

Probiotics and Its Therapeutic Effects: A Review

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ABSTRACT

Mankind has been exploiting microorganisms involuntarily from the very beginning until Louis Pasteur proposed the role of microorganisms in fermentation. However, the ability of these microorganisms to reshape the human life came into frame through the pioneering studies by ‘The father of Probiotics’, Ellie Metchnikoff in the beginning of 20th century. Replacement of putrefactive bacteria in the gut micro biome by probiotics microorganisms has shown to restore and maintain the gastrointestinal health. Probiotics by definition is “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. Though the most common strains of probiotics employed are *Lactobacillus* and *Bifidobacterium* sp., the prospect of other microorganisms are still being explored. This review mainly focuses on the potential therapeutic effects of probiotics on different classes of diarrhea such as acute infectious diarrhea, traveler’s diarrhea, Antibiotic associated diarrhea, inflammatory Bowel Syndrome, Necrotizing Enterocolitis as well as the its effects on various skin diseases such as Atopic dermatitis, Psoriasis, Acne, Rosacea along with some miscellaneous effects Hypercholesteremia, wounds, urogenital tract infections, etc.

Keywords: Probiotics, Therapeutic effects

INTRODUCTION

Probiotics meaning ‘fit for life’ are live microorganisms that have numerous health benefits on the lives of humans and animals. According to FAO and WHO probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”. Adequate doses of probiotics can contribute to the betterment of gut micro flora. These are known to be the exact opposite of antibiotics since one microorganism can stimulate the growth of another. *Lactobacillus* and *Bifidobacterium* are the most commonly used strains for Probiotics. However further studies have proved that strains of *Bacillus*, *Pediococcus* and some yeasts are potential candidates [1, 2]. Viable and stable strains are used. Bacteria that are generally not found in the intestinal tract are also classified as probiotics. These strains do not populate the intestinal tract. *Lactobacillus bulgaricus*, *Streptococcus thermophilus*, and *Leuconostoc* and *Lactococcus* species belongs to this category and are used as starters in dairy products [3]. Both fermented dairy and non- dairy products accommodate a wide range of Probiotics. Some probiotic strains are proteolytic and grow well in milk, while some need stimulants to grow. Presence of probiotics in dairy products has contributed to an increase in its market value. The emergence of fermented dairy products was mentioned in the bible as well as in the sacred hindu books. Nobel Prize winner Elie Mechnikoff is considered as the grandfather of modern probiotics. He

theorized that, the enhanced health and delayed senility in the population of Bulgarian peasants is due to the regular intake of fermented dairy products, yoghurt being an example [4]. Lilly and Stillwell coined the term probiotics in the year 1965 to describe the 'substances secreted by one micro-organism that stimulate the growth of another'. In 1974, Parker defined probiotics as 'organisms and substances which contributes to intestinal microbial balance' [5]. Marteau stated that probiotics are 'microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being. Salminen quoted that probiotics are 'food which contain live bacteria that are beneficial to health'.

Primary requirements for a probiotic to be effectual are listed below:

- When taken, the microorganisms contained must be live in sufficient number.
- The strains are to identify using appropriate studies before trying it on the host.
- A single strain cannot always be effective for multiple conditions.
- Should have resistance to low pH and acids.
- Despite the fact that some probiotics strains cannot colonize the gut, they must be able to persist in the intestine.
- Should adhere to the epithelium of the gut to overcome the flushing effect due to peristalsis.
- Probiotics should have the ability so that it can influence the local metabolic activity.
- Probiotics must show resistance to processing.
- Must be non-pathogenic.
- The microorganisms used must be Generally Recognized as Safe [6, 7].

PROBIOTICS FOR GASTROINTESTINAL AILMENTS

Since most of the microbial fermented dairy products are rich in Lactic acid bacteria (LAB), they have been used as medication for various ailments such as gastrointestinal diseases, liver diseases, arthrosclerosis etc. The common characteristic of LAB which makes it effective as a remedy for these ailments include anaerobic digestion of saccharides, production of lactic acid, resistance to low pH and wide range of temperature. The common disorder related to gastrointestinal area is diarrhea.

Diarrhea

Diarrhea is characterized by loose, watery stools (Bowel movement) occurring three or more times in a row in a period of 24 hours. It can also be accompanied by dehydration, vomiting, nausea, abdominal pain, and fever. It could be either due to bacteria, parasite or virus. The impact of diarrhea can vary with different person. Improving the nutritional status has a key role in decreasing the burden of diarrheal disease. Curative effect of probiotics is finding prevalence through recent studies. Single strain or mixed culture of *Lactobacillus reuteri*, *L.rhamnosus GG*, *L.casei*, *L.acidophilus*, *Escherichia coli strain* and strains of Bifidobacteria and enterococci and probiotics yeast *saccharomyces boulardii* are found to be preventive as well as curative against various etiologies of diarrhea.

Acute Infectious Diarrhea

Acute infectious diarrhea is defined as a loss of stool consistency, with pasty or liquid stools, and/or an increase in stool frequency to more than three stools in 24 hours, with or without fever or vomiting [8]. Diarrhea usually lasts less than 7 days; if it lasts longer than 14 days, it is called protracted diarrhea [10]. The effect of probiotics on acute infectious diarrhea showed a significant decrease in the symptoms. In a study performed in France and Lebanon (2010), administering probiotics through milk showed a

decreased rate of diarrheal symptom accompanied with an increase in weight. In Brazil, 186 children between the age group (6-48 months) were hospitalized for acute diarrhea. Supplementation of probiotics *Saccharomyces boulardii* reduced the duration of symptoms and was seen to shorten the duration of diarrhea. However, it was found that the probiotics was effective only if it was administered within 72 hours from onset period [10]. Other studies indicated that probiotic supplemented to Rotavirus positive patients had more beneficial effects. Two probiotics *Lactobacillus rhamnosus* 19070 and *L.reuteri* DSM 12246 reduced the symptoms concerned with acute diarrhea in hospitalized children [11]. A systematic review of randomized controlled trials revealed a 14% reduction in diarrhea duration among those who received probiotics compared to those who received placebo. Recovery time was reduced in treatment group when compared with placebo group (49.03 hours v/s 73.03 hours) [12]. A clinical trial, carried out in three hospitals in Jakarta, where most of the candidates were females, showed that the probiotics supplementation appears to be a therapeutic agent for the effective treatment of acute diarrhea [13]. A randomized control trials were carried out in children aged between 3-36 months. Probiotics were prescribed for 5 days and orally administered in 20ml water. The primary outcome showed a reduction in total duration of diarrhea of which the children who received *Lactobacillus rhamnosus* GG had a much more significant reduction [14].

Traveller's Diarrhea

The classic definition of traveler's diarrhea is three or more unformed stools in 24 hours with at least one of the following symptoms: fever, nausea, vomiting, abdominal cramps, tenesmus, or bloody stools. Milder forms can present with fewer than three stools (e.g., an abrupt bout of watery diarrhea with abdominal cramps). Though it is not life threatening, it can hinder the day to day activities and can interrupt a normal life. *E. coli* such as enteroaggregative *E. coli* have been recognized as common causes of traveler's diarrhea (80% caused by *Escherichia coli*) [10]. Other organisms include shigellae and salmonellae along with campylobacter species and protozoa [15]. Traditional medication for traveler's diarrhea includes bismuth subsalicylate and prophylactic antibiotics. A study by McFarald showed the effect of probiotics against travelers' diarrhea using *Saccharomyces Boulardii* [10]. In 2 placebo-controlled studies using *Lactobacillus rhamnosus* GG as prophylaxis a reduction in duration of diarrhea was noted in tourists travelling to Turkey and in second study similar results were found in tourists travelling to Mexico when administered with *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*. However, not all probiotics are effective. *L.fermentum* did not bring the expected result. An experiment using for different species of lactobacillus involving *L.casei*, *L.fermentum*, *L.rhamnosus* and *L.acidophilus* demonstrated inhibition against pathogenic microorganisms. It also showed that live cultures of probiotics had a significant role in inhibiting Enterotoxigenic *Escherichia coli* (ETEC) and enterohaemorrhagic *Escherichia coli* (EHEC) which are a major food and water borne pathogens [16, 17]. However, due to lack of experimental research, probiotics are not medically recommended for traveler's diarrhea.

Antibiotic Associated Diarrhea

Antibiotic associated diarrhea results from disruption of the normal microflora of the gut by antibiotics. This micro flora, composed of 10^{11} bacteria per gram of intestinal content, forms a stable ecosystem that permits the elimination of exogenous organisms. Antibiotics disturb the composition and the function of this flora and enable overgrowth of micro-organisms that induce diarrhea. AAD affects the electrolyte

balance and the complications include dehydration, pseudo membrane colitis and toxic megacolon. *Clostridium difficile* has emerged as one of the most potent enteropathogen for antibiotic associated diarrhea. Extreme cases of antibiotic associated diarrhea can result in pseudo membranous enterocolitis which is also caused by *Clostridium difficile* [18]. Restoring the gut micro biome has shown significant result in reducing the symptoms of AAD. A study by Hickson et.al showed patients undergoing antibiotic therapy had a lower risk of getting AAD when they were administered with 100g of activated yoghurt. The most effective organisms were found to be *S.boulevardii*, *Lactobacillus GG*, and other probiotics mixture [10]. The effect of lactobacillus GG in preventing AAD was demonstrated through two clinical trials in adults. Asymptomatic *Helicobacter pylorii* infected patients when given a ripple therapy along with a probiotics strain showed a significant reduction in the occurrence of diarrhea, nausea and taste disturbances. *Lactobacillus rhamnosus GG* increases the number of cells that secrete immunoglobulin A and stimulates the local release of interferon. Three different randomized placebo controlled studies demonstrated a decrease in the risk of AAD in participants administered with *Saccharomyces Boulardii* [19].

Inflammatory Bowel Syndrome

Irritable bowel syndrome (IBS) is a complex, functional gastrointestinal disorder characterized by chronic abdominal pain or discomfort and altered bowel habits. The common symptoms include abdominal pain, stool pattern alterations, bloating, straining, etc. Ulcerative colitis and Chron's disease comes under the category of IBS [10]. The types of IBS according to Rome III criteria are diarrhea predominant IBS, constipation predominant IBS, alternating diarrhea IBS and undefined IBS [20]. IBS affects some 12% of the global population and has a significant disease burden in terms of increased absenteeism from school or work and reduced health-related quality of life. The major cause for IBS is said to be impaired intestinal micro flora. Lactobacillus and Bifidobacterium has shown its action in the conjugation of bile acids. Administering IBS patients with *B.infantis* has shown to improve the symptom profile of patients as well as alters the gut flora [21]. Recent clinical trials have confirmed the efficacy of probiotics in eliminating these gastrointestinal symptoms. Several trials of probiotics on IBS have shown *Lactobacillus plantarum 299v* to be the main organism [22]. A study was conducted in 36 patients diagnosed with IBS-D by supplementing them with probiotics *B.coagulancemcc 5856* for 90 days showed a significant improvement with the symptoms concerned with IBS. In another study administering probiotics such as *B.animalis*, *L.acidophilus*, *L.delbreukii* and *S.thermophilus* for a four week period in 108 participants showed a significant improvement in abdominal pain. VSL# 3, consisting of *L.casei*, *L.plantarum* and *L.streptococussalivarius subspecies thermophilus* is usually used a medication for IBS [23]. Various clinical trials show that probiotics are highly beneficial and effective against Irritable bowel syndrome.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is the most common inflammatory gastrointestinal disease largely affecting the preterm infants. It is generally is initiated during external feeding. Factors affecting necrotizing enterocolitis include prematurity, external feeding, bacterial colonization, etc [24]. Necrotizing enterocolitis is characterized by various other factors such as intestinal ischemia, substrate in the gut's lumen and bacterial colonization [25]. Complications of NE include abdominal distension, bilious vomiting, bloody diarrhea, lethargy, apnoea and bradycardia. It is reported that 10-25% of pre

term infants are admitted to neonatal intensive care unit (NICU) and might affect 1/3 to 1/2 of all low birth weight infants. Several clinical trials have depicted the preventive action of probiotics supplementation against NE. Probiotics acts by enhancing the epithelial barrier function, competing with the pathogens in gut and through direct anti-inflammatory effects on epithelial signalling pathways. Probiotics also acts by the modulating the enterocyte genes that regulates the innate immune mediated inflammation in infants. A study by Mohan and his co-workers showed that preterm infants supplemented with probiotics had lower counts of pathogenic species, such as Enterobacteriaceae and Clostridium spp compared to the control group. Furthermore, with *L. rhamonosus* GG administration, Manzoni and his team demonstrated decreased stool colonization with *Candida* in treated preterm infants compared with controls. Hoyos administered the probiotics *Lactobacillus acidophilus* and *Bifidobacterium brevis* to newborns in neonatal intensive care unit in Columbia. It showed a decrease in incidence of necrotizing enterocolitis in treated compared to control group (2.9% vs 6.6%) [26]. A clinical trial performed in Israel demonstrated a decreased incidence of necrotizing enterocolitis in preterm infants administered with *Bifidobacterium infantis*, *Streptococcus thermophilus* and *Bifidobacterium bifidus* [27]. A randomized blind study in Taiwan showed a decrease in NE when supplemented with probiotics [25, 28]. The combination of *Lactobacillus acidophilus* and *Bifidobacterium infantis* has clinically proven to prevent necrotizing enterocolitis. Though several data and studies prove the preventive effect of probiotics against NE, FDA prohibits the standard administration of whole bacteria to neonates without the approval of Institutional Review Board (IRB) [29].

EFFECT OF PROBIOTICS ON SKIN DISEASES

The relation between the gut micro biome and its effect on skin is being extensively studied. Gut microbiome refers to the set of microorganisms that live on or inside the organism. The skin performs various functions such as temperature regulation, protection, water retention etc. It also acts as an immunogenic organ and a biosensor in all organisms [30]. The gut micro biome affects skin homeostasis through its influence on the signaling pathways that coordinate epidermal differentiation. The relationship between gut and skin was also proposed by John H Stokes and Donald M Pillsbury in 1930 in a theory known as Gut –Brain-Skin theory which suggests that gastrointestinal regulation mediates the influence of emotional and nervous states on the skin [31]. Even in the earlier days, probiotics was known to reduce ageing by restoring the gut micro flora with good bacteria and eliminate toxic biochemicals produced by proteases such as *Clostridium* species. In a study supplementing middle aged women with *L.lactis* H61 for 8 weeks showed improvement on skin elasticity and body characteristics. Administering *L.plantarum* HY7714 in women aged between 41-59 years had an overall improvement in skin moisture, decreased wrinkles, improved skin gloss, increased melanin and decrease in trans epidermal water loss [32]. Probiotics as new tools for skin disorder management is a need of the hour.

Atopic Dermatitis

Atopic dermatitis or eczema is a skin disease characterized by compromised skin barrier integrity, heightened inflammatory response against stimulants and diminished antimicrobial responses [33]. Even now, AD is considered to be an economic and social burden. Eczema, being relapsing is known to affect approximately 20% of children in both developed and developing countries. It is distinguished by dry skin, intractable pruritis and current relapses [34]. It is caused by the deficiency of structural protein

filaggen and is contributed by genetics and pre/post natal environmental factors [35]. It is seen that early life supplementation in children reduces the risk of developing AD. AD is a precursor for the evolution of a chain of hypersensitivity reactions which includes asthma, food allergies, allergic rhinitis, etc. Specific probiotic microorganism, especially *Lactobacillus* (being predominant during birth) has preventive role on AD [35]. In a study a mixture of *L.rhamnosus* and *L.reuteri*, when administered improved the severity of eczema by 56%. Infants at high risk of getting atopic dermatitis when administered a mix of probiotics (during pregnancy and after birth) showed a reduction in intense eczema [32]. *Bifidobacterium brevis* M-16V and *Bifidobacterium longum* BB536 when given 1 month prenatally, 6 months infancy and follow up of 18 months lowered the incidence of AD than placebo controlled groups [33]. Probiotics has shown to reduce Th2 cytokines responsible for induction of IgE activation of eosinophiles, increases production of interleukin-10 serum (IL 10) and transforming growth factor (TGFβ). A Finnish group headed by Isolauri in the year 1997 was the first ones to show the significant reduction in SCORAD (SCORing Atopic Dermatitis, a clinical tool used to assess the extent and severity of eczema) in probiotics group compared to placebo group. After a period of 4 years, the group showed a positive outcome in prevention of AD [34]. However, few studies have proven that probiotics are ineffective against the controlling of AD or only moderately effective against atopic dermatitis as well as IgE associated atopic dermatitis in infants [36].

Psoriasis

Psoriasis is an immune mediated inflammatory skin disease caused by the hyper proliferation of keratinocytes with keratinocyte hyperplasia [35]. Psoriasis is often associated with gut dysbiosis or Inflammatory Bowel Disease (IBD) (7-11%) [30]. The reduction in bacterial diversity of gut found in most of the psoriatic patients resembles the pattern of dysbiosis observed in the case of IBD. The characteristic morphological features of psoriasis include well demarcated, erythematous, scaly and painful skin plaques [30]. The degree and clinical activity of psoriasis is examined using Psoriasis Area Surface Index (PASI) [37]. The application of oral probiotics in management of the disease was studied through 3 trials and it showed a significant improvement [35]. In another study, administering *Lactobacillus pentosus* GMNL-77 in imiquimod induced psoriasis mouse model showed less erythema, scaling and epidermal thickening [38]. In a study performed by Groeger David and his coworkers in the year 2013 demonstrated the advantageous and beneficial use of the probiotics *Bifidobacterium infantis* 35624 against psoriatic arthritis in patients who were not administered anti- psoriatic drugs [39]. However, enough experimental records for the action of probiotics on psoriasis are absent.

Acne

Acne (Acne vulgaris) is a chronic inflammatory disease affecting face, chest, arms and back, seen mainly in adolescents although it has been reported in adult population too [40]. It is mainly caused by excess sebum production hyper proliferation of cutibacterium acne hyperkeratinisation of pilosebaceous follicles and other inflammatory mechanisms [41]. Cutibacterium acne has been found to be most common form and is caused by *Staphylococcus aureus* and *S.epidermis*. Acne formation is dependent on several factors such as increased sebum production, abnormal keratinisation of sebaceous canal Propionibacterium acne colonization, etc. The first clinical trial to use probiotics against acne was done by Robert H. Silver in 1961 where 300 patients were supplemented with probiotics such as *L.bulgaricus*

and *L.acidophilus*. It showed an improvement in 80% of the subjects³¹. Probiotics have a two way mechanism in the preventive treatment of acne:

1. It alters the micro biota by preventing the growth of undesirable or opportunistic organisms and it inhibits cytokine interleukin-8 in epithelial cells.
2. Probiotics bind to the epidermal surface which results in the production of antimicrobial substances and increase the immunomodulators. Immunomodulators inhibits cytokine interleukin-8 in epithelial cells [42].

Probiotics also inhibits cutibacterium acne by the production of antibacterial proteins. The general medication for severe acne is the oral administration of isotretinoin [43]. *Lactobacillus salivaris* – LSO3 has shown to reduce total facial lesion count [44]. In a clinical trial carried out in 2016, 57 patients with acne, dermatitis and rosacea was administered with *E.coli Nissle*. It showed an improvement of 89% and reduced skin eruptions. Administration of Konjacglucomannanhydrolylates along with probiotics *L.casei*, *L.planterum* and *L.lactis* showed an inhibitory action towards cutibacterium acne [45]. In a randomized placebo controlled study 20 adults with acne vulgaris were administered with *L.rhamnosus* GG for a period of 12 weeks showed a significant improvement in acne [41]. In 2021 two studies using *Lactiplantibacillusplantarum* and *Weissellaviridescens* exhibited a positive effect against acne [44]. An invitro study showed the inhibitory effect of bacteriocin produced by Lactococcus species HY449 on pathogenic bacteria hence it is recommended to use as an antimicrobial in cosmetic formation [42]. The probiotics Bifidobacterium (*B.infantis* and *B.longum*) is known to produce vitamin B12 the deficiency of which causes skin acne [35]. The most common probiotics used for inhibiting cutibacterium acne are *B.subtilis* and *L.acidophilus*.

MISCELANEOUS EFFECTS

The gut micro biome has a pivotal role in maintaining human health and has its influence on several other organs apart from gastro intestinal tract. Dysbiosis, the compositional changes of the gut micro biome, contributes to various conditions such as obesity, diabetes and cancer [46]. Tumerogenesis of Gastro-intestinal cancer could be due to this compositional change. Various researches on probiotics as an anti-cancer agent proved its potential. The mechanism of action of probiotics against cancer involves antiproliferative action and proapoptotic effect and hence it can be used along with chemotherapy treatment. The pioneering study on the relationship between Lactobacillus and its effect on incidence of colorectal cancer was established by Goldin and Gosbach [47]. Lactic acid bacteria modify the gut flora, bind to the intestinal mutagens and repress the growth of those bacteria which transform procarcinogens to carcinogens [7].

Hypercholestrolemia is a medical condition caused by elevated levels low density lipoprotein (LDL) cholesterol compared to high density lipoprotein (HDL) cholesterol. It hardens and narrows blood vessels resulting in premature coronary artery disease. Supplementation of probiotics along with diet is a natural way to reduce blood cholesterol level. *Lactobacillus acidophilus* being the predominant probiotic in the intestine, is usually exploited for these. Yoghurt fermented with this microorganism along with *Bifidobacterium longum* increased the level of HDL thus maintaining the serum cholesterol level. Two controlled clinical studies performed by Anderson and Gilil and demonstrated a reduction in serum cholesterol on consumption of yoghurt on a daily basis. Another study showed that the cholesterol reducing effect of *L.plantarum*CK 102 can be used as an additive for health assistance food. A randomized cross over trial involving 54 participants showed a reduction serum cholesterol (5-10%)

after consumption of yoghurt fermented with *Lactobacillus bulgaricus* and *Streptococcus thermophiles* [48, 49].

Rosacea is a chronic inflammatory skin disease characterized by erythema and telangiectasia on face. This is often associated with IBD. In a case study, a patient administered with doxycycline along with probiotics had significant result in the management of the disease which could be a potential hint on the ability of probiotics to act as a remedy [35]. Probiotics are also used for healing wounds and surgical infections. A study demonstrated an improvement in healing process of burnt wound with *Saccharomyces cerevisiae*. Some probiotics such as *L.acidophilus* and *L.casei* has shown antibacterial property against methicillin resistant *Staphylococcus aureus* which has the ability to infect wounds [32]. *S.aureis* is also inhibited by *L.fermentum* RC 14 by preventing its adherence to surgical implants. Probiotics are also known to decontaminate the intestine preceding gut surgery [7, 32].

Lactobacillus GG (ATCC 53103) and *Lactobacillus rhamnosus* GR1 colonize and protects the urogenital tract against infections. Probiotics also nreduce bacterial vaginosis and thus reduces the infant mortality rate as well as pre-term labor in pregnant women. Lactobacilli reduce the vaginal microflora and show a positive result against the transmission of AIDS and STDs. However enough evidences are not yet available [7].

CONCLUSION

Probiotics, live microorganisms, are finding its place as a potential medication for various illnesses. These organisms restore the intestinal micro biota and prevent the proliferation of pathogenic bacteria. The therapeutic effect of probiotics on gastrointestinal ailments and skin disorders has been well established through innumerable clinical trials and studies. They not only influence the gastrointestinal tract but also have beneficial effects on other distal organs such as liver, kidney, pancreas, etc. The gut brain skin theory explains the relationship between the gut micro biome and skin and modifying these by the action probiotics brings about a favorable response to skin disorders. Lactobacillus and Bifidobacterium are the most common probiotics administered as supplements. Their supplementation is also ensured with the consumption of fermented dairy products. Probiotics improves the overall health of an individual and plays a pivotal role in preventing diseases like cancer, hypercholesterolemia, rosacea, etc. However there is still much more scope for research in the therapeutic effect of probiotics in various fields of health and medicine.

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