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Potential Role and Mechanism of Probiotics

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Abstract:
Probiotics can be defined as the group of microorganisms having beneficially effects for health if they encounter with an appropriate amount. They provide vital metabolites with nutritional and therapeutic properties that provide countless health benefits. Probiotics have been demonstrated toprevent somedigestive disorders such as infectious diarrhea, helicobacter pylori infection, antibiotic-associated diarrhea (AAD), necrotizing enterocolitis(NEC), chronic kidney disease (CKD), Irritable Bowel Syndrome (IBS). The most widely used probiotic species are*Bifidobacterium* and some lactic acid bacteria strainsthat are used in wide range of functional foodsas well as in dietary supplements. For sake of an additional information , probiotics are responsible for treatment of several disorders like type 2 diabetes, non- alcoholic fatty liver dysfunctions also acts an co adjuvant many metabolic diseases and in obesity too. Therefore, the action mechanismof probiotics includeddiversified, strain specified as well as miscellaneousthat have examined some monitoring. The main focus of the research is to reconsideration Probiotics's assorted action mechanisms.Further attempts have been made to isolate the new probiotics from unexplored microflora and to investigate their mechanisms of action.
Keywords: antibiotic-associated diarrhea, necrotizing enterocolitis, Irritable Bowel Syndrome

INTRODUCTION

Nowadays, in addition to the fundamental nutritional role of providing the needed nutrients for the organism's growth and development, some extra elements are becoming progressively crucial, including health maintenance and disease counteraction. In the globe of extremely processed foods, specific consideration is paid to the structure, safety and wellbeing of the consumed products. The fermented food contains some organisms which bestow health benefits and are generally regarded as 'probiotics'. And according to the (FAO) Food and Agriculture Organizationand (WHO) World Health Organization,these probiotics are "live microorganisms which when administered in adequate amounts confer a health benefits on the host". [Paulina*et al.*, 2017].

Probiotics are potentially useful micro biota playing a wide variety of vital roles in several different fields including improvement of digestion, intestinal health, and in inhibition of pathogenic bacteria in gastric tract, for the enhancement of immune system, production of cofactors and vitamins, prevention of tumors and cancers and also helps in the reduction of blood pressure[Nasr *et al.*,2018].

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The probiotic bacteria are found mainly in dairy products and in fermented products. These foods play a predominant role in upgrading the positive image of probiotics in the field of health. Probiotics are used as starter culture in the fermented foods. There are several factors that can be considered when these bacteria are added to the fermented foods that influence the potential of probiotics in order to survive in the food products and become active when enters into the gastrointestinal tract of consumers. These factors include the physical conditions of products storagethe chemical composition of products(i.e. nitrogen contents, oxygen content, carbohydrate content, water activity), possible interactions between probiotics and starter culture (i.e. synergism, bacteriocin production and antagonism) [Senok*et al.,* 2005].There has been a growing interest of fermented foods in the field of food microbiology in upcoming years[Wenbin*et al.,* 2019]. *Lactobacillus* spp. are the most frequent species used in the fermented dairy products. These can convert carbohydrates (i.e. lactose) into lactic acid. Lactic acid protects dairy products from being corrosive. Their count per diet should be 1×10^9 CFU. Depending on age, genetics and nutrition, it is essential to maintain the equilibrium between healthy (85%) and damaging bacteria (15%).Probiotic species selection depends upon their long term history of utilization without harming side effects. Other appropriate criteria for the utilization of suitable bacterial species are resistance and endurance in the host's digestive system which implies stomach acid and bile resistance, capacity to append and colonize the intestinal's epithelial cells, the power to inhibit pathogens by making antibacterial compounds(Yousef*et al., 2019)*

It is currently recognized that intestinal dysbiosis relates to modifications in the quantitative a nd qualitative structure of microbiota, which can lead to modified microbial interactions of th e host, which can often contribute to a condition with inflammation. And this linked to the growth of many non communicable human illness, but the process used to maintain homeostasis is not fully understood [Plaza*et al.,* 2018].

Recent research has suggested that epithelial hypoxia limits the accessibility of oxygen in the colon during homeostasis, resulting in the maintenance of healthy microbiome that acts as microbial origin, generating metabolites that add to the host's nutrition and niche safety [Julio *et al.,* 2018].

Probiotic is an ongoing approach to treat the various diseases, and alter the disturbed intestinal microflorawith a particular action mechanism that has not been completely explained. That's why we conducted a literature survey of the probiotics diverse mechanism of action to know the contribution of different strains in a host's homeostasis.

Various organisms come under the spectrum of probiotics some of them are listed as below:
According to FDA (Food and drug administration), probiotics are regulated as GRAS (i.e. Generally Regarded As Safe) [Anadon*et al.,* 2006]. Microbes including bacteria such as *Lactobacillus species* like*Lactobacillus casei, L. bulgaricus, L. fermentum , L. crispatus, L. acidophilus,L. johnsonii, L. gasseri, L. plantarum, L. reuteri, L. lactis,* and some *Bifidobacterium species* andyeast like*Saccharamycesbaulardi*[Santosa*et al.,* 2006].*Lactobacillus* is a anaerobic facultative,non-spore forming gram-positive microscopic

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microbesthat are mostly found in the oral cavity, intestine and in vagina. *Bifidobacterium*is obligate anaerobe, non-spore forminggram-positive bacteria which produces acetic acid and also lactic acid in the ratio of 3:2[Shigeru*et al.,* 2019].

Applications of probiotics in gut health:

It is now widely acknowledged that the entity of microbes that colonize the human microbiota and human epithelial surfaces incorporates a key role in decisive human health. Large numbers of intestinal disorders are associated with the unbalanced GIT (gastrointestinal tract)microbiota. Scientific evidences upgrade the important and vital role of probiotics the digestive system, their consequential effects in decompressing the symptoms of various diseases. Several clinical investigations have demonstrated that probiotics are effectual in the treatment of various diseaseslike:

Infectious diarrhea: Among the various microorganisms, rotavirus is a most common that cause infectious diarrhea mostly in infants. The acute symptom is additionally frequent among the travellers, in whom the enterotoxigenic*E.Coli* is common.. It is also caused by the pathogenic bacteria like *Shigella*,*Campylobacter*, and *Salmonella*. In Infectious diarrhea, probiotics act against pathogenic bacteria by competing for accessible nutrients, binding sites, manufacturing a range of chemicals, making the gut contents acid, and increasing the specific as well as nonspecific immune responses(Allen *et al*., 2011).

Helicobacter pylori infection: *Helicobacter pylori*, is a high prevailing pathogenic bacteria which causes gastric malignancies,peptic ulcers and chronic gastritis. Probiotics were tested to inhibit the*Helicobacter pylori* not solely in vitro, but also in vivo studies. The rationale for using probiotics against the *H. pylori* infection is the competition for nutrients, competitive inhibition of adherence, production of bactericidal substances and also the stimulation of host functions as well as immunity. Additionally, probiotics are clinically tried for eradication therapy for the treatment of *H. pylori* infection. [shigeru*et al.*,2019].

Antibiotic-associated diarrhea (AAD): The commonly reported AAD pathogens are *Clostridium difficile, Clostridium perfringens, Staphylococcus aureus* and *Klebsiellaoxytocaare*. It alters enteric microflora membrane integrity, nourishment and mineral metabolism and if severe might causes electrolyte disturbances, crampy, abdominal pain, dehydration premature termination of antibiotic therapy, toxic megacolon, pseudomembranous colitis and probably death [Johnston *et al.*, 2004]. As the increase in number of clinical investigations, it provided the data format analysis to assess the adequacy of probiotics (i.e. *Lactobacillus GG strain* and *S.boulardii* strain) for the protection as well as the relapse of CDAD [Jacob*et al.*, 2016]. During the antibiotic treatment of AAD, the consumption of probiotics reduced the duration of AAD. Many probiotic products can diminished the risk of AAD by over 40% where as some probiotics are also reported to reduce*C.difficile* associated diarrhea by upto 60%[szajewska*et al.*, 2006].

Necrotizing enterocolitis (NEC): Itis an inflammatory necrosis occurs in the gut of premature infantsdemonstrating the symptoms like feeding intolerance, sensitive and bloated

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abdomen. It also results in gastrointestinal aperture. It is a significant reason for mortality (i.e.20–50%) in neonatal intensive care units throughout the world [Neu*et al.,* 2011]. NEC is affected by many factors like enteral feeding, gestational prematurity, mucosal injury, bacterial translocation, host geneticsand inflammatory responses. Multiple meta-analyses have concluded that probiotic treatment reduces the inflammatory disease and death in premature infants. Various probiotics seem to be efficacious and suggesting additional generalized mode of action.

Chronic kidney disease (CKD): It is a worldwidemedicalproblem with high economic costs to healthcare and one of the high risk issue of cardiovascular disease (CVD). Every stage of CKD is associated with attenuate quality of life. CKD is typically the asymptomatic till later stages. Diuretic, phosphate and RAAS inhibitors as well as potassium binders are commonly used for the treatment of CKD. Probiotics is new approach to control CKD. It not only reduces the blood uremic toxicity but also offers the advantages to the patient by restoring the microbial equilibrium that altered the gut microflora[Mayuresh*et al.,* 2019].

Irritable Bowel Syndrome (IBS): It is a severe gastricproblem including the symptoms such as incomplete evacuation, abdominal pain, straining, bloating, bowel function and constipation [Snigda*et al.,* 2019]. Growing evidences suggest the possible role in the physiology and symptom generation of intestinal microflora. For that, different testing trials in previous years and although the findings suggest that probiotic use should be benefit in the alleviation of the IBS symptom. Strains like *Bifidobacteriuminfantis, E.Coli*and *L.plantarum* are efficient against IBS [Borja*et al.,* 2016].

Mechanism of Action of Probiotics: Probiotics in human species have countless advantageous features. Their primary benefit is the impact on the growth of the organism's microbiota in order to ensure a correct equilibrium between pathogens and bacteria needed for the ordinary function of the organism. Live microbes that meet the applicable necessities are utilized in manufacturing of functional foods. Their beneficial impact is used after antibiotic treatment to restore natural microbiota [Johnston *et al.,* 2006]. Another role is to counteract the pathogenic intestinal microbiota activity that has been brought from the contaminated environment. Probiotics can therefore inhibit the pathogenslike *Clostridium perfringens, Salmonella enteritidis*[Cameron & Carter, 1992], *Campylobacter jejuni* [Jimmysaint*et al.,* 2017], and various species of *Staphylococcus* [Sirkoska*et al.,*2013] and *Yersinia* [Demontijo*et al.,* 2015] and thus preventing from food poisoning. Probiotics have been confirmed to have a beneficial impact on digestion procedures, food allergy, candidosis and dental caries. Probiotic microorganisms like*Lactobacillus reuteri, Lactobacillus plantarum, Bifidobacteriumpseudocatenulatum* and *Bifidobacteriumadolscentis* are the natural producers of somevitamin B. Probiotics can also generate enzymes like esterase, lipase and coenzymes like A, Q, NADP and NAD [Paulina *et al.,* 2017].

Probiotic exert its benefits through differentmode or mechanism of action:
1. Antagonism effect through the production of antimicrobial substances
2. Competition with pathogens for the purpose of adhesionto the epithelium
3. Immunomodulation of the host

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4. Inhibition of bacterial toxin production [Hill *et al.*,2014]
5.Functioning of probiotics with TLRs and cell cascade signalling [Julio *et al.*,2019]

The first two processes are linked directly to their impact on their microorganisms. These mechanisms are essential for prophylaxis and infection therapy as well as for maintaining the host's intestinal microbiota equilibrium.

Antagonism effect through the production of antimicrobial substances: It this mode of action, the co aggregate capacity of probiotic strains may contribute as a protective barrier that prevent pathogens from epithelium colonization. It has been shown that several *Lactobacillus* proteins encourage this adhesion which exhibit surface adhesives that facilitate attachment to the mucous layer. Probiotics can adhere to the epithelial cells and therefore block pathogens. That mechanism has a significant effect on the health situation of host. In addition, the adherence of probiotics to epithelial cells can cause a signalling cascade that results in immunological modulation which release certain soluble elements can cause immunological cells to activate directly or indirectly (through epithelial cells) [Oelschlaeger*et al.,* 2010]. This impact plays a major role in the treatment of infectious diseases and the prevention of chronic inflammation of food tract.

L. rhamnosus was screened in the presence of *E.coli*, F-4 expressing strain in the intestinal epithelial porcine J2 cells. Toll like receptor (TLR)-4 expression and the nucleotide binding oligomerization domain comprising protein (NOD2) was increased in the presence of *E.coli* and these rises were weakenby *L. rhamnosus* treatment. In response to bacterial infection, the probiotic retained the epithelial barrier and encouraged bowel epithelial cell activation [Zhang *et al.,* 2015]. From the certain investigation, this thin is suggested that probiotics may play a part in the cancer cell elimination [Collado*et al.*, 2015].

Competition with pathogens for the purpose of adhesion to the epithelium and for nutrients: Most trials concentrated on reducing human pathogens like *Salmonella typhi* and strain *E.Coli*. The probiotic metabolites therefore come to play a part in the cell modulation of various signalling as well as metabolic pathways. Some strains of *Lactobacilli* and *Bifidobacteria* may produce the antibacterial peptides called 'bacteriocins' that stop selected pathogen from proliferating. Bacteriocins are the small cationic molecules made up of approximately 30-60 amino acids [Umu*et al.,* 2017]. Bacteriocins are categorized into four major kinds i.e. their primary structures, genetic characteristics, molecular weight and translation modifications [Mokoena*et al.,* 2017]. Some of these substances are produced by*L. plantarum* and strain *L. acidophilus,* and it has been shown that they stop the growth of *rotavirus, C. difficile* and some multidrug resistant species of *Shigella*, *E.Coli* in many gastrointestinal conditions [Kumar *et al.,* 2016].

Immunomodulation of the host: The gut microbiota of the host regulates the immune system by producing molecules capable of activating immune cells with immunomodulatory as well as anti inflammatory functions. The relationship of probiotic with monocytes, epithelial cells, macrophages or with lymphocytes causes these immunomodulatory impacts [Damelio*et al.,* 2017].

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The immunomodulatory impact of the intestinal microflora is based on following apparently contradictory events [Borcherset *al.*, 2019]:

(1) Induction and the maintenance of immunological tolerance state to environmental antigens

(2) Induction and control of the immunological reactions againstmany bacterial and viral origins's pathogen

(3) Inhibition of auto aggressive and allergic reaction

Probiotics can affect the congenital and acquired immune system through some metabolites and cell wall elements. Intestinal immune cells and intestinal epithelial cells are the main host cells which are used in the framework of immune response [Paulina *et al.*, 2017].

Macrophage activity is stimulated by the components of lactic acid bacteria's cell wall. Probiotic bacteria can also regulate the development of cytokines through the gastrointestinal tract's immune competent cells [Marteau*et al.*, 2003].

Inhibition of bacterial toxin production: Bacterial toxin inhibition is focused on the actions that lead to inactivation of toxins and contribute to the removal of toxins from the body [Nikbakht*et al.*, 2013]. Nevertheless not all probiotics are detoxifying because they are a part of the strain. Therefore, studies should be performed in order to select the potent strain with such features.

Thus the reduction of some metabolic reactions can lead to the production of various toxins that associates with pathway stimulation which lead to the manufacturing of indigenous antimicrobial substances, enzymes and vitamins [Paulina *et al.*, 2010].

Functioning of probiotics with TLRs and cell cascade signalling: TLR is a family that includes 11 proteins in mammals (i.e. from TLR1-TLR11) and their activation occurs after binding the legand to extra cellular leucine-rich repeats. In humans, TLR1, TLR2, TLR4, TLR5, TLR6 and TLR19 are associated with outer membrane and then primarily react to the bacterial surface associated PAMPs.whereas TLR3, TLR7, TLR8 and TLR9 are present on the endosome surfaces where they mainly react to virus and bacterial and with bacterial nucleic acid-based PAMPs. The TLR signalling pathway (except TLR3) includes the enrolment of the main 88 myeloid differentiation reaction, which activates the signalling pathways for MAPK and NF-κB. TLR3 uses the adaptor protein which results in type 1 IFNs being expressed [Julio *et al.*, 2019]. TLR9 signaling is crucial to moderate the anti inflammatory impact of probiotics [Bermudez *et al.*, 2012].

Probiotics are capable to prevent the intestinal inflammation by reducing the regulation of TLR expression, secreting metabolites which prevent TNFα from entering mononuclear cells in the blood and inhibiting enterocyte signals of NF-κB [Thomas *et al.*, 2011].

In this context, signalling of Lactobacilli cell wall elements can possibly happen through the bonding of TLR2 and TLR6 which stimulates the development of cytokine. The related immune cells of casei and gut induce the amount of receptors CD-206 and TLR2. Furthermore, multiple strains like *L.CCFM634 plantarum, L. CCFM734 plantarum, L.*

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CCFMM381, *L. fermentum CCFM137* are TLR2/TLR6 stimulus. Thus, in immune regulatory processes TLR2/TLR6 signaling is crucial.

CONCLUSIONS

Probiotics are safe microbes that give some positive impacts to the host when it get administered in adequate doses at suitable time. The mechanism of action of probiotics involve antagonism through the production of some antimicrobial substances, immunomodulatison of the host, competition with pathogens, inhibition of bacterial toxin production, interaction of probiotics with TLR's and cell cascade signalling that plays a vital role in maintaining the homeostasis and in regulating the peripheral tissue functionality. All of the above mentioned action mechanisms should encourage researchers, stakeholders and customers to know about the impacts of probiotics that demonstrate promising outcomes.

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