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Review Article

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Probiotics and its Effect on Slow Colonic Transit

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Abstract

Slow colonic transit is a common disorder that is a contributing factor to various diseases. Most notably, it is associated with constipation and thereby affects quality of life. Various physiological factors affect colonic transit and may be influenced by microbes in general and probiotics in particular. Probiotics can be delivered in various formats with; mainly as fermented dairy products or as supplements; each with their own specific technological challenges. Probiotics have been tested in various formats for their ability to improve slow colonic transit. A search of the literature yielded 13 reports on the effects of probiotics on either colonic or oro-anal transit. The quality of the studies is variable and several are uncontrolled. Although most studies indicated a reduced transit time for the probiotics group; not all did so. Notwithstanding the fact that a wide range in the doses tested, no relation between dose and effect size could be observed. From a regulatory perspective, only in Switzerland a claim for probiotics on reducing long intestinal transit has currently been approved.

Keywords

Probiotics; Colonic transit; Constipation; Health claim; *Bifidobacterium; Lactobacillus;* Metabolic activity

Introduction

The most generally accepted definition of probiotics was proposed by a FAO/WHO work group: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" [1]. This definition focuses on the viability of probiotics at the moment of consumption. Serious manufacturers of probiotic supplements and foods assure that sufficient viable probiotics are present at the end of shelf life. For certain health benefits, such as slow colonic transit it may be required that probiotics remain viable during gastrointestinal transit as metabolites are considered to contribute to the effect. In order to achieve this, probiotics that are intrinsically robust are usually selected and they are produced in a way that improves their stability. Furthermore, the delivery format is chosen such that pH, water activity, temperature and redox potential support the survival of the strain during storage.

A probiotic may belong to any genus or species as long as it fulfils the requirements for the definition. Most commonly used probiotics belong to the genera *Lactobacillus* and *Bifidobacterium*; these are also the genera we will be considering here below. Specific probiotic strains have various documented health benefits; such as reduction of risk for antibiotic associated diarrhoea [2], reduced risk for respiratory tract infections [3], reduced risk for development of atopic dermatitis [4], risk for necrotising enterocolitis [5], pregnancy complications [6] and slow colonic transit [7].

Colonic transit varies between subjects. In most studies, the mean colonic transit time is 30–40 h with an upper limit of 70 h in mixed populations. Women have a longer maximum colonic transit time (70–106 h) then men (around 50 h). Differences in colonic transit time reported between studies may be explained by differences in age and gender ratios and the methodology used in studies [8].

Although constipation is a relatively benign disorder, it greatly affects quality of life. Slow colonic transit may manifest itself as constipation, though not all constipation is caused by slow colonic transit [9]. Anorectal obstruction may cause constipation with normal colonic transit [10]. Therefore different treatments maybe required for the management of constipation.

Among the health risks of slow transit, increased risk for colonic cancer [11] and diverticulitis have been mentioned; it furthermore affects physical and psychological functioning. Increased fibre intake and laxatives are commonly advised to treat slow colonic transit and constipation. However, also specific probiotic strains may aid in improving slow colonic transit [7].

The Use of Combination Products to Increase the Beneficial Effect of Probiotics

Multi strain products

It has been a matter of debate if probiotic strains should be used single or in combinations [12]. A combination of several probiotic strains in one product does not automatically lead to an additive or possibly even synergistic effect. Also a high number of different strains is in itself not indicative of greater efficacy than a lower number of strains. Each combination of strains needs to be investigated what the interactions are between the combined strains and to prove its possible health effect [13,14]. For transit, no conclusions can be drawn as the same strain has not been tested single or in combination (Table 1).

Combinations with prebiotics or dietary fibers

When considering combining probiotics with other ingredients to increase or extend the beneficial effect of a food product, especially in the area of digestive health, dietary fibers or prebiotics present an obvious choice. Dietary fibers are various forms of complex carbohydrates that are resistant to hydrolysis and human digestion, which allows the fiber to reach the colon undigested. This results in increased fecal bulk and may promote bowel movements; alleviating constipation, as confirmed in several studies [15]. The health benefits of dietary fiber have long been appreciated, however fiber intakes globally are still below recommended levels. Increasing fiber consumption by food supplementation is a desirable goal [16,17].

Prebiotics are a specific group of dietary fibers, both share many properties, but they are not necessarily the same. Beyond the general properties of dietary fibers, prebiotics are defined as 'non-digestible food ingredients that, when consumed in sufficient amounts,

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Table 1: Study Characteristics (Modified from Miller & Ouwehand 2013).

Study	Study Design	N Active: Control	Transit Time Outcome, Method	Probiotic Strain	Daily Dosage (109 CFU)	Delivery Method	Treatment Duration (days)	Effect (h) Active: Control
[60]	Parallel groups	17:17	CTT, radiopaque markers	*B. lactis* DN-173 010	25.0	Active: Yogurt + probiotic Control: Non fermented milk-based product	28	-12.2:+3.7†‡
[61]	Cross-over	32	CTT, radiopaque markers	*B. lactis* DN-173 010	18.75	Active: Yogurt + probiotic Control: Yogurt	10	-3.7:+5.5
[62]	Parallel groups	36:36	CTT, radiopaque markers	*B. lactis* DN-173 010	97.5	Active: Probiotic fermented milk Control: Heat-treated probiotic fermented milk	11	-6.8:+0.5‡
[63]	Parallel groups	24	OATT, carbon + carmine red	*B. lactis* DN-173 010	25	Active: : Yogurt + probiotic Control: None	14	-24.6‡
[63]	Parallel groups	20	OATT, carbon + carmine red	*B. lactis* DN-173 010	37.5	Active: : Yogurt + probiotic Control: None	14	-28.6‡
[64]	Parallel groups	40	OATT, carbon + carmine red	*B. lactis* DN-173 010	12.5	Active: Yogurt + probiotic Control: None	14	-9.5‡
[64]	Parallel groups	41	OATT, carbon + carmine red	*B. lactis* DN-173 010	25	Active: Yogurt + probiotic Control: None	14	-19.6‡
[65]	Cross-over	12	OATT, radiopaque markers	*B. longum*	>0.5	Active: Yogurt with 2.5g lactulose + probiotic Control: Yogurt	21	38.1:40.1◊‡
[66]	Parallel groups	12:10	OATT, radiopaque markers	*L. rhamnosus* GG	20	Active: Buttermilk + probiotic & white wheat bread Control: White wheat bread	21	67.0:65.5◊
[67]	Parallel groups	16:14	OATT, radiopaque markers	*L. rhamnosus* GG	15	Active: Yogurt + probiotic & low fiber toast Control: Low fiber toast	21	+8.4†:+18†
[68]	Parallel groups	12:12	CTT, radiopaque markers	*L. casei* Shirota	6.5	Active: Probiotic fermented milk drink Control: Non fermented milk drink	28	-19.1:-8.7‡
[69]	Cross-over	83	OATT, carmine red	*B. lactis* BB12 *L. casei* CRL 431	2-20 2-12	Active: Yogurt with 0.625g inulin & oligofructose + probiotic Control: Yogurt	15	-16.6:-3.68‡
[70]	Cross-over	13	OATT, radiopaque markers	*L. rhamnosus* 19070-2, *L. reuteri* DSM 12246	20 20	Active: Freeze-dried powder + probiotic Control: Skimmed milk powder w/ dextrose	18	46:40◊
[70]	Cross-over	13	OATT, radiopaque markers	*L. casei* subsp. *alactosus* CHCC 3137, *L. delbrueckii* subsp. *lactis* CHCC 2329, *L. rhamnosus* GG	20 20 20	Active: Freeze-dried powder + probiotic Control: Skimmed milk powder w/ dextrose	18	45:40◊
[71]	Parallel groups	22:20	CTT, radiopaque markers	*B. longum* BB536, *B. lactis* 420, *L. acidophilus* 145	2.4-18* 0.48	Active: Probiotic fermented milk Control: Fermented milk	21	-1.3:-2.2
[72]	Parallel groups	33:34	CTT; radiopaque markers	*B. lactis* HN019	1.8	Active: Capsule, maltodextrin, probiotic Control: Capsule, maltodextrin	14	-18.5:+1.3‡

[72]	Parallel groups	33:34	CTT; radiopaque markers	*B. lactis* HN019	17.2	Active: Capsule, maltodextrin, probiotic Control: Capsule, maltodextrin	14	-28.1:+1.3‡

CFU: Colony Forming Units; CTT: Colonic Transit Time; OATT: Oro-Anal Transit Time
*Represents the reported range of total Bifidobacterium
‡Significant
†Estimate
◊End of study transit time, no pre-intervention transit time given

selectively stimulate the growth and/or activity of one or a limited number of microbes in the colon resulting in documented health benefits' [18]. Dietary fibers and prebiotics exhibit a diverse range of compounds, so it is clear that not all are equal in terms of the types and extent of health benefits they provide as well as their applicability in food products [17]. Prebiotics may also lead to faecal bulking or may contribute to an osmotic effect by virtue of their own small size or through their fermentation products; mainly short chain fatty acids (SCFA).

Because of their application, health target and mechanisms it is obvious that combinations of probiotics and prebiotics should be investigated, as they may have synergistic effects; in particular in the field of colonic transit. For such mixtures the term 'synbiotic' was introduced. However, it cannot generally be assumed that any combination of the two will yield a synbiotic. For a synbiotic, a true synergy is expected between the two components and not just a combination of single effects. In practice, this appears to be difficult to obtain, even when the two have been tailored for each other in order to interact appropriately and indeed provide synergy [14,19].

From an application perspective, combining prebiotics, fibers or other dietary ingredients may provide challenges. Product formulation might confer direct effects on probiotics such as providing a physiochemical barrier against gastric acid or specific nutrients that can be selectively metabolized by the probiotic in the consumer product or the gut. These matrix effects differ among bacterial species, as shown for strains of *Bifidobacterium* and *Lactobacillus* in capsules, cheese, and yogurt [20]. Furthermore, the often higher water activity of 'dry' components such as fibers and prebiotics may lead to reduced viability of the probiotic during storage. If metabolic activity is required during intestinal passage, such as for influencing transit, this may influence efficacy.

Clinical Data

A search of available literature revealed 13 studies with probiotics on intestinal transit; four of these concerned two interventions, Table 1. The quality of the studies varies as a number of them are not controlled or not appropriately controlled. Some studies are confounded by the inclusion of prebiotics such as lactulose, inulin and fructo-oligosaccharides. The majority of studies used fermented milk, usually yogurt, as format of administration. Besides the presence of yogurt starter cultures (*Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*) combinations of other lactic acid bacteria have been tested.

Most studies used radio-opaque pellets and abdominal X-ray as method to determine transit; a technique commonly used in clinical practice [10]. The subject consumes on three consecutive days capsules with pellets of different shape. X-ray reveals if any pellets from previous days have been retained and where they are located in the colon. This methodology allows for the determination of colonic transit time and also for transit times in different sections of the colon. Some studies evaluated the excretion of radio-opaque pellets by X-ray of the faeces; this gives information on oro-anal transit time. Similarly, some studies used marker dyes; carmine red and coal to determine oro-anal transit time. The latter two methods are less accurate as defecation may not be affected and it does not distinguish between slow colonic transit and anorectal obstruction.

The studies are in general performed with relatively few subjects; between 12 and 83 (mean 46). The study duration ranged from 10 to 28 days and the dose administered ranged from 0.48×10^9 to 97.5×10^9 CFU/day, (Table 1).

Despite these short comings and variations in study design, the majority of studies observed a significant effect of the consumption of probiotics on colonic transit time: 11 out of 17 interventions. A recent meta-analysis also concluded that short term consumption of probiotics resulted in a shortening of colonic transit time [7]. The delivery format; fermented milk or supplement, did not seem to affect the efficacy, although no strain was tested in different formats. The study duration was not found to correlate with the observed effect size. Neither was the dose found to correlate with the observed effect size. However, the studies that did test different doses (with *B. lactis* DN 173 010 and *B. lactis* HN019) did observe an increased effect with an increased dose, although this difference between the doses was usually not significant.

B. lactis DN-173 010 has been the most investigated strain in terms of colonic transit and has shown repeatable results. *L. rhamnosus* GG, however, was tested twice with neither of the studies reporting any effect on oro-anal transit time.

Potential Mechanisms

Microbiota

The human colonic microbiota represents a complex ecosystem that plays a key role in maintenance of health and physiological functions of the host. This microbiota is mostly anaerobic and can metabolize a large variety of compounds and participates thus in e.g., host nutrition, pathogen resistance, production of metabolic compounds from dietary and endogenous substrates. Disturbances within this microbial ecosystem may lead to different digestive health problems like constipation, diarrhea and inflammatory bowel diseases. Selected probiotics, such as e.g. *B. lactis* HN019 [21] and *L. rhamnosus* GG [22] have been observed to change the composition of the faecal microbiota; such change may be a contributing mechanism by which probiotics can shorten colonic transit, (Figure 1).

Short chain fatty acids

The metabolism of carbohydrates by the gut microbiota is an important process that allows a supply of nutrients and energy to the host [23]. Simple monosaccharides can be directly absorbed by the host, while many disaccharides can be hydrolyzed to their respective monosaccharides, but digestion of complex plant polysaccharides,

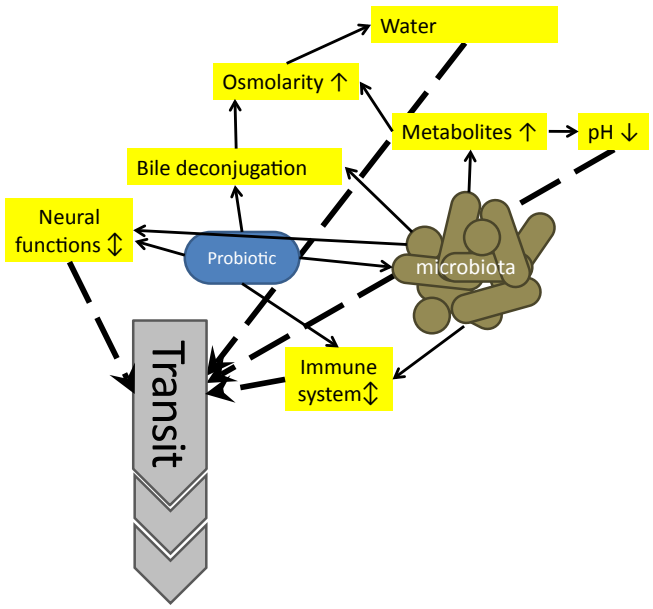

Figure 1: Schematic representation of potential mechanisms by which probiotics can influence slow colonic transit.

fiber and prebiotics (see above), is very limited [24,25]. The fermentative process of different carbohydrates is complex and involves interaction of several functional bacterial groups in order to ensure the biotransformation of polymers into end-products, mainly short chain fatty acids (SCFA) and H_2, CO_2, and CH_4 [26]. The main SCFAs produced are butyrate, propionate and acetate which can be utilized by the host. Other organic acids such as, lactate or succinate and branched-SCFA (generated from amino acids) are found in much smaller amounts. Butyrate is utilized by the colonocytes, while propionate and acetate reach the hepatic cells where they are used for gluconeogenesis and lipogenesis, respectively [24]. The intestinal pH is lowered due to production of SCFA, and this results in enzymatic inhibition of a dehydroxylase that catalyses secondary bile acid formation, and the further reduction of secondary bile acid concentrations due to precipitation, (Figure 1). Also, lactic, acetic and other acids results in a lower pH in the colon. A lower pH enhances peristalsis of the colon and subsequently decreases colonic transit time which is beneficial in the treatment of constipation [25]. The production of short chain fatty acids may also increase the osmolarity and leads to a higher water content of the digesta and thereby increased motility, (Figure 1). In the presence of a fermentable carbon source, probiotics can produce *in situ* short chain fatty acids. This assumes that probiotics are not only viable at the time of consumption, but also alive and metabolically active in the intestine; this seems to be the case for most probiotics [27-29].

Bile acid deconjugation

Bile acids are synthesized in the liver, released into the proximal intestine during intestinal contraction, and reabsorbed in the distal intestine [30]. Bile acids are absorbed by passive diffusion along the entire gut and by active transport in the terminal ileum [31]. Part of the primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), are modified within the intestinal lumen by intestinal bacteria into secondary bile acids, deoxycholic acid (DCA) and lithocholic acid (LCA) [30,32]. It is known that an elevated concentration of CDCA or DCA in the colon induces water secretion, thus causing looser stools. An increase has been reported to accelerate colonic transit [33], (Figure 1).

Prior to secreting any of the four bile acids, they maybe conjugated in the liver with one of two amino acids, glycine or taurine, to form a total of eight possible conjugated bile acids. The conjugated bile acids are usually referred to as bile salts [23]. Bile acids make several enterohepatic circulation rounds per day and in each tour [30,32], most of them are absorbed, while about 5% of the total bile acid pool per day is lost in the faeces, and may thus be modified by the indigenous intestinal bacteria [34]. Different bile acid transporters are all highly expressed in the ileum but not in the liver, jejunum or colon [35]. A reduced expression makes the intestine less efficient at bile acid resorption, while if the bile acids are e.g. deconjugated by small intestinal bacterial overgrowth, absorption is less efficient [35,36]. Deconjugation must occur before further modifications are possible [37]. The bile salt hydrolase (BSH) enzymes catalyze deconjugation by hydrolyzing the amide bond and thereby liberating the glycine/taurine moiety from the steroid core. The resulting acids are termed unconjugated or deconjugated bile acids [23]. BSH activity has been detected in several different bacterial species, mostly gram-positive bacteria, such as *Lactobacillus* [38,39], *Bifidobacterium* [40], *Enterococcus* [41], and *Clostridium* [42]. In particular *B. lactis* appears to express BSH; which may partially explain why some strains of this species have been successful in shortening colonic transit times [43].

Gas formation

H_2 is the main gas produced from fermentation of organic material, and elimination of it, is essential to maintain an efficient fermentation in the gut [44]. Certain bacterial classes can shift between the substrates freely, while others are more specific to a particular substrate. Abnormal microbial fermentations have been suggested in irritable bowel syndrome (IBS) patients [44,45]. If bacterial overgrowth occurs, fat malabsorption is caused by bile acid deconjugation. Also carbohydrates are blocked from being absorbed. Instead, they continue to the colon where they ferment, resulting in gas, bloating, pain, mucus in stools, foul-smelling gas and stools, and diarrhea. However, gas and bloating are often experienced alongside with constipation. The composition of gastrointestinal gases not only varies between individuals and health of individuals but depends also on the site along the gastrointestinal tract. While the composition of stomach gases is quite similar to the air, the composition of flatus is much more variable. The primary constituents of flatus are N_2, H_2, CO_2, CH_4, and H_2S. The presence of CH_4 is extremely variable, presence ranging from 0 to 30.3% of the flatus. H2 and CH_4 are thought to be produced exclusively by anaerobic fermentation in the gut [46]. CH_4 also affects colonic transit; constipated people are more likely to produce detectable amounts of methane. Since CH_4 is not utilized by humans, it is excreted either as flatus, or crosses the intestinal mucosa to the systemic circulation and is then excreted unchanged through the lungs [47]. Production of CH_4 is more prevalent in constipated conditions, and much less frequent in predominantly diarrheal conditions such as inflammatory bowel disease [48]. It is difficult to separate cause and effect here. However, as probiotics can modulate intestinal microbiota composition (see above); reducing the level and activity of methanogens may positively influence colonic transit time. H_2 can be converted to either CH_4 or H_2S by methanogenic archeabacteria or sulfate-reducing bacteria, respectively [49].

Immune effects

The intestinal microbiota has been considered to play a paramount role in the development of the immune system; this is

most obvious in germfree animals [50]. Also selected probiotics have been documented to modulate the immune system [51]. Probiotic modulation of the immune system could therefore be hypothesized to be a mechanism by which probiotics can influence intestinal motility. Inflammatory diseases of the intestine; such as Ulcerative Colitis and Crohn's Disease are characterized by diarrhea. Despite their anti-inflammatory potential have probiotics in general not been very successful in treatment or maintenance of remission in inflammatory bowel disease [52]. It is therefore uncertain to what extent probiotic immune modulation plays a role in modulating intestinal and in particular colonic transit, (Figure 1).

Neurological effects

That there is a connection between the enteric nervous system and the central nervous system has long been know; the so-called gut-brain axis. However, the recognition that the intestinal microbiota has a direct influence on the brain and wider neurological function is relatively new, much remains to be explored on this topic as well as the role probiotics may play in the respect, including influencing motility. The intestinal microbiota is directly influencing intestinal motility as can be observed by the disturbed motility in germ-free animals. The microbiota influences also the brain through the so-called gut-brain axis and can so influence the perception of visceral pain [53] and indeed probiotics have been documented to be beneficial in the relief of irritable bowel syndrome [54]. Probiotics [55] and their metabolites [56] have also been documented induce intestinal smooth muscle contraction. Increased smooth muscle contraction may contribute to improved intestinal peristalsis and may be a mechanism by which certain probiotics contribute to shortened transit times, e.g. through stimulation of 5-hydroxytryptamine (5-HT) receptors by tyramine [57], (Figure 1).

Regulatory

European union

In the European Union (EU) the use of health claims for food products including food supplements was recently harmonised by the implementation of REGULATION (EC) No 1924/2006 on nutrition and health claims made on foods. This Regulation lays down measures across the EU to ensure that consumers are not misled and only accurate and evidence based claims are made on foods in labeling, presentation or marketing in the EU.

The Nutrition and Health Claims regulation (NHCR) defines different types of health claims that all need evaluation and authorization. These are the so-called Article 13 claims describing functional health claims like "X contributes to an acceleration of intestinal transit" as well as claims referring to reduction of disease risk and claims referring to child development and health (Article 14).

The NHCR mandates the European Food Safety Authority (EFSA) to perform and ensure a harmonized scientific assessment of the applications through the Panel on Dietetic products, Nutrition and Allergies (NDA); the Commission then makes a decision on the use of the claim on the basis of the EFSA's opinion. According to the NHCR, the use of health claims shall only be permitted if the food/constituent, for which the claim is made, has been shown to have a beneficial physiological effect.

The first list of permitted Article 13 health claims made on foods came into effect in December 2012 (Commission Regulation (EU) No 432/2012) so far without any positive opinions related to the benefits of probiotics.

Between 2011-2012 the NDA panel published guidelines on the scientific requirements for health claims related to gut and immune function, antioxidants, oxidative damage, cardiovascular health, appetite ratings, weight management, bone, joints, skin and oral health, physical performance and functions of the nervous system; including psychological functions. In the guidance related to gut and immune function the NDA panel remarks that changes in bowel function such as reduced transit time, more frequent bowel movements, increased fecal bulk, or softer stools, may be considered beneficial physiological effects. It is also indicated that these effects could be appropriate outcome measures of the claimed effect in human studies [58].

Outside EU

Outside the EU there is a very diverse interpretation of probiotics with regard to efficacy demonstration of health benefits and the allowance to claim.

In Switzerland, nutritional and health related claims have been governed since March 2008 by the Ordinance on labeling and advertising of foodstuffs (FLO). The provisions are closely aligned with those of the EU and claims that are not listed among the more than 200 generic health claims; which is the case for probiotics, are subject to approval by the Swiss Federal Office of Public Health (FOPH). However, in contrast to the EFSA the FOPH in Switzerland has recently authorized 4 health claims on probiotics with the most recent being a health claim for *Bifidobacterium lactis* HN019 allowing the product to claim "contributes to normal digestion by shortening the intestinal transit time".

In Brazil there are 2 types of claims defined by Resolution 19/1999, ANVISA; functional claims and health claims. Today all the approved claims are functional. Registration at the National Health Surveillance Agency (ANVISA) is mandatory for the final product but there is a functional claim pre-established for probiotics "balances intestinal flora". Thus, in Brazil no claims are approved for probiotics improving slow intestinal transit.

In Canada, The Natural Health Products Directorate (NHPD) approves the use of the following non-strain specific claims for a list of species from the genera *Lactobacillus* and *Bifidobacterium* [59]:

- Probiotic that naturally forms part of the gut flora.

- Provides live microorganisms that naturally form part of the gut flora.

- Probiotic that contributes to healthy gut flora.

- Provides live microorganisms that contribute to healthy gut flora.

The NHPD has also recently approved condition-specific health claims for digestive health on final probiotic products claiming "Restoring and maintaining intestinal flora"; "Helps to reduce the risk of traveler's diarrhea" and "Helps to reduce the risk of antibiotic associated diarrhea". However, no claims on improving slow intestinal transit have been approved for probiotics in Canada.

In the US, the FDA distinguishes between general structure/function claims, where a dietary ingredient affects or maintains the normal structure or function in humans, and health claims where the effect is on a disease or symptoms of a disease. A structure function claim such as "Y may contribute to maintenance of heart health" does not need preapproval by the FDA, but the manufacturer must possess substantiation (clinical studies or similarly) to show that the claim is truthful and not misleading (21 U.S.C. 343(r)(6); 21 CFR 101.93[1]).

Health claims indicate that the specific food or food supplement will reduce the risk of developing a disease or condition like "Z can reduce cholesterol, which will lower the chances of developing serious heart conditions". Health claims are regulated by the FDA through the Code of Federal Regulations Sec. 101.14. Health claims need to be authorized by FDA based on a review of available scientific evidence to determine that the nutrient/disease relationship is well established.

Conclusions

Although the majority of studies reported a reduction in transit time, this did not reach statistical significance for all of them. This may be explained by the relatively small number of subjects in most groups and strain differences. While there are several potential mechanisms by which probiotics can exert this activity, none of these mechanisms is generally accepted. Against this background, it is maybe not surprising that few claims on reducing slow intestinal transit have been accepted by authorities. Nevertheless, a recent meta-analysis reported a positive effect of probiotics [7], suggesting that improving slow intestinal transit is a promising health target for selected probiotic strains.

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