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Medical, nutritional and technological properties of lactulose. An update

Summary The undigestable disaccharide lactulose has been in medical use for over 40 years, mainly in the treatment of portosystemic encephalopathy and of constipation. Pharmacodynamics of lactulose make it an efficacious and safe drug in these indications. But the reason for its numerous potential benefits are under research now. The major principle of action is the promotion of growth and activity of lactic acid bacteria in the gut which counteract detrimental species such as clostridia or salmonellae. This shows that prebiotic action, if used accordingly, can have medically significant effects. The mechanism of action, medical and prebiotic effects, veterinary uses, and technological properties of lactulose, e. g. in yoghurt production are reviewed.

Key words lactulose – constipation – portosystemic encephalopathy – prebiotic – prevention – nutrition – feed – milk

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Description

Lactulose is a semi-synthetic disaccharide made from lactose by a chemical reaction which was first described in 1930 [1]. Though not present in nature lactulose occurs in heat-treated milk products as a result of catalyst-free isomerisation of lactose. Since the 1950s lactulose has been used in humans for the treatment of specific medical conditions but as a prebiotic as well (at that time named "bifidus factor"), although the nomenclature of pro- and prebiotics has only come into use much later. For this reason lactulose became known to science first as a medicinal product and not as a prebiotic food additive. This history of use and the semi-synthetic character explains the legal status of lactulose, which differs clearly from other prebiotics. These are usually no drugs but food components or additives. Lactulose is classified as a drug despite its very close chemical and physiological relation to other prebiotics. Exceptions to this rule are Italy, Japan, and the Netherlands where lactulose is sold either as food or drink additive, in infant formula, or as a pure prebiotic.

Chemistry, occurrence and general properties

Lactulose (4-O-β-D-galactopyranosyl-D-fructose) is an isomerisation product from lactose and thus both are identical regarding the empirical formula ($C_{12}H_{22}O_{11}$) and the molecular weight (342.3). Alkali hydroxides and boric acid are typically used to catalyse this isomerisation. Refined edible lactose qualities are used for this process. Chemical structures of lactose and lactulose are shown in Fig.1.

Lactulose liquid (syrup) is a yellowish, odourless clear syrup with a sweet taste which is largely due to the content of other sugars (see Table 1).

Lactulose dry is a white to almost white odourless crystalline powder of sweet taste (sweetness 0.6–0.8 relative to sucrose, [2]), soluble in water, slightly soluble in methanol, and insoluble in ether. Melting point is between 168.5 and 170 °C.

Some commercially available liquid products are mixed with flavours. The reasoning behind that is to cover the sweetness which for some patients may lead to signs of intolerance. However, only very rarely do patients stop taking lactulose because of the sweetness; on the other hand, flavours may provoke intolerance in terms of allergic or hypersensitivity reactions.

European Journal of Nutrition, Vol. 41, Supplement 1 (2002)

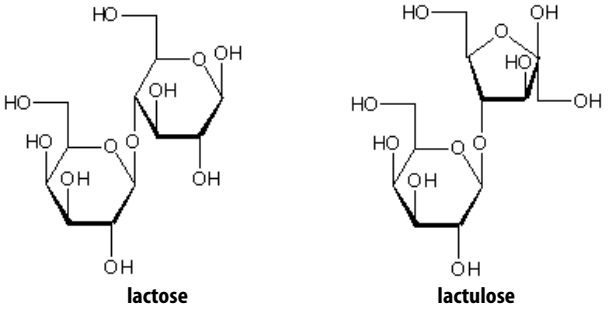

Fig. 1 Structural formula of lactulose and lactose

Table 1 Principle composition of lactulose liquid and dry

Component	Liquid (g/l, range)	Dry (g/100 g; range)
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

Note: these are pharmakopoeia requirements; sugars other than lactulose are usually much less concentrated. Differences in composition are pharmaceutically and pharmacologically unimportant; by very low residual-sugar concentrations and/or high lactulose concentrations the syrup becomes microbiologically instable

In contrast to most other prebiotics, lactulose is not present in nature and does not occur naturally, e. g. as a product of hydrolysis or enzymatic synthesis from lower sugars. Nevertheless, lactulose does occur in very small amounts in heated milk as a product of noncatalysed isomerisation. In contrast to its substrate lactose, lactulose can not be split by human intestinal enzymes at the β-1-4-glycosidic bond. While lactose can be digested and absorbed by most of the white, Caucasian population, lactulose can not be absorbed and is mainly metabolised by saccharolytic intestinal (colonic) bacteria. Lactulose constitutes a favourable food for lactic acid bacteria over numerous pathogenic (proteolytic) species. The biological/medical potential of such a characteristic is manifold and compares well with the effects of other prebiotics although clear differences do exist. For instance, lactitol has the same empirical formula and molecular weight as lactulose, nor is it split in the small intestine, but still it shows very different effects on several parameters of bacterial metabolism, faecal pH, and transit time [3–6, Huchzermeyer H & Schumann C, unpubl. results]. Lactitol has been shown to be significantly less effective at the same dosage. It has been suggested that only the cyclic part of this sugar-alcohol acts as a prebiotic while the alcohol residue is thought to act in an osmotic manner [5]. Direct comparisons of lactulose and other prebiotics are scarce [7].

Applications

In contrast to other prebiotics lactulose has up to now been mainly used as a medicinal drug. In 1957 Petuely [8] published the basic work about lactulose as "the bifidus factor" which was confirmed by MacGillivray et al. [9]. They found that the composition of the colonic microflora of bottle-fed babies is very much like that of adults while if lactulose is added to the formula milk such babies have the same composition as breast-fed babies (Table 2).

Especially the Japanese took advantage of this early and added lactulose to products for babies. No other bifidogenic compounds were known at that time. On the other hand, in the European Union lactulose – and other prebiotics – are not allowed in weaning food (an EU directive). Thus, lactose remains the major carbohydrate source in formula milks.

Lactulose as a medicinal drug is registered in over 100 countries. Indications are hepatic encephalopathy and constipation and in some countries the treatment of salmonella carrier state. Dosages in these indications are rather different: for constipation usually 10–40 g per day are recommended, while in hepatic encephalopathy (HE) the dosages applied range up to 90 g/day depending on the severity.

Constipation and hepatic encephalopathy

Mayerhofer and Petuely [10] were the first to suggest lactulose for a therapeutic use, constipation in children. Due to the safety profile in long-term use and due to the reliable efficacy of lactulose, chronic constipation in general has become the largest indication while in hepatic encephalopathy (HE) lactulose is the standard treatment world-wide in prophylaxis and treatment [11]. Bircher et al. [12] published the first evidence that lactulose is effective in this indication. Since Conn et al. [13] showed superiority of lactulose over the standard treatment up to that time it has been used successfully in all degrees of severity of HE including the subclinical state and hepatic coma where lactulose is also applied via gastric tube or as enema. All aspects of HE and the use of lactulose in this indication have been reviewed by Conn [14]. In addition to the HE-related effects of lactu-

Table 2 Major components of colonic microflora of babies fed different food

Species of the Colonic microflora	count per gramme faeces		
	breast-fed	bottle-fed	bottle-fed + lactulose
Bifidobacterium spec.	10^9	10^{10}	10^9
All anaerobes	10^9	10^{11}	10^9
All aerobes	10^{7-8}	10^8	10^{7-8}

lose in the colon some evidence from animal trials is available for a lactulose-mediated reduced production of glutaminergic ammonia in the small intestines [15]. Trapping of ammonia by lactulose molecules is the assumed mechanism [16].

Salmonella carrier state

Hoffmann [17] like others later on demonstrated the potential of lactulose for a medically meaningful use as a powerful prebiotic in (non-typhoid) salmonella carriers. In this indication lactulose is used in dosages of up to 60 g per day. It is believed that this leads to a sharp drop of the colonic pH, which makes survival of salmonella difficult.

This indication is registered in only a few countries which is due to national legislation regarding salmonella carriers. It is, however, a rather old indication of the prebiotic efficacy of lactulose.

Safety and tolerance

Lactulose has been used for 40 years in the treatment of constipation [10] and for more than 30 years for portosystemic encephalopathy (PSE) [12]. The dosages used in PSE are up to four times higher than those usually applied in constipation. PSE patients are frequently chronic users of lactulose and, in contrast to most laxative users, are under regular medical supervision. No putative or definite evidence of mutagenic, genotoxic or teratogenic effects of lactulose has been obtained in human use. Animal studies in rats and rabbits also did not reveal any teratogenic or reproduction-toxicologic effects, and even high dosages have had no deleterious effects [18].

Generally, it can be stated that the safety of lactulose as a laxative is reflected above all by the absence of publications on this topic. Conn & Bircher [10] comment in this respect: "A chapter dealing with the complications of lactulose use cannot be very long. Despite gastrointestinal side effects, this indigestible carbohydrate or its biodegradation is not expected to produce any toxic intermediates." Nunez and Robinson [20] regard lactulose as one of the safest laxatives. Most frequent side effects are transient flatulence and other gas-related symptoms. Recently, Baskaran et al. [21], in view of the addition of lactulose to food and infant formula, investigated the safety of lactulose in growing rats and found very high calculated LD_{50} and maximum tolerated dosages (> 10 g/kg body weight) and neither mortality or clinical signs of toxicity nor effects on food consumption have been found. At higher dosages mild diarrhoea was observed, but only during the first 5 hours of lactulose treatment.

Potential claims (indications)

Besides the registered indications mentioned above, evidence has accumulated about further effects of lactulose in several disease states. The majority of these potential applications aim at prevention. Thus, lactulose is comparable to claims of other prebiotics. However, while most of the claims made by non-drug prebiotics such as inulin or oligofructose are based mainly on animal or in vitro trials, lactulose data to a considerable extent are based on clinical research (for references see [22]).

Circulating bile acids

The first ideas about further indications and especially uses which would now be called prebiotic arose from thoughts by Ebner [23] and subsequent work reporting the first evidence for a hypolipidaemic effect of lactulose [24]. In an open trial the group showed in hyperlipidaemic patients a decrease of serum cholesterol by 17 % after 4 week's treatment with lactulose and, even more important, values had remained low after another 4 weeks without treatment [24]. In hamsters lactulose plus lignin decreased serum cholesterol and the lithogenic index of bile significantly more than did lignin alone [25]. In 1979 a preventive effect of lactulose in colorectal carcinoma was hypothesised [26], and in 1981 it was shown that the lithogenic index can be reduced significantly by lactulose [27], thus decreasing the risk for developing cholesterol gallstones. These results were reproduced by Van Berge Henegouwen et al. [28]. This working group also considered lactulose as protective in colorectal carcinogenesis [29].

The common basis for these effects is seen in a shift of the bacterial composition and of the bacterial metabolism leading to a much reduced activity of 7-α-dehydroxylase which produces secondary bile acids. These are suggested as being co-carcinogens and they are enterohepatically recycled, their concentration affecting hepatic bile acid and cholesterol synthesis [30]. 7-α-dehydroxylase and other bacterial enzymes with potentially toxic products are significantly reduced by lactulose [5]. Reduced production of other potential carcinogens such as ammonia may contribute to the protective effect of lactulose (Table 3). A third mechanism might be seen in the DNA-protective effects of butyrate. Much research is being done in the effects of this SCFA; however, most of it is related to anti-inflammatory effects. A potential use of lactulose in inflammatory bowel disease has been postulated [31] and the anti-inflammatory effects of lactulose and prebiotics in general have been reviewed [32].

Though some work has been done on the indications related to bile acid turnover a final proof of efficacy in

European Journal of Nutrition, Vol. 41, Supplement 1 (2002)

Table 3 Bacterial enzymes, products and potential effects

Enzyme	product	potential effect
Azoreductase	aromatic amines	cancero-/mutagenic
7α-dehydroxylase	desoxycholic acid	cell proliferation
β-glucuronidase	aglycones (laxatives)	cancero-/mutagenic
Nitroreductase	1-aminopyrene	mutagenic
Urease	ammonia	co-carcinogenic

one of them has not yet been published. A prevention trial over five years showed that lactulose was as effective as antioxidative vitamins (A, C, E) and superior to placebo in preventing recurrence of adenomas after polypectomy [33]. This trial, however, needs confirmation. Numerous effects may contribute to such a protective role of lactulose: transit time, increased excretion of neutral sterols as a sign of reduced cholesterol absorption, reduced secondary bile acids and other toxins, and protective effects of butyrate.

Tumour prevention/immunology

A considerable amount of work in the area of tumour prevention by bifidobacteria has been done showing efficacy also in the prevention of mammary and liver carcinogenesis induced, e. g. by 2-amino-3-methylimidazo-(4,5-f)-quinolone [34]. Recently, the DNA-protective effect of lactulose in human flora-associated rats exposed to dimethylhydrazine has been demonstrated [35]. Japanese workers concentrated on the effects of bifidobacteria in carcinoma prevention. They described numerous specific and non-specific anti-tumour and immunologic effects exerted by bifidobacteria (reviewed in [36]). Since most Bifidobacteria metabolise lactulose very well this immunologic and anti-tumour effects of bifidobacteria can most likely be triggered by feeding lactulose.

Recently, another potential use has come into discussion: atopic disease in early life. Related skin reactions of new-borns have been successfully treated by application of specific strains of probiotic bacteria [37]. Their use in new-born babies, however, has been questioned ethically. Therefore, an equally safe and successful bacteria-free treatment would be welcome. Lactulose has the potential for such effects. Preliminary data are promising [38].

Direct immunologic effect

Although lactulose is for the most part not absorbed and passed on to the liver and the systemic circulation the small amounts which are absorbed (0.25–2 %) are sufficient for immunologic reactions (~30 μg/ml). As has already been shown [39, 40] lactulose does also show specific immunologic effects if given intravenously or in the in vitro setting. After galactosamine challenge of rats i. v. lactulose nearly completely prevented necrosis of hepatocytes and inflammatory reactions of liver tissue; Greve and coworkers found in vitro that the endotoxin-inactivating capacity of lactulose is limited but that the endotoxin-induced production of tumour necrosis factor by monocytes is significantly reduced. These results have been followed up and preliminary results (unpublished) of in vitro trials show that macrophages activated by endotoxins of different origin (Salmonella, E. coli, Pseudomonas) show differentiated reactions with regard to TNF-α, IL-1β, GM-CSF, IL-8, IL-2, TGF-β1, IL-10, IL-12, and IFN-γ. This suggests a direct immunologic action of absorbed lactulose in addition to the indirect effects by bifidobacteria. Currently these data do not allow any further conclusion, because the cytokine reactions require a differentiated evaluation.

Anti-endotoxin effects

As early as 1980 an anti-endotoxin effect had been suggested [39]. Endotoxins trigger inflammatory reactions if they are translocated from the gut into the systemic circulation. Translocation can especially take place when the gut permeability is disturbed. This may be caused by all kinds of trauma, e. g. burns, surgery, and even in stress. In inflammatory bowel disease (Crohn's, ulcerative colitis) permeability is increased as well and may depend on the state of the disease. Clinically, the anti-endotoxin effect of lactulose has been repeatedly investigated in patients who underwent surgery of obstructive jaundice. Lactulose treatment during 2–3 days prior to operation nearly completely prevented endotoxin-dependent complications [42, 43] such as renal dysfunction.

The anti-endotoxin effect of lactulose may receive a much broader meaning once the connection with metabolic diseases like the hepatorenal syndrome [44], exocrine pancreatic dysfunction [45], diabetes mellitus [46, 47], and hypercholesterolemia [48] are better understood.

Infection prevention

In a retrospective trial lactulose showed significantly decreased rates of urinary tract infection (UTI) and of pneumonia [49]. A placebo-controlled trial confirmed the UTI-preventive efficacy of lactulose in bedridden, elderly females; the incidence of UTI after 6 months treatment had decreased to 12 % compared to 35 % in the placebo group [59]. Recurrent vaginal mycosis have also been successfully prevented with lactulose [51]. High candida counts in faeces react on treatment with

specific strains of bifidobacteria [52] but lactulose treatment as well [53, 54].

Blood glucose and insulin

In a small cross-over trial preliminary results showed a statistically significantly reduced increase of blood glucose after oral glucose tolerance testing after 10 days pretreatment with lactulose as compared to no treatment [55]. Further evidence for glucose-lowering effects of lactulose was provided by Bianchi et al. [56]. Hosaka et al. [57] showed in the isolated jejunal loop of rats that lactulose reduced the absorption of glucose by 40 % without affecting the uptake of amino acids. Unpublished data (on file: International Lactulose Application Committee, Hanover, Germany) show that the reduced glucose and insulin responses after lactulose administration are not due to α-glucosidase inhibiting properties. Cornell [58] suggested that endotoxins might reduce pancreatic insulin production and that endotoxin-reducing substances might have antidiabetic effects.

Diagnostic applications

Lactulose is applied in the determination of the orocaecal transit time by means of the *H_2-breath test* in order to assess a) lactase deficiency and b) small intestinal bacterial overgrowth.

The principle is based on the bacterial hydrogen production from undigested(able) disaccharides. Hydrogen is quickly absorbed and exhaled and can be measured easily. Lactulose in this diagnostic procedure is used as a standard. Usually, hydrogen is measured over a period of 2–3 hours after ingestion of 10–25 g lactulose in 10–30 minutes intervals. In the fasting state a peak is usually seen after 80–110 minutes. A test sugar, mainly lactose is applied on another day and peak hydrogen concentration in the exhaled air is determined. In lactose-intolerant persons the peak value should occur at about the same time after ingestion of the two sugar solutions.

In small intestinal bacterial overgrowth occasionally the lactulose H_2-breath test is used for diagnosis. In positive cases an early peak can be found before the large peak occurring after the substrate has reached the large intestines.

In determinations of the orocaecal transit time as the target parameter of the physiologic action of the stomach and the small intestines lactulose and other undigestible carbohydrates are not suitable since in the fasting state they are moved forward at higher speed than normal mixed food. Thus, results of such tests can only be relative but are not suitable to measure transit times of food.

In numerous conditions an increased *gut permeability* can be found. For diagnosis differently absorbed sugars (e. g. rhamnose/lactulose) are applied; urinary excreted amounts of these sugars are determined and the quotient used for quantification of the disturbed permeability.

Lactulose as food additive

Currently, lactulose is not present naturally in any food. However, a series of tests with lactulose has been performed on yoghurt, cookies, cake, chocolate, etc. regarding the behaviour during processing, sensory properties, influence on taste, browning, etc. [2]. Major aspects are the highly flavour enhancing properties, a favourable browning behaviour, excellent solubility in water, and a viscosity which allows substitution of sucrose (Table 4).

Physiological properties

Although never stated clearly, lactulose is the original prebiotic, known since 1957, impressively researched with thousands of publications and numerous, also human, data about its prebiotic actions. Most of the data have already been discussed in detail in the application section. An overview of the mechanism of action of lactulose is given in Fig. 2.

Not shown in Fig. 2 are the general consequences of feeding lactulose to the indigenous flora of the intestinal tract. These are manifold and a summary overview is given in Table 5. As can be clearly seen from the lactitol example [3, 5] and from oligofuctose and inulin [7] even very closely related prebiotics may constitute differently valuable nutrients for intestinal bacteria. Consequently, the bacterial actions listed in Table 5 will be promoted quite differently by different prebiotics.

In the fasting state lactulose may reach the colon within about 1.5 hours as could be concluded from H_2-breath test results (see diagnostic applications section). Lactulose entering the caecum is quickly metabolised. This results in a moderate rise of the osmotic pressure and a clear and dose-dependent drop of the caecal pH.

Table 4 Chemical/physical and selected physiological properties of lactulose powder (from Battermann 1997)

Taste improvement
Texturising effect
Stabilising effect
Good solubility in water
Viscosity closely resembles that of sucrose
Rel. sweetness 0.6–0.8 that of sucrose
Low energy value (2.0 kcal/g)
Does not cause dental plaque

European Journal of Nutrition, Vol. 41, Supplement 1 (2002)

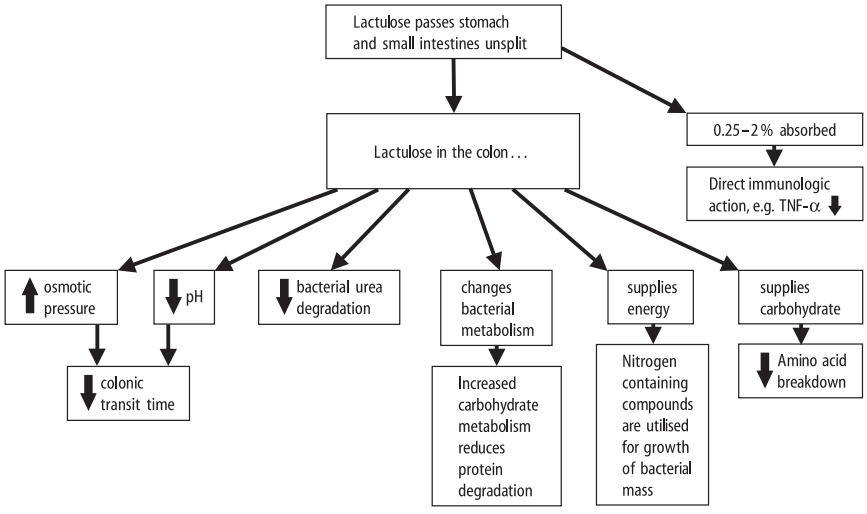

Fig. 2 Principle mechanism of action of lactulose. Principle consequences of the bacterial metabolism of lactulose are displayed. It is not known to which extent the individual physiological actions contribute to a certain effect

Table 5 General prebiotic effects of lactulose

Acidification of gut contents
Ammonia depletion
Increased peristalsis
Increased osmotic pressure
Softening of stool
Facilitated defaecation
Selective bacterial growth
Stabilisation of ecosystem
Inhibition of toxin-producing enzymes
Prevention of gallstones
Decrease of serum lipids
Shorter residence time of toxins
Prevention of carcinoma (colorectal and maybe other organs)
Prevention of gastrointestinal infections (Rotavirus, Candida, etc.)
Prevention of urogenital infections
Prevention of radiation enteritis
Anti-endotoxic (numerous applications possible)
Glucose- and insulin control
Improved mineral absorption
Prevention (therapy) of inflammatory diseases (e. g. diverticulitis)

Table 6 Concentration of volatile fatty acids in faeces of healthy volunteers after 4 weeks treatment with 2 x 10 g lactulose or placebo (mmol/l) (from [5])

Acid	Placebo	Lactulose
Lactic acid	14.7	19.6
Acetic acid	54.8	71.3
Propionic acid	13.0	11.1
Butyric acid	5.4	4.4

Physiologically, these two effects in combination lead to an increased peristaltic action. After low dosages, which do not decrease the colonic transit time much, faecal pH is not affected. Major end products of bacterial metabolisation are lactic acid and short chain fatty acids (SCFA)(Table 6).

Secondary effects are changes in bacterial metabolism and bacterial composition; in addition a quick (< 24 hours) and clinically relevant drop of the blood ammonia level in hepatic encephalopathy patients has been observed.

Recent *in vitro* and *in vivo* trials show clear prebiotic effects of lactulose [4, 5, Gibson 2000, pers comm.]. While bifidobacteria, lactobacilli and to a certain extent streptococcus species increase, *Bacteroides*, Clostridia, coliforms, and eubacteria decrease significantly. The effect of, e. g., lactitol is much less pronounced. This differential growth of colonic bacteria is reflected in changes in enzymatic activities which decrease by 50–70 %. Products of these enzymes and their potential effects are displayed in Table 3.

Recently, a trial has been completed which measured the calcium absorption after lactulose or placebo in healthy post-menopausal women. The authors found a significant increase of Ca absorption without increased urinary excretion [59]. These data confirm results from animal experiments showing increased bone strength and reduced breakability after feeding lactulose as compared to either inorganic calcium or whey [60, 61]. The favourable effect of lactulose on absorption of calcium, magnesium, iron and zinc has recently been reviewed [62].

One aspect of feeding prebiotics is the bacterial production of gas. This may occasionally lead to meteorism and flatulence and seems to be differently pronounced depending on the prebiotic [3, 7]. Data about this aspect are rare.

Veterinary uses

Only very recently has lactulose become subject of veterinary research. Today, while more and more countries ban antibiotics in the breed and nutrition of cattle, pork and poultry, lactulose has gained remarkable interest as a replacement additive to fed. Here, lactulose is interesting in at least two aspects:

- Prevention and treatment of infection or carrier-states
- Growth enhancement.

Numerous trials are going on to determine cost-effectiveness of lactulose in various conditions of major groups of housestock. Preliminary results are promising [63].

As compared to antibiotics, and if further proof of effectiveness becomes available, the use of lactulose in the feed would fulfil important contemporary conditions:

- no chemical residues
- no amplification of bacterial resistances.

Medically and nutritionally important technical information

Commercially, lactulose is produced by catalytic isomerisation from lactose. Two different major end-products of anhydrous lactulose are in world-wide use: a 50/50 (w/w) liquid containing about 20 % other saccharides (Table 1), and dry lactulose as a powder or granulated. Also, a freeze-dried syrup containing other sugars like liquid lactulose is available. Another, minor product is lactulose trihydrate.

The current potential world production is estimated at about 50,000 tons of liquid and dry lactulose per year distributed rather unevenly over 7 producers.

Analytical methods

Currently lactulose is rarely processed as a food ingredient except for infant formula. This is due to the drug status lactulose still has in most countries. Except for quality assurance in the pharmaceutical industry determination of lactulose is performed in mainly two settings: 1) the diagnostic application of lactulose used for the determination of gut permeability (see above) and 2) detection in processed dairy products, especially in UHT milk [64]. Lactulose is also present in corn syrup [65].

In permeability testing lactulose determination is usually performed either by gas chromatography [66] or by means of simultaneous HPLC determination of lactulose and mannitol, for example, although other or refined methods for determination from serum also are possible [67–70].

Lactulose does occur in UHT milk at concentrations up to 0.5 % but not in high pasteurised milk [71]. Methods for determination of lactulose in milk products are described by Clawin-Rädecker et al. [72] and Villamiel et al. [73].

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European Journal of Nutrition, Vol. 41, Supplement 1 (2002)

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