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Probiotics: A Friend with Benefits

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Abstract: Gut paves the way for well-being and consumption of probiotics to promote the gut micro-organisms thereby the health has increased significantly worldwide in recent years. Probiotics induce the health as a benevolent despot and its physiological effects are strain-dependent. Several studies revealed the importance of probiotics in interaction with the indigenous micro-biome to enhance the health profile of an individual. While there has been a surge in awareness about the health benefits of probiotics amongst world community, care needs to be taken to enhance its efficacy. The variation in the composition of gut micro-biome possesses control over a wide array of ailments including cancer. This review emphasizes the conventional role of probiotics in disease prevention, immune-modulation and several other health benefits to promote substantiate research in understanding the benefit mechanism of probiotics and to devise apt formulations for the therapeutic industry.

Keywords: probiotics, cancer, micro-biome, disease prevention.

I. INTRODUCTION

Humans and many animals are suitable for inhabitation by microbes and comprise the most significant association in terms of improving the health of the host. A viable mono or mixed culture of bacteria which enhances the beneficial properties of the indigenous flora of the host may be termed as probiotics [1]. Several works have been done in establishing micro-flora inside the animal system as beneficial, and the noted work was of Henry Tissier who observed the concentration of a particular type of bacteria more in the stool of healthy individuals than infected individuals [2]. As probiotics modulate the intestinal flora its consumption imparts various beneficial and therapeutic effects which include intestinal health improvement, immune-modulation, synthesizing and enhancing the bioavailability of nutrients, lactose hydrolysis to prevent its intolerance, and reducing the risk of some other diseases [3-6]. In people aged > 60 years, age-specific compositional shifts were reported in gut microbiota composition and the Bacteroidetes/Firmicutes ratio observed to be dwindling along with *bifidobacteria* [7]. Apart from the beneficial effects associated with probiotics, several challenges need to be addressed. For instance the probiotic micro-organisms must be able to grow and survive in the conditions of the host system in which they have been administered and should properly proliferate at the site of action to show its maximum activity. Preferably probiotics should be of human origin [8], and must be able to tolerate high concentration of enzymatic secretions and low pH conditions. The probiotic strains used need to be non-pathogenic, non-allergic and must be tolerated by the human immune [9]. Major health organization has marked some stringent guidelines in order to systematically evaluate the health benefits claimed by use of probiotics in food. The mind to gut communication has influence of gut micro-flora composition along with notable impact on metabolism and digestion [10]. To combat obesity, probiotics are helpful and have essential physiological functions to the health of the host environment regulating microbes [11]. Probiotics modify, induce and regulate the host's immune response by activating certain genes involved in cascade of reactions. The neuronal signaling regulates the gut-brain communication and brain activity corresponds to the signals imparted by gut micro-biome [12]. A wide array of metabolic disorders can be regulated in addition to the nutritional optimization by the benevolent probiotics [13]. Apart from the known beneficial effect via use of probiotics as supplements hefty researches required to validate use of certain strains as potential probiotics in elevating the human health.

II. SOURCES OF PROBIOTICS

Probiotics can be obtained from different sources such as conventional and unconventional as shown in Table 1. The fermented food products and plants are the conventional sources of probiotics. Various microorganisms have potential for probiotics, which are non-intestinal sources and non-dairy fermented food products, fermented drinks, vegetables, and fruit juices. Different raw materials and ingredients are used to produce fermented and non-fermented foods from different available species or strains of probiotics. Lactic Acid Bacteria (LAB) species primarily *Lactobacillus plantarum* is present in many types of fruits and juices, whereas *Leuconostoc mesenteroides* is most commonly found in tomatoes and rarely found in fruits. Probiotics isolated from non-intestinal sources such as several fresh fruits and vegetables, including the dragon, durian, ginger, papaya does not produce any bacteriocin-like substance e.g, *L. plantarum.*

Table 1. Conventional and unconventional sources of probiotics.

Strain	**Conventional sources**	**Unconventional sources**
Lactic Acid Bacteria (LAB)	Fermented meats and pla	Fruits, juices, vegetables
Lactobacillus plantarum	Fermented idli	Ginger, papaya
Lactobacillus pentosus	Green and black olives, human breast milk and fe	-
Lactobacillus paracasei	Green olives	-
Lactobacillus	Kitchen waste	-

delbrueckii		
Lactobacillus salivarius	Human breast milk	-
Lactobacillus kunkeei	-	Giant honey bees, flesh, long grass and milk whey
Leuconostoc mesenteroids	Black olives	Fruits mainly tomatoes
Pediococcus pentosaceous	Fermented beef sausage	-
Bacillus subtilis	Weaned pig	-
Bifidobacterium pumilus	Sea water	-
Streptomyces spp.	Indigenous and broiler ch	-

III. PROBIOTICS AGAINST PATHOGENIC MICROORGANISMS

Unlike conventional antibiotics, probiotics did not alter the complex population of gut microbiota, thereby acting as the most useful properties of probiotics. Studies on probiotics have been focused on the investigation of their activity against pathogenic microorganisms. Tejero-Sarinena *et al*. [14] has reported the antagonistic activity of probiotics against *Salmonella enterica*, *Serovar typhimurium* and *Clostridium difficile* through *in vitro* model system which was explained due to short-chain fatty acids (SCFAs) production, such as acetic, propionic, butyric and lactic acids by probiotics. These SCFAs help to maintain an appropriate pH in the colonic lumen, required for the expression of numerous bacterial enzymes and metabolism of foreign compounds and carcinogens in the gut [15]. Islam [16] reported inhibitory activity of probiotics was due to the production of compounds, like bacteriocins, organic acids, acetaldehydes, diacetyl, hydrogen peroxide, ethanol and peptides. Out of these compounds, peptides, and bacteriocins, showed the killing of cells by increasing the permeability of cell membrane and depolarization of the membrane potential [17]. While, the production of H_2O_2 by these bacteria leads to denaturation of several enzymes involved in the membrane integrity, thereby increasing permeability of the membrane of pathogenic microorganism and consequently, leads to cell death [18]. A few compounds resulted in the production of organic acids which lower the pH of the cell [15]. Along with production of anti-pathogenic molecules, probiotics also boost defense system of the host cell by producing defensins which is a cationic anti-microbial peptides [19]. Another mechanism by which probiotics exert anti-pathogenic activity is by competing for pathogen binding and receptor sites, as well as for available nutrients and growth (Fig. 1).

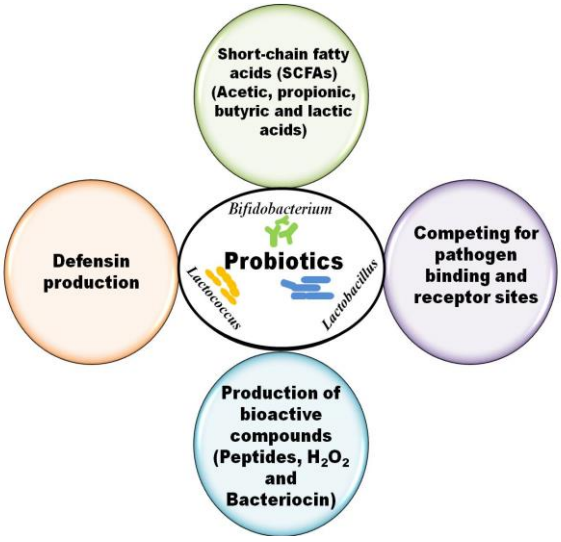

Fig. 1. Mechanism of action of anti-pathogenic activity of Probiotics

IV. PREVENTION FROM OBESITY AND DIABETES

The role of gut flora in the pathology of insulin resistance (type II diabetes) and obesity has been reported by Ley *et al*. [20]. Studies conducted on animal and human models suggested the role of gut flora in enhancement of body weight and insulin resistance, and these characteristics are transmittable with gut flora when microbiota from obese is transmitted to normal and germ-free mice [21-22]. This gut flora-mediated pathology of obesity and diabetes was possibly due to increased energy harvest; increased LPS levels in the blood (endotoxemia) and low inflammatory activity [23]. Therefore, to treat obesity and diabetes, modulation of gut flora can be used as a more effective tool. Probiotics are novel gut flora modulators, and have protective role in the prevention and treatment of diabetes and obesity [24-25]. Yadav *et al.* [25-26] suggested that probiotic-supplemented fermented milk product i.e. Dahi (yogurt) help to lower diet-induced insulin resistance and protect from streptozotocin-induced diabetes in animal models. Moreover, this probiotic Dahi also suppress the progression of diabetes and its complication by boosting the antioxidant system of the body [26]. Recent studies have suggested the positive effect of selective strains of *Lactobacilli* and *Bifidobacteria* against obesity and type-2 diabetes [27]. Andreasen *et al.* [28] reported that *L. acidophilus* lowers the insulin resistance and expression of inflammatory markers in human. Although several studies conducted on animal were successful in probiotic mediated suppression of obesity and diabetes, there are only very few studies in humans showing the significant effects.

V. ROLE OF PROBIOTICS AGAINST DIARRHOEA

Several studies have reported the protective role of probiotics against different types of diarrhoea, principally in traveller's diarrhoea, antibiotic-induced diarrhoea, radiation-

induced diarrhoea, *Clostridium difficle* infection and diarrhoeal diseases in young children caused by rotavirus.

A. Antibiotic-Associated Diarrhoea

The most common side effects of antibiotic therapy are mild or severe diarrhoea because of overgrowth of pathogenic strains and the suppression of normal microflora. The diarrhoea may be mild which is without mucosal abnormality to *Pseudomembranous colitis* (*Clostridium difficile*). Conventional treatment of this type of diarrhoea involved the causal antibiotic agent removal, correction of the electrolyte disorders and treated with metronidazole or vancomycin therapy in severe cases. Clinical studies involving treatment with probiotics such as *S. boulardii* and *L. rhamnosus* suggested that the use of probiotic resulted in reduced risk of antibiotic-associated diarrhoea [29-30]. However, there is need to prepare an optimum dose of the probiotics and to compare effectiveness of different probiotic interventions [31].

B. Infectious Diarrhoea

Probiotics are helpful in the treatment and prevention of infectious diarrhea. Rotavirus is the most common cause of acute infantile diarrhoea and is responsible for infant mortality in the world. Administration of probiotic supplements under well-controlled clinical studies have suggested that probiotics supplements from *L. rhamnosus* GG, *L. reuteri, L. casei* Shirota, and *B. animalis* Bb12 can lower the duration of acute rotavirus induced diarrhea in children [32-35]. The mechanism behind the reduction of rotavirus diarrhoea may be competitive blockage of receptor site signals, enhancement of the immune response, and production of antiviral substances. Other than rotavirus infection, studies have shown the role of food and non-food probiotic strains in inhibiting the growth and adhesion of a range of diarrhoeal syndromes. Several studies have reported the protective activity of probiotics against travelers' diarrhoea in adults. Furthermore, few animal studies resulted that bacteriocins produced by probiotics are responsible for inhibitory activity of probiotics against enteropathogens [36].

VI. PROBIOTICS AGAINST LACTOSE INTOLERANCE

Lactose intolerance a genetic disorder caused due to deficiency of beta-galactosidase caused due to pelvic radiotherapy, rotavirus infection and short bowel syndrome. Lactose intolerant (LI) individuals are more prone to diarrhoea, abdominal discomfort, after consumption of milk or milk products. Probiotics have gained high interest in recent years as potential compensation for lactase insufficiency. Probiotics belonging to *Bifidobacterium* and *Lactobacilli* are the predominant groups of the gastrointestinal microbiota, which are the most widely used probiotic bacteria [37-38]. Probiotics promote lactose digestion in lactose intolerant individuals by increasing the overall hydrolytic capacity in the small intestine and increasing the colonic fermentation [39]. Probiotics can lower the level of lactose in fermented products, and help to increase the entry of active lactase enzyme in the small intestine with the fermented products [40]. Studies have noted the protective effect of *B. animalis* against diarrhea and its role in modulating the colonic microbiota [41-42]. In the study of Le Luyer *et al.* [41], *B. animalis* and *B. longum* supplementation modified the composition and metabolic activities of the colonic microbiota. However, the mechanisms by which *B. animalis* exerts its effects are currently not fully understood, however, contributive factors may include (1) modifying gut pH, (2) expressing beta-galactosidase, and (3) positively influencing intestinal functions and colonic microbiota. However, further studies are needed to determine the varying efficacies of oral probiotic supplementation and their mechanisms of action.

VII. ROLE OF PROBIOTICS AGAINST ALLERGY

Probiotics also find their application in protection and management of allergic diseases caused due to immune disorders. Song *et al.* [43] reported the protective role of *Lactobacillus plantarum* L67 against allergy-associated disorders with the production of interleukin-12 and interferon-G in their host. Study conducted on mice showed that *L. plantarum* 06CC2 help to lower the effect of allergy by reducing the level of total immunoglobulin E, ovalbumin-specific immunoglobulin E, and histamine in the sera of ovalbumin-sensitized mice and increased secretion of interferon-G and interleukin-4 in spleen cells [44]. Further studies need to be extended in evaluating the anti-allergic role of probiotics and mechanism underlying the activity.

VIII. ROLE OF PROBIOTICS AGAINST INFLAMMATION

Crohn's disease (CD) and ulcerative colitis (UC) are among the most chronic inflammatory diseases of the GIT and are collectively called inflammatory bowel disease (IBD) [45]. Studies have shown the positive correlation of imbalance in the gut microbiota with the pathophysiology of IBD and this can be prevented by using different probiotics supplementation [46-48]. IBD resulted in an imbalance of SCFAs such as acetate, butyrate, and propionate. Moreover, these SCFAs help to regulate colonic homeostasis, improve the propulsive colonic function and prevent inflammatory effects [49]. Nowadays, several genetically engineered probiotic bacteria have developed which have ability to produce and secrete immunomodulators, such as interleukin-10, trefoil factors (compact proteins co-expressed with mucins in the GIT), or lipoteichoic acid (a major constituent of the cell wall of Gram-positive bacteria) that can impact the host immune system, thereby help in restoring of the level of protective commensal bacterial species [50]. Apart from bacteria such as *Lactobacillus, Bifidobacterium*, *Enterobacter* and *E. coli*, new or genetically modified should be developed to counteract IBD [51].

IX. PROBIOTICS FOR THE TREATMENT OF CANCER

According to the WHO Cancer fact sheet [52], cancer has become a dreadful disease affecting people globally and approximately 14 million new cases and 8.2 million cancer-

related deaths added till 2012. People from Asian, African, and American continents are more prone to death due to cancer [53]. Lots of research has been going on towards solving the mystery of cancer and many new drugs have been discovered using biotechnology and nanotechnology. But due to side effects caused by these new drugs, research has been shifted towards natural sources in previous years [54]. These probiotics can be used by clinical nutritionists, scientists, and industrialists to fight against cancer and to prepare a drug with more effectiveness and minimal or no side-effects [55-57]. Probiotic strains such as *Lactobacillus fermentum* NCIMB-5221 and *L. fermentum* NCIMB-8829, have gained application in suppressing colorectal cancer cells and promoting normal epithelial colon cell growth *in vitro*, by producing SCFAs (ferulic acid). Similar activity was also reported by other probiotic bacteria, namely *L. acidophilus* ATCC 314, *L. rhamnosus* ATCC 5130 [58], *L. acidophilus* LA102 and *L. casei* LC232 against two colorectal cancer cell lines (Caco-2 and HRT-18) [59]. Although probiotics showed promising results against cancer, but only *in vitro* research has been carried out so far. Hence, the potential of probiotics against cancer must need to be proven *in vivo* models and proceed towards animal testing and clinical trials. Nowadays, probiotics have also gained their application in treatment of cardiovascular diseases also [60, 61]. Summary of beneficiary effect of probiotics was summarized in Fig. 2.

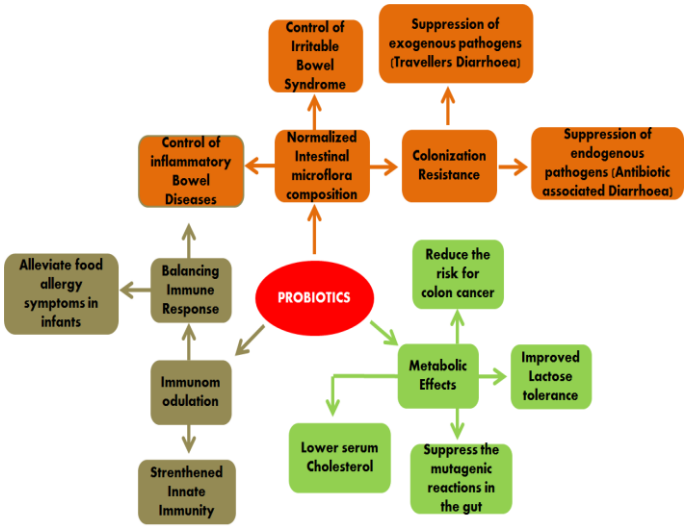

Fig. 2. Therapeutic benefits of Probiotics. (Adapted and modified from Mahajan and Singh [13].

X. CONCLUSION

With the advent of the functional food concept, the use of probiotics in human health is the most sought approach. Rigorous research needs to be undertaken to validate probiotics as a superior alternative to existing therapies. In promoting health beneficial effect, it has tremendous promise; but is it long term or it has some detrimental side effect on the human body as a result of long term consumption needs to be figured out. Thereby, the immune system stimulation from the gut by microbiota and the mechanism governing such stimulation is an area that is still unexplored. To develop new disease-specific probiotic strains, to facilitate the understanding of when to use probiotics and how they affect specific pathological states more significant stones needs to be unturned. Elucidation of mechanisms of activity of a probiotic can be helpful in preparing specific and targeted probiotics. Although consumer have resisted the utilization of genetically modified organisms, but GMO probiotic foods with potential clinical applications may be more rapidly acknowledged.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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