Therapeutic Role of Probiotics In Managing Various Diseases

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ABSTRACT
Since last few decades, probiotics gained the attention of clinicians for their use in the prevention and treatment of multiple diseases. Probiotic bacteria play a critical and functional role in clinical and nutritional applications. In the last decades, a wide number of scientific works and studies shed light on the crucial role of probiotic microorganisms and their potential to cure various ailments and disorders based on the promising findings and results of different in vitro and in vivo investigations, suggesting a powerful connection flanked by these so-called probiotics and the human immuno-modulatory responses. The issues that were noticed are included: fibrocystic, diabetes, acne, colon cancer, cardiovascular, urinary tract infections, atopic eczema syndrome, food allergies and obesity. Probiotics main mechanisms of action include enhanced mucosal barrier function, direct antagonism with pathogens inhibition of bacterial adherence and invasion capacity, boosting of the immune system and regulation of the central nervous system. Enhancement in using drug treatment has led to the appearance of drug-resistance concern, thus probiotics can be a suitable choice. There is a mutual communication between the central nervous system and the liver, the so-called "microbiota-gut-liver axis" as well as a reciprocal communication between the intestinal microbiota and the central nervous system through the "microbiota-gut-brain axis". This review focuses on the effect of probiotic bacteria and their metabolites on immune-boosting, prevention and treatment of these diseases.
Keywords: Gut microbiota; immuno modulatory response; invasion; metabolites; probiotics

INTRODUCTION

Over the past decades, scientific investigations keen on probiotics and their health benefits have rocketed sky-high. Regardless of the beneficial effects on human health as good bacteria, probiotics have shown high potential in clinical practice. The human intestinal flora contains a variety of bacteria species. Environmental stresses and illnesses can lead to disruption in intestinal flora balance. Some of these bacteria are known as probiotic which addition to digestion aid, produce complex compounds such as vitamins and antibiotics and can be helpful for the body. World Health Organization (WHO), reported that there are four group of complications in patients with medical conditions, which are: Systemic infections, detrimental metabolic activity, overstimulation of immunocompromised individuals, and gene transfer (Hashempour et al, 2021). Some of disorders side effects have been reported in the gastrointestinal tract, such as vomiting, nausea, spasms, diarrhea, bloating, thirst, and taste disturbances. Some of them can change the natural microbial flora of the skin and irritate the skin rash and acne.

Probiotics by stimulation of lactase activity and assistance in lactose digestion can be useful against various diarrhea and lactose intolerance diseases. Some strains of *E. coli*, as well as *Salmonella spp, Shigella spp*, *Campylobacter spp*. and viruses like Rotavirus, Norovirus etc are among the most frequent causes of gastroenteritis leading to inflammation of the intestine (Stavropoulou E and Bezirtzoglou E, 2020). Lactobacillus strains are the main players of the commercially available probiotics. There are reliable proofs that probiotic microbes can hamper various ailments and infections or be useful in their health, particularly in direct connection to numerous gastrointestinal disorders, in both cases, with children and adults. They use enzymatic mechanisms to block toxin-mediated pathology and modify toxin receptors. In addition, Lactobacillus sp. bind to mutagenic compounds in the gut, preventing or delaying tumor progression and cancer. Furthermore, the most significant property of probiotics is the increase in the amount of IgA-producing cells (Adorini et al, 2002), which is effective in controlling allergies. Overall, an ideal probiotic should be generally recognized as safe, resistant to bile, hydrochloric acid and pancreatic water, has anti-cancer activity, reduces intestinal permeability, produces lactic acid (Hashempour et al, 2021; Arvola et al, 1999), stimulate the immune system, resistant to both acidic (stomach) and alkaline (duodenal) conditions.

Sources of Probiotic Strains

The main sources may emanate from human origins like human large intestine, small intestine, or even breast milk. It can also be from animal origins, various food biotopes such as raw milk or fermented food products. Probiotic strains isolated from human microflora are well characterized by high adhesive levels to the human intestinal epithelial barrier than others and more likely to be safe. Nevertheless, several probiotic dietary foods and supplements may carry different bacteria and microbes with no history of safe use in humans or in other animals. The bacterial strains used in probiotics help in Cholesterol lowering and its metabolism (Stavropoulou et al, 2020), colonization in the intestinal, respiratory and urogenital tracts, inhibition of the carcinogenesis, directly or/and indirectly, via the stimulation of the immune system, the metabolism of lactose, the absorption of calcium and the potential of vitamin synthesis. Probiotics also produces many useful metabolites during their growth and metabolism (Stavropoulou et al, 2020; Hashempour- et al, 2021) e.g. production of bioactive compounds, conjugated linolenic acid, propionic acid, etc (Guillot et al, 2003). Increasing knowledge on human intestinal microbiota and microbiota development enables the design of new more specific and unknown probiotics and prebiotics. Also, they can be used instead of drug treatments and lead to prevent the drug resistance issue.

Mechanisms of action and properties of probiotics

Antagonism between pathogenic bacteria and probiotics which is produced by competition for nutrients found in limited quantities in the intestine (Rao et al, 2013) or by pH modulation. Maintenance of an acid pH on the epithelium by probiotics (Fig. 1).

Maintenance of mucosal integrity

The intestinal mucosa has two more layers, the lamina propria and the muscularis mucosae, which bracket the epithelial monolayer. Probiotics show a cytoprotective action upon the gastric mucosa integrity by strengthening the epithelial junctions and preserving the mucosal barrier function (Krishna et al, 2013).

Enhance intestinal barrier function

Preservation of the microbial intestinal balance via the barrier effect.

Regulation of gut motility

Intestinal motility as well as reflexes and secretory functions of the gastrointestinal tract are regulated by the Enteric Nervous System (ENS) found in the intestinal wall. There is a reciprocal communication between Central Nervous System (CNS) and bacterial flora in the intestine (Stavropoulou et al, 2020).

Anti-carcinogenic, antimutagenic and anti-allergic activities

Studies in animals as well as cohort studies in humans have demonstrated a correlation between consumption of dairy products and the risk of colorectal cancer (Stavropoulou et al, 2020; Goldenberg et al, 2017). Anticancer activity of some strains is associated to the capacity of the probiotic strain to inhibit DNA destruction in the very first stages of carcinogenesis.

Hypocholestaemic action

Hypocholestaemic effect is bacterial species related. Different mechanisms have been proposed. Deconjugation of bile acids, assimilation of endogenous or exogenous cholesterol (Adorini et al, 2002; Guillot et al, 2003), binding of cholesterol and free bile acids to the microbial cell or coprecipitation of the free bile acids **(**Goldenberg et al, 2017).

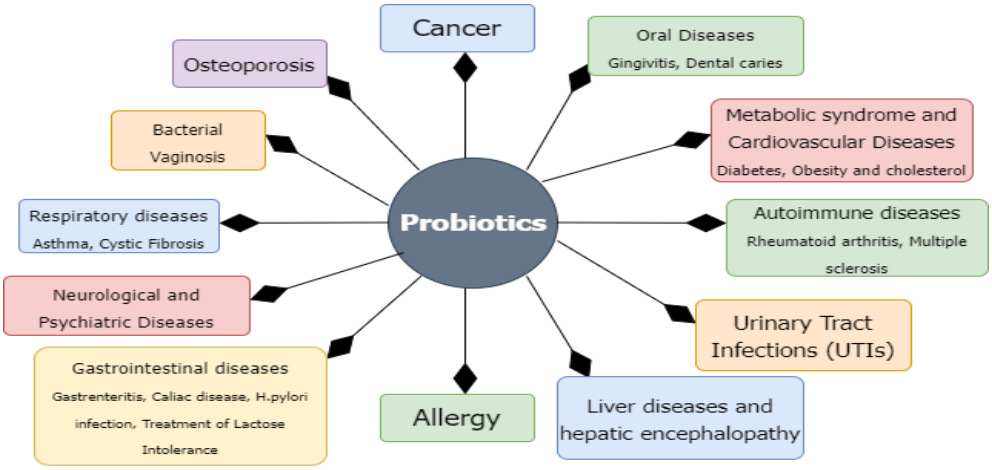

Fig. 1 Mechanism of action and properties of Probiotics

The effect of probiotics on different diseases

Inflammatory bowel disease

Probiotics seem to have an effect on inflammatory bowel disease. Administration studies of the various probiotics remain differentiated in terms of treatment effectiveness (Table 1). While some authors report that there is no difference in the relapse rate but simply a longer interval without relapse for the

treatment of ulcerative colitis with probiotics such as *Escherichia coli* or *Lactobacillus* GG, others accept that supplementation of medical treatment with Bifidobacterium spp. and *L. acidophilus* improves clinical response (Barbut et al, 1992; Mater et al, 2008).

Treatment of Lactose Intolerance

Lactose intolerance is due to the inability to digest lactose in dairy products. It has 60% effect of the world's population. Lactose malabsorption varies considerably in the different countries. *Lactobacillus delbrueckii* subspecies *Bulgaricus* sp, and S. thermophilus in yoghurts improve the intolerance to lactose as they possess the enzyme beta- galactosidase (Arthur et al, 2011). Recent studies showed the efficiency of probiotic bacteria in fermented and unfermented milk preparations given to alleviate the clinical symptoms of lactose malabsorption.

Colon Cancer

Colon Cancer is a multifactorial disease in which irregular and uncontrolled cell growth is one of its most prominent features. Various pathogenic bacteria such as *Escherichia coli* and Clostridium perfringens have mutagenic effect and are associated with the progression of colon cancer. Probiotics such as Bifidobacterium inhibit the growth of these pathogenic bacteria and create a favorable environment that modulates bacterial enzymes, which affect the immune response and destroy tumor cells in the early stages of growth. They can also have synergistic effect with anti-cancer and immunological drugs. The interaction between probiotics and intestinal microbiota can lead to: neutralizing cancer, improving intestinal barrier function (Cao et al, 2015; Hashempour et al, 2021).

Allergy

Allergy results from an exacerbated hypersensitivity response of the immune system to harmless triggering substances in the environment that include drugs, foods, grass and tree pollen, insects, insect's bites and stings. Probiotics have been successfully used in the treatment of allergic diseases such as allergic rhinitis, asthma, atopic dermatitis and food allergy (Guillot at al, 2003). The use of probiotics in allergic conditions such as atopic dermatitis is promising. Lactobacillus casei administered in children with mite allergies decreased the frequency and severity of symptoms (Ouwehand et al, 2009). The combination of Lactobacillus+Bifidobacterium in treatment seems to be the more popular and successful for the allergic rhinitis (Zhang et al, 2012).

Asthma

The modulation of the normal gut microbiota in an experimental model of asthma in animals has been registered. Children at risk of asthma showed microbial dysbiosis in their intestine with Enterococcus faecalis FK-23 suppresses the asthmatic hypersensibility (Aronsson et al, 2010).

Obesity

Obesity is caused by an imbalance between energy intake and consumption, which lead to fat accumulation in body. Probiotics are believed to help obesity and weight management by act important role in gut (Adorini et al, 2002; Arthur et al, 2011). Studies in humans and animals have shown

that the intestinal bacteria of normal weight individuals are more diverse than those of overweight individual. Some species of the Lactobacillus family prevent the absorption of dietary fat in the body and thus increase the fat excreted in the feces and obese individuals have more firmomycetes and fewer bacterioids (Johnson et al, 2018) than normal-weight individual.

Urinary infections

Urinary tract infections (UTIs) are among the most common infections. Shortness of the women urethra is associated with more frequent urinary tract infections in women. They are divided into complicated and include cystitis, pyelonephritis, febrile UTIs, prostatitis and urinary-source bacteria. It seems that probiotics' activity and efficiency is closely related to the specific administered strain and efficient as prophylaxis against potential (Bordalo et al, 2017) pathogenic bacteria of the urinary tract.

Diabetes

Diabetic subjects are characterized by constant systematic inflammation with high levels of proinflammatory cytokines (TNF-a, IL-6, b kinase inhibitor (IKKb), and Jun N-terminal kinase (JNK)) which exert a negative effect on insulin (Cox et al, 2010). Lactic acid bacteria have positive clinical effects on the treatment of specific populations with type 2 diabetes by modulating the inflammatory status. The consumption of yogurt with live probiotics seems to touch up the antioxidant status and fasting plasma glucose (FPG) levels in type 2 diabetic patients (Cox et al, 2010).

Vaccine adjuvant: Lactobacillus casei was used for boosting of the immune response and *Lactobacillus fermentum* strain VRI 003 as an adjuvant to flu vaccine and athletic endurance **(**French et al, 2009). Probiotics were shown effective in increasing immunogenicity levels by auctioning upon seroconversion and seroprotection rates (Agerholm et al, 2000) in adults inoculated with Influenza vaccines.

Table 1: Clinical effect of probiotic strains on human health

Probiotic Microorganisms	**Reported Specific Benefits in Indicated References**	**References**
	Overweight Obesity	
Enterococcus faecium, *Streptococcus thermophilus*	Reduction in body weight, systolic Blood Pressure LDL-C (Low-Density Lipoprotein Cholesterol) and increase in fibrinogen levels.	Ejtahed et al, 2011
	Type-2 diabetes and Dyslipidemia	
Lactobacillus acidophilus La5, Bifidobacterium lactis Bb12	Total cholesterol (TC) and LDL-C improvement.	Ejtahed et al, 2011
	Constipation	
Bifidobacterium lactis	Improvement of the whole gut transit time, stool frequency, and stool consistency.	Hertzler et al, 2003

	Antibiotic-Associated Diarrhea, Diarrheas, Colic, Ulcerative colitis	
Saccharomyces cerevisiae, Saccharomyces boulardii	Reduction of diarrhea rates in children receiving probiotic yeast (7.5%) compared to those receiving placebo (23%).	Hertzler et al, 2003
	Allevation of lactose intolerance	
Streptococcus lactis, Streptococcus plantarum, Streptococcus cremoris, Streptococcus casei, Streptococcus diacetylactis, Streptococcus florentinus, Streptococcus cremoris	Improved lactose digestion and tolerance	Turner et al, 2015
	Allergic Rhinitis	
Streptococcus paracasei-33	Clinical improvements in nasal blockage, rhinorrhea, and nasal itching.	Weston et al, 2005
	Blood Pressure	
Lactobacillus helveticus and *Saccharomyces cerevisiae*	Reduction of hypertension effects	Weston et al, 2005
	Atopic Dermatitis	
Lactobacillus fermentum VRI 033 PCC™	Reduction in SCORAD (SCORing Atopic Dermatitis)	Marcone et al, 2010
	Cancer and side effects	
Lactobacillus acidophilus, Bifidobacterium bifidum	Reduction in incidence of diarrhea and better stool consistency.	Marcone et al, 2010
	Bacterial Vaginosis	
Lactobacillus rhamnosus	The vaginal administration of the probiotic strain leads to stabilization of the vaginal flora with obvious reduction of bacterial vaginosis recurrence.	Patel et al, 2014
	Depression, Anxiety and Mental disorders	
Lactobacillus helveticus R0052 Bifidobacterium longum R0175	Probiotic supplementation reduced aggressive and ruminative thoughts in response to sad mood.	Patel et al, 2014

Safety of Probiotics

The world of probiotics is continuously growing, not only by the increasing number of people who use probiotics but also by the variety of probiotic products and novel probiotic strains. Future investigations and scientific studies need to report a more detailed description of the tested probiotic microbe encompassing the genus, species, and strain level, additionally to the daily dose and the duration of the treatment. Generally, probiotic microorganisms are

distinguished by their safe aspect with GRAS status (Generally Regarded as Safe) by the World Health Organization (Shanahan et al, 2012). Safety for human health corresponds to the salient determinant for probiotics selection. Probiotic strains should be characterized by the absence of their virulent profile and their low resistance to antibiotics. These beneficial microbes have a good safety record during history, primarily related to the use of Lactobacilli and Bifidobacteria strains. New probiotic bacteria must belong to genera and strains commonly found in the healthy human intestinal microbiota. Three major elements composed from the public, healthcare providers and manufacturers have to win the challenges face to face to probiotics, in purpose to focus on international regulations and standards and to provide guidance for strain-specific evidence-based therapy.

CONCLUSION

Probiotics and their metabolites as biological control agents play an important role in prevention and treatment of various diseases, especially those related to the gastrointestinal tract. Probiotics seem to be a modern approach to prevent and reduce the symptoms of these diseases or as an adjuvant therapy by maintaining the proper balance of our intestinal microbiota. The biodiversity of GI microbes usually decreases with age and antibiotics therapy. This dysbiosis has been remarkably linked to several infectious, metabolic, or inflammatory diseases and conditions such as malnutrition, colon cancer, obesity, diabetes, and atherosclerosis. A plethora of commercial products with differences in strain(s) composition and potentiality have been developed as probiotics and functional foods; Align B. infantis, Activa yogurt, Culturelle, Florajen, Kefir etc. For instance, ensuring a strong correlation linking three central sectors, including the food, health, and medicine around the globe, is a major key to the pursuit of this battle. Currently, *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* represent the most and the best-studied strains, and research supplies positive data on *L. reuteri*. Probiotic consumption could be a safe choice for boosting immune system, prevention and treatment of different diseases. The divergence in terms of the definition of probiotics led to an imperative new approach and conceptualization in probiotic terminology to be developed for global usage in all scientific literature. Certainly, future research is suggested to determining the best probiotic and its ideal dose for each disease.

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