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A Review: Probiotics - A Good Bug For Healthy Gut

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Abstract:
As per the old age quote by Hippocrates, "Let food be thy medicine and medicine be thy food" is the ideology of today's health conscious population. As intestine is a home for more than 100 trillion of microorganisms but only few are beneficial microbes. The prolonged use of antibiotics disrupts the healthy intestinal flora. As a result the healthy gut has to be supplemented in the form of probiotics. Probiotics are live microorganisms have obtained increasing medical importance because of their beneficial effects on the host health. Oral administration of probiotics has multiple effects such as normalization of the intestinal microflora, improvement of the gastrointestinal barrier, inhibition of potential pathogens or carcinogenesis in the gut. Together with the enhancement of systemic immune and anti-inflammatory activities, probiotics may play a part in reducing the risk of multiple chronic diseases including cancer, high serum cholesterol-associated diseases, allergy and many chronic diseases like vaginosis, antibiotic associated diarrhea, irritable bowel syndrome, anti-cholesterol effect, anti–obesity effect etc., Therefore, the present review discussed on the potential preventive and therapeutic role of probiotics with possible mechanism of action. Based on this idea, the current review concentrated on delivering the potential role of probiotic organisms for a healthy gut with their possible mechanism of action.

Keywords: Probiotics, Lactic Acid Bacteria, Health benefits, Commercial products

1. INTRODUCTION

There are more than 400 bacterial species that inhabits the large intestine and make up the gut flora. Nearly we have 20 times more bacteria in the body than the cells and even more than total number of people that ever lived on earth. Therefore having right kind of bacteria in gut is very important because "Intestinal Tract is home" to some 100 trillion of microorganisms but only few are friendly microbes. The antibiotics and bad bugs can kill the good bugs in intestines and upset the balance of healthy colonies in the body. In the early 1500's, king Francis of France reported that, "Cure of an illness after eating yoghurt" describes that probiotics have been around for more than 500 years.

In 1907, Eli Metchnikoff, the Russian Nobel prize winner was the first one to recognize the beneficial role of selective Lactic Acid bacteria on gastrointestinal tract of humans. Subsequently the "Theory of Longevity" by Metchnikoff was correlated with

prolonged youth and a healthy old age, observed largely in Balkan peasants of those times, who used cultured milks in their diet (Kavita R.Pandey, Suresh R.Naik and Babu V.Vakil, 2015).

The concept of Functional foods emphasizes that food not only are vital for living but also play a role in the prevention and reduction of risk factors for several diseases and are also capable of enhancing certain vital physiological functions. Functional foods also provide the body with required amount of vitamins, fats, proteins, carbohydrates, etc., (Cencic and Chingwaru, 2010).

2. SOURCES, SELECTION AND CHARACTERISTIC FEATURES OF PROBIOTICS

Probiotics are defined as 'live microorganisms which when administered in adequate amount confer health benefits to the host' (FAO/WHO, 2002). Alternatively, probiotics have been defined as live microbial feed supplements that beneficially affect the host animal by improving its intestinal microbial balance. Probiotics were originally used to improve the health of both animals and humans through the modulation of the intestinal microbiota. At present, several well-characterized strains of Lactobacilli and Bifidobacteria are available for human use to reduce the risk of gastrointestinal (GI) infections or treat such infections (Salminen et al., 2005). The sources, isolation, identification and characterisation of probiotics are illustrated in Figure 1. The best source for probiotics is found to be dairy and dairy related products, fermented foods, breast milk and human GastroIntestinal Tract (Luis Fontana et al., 2013)

Dairy and dairy-related products are a good source of probiotics (1). Within this context, lactic acid bacteria (LAB), bifidobacteria and other microorganisms obtained from fermented milks have been used for centuries. Spontaneous milk fermentation has a long history in different regions of Mongolia or Africa, and the use of beneficial microorganisms in fermented dairy products has been practised for many generations

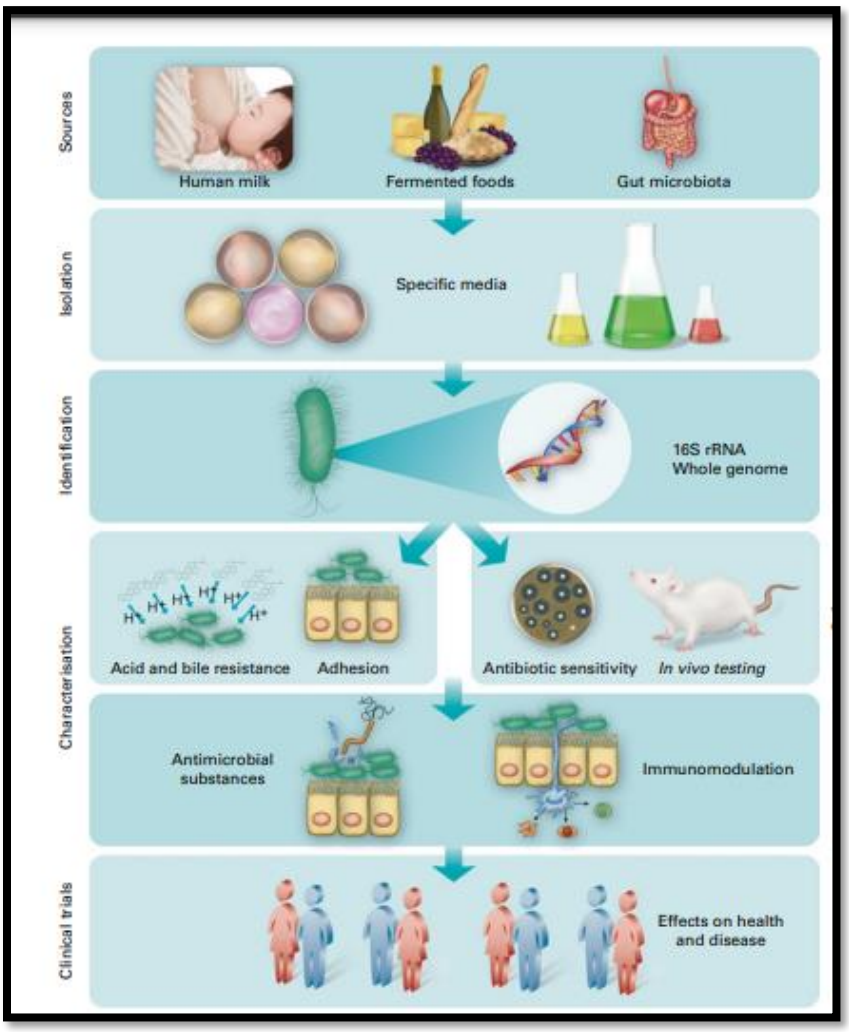


Figure 1: Sources, Isolation, Identification, Characterisation and Clinical Trials of Probiotics

The diverse characteristics of probiotics have been recognized as key health promoters. The studies focused on investigating the culture conditions and viability of probiotic strains during processing and storage; strain should exert a beneficial effect on host animal by surviving and metabolizing in the gut, non pathogenic, non toxic, resistant to low pH, organic acid, gastric fluid, bile, pancreatic and intestinal fluids. The strain should have potential adherence to isolated cells or cell cultures, colonize and interactions with other pathogenic microorganisms by good cell surface hydrophobicity as well as production of antimicrobial substances, bacteriocins for inhibiting the growth of pathogens (Fuller, 1989 & Sonal et al., 2008).

Probiotics for human should have GRAS - 'Generally Regarded As Safe' status, with a proven low risk of inducing or being associated with the etiology of disease. The probiotic organisms should preferably be of human origin, must be able to survive and grow in the in vivo conditions of the desired site of administration, and thus must be able to tolerate low

pH and high concentration of both conjugated and deconjugated bile acids. For successful application in foods, the probiotic used should also be technologically compatible with the food-manufacturing process. In addition to that, the foods containing the probiotic bacteria must maintain the characteristic sensory attributes of the traditional food (Collins et al., 1998).

3. POTENTIAL PROBIOTIC MICROFLORA

An optimum balance in microbial population in the gut has been associat3ed with good nutrition and health. The most microorganisms associated with this balance belongs to Lactic Acid Bacteria family. Probiotics can be a bacteria, molds and yeasts. A selective list of different bacterial species that are actively used as probiotics is listed in Table 1(Rout George Kerry et al., 2018).

Table 1. Microflora Used As Probiotics

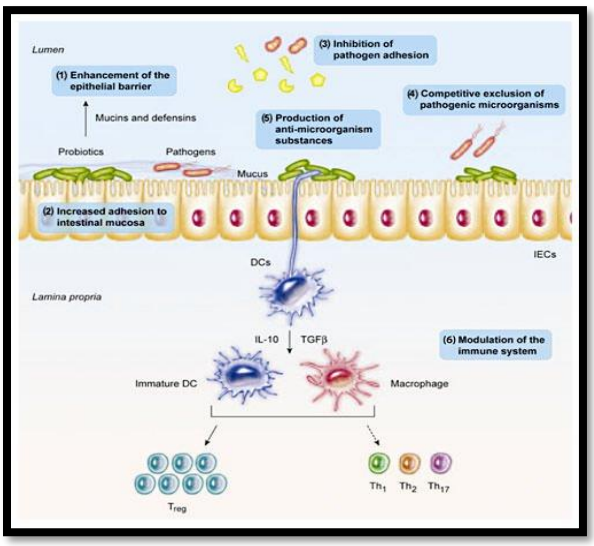
S. No.	Probiotic Bacterial Genera	Species Involved
1.	Lactobacillus	Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus reuteri, Lactobacillus bulgaricus
2.	Propionibacterium	Propionibacterium jensenii, Propionibacterium freudenreichii
3.	Peptostreptococcus	Peptostreptococcus productus
4.	Bacillus	Bacillus coagulans, Bacillus subtilis, Bacillus laterosporus
5.	Lactococcus	Lactococcus lactis, Lactococcus reuteri, Lactococcus rhamnosus, Lactococcus casei, Lactococcus acidophilus, Lactococcus curvatus, Lactococcus plantarum
6.	Enterococcus	Enterococcus faecium
7.	Pediococcus	Pediococcus acidilactici, Pediococcus pentosaceus

S. No.	Probiotic Bacterial Genera	Species Involved
8.	Streptococcus	Streptococcus sanguis, Streptococcus oralis, Streptococcus mitis, Streptococcus thermophilus, Streptococcus salivarius
9.	Bifidobacterium	Bifidobacterium longum, Bifidobacterium catenulatum, Bifidobacterium breve, Bifidobacterium animalis, Bifidobacterium bifidum
10.	Bacteroides	Bacteroides uniformis
11.	Akkermansia	Akkermansia muciniphila
12.	Saccharomyces	Saccharomyces boulardii

4. MECHANISM OF ACTION OF PROBIOTICS

Probiotics have various mechanisms of action although theexact manner in which they exert their effects is still not fully elucidated. Major probiotic organisms possess the mechanisms of action includes enhancement of the epithelial barrier, increased adhesion to intestinal mucosa, and concomitant inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, production of anti-microbial substances and modulation of the immune system is depicted in figure 2. (Bermudez-Brito et al., 2012). These range from bacteriocin and short chain fatty acid production, lowering of gut pH, and nutrient competition to stimulation of mucosal barrier function andimmunomodulation. The latter in particular has been the subject of numerous studies and there is considerable evidence that probiotics influence several aspects of the acquiredand innate immune response by inducing phagocytosis andIgA secretion, modifying T-cell responses, enhancing Th1 responses and attenuating Th2 responses (Guarner and Malagelada,2003)

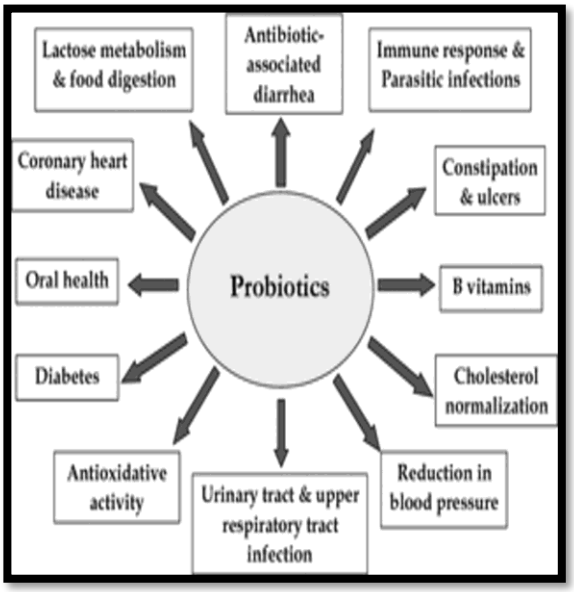
Figure 2: Major Mechanisms Of Action Of Probiotics



5. POTENTIAL APPLICATION OF PROBIOTICS

There is increasing evidence in favour of the claims of beneficial effects attributed to probiotics, including improvement of intestinal health, enhancement of the immune response, reduction of serum cholesterol, and cancer prevention. There is substantial evidence to support probiotic use in the treatment of acute diarrheal diseases, prevention of antibiotic-associated diarrhoea, and improvement of lactose metabolism, but there is in sufficient evidence to recommend them for use in other clinical conditions (Maria Kechagia et al., 2012). There are many applications of probiotics both in case of humans and animal studies. The different beneficial properties of probiotics are listed in figure 3 (Ravinder Nagpal et al., 2012)

Figure 3: Beneficial Properties of Probiotic Organisms



5.1. Antimicrobial Activity

Tejero-Sarinena et al., 2013 investigated the influence of probiotics on the survival of Salmonella enterica, Serovar typhimurium and Clostridium difficile in an in vitro model and postulated that probiotics inhibit pathogens by the production of short-chain fatty acids (SCFAs), such as acetic, propionic, butyric and lactic acids. Short Chain Fatty Acids help to maintain an appropriate pH in the colonic lumen, which is imperative in the expression of numerous bacterial enzymes and in metabolism of foreign compounds and carcinogens in the gut (Kareem et al., 2014)

5.2. Antibiotic Associated Diarrhea

Mild or severe episodes of diarrhoea are common side effect of antibiotic therapy as the normal microflora tends to be suppressed, encouraging the overgrowth of opportunistic or pathogenic strains. The spectrum may range from diarrhoea without mucosal abnormality to pseudomembranous colitis. The latter is a severe form of antibiotic-associated diarrhoea (caused by Clostridium difficile, cytotoxic strains of which may emerge after antibiotic use). Treatment with probiotics has been used in clinical practice with Lactobacillus rhamnosus and Saccharomyces boulardii being administered. Several studies that have been carried out suggest that probiotic use is associated with a reduced risk of antibiotic-associated diarrhoea (McFarland, 2006 & Sazawal et al., 2006]. A recent meta-analysis evaluating the available evidence on probiotics for the prevention and treatment of antibiotic-associated diarrhoea concluded that probiotic administration-namely, Lactobacillus rhamnosus, Lactobacillus casei, and the yeast Saccharomyces boulardii, as these are the probiotics predominantly included in the majority of trials is associated with a reduced risk of the condition (Hempel et al., 2012)

5.3. Infectious Diarrhea

Treatment and prevention of infectious diarrhoea are probably the most widely accepted health benefits of probiotic microorganisms. Rotavirus is the most common cause of acute infantile diarrhoea in the world and a significant cause of infant mortality. Probiotic supplementation of infant formulas has been aimed both at the prevention of rotaviral infections and the treatment of established disease. Well-controlled clinical studies have shown that probiotics such as Lactobacillus rhamnosus GG, Lactobacillus reuteri, Lactobacillus casei Shirota, and Bifidobacterium animalis Bb12 can shorten the duration of acute rotavirus diarrhoea with the strongest evidence pointing to the effectiveness of Lactobacillus rhamnosus GG and Bifidobacterium animalis Bb12 [Szajewska et al., 2001]. For example, in a prospective, randomized, controlled french study conducted among children in day care, the administered probiotic yoghurt product containing Lactobacillus casei shortened the mean duration of diarrhoea significantly compared to the conventional one

[Pedone et al., 1999]. Furthermore, numerous animal studies have indicated an inhibitory effect of probiotics against enteropathogens mainly through the production of bacteriocins (Moslehi-Jenabian , Nielsen and Jespersen, 2011).

5.4. Lactose Intolerance

Lactose intolerance is a genetically determined beta galactosidase deficiency resulting in the inability to hydrolyse lactose into the monosaccharides glucose and galactose. Upon reaching the large bowel the undigested lactose is degraded by bacterial enzymes leading to osmotic diarrhoea. Acquired, usually reversible, causes of beta - galactosidase deficiency include pelvic radiotherapy which damages the mucosa, as well as infection with rotavirus which infects lactase producing cells, and short bowel syndrome. Lactose intolerant individuals develop diarrhoea, abdominal discom- fort, and flatulence after consumption of milk or milk products. Although conventional yoghurt preparations, using Streptococcus thermophilus and Lactobacillus delbrueckii spp. bulgaricus, are even more effective in this direction, partly because of higher beta- galactosidase activity, improvement of lactose metabolism is a claimed health benefit attributed to probiotics and seems to involve certain strains more than others and in specific concentrations. Therefore certain individuals have responded positively to probiotic supplementation, clinicians should consider it as a therapeutic alternative (M. de Vrese et al., 2001 & Levri et al., 2005).

5.5. Anti-Allergic Effect

The role of intestinal microbiota in allergy is supported by observations of their quantitative as well as qualitative difference among children and infants suffering from allergies and healthy ones, the former exhibiting colonization by a more adult-like type of microflora. These probiotic effects seem to particularly involve food allergy and atopic dermatitis. The latter is a common chronic relapsing skin disorder of infancy and childhood with hereditary predisposition being an important component of its pathogenesis together with the individual's exposure to environmental allergens. A limited number of strains have been tested for their efficacy in the treatment and prevention of allergy in infants. In a recent study of breast fed infants suffering from atopic eczema, Bifidobacterium lactis and Lactobacillus rhamnosus GG were found to be effective in decreasing the eczema severity. Furthermore Lactobacillus rhamnosus GG has been found successful in preventing the occurrence of atopic eczema in high risk infants, when supplied prenatally to selected mothers who had at least one first degree relative with atopic eczema, allergic rhinitis, or asthma (Isolauri et al., 2000)

5.6. Antimutagenic Effect

Live cells of probiotic bacteria showed higher antimutagenic activity and their efficiency in inhibiting the mutagens was better than killed bacterial cells. Live bacterial cells bound or inhibited the mutagens permanently, whereas killed bacteria released mutagens upon

extraction with dimethyl sulfoxide. Among the organic acids, butyric acid showed highest inhibition of mutagens 9 N-methyl, N'-nitro, N-nitrosoguanidine; 2-nitroflourene; 4-nitro-O-phenylenediamine; 4-nitroquinoline-N-oxide; Aflatoxin-B; 2-amino-3-methyl-3H-imidazoquinoline; 2-amino-1-methyl-6-phenyl-imidazo (4,5-b) pyridine, and 2-amino-3-methyl-9H-pyrido (3,3-6) indole.) followed by acetic acid. Lactic and pyruvic acids did not show appreciable levels of inhibition (Lankaputhra and Shah, 1998).

5.7. Anti - Cholesterolaemic Effect

Bile, a water-soluble end product of cholesterol in the liver, is stored and concentrated in the gallbladder, and released into the duodenum upon ingestion of food. It consists of cholesterol, phospholipids, conjugated bile acids, bile pigments and electrolytes. Once deconjugated, bile acids are less soluble and absorbed by the intestines, leading to their elimination in the feces. Cholesterol is used to synthesize new bile acids in a homeostatic response, resulting in lowering of serum cholesterol (Begley , Hill and Gahan , 2006). In an in vitro study, Jones et al., 2004 evaluated the role of bile salt hydrolase in cholesterol-lowering using Lactobacillus plantarum 80 (pCBH1). Bile salt hydrolase (BSH) is the enzyme responsible for bile salt deconjugation in the enterohepatic circulation. It has been detected in probiotics indigenous to the gastrointestinal tract. The authors found that bile salt hydrolase activity was able to hydrolyze conjugated glycodeoxycholic acid and taurodeoxycholic acid, leading to the deconjugation of glyco and tauro bile acids.

Possible conversion of cholesterol into coprostanol by bacteria has been evaluated by in one of the study, where the authors found that cholesterol dehydrogenase/isomerase produced by bacteria such as Sterolibacterium denitrificans was responsible for catalyzing the transformation of cholesterol to cholest-4-en-3-one, an intermediate cofactor in the conversion of cholesterol to coprostanol. This served as a fundamental for further evaluations using strains of probiotic bacteria. In a recent in vitro study, Lye et al., 2010 evaluated the conversion of cholesterol to coprostanol by strains of lactobacilli such as Lactobacillus acidophilus, Lactobacillus bulgaricus and Lactobacillus casei ATCC 393 via fluorometric assays. The authors detected both intracellular and extracellular cholesterol reductase in all strains of probiotics examined, indicating possible intracellular and extracellular conversion of cholesterol to coprostanol. The concentration of cholesterol in the medium also decreased upon fermentation by probiotics accompanied by increased concentrations of coprostanol. This mechanism warrants further evaluations as cholesterol reductase is also directly administered to humans to convert cholesterol to coprostanol in the small intestines for a bloodstream cholesterol-lowering effect (Lay Gaik Ooi and Min-Tze Liong, 2010).

5.8. RELIEF OF CONSTIPATION

Ingestion of Lactobacillus acidophilus influenced the bowel function of patients had an effect on constipation (Rettger and Cheplin, 1931).

5.9. ANTI-TUMOR ATIVITY

The anticarcinogenic properties of Lactic Acid Bacteria falls into three categories such as inhibition of tumor cells (Reddy et al., 1973) the suppression of bacteria which produce enzymes such as β-glucosidase,β-glucuronidaseand azoreductase which are responsible for the release of carcinogens from innocuous complexes (Goldin and Gorbach, 1977) and the destruction of carcinogens such as nitrosoamines and suppression of nitroreductase involved in synthesis of nitrosoamines (Rowland and Grasso, 1975)

5.10. ENHANCEMENT OF IMMUNE SYSTEM

The effectiveness of probiotics is related to their ability to survive in the acidic environment of stomach and alkaline conditions in the duodenum as well as their ability to adhere to the intestinal mucosa of colon Typical doses of probiotics (1 to 1o billion) are taken few times a week to maintain their effect on microecology. The probiotic organisms need to be alive when they are consumed and therefore maintaining suitable conditions for thir storage and transport before consumption is important. The probiotic organisms modulates the immune systemby stimulating the protective cytokines such as Interleukins (IL10), Transforming Growth Factor (TGF), suppression of pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF) in the mucosa of patients with pouchitis and crohn's diseases. Sacharomyces boulardii may limit the migration of T-Helper 1 (TH1) cells in inflamed colon tissue in inflammatory bowel disease (IBD) in experimental studies (Lebenthal and Lebenthal, 2002).

5.11. VAGINITIS

Based on the recent research on the prevention of recurrent bacterial vaginosis with probiotics, Lactobacillus supplementation may be appropriate for select patients with bacterial vaginosis. Probiotics could be started concurrently with antibiotic treatment, or after completion of antibiotics, and continued for several weeks to prophylactically treat and prevent a recurrence. However, studies are limited and small, with a large variety in treatment protocols (Webb, Lauren DMSc and PA, 2021). Probiotic strains administeredin dairy products have shown to improve the therapeutic outcome in women with bacterial vaginosis, most probably bysupporting the normal vaginal Lactobacilli microbiota (Falagas, Betsi and Athanasiou, 2007).

5.12. ANGIOGENIC ACTIVITY

Angiogenesis has been an important phenomenon and is necessary for wound healing process through delineated cellular responses to regenerate damaged tissues. The angiogenic program consists of a deliberately orchestrated series of cellular events by which

new vessels arise from pre-existing ones by promoting recruitment of inflammatory cells and producing cytokines, matrix-degrading enzymes and chemokines. Deregulated angiogenesis has a prominent impact on major human diseases, such as cancer, diabetic retinopathy, and IBD including CD and UC (Folkman, 2006) Non-pathogenic probiotic yeast, Saccharomyces. boulardii, has been reported to protect against intestinal injury and inflammation. The molecular mechanisms by which probiotics mediate these beneficial effects however remain unclear. (Folkman, 2007)

5.13. ANTI OBESITY ACTIVITY

Probiotics possess physiological functions that contribute to the health of host environment regulating microbes. In most instances, weight loss is facilitated by thermogenic and lipolytic responses through stimulating the sympathetic nervous system. Probiotic strains, Lactobacillus gasseri BNR17 have shown properties of inhibiting the increase in adipocyte tissue that are the main source of leptin and adiponectin and thereby, limiting leptin secretion (Khang etal., 2013). Other probiotic microbes such as Lactobacillus casei, Lactobacillus acidophilus and Bifidobacterium longum have also been reported to have hypocholesterolemic effects (Karim et al., 2014).

6. COMMERCIAL FORMS OF PROBIOTIC PRODUCTS

There are two main forms in which probiotic organisms can be ingested—fermented foods and supplements. Fermented foods can be of both dairy and vegetable origin, with the most commonly known of each being yogurt and sauerkraut, respectively. Probiotic supplements consist of freeze-dried (lyophilized) bacteria in powder, capsule, or tablet form. Regardless of the form in which the microorganisms are consumed, for clinical efficacy, products containing probiotic organisms must provide live organisms in sufficient numbers to exert therapeutic effects. Both types of fermented foods and supplements are able to do this. Pros and cons of common probiotic delivery systems are compared in Table 2. (Amirreza Khalighi, Reza Behdani and Shaabnam Kouhestani, 2016).

Table 2. Pros and Cons of Different Probiotic Delivery Systems

Delivery system	Pros	Cons
Fermented dairy	-Affordability and easy Availability -Ease of incorporation into daily patterns -Additional nutritional benefits -Enhanced bacterial survival through upper GI tract (100× less	-Contains dairy proteins and lactose -Taste can be issue -Not suitable when travelling -Not suitable for vegans

Delivery system	Pros	Cons
	bacteria can be given per dose) -Effective in the upper GI tract	
Capsules	-Ease of administration -Contain no binders	-Not therapeutic in upper GI tract (unless opened or chewed) -May contain allergenic excipients -Higher cost
Tablets	-Ease of administration -Effective in the upper GI tract	-May contain allergenic or otherwise problematic binders and excipients (e.g., gluten) -Higher cost
Powders	-Effective in the upper GI tract -Dosages can be easily adjusted -Can be incorporated into foods or drinks -Contain no binders	

7. DOSAGE

The dosage of probiotic foods and supplements is based solely upon the number of live organisms present in the product. Successful results have been attained in clinical trials using between $10^7$and 10^{11} viable bacteria per day. Interestingly, it appears that 100 times fewer viable bacteria need to be given in a dairy medium than in a freeze-dried supplement to achieve similar numbers of live bacteria in the lower bowel. Dairy appears to work as an ideal transport medium for the bacteria, enhancing their survival through the upper GI tract (Amirreza Khalighi, Reza Behdani and Shabnam Kouhestani)

CONCLUSION

There are lots of scientific evidence supporting incorporation of probiotics in nutrients as means of derivation of health benefits. Over the last decade, progress in the microbiology, genetics and molecular taxonomy of probiotic cultures has virtually eliminated issues concerning strain identification and tracking. Significant progress has also been made in developing high quality probiotic cultures that exhibit levels of viability and activity that are more stable and better suited for use in clinical investigations. Therefore, the stage is set to carry out well-designed investigations on the clinical and in vivo effects of probiotics. The

current review includes the effects of probiotic organisms against bowel disorders, (lowers cholesterol,antibiotic associated diarrhea, infectious diarrhea etc.,) implies their potential in various health condition. Still the development of consumption of prrobiotics is still in infancy stage.Further research is needed to determine type of organisms and dosage are associated with greatest efficacy for patients to demonstrate their safety and limitations. Hence the role of probiotics in nutrition and medicine will increase in next decade with the support of medical professionals and promoted by food industries for consumption.

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