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Review

Isomerization of lactose and lactulose production: review

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Lactulose is widely used in pharmaceutical, nutraceuticals and food industries because of its beneficial effects on human health. Technology of lactulose production is mainly based on the isomerization reaction of lactose in alkaline media. However, information available on this subject is very varied. This study is a summary of the principal techniques used for lactulose production in order to gather maximum information in one manuscript for a better comprehension of the technological characteristics and specificities of lactulose synthesis.

Introduction

Significant part of the world population suffers from gastrointestinal diseases of various types. Several of these diseases are caused by pathogenic bacteria which invade the human intestine. A few days after the birth, the human intestine is colonized mainly by bifidobacteria which play a very important role in the maintenance of a good health. By changing the nutrition regime and children passage from mother's milk nutrition to ordinary food regime, the pathogenic bacteria which infiltrated into the human intestine cause diseases of various types. In order to solve this health problem, food industry and in particular dairy technology has developed dairy bio-products enriched with probiotics like lactobacillus (*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, etc.) and bifidobacteria (*Bifidobacteria bifidum*, *Bifidobacteria longum*, *Bifidobacteria infantilus*, *Bifidobacteria adolescentis*) (Clark & Martin, 1994; Donkor, Nilmini, Stolic, Vasiljevic, & Shah, in press; Katz, 2006; Ninonuevo *et al.*, 2007; Olguin, *et al.*, 2005; Wainwright, 2006). However, because of various reasons, this solution did not solve the problem. These reasons could be resumed by the following: a great loss of bacterial cells during the production process of different dairy products noticed by several researchers, a considerable reduction of the total of bacterial number due to storage at pH values lower than 5.5 as well as because of the strong acid medium in the stomach (pH $\cong$ 1.5) and the negative effect of bile salts (Chou & Hou, 2000; Lankaputhra & Shah, 1995; Lian, Hsiao, & Chou, 2002). An alternative to the resolution of this problem consists in an internal stimulation of the bifidobacteria which are already present in the intestine (Bouhnik *et al.*, 1990; Delzenne, 2003; Gibson, Beatty, Wang, & Cummings, 1995; Mizota, Tamura, Tomita, & Okonogi, 1987). This method consists in using bifidogenic functional food ingredients, known under general name of prebiotics (Kaplan & Hutkins, 2000; Marteau & Boutron-Ruault, 2002; Roberfroid, 2002; Saarela, Hallamaa, Mattila-Sandholm, & Matto, 2003; Ziemer & Gibson, 1998). These bifidogenic ingredients stimulate the growth of bifidobacteria (Tamura, Mizota, Shimamura, & Tomita, 1993). Lactulose is one of these ingredients (Alander et al., 2001; Ballongue, Schumann, & Quignon, 1997; Saarela *et al.*, 2003). Lactulose is a synthetic disaccharide obtained by an isomerization reaction of lactose whose milk and lactoserum are very rich (Zokaee, Kaghazchi, Zare, & Soleimani, 2002). The average lactose content in milk or milk whey is approximately 4.5% (Lindmark-Mansson, Fonden, & Pettersson, 2003). Several studies showed the effectiveness of lactulose to stimulate the growth of bifidobacteria (Martin, 1996; Mizota, 1996; Sako, Matsumoto, & Tanaka, 1999; Shin, Lee, Petska, & Ustunol, 2000; Strohmaier, 1998). Moreover, lactulose is widely used in pharmaceutical industry as an effective drug against different diseases like acute and chronic constipation (Mizota, Tamura, Tomita, & Okonogi, 1987; Tamura et al., 1993).

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Taking into account all these considerations, one can deduce the great need for a large scale production of lactulose for food, nutraceuticals and pharmaceutical purposes. The raw material for this production is largely available in great quantity on the market (lactoserum as by-product of the cheese industry). Annual whey production in the world is estimated to be 72 million tons, which means that about 200,000 tons of milk proteins and 1.2 million tons of lactose are transferred into whey annually. Even though many uses of whey and some whey solids have been developed recently, only a little amount of the available whey solids are utilized as ingredients in the human nutrition and animal feed (Kosaric & Asher, 1982). Ghaly, Ramkumar, Sadaka, and Rochon (2000) estimated that in 1998 about 137.9 million tons of whey were produced in the world. As a particular case, in Canada, the annual cheese production increased by 22% between 1994 and 2004. Total cheese production in Canada in 2004 was estimated at 0.34 million tons, which implies that over 0.27 million tons of whey was produced that year (Ferchichi, Crabbe, Gil, Hintz, & Almadidy, 2005). Even though there are a multitude of technological developments in the transformation of milk whey to other useful products, utilisation or disposal of whey remains one of the most significant problem in the dairy industry (Calli & Yukselen, 2004; Mawson, 1994).

Prebiotics

Prebiotics are defined as non-digestible food ingredients that may beneficially affect the host by selectively stimulating the growth and/or the activity of a limited number of bacteria in the colon. Thus, to be effective, prebiotics must escape digestion in the upper gastrointestinal tract and be used by a limited number of the microorganisms comprising the colonic microflora. Prebiotics are principally oligosaccharides. They mainly stimulate the growth of bifidobacteria, for which reason they are referred to as bifidogenic factors (Durand, 1997; Berg, 1998; Gibson & Roberfroid, 1995; Macfarlane & Cummings, 1999; Roberfroid, 2000). So that a food ingredient can be regarded as prebiotic, it must meet certain characteristics which were defined gradually after the initial work of Gibson and Roberfroid (1995). Food ingredient can be regarded as prebiotic if it satisfies some criteria (Gibson & Roberfroid, 1995): not digestible nor absorbed before reaching the colon; to be a selective substrate of one or several (preferably a low number) bacteria having a probable or definitively established beneficial role; to be able to modify the composition of the colic flora for better health by supporting the growth and/or the metabolic activity of *Lactobacillus* sp. or *Bifidobacteria* sp. (Gibson & Roberfroid, 1995); more rarely by attenuating the virulence of pathogenic bacteria like *Listeria monocytogenes* (Park & Kroll, 1993).

Some researchers reported some information, where the role of the prebiotics is not totally clear. In was postulated that prebiotic ingestion may contribute to normalize the gastrointestinal barrier function in burn patients (Olguin *et al*., 2005). This hypothesis was based on observations that burn injury is associated with dramatic alterations of the intestinal microbiota and gastrointestinal permeability, and that increasing luminal lactobacilli and bifidobacteria through the ingestion of prebiotics or probiotics is associated with recovery of the gastrointestinal barrier function. This postulate was based on the observation that regular intake of *Lactobacillus* spp. decreased the gastric permeability alterations. In relation to burn injury, a decrease of the intestinal anaerobic microbiota, including bifidobacteria, has been observed in rats, while at the same time aerobic bacteria and fungi increase. This resulted in an imbalance of the aerobic/anaerobic ratio and in a decrease of colonization resistance in these animals. These changes were associated with increased bacterial translocation and endotoxinemia, histological lesions of the mucosa. Similar alterations have been observed in burn patients. Supplementation of burn rats with a bifidobacteria preparation reduced the imbalance of the aerobic/aerobic ratio, the endotoxinemia and the mucosal lesions; the same preparation with bifidobacteria decreased gastrointestinal symptomatology and diarrhea in humans who suffered burns (Chen, Zhang, & Xiao, 1998; Gotteland, Cruchet, & Verbeke, 2001; Olguin et al., 2005). Stimulation of endogenous lactobacilli or bifidobacteria by prebiotics may also exert a protective effect against gastrointestinal mucosa alterations. Lactosucrose, for example, has been shown to protect against indomethacin-induced gastric ulcerations in rats (Honda *et al*., 1999). Although a number of studies have been carried out in animal models, data are scarce in humans. In the study reported by Olguin *et al*. (2005), oligofructose, whose administration is known to dose-dependently increase fecal bifidobacteria in humans, was used. This prebiotic did not improve the gastrointestinal barrier function alterations. A possible explanation for this lack of effect is the use of high doses of antibiotics in all these patients, which may interfere with lactobacilli and bifidobacteria growth even after stimulation by the administrated prebiotic (oligofructose). In the case of probiotics, this may be overcome by the continuous administration of these exogenous, live bacteria which may compensate for the mortality induced by antibiotics; prebiotics, however, act by stimulating the growth of endogenous bacteria, and this is probably decreased when these microorganisms are affected by antibiotics. The results obtained in the above mentioned studies may be interpreted as suggesting that prebiotics probably are not the best option for subjects on high doses of antibiotics, and that administration of probiotics or symbiotic, a mixture of pre and probiotics may be a better choice for these patients (Olguin *et al*., 2005). However, even if the used prebiotic showed some negative aspects, we can not generalise this conclusion to all the prebiotics, including lactulose. The use of antibiotics would be the