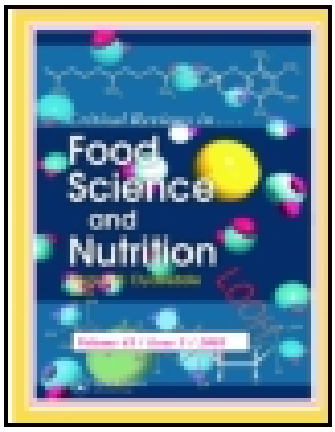

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The comparison of food and supplement as probiotic delivery vehicles

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The comparison of food and supplement as probiotic delivery vehicles

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Abstract

Probiotics are live bacteria which have frequently been reported to be beneficial in preventing a wide range of diseases as well as playing a major role in treating the existing ailments. Thus far, a variety of probiotic products have been developed which can be categorized into two groups: probiotic foods and supplements. Both foods and supplements have been able to confer the health benefits claimed for them. However, it is not known which one can be clinically more efficient, and to the best of our knowledge, until now no research has been conducted to investigate this issue. The present review aims to discuss this matter, based on the evidence available in the literature. To do so, articles indexed in Pubmed and ScienceDirect between 2000 and 2011 were reviewed. The articles included the clinical trials in which either foods or supplements were used to administer the probiotics to either patients suffering from different diseases or healthy subjects. Although both foods and supplements seem to have been efficient carriers for the beneficial bacteria, to generally promote public health in communities, probiotic foods appear to be preferred to probiotic supplements.

Key words

Probiotic products, health benefits, efficacy

Introduction

The history recording beneficial properties of fermented products dates back many centuries. Hippocrates prescribed yogurt to his patients to cure diarrhea and other intestinal disorders (Lourens-Hattingh & Viljoen, 2001). It was early 20th century when Metchnicoff extolled the virtues of consuming fermented dairy products and postulated his "Longevity without aging" theory, in which he claimed that replacing the harmful bacteria indigenous to the intestines by lactic acid producing bacteria can prolong life (Hughes & Hoover, 1995). Tissier was another scientist who, almost at the same time, suggested that bifidobacteria which are the predominant component of breast fed infants' gut microbiota, can relieve diarrhea in non-breast fed children by replacing the putrefactive bacteria (Ishibashi & Shimamura, 1993).

Probiotics are defined as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host” by the FAO/WHO (Anonymous (WHO/FAO), 2002). In Japan a product must contain a minimum of 10^7 colony forming unit (CFU)/gr of probiotic bacteria to be considered a probiotic one while the USA has developed a standard which requires at least 10^8 CFU/gr of the product to label it as probiotic (De Vuyst, 2000). Generally, it is believed that a probiotic product should provide $>10^6$–10^8 CFU/g, or $>10^8$–10^{10} CFU/day of viable cells to be clinically efficacious. There is no cell count level demonstrated to guarantee a health effect though (Champagne et al., 2011). Some of the genera used in probiotic products are: 1) Lactic acid producing bacteria (LAB): *lactobacillus*, *bifidobacterium*, *streptococcus*; 2) Non-lactic acid producing bacteria: *bacillus*, *propionibacterium*; 3) Non-pathogenic yeasts: *saccharomyces*; 4) Non spore forming and non flagellated rod or *coccobacilli* (Saraf et al., 2010).

A microorganism to be called probiotic must fulfill the criteria below:

1) Its culture can be produced in industrial scale; 2) It can survive during production and storage; 3) It can tolerate the gut environment of the host and 4) It exerts health effects when consumed (Anonymous (WHO/FAO), 2002).

Clinical benefits of probiotics in foods versus supplements

Traditionally yogurt was the first food to which probiotics were added. Recently development of novel probiotic foods has attracted a great attention and manufacturers are coming out with new probiotic foods including ice-cream, cheese, chocolate, beverages, cereals and vegetable products (Ranadheera et al., 2010). Different forms of probiotic supplements are also available in the market today, including pills, capsules, tablets, caplets, gelcaps, liquids and powders (Brink et al., 2005). To investigate the health benefits of probiotics, both foods and supplements have been used as delivery vehicles in clinical trials; however, no studies have been performed to compare the efficacy of the two forms of carriers regarding clinical benefits, as far as our literature review goes.

Probiotics have been shown to be effective against a number of disorders. Three of the mostly documented benefits of probiotics include alleviation of gastrointestinal disorders, affecting the elements of metabolic syndrome and modulation of immune system function, which are among the most important health issues throughout the world. Thus in this review article, it has been concentrated on these three conditions.

Articles were searched in two databases: Pubmed and ScienceDirect. In both databases "Probiotics" was used as the key word. In Pubmed, search was limited to the last 11 years in the

"dates", clinical trials in the "type of article" and English in the "languages" bar. In ScienceDirect, the key word was searched in the title, keyword or abstract and years 2000-2011 was selected in the date range. Then clinical trials were searched within the results.

Probiotics in gastrointestinal disorders

Diarrhea is a common gastrointestinal tract disorder for the prevention and treatment of which, probiotics have been reported to be beneficial. There are different types of diarrhea regarding their etiology. Antibiotic-associated diarrhea (AAD) is a common complication of antibiotic use. Also hospitalized patients exposed to antibiotics may develop Clostridium difficile disease (CDD). Diarrhea in these two conditions is attributed to disruption of intestinal microbiota by antibiotics. Probiotics may be a suitable option for treating diarrhea in AAD and CDD by reestablishing the disrupted intestinal microbiota, enhancing immune responses and clearing pathogens and their toxins from the host (Mcfarland et al., 2006). However, more clinical trials are warranted to propose the most suitable strain and dosage to most efficiently alleviate diarrhea in these cases (Ejtahed & Homayouni, 2010). Diarrhea can also be a result of radiation therapy to pelvic malignancy. Radiation causes changes in bacterial flora, the vascular permeability of the mucosal cells and intestinal motility. Animal and human studies have revealed that probiotics can reduce the incidence and severity of diarrhea during pelvic radiotherapy. There in need for more clinical trials to draw a critical conclusion in this regard (Chitapanarux et al., 2010; Ejtahed & Homayouni, 2010). Bacterial diarrhea is a common problem for many travelers. *Saccharomyces cerevisiae* has been shown to efficiently alleviate diarrhea in travelers, but *lactobacillus GG* and *lactobacillus acidophilus* have failed to ease the symptoms. This may

indicate that bacterial diarrhea is affected only by *saccharomyces cerevisiae*, while *lactobacilli* are more effective in viral diarrheas (Briand et al., 2006; Ejtahed & Homayouni, 2010).

Acute diarrhea typically affects infants and children. This type of diarrhea is associated with 20 viruses, bacteria and parasites; but worldwide, rotavirus is the most common cause of severe diarrhea and diarrhea mortality in children (Allen et al., 2010). This review has mainly focused on acute infectious diarrhea, since it is more prevalent and the majority of studies linking probiotics to diarrhea have been performed in this field. In table 1, clinical trials investigating the effects of probiotic supplementation on acute infectious diarrhea have been summarized. In these trials, incidence, frequency and duration of diarrhea, hospital stay and fecal rotavirus excretion have been used as indicators of the effect probiotics have left on patients. Figure1 shows the many routes through which probiotics may be effective in reducing incidence, severity and duration of diarrhea (Allen et al., 2010; Ejtahed & Homayouni Rad, 2010; Homayouni Rad, 2008).

Probiotics have also been tried in attempt to improve symptoms of lactose maldigestion or intolerance. It's crucial to discriminate between these two concepts. Lactose maldigestion results from lower than normal concentration of lactose cleaving enzyme, β-galactosidase (also called lactase) in the brush border membrane of the mucosa of the small intestine. There are several forms of lactose maldigestion; in primary lactose maldigestion or adult maldigestion, lactase concentration is high at birth but decreases gradually as the age goes up and reaches a stable level at adulthood. This type of lactose maldigestion is a physiologic situation for mammals and humans. Secondary forms of maldigestion can result from inflammation or functional loss of the small intestinal mucosa and by protein-energy malnutrition. Secondary lactose maldigestion is

usually irreversible even after the recovery of the original disease. Congenital lactose maldigestion is a rare autosomal-recessive heritable genetic defect and can be detected immediately after birth, as the infant responds to the first milk with diarrhea. Breath hydrogen is a reliable indicator for lactose maldigestion. Lactose maldigestion accompanied by clinical symptoms such as bloating, flatulence, nausea, diarrhea and abdominal pain is defined as lactose intolerance. Studies have shown that reduction in breath hydrogen is not necessarily followed by improvement of clinical manifestations. Fermented dairy products have been shown to efficiently reduce the symptoms of lactose intolerance in lactose maldigesters. This has been attributed to microbial β-galactosidase content of the (fermented) milk product, delayed gastrointestinal transit, positive effects on intestinal functions and colonic microbiota, and reduced sensitivity to symptoms. Studies have revealed that probiotics, in order to alleviate symptoms in lactose intolerant subjects, must be alive or at least have an intact cell wall once they reach the small intestine. This is crucial for the protection of enzyme, β-galactosidase from the acidity of the stomach (Mustapha et al., 1997; Rampengan et al., 2010; De Vrese et al., 2001). A systemic review article by Levri and colleagues (2005), based on results from studies performed between 1966 and 2002, concluded that only specific strains, concentrations and preparations of probiotics might be effective in reducing the symptoms in lactose maldigesters. Clinical trials performed in the last 11 years on the effect of probiotics in lactose intolerant patients have been presented in table 1.

The number of clinical trials in which foods were used as probiotic delivery vehicles, are limited. This may be justified by the fact that it is easier to administer supplements than foods to the infants in which acute diarrhea is most prevalent and who are the major target group when

studying the effects of probiotics in alleviating acute diarrhea. Though not conclusive, all these trials revealed that probiotic foods could be beneficial in children affected by acute diarrhea, in some way (Pedone et al., 2000, Chouraqui et al., 2004, Lei et al., 2006). As far as our review goes, no clinical trial was performed to investigate the effects of probiotic foods in lactose maldigesters.

Supplementation with probiotics has been beneficial for the patients with acute diarrhea (Guandalini et al., 2000, Lee et al., 2001, Rosenfeldt et al., 2002, Sarker et al., 2005, Szimanski et al., 2006, Vivatvakin et al., 2006, Canani et al., 2007, Basu et al., 2009, Kianifar et al., 2009, Chen et al., 2010, Ritchie et al., 2010) and lactose intolerants (He et al., 2008, Rampengan et al., 2010) in most trials. However, some investigations have failed to exert such effects (Costa-rebeiro et al., 2003, kowalska-Duplaga et al., 2004, Basu et al., 2007, Yesovitch et al., 2004). Varying outcomes from different studies may result from different study settings. It is also noteworthy that different populations may respond differently to the same intervention, for they have different gut microbiota as a result of different styles of life and nutrition.

Probiotics in metabolic syndrome

The metabolic syndrome, a concurrence of disturbed glucose and insulin metabolism, overweight and abdominal fat distribution, mild dyslipidemia and hypertension is such an important issue in today's world, mostly because of its association with subsequent development of type 2 diabetes mellitus and cardiovascular diseases (Lakka et al., 2002). It has been shown that the composition of intestinal microbiota in obese subjects differs from that of lean ones. Human studies on fecal microbial ecology have revealed some connection between weight loss and the abundance of

bacteroides-related taxa. However these results are not conclusive. Unlike human studies, animal studies have come up with less variable outcomes; results generally support patterns of greater *firmicutes*/*bacteroidetes* ratios in obesity models. In addition, specific bacteria were related to the obese phenotype (*halomonas* and *sphingomonas*), as were lower total bacterial counts and lower bifidobacterial counts. The question whether changes in gut microbiota is only a result of obesity or can play a causal role in its development, has been answered by animal studies in which gut microbiota was manipulated by administering particular bacteria to germ-free rodents. Results showed that animals fed obese microbiotas gained greater weight compared to the other group, on an isocaloric diet (Ley, 2010). Not many clinical trials have used probiotics to modify the gut microbiota in order to combat obesity. Possible mechanisms through which intestinal microbiota can affect body weight are summarized in figure 2 (Musso et al., 2010). Three main ways through which energy harvest is implicated by gut microbiota are: 1) obese gut microbiome is depleted of genes involved in motility (chemotaxins, motility proteins, flagellar assembly) and enriched in enzymes capable of breaking down otherwise indigestible alimentary components, 2) gut microbiota on a high-fat diet may convert dietary choline into hepatotoxic methylamines, reducing bioavailability of choline, which is necessary for the assembly and secretion of very low density lipoproteins (VLDLs) and ultimately enhancing hepatic steatosis, insulin resistance and lipoperoxidation, 3) microbiota may modulate host hepatic and systemic lipid metabolism through modification of bile acid conjugative patterns, directly influencing emulsification and absorption properties of bile acids and indirectly affecting hepatic fat storage and lipoperoxidation through bile acid signaling properties. Gut microbiota can also affect fatty acid metabolism; mammalian intestinal *lactobacilli* and *bifidobacteria* can synthesize bioactive

isomers of conjugated linoleic acid from free linoleic acid. The isomers of conjugated linoleic acid have antidiabetic, anti-atherosclerotic, immunomodulatory, and anti-obesity properties (Ley, 2010).

Bacteria residing the gut can ferment indigestible carbohydrates to short chain fatty acids (SCFAs), mainly acetate, propionate and butyrate. SCFAs bind G-protein-coupled receptors, Gpr41 and Gpr43. These receptors stimulate secretion of PYY, a gut secreted hormone which inhibits gut motility and slows intestinal transit thus enhances nutrient absorption (Delzenne & Cani, 2010; Ley, 2010). PYY decreases appetite as well. This may explain how SCFAs produced by probiotics can play a role in combating obesity (Chaudhri et al., 2008). Gut microbiota fermentation of prebiotics has been shown to promote L-cell differentiation in the proximal colon. These cells secrete glucagon-like peptide (GLP) 1 and 2. GLP1 is an anorexigenic peptide which decreases postprandial blood glucose by stimulating insulin secretion and inhibiting glucagon release. GLP2 plays a role in modulating gut barrier integrity (Sanz et al., 2010; Ley, 2010).

Low-grade metabolic inflammation is recognized as an important element in obesity and metabolic syndrome. Metabolic systems are incorporated functionally and molecularly with immune responses. For example the increase in pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF -α), typical of obesity-related inflammation, has been shown to result in insulin resistance. Studies have found that gut bacteria can initiate the inflammation and insulin resistance associated with obesity. On the other hand, probiotics, through modulating the immune system function, have performed well in reducing inflammation and the insulin resistance following it. Activity of lipopolysaccharide (LPS), an essential component of the cell

walls of Gram-negative bacteria such as the *bacteroidetes* is one main route by the means of which, bacteria can impact inflammation and insulin resistance. LPS can trigger the inflammatory process by binding to the CD14 toll-like receptor-4 (TLR-4) complex at the surface of innate immune cells (Caesar et al., 2010; Duncan et al., 2003; Ley, 2010; Lye et al., 2009; Pickup, 2004). More details on how probiotics can trigger different aspects of immune system are presented in the upcoming section.

Hypertension may be either primary which is diagnosed with no known cause, or secondary which may result from pregnancy, diseases such as sleep apnea, Cushing's syndrome, kidney malfunction, and as a side-effect of various drugs. The exact causes of primary hypertension remain unclear; however, factors that augment the risks of primary hypertension have been identified including obesity, hypercholesterolemia, diabetes, increased physiological production of renin and an imbalanced sexual hormones profile. Obesity results in increased leptin production from adipocytes. Leptin over-activates sympathetic nervous system which leads to lipid profile alters and increased blood pressure by causing peripheral vasoconstriction and increasing renal tubular sodium reabsorption. Insulin's vasodilatory effects are prevented and sympathetic and the antinatriuretic tone, are upregulated as a result of insulin resistance and its attendant hyperinsulinemia. Rennin is a proteinase which plays a key role in renin-angiotensin system by hydrolyzing angiotensinogen to yield the inactivate angiotensin I. Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II which causes vasodilation and induces release of aldosterone and thus increases sodium concentration which in turn elevates blood pressure. Moreover, hypertension can result from imbalances in hormones such as estrogen, progesterone and aldosterone (Lye et al., 2009).

There is strong evidence that probiotics can exert antihypertensive properties through modulating the underlying causes of primary hypertension, mentioned herein. How probiotics can affect body weight and insulin resistance, was briefly discussed above (Lye et al., 2009). Figure 3 presents the possible routes by the means of which probiotics can impact blood cholesterol level (Lye et al., 2009; Ooi & Liong, 2010). As mentioned previously, angiotensin II, the potent vasoconstrictor is converted from angiotensin I by ACE. ACE can contribute to elevations in blood pressure by inactivating the vasodilator, bradykinin as well. Hence, both angiotensin II and bradykinin levels which play the major role in regulating blood pressure are dictated by ACE. ACE inhibitory peptides which reduce production of angiotensin II and inhibit degradation of bradykinin are inactive within the sequence of a parent protein. Release of ACE inhibitory peptides from the parent protein through proteolytic action explains how probiotics can exert antihypertensive effects (Lye et al., 2009).

There is strong epidemiological evidence that hypertension is associated with hormonal imbalances. Estrogen and progesterone serve as antihypertensive sex hormones, antagonizing the pro-hypertensive effects of testosterone with direct effects on the vascular, renal and heart cells; or even via indirect effects mediated by humoral factors. Hormone replacement therapy is usually prescribed to postmenopausal women or men, to prevent hypertension. Phytoestrogens are naturally occurring dietary compounds which can mimic the physiologic roles of estrogen. Phytoestrogens are more efficiently absorbed when the glycoside on their phenolic ring is hydrolyzed. Probiotics can facilitate phytoestrogen take up for they contain β-glucosidase (Lye et al., 2009). Clinical trials investigating the effects of probiotic supplementation on different aspects of metabolic syndrome are summarized in table 2. Only one clinical trial was performed

in which the effect of probiotic ingestion in preventing obesity was investigated. Fermented milk was used as the delivery vehicle in this study. The intervention could decrease abdominal, visceral and subcutaneous fat significantly (Kadooka et al., 2010). Based on the results from different studies performed in various disorders related to metabolic syndrome including obesity, diabetes, hypertension and hypercholesterolemia, foods have been better carriers for probiotics than supplements in conferring the desired benefits.

Probiotics in immune function

Our intestine is colonized by a great number of microorganisms, the composition of which is influenced by the combination of food practices, geographical localization, various levels of hygiene or various climates. This colonization facilitates the formation of a physical and immunological barrier between the environment and us. The immune properties of the digestive mucosa are provided by the gut-associated lymphoid tissue (GALT). GALT is composed of lymphoid aggregates, including the Peyer's patches (located mainly in the small intestinal distal ileum), where stimulation of immune responses occurs, and mesenteric lymphoid nodes. In addition, there are large amounts of immune-competent cells in the lamina propria and the mucosal epithelium. The intestine also protects us from pathogens because its epithelium is covered by mucus and avoids any direct contact with the microorganisms.

Many in vitro and in vivo studies have been performed to investigate the effects of probiotic bacteria on different aspects of immune function. Results have revealed that probiotics can affect immune function in many ways and the outcomes are strongly strain specific. It has also been shown that probiotics, not only stimulate immune system locally, but also affect both innate and

adaptive immune responses, systemically. It is also noteworthy that direct contact between the probiotic bacteria and the epithelial cells has been proposed to be essential for the GALT to be induced (Delcenserie et al., 2008). The possible mechanism through which probiotics induce immune response is presented in figure 4. Dentritic cells (DCs) present in the lamina propria can sample the luminal bacterial antigens through two routes, either by passing their dendrites between intestinal epithelial cells (IECs) into the gut, or by direct interact with the bacteria that have gained access to the dome region of the GALT which is due to the specialized cells called microfold cells (M cells) that can transfer the bacteria intact to the lower layers. The microorganism-associated molecular patterns (MAMPs) that are present on the surface macromolecules of probiotic bacteria are recognized by the host pattern recognition receptors (PRRs). PRRs which can perceive probiotic signals include Toll-like receptors (TLRs) and the C type lectin DC-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN). Important responses of DCs against probiotics include the production of cytokines, major histocompatibility complex (MHC) molecules for antigen presentation and co-stimulatory molecules that polarize T-cells into T helpers or regulatory T cells in the mesenteric lymph nodes (MLNs) or subepithelial dome of the GALT (Lebeer et al., 2010). Clinical trials published in Pubmed and ScienceDirect during the last 11 years in this regard are presented in table 3. Both foods and supplements have widely been used as carriers to provide the subjects with probiotics in trials investigating the effects of probiotics on immune system function. Among studies in which food was used as probiotic delivery vehicle, some trials showed the results expected for probiotics, while the others did not. This was the case for studies in which supplements were used to administer probiotics as well. Since it is always emphasized that the effects of probiotics

in different aspects of immune system function is strongly strain specific, this was predictable in both food and supplement studies.

Comparison

Unfortunately thus far no studies have been performed to compare the efficacy of foods versus supplements as probiotic delivery vehicles. Even regarding the results from the clinical trials presented in the tables (1-3), it seems hard to judge whether foods or supplements have acted more efficiently in exerting the claimed health effects; mainly because the results of different studies is strongly dependant on the strain, dosage, period of intervention and the condition studied.

The efficacy of probiotic bacteria is mainly based on two factors: viability (being live in food products and supplements) and survivability (sustaining their life through harsh conditions) as well as activity (De Vrese & Schrezenmeir, 2008). Several parameters including probiotic strain, pH of the matrix, nutritional composition of the carrier and heat treatment can affect viability and survivability (Bazrafshan & Homayouni Rad, 2010; Homayouni Rad et al., 2008a; Kailasapathy & Chin, 2000; Kolida et al., 2000; Ranadheera et al., 2010; Sleator & Hill, 2008). Some techniques have been developed for increasing bacterial viability and survivability including pre-exposing to sublethal stresses such as salt, heat, bile and low pH, immobilized cell technology, micro-encapsulation, genetic modification, combining different synergistic strains and incorporation of nutrients and prebiotics to the matrix. Selection of the proper method depends

on the type of product probiotic bacteria will be added to (Alizadeh et al., 2008; Farnworth, 2008; Homayouni Rad et al., 2008b; Homayouni Rad et al., 2008c; Sleator and Hill, 2008). Factors affecting bacterial activity are water activity of the carrier, access to essential nutrients for probiotic growth, pH of the matrix and growth promoters (De Vuyst, 2000).

Only one study has compared the survivability of probiotic bacteria in food vs. supplements thus far, in which fecal bacterial count was considered the indicator of survivability. The results showed that matrix did not influence survival of *lactobacilli* strains but *bifidobacteria* survived better in yogurt (Saxelin et al., 2010). However, the magnitude of health effects was not investigated and compared for different matrices in this study.

Conclusion

Returning to the hypothesis posted at the beginning of this study, it is now possible to state that both foods and supplements have performed well as probiotic delivery vehicles. However, foods may be preferred to supplements when public health promotion is aimed. This may be due to the buffering properties of foods for probiotics during passage through the gut, provision of essential nutrients for maintaining the activity and efficacy of the probiotic bacteria, synergistic effects of food ingredients on probiotic growth and consumer attitude towards probiotic foods vs. supplementation with tablets, capsules and other drug forms (Del Piano et al., 2011; Ranadheera et al., 2010; De Vrese & Schrezenmier, 2008).

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Figure legends

Figure 1) routes through which probiotics may be effective in alleviating diarrhea

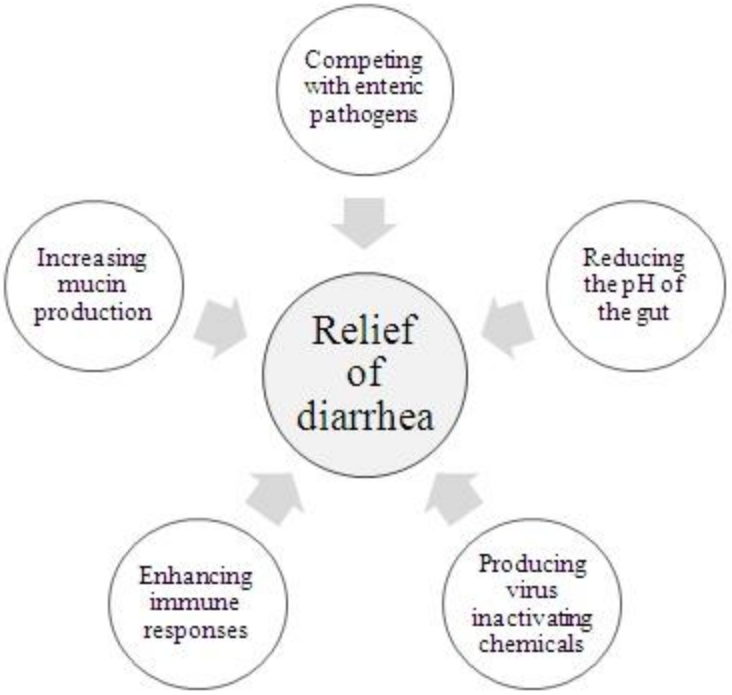


Figure 2) possible mechanisms through which intestinal microbiota can affect body weight

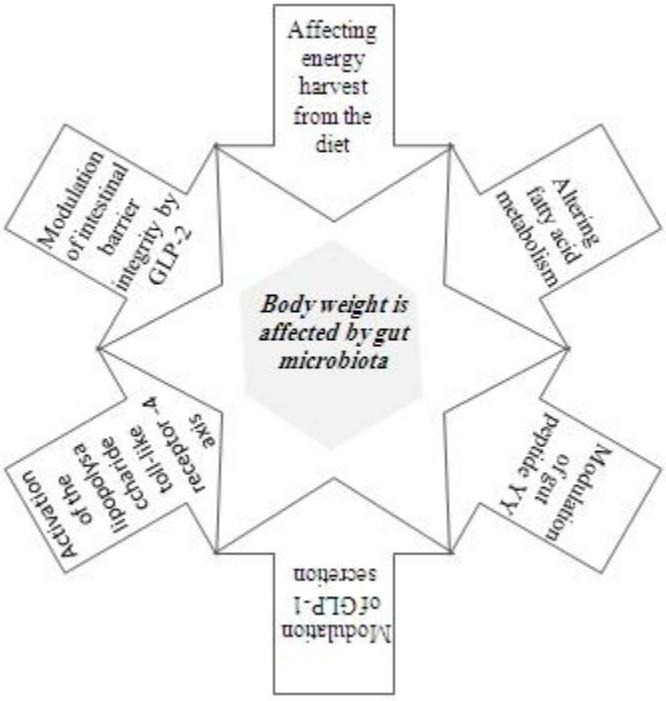


Figure 3) possible mechanisms for the cholesterol lowering property of probiotics

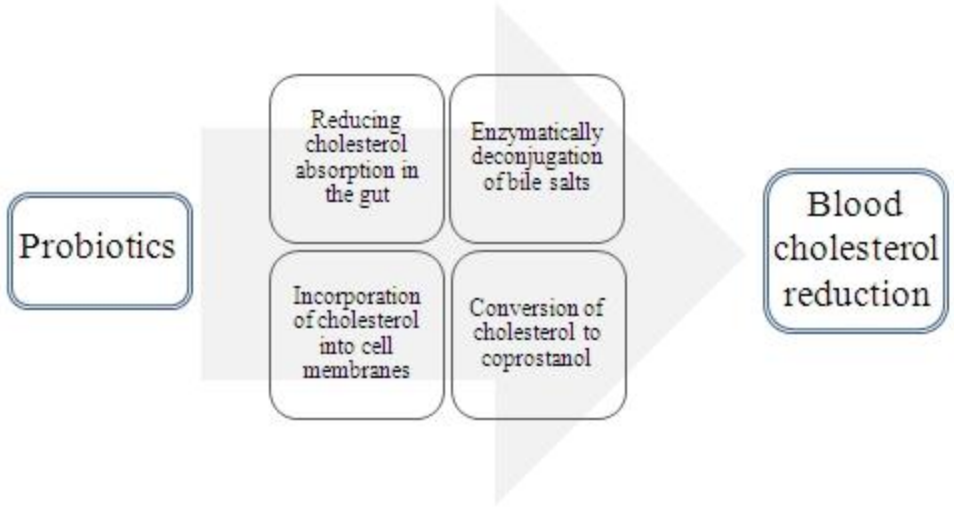
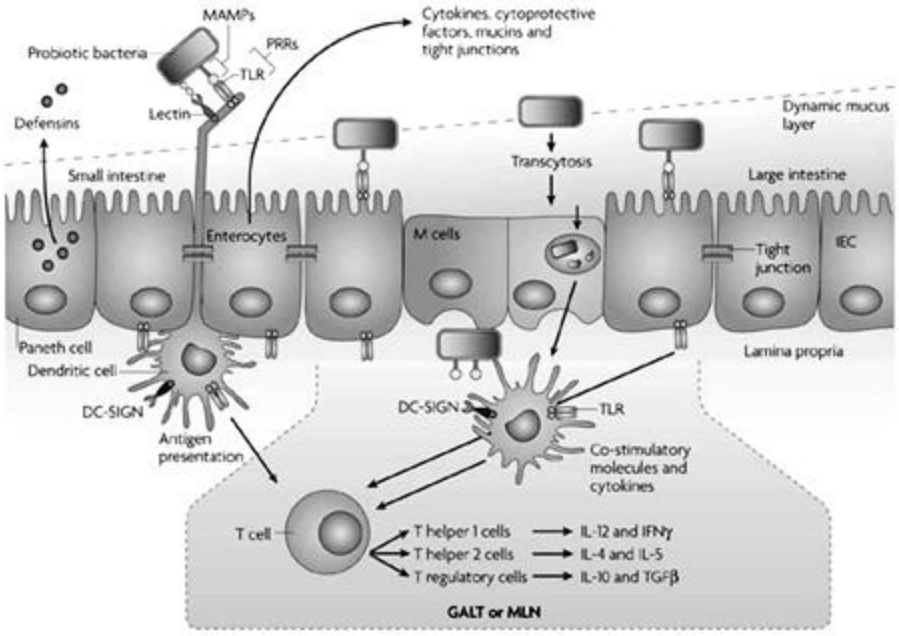


Figure 4) possible mechanism through which probiotics induce immune response



Tables

Table 1) Results from studies on the effect of probiotics on acute diarrhea and lactose intolerance, performed between 2000 and 2011

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
Food	Yogurt	Yogurt cultures and *L.casei DN-114 001*	10^{10} CFU/day	Over 4 months	Diarrhea	Incidence of diarrhea was significantly reduced	Pedone et al., 2000
	Acidified formula	*B. Bifidum BbF*	Not mentioned	During stay in the care center	Diarrhea	Less chance to get diarrhea during stay, later occurrence of the episodes and shorter duration of the episodes were seen for the probiotic group	Chouraqui et al., 2004
	Millet	Lactic acid bacteria, which was dominated by *W. confusa* and *L. fermentum*	3×10^{10} CFU/day	5 days	Diarrhea	stool frequency, stool consistency and duration of diarrhea were not affected, however well being increased	Lei et al., 2006

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
Supplement	Powder	*L.GG ATC 53103*	10^{10} CFU/day	Until diarrhea stopped	Diarrhea	Shorter duration of diarrhea, less chance of a protracted course, and faster discharge from the hospital were observed	Guandalini et al., 2000
	Capsule	*L.acidophilus B.infantis*	10^{9} CFU/day 10^{9} CFU/day	4 days	Diarrhea	The duration of diarrhea during hospitalization in study group decreased	Lee et al., 2001
	Capsule	*L.rhamnosus 19070-2 L.ruteri DSM 12246*	2×10^{10} CFU/day 2×10^{10} CFU/day	5 days	Diarrhea	Supplementation reduced the period of rotavirus excretion and reduced length of hospital stay	Rosenfeldt et al., 2002
	Capsule	*L.GG*	10^{9} CFU/day	7 days	Diarrhea	There was no significant reduction in diarrhea duration and stool output in the *L.GG*	Costa-rebeiro et al., 2003
	Capsule	*L.acidophilus LaCH-5*	1.6×10^{9} CFU/day	5 days	Diarrhea	Supplementation was only	Kowalska-

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
		B.bifidum Bb-12 L.bolgaricus Lb-Y 27				moderately effective in shortening the course of acute diarrhea group	Duplaga et al., 2004
	Powder	*L.paracasei ST11*	10^{10} CFU/day	5 days	Diarrhea	Supplementation had a clinically significant benefit in the management of children with non rotavirus-induced diarrhea, but it is ineffective in those with rotavirus diarrhea	Sarker et al., 2005
	Capsule	*L.Rhamnosus 573L/1; 573L/2; 573L/3*	2.4×10^{10} CFU/day	5 days	Diarrhea	Supplementation shortened the time of intravenous rehydration	Szymanski et al., 2006
	Capsule	*Lactobacillus B.infantis*	3×10^{9} CFU/day	5 days	Diarrhea	Diarrhea duration was shortened	Vivatvakin et al., 2006
	Powder	Either of 4	Approximat	5 days	Diarrhea	*L.GG*	Canani et

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
		strains or a mixture of four probiotic bacteria	ely 10^9 CFU of each			reduced the duration of the diarrhea	al., 2007
	Powder	*L.GG*	12×10^7 CFU/day	7 days or till diarrhea ceased	Diarrhea	No effects were observed	Basu et al., 2007
	Powder	*L.GG*	2×10^{10} CFU/day Or 2×10^{12} CFU/day	7 days or till diarrhea ceased	Diarrhea	Duration and frequency of diarrhea and hospital stay decreased	Basu et al., 2009
	Powder	*L.acidophilus* *B.bifidum*	10^9 CFU 10^9 CFU (the combination administered 3 times daily)	5 days	Diarrhea	The treatment decreased duration and frequency of diarrhea and hospital stay	Kianifar et al., 2009
	Powder	Bio three composed of: *B.mesenteri cus* *E.faecalis* *C.butyricum*	2.5×10^7 CFU/kg/day in 3 divided doses	7 days	Diarrhea	The severity of diarrhea and hospital stay decreased	Chen et al., 2010
	Capsule	*L.GG*	15×10^9 CFU/day	3 days	Diarrhea	No effects were seen except that diarrhea frequency decreased on	Ritchie et al., 2010

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
						day 2	
	Yogurt + capsule	*L.bolgaricus* *S.thermophilus* *B.animalis* *B.longum*	3.8×10^{10}CFU 1.8×10^{9}CFU	2 weeks	Lactose intolerance	Faecal β-galactosidase activity increased significantly and symptom score decreased	He et al., 2008
	VSL3 capsule	A mixture of probiotic bacteria	Either of 450×10^{9} or $4\times450\times10^{9}$ CFU	17 days	Lactose intolerance	No effects were seen	Yesovitch et al., 2004
	Capsule+ Satch	Lacidophil Dialac	Not mentioned	2 weeks	Lactose intolerance	Breath hydrogen decreased	Rampengan et al., 2010

Table 2) Results from studies on the effects of probiotics on elements of metabolic syndrome, performed between 2000 and 2011

Carrier	Type	Species/strain	Dose	Period	Heath condition	Effect	Ref.
Food	Fermented milk	*L.gasseri SBT2055*	10^{11} CFU/day	12 weeks	Obesity	Abdominal, visceral and subcutaneous fat areas significantly decreased	Kadooka et al., 2010
	Yogurt	*L.acidophilus LA-5* *B.lactis Bb12*	1×10^{9} CFU/day 9×10^{8} CFU/day	8 weeks	Diabetes	The treatment reduced LDL-cholesterol	Ejtahed et al., 2010; Ejtahed et al., 2011a; Ejtahed et al., 2011b
	Yogurt (NY-YP901)	A mixture of probiotic bacteria plus functional ingredients	Different doses for the bacteria	8 weeks	Metabolic syndrome	The treatment significantly decreased total and LDL cholesterol as well as body weight and BMI	Chang et al., 2011
	Proviva (drink)	*L.plantarum 299v (DSM 9843)*	2×10^{10} CFU/day	6 weeks	Hypertension	Systolic blood pressure, leptin and fibrinogen decreased significantly	Naruszewicz et al., 2002
	Powdered	*L.helveticus CM4*	Not mention	4 week	Hypertension	Intervention decreased	Aihara et al., 2005

Carrier	Type	Species/strain	Dose	Period	Heath condition	Effect	Ref.
	fermented milk (tablets)		ed	s		diastolic blood pressure significantly	
	Sausage	*L.paracasei LTH 2579*	5×10^{9} CFU/day	5 weeks	Hyper-cholesterolemia	No effects were observed in lipid profile, a significantly higher titer of antibodies against oxidized LDL was observed	Jahreis et al., 2002
	Milk	*B.longum BL1*	9×10^{10} CFU/day	4 weeks	Hyper-cholesterolemia	Total cholesterol decreased particularly in those with mild hyper-cholesterolemia	Xiao et al., 2003
	Yogurt	*L.acidophilus B.lactis*	3×10^{8} CFU/day	6 weeks	Hyper-cholesterolemia	Only total cholesterol decreased significantly	Ataie-Jafari et al., 2009
Supplement	Capsule	*L.acidophilus NCFM*	10^{10} CFU/g	4 weeks	Diabetes	Supplementation preserved insulin sensitivity but did not affect systemic inflammator	Andreasen at al., 2010

Carrier	Type	Species/strain	Dose	Period	Heath condition	Effect	Ref.
						y responses	
	Capsule	*L.acidophilus LA-1*	6×10^{10} CFU/day	6 weeks	Hyper-cholesterolemia	Cholesterol was decreased in vitro, but throughout the study no changes were observed	Lewis & Burmeister., 2005
	Capsule	PCC® *L.fermentum*	4×10^{9} CFU/day	10 weeks	Hyper-cholesterolemia	No effects were seen	Simons et al., 2006
	Capsule	*L.rhamnosus LC705 P.freudenreichii ssp shermanii JS*	4×10^{10} CFU/day	4 weeks	Hyper-cholesterolemia	No effects were seen	Hatakka et al., 2008

Table 3) Results from studies on the effects of probiotics on immune system function, performed between 2000 and 2011

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
Food	Milk	*B.lactis HN019*	5×10^9 CFU/day Or 5×10^{10} CFU/day	3 weeks	Immunity of elderly subjects	Increased CD4+, CD25+, natural killer cells and phagocytic capacity of immune cells were seen	Gill et al., 2001
	Fermented milk	*L.casei DN114001*	10^8-10^{10} CFU/day	8 weeks	Immunity of healthy subjects	No changes in immune cell proportions were detected but oxidative burst capacity of monocytes and NK cells tumoricidal activity increased	Parra et al., 2004
	Formula	*B.animalis Bb-12*	6×10^9 CFU/100 ml	32 weeks	Immunity of non-breastfed newborns	No effects on fecal SIgA were observed	Bakker-Zierikzee et al., 2006
	Fermented product	*L.gasseri CECT 5714* and *L.coryniformis CECT 5711*	Not mentioned	4 weeks	healthy adult human volunteers	The treatment induced an increase in the proportion of	Olivares et al., 2006

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
						natural killer (NK) cells and in IgA concentrations which suggests regulation of the immune system	
	Yogurt	*L.acidophilus 74-2 B.lactis subsp lactis DGCC 420*	27.9×10^{10} CFU/day 9×10^{8} CFU/day	5 weeks	Immunity of healthy subjects	Percentages of granulocytes and monocytes showing phagocytic activity were significantly elevated	Klein et al., 2008
	Formula	*B.bifidum S.thermophilus*	2.5×10^{10} CFU/day	8 weeks	Immunity of HIV infected children	There was an increase in the mean CD4 count	Trois et al., 2008
	Yogurt	*L.gasseri CECT5714 L.coryniformis CECT5711*	2×10^{8} CFU/day 2×10^{8} CFU/day	12 weeks	Immunity of allergic children	Serum IgE decreased and regulatory T cells and natural killer cells increased	Martinez-Canavate et al., 2009
	Milk	*L.casei Shirota*	1.95×10^{10} CFU/day	4 weeks	Immunity of healthy men with a reduced NK lytic	Intervention didn't increase NK cell activity in healthy	Seifert et al., 2011

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
					function	men	
	Extensively hydrolysed casein formula	*L.rhamnosus GG (ATCC 53103)*	3.4×10^9 CFU/day	12 weeks	Immunity of infants with atopic dermatitis	IgA and IgM secreting cells decreased and CD19(+) CD27(+) B cells increased	Nermes et al., 2011
	Powdered skimmed milk	*L.plantarum CECT 7315* and *CECT 7316*	Either of 5×10^8 CFU/day Or 5×10^9 CFU/day	12 weeks	Immunity of elderly subjects	Depending on the dose, *L. plantarum* has different immune-enhancing effects in elderly subjects	Mane et al., 2011
Supplement	Suspension	*E.coli Nissle 1917*	1 ml at a time	5 days and three times a week for 3 more weeks	Immunity of premature infants	Significantly higher amounts of specific anti-*E. coli Nissle* 1917 antibodies (Ab) of immunoglobulin (Ig)A isotype and nonspecific polyclonal IgM were found in the blood of colonized infants	Cukrowska et al., 2002

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
	Tablet	*L.gasseri PA 16/8 B.longum SP 07/3 B.bifidum MF 20/5*	5×107 CFU/day	12 weeks	Immunity of healthy subjects	Symptoms and duration of cold decreased. Sytotoxic T cells and suppressive T cells and helper T cells were enhanced	De Vrese et al., 2005
	Capsule	*L.rhamnosus GG (ATCC 53103)*	10^{10} CFU/day	4 weeks before expected delivery and 6 months to the infants	Gut microecology and Immunity of infants	(Ig)G-secreting cells in Probiotic group exceeded the placebo group which correlated with concentration of sCD14 in colostrum	Rinne et al., 2005
	Capsule	*B.lactis ssp. lactis (BB-12) L.paracasei ssp. paracasei (CRL-431)*	10^{8}, 10^{9}, 10^{10}, or 10^{11} CFU/day	3 weeks	Immunity of healthy subjects	No effects were observed	Christensen et al., 2006
	Capsule	*L.casei Shirota*	19.5×10^{9} CFU/day	4 weeks	Immunity in cirrhotic patients	The treatment restored neutrophil phagocytic capacity, possibly by	Stadlbauer et al., 2008

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
						changing IL10 secretion and TLR4 expression	
	Capsule	*L.coagulans GBI-30*	2×10^9 CFU	4 weeks	Immunity in healthy adults	The treatment significantly increased T-cell production of TNF-α in response to adenovirus exposure and influenza A exposure, but it did not have a significant effect on the response to other strains of influenza	Baron, 2009
	Powder	*B.mesentericus E.faecalis C.butyricum*	3×10^7 CFU/day	7 days	Immunity of children	IL-10 was increased in the serum and supernatants of cell culture and tumor necrosis factor alpha values were down-regulated. Interferon gamma and	Chen et al., 2010

Carrier	Type	Species/strain	Dose	Period	Health condition	Effect	Ref.
						IL-12 were mildly elevated in the probiotics group	
	Capsule	*L.salvarius CECT5713*	2×10^8 CFU/day	4 weeks	Immunity of healthy adults	Percentage of NK cells and monocytes, as well as the plasmatic levels of immuno-globulins M, A and G, and the regulatory cytokine IL-10	Sierra et al., 2010
	Capsule	*L.plantarum HEAL 9 L.paracasei 8700:2*	10^9 CFU/day	12 weeks	Immunity of healthy subjects	The risk of acquiring common cold infections was decreased	Berggren et al., 2011