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RECENT TRENDS IN PROBIOTICS AND HEALTH MANAGEMENT: A REVIEW

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ABSTRACT: Probiotics are defined as "Live microorganisms" which when administered in sufficient amounts confer a health benefit to the host. They are consumed as microbial food supplements. The mechanism of action of probiotics is associated with their ability to enhance immune response, compete with pathogenic microbes for adhesion sites, to antagonize these pathogens and production of antimicrobial substances. Immunomodulatory effect of probiotics can be explained by molecular and proteomic studies. Health benefits of probiotics includes prevention and treatment of various health conditions and diseases such as gastrointestinal disorders, lactose intolerance, irritable bowel syndrome, inflammatory bowel disease, Necrotising colitis, allergies, urogenital infections, various cancers, Arthritis, AIDS, Upper respiratory infections, oral health such as prevention of dental caries, periodontal diseases and haliotis as well as many other effects which are under exploration. The result of several clinical investigations proposes that probiotics may exert beneficial effect in preventing and treating various diseases to manage human health. Though, many of this clinical research needed validation to provide results for clinical regime. This review illustrates the health benefits of probiotics in various diseases and their possible mechanism and also highlights current challenges for future studies.

INTRODUCTION: Probioticsare microorganisms that contribute some form of health benefit to the host. They can be found in a variety of different foods. They are considered to be "live microorganisms which when administered in adequate amounts confer a health benefit on the host", according to the World Health Organization [1], the successful growth of probiotic bacteria depends on indigestible carbohydrates that are available in thousands of diverse plants and fruits.

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Collectively the nutrients that probiotics require for "survival" are called prebiotics. The term synbiotic is used for the combination of probiotics and prebiotics [2]. Probiotics are usually consumed in the form of fermented foods with active live cultures such as yogurt. The most commonly used bacterial genera in probiotic food are *Lactobacillus* and *Bifidobacterium.*

Probiotics are believed to play very important roles in regulating correct intestinal function and digestion by balancing intestinal microflora. Probiotics act through diverse microflora. Probiotics act through diverse mechanisms that affect the microbiota [3, 4]. Molecular mechanism facilitates to identify immunomodulation property of probiotics. Traditionally, probiotics considered to be related with gut health.

However, during the last decade, a rising number of established and proposed beneficial health effects of probiotic bacteria have been reported, including treatment or prevention of urogenital, oral and respiratory tract infections, and prevention or alleviation of allergies, regulation of brain function, atopic disease in infants and prevention of skin infection. These benefits further tend to increase with the development of more advanced research methods utilized in studying the microbe-host interactions [5]. The literature on the health benefits of probiotics has often focused on disease states using either animal models of such diseases or studies in human populations by clinical trial [6]. The present review summarizes the preventive and therapeutic effects of probiotics in various health condition and disease.

Histroy of Probiotics: The term 'probiotic' was derived from the Greek word meaning "for life". This term was first used by Lilly and Stillwell in 1965, for describing substances secreted by one organism which stimulate the growth of another [7]. The first scientific assessments of probiotics were made in 1908, based on the work of the Russian Nobel Prize Laureate Elie Metchnikoff. He first hypothesized that a high concentration of lactobacilli in intestinal flora were significant for health and longevity in Bulgarian population. In addition he contributed to the adoption of the name of the species, lactobacillus bulgaricus, one of the two essential yoghurt starter microorganisms. This made the birth of modern dairy industry [8]. Metchnikoff proposed that regular consumption of fermented milk would repopulate the intestine with beneficial lactic-acid bacteria and the products from the probiotic organisms able to decrease the intestinal pH and subsequently suppress the growth of harmful bacteria.

Microorganism with Function as Probiotics: Some of the most significant representatives are listed in **Table 1.** According to mode of nutrition Lactic acid bacteria are significant and among them the ones with the most important properties in an applied perspective are those belonging to the genera *Lactobacillus* and *Bifidobacterium* [9].

TABLE 1: ADAPTED FROM HOLZAPFEL *ET AL* [9]

Microorganisms considered as probiotics	
Lactobacillus species	*Bifidobacterium* species
L. acidophilus *L. casei* *L. crispatus* *L. gallinarum*[1] *L. gasseri* *L. johnsonii* *L. paracasei* *L. plantarum* *L. reuteri* *L. rhamnosus*	*B. adolescentis* *B. animalis*[2] *B. bifidum* *B. breve* *B. infantis* *B. lactis* *B. longum*
Other lactic acid bacteria	**Nonlactic acid bacteria**
Enterococcus faecalis[1] *E. faecium* *Lactococcus lactis*[3] *Leuconostoc mesenteroides* *Pediococcus acidilactici*[3] *Sporolactobacillus inulinus*[1] *Streptococcus thermophillus*[3]	*Bacillus cereus* [1] *Escherichia coli strain nissle* *Propionibacterium freudenreichii* *Saccharomyces cerevisiae* *S. boulardii*

[1]Mostly used for animals. [2]Recently reclassified as *B. animalis* subsp. Lactis [10]. [3]Little is known about probiotic properties.

How Probiotics Acts? Probiotics have various mechanisms of action although the exact manner in which they exert their effects is still not fully elucidated. In vitro and animal studies revealed some of the properties and modes of action of these beneficial micro-organisms. The mechanism of action of probiotic microorganisms can be elucidated by promotion of digestion and uptake of dietary nutrients, strengthening of intestinal barrier function, modulation of the innate and acquired immune response of the host, production of antimicrobial substances and competition with pathogens for binding sites [11]. In addition probiotics show adhesion and colonization of the different sites of human body which may increase their retention time thus provides prolonged probiotic activity [12].

Immunomodulation has been the topic of several studies and there is significant evidence that probiotics influence many aspects of the acquired and innate immune response by inducing phagocytosis and IgA secretion, modifying T-cell responses, enhancing Th1 responses, and attenuating Th2 responses [13]. Further Probiotics may modulate the host's non-specific and specific immune response by products like metabolites, cell wall components and DNA. Sometimes probiotics may increase intestinal mucin production [14]. They may modify the structure of potentially harmful antigens and thereby alter the mode of their immunogenicity [15].

The another important mechanism of probiotics action is production of substances that inhibit pathogens – low-molecular-weight substances, low- and high-molecular-weight bacteriocins, antibiotics and microcins [16]. Furthermore, these good bacteria exert direct, mechanical effects on pathogens. These mechanical properties allow them to antagonize and to compete with pathogens for binding sites, adhesion, nutrients and space, without influencing the metabolism neither of the host, nor of the pathogen [17]. Lactic Acid Bacteria (LAB) produce a variety of substances that exhibit antagonistic activity against other bacteria [18, 19]. Probiotic action may direct at the host, the pathogen or both.

The properties and modes of action vary among probiotic strains. In addition, the mechanical properties are as well location specific. Thus, a single probiotic cannot be a cure for all diseases. This explores the importance of choosing the suitable strain for a given condition [20].

Molecular Mechanism of Probiotics: Beneficial health effects and clinical application of probiotics evidenced by numerous studies but the molecular basis of their action is still under question. In vitro and in vivo studies supported the proteomics in past few years. Proteomics analysis chiefly applied to the investigation of the immunomodulatory mechanisms mediated by extra-cellular proteins. Six proteins with potential immnunogenic characteristics were recognized in the extracellular proteome of B. *animalis* BB12.

p40 and p75 protiens were identified in *Lactobacillus GG* which are able to stimulate the activation of Akt (protein kinase B protein family) in intestinal epithelial cells and to inhibit intestinal epithelial cells apoptosis induced by TNF [21, 22]. Immunomodulatory function of moonlighting proteins EF-Tu and GroEL of L. johnsonii NCC533 revealed by proteomics studies they are able to stimulate IL-8 secretion in macrophages and HT29 cells in CD14-dependent proinflammatory response [23]. The metabolic approach to understand the probiotic ability to reduce serum cholesterol levels in humans is still unclear [24].

Recently proteomic and genetic studies exposed catabolite control protein A (CcpA) might be a novel factor involved in the *L. acidophilus* A4 ability to lower serum cholesterol which mainly affecting the expression level of membrane associated proteins. The development of new molecular techniques and design of prteomic studies will be paramount to open novel perspectives in this area [25].

Health Benefits of Probiotics: There is emerging evidence in favour of the claims of beneficial effects exerted by probiotics, includes enhancement of the immune response, prevention and treatment of gastrointestinal disorders such as antibiotic associated-diarrhoea, inflammatory bowel diseases,

irritable bowel syndrome, neonatal necrotizing enterocolitis and so on, as well as allergies, intolerances, reduction of cholesterol levels and lowering of blood pressure **(Fig. 1).** These health properties are strain specific and are influenced by the various mechanisms mentioned above. While a few of the health benefits are well known others require further studies in order to be established.

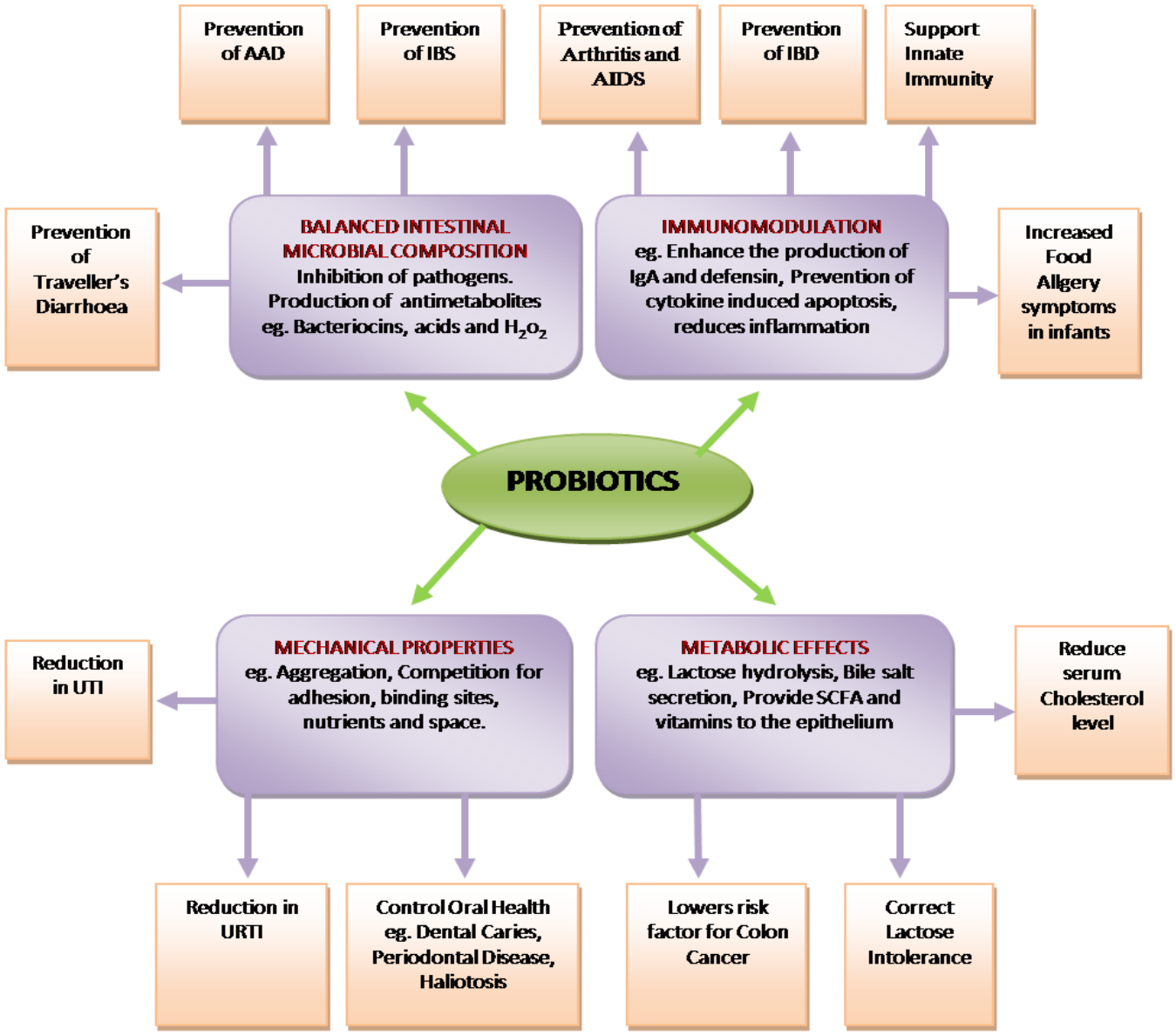

FIG. 1 HEALTH BENEFITS OF PROBIOTICS AND THEIR PROPOSED MECHANISMS.

AAD-Antibiotic associated diarrhoea, IBS-Irritable bowel syndrome, IBD- Inflammatory bowel disease, UTI-Urinary Tract Infection, URTI- Upper respiratory tract infection , AIDS-Acquired Immuno Deficiency Syndrome

Prevention of Various Types of Diarrhoea: Numerous studies have reported efficiency of probiotics in prevention and treatment of various diarrhoeal diseases, principally in traveller's diarrhoea, antibiotic induced diarrhoea, Radiation induced diarrhoea, *Clostridium difficle* infection and diarrhoeal diseases in young children caused by rotavirus.

Infectious Diarrhoea Prevention and treatment of infectious diarrhoea are probably the most extensively accepted health benefits of probiotic microorganisms. Probiotic supplementation of infant formulas has been intended both at the prevention of rotaviral infections and the cure of established disease.

Well-controlled clinical studies have revealed that probiotics such as *L. rhamnosus* GG, *L. casei* Shirota, *L. reuteri,* and *B. animalis* Bb12 can shorten the period of acute rotavirus diarrhoea with the immense data pointing to the efficiency of *L. rhamnosus* GG and *B. animalis* Bb12 [26]. The proposed mechanisms behind this effectiveness include competitive blockage of receptor site signals which regulates secretory and motility defences, enhancement of the immune response, and production of substances that directly inactivate the viral particles. Probiotics increases IgA level and other immunoglobulins secreted cells in the intestinal mucosa and stimulate local discharge of interferons. It facilitates antigen transfer to principal lymphoid cells, which serves to enhance antigen uptake in Peyer's patches [27].

Antibiotic-Associated Diarrhoea The most common side effects of antibiotic therapy are mild or severe case of diarrhoea because the normal microflora tends to be suppressed, encouraging the overgrowth of opportunistic or pathogenic strains. Treatment consists of removal of the underlying antibiotic agent, correction of the electrolyte disorders, and in severe cases remedy with metronidazole or vancomycin. Several studies that have been carried out proposed that probiotic (*L. Rhamnosus L. casei,* and *S. Boulardii)* use is linked with a reduced risk of antibiotic-associated diarrhoea [28]. Matters for prospect research include the optimal dose of the probiotic preparation and the comparative efficiency of several probiotic interventions [29].

Lactose Intolerance: Lactose intolerance is a genetically characterized beta-galactosidase deficiency resulting in the failure to hydrolyse lactose into the monosaccharides glucose and galactose. Lactose intolerant persons develop diarrhoea, abdominal discomfort, and flatulence after consumption of milk or milk products. Even though conventional yoghurt preparations, with *S. thermophilus* and *L. delbrueckii* ssp. *Bulgaricus,* are even more effective in this course, somewhat due to higher beta-galactosidase activity, correction of lactose metabolism. It's a known health benefit of probiotics which include specific strains more than others and in definate concentrations. Moreover some individuals have shown positive result to probiotic supplementation hence, medical practitioner should consider it as a therapeutic alternative [30].

Irritable Bowel Syndrome: IBS is the most common intestinal disorders in industrialised and developing countries which cause major healthcare expenses [31]. Presently IBS is distinct by symptom criteria, which comprise chronic recurring episodes of abdominal pain and discomfort related with altered bowel habits in the absence of organic malady [32]. Many studies reported that intestinal microbiota and probiotics influence enteric nervous system and brain signalling. Few beneficial effects of probiotics on visceral nociceptive reflexes in rodents have also been reported [33, 34]. An increasing number of meta-analyses differ in their conclusions on the efficiency of probiotics against IBS, because of insufficient sample size, poor study design and use of several probiotic strains in the reviewed studies [35, 36].

Inflammatory Bowel Disease: Probiotics shows promising approach to prevent chronic inflammatory bowel disease because of their immunomodulatory and bowel flora correcting properties but the beneficial effect of probiotics on IBD have yet to reach the high expectations predicted by mechanistic and animal studies, particularly for Crohn's disease [37, 38]. Use of probiotics in combination with prebiotics shows an alternative approach to prevent IBD in many studies. For example, prebiotics such as inulin or fructose oligosaccharides enhance luminal numbers of *Bifidobacterium* species and concentrations of protective short-chain fatty acids, which are significant metabolic substrates for colonic epithelial cells [39, 40]. Further studies are needed to assess the accurate place of probiotics within a treatment regimen for inflammatory bowel disease.

Necrotising Enterocolitis: Probiotics have been reported to prevent NEC in infants [41]. The microbiota of infants with NEC vary from other low-birth-weight infants, [42] currently, NEC is related with 30% mortality. The immature intestine of preterm infants is particularly prone to inflammation and loss of epithelial integrity [43].

Probiotics have potential to interfere with this progression; they have been tested clinically for NEC. Various meta-analyses of probiotic studies with strains of *Bifidobacterium, Lactobacillus, Saccharomyces* and/or *S thermophilus* to prevent NEC show reduction in the occurrence and reduction in overall mortality [44]. Probiotics have potential role to prevent NEC which have been tested clinically.

Probiotics and Arthritis: Several studies have been conducted to assess the role of probiotics in Rheumatoid arthritis. It is a chronic autoimmune disease which leads to harsh joints pain and associated with damage to both cartilage and bone. Probiotic (*L. casei*) have shown the influential preventive effect against the chronic inflammation and arthritis induced by collagen. *L. casei* exerts an anti-inflammatory effect against CIA model. This effect would be the result of COX-2 and NF-κB inactivation which are the potent mediators liable for inflammatory reactions related with rheumatoid arthritis.

Some more studies needed in this direction for the evaluation of cyclooxgenase inhibition by using *Lactobacillus* species either alone or in combination to reveal the reason behind the antiarthritic property of *Lactobacillus* species [45]. In another study Probiotics (*L. casei* and *L. Acidophilus)* were found to suppress the first stage of carrageenan-induced paw edema, which confirmed its NSAID-like property. *L. Casei* and *L. acidophilus* significantly reduce the inflammatory reactions induced by carrageenan [46]. Further more studies are require to obtain exact role of probiotics in prevention of Arthritis.

Probiotics and Urinary Tract Infection (UTIs): Studies have shown the protective role of probiotics in Urinary tract infection (UTI). About 50–60% of women probably come across with UTI in their lifetime [47]. Decrease in number of *Lactobacillus* increases the risk of UTI [48]. Poor colonization of vaginal flora causes imbalance which is responsible for bacterial vaginosis, *Candida* vaginitis, and other gynaecological infection [49]. Normal vaginal flora can be regain by administration of probiotics [50].

The desquamated vaginal epithelial cells liberate glycogen which provides nutrients to probiotics bacteria. These probiotics degrade glycogen and generate an acidic environment which limits the growth of pathogenic microorganism [51].

Application of probiotics through the urogenital tract has been investigated by Bastani *et al* [52] Moreover, both oral and vaginal administration of *Lactobacilli* may help in treatment of bacterial vaginosis.

Probiotics and Cancer: Several studies shows preventive effect of probiotics on colorectal cancer (CRC). It is one of the most common cancers worldwide. Many studies in rodents have yielded consistent, beneficial effects of probiotics on precancerous lesions and tumours [53]. The potential mechanisms includes alterations in microbiota species and metabolism, changes in colonic pH, enhanced immune responses, binding or inactivation of carcinogens, decreased colonic inflammation, reduced epithelial proliferation and increased apoptos [54].

Biomarker studies in humans explain that synbiotics lowered faecal-water-induced genotoxic damage and enhance transepithelial resistance [55]. An human study illustrate *L. casei* administration reduced the rate of recurrence of adenoma atypia [56]. Further research is needed in this direction.

Probiotics and AIDS: Health benefit of probiotics in management of AIDS reported by few studies. One study shows the relationship between probiotic consumption through yogurt and the gastrointestinal health of individuals with HIV. However HIV infection can upset the natural balance of healthy bacteria in the intestine, which can be restored by adding probiotics in diet [57].

Many evidences available that shows the probiotics may help in improving the health of individuals with HIV. The reason behind this event people with HIV tend to have reduced number of T cells, including CD4 cells, than healthy people. The probiotics may help in restoring CD4 counts so that the immune system is more prepared to battle against HIV associated infections.

Probiotics and Allergy: Allergic disorders and their factors such as birth delivery mode [58], antibiotic use in the newborn and infant, and non-breast-milk diets are linked with shifts in the intestinal microbiota [59]. Probiotics have been studied as possible dietary interventions to interrupt progression of eczema to rhinitis and rhinitis to asthma [60, 61]. Probiotics may provide safe alternative microbial stimulation and improve mucosal barrier function, considered to contribute in moderating allergic response. The role of gut microbiota in allergy is explained by observations of their quantitative and qualitative differences among children and infants suffering from allergies and healthy ones [62]. These probiotic effects seem to predominantly involve food allergy and atopic dermatitis. Furthermore *L. rhamnosus* GG and *B. lactis* shows preventive effect in the occurrence of atopic eczema in high risk infant [63].

Probiotics and Upper Respiratory Tract Infection (URTI): Various studies in both children and adults have indicated that probiotics may lower the frequency, duration and symptoms of upper respiratory tract infections (URTIs). In vitro and animal studies have revealed some of the mechanical properties and modes of action of the tested probiotics. addressing The effect of probiotics in URTIs and otitis assesd by clinical trials for example out of 21 clinical trials, four trials have reported no significant difference in the outcome measures between the probiotic and placebo groups [64, 65].

All the other trials reported a beneficial effect of the probiotic in URTI. Immunomodulation and mechnanical properties exerted by probiotics are responsible for pathogen inhibition. More clinical trials are needed to understand the strain and dose specificity of probiotics in prevention of URTI.

Oral Health:

Probiotics and Dental Caries Probiotics have a beneficial effect in limiting dental caries, because they are able to adhere to dental surfaces and integrate into the bacterial communities to produce the dental biofilm. Some probiotic bacteria capable to compete with and antagonize the cariogenic bacteria which prevent their proliferation. Comelli and colleagues investigated the 23 bacterial strains used in the dairy industry, *Streptococcus thermophilus* and *Lactobacillus lactis* ssp. *lactis* were the only ones with the ability to incorporate into a biofilm present on a hydroxyapatite surface and to interfere with development of the cariogenic species *Streptococcus sobrinus* [66].

Probiotics and Periodontal Diseases

Probiotic bacteria reported to favour periodontal health if they are able to integrate themselves in oral biofilm and inhibit pathogen growth and metabolism. Merely few clinical studies established to investigate probiotic effectiveness in periodontal disease [67, 68].

Probitics and Halitosis: Halitosis, or bad breath, is a situation affecting comparatively large segment of the population. It has been shown that bacteriotherapy can also recover this condition. Colonization of probiotic bacterial strains replaced the bacteria implicated in haliotis and they have prospective application as adjuncts for the prevention and treatment of halitosis [69].

Other Benefits: Several evidences suggested that food products containing probiotic bacteria probably contribute to coronary heart disease prevention by lowering serum cholesterol levels as well as to blood pressure control. The Proposed mechanisms comprise interference with cholesterol absorption from the intestine, direct cholesterol assimilation, and production of end fermentation products that influence the systemic levels of blood lipids and mediate an antihypertensive result. However, these probiotic effects are still an issue of debate as further research is recquired in long-term human studies.

CONCLUSION: Probiotic therapeutic approach made its way for several diseases. The evidence suggests adequate data about the prevention and treatment of certain conditions while simply emerging or even controversial when it comes to others. Molecular and Proteomic studies needed to describe the immunomodulatory and other properties of probiotic microorganism.

The best recognized effects include gastrointestinal disorders such as, antibiotic-associated diarrhoea, infectious diarrhoea, lactose intolerance, IBD, IBS, Upper respiratory infections and allergy, and emerging evidence required to understand potential role in various other conditions. Furthermore research, in the form of controlled human clinical studies, is essential to establish which probiotics and which dosages are related with the maximum effectiveness and for which patients, as well as to reveal their safety and limitations. The Present reviews summarize health benefits of probiotics and describe future perspectives for further research in this field.

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