al. 2009; Gallardo-Escamilla et al. 2007; Pescuma et al. 2008, 2012; Saeed et al. 2015; Skryplonek 2018; Schirabi et al. 2016)~~, demonstrating the promising starters also for whey fermentation. Other authors ~~, instead,~~ demonstrated the capability of many LAB to produce flavoring compounds (Mauriello et al. 2001; Ricciardi et al. 2019)~~(Mauriello et al. 2001; Ricciardi et al. 2019)~~ and to scavenge radicals (Virtanen et al. 2007)~~(Virtanen et al. 2007)~~ when cultivated in whey-based medium.~~, suggesting their effectiveness for the production of whey-derived drinks.~~

The challenge in whey-beverage segment, however, is certainly the use of probiotic strains. ~~to develop functional drinks. The strains~~ The species principally used for the production of ~~fermented probiotic~~functional whey beverages ~~belong to the species~~are *L. acidophilus, L. casei, L. rhamnosus* and *L. reuteri* (Turkmen et al. 2019)~~(Turkmen et al. 2019)~~. Several authors (Tripathi and Jha 2004; Castro et al. 2013a; Bulatović et al. 2014)~~(Bulatović et al. 2014; Castro et al. 2013a; Tripathi and Jha, 2004)~~ demonstrated that different probiotic lactobacilli (i.e.

~~the same strain was used in co-culture with *L. acidophilus* La-5 and *S. thermophilus* St-36 for the production of milk-whey beverages (Yerlikaya et al. 2012), and with *L. rhamnosus* GG for the production of mulberry whey drinks (AbdulAlim et al. 2018). Combination of *B. lactis* Bl-07 and *L. acidophilus* La-14 were used as probiotic adjunct in milk-beverages supplemented with different whey concentrations (Castro et al. 2013b). Hernandez-Mendoza et al. (2007) used different ratio of *L. reuteri* NRRL1417 and *B. bifidum* NCFB271 to ferment whey beverages that preserved acceptable flavor and significant level of survived probiotics during the storage period.~~

Combination of LAB and yeasts have been used for the production of kefir-like whey-beverages using kefir grains (including *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Streptococcus spp*., and *Kluyveromyces*, *Torula*, *Candida* and *Saccharomyces spp.*) for fermentation process (Koutinas et al. 2007; Magalhães et al. 2010; Sabokbar and Khodaiyan 2016)~~(Koutinas et al. 2007; Magalháes et al. 2010, 2011a,b; Sabokbar and Khodaiyan, 2016)~~. These products had interesting aroma profile, sensory properties and antioxidant capability, suggesting that kefir grains may be potential starters for the production of whey-based beverages.

Although fermented whey-drinks may offer greater benefits than unfermented ones, to date the marketed products containing LAB cultures and/or probiotics are very limited. To our knowledge, "Gefilus" (Valio Ltd Company, Finland), containing *L. rhamnosus* GG, lactose-hydrolyzed and demineralized whey or whey protein concentrates, fruit juices or fruit aromas and fructose as sweetening agent, is the only probiotic drink commercially available.

Compared to whey-based products, fermented milks with probiotic supplementation (see a list in Turkmen et al. 2019), remain the mainstay of functional beverage market. The currently marketed whey-drinks are still mainly recognized as energy-sport drinks with specific functions (e.g. recovery of muscle and muscle cramps, increase in lean weight, neurostimulant). On the contrary, the fermented whey beverages can be used to formulate different products with multiple applications and functionalities, allowing to retain different groups of health-conscious consumers. Furthermore, the production costs of fermented whey drinks would be comparable to those of fermented milks, since cheese whey and derivatives are cost-effective substrates.

Bioconversion into fermented beverages, would allow cheese whey valorization also in small and medium scale cheese plants, which cannot sustain the operational and equipment costs for the production of other whey-derived products (e.g. whey protein isolates, whey protein concentrates, purified organic acids).

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Alcoholic and low and low acetic beverages

The bioconversion of whey and derivatives into low-alcoholic and acetic beverages, including vinegar, is an interesting alternative to lactic drinks for producing new food commodities from the dairy waste.

Alcoholic fermentation

Ethanol production worldwide has strongly increased since the oil crises in 1970. Its market grew from less than a billion liters in 1975 to more than 39 billion liters in 2006, and reached 100 billion liters in 2015. Significant amounts of renewable ethanol are produced not only as biofuel but also for beverage and industrial end-uses. In 2018 EU produced 5.81 billion liters of bioethanol, 9% of which was food-grade ethanol (www.epure.org). The biological production of ~~bio~~ethanol from whey requires microorganisms, generally yeasts, suitable to assimilate lactose into ethanol~~.~~. ~~The main applications of yeasts in ethanol bioconversion are reported in Table SX. The best alcohol-producer yeast *Saccharomyces cerevisiae* does not have the pathway for lactose assimilation, and thus it cannot be exploited to produce ethanol from CW and other derivatives (SCW and whey permeate) without any preliminary enzymatic hydrolysis of lactose into glucose and galactose (Das et al. 2016).~~

~~By contrast the~~ The ~~yeast~~ species *Kluyveromyces lactis* and *Kluyveromyces marxianus* (synonyms *Kluyveromyces fragilis* nom. inval. and *Candida pseudotropicalis*) are lactose-fermenting yeasts thanks to ~~assimilate lactose as unique carbon source. This ability depends upon two genes not found in *S. cerevisiae*,~~the genes *LAC12* and *LAC4*, encoding for lactose permease and intracellular β-galactosidase, respectively (Varela et al. 2017)~~(Varela et al. 2017)~~. Both yeasts are commonly isolated from food, fruits and plants, as well as from fermented dairy products, thus they gained the European Food Safety Authority (http://www.efsa.europa.eu/) Qualified Presumption of Safety (QPS) status and are Generally Regarded as Safe (GRAS) organisms (Coenen et al. 2000)~~(Coenen et al. 2000)~~. Despite their phylogenetic closeness, *K. lactis* and *K. marxianus* differ in sugar metabolisms. *K. marxianus* engages better in fermentative metabolism than the respiring yeast *K. lactis* even at high temperature (45-50°C), and therefore it is preferred over *K. lactis* for bioethanol conversion (van Dijken et al. 1993; González Siso 1996)~~(van Dijken et al. 1993; Siso et al. 1996)~~. However, whey fermentation by *K. marxianus* suffers of low ethanol yield. The maximum theoretical yield of ethanol from lactose is 0.538 g ethanol/g lactose, thus the fermented product contains approximately 3-5% ethanol, depending upon strain and fermentation technology adopted. The fermentation product is then centrifuged to remove the biomass, and sent to a distillation column where the alcohol content is increased to 95 v/v%. *K. marxianus* exhibits a great strain variability in lactose utilization, so an accurate strain selection is essential to optimize ethanol yields. Selected strains should exhibit ethanol- and thermo-tolerance in order to avoid inhibitory effects on yeast growth due to catabolite repression and reduce cooling cost in ethanol production bioprocesses, respectively. Furthermore, high lactose-utilizsing~~selected~~ yeasts should possess a functional KmLac12 transport~~protein~~ which efficiently ~~transports~~ catalases the lactose ~~into the cell~~uptake (Fonseca et al. 2008)~~(Fonseca et al. 2008)~~.

Feeding, oxygen, temperature and fermentative modes also strongly contribute to alcohol productivity (Sansonetti et al. 2009) ~~(Sansonetti et al. 2009)~~. In batch processes, high lactose, relatively low temperature and low oxygen levels generally increased alcoholic fermentation (Sansonetti et al. 2009; Sansonetti et al. 2010; Sansonetti et al. 2011)~~(Sansonetti et al. 2009, 2010, 2011)~~. Lactose amount in the range of 50-200 g/L enhanced ethanol productivity, while values higher than 200 g/L negatively affected yeast growth (Ferreira et al. 2015)~~(Ferreira et al. 2015)~~. Empirical models indicated 32.3°C as the best operating temperature (Sansonetti et al. 2010)~~(Sansonetti et al. 2010)~~, whereas temperature higher than 35-37°C increased the lag phase (Christensen et al. 2011)~~(Christensen et al. 2011)~~. Oxygen depletion reduced biomass and glycerol (required for NADH oxidation) production in favour of ethanol (Sansonetti et al. 2009)~~(Sansonetti et al. 2009)~~. Cells immobilization in batch bioreactor (Roohina et al. 2016)~~(Roohina et al. 2016)~~, fed-batch processes (Brady et al. 1997; Kourkoutas et al. 2002) ~~(Brady et al. 1997; Kourkoutas et al. 2002)~~ and continuous cultivation (Kourkoutas et al. 2002; Sansonetti et al. 2011; Gabardo et al. 2014; Hadiyanto et al. 2014)~~(Gabardo et al. 2014; Kourkoutas et al. 2002; Hadiyanto et al. 2014; Sansonetti et al. 2011)~~ modes coupled with immobilized *K. marxianus* cells overcame free cells in batch bioreactor in alcohol productivity, as new substrate was available without any catabolite repression.

Differently from *Kluyveromyces* spp., the best alcohol-producer yeast *Saccharomyces cerevisiae* is unable to assimilate lactose, and thus it cannot be exploited to produce ethanol from CW and other derivatives (SCW and whey permeate) without any preliminary enzymatic hydrolysis of lactose into glucose and galactose (Guimarães et al. 2010; Das et al. 2016)~~(Guimarães et al. 2010; Das et al. 2016)~~. Alternatively, *S. cerevisiae* [illegible] sequential process or, alternatively, in co-immobilized state to avoid enzyme and cell washing-out. Bioreactors with direct contact membrane distillation allowed for the continuous removal of ethanol and increased the efficiency of sugar conversion to ethanol, by-passing catabolite repression (Tomaszewska and [illegible] heterologous expression of *Kluyveromyces LAC12* and *LAC4* genes (Domingues et al. 2010)~~in *S. cerevisiae* (Domingues et al. 2010)~~. These engineered strains generally exhibited more ethanol yield than *K. marxianus*, but should be discarded for the production of food-grade ethanol. Furthermore, ~~However~~, in presence of glucose and galactose, *S. cerevisiae* preferentially consumes glucose due to catabolic repression of enzymes necessary for galactose uptake. ~~Then, d~~Diauxic shift to galactose imposes the synthesis of novel enzymes for galactose catabolism, leading to a [illegible]

Data on economic sustainability of bioethanol conversion from whey permeate are generally poorly available. Cost-benefit analysis performed by Utama et al. (~~Utama et al.~~ 2017)~~(2017)~~ showed that ethanol production from cheese whey and napa cabbage covered the wastes disposal costs, leading to a financial benefit up to US$ 3 816.96 per month, and attained the breakeven point in 3.53 months. Conversely, ~~Da~~ Silva et al. ~~(Silva et al.~~ (-2015)~~(2015)~~ suggested that production of WPC was more economically sustainable when coupled with lactose powder production than with ethanol bioconversion of whey permeate due to high production cost for ethanol.

Acetic acid fermentation

CW and derivates after alcoholic fermentation can reach an ethanol amount around 6% (v/v) which allow the production of both vinegar and low acetic beverages. This way to valorize CW is in tune with consumer's demand for high value-added products and government initiatives promoting healthy food and drink. Health based recommendations include reducing alcohol consumption; calories from added sugars; and limiting the

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consumption of foods that contain refined grains, especially refined grain foods that contain added sugars and sodium. Foods and beverages with added sugars are higher in energy and low in essential nutrients or dietary fiber. Moreover, the safe use of non-nutritive sweeteners, like aspartame, is currently under on-going scientific debate, opening the avenue for alternative low caloric sweeteners.

Overall, these issues raise the opportunity for the beverage industry with fermentation background to make a dynamic comeback with the production of new whey-based and alcoholic-free fermented beverages.

From the biotechnological point of view, the conversion of ethanol produced from CW and its derivates into acetic acid by AAB is highly feasible. AAB are able to produce acetic acid in fermenting liquids, in which ethanol content ranges from 2-3% to 15-18%, according to the fermentation system and the microbial strain used (Gullo et al. 2014)~~(Gullo et al. 2014)~~. This wide range allows to design versatile bioprocesses obtaining vinegars and drinks at variable acetic acid content and residual ethanol. Besides the protective action of residual alcohol or acids on acetic drinks, the fermentation process can have additional roles. Microbial secondary metabolites produced by AAB can improve the functional properties and reduce or eliminate some compounds while maintaining or even increasing others.

In this scenario the exploitation of AAB by selective fermentations producing ethanol-free drinks, containing low amount of acetic acid, fructans, while reducing the content of sugar, is a challenge.

Among fructans, levan-type exopolysaccharides (LT-EPS) are synthesized by the extracellular enzyme levansucrase (or sucrose 6-fructosyltransferase), which catalyses the transfer of D-fructosyl residues from sucrose to a growing fructan chain by trans-fructosylation (Donot et al. 2012)~~(Donot et al. 2012)~~. After sucrose depletion, levansucrase cleaves the ß(2-6) linkages of the newly-formed levan chain, causing the consecutive release of the terminal fructose units until a branching point is reached (Méndez-Lorenzo et al. 2015)~~(Méndez-Lorenzo et al. 2015)~~.

The interest for bacterial fructans arises from some their properties, like bio-compatibility, bio-degradability and biomedical properties such as antioxidant, anti-inflammatory, anti-tumor and cholesterol-lowering agents. Moreover, they are considered prebiotic molecules since their hydrolysis products, which are short-chain fructooligosaccharides, show the ability to preferentially stimulate the growth of intestinal bifidobacteria (Roberfroid et al. 1998)~~(Roberfroid et al. 1998)~~.

Some studies focused fructans production by AAB, especially for food and beverages industry applications, but they are rarely applied in the food industry due to the lack of defined commercially preparations. However, they are used for some non-alcoholic beverages (e.g. in some ultra-high-fructose syrups) as sweetener or dietary fiber (La China et al. 2018)~~(La China et al. 2018)~~.

Among AAB, the strain *Gluconacetobacter diazotrophicus* SRT4 highlighted the ability to synthetize high amount of branched LT-EPS with a molecular weight above 2 x 10^6 Da. The ability to synthetize LT-EPS was also found among *Komagataeibacter xylinus* strains (see La China et al. 2018 for references). Recently, Jakob and co-workers quantified and characterized the LT-EPS produced by strains of the species *Gluconobacter frateurii*, *G. cerinus*, *Neoasaia chiangmaiensis* and *Kozakia baliensis*, by a combination of NMR and AF4-MALS-RI analysis (Jakob et al. 2013)~~(Jakob et al. 2013)~~. These latter studies showed that the molecular weight of LT-EPS has a high variability among AAB species, ranging from 4 MDa (*G. frateurii*) to 2000 MDa (*K. baliensis*). This aspect deeply influences the physiochemical properties (different rheology) as well as the function (changes in antitumor and antiviral activities) of LT-EPS. Although a number of studies highlighted the high potential applying AAB able to produce both acetic acid and LT-EPS, no commercial products are available in the market.

Whey vinegars

The conversion of cheese whey into whey vinegars represents a valuable option to recycle whey in traditional fermented food chain and to circumvent the main disadvantage of low productivity found in bioethanol production from whey. The basic process is the bioconversion of sugars into ethanol by lactose-fermenting *Kluyveromyces* yeasts, which is further converted into acetic acid by AAB (Parrondo et al. 2009)~~(Parrondo et al. 2009)~~.

FAO/WHO defines vinegar as any liquid, fit for human consumption, obtained exclusively by the biological process of double fermentation, alcoholic and acetous, from liquids or other substances of agricultural origin (Joint FAO/WHO Food Standards Programme, 1998. Codex Alimentarius 1987). In the USA, the Food and Drug Administration (FDA) requires that vinegar products must contain a minimum acidity of 4 g per 100 g. There are currently no standards to identify vinegars, however FDA has established “Compliance Policy Guides” that the Agency follows regarding labelling of vinegars, such as cider, wine, malt, sugar, spirit and vinegar blends (FDA/ORA CPG 7109.22). In EU, each country has specific regional standards for vinegar produced or sold in the national area. Unlike the USA law, EU has established a minimum threshold of 5% (w/v) and a maximum threshold of 0.5% (v/v) for acidity and ethanol, respectively, when the raw material for acetic acid fermentation is not wine.

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The most famous vinegars are from wine or cider, however, vinegars can be produced from other non-conventional sources containing sugars, like lactose-rich CW and SCW. Actually, vinegars from CW and its derivates are produced mainly in Switerland, but they are poorly known.

As ethanol amount higher than 5-6% could inhibit AAB, *Kluyveromyces* yeasts grown on whey permeate with lactose up to 200 g/L assure enough alcohol for the subsequent acetic acid production. Parrondo et al. (~~Parrondo et al.~~ 2003)~~(2003)~~ produced vinegar with acetic acid content between 5 and 6% (v/v) by sequential fermentation of *K. marxianus* and *Acetobacter pasteurianus*. Using whey permeate with 135 g/L of lactose, *K. marxianus* produced whey liquor with a final concentration of ethanol around 55 g/L within 48 hours at optimal temperature of 30°C. Ethanol was converted into acetic acid by *A. pasteurianus* in four days with an efficiency of around 84%. Similarly, *K. marxianus* strains fermented three-fold concentrated whey, producing a whey liquor containing 8% ethanol (Tamura 2000). It was two-fold diluted before oxidization of ethanol to acetic acid by *A. pasteurianus* IFO 14814. The resulting whey vinegar contained 5.2% acetic acid and exhibited a faint odour of cow milk as well as a mellow acidic taste. Whey vinegar was also proposed as stable nutrient ingredient in dairy cattle diet (Lustrato et al. 2013)~~(Lustrato et al. 2013)~~. Sequential fermentation of *K. marxianus* and *Acetobacter aceti* led to average lactose consumption of 56%, ethanol yield of 6.7 g/L/d and acetic acid production of 4.35 g/L/d.

Commentato [CP4]: sono ripartita da qui

The current vinegar market offers a number of products with peculiar attributes, especially those containing healthy and functional compounds, which number continuously, increase. These vinegars originate from different raw materials such as fermentable fruits and vegetables. CW and its derivates are suitable raw materials to design innovative bioprocesses conducted by selected yeasts an AAB strains to produce added value vinegars.

Distilled whey-based spirit (whey vodka)

Once produced, bioethanol should be distilled and/or concentrated for food or biofuel usage. Developed since 1940 in Ireland, the so called Carbery's process represents the first and most common mode to produce potable whey spirits from whey permeate on industrial scale. It relies on batch or fed-batch fermentations by *K. marxianus* coupled with continuous extractive distillation. The resulting distillate (95% by volume ethanol) is further diluted with water and redistilled to remove impurities and to produce potable whey spirits. The Carbery's process is currently used ~~by a~~in Ireland to produce 11 thousand tonnes of ethanol per year. Also, in New Zealand ~~company to produce~~ over 18 million ~~litres~~liters of ethanol were produced annually from whey through Carbery's process the and ~~annually, which are~~ exported to Asian market (Hughes et al. 2019)~~(Hughes et al. 2018)~~(Risner et al. 2018). The concept of producing whey-based spirits has been recently shifted to small craft distilleries which used pot distillation instead of extractive method. Based on life cycle analysis, production of distilled whey-based spirit resulted more sustainable than the conventional method for unaged spirit production from malted barley in terms of carbon dioxide-equivalent (CO2e) emissions and water usage (Risner et al. 2018)~~(Risner et al. 2018)~~. Volatilome of distillates changed depending upon wheys, with sweet whey distillates enriched in alcohols, acids, esters, and ketones, whereas acid whey distillates in aldehydes, terpenes, and terpenoids (Risner et al. 2019)~~(Risner et al. 2019)~~.

Although this is a means to reduce CW waste, it cannot considered among healthy strategies to valorize dairy wastes since alcoholic beverages are not in tune with healthy recommendations.

Biopolymers

The environmental problems associated with the accumulation of traditional petrol-derived plastics make urgent to find new alternatives (European Commission 2013). The real opportunity to overcome the state of emergency caused by environmental pollution related to the dispersion of plastics and issues relating to their disposal, results in the use of bio-polymers of bacterial origin. In order to reconcile food security and natural resource scarcity and environmental sustainability, the side-products of cheese production can also be used to produce biopolymers such as PHAs and BC. These biopolymers are promising candidates for industry to substitute the traditional fossil fuel derived plastics. However, the industrial production of PHA and BC, by fermentation, is a challenge in terms of economic sustainability of the process. By contrast the production cost of plastics from petrochemical product is still more competitive and preferred by industrial companies compared to biopolymer production. In fact, in order to be competitive with petrol-derived plastics, the selling price of biopolimers should not exceed 2000 €/ton. At present, unfortunately, a prediction on the revenues obtainable from products derived from biopolymers is difficult and no evidences are present in bibliografy. This depend on both type of raw material used, which is 20% to 80% higher than the cost of raw materials of conventional plastics and type of products obtained from biopolymers. It is expected that advancement in the industrialization process of PHA would drive the cost of PHA and make it an effective alternative for conventional plastic (Research and Markets, 2019a).

The PHAs are polymers of carbon and energy of reserve accumulated in the cytoplasm of many bacterial species under particular conditions of excess of carbon availability, while some other factor is limiting (i.e. N, P, S, etc). Considering that, whey can be considered as one favorite substrate for PHAs production, due to its relatively high organic load (lactose 39-60 g/L, fats 0.99-10.58 g/L, proteins 27-60 g/L, and mineral salts 4.6-8 g/L) (Colombo et al. 2016)~~(Colombo et al. 2016)~~. The use of this waste materials, among several others

Commentato [LI5]: Non so se inserirla questa frasetta

Commentato [LI6]: Research and Markets 2019 a. World Polyhydroxyalkanoate (PHA) Market - Opportunities and Forecasts, 2017 - 2023

Formattato

(Anjum et al. 2016; Koller et al. 2017)~~(Koller et al. 2017; Anjum et al. 2016)~~ as carbon source for microbial-derived PHA production has the dual function of reducing both PHA production costs and waste management costs, and it has been recently extensively reviewed by Amaro et al.~~ 2019~~ (~~Amaro et al.~~ 2019). PHAs are the only "bio-plastics" with a whole "green" life-cycle: renewable resources act as feedstock of the production (bio-based), living cells are responsible for both synthesis of their monomeric building blocks, and their subsequent polymerization (bio-synthesized), no adverse effects on the biosphere (bio-compatibility) and, lastly, they endure degradation by the action of living organisms (biodegradability) (Verlinden et al. 2007; Koller et al. 2013)~~(Koller et al. 2013; Verlinden et al. 2007)~~, such as Gram-positive and Gram-negative bacteria, *Bacillus* spp., *Pseudomonas* spp., *Streptomyces* spp. and fungi as *Aspergillus fumigates* (Bugnicourt et al. 2014)~~(Bugnicourt et al. 2014)~~.

PHA has been used in the fixation and orthopedic applications, tissue engineering, production of bioplastic, food services, in packaging, pharmaceutical industry and agriculture. According to Research and Markets (2019b), the global polyhydroxyalkanoate market accounted for $78.20 million in 2017 and is expected to reach $135.78 million by 2026 growing at a CAGR of 6.3%.

Commentato [LI7]: Research and Markets July 2019. Polyhydroxyalkanoate - Global Market Outlook (2017-2026)

~~The PHAs are of great interest for potential applications that may arise, such as packaging materials, biomedical applications and bio-fuels.~~ These polymers can be synthesized in different types of PHA that microorganisms accumulate as insoluble inclusion bodies. The first PHA identified was the homopolymer poly-3-hydroxybutyrate (PHB) Lemoigne (1927), a semi-crystalline isotactic polymer that endures surface erosion due to the hydrophobicity of the backbone and its crystallinity. Moreover, hydrolytic degradation of PHB ends in the formation of D-(-)-3-hydroxybutyric acid, a normal blood constituent, making it an excellent candidate for use in long-term tissue engineering applications being biocompatible, workable, and degradable (Ulery et al. 2011)~~(Ulerly et al. 2011)~~. It can be applied also in many types of implant applications including orthopedic, craniomaxillofacial, dental, and cardiovascular, as well as in cardiology, plastic and reconstructive surgery, general surgery, ear, nose, and throat surgery, and oral surgery. While the PHAs offer a wide range of mechanical properties, which are potentially useful in medical applications, their use particularly in vivo as bioresorbable polymers has been limited by their slow hydrolysis (Niaounakis 2015)~~(Niaounakis et al. 2015)~~. Other general characteristics of PHAs are: water insoluble and relatively resistant to hydrolytic degradation; good ultra-violet resistance but poor resistance to acids and bases; soluble in chloroform and chlorinated hydrocarbons; sinks in water, facilitating its anaerobic biodegradation in sediments; nontoxic; less "sticky" than others polymers when melted (Bugnicourt et al. 2014)~~(Bugnicourt et al. 2014)~~. These properties make PHA also good candidates for food packaging. Koller (~~Koller~~ 2014)~~(2014)~~ reviewed the main aspects to be considered when PHA are used for this purpose: purity and sensory quality, in which a specific role is played by the extraction and purification methods in order to avoid typical rancid odor and smell of the material that can easily and negatively affect the quality of the packaged food. Moreover, particular attention has to be given to the removal of remaining lipids and pyrolytic lipopolysaccharides (endotoxins) that are frequently spotted attached to PHAs from Gram negative strains (Furrer et al. 2007)~~(Furrer et al. 2007)~~; the oxygen barrier of the film depends on the composition of PHAs on the monomeric level; water barrier, PHA polyesters show the advantage of substantial hydrophobicity in comparison to other biopolymers of natural origin (starch). Generally, values for PHB are similar to petrochemical opponents (PET) and poly(vinyl chloride) (PVC); high barrier for flavouring substances to protect the flavour of the food; chemical resistance, PHAs are easily subjected to acid-catalysed hydrolytic degradation, so the performance and the suitability of biopolymers stored with common food packaging solution as a function of time has to be assessed. Bugnicourt et al. (2014) and Koller (2014) summarized the most known commercially available PHAs.

Since the first discovery by Lemoigne (1927), a number of studies indicated many microbial species able to synthesize PHAs, and the most important are *E. coli* (engineered culture) and *Cupriavidus necator*. These bacterial species are the most used for industrial application since they associate high productivity to reduced times of accumulation, ranging from 0.02 to 5.2 g/L/h (Amaro et al., 2019). Unfortunately, as reviewed by Amaro et al. (2019), despite whey is a rich media that supports microbial growth, some of the best-described PHA-producing microbial species have been shown to be unable to directly produce PHA from whey, due to its carbon source, the lactose. *Alcaligenes latus, Bacillus spp., Bacillus megaterium, Sinorhizobium meliloti, Sinorhizobium spp., Bacillus cereus, Pseudomonas aeruginosa, Hydrogenophaga pseudoflava, Pseudomonas hydrogenovora, Haloferax mediterranei, Thermus thermophiles, Methylobacterium spp.,* and *Halomonas halophila* were the species used until now to produce PHAs from whey and a comparison among used substrate, type of culture, microorganism, culture method, productivity and type of PHA has been reported in Amaro et al. (2019). Alternatively, mixed microbial cultures (MMCs) enriched in PHA-storing bacteria within the classes of *Alphaproteobacteria*, *Betaproteobacteria* and *Gammaproteobacteria* have been exploited (Morgan-Sagastume 2016; Amaro et al. 2019)~~(Morgan-Sagastume, 2016; Amaro et al. 2019)~~.

MMCs are used using feast and famine cycles in order to enrich the strains that are able to use accumulate PHAs. While MMCs were associated with lower yields of PHA production in respect to the pure strains (0.0035-0.56 g/L/h vs 0.0039-0.17 g/L/h),, they have the advantage of not requiring sterile condition (Amaro et al., 2019).

Cellulose is the most abundant biopolymer on earth, recognized as the major component of plant biomass, but also as a representative of microbial extracellular polymers. BC is a highly pure form of cellulose with the same chemical structure as plant cellulose, but having superior physical and chemical properties (eg. stability at high temperature, purity, biodegradability and water holding capacity (Gullo et al. 2017)~~(Gullo et al. 2017)~~. These properties result from a higher degree of polymerization and ultrafine network architecture. Moreover, BC does not contain hemicellulose or lignin and it shows a more crystalline structure with respect to plant cellulose. Because of its unique properties, BC has found a multitude of applications in food, paper, textile industries, as well as in cosmetic and medicine fields (Gullo et al. 2018)~~(Gullo et al. 2018)~~. Many BC-based scaffolds are approved by the Food and Drug Administration (FDA) because of the low proteins and endotoxic units content (Petersen and Gatenholm 2011)~~(Petersen and Gatenholm 2011)~~.

The global BC market is valued at 207.36 million USD in 2016 and is estimated to reach 497.76 million USD by the end of 2022 (QYResearchReports, 2017). However, until now the industrial production of BC suffers from the low production yield. BC production can be properly optimized to overcome these limitations. The design of a rational selection strategy to recover suitable producing strains is the first step to obtain functionalized BC for different applications.

The use of biodegradable BC-based material can be an outstanding alternative to substitute materials currently used in food packaging (Umaraw and Verma 2017)~~(Umaraw and Verma 2015)~~. According to American Society for Testing and Materials (ASTM Standard D-5488-94d), a biodegradable material is defined as a material able of undergoing decomposition into carbon dioxide, methane, water, inorganic compounds, or biomass in which the predominant mechanism is the enzymatic action of microorganisms, that can be measured by standardized tests, in a specified period.

BC as eco-friendly polymer, has received considerable attention especially to produce composite materials aimed to increase the shelf life of foods. Due to its specific properties, BC can be functionalized to fabricate innovative materials for the development a new generation of active packaging, in which antimicrobial agents are combined into the packaging material creating a protective layer.

Highly interesting seems the development of biodegradable active food packaging with improved physical, mechanical, barrier and additional bioactive function to ensure food safety and to extend the shelf-life of foods. Moreover, BC activated with antimicrobial compounds and probiotic can be effective against bacterial food pathogen infection, thus extending the shelf life of food products.

Some studies showed the antimicrobial effect of a BC packaging embedded with sorbic acid in mono- and multilayer BC against *E. coli* (K12-MG1655) (Jipa et al. 2012)~~(Jipa et al. 2012)~~.

Among the strictly aerobic AAB, different species synthetize BC which production yield largely differs, but the most important one is *K. xylinus* (Chawla et al. 2009; Gullo et al. 2019)~~(Chawla et al. 2009; Gullo et al. 2019)~~.

To reduce the costs of feedstock while contributing to environmental impact reduction, various low-cost alternative carbon sources for producing BC have been valued. In particular, researches focused on cheap agricultural products or waste containing suitable carbon sources (Thompson and Hamilton 2001; Kuo et al. 2010)~~(Thompson and Hamilton 2001; Kuo et al. 2010)~~. Although results are encouraging, many issues related to the yield and quality of the BC produced are still to be solved.

Few studies evaluate the use of CW and derivates for BC production. However, recently agri-food waste such the residual liquid of grape in combination with cheese whey was evaluated for BC synthesis (Bekatorou et al. 2019)~~(Bekatorou et al. 2019)~~. As for other raw material, no optimized bioprocesses are available and the main issues are related to the low BC production yield and pro and cons are related to costs and quality of BC produced. In this ~~light~~light, the exploitation of CW and derivates in producing BC is highly appealing.

Conclusion and perspectives

CW and SCW are main waste of dairy industry responsible for a high organic load. Although existing strategies to manage these wastes contribute to reduce their amount, there is a need to further valorize them. Among biological treatments, fermentative approaches using yeasts, LAB and AAB offer the opportunity to consolidate already used bioprocesses and to introduce innovative bioprocesses combining the valorization of these wastes with the need to produce healthy food commodities.

Considering the fermented beverages sector, the selection of appropriate microbial culture of yeasts, LAB and AAB could reinforce the valorization of CW and its derivates by increasing the yield of the main fermentation compounds and offering the opportunity to design and produce new functional beverages with healthy attributes.

The production of biopolymers such PHAs and BC from food wastes is of great interest by the biotechnological industry. On the basis of the current knowledge there is a wide potential but further optimization steps are needed to enhance the industrial feasibility.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical statement approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

AbdulAlim TS, Zayan AF, Campelo PH, Bakry AM (2019) Development of new functional fermented product: mulberry-whey beverage. J Nutr Food Res Technol 1:64–69 . doi: 10.30881/jnfrt.00013

Almeida KE, Tamime AY, Oliveira MN (2009) Influence of total solids contents of milk whey on the acidifying profile and viability of various lactic acid bacteria. LWT - Food Sci Technol 42:672–678 . doi: 10.1016/j.lwt.2008.03.013

Amaro TMMM, Rosa D, Comi G, Iacumin L (2019) Prospects for the use of whey for polyhydroxyalkanoate (PHA) production. Front. Microbiol. 10

Anjum A, Zuber M, Zia KM, Noreen A, Anjum MN, Tabasum S (2016) Microbial production of polyhydroxyalkanoates (PHAs) and its copolymers: A review of recent advancements. Int. J. Biol. Macromol.

Bekatorou A, Plioni I, Sparou K, Maroutsiou R, Tsafrakidou P, Petsi T, Kordouli E (2019) Bacterial cellulose production using the corinthian currant finishing side-stream and cheese whey: Process optimization and textural characterization. Foods 8: . doi: 10.3390/foods8060193

Brady D, Nigam P, Marchant R, McHale AP (1997) Ethanol production at 45°C by alginate-immobilized Kluyveromyces marxianus IMB3 during growth on lactose-containing media. Bioprocess Eng 16:101 . doi: 10.1007/s004490050295

Bugnicourt E, Cinelli P, Lazzeri A, Alvarez V (2014) Polyhydroxyalkanoate (PHA): Review of synthesis, characteristics, processing and potential applications in packaging. Express Polym Lett 8:791–808 . doi: 10.3144/expresspolymlett.2014.82

Bulatović ML, Krunić T, Vukašinović-Sekulić MS, Zarić DB, Rakin MB (2014) Quality attributes of a fermented whey-based beverage enriched with milk and a probiotic strain. RSC Adv 4:55503–55510 . doi: 10.1039/c4ra08905g

Carvalho F, Prazeres AR, Rivas J (2013) Cheese whey wastewater: Characterization and treatment. Sci Total Environ 445–446:385–396 . doi: 10.1016/j.scitotenv.2012.12.038

Castro WF, Cruz AG, Bisinotto MS, Guerreiro LMR, Faria JAF, Bolini HMA, Cunha RL, Deliza R (2013a) Development of probiotic dairy beverages: Rheological properties and application of mathematical models in sensory evaluation. J Dairy Sci 96:16–25 . doi: 10.3168/jds.2012-5590

Castro WF, Cruz AG, Rodrigues D, Ghiselli G, Oliveira CAF, Faria JAF, Godoy HT (2013b) Short communication: Effects of different whey concentrations on physicochemical characteristics and viable counts of starter bacteria in dairy beverage supplemented with probiotics. J Dairy Sci 96:96–100 . doi: 10.3168/jds.2012-5576

Chavan RS, Shradda R, Kumar A, Nalawade T (2015) Whey Based Beverage: Its Functionality, Formulations, Health Benefits and Applications. J Food Process Technol 6: . doi: 10.4172/2157-7110.1000495

Chawla PR, Bajaj IB, Survase SA, Singhal RS (2009) Microbial cellulose: Fermentative production and applications. Food Technol. Biotechnol. 47:107–124

Christensen AD, Kádár Z, Oleskowicz-Popiel P, Thomsen MH (2011) Production of bioethanol from organic whey using Kluyveromyces marxianus. J Ind Microbiol Biotechnol 38:283–289 . doi: 10.1007/s10295-010-0771-0

Coenen TMM, Bertens AMC, De Hoog SCM, Verspeek-Rip CM (2000) Safety evaluation of a lactase enzyme preparation derived from Kluyveromyces lactis. Food Chem Toxicol 38:671–677 . doi: 10.1016/S0278-6915(00)00053-3

Colombo B, Sciarria TP, Reis M, Scaglia B, Adani F (2016) Polyhydroxyalkanoates (PHAs) production from fermented cheese whey by using a mixed microbial culture. Bioresour Technol 218:692–699 . doi: 10.1016/j.biortech.2016.07.024

da Silveira EOD, Lopes Neto JH, Silva LA d., Raposo AES, Magnani M, Cardarelli HR (2015) The effects of inulin combined with oligofructose and goat cheese whey on the physicochemical properties and sensory acceptance of a probiotic chocolate goat dairy beverage. LWT - Food Sci Technol 62:445–451 . doi: 10.1016/j.lwt.2014.09.056

Das B, Sarkar S, Maiti S, Bhattacharjee S (2016) Studies on production of ethanol from cheese whey using Kluyveromyces marxianus. In: Materials Today: Proceedings. Elsevier Ltd, pp 3253–3257

de Castro FP, Cunha TM, Ogliari PJ, Teófilo RF, Ferreira MMC, Prudêncio ES (2009) Influence of different content of cheese whey and oligofructose on the properties of fermented lactic beverages: Study using response surface methodology. LWT - Food Sci Technol 42:993–997 . doi: 10.1016/j.lwt.2008.12.010

Domingues L, Guimarães PMR, Oliveira C (2010) Metabolic engineering of Saccharomyces cerevisiae for lactose/whey fermentation. Bioeng Bugs 1:164–171 . doi: 10.4161/bbug.1.3.10619

Donot F, Fontana A, Baccou JC, Schorr-Galindo S (2012) Microbial exopolysaccharides: Main examples of synthesis, excretion, genetics and extraction. Carbohydr. Polym. 87:951–962

Faisal S, Chakraborty S, Devi WE, Hazarika MK, Puranik V (2017) Sensory evaluation of probiotic whey beverages formulated from orange powder and flavor using fuzzy logic. Int Food Res J 24:703–710

Ferreira PG, da Silveira FA, dos Santos RCV, Genier HLA, Diniz RHS, Ribeiro JI, Fietto LG, Passos FML, da Silveira WB (2015) Optimizing ethanol production by thermotolerant Kluyveromyces marxianus CCT 7735 in a mixture of sugarcane bagasse and ricotta whey. Food Sci Biotechnol 24:1421–1427 . doi: 10.1007/s10068-015-0182-0

Fonseca GG, Heinzle E, Wittmann C, Gombert AK (2008) The yeast Kluyveromyces marxianus and its biotechnological potential. Appl. Microbiol. Biotechnol. 79:339–354

Furrer P, Panke S, Zinn M (2007) Efficient recovery of low endotoxin medium-chain-length poly([R]-3-hydroxyalkanoate) from bacterial biomass. J Microbiol Methods 69:206–213 . doi: 10.1016/j.mimet.2007.01.002

Gabardo S, Rech R, Rosa CA, Ayub MAÔZ (2014) Dynamics of ethanol production from whey and whey permeate byimmobilized strains of Kluyveromyces marxianus in batch andcontinuous bioreactors. Renew Energy 69:89–96 . doi: 10.1016/j.renene.2014.03.023

Gallardo-Escamilla FJ, Kelly AL, Delahunty CM (2007) Mouthfeel and flavour of fermented whey with added hydrocolloids. Int Dairy J 17:308–315 . doi: 10.1016/j.idairyj.2006.04.009

González Siso MI (1996) The biotechnological utilization of cheese whey: A review. Bioresour. Technol. 57:1–11

Guimarães PMR, Teixeira JA, Domingues L (2010) Fermentation of lactose to bio-ethanol by yeasts as part of integrated solutions for the valorisation of cheese whey. Biotechnol Adv 28:375–384 . doi: 10.1016/j.biotechadv.2010.02.002

Gullo M, La China S, Falcone PM, Giudici P (2018) Biotechnological production of cellulose by acetic acid bacteria: current state and perspectives. Appl. Microbiol. Biotechnol. 102:6885–6898

Gullo M, La China S, Petroni G, Di Gregorio S, Giudici P (2019) Exploring K2G30 genome: A high bacterial cellulose producing strain in glucose and mannitol based media. Front Microbiol 10: . doi: 10.3389/fmicb.2019.00058

Gullo M, Sola A, Zanichelli G, Montorsi M, Messori M, Giudici P (2017) Increased production of bacterial cellulose as starting point for scaled-up applications. Appl Microbiol Biotechnol 101:8115–8127 . doi: 10.1007/s00253-017-8539-3

Gullo M, Verzelloni E, Canonico M (2014) Aerobic submerged fermentation by acetic acid bacteria for vinegar production: Process and biotechnological aspects. Process Biochem.

Hadiyanto, Ariyanti D, Aini AP, Pinundi DS (2014) Optimization of ethanol production from whey through fed-batch fermentation using kluyveromyces marxianus. In: Energy Procedia. Elsevier Ltd, pp 108–112

Hernandez-Mendoza A, Robles VJ, Angulo JO, De La Cruz J, Garcia HS (2007) Preparation of a whey-based probiotic product with Lactobacillus reuteri and Bifidobacterium bifidum. Food Technol Biotechnol 45:27–31

Hughes P, Risner D, Meunier Goddik L (2019) Whey to Vodka. In: Whey - Biological Properties and Alternative Uses. IntechOpen

Jakob F, Pfaff A, Novoa-Carballal R, Rübsam H, Becker T, Vogel RF (2013) Structural analysis of fructans produced by acetic acid bacteria reveals a relation to hydrocolloid function. Carbohydr Polym 92:1234–1242 . doi: 10.1016/j.carbpol.2012.10.054

Jipa IM, Stoica-Guzun A, Stroescu M (2012) Controlled release of sorbic acid from bacterial cellulose based mono and multilayer antimicrobial films. LWT - Food Sci Technol 47:400–406 . doi: 10.1016/j.lwt.2012.01.039

Koller M (2014) Poly(hydroxyalkanoates) for food packaging: Application and attempts towards implementation. Appl. Food Biotechnol. 1:3–15

Koller M, Maršálek L, de Sousa Dias MM, Braunegg G (2017) Producing microbial polyhydroxyalkanoate (PHA) biopolyesters in a sustainable manner. N. Biotechnol.

Koller M, Salerno A, Muhr A, Reiterer A, Braunegg G (2013) Polyhydroxyalkanoates: Biodegradable polymers and plastics from renewable resources. Mater Tehnol 47:5–12

Kourkoutas Y, Dimitropoulou S, Kanellaki M, Marchant R, Nigam P, Banat IM, Koutinas AA (2002) High-temperature alcoholic fermentation of whey using Kluyveromyces marxianus IMB3 yeast immobilized on delignified cellulosic material. Bioresour Technol 82:177–181 . doi: 10.1016/S0960-8524(01)00159-6

Koutinas AA, Athanasiadis I, Bekatorou A, Psarianos C, Kanellaki M, Agouridis N, Blekas G (2007) Kefir-yeast technology: Industrial scale-up of alcoholic fermentation of whey, promoted by raisin extracts, using kefir-yeast granular biomass. Enzyme Microb Technol 41:576–582 . doi: 10.1016/j.enzmictec.2007.05.013

Kumar R S (2015) Development, Quality Evaluation and Shelf Life Studies of Probiotic Beverages using Whey and Aloe vera Juice. J Food Process Technol 06:9 . doi: 10.4172/2157-7110.1000486

Kuo CH, Lin PJ, Lee CK (2010) Enzymatic saccharification of dissolution pretreated waste cellulosic fabrics for bacterial cellulose production by Gluconacetobacter xylinus. J Chem Technol Biotechnol 85:1346–1352 . doi: 10.1002/jctb.2439

La China S, Zanichelli G, De Vero L, Gullo M (2018) Oxidative fermentations and exopolysaccharides production by acetic acid bacteria: a mini review. Biotechnol. Lett. 40:1289–1302

Lappa IK, Papadaki A, Kachrimanidou V (2019) Cheese Whey Processing : Integrated Biorefinery. Foods 8:347 (8–15) . doi: 10.3390/foods8080347

Lustrato G, Salimei E, Alfano G, Belli C, Fantuz F, Grazia L, Ranalli G (2013) Cheese whey recycling in traditional dairy food chain: effects of vinegar from whey in dairy cow nutrition. Acetic Acid Bact 2:8 . doi: 10.4081/aab.2013.s1.e8

Magalhães KT, Pereira MA, Nicolau A, Dragone G, Domingues L, Teixeira JA, Batista De Almeida Silva J, Schwan RF (2010) Production of fermented cheese whey-based beverage using kefir grains as starter culture: Evaluation of morphological and microbial variations. Bioresour Technol 101:8843–8850 . doi: 10.1016/j.biortech.2010.06.083

Mauriello G, Moio L, Moschetti G, Piombino P, Addeo F, Coppola S (2001) Characterization of lactic acid bacteria strains on the basis of neutral volatile compounds produced in whey. J Appl Microbiol 90:928–942 . doi: 10.1046/j.1365-2672.2001.01327.x

Méndez-Lorenzo L, Porras-Domínguez JR, Raga-Carbajal E, Olvera C, Rodríguez-Alegría ME, Carrillo-Nava E, Costas M, Munguía AL (2015) Intrinsic levanase activity of bacillus subtilis 168 levansucrase (SacB). PLoS One 10: . doi: 10.1371/journal.pone.0143394

Mills O (1986) Sheep dairying in Britain — a future industry. Int J Dairy Technol 39:88–90 . doi: 10.1111/j.1471-0307.1986.tb02378.x

Mollea C, Marmo L, Bosco F (2013) Valorisation of Cheese Whey, a By-Product from the Dairy Industry. doi: 10.5772/53159

Morgan-Sagastume F (2016) Characterisation of open, mixed microbial cultures for polyhydroxyalkanoate (PHA) production. Rev. Environ. Sci. Biotechnol. 15:593–625

Niaounakis M (2015) Medical, Dental, and Pharmaceutical Applications. In: Biopolymers: Applications and Trends. Elsevier, pp 291–405

Panesar PS, Panesar R, Singh RS, Kennedy JF, Kumar H (2006) Microbial production, immobilization and applications of β-D-galactosidase. J. Chem. Technol. Biotechnol. 81:530–543

Parrondo J, Garcia LA, Diaz M (2009) Whey vinegar. In: Vinegars of the World. Springer Milan, pp 273–288

Parrondo J, Herrero M, García LA, Díaz M (2003) A Note - Production of Vinegar from Whey. J Inst Brew 109:356–358 . doi: 10.1002/j.2050-0416.2003.tb00610.x

Patel S (2015) Emerging trends in nutraceutical applications of whey protein and its derivatives. J. Food Sci. Technol. 52:6847–6858

Pescuma M, Hébert EM, Bru E, de Valdez GF, Mozzi F (2012) Diversity in growth and protein degradation by dairy relevant lactic acid bacteria species in reconstituted whey. J Dairy Res 79:201–208 . doi: 10.1017/S0022029912000040

Pescuma M, Hébert EM, Mozzi F, Font De Valdez G, Heert EM, Mozzi F, Font De Valdez G (2008) Whey fermentation by thermophilic lactic acid bacteria: Evolution of carbohydrates and protein content. Food Microbiol 25:442–451 . doi: 10.1016/j.fm.2008.01.007

Petersen N, Gatenholm P (2011) Bacterial cellulose-based materials and medical devices: Current state and perspectives. Appl. Microbiol. Biotechnol. 91:1277–1286

Prazeres AR, Carvalho F, Rivas J (2012) Cheese whey management: A review. J Environ Manage 110:48–68 . doi: 10.1016/j.jenvman.2012.05.018

Ricciardi A, Zotta T, Ianniello RG, Boscaino F, Matera A, Parente E (2019) Effect of respiratory growth on the metabolite production and stress robustness of lactobacillus casei N87 cultivated in cheese whey permeate medium. Front Microbiol 10: . doi: 10.3389/fmicb.2019.00851

Risner D, Shayevitz A, Haapala K, Meunier-Goddik L, Hughes P (2018) Fermentation and distillation of cheese whey: Carbon dioxide-equivalent emissions and water use in the production of whey spirits and white whiskey. J Dairy Sci 101:2963–2973 . doi: 10.3168/jds.2017-13774

Risner D, Tomasino E, Hughes P, Meunier-Goddik L (2019) Volatile aroma composition of distillates produced from fermented sweet and acid whey. J Dairy Sci 102:202–210 . doi: 10.3168/jds.2018-14737

Roberfroid MB, Van Loo JAE, Gibson GR (1998) The Bifidogenic Nature of Chicory Inulin and Its Hydrolysis Products. J Nutr 128:11–19 . doi: 10.1093/jn/128.1.11

Roohina F, Mohammadi M, Najafpour GD (2016) Immobilized Kluyveromyces marxianus cells in carboxymethyl cellulose for production of ethanol from cheese whey: experimental and kinetic studies. Bioprocess Biosyst Eng 39:1341–1349 . doi: 10.1007/s00449-016-1610-0

Sabokbar N, Khodaiyan F (2016) Total phenolic content and antioxidant activities of pomegranate juice and whey based novel beverage fermented by kefir grains. J Food Sci Technol 53:739–747 . doi: 10.1007/s13197-015-2029-3

Saeed M, Anjum FM, Khan MR, Khan MI, Nadeem M (2013) Isolation, characterization and utilization of starter cultures for the development of wheyghurt drink. Br Food J 115:1169–1186 . doi: 10.1108/BFJ-10-2011-0274

Sansonetti S, Curcio S, Calabrò V, Iorio G (2009) Bio-ethanol production by fermentation of ricotta cheese whey as an effective alternative non-vegetable source. Biomass and Bioenergy 33:1687–1692 . doi: 10.1016/j.biombioe.2009.09.002

Sansonetti S, Curcio S, Calabrò V, Iorio G (2010) Optimization of ricotta cheese whey (RCW) fermentation by response surface methodology. Bioresour Technol 101:9156–9162 . doi: 10.1016/j.biortech.2010.07.030

Sansonetti S, Hobley TJ, Calabrò V, Villadsen J, Sin G (2011) A biochemically structured model for ethanol fermentation by Kluyveromyces marxianus: A batch fermentation and kinetic study. Bioresour Technol 102:7513–7520 . doi: 10.1016/j.biortech.2011.05.014

Shukla M (2012) Development of Probiotic Beverage from Whey and Pineapple Juice. J Food Process

Technol 04:4–7 . doi: 10.4172/2157-7110.1000206

Silva AN da, Perez R, Minim VPR, Martins DDSA, Minim LA (2015) Integrated production of whey protein concentrate and lactose derivatives: What is the best combination? Food Res Int 73:62–74 . doi: 10.1016/j.foodres.2015.03.009

Silva e Alves A, Spadoti L, Zacarchenco P, Trento F (2018) Probiotic Functional Carbonated Whey Beverages: Development and Quality Evaluation. Beverages 4:49 . doi: 10.3390/beverages4030049

Skryplonek K (2018) The use of acid whey for the production of yogurt-type fermented beverages. Mljekarstvo 68:139–149 . doi: 10.15567/mljekarstvo.2018.0207

Sohrabi Z, Eftekhari MH, Eskandari MH, Rezaeianzadeh A, Sagheb MM (2016) Development and characterization of fermented and unfermented whey beverages fortified with vitamin E. J Agric Sci Technol 18:1511–1521

Thakkar P, Vaghela B, Patel A, Modi HA, Prajapati JB (2018) Formulation and shelf life study of a whey-based functional beverage containing orange juice and probiotic organisms. Int Food Res J 25:1675–1681

Thompson DN, Hamilton MA (2001) Production of bacterial cellulose from alternate feedstocks. In: Applied Biochemistry and Biotechnology - Part A Enzyme Engineering and Biotechnology. pp 503–513

Tomaszewska M, Białończyk L (2016) Ethanol production from whey in a bioreactor coupled with direct contact membrane distillation. In: Catalysis Today. Elsevier, pp 156–163

Tripathi V, Jha YK (2004) Development of Whey Beverage with Antagonistic Characteristics and Probiotics. Int J Food Prop 7:261–272 . doi: 10.1081/JFP-120030037

Turkmen N, Akal C, Özer B (2019) Probiotic dairy-based beverages: A review. J Funct Foods 53:62–75 . doi: 10.1016/j.jff.2018.12.004

Ulery BD, Nair LS, Laurencin CT (2011) Biomedical applications of biodegradable polymers. J Polym Sci Part B Polym Phys 49:832–864 . doi: 10.1002/polb.22259

Umaraw P, Verma AK (2017) Comprehensive review on application of edible film on meat and meat products: An eco-friendly approach. Crit Rev Food Sci Nutr 57:1270–1279 . doi: 10.1080/10408398.2014.986563

Utama GL, Kurnani TBA, Sunardi S, Cahyandito MF, Balia RL (2017) Joint cost allocation of cheese-making wastes bioconversions into ethanol and organic liquid fertilizer. Bulg J Agric Sci 23:1016–1020

van Dijken JP, Weusthuis RA, Pronk JT (1993) Kinetics of growth and sugar consumption in yeasts. Antonie Van Leeuwenhoek 63:343–352 . doi: 10.1007/BF00871229

Varela JA, Montini N, Scully D, Van der Ploeg R, Oreb M, Boles E, Hirota J, Akada R, Hoshida H, Morrissey JP (2017) Polymorphisms in the LAC12 gene explain lactose utilisation variability in Kluyveromyces marxianus strains. FEMS Yeast Res 17: . doi: 10.1093/femsyr/fox021

Verlinden RAJ, Hill DJ, Kenward MA, Williams CD, Radecka I (2007) Bacterial synthesis of biodegradable polyhydroxyalkanoates. J Appl Microbiol 102:1437–1449 . doi: 10.1111/j.1365-2672.2007.03335.x

Virtanen T, Pihlanto A, Akkanen S, Korhonen H (2007) Development of antioxidant activity in milk whey during fermentation with lactic acid bacteria. J Appl Microbiol 102:106–115 . doi: 10.1111/j.1365-2672.2006.03072.x

Yadav JSS, Yan S, Pilli S, Kumar L, Tyagi RD, Surampalli RY (2015) Cheese whey: A potential resource to transform into bioprotein, functional/nutritional proteins and bioactive peptides. Biotechnol. Adv. 33:756–774

Yerlikaya O, Asli A, Kpinar, Torunoglu FA, Kinik O, Akbulut N, Uysal H (2012) Effect of some prebiotic combination on viability of probiotic bacteria in reconstituted whey and milk beverages. Agro Food Ind Hi Tech 23:XXVII–XXIX

Zoellner SS, Cruz AG, Faria JAF, Bolini HMA, Moura MRL, Carvalho LMJ, Sant'ana AS (2009) Whey beverage with acai pulp as a food carrier of probiotic bacteria. Aust J Dairy Technol 64:177–181

~~Amaro TMMM, Rosa D, Comi G, Iacumin L (2019) Prospects for the use of whey for Polyhydroxyalcanoate (PHA) production. Frontiers in Microbiol 10, 992. doi: 10.3389/fmicb.2019.00992~~

Becerra M, Cerdán ME, González-Siso MI (2015) Biobutanol from cheese whey. Microb Cell Fact 14:27-41. doi: 10.1186/s12934-015-0200-1

[illegible] supplemented whey permeate using immobilized *Lactococcus lactis* UL719. Int Dairy J 11:953-960. doi: 10.1016/ S0958-6946(01)00129-7

[illegible] recent studies and applications. J Food Sci 84, Iss. 7. doi: 10.1111/1750-3841.14686

~~**Carvalho F, Prazeres AR, Rivas J (2013) Cheese whey wastewater: characterization and treatment. Sci Total Environ 445-446:385–396. doi: 10.1016/j.scitotenv.2012.12.038**~~

[illegible] enriched whey permeate in batch fermentation processes. J Food Agric Environ 4:85-88.

~~European Commission (2013) Analysis of the public consultation on the green paper "European strategy on plastic waste in the environment". EU DG ENV. http://ec.europa.eu/environment/ waste/studies/pdf/green_paper_plastic.pdf.~~

~~**Faisal S, Chakraborty S, Devi WE, Hazarika MK, Puranik V (2017) Sensory evaluation of probiotic whey beverages formulated from orange powder and flavor using fuzzy logic. Int Food Res J 24(2):703-710.**~~

~~**Guimarães PMR, Teixeira JA, Domingues L (2010) Fermentation of lactose to bio-ethanol by yeasts as part of integrated solutions for the valorisation of cheese whey. Biotechnol Adv 28:375-384. doi: 10.1016/j.biotechadv.2010.02.002**~~

[illegible] 95:756-774. doi: 10.3168/jds.2012-5732

~~**Hernandez-Mendoza A, Robles VJ, Angulo JO, De La Cruz J, Garcia HS (2007) Preparation of a whey-based probiotic product with *Lactobacillus reuteri* and *Bifidobacterium bifidum*. Food Technol Biotechnol 45:27-31.**~~

~~**Koller M (2014) Poly(hydroxyalkanoates) for Food Packaging: Application and attempts towards implementation. Appl Food Biotechnol 1(1), 1-13. doi: 10.22037/afb.v1i1.7127**~~

~~Lappa IK, Papadaki A, Kachrimanidou V, Terpou A, Koulougliotis D, Eriotou E, Kopsahelis N (2019) Cheese whey processing: integrated biorefinery concepts and emerging food applications. Foods 8:347. doi: 10.3390/foods8080347~~

Liao C, Yousef AE, Richter ER, Chism GW (1993). *Pediococcus acidilactici* PO2 bacteriocin production in whey permeate and inhibition of *Listeria monocytogenes* in foods. J Food Sci 58:430-434. doi: 10.1111/j.1365- 2621/1993.tb042291.x

Liu X, Chung YK, Yang ST, Yousef AE (2005). Continuous nisin production in laboratory media and whey permeate by immobilized *Lactococcus lactis*. Process Biochem 40:13-24. doi: 10.1016/j.procbio.2003.11.032

Liu L, Zhu Y, Li J, Wang M, Lee P, Du G, Chen J (2012) Microbial production of propionic acid from propionibacteria: Current state, challenges and perspectives. Crit Rev Biotechnol 32: 374-381

Lo YM, Argin-Soyal S, Hsu C (2007) Bioconversion of whey lactose into microbial exopolysaccharides. Chapter 22 In Bioprocessing for Value-Added Products from Renewable Resources - New Technologies and Applications, Edited by: Shang-Tian Yang, pages 559-583.

Longanesi L, Frascari D, Spagni C, DeWever H, Pinelli D (2018) Succinic acid production from cheese whey by biofilms of *Actinobacillus succinogenes*: packe d bed bioreactor tests. J Chem Technol Biotechnol 93: 246–256.

Lule VK, Singh R, Pophaly S, Poonam, Tomar SK (2016). Production and structural characterisation of dextran from an indigenous strain of *Leuconostoc mesenteroides* BA08 in whey. Int J Dairy Technol. doi: 10/1111/1471-0307.12271

[illegible] exopolysaccharide production by *Lactobacillus rhamnosus* RW-9595M in a whey permeate. Int Dairy J 12:419-426. doi: 10.1016/S0958-6946(01)00173-X

~~Magalhães KT, Pereira MA, Nicolau A, Dragone G, Domingues L, Teixeira JA, de Almeida Silva JB, Schwan RF (2010) Production of fermented cheese whey-based beverage using kefir grains as starter culture: evaluation of morphological and microbial variations. Biores Technol 101:8843-8850. doi: 10.1016/j.biortech.2010.06.083.~~

Nath A, Verasztó B, Basak S, Koris A, Kovács Z, Vatai G (2016) Synthesis of lactose-derived nutraceuticals from dairy waste whey-a Review. Food Bioprocess Technol 9:16-48. doi: 10.1007/s11947-015-1572-2

~~Niaounakis M (2015). Medical, Dental, and pharmaceutical applications. Biopolymers: applications and trends, 291-405. ISBN: 9780323353991~~

O'Brien DJ, Panzer C, Eisele W (1990) Biological production of acrylic acid from cheese whey by resting cells of *Clostridium propionicum*. Biotechnol Prog 6(4):237-242. Doi:10.1012/bp00004a001

Pagliano G, Ventorino V, Panico A, Romano I, Pirozzi F, Pepe O (2019) Anaerobic process for bioenergy recovery from dairy waste: meta-analysis and enumeration of microbial community related to intermediates production. Front Microbiol 9:3229. doi: 10.3389/fmicb.2018.03229

~~Panesar PS, Panesar R, Singh RS, Kennedy JF, Kumar H. (2007) Microbial production, immobilization and applications of β-D-galactosidase J Chem Technol Biotechnol 81:530-543. doi: 10.1002/jctb.1453~~

~~Parrondo J, Garcia LA, Diaz M (2009) Whey Vinegar. In: Solieri L, Giudici P (eds) Vinegars of the World. Springer-Verlag: Milan, Italy, pp 273-288.~~ **fermentation. Appl Microbiol Biotechnol 99:6183-6196. doi: 10.1007/s00253-015-6766-z**

~~Pescuma M, Hébert EM, Bru E, de Valdez GF, Mozzi F (2012) Diversity in growth and protein degradation by dairy relevant lactic acid bacteria species in reconstituted whey. J Dairy Res 79:201-208. doi: 10.1017/S0022029912000040~~

Regulation (EC) No 1069/2009.

~~**Roberfroid MB, Van Loo JA, Gibson GR (1998) The bifidogenic nature of chicory inulin and its hydrolysis products. J Nutr 128:11-19. https://doi.org/10.1093/jn/128.1.11**~~
Xanthomonas campestris **using whey permeate medium. World J Microbiol Biotechnol 28:2759-2764. doi: 10.1007/s11274-012-1087-1.**

~~**Shukla M (2012) Development of probiotic beverage from whey and pineapple juice. J Food Process Technol 04:4-7. doi: 10.4172/2157-7110.1000206**~~

~~**Sohrabi Z, Eftekhari MH, Eskandari MH, Rezaeianzadeh A, Sagheb MM (2016) Development and characterization of fermented and unfermented whey beverages fortified with vitamin E. J Agr Sci Technol 18:1511-1512.**~~

~~**Thakkar P, Vaghela B, Patel A, Modi HA, Prajapati JB (2018) Formulation and shelf life study of a whey-based functional beverage containing orange juice and probiotic organisms. Int Food Res J 25(4): 1675-1681.**~~

~~Varela JA, Montini N, Scully D, Van der Ploeg R, Oreb M, Boles E, et al. (2017) Polymorphisms in the *LAC12* gene explain lactose utilisation variability in *Kluyveromyces marxianus* strains. FEMS Yeast Res 17:fox021. doi: 10.1093/femsyr/fox021~~

~~**Verlinden RA, Hill DJ, Kenward MA, Williams CD, Radecka I (2007) Bacterial synthesis of biodegradable polyhydroxyalkanoates. J Appl Microbiol 102, 1437-1449. doi: 10.1111/j.1365-2672.2007.03335.x**~~

Wan C, Li Y, Shahbazi A, Xiu S (2008) Succinic acid production from cheese whey using *Actinobacillus succinogenes* 130 Z. Appl Biochem Biotechnol 145:111-119.

Figure captions

Fig.1 Outline of value-added products obtained from cheese whey and whey-derivates through microbial fermentations.

Commentato [CP8]: Tutti questi in giallo nel testo non ci sono più

Formattato: Evidenziato