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The prebiotic potential of lactulose: A review

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Review Article

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ABSTRACT

Synbiotic foods containing both probiotics and prebiotics have got wide acceptance owing to its health benefits. Lactulose one of the established prebiotic substances is derived by isomerization of the lactose. Lactulose is commonly called as 'bifidus factor' as it enhances the growth of the *Bifidobacterium spp*. Apart from enhancing the growth of probiotic strains, lactulose is also used in treatment of constipation, detoxifying agent at higher doses. Lactulose is reported to possess many health benefits including antidiabetic activity, preventing systemic endotoxemia, anti-carcinogenic activity, preventing the growth of pathogens.

Keywords: Bifidus factor, Probiotics, Synbiotics, Health benefits.

INTRODUCTION

The demand for food products holding potential health benefits apart from nutrition, famously called functional foods, are increasing owing to the increasing number of health-conscious consumers. One of the leading categories among the functional foods, particularly dairy based, are the probiotic, prebiotic and synbiotic foods. In the development of such synbiotc foods, the synergistic effect of probiotic strains and prebiotics are very important for getting the potential health benefits. Several studies have found that combining prebiotics and probiotics may reduce the risk of intestinal diseases and eliminate specific microbial disorders. Synbiotics aid in the proper functioning of the digestive system, thereby improving overall human and animal health. Synbiotics have evolved into the most effective and safest solutions for combating specific bacterial pathogens and improving gut health.

Lactulose is a semi-synthetic disaccharide which has been used as a potential prebiotic in various milk products and is a proven bifidus factor. Since 1950, lactulose has been used in the treatment of constipation and Hepatic Encephelopathy (HE). The World Health Organization has listed lactulose in the category of essential medicine.

Many countries use it as a medicine, and it comes as solution, powder and in rectal formulations. Furthermore, it is available in some countries as a food or drink additive (for example, Italy, Japan, and the Netherlands). Comparing with other laxatives, lactulose has multiple modes of action, which gives numerous benefits.

Lactulose: General Properties and Structure

Lactulose chemically called 4-*O*-β-d-galactopyranosyl-d-fructofuranose is obtained from lactose via an isomerization process in which the monomer glucose in lactulose is converted into fructose, resulting in a galactose and fructose disaccharide linked together via a β-1-4 glycosidic linkage (Figure 1). It is formed in milk during ultra-high temperature heat treatment (UHT). During the normal pasteurization process, very little lactulose is formed. This makes it a useful indicator of thermal processing intensity [1]. The concentration of lactulose in UHT milk and sterilized milk ranges to 0.3 g/L and 1.6 g/L respectively [2]. Some of the general properties of lactulose is listed in Table 1.

Unlike most other prebiotics, lactulose does not occur naturally and it occurs only in very small quantities in heated milk. Lactulose is primarily metabolized by saccharolytic intestinal (colonic) bacteria because it cannot be hydrolyzed by enzymes present in the human intestine. Over a wide range of pathogenic (proteolytic) species, lactic acid bacteria prefer lactulose as a food source [3]. Lactulose is available in both liquid and dry forms. Lactulose syrup is a yellowish, odourless clear syrup with a sweet taste owing to the presence of other sugars. Lactulose dry is an odourless, white to almost white crystalline powder with a sweet taste that is water soluble, slightly soluble in methanol, and ether insoluble [4]. Duphalac, Bifiteral, Chronulac, Cephulac, etc. are some of the commercial preparations of lactulose and these liquid products are blended with flavours to mask the sweetness that may cause intolerance in some patients. Detailed compositional difference between dry and liquid lactulose is shown in Table 2.

Table 1: General properties of lactulose

Solubility in water	76.4% (w/w) at 30°C and 86% at 90°C
Melting point	168.5 – 170.0°C
Sweetening power	0.48 – 0.62 times sucrose and 1.5 times lactose
Energy value	2 kcal/g

Table 2: Compositional difference between liquid and dry lactulose

Constituent	Syrup (g/L)	Powder (g/100g)
Lactulose	634 - 700	95.0
Galactose	≤ 150	≤ 2.5
Lactose	≤ 90	≤ 2.0
Epilactose	≤ 70	≤ 1.5
Tagatose	≤ 30	≤ 3.0
Fructose	≤ 10	≤ 1.0

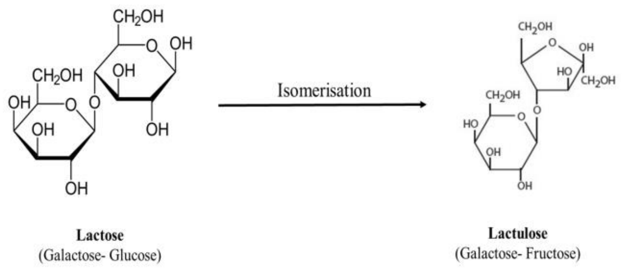

Figure 1: Structure and formation of lactulose

Lactulose as Prebiotic

The prebiotic concept was introduced for the first time by Glenn Gibson and Marcel Roberfroid in the year 1995. They described prebiotic as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health". Dietary Prebiotics were defined as "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health" [5]. The characteristics of ideal prebiotics include the following.

(1) Mammalian tissues or enzymes should not absorb or hydrolyze them.

(ii) Selectively enhance the growth and multiplication of beneficial microbes.

(iii) Impart a positive effect on the activity of the intestinal microflora.

(iv) Possessing a positive influence on the defence mechanism of the host.

(v) It has to be stable in the stomach and colon over a wide pH range.

Lactobacilli and faecal Bifidobacteria have the properties for improving the health. Their growth can be augmented when lactulose was administered at low dose for a particular time period. Studies proved that 10g of lactulose/day is connected with an increase in faecal Bifidobacterial counts, indicating that lactulose meets the criteria for being considered a prebiotic [6].

In a study, the dose-dependent prebiotic effect of lactulose in a computer-controlled *in vitro* model of the human large intestine was evaluated. They observed that lactulose at 2g results in an increase in short chain fatty acids (SCFAs), chiefly acetate, whereas lactulose at 3 or more grams was required for increase in butyrate. The reduction in ammonia was as noticeable at 4 g Lactulose whereas at 5g lactulose the growth of *Bifidobacterium*, *Lactobacillus*, and *Anaerostipes* was most prominent. According to the findings, daily dose of maximum 5g for five days can have a full beneficial prebiotic effect. Branched chain fatty acids (BCFA) are produced by the proteolytic bacteria upon the degradation of protein. Presence of such proteolytic bacteria is getting reduced after the lactulose administration which accounts for the lower BCFA content [7].

Comparative analysis of lactulose and fructooligosaccharide (FOS) on growth kinetics, fermentation, and antioxidant activity of common probiotics were studied. The results revealed that lactulose increased percentage lactic acid (%LA) than FOS of the two prebiotic supplements. The most noticeable difference was found in *L. casei LcS*. *Bifidobacterium spp*. could ferment FOS, but lactulose was preferred over FOS for enhancing the fermentation ability. *E. coli Nissile* and *B. coagulans* produced higher %LA and lower pH when lactulose was used. When given lactulose as the prebiotic, all the probiotic strains used in this study (*Lactobacillus spp.*, *Bifidobacterium spp.*, *E. coli Nissile*, *B. coagulans*) produced lower pH and higher %LA. These findings indicate that lactulose has prebiotic potential [8].

A study regarding the effect of lactulose intervention on gut microbiota and SCFA composition of C57BL/6J mice revealed that lactulose administartion enhanced the growth of probiotic bacteria *Bifidobacteriaceae* and *Lactobacillaceae*, hydrogen producing bacteria like *Prevotellaceae* and *Rikenellaceae*, and mucin-degrading bacteria such as *Akkermansia* and *Helicobacter*. The growth of *Desulfovibrionaceae* and harmful metabolites were reduced after lactulose intervention. SCFA's concentartion were maintained stable during period with decrease in branched chain fatty acid level. The addition of lactulose enhanced the growth of hydrogen producing bacteria, including *Rikenellaceae* and *Prevotellaceae*. Hydrogen has the ability to selectively neutralise reactive oxygen species while also protecting the cells from oxidative stress injuries [9].

A study was performed to evaluate the prebiotic effect of lactulose at low doasge in japaneese women and found that the defecation frequency, number of defecation days and the faecal bifidobacterial count was increased when lactulose was consumed at a doses of 1, 2, and 3 g/day. The study revealed that lactulose at 1 g/day is associated with a prebiotic effect [10].

In a study the effect of selected prebiotics on the growth of lactic acid bacteria and physicochemical properties of yoghurts were analysed and they observed that supplementation of lactulose at 4% leads to a significant increase in the growth count of the starter organisms used. Growth of *Lactobacillus delbrueckii ssp. bulgaricus* was enhanced more when lactulose was added at 4% rate. Cell viability was increased till the 14th day of storage. After the addition of lactulose, the total bacterial count remained higher with respect to the control. The viability of *L. delbrueckii ssp. bulgaricus* was enhanced during lactulose addition at various dosages [11].

In a study the use of lactulose as prebiotic and its influence on the growth, acidification profile and viable counts of different probiotics in fermented skim milk were evaluated using probiotic co-cultures

L.acidophilus (La), *L.rhamnosus*(Lr) and *B.lactis*(Bl) in combination with *S. thermophilus*(St). Addition of lactulose to skim milk increased the acidification rate (V_{max}) while decreasing fermentation time (t_{max}) and time required to reach the pH 4.5 ($t_{pH4.5}$). All the probiotic bacteria grew faster after being exposed to lactulose. After day 7, there was no significant decrease in the count of all probiotic strains. The cell count of Bl in St-Bl co-culture was significantly higher than other microorganism which proves that lactulose is a bifidus factor. They found that the quality of fermented skim milk was improved upon the addition of lactulose [12].

Lactulose causes a decline in the colon pH, making *Salmonella* difficult to survive. As a result, lactulose can act as an effective prebiotic for (non-typhoid) *Salmonella* carriers. Lactulose intervention decreases the occurrence of respiratory tract infections and urinary tract infections by clearing faecal *Salmonella* and *Shigella* species. Lactulose administration orally eliminates and prevents systemic endotoxemia of gastrointestinal origin. As a result, lactulose may be used to treat Inflammatory Bowel Diseases (IBD) [4]. Lactulose has its potential prebiotic application in prevention of various types of infections [13,14,15] which were given in Figure 2. Lactulose cam be used in the treatment of obstructive jaundice [16]. A substantial amount of mobilised endogenous hydrogen produced after metabolism of lactulose reduces the oxidative stress, improve IBD symptoms in humans, and also protect against DSS-induced colitis [17].

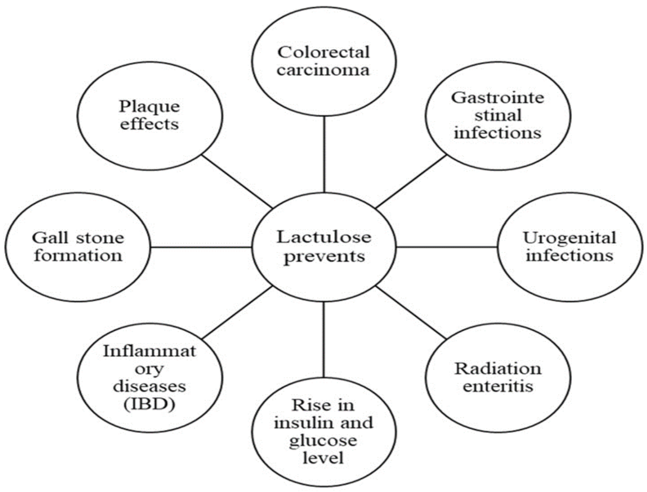

Figure 2: Potential prebiotic effects of lactulose

Mechanisms of Action

Lactulose reaches the colon without being hydrolysed by the intestinal enzymes and is metabolized by the colonic bacteria into its monomers and are the transformed into short chain fatty acids (SCFA's), hydrogen, and methane. Detailed mechanism of action of lactulose shown in Figure 3. There are mainly three ways in which lactulose reduces the production and absorption of the ammonia in the intestine [18];

1. Colonic lactulose metabolism produces a laxative effect by increasing osmolality and intraluminal gas formation, which results in a decrease in intestinal pH and transit time. This laxative effect can also help with constipation.

2. Lactulose increases ammonia intake by colonic bacteria as a nitrogen source for protein synthesis. This process is aided by lowering the intestinal pH, which also favours the conversion of ammonia (NH_3) into ammonium (NH_4^+) ion, which is impermeable across the biological membranes.

3. Lactulose reduces ammonia production in the intestine. The acidic pH eliminates urease-producing bacteria, which produces ammonia. It also retards the intestinal glutaminase activity, which prevents glutamine uptake and its metabolism to ammonia.

The decrease in the colonic pH due to lactulose metabolism has led to the increased solubility of calcium of magnesium salts. The increased solubility can lead to increased absorption of these salts in the GUT. Thereby lactulose can improve the bone health.

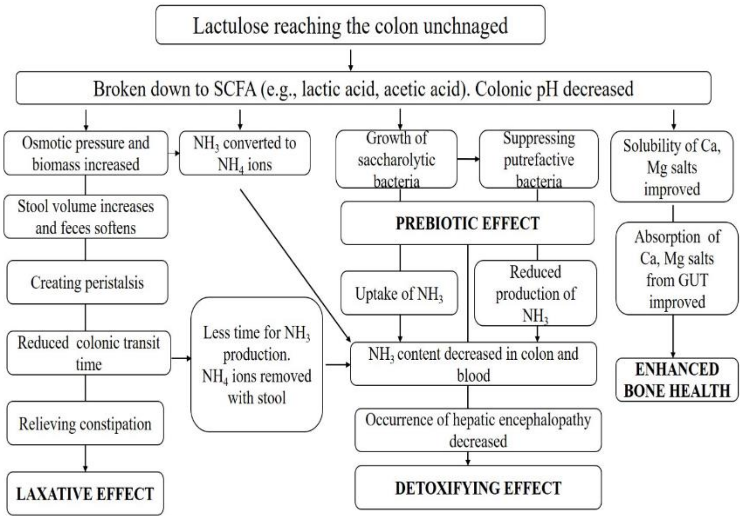

Figure 3: Mechanisms of action of lactulose

Safety and Tolerance

Lactulose has a history of over 40 years and 30 years in the treatment of constipation and portosystemic encephalopathy (PSE) respectively [13]. The dosage of lactulose in the treatment of PSE are up to four times higher than those used to treat constipation. Mutagenic, genotoxic or teratogenic effects of lactulose was not found in human use. Animal studies carried out in rats and rabbits found no teratogenic effects, and even high doses had no negative effects [18]. Lactulose and its metabolized products do not produce any toxic intermediates. Lactulose was regarded as one of the safer laxatives. Most common side effects of lactulose include flatulence and some gas related issues. At higher dosage levels of lactulose diarrhoea was observed and that too during the first five hours of treatment [19].

Dosage and Administration

As the severity and the type of disease condition varies, the dosage of lactulose also varies. Low dose of 10 g/day is associated with increase in count of faecal *Bifidobacteria* [6]. The dose of lactulose orally for constipation in adults is 15-30 mL/day, and if necessary, it can be increased to 60 mL/day [20]. To prevent opioid-induced constipation, 60 mL of lactulose per day should be taken [21]. The dosage for children with constipation is 0.7-2 g/kg/day in divided doses; the dosage should not exceed 40 g/day (60 mL/day) [22]. The amount of lactulose required to treat hepatic encephalopathy is much higher than that required to treat constipation. At varying doses, lactulose can be used for various treatments (Figure 4).

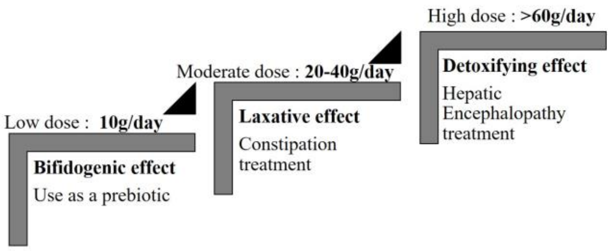

Figure 4: Dose dependent effect of lactulose

Production Methods

Lactulose can be manufactured by chemical and enzymatic methods (Figure 5). Lactulose is industrially produced by chemical isomerization of lactose using Lobry de Bruyn-Alberda van Ekenstein (LA) rearrangement. Alkaline catalyst that are being used involves calcium hydroxide, sodium hydroxide, magnesium oxide, tertiary amines. Alkaline ions like magnesium, lithium, sodium, potassium and caesium have also been used in the chemical isomerization process for the manufacture of lactulose. The enzymes β-galactosidase and glycosidase are commonly used in the production of lactulose by enzymatic method. β-Galactosidase (EC.3.2.1.23) is a well-established enzyme for use in the trans-galactosylation reaction [23]. Enzymes β-galactosidase from *Aspergillus oryzae* and the hyper thermostable β-glycosidase from *Pyrococcus furiosus* are used in the enzymatic transgalactosylation of lactose to fructose. Lactulose production from *Pyrococcus furiosus* were 46 mmol/L and 30 mmol/L for *A. oryzae* β-galactosidase [24]. Whole cells have several advantages over free enzymes in the manufacture of lactulose. However, the cell envelope's permeability barrier is the major constraint involve in the process. Permeability barrier can be reduced by permeabilizing the yeast cells making the whole cells with high activities [4].

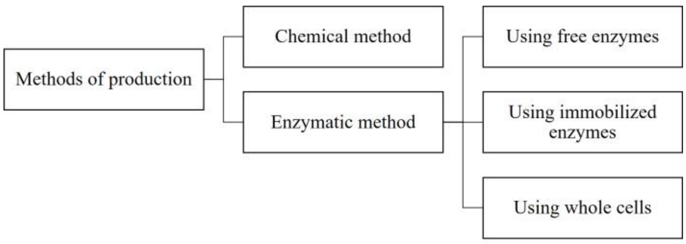

Figure 5: Manufacturing methods to produce lactulose

Food Applications

Lactulose being a bifidus factor is used in wide range of foods as a functional ingredient. Apart from imparting health benefits lactulose is useful in modifying food flavour and physicochemical properties. Lactulose is also being used for various purposes like sweetener for diabetic patients, replacing the sugar in confectionaries, infant milk powders, beverages, bakery products, yoghurts etc. Some of the desirable properties of lactulose in food products includes; flavour enhancement, enhancing the browning properties and excellent water solubility, and so on. Many researches were conducted on yoghurt, cookies, cake, chocolate, and other products to determine how lactulose behaves during product processing [4].

The use of lactulose syrup is permitted by FSSAI in the following foods [25]:

- In special milk based infant food formulations: Max 0.5% of final food subject to label declaration.
- In bakery products: Max 0.5% by weight

CONCLUSION

Lactulose is being used as a potential prebiotic owing to its health benefits attributed upon ingestion of the disaccharide. It widely enhances the growth of the genus *Bifidobacteria* and is called as a Bifidus factor. The utilization of lactulose by gut microbiota is highly strain specific. Lactulose helps in prevention of various types of infections. The effect of lactulose on human body is dose dependent. Various food applications along with the rising market demand makes lactulose an ideal ingredient in the manufacture of synbiotic dairy foods.

Conflict of Interest

None declared

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