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PROBIOTICS AND INFECTIOUS AGENTS

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ABSTRACT

A well known adverse effect of the use of antibiotics as growth promoters/ chemotherapeutics often used indiscriminately for controlling infections is the emergence of antibiotic resistance strains, referred to as 'superbugs'. Antibiotic resistance is of great concern for scientists and medical professionals across the globe, and accordingly WHO recommends the use of alternative methods in order to curb the further emergence of antibiotic resistance strains. One such alternative and promising emerging concept is that of 'probiotics'. Probiotics have been found to have protective effects on infectious agents like *Salmonella*, *E. coli*, *Shigella*, *Klebsiella*, *Proteus* and many others in various *in vitro* and *in vivo* studies which have been reviewed in this article.

KEYWORDS

Probiotic, *Lactobacillus*, *Saccharomyces*, *Salmonella*, *E. coli*.

INTRODUCTION

A continuous search for newer methods of combating bacterial infections has attracted the attention of the scientists worldwide; particularly due to an increased frequency of opportunistic infections in immunocompromised patients, and the emergence of new types of pathogens often with increased antibacterial resistance. The need for the same is being strained on us by the long intervals in the development of new antibacterial agents. Moreover, it is well established that antibacterial agents disturb normal human flora, which may further reduce our defence mechanisms against infection. Although, the antibacterial agents are still in the process of development but they may not solve current problems related to resistance, which is at present "a major public health problem in both developed and developing countries throughout the world" and has been the focus of discussion at a The World Health Organization (WHO) conference[1]. Keeping this in view, the WHO recommends global programs to trim down the use of antibiotics with amplified efforts to prevent' diseases through the development of novel, more efficient and secure therapies. Accordingly, bacteriotherapy *i.e.* the use of harmless bacteria for the displacement of pathogenic organisms may serve as an alternative and promising way[2].The microorganisms used to achieve this goal are called probiotics.

Probiotics are live microorganisms which when administered in appropriate doses result in significant beneficial effects on health of human beings and animals which have been well documented through an array of scientific research and include prevention or treatment of disorders associated with the gastrointestinal tract (mainly diarrhoea caused by certain pathogenic bacteria and viruses, inflammatory diseases, bowel syndromes and constipation); cardiovascular diseases, urogenital tract disorders (bacterial vaginosis, yeast vaginitis and urinary tract infections) and cancer besides providing improvement of hypertension, immunomodulation, cholesterol lowering and anti-allergic effects amongst many others. Also, the increase in productive parameters like growth rate and feed conversion ratio in animals are the other favourable effects[3].

HISTORY IN BRIEF

The word 'probiotic' originated from the Greek word ('*pro bios*' which means 'for life'). This apparently new term has references in the Holy Bible and the sacred books of Hinduism and their usage was in vogue since the early days of human civilization[4]. The term 'probiotic' was originally coined by Lilly and Stillwell in 1965 and its definition has progressively been changed from 'the substances secreted by one microorganism that stimulate the growth of another,[5] to the most recent one ‘live microorganisms which, when administered in adequate amounts, confer a health benefit on the host' as given by the Food and Agriculture Organization of the United Nations/World Health Organization[6] and approved by the International Scientific Association for Probiotics and Prebiotics[7].

Interestingly, the definitions have undergone continuous modifications like 'the organisms and substances which contribute to intestinal microbial balance'[8,9]; 'the food which contains live bacteria beneficial to health'[10]; 'microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being'[11], 'a live microbial feed supplement which beneficially affects the host animal by

improving its intestinal balance'[12], 'a viable mono or mixed culture of bacteria which, when applied to animal or man, beneficially affects the host by improving the properties of the indigenous flora'[13], 'live microorganisms, which when consumed in adequate amounts, confer a health effect on the host'[14] to reach the present day one.

By defining probiotics as 'microorganisms which, when ingested, may have a positive effect in the prevention and treatment of a specific pathologic condition' Charteris *et al.*[15] emphasised on the preventive or therapeutic properties of probiotics. Since probiotics have demonstrated effectiveness in the treatment of many gastrointestinal diseases[16] they can be considered to be therapeutic agents. These microorganisms contribute to intestinal microbial balance and play a role in maintaining health.

Timmerman *et al.*[16] defined the following three types of probiotic products used in the research: 1) Monostrain probiotics - containing one strain of a certain species; 2) Multistrain probiotics - containing more than one strain of the same species or closely related species (e.g. *Lactobacillus acidophilus* and *Lactobacillus casei)* and 3) Multispecies - containing strains of different probiotic species that belong to one or preferentially more genera (e.g. *L. acidophilus, Bifidobacterium longum, Enterococcus faecium* and *Lactococcus lactis).*

Although, the main probiotic clusters are *Lactobacillus* and *Bifidobacterium;* the probiotic potential of different strains of species, *viz. Streptococcus, Peptostreptococcus, Pediococcus, Lactococcus, Bacillus, Escherichia* and yeast *Saccharomyces* has also been reported.

There are a number of pathogens on which the antagonistic effects of probiotic studies, both *in vivo* and *in vitro*, have been carried out. Apart from enteric pathogens, the effects on the urogenital infectious agents have also been studied. In majority of these studies, the probiotics were having significant antagonistic effects on these pathogens. Nevertheless, no promising results have been observed. Moreover, there is a dearth of data related to the safe use of probiotics and their exact mechanisms of action due to which the studies to explore this field are needed to be conducted. In this article, we have reviewed the effects of probiotics exhibited on various pathogens in several *in vivo* and *in vitro* studies based on different experimental models.

ANTAGONISTIC EFFECTS ON PATHOGENS

Probiotics have been reported to possess inhibitory activity toward the growth of pathogenic bacteria such as *Escherichia coli, Listeria monocytogenes, Salmonella* spp., *Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp., *Staphylococcus, Candida* spp., *Shigella* spp., *Helicobacter* spp. and many others[17,18,19,20].

IN VITRO EXPERIMENTS

A number of experimental studies have been conducted *in vitro* using different assays like agar well diffusion method, disk diffusion method, multilayer inhibition assay, broth inhibition assays. Many cell lines have been used in order to elucidate the interactions of probiotics with various cells and pathogens like adhesiveness, competition for binding sites, inhibition of penetration by pathogens and to understand the mechanistics of probiotics.

Probiotic *Lactobacillus* strains, including *L. acidophilus* LB[21,22,23], *L. rhamnosus* GG[24,25,26,27], *L. casei* Shirota YIT9029[25,26,27] , *L. acidophilus* HN017[28], *L. rhamnosus* DR20[28], *L. gasseri* K7[29] and *L. johnsonii* La1[30] are capable of inhibiting the adhesion of enterovirulent pathogens to and/ or the cell entry into cultured human intestinal cells.

Fayol-Messaoudi *et al.*[31] reported that *L. plantarum* strain ACA-DC287 displayed in vitro killing activity against *Salmonella*, similar to that exhibited by the established probiotic strains *L. rhamnosus* GG, *L. casei* Shirota

YIT 9029 and *L. johnsonii* La1 and observed an ability of *L. plantarum* strain ACA-DC287 to inhibit the penetration of *Salmonella* Typhimurium (*S.* Typhimurium) SL1344 into cultured human intestinal Caco-2 / TC7 cells in competitive condition. An antagonistic activity against *S.* Typhimurium invading the cultured human enterocyte-like Caco-2 cells by a culture containing *L. casei* GG, which reportedly adheres to the Caco-2 cells in vitro. Two lactobacillus strains isolated from kefir, *L. acidophilus* CYC 10051 and *L. kefiranofaciens* CYC 10058 strains, adhered onto human enterocyte-like Caco-2 cells, reportedly developed antimicrobial activities against enteropathogenic bacteria and inhibited attachment of *S.* Typhimurium to Caco-2 cells[32].

Bifidobacteria too have been proved to exhibit inhibitory effects on many other pathogenic organisms. In another study, *Bifidobacterium* strains isolated from infant stools, *Bifidobacterium* spp. CA1 and F9, have been reported to inhibit the entry of *S.* Typhimurium into Caco-2 cells[33]. The inhibitory effect of *B. breve* and *B. infantis* strains isolated from human adult subjects, on the colonization of an intestinal cell monolayer by a variety of diarrhoea pathogens has reportedly demonstrated a marked and concentration dependent inhibition on the association between enterotoxigenic; enteropathogenic; diffusely adhering *E. coli* and *S.* Typhimurium strains; and enterocytic Caco-2 cells[34]. *In vitro*, *B. lactis* DR10 has been shown to inhibit the binding of *E. coli* O157:H7 to an intestinal cell monolayer and thereby reducing its invasiveness[28].

Various Lactobacillus strains including *L. rhamnosus*, *L. gasseri*, *L. casei* and *L. plantarum*, inhibit enterohemorrhagic *E. coli* infection in the human colon epithelial cell line, C2BBe1[35]. Moreover, strongly adherent *L. gasseri* bacteria were found to inhibit the attachment of *E. coli* O111 to intestinal Caco-2 cells under the condition of exclusion[36]. *L. rhamnosus* DR20 and *L. acidophilus* HNO17 strains reduced cell invasion by this enterovirulent strain and inhibited colonization of the intestinal cell monolayer by *E. coli* O157:H7[28]. *L. rhamnosus* has shown to be a promising probiotic in preventing the colonization of the gastrointestinal tract by pathogenic bacteria such as enteropathogenic *E. coli,* enterotoxigenic *E. coli,* and *Klebsiella pneumoniae* (*Kl. pneumoniae*) using *in vitro* model with Caco-2 cell line[37].

L. rhamnosus GG and *L. casei* Shirota strains excluded pathogenic *E. coli* and *Salmonella* spp. adhering onto human intestinal mucus glycoproteins and Caco-2 cell surfaces due to their ability to compete with them[26]. Moreover, *L. rhamnosus* GG was reported to increase the inhibition of bacterial translocation by mediating the up-regulation of epithelial MUC-2 in human enterocyte Caco-2 cells[38].

Several experimental studies show that probiotics, especially lactic acid bacteria, could be helpful in the treatment and prevention of *Helicobacter pylori,* the cited causative agent of ulcers. *In vitro* studies suggest that by acting as a bactericide, lactic acid bacteria may inhibit or kill *H. pylori*[39,40]. Growth or attachment of *H. pylori* may be inhibited by *Bifidobacteria* and *B. subtilis*[41].

In vitro, *Saccharomyces boulardii* (*Sac. boulardii*) reduces the growth of *Candida albicans, E. coli, Shigella* species, *S.* Typhi, *Pseudomonas aeruginosa, Staphylococcus aureus* and other microorganisms[42]. *Sac. boulardii* has been shown to inhibit the growth of *Pseud. aeruginosa* and *Staph. aureus* in an enteral nutrient liquid into which these pathogens had been inoculated[43]. *In vitro*, *Sac. boulardii* significantly reduces the number of red blood cells which adhere to *Entamoeba histolytica,* and the number of *Ent. histolytica* organisms in which red blood cells are found[44].

IN VIVO EXPERIMENTS

The efficacy of the probiotic strains have been tested in several anti-infection animal models, including protection against *Salmonella, E. coli* and rotavirus and found to

possess high antibacterial properties. Obadina *et al.* showed that all the isolates of *L. rhamnosus* and *L. plantarus* exhibited high antibacterial potential against *S.* Typhi, *Proteus vulgaris* and *Kl. pneumoniae*[45]. Another study, Perdigon *et al.* reported the *L. acidophilus* and *L. casei* fermented milk in preventing colonisation of *S.* Typhimurium in liver and spleen[46]. Similarly, *L. plantarum* strain ACA-DC287, *L. rhamnosus* GG, *L. casei* Shirota YIT9029 and *L. johnsonii* La1 strains exhibited anti-*Salmonella* activity in mice[31].

Varied results have been reported on the use of probiotics in *Salmonella* spp. infection models. Although, Pascual *et al.*[47] noted complete exclusion of *S.* Enteritidis by 21 days using *L. salivarius* in chickens whereas Nisbet *et al.*[48] reported a significant reduction in mortality due to *S.* Gallinarum infection in chicks treated with a commercial probiotic mixture. La Ragione *et al.*[49] observed no beneficial effect on fecal numbers or colonization of the intestine by *S.* Enteritidis when chickens were pretreated with *L. johnsonii.* Even though the same authors found reduction in *E. coli* numbers in the small intestine but did not find the same in the colon, cecum or feces. Moreover, they also claimed the strain to be very effective against *Clostridium perfringens.*

Fayol-Messaoudi *et al.*[31] showed complete inhibition of the growth of *S.* Typhimurium SL1344 induced by *Lactobacillus* strains, resulting mainly due to the effect of an acidic/lowered pH. They reported that *L. plantarum* strain ACA-DC287 isolated from Xynotyri cheese displayed *in vitro* killing activity against *Salmonella* and reduced the levels of viable *Salmonella* associated with the intestinal epithelium and the intestinal contents in infected mice[31]. The *L. rhamnosus* HN001 is capable of conferring immune enhancement and protection to BALB/c mice when challenged orally with *S.* Typhimurium 1772[50]. Furthermore, normal commensal *L. salivarius* CTC2197 prevents *S.* Enteritidis colonization in leghorn chickens[47].

Sac. boulardii and *B. lactis* were shown to provide protection against *S.* Typhimurium challenge in conventional and gnotobiotic mice by Rodrigues *et al.*[51] and Silva *et al.*[52], respectively. In another study, Martins *et al.* observed the protective effects of *Sac*. *boulardii* against *S.* Typhimurium infection in mice[53]. The study also demonstrated that *Sac. boulardii* modifies the invasive properties of *Salmonella.* Also, *Sac*. *boulardii* has antagonistic effects on *Candida* species[54] besides possessing immunostimulatory effects[55.] *Sac*. *boulardii* has been shown to increase the survival ratio in *Sh. flexneri, S.* Typhimurium and *Staph. aureus* infection[51,56].

Further, Hudault *et al.* reported that *L. casei* GG significantly reduced the level of viable *S.* Typhimurium C5 in mice faeces in comparison to the untreated group[24]. Fedorka- Cray *et al.* also reported that application of competitive exclusion culture of swine origin led to reduced number of *Salmonella* in their cecal contents and the ileocolic junction in *S.* Choleraesuis-challenged piglets[57]. The level of viable *S.* Typhimurium in the faeces of infected conventional mice was decreased by oral administration of probiotic *L. johnsonii* La1 or *L. acidophilus* LB[30,58]. Paubert-Braquet *et al.*[59] reported more protection upon feeding the mixture of *L. casei* LAB-1 plus yoghurt to mice orally infected with S. Typhimurium.

Bifidobacterium species exhibit a protecting role against *Listeria monocytogenes*[60], *Campylobacter jejuni*[61] and *Bacteroides vulgatus*[62]. *B. longum* has been reported to provide benefits against the pathogenic challenge of *S.* Typhimurium in animal models[52,63]. In two different studies involving *B. longum,* Silva *et al.*[63] and Lima-Filho *et al.*[64] observed higher survival rate in probiotic-treated mice compared to control group. In a similar way, Henriksson and Conway (2001) found that oral administration of certain human *Bifidobacteria* protect mice against *Salmonella* infection[65]. Silva *et al.* observed improved survival rate for mice pretreated with *B. longum* during challenge

with *Salmonella* spp. but no effect on numbers of the pathogen. Mice were reported to be protected against the challenge with *S.* Typhimurium by *B. longum*, on the basis of survival rate, histopathological and morphometric data[63].

Feeding *B. lactis* HN019 conferred significant protection against single or multiple oral challenges of *S.* Typhimurium in a BALB/c model was demonstrated by a study conducted by Shu *et al.*. The authors reported a ten-fold increase in survival rate; significantly higher postchallenge feed intake; weight gain; and reduced pathogen translocation to visceral tissues. *B. lactis* HNO19 offered significant protection against *Salmonella* infection by enhancement of various immune function parameters related to the immunological control of salmonellosis[66].

Many researchers reported protection of mice from lethal infection with shiga-toxin-producing E. coli 0157:H7 by *B. breve* and *B. pseudocatenulatum*[67,68]. Shu and Gill[69] suggested that *B. lactis* HN019 could reduce the severity of enterohemolytic pathogen *E. coli* 0157: H7 infection and ascribed protection conferred to this probiotic responsible for the reduction. Lema *et al.* observed no beneficial effects in lambs infected with *E. coli* 0157:H7 and subsequently administered *L. acidophilus*[70].

Cole and Fuller reported the successful suppression of the growth of *E. coli* in the gut of new-born rats using *L. salivarius*[71]. Similarly, another strain *L. lactis* associated with the small intestine epithelial surface of pigs showed reduction in *E. coli* count in the gut[72]. Similarly, another study showed the efficacy of *B. lactis* HN019 in reducing the severity of *E. coli* 0157:H7 infection and resultant a lower cumulative morbidity rate as compared to control mice[73]. Ogawa *et al.* reported that the use of *L. casei* Shirota reduced colonization levels and decreased the severity of diarrhoea in infant rabbits infected with *E. coli* 0157: H7[74]. In another study, Ishida-Fuji *et al.* reported significantly increased survival rate of mice infected with pathogenic *E. coli* Juhl by L. *casei* I-5[75]. Inhibitory activity against *E. coli* growth was exhibited by *Lactobacillus* strains isolated from traditional product Caprino d' Aspromonte cheese[76].

Antagonistic action of the probiotics against *H. pylori*[77,78,79], a Gram-negative bacterium associated with the development of chronic gastritis, peptic ulcers and gastric cancer was reported in various studies. L. *salivarius* was reported to inhibit the colonization and the release of interleukin-8 in *H. pylori* inoculated gnotobiotic mice[80]. Another double-blind, randomized, controlled clinical trial conducted by Cruchet *et al.* to investigate the effects of *L. johnsonii* La 1 on *H. pylori* colonization in children found it's interference with colonization of *H. pylori* by restricting the population of pathogen and delaying of colonization[39]. Sakamoto *et al.* reported that *L. gasseri* OLL 2716 (LG21) eradicated *H. pylori* in gnotobiotic murine models[78]. Using mice, Johnson-Henry *et al.* found a reduction in bacterial colonization in *H. pylori*-infected animals using a mixture of *Lactobacillus* spp[81].

Some studies on competitive exclusion of *E. coli* 078:K80 by *Bacillus subtilis*[82] and the suppression of *Vibrio harveyi* in shrimp by several *Bacillus* spore formers[83] show that these strains have probiotic potential. Positive effects have been shown by *L. casei* Shirota strain YIT9029 on oral infection of conventional Wistar rats with *Listeria monocytogenes*[84]. Likewise, the protection to the animals against the same pathogen was demonstrated by prophylactic treatment of gnotobiotic and conventional mice with the *L. delbrueckii* H2B20 or *Sac. boulardii,* respectively, by involvement of immune mechanisms[85,86].

Several non-pathogenic *E. coli* strains have also been used as probiotics. Duval-Iflah *et al.* successfully showed that by inoculating children with a plasmid-free human *E. coli* (EMO strain) just after birth, there is reduction in the number of antibiotic-resistant *E. coli* in infant feces, by suppressing the multiplication of plasmid-

bearing strains present in the intestinal tract[87].

Candida species is one of the most common causes of frequently recurrent and chronic vaginal infection. Probiotics are reported to be usefull in it's treatment[88.89]. The oral administration of *L. acidophilus* significantly reduced vaginal colonization with *Candida* species and a 7-day course of vaginal suppositories of LGG showed clinical improvement in women with recurrent vaginitis in separate studies carried out by Hilton *et al.*[90.91]. Significant reduction in *Candida albicans* in the digestive tract of both normal and antibiotic treated rats was shown by ingestion of *Sac. cerevisiae* by Seguela *et al.*[92]. Identical antagonistic effects against C. *albicans* have been reported by Ducluzeau and Bensaada in mice[54]. Even though, *Sac. cerevisiae* has antagonistic effect against *Candida krusei* and *Candida pseudotropicalis* but it was reportedly ineffective against *Candida tropicalis.* The antagonistic actitivty disappeared up on killing *Sac. cerevisiae* cells by heating[54]. *In vivo*, *Sac. boulardii* reportedly reduces the *C. albicans* population in mice 10-50-fold. In immunodepressed mice (antibiotic decontamination and prednisolone injections), the administration of *Sac. boulardii* significantly reduced the incidence of translocation of *C. albicans* to the mesenteric lymph glands, liver and kidneys[93].

Lactobacillus strains have been reported to inhibit the growth of Gram negative pathogenic bacteria[94]. Several strains of *L. acidophilus*, *L. rhamnosus* and *L. bulgaricus* inhibited the growth of clinical isolates of *H. pylori*[95,96], while *L. rhamnosus* strain Lcr35 reduced the growth of enteropathogenic *E. coli,* enterotoxigenic *E. coli* and *Kl. pneumoniae*[37].

A significant reduction in the number and severity of signs of disease was observed in rats inoculated with *Entamoeba histolytica* when *Sac. boulardii* was administered[54]. Substances produced by *Sac. boulardii* compete with the receptors of the target cells for *E. histolytica*[44]. Similarly, *Sac. boulardii* was shown to significantly increase the survival ratio in *Sh. flexneri* infection and *Staph. aureus* infection and in *S.* Typhimurium infection [51,56].

MECHANISM OF ACTION

Potential health benefits of probiotics include stimulation of immune system, alleviation of lactose intolerance, hypocholesterolaemic effect, and prevention of cancer recurrence etc.[97,98,99].

Probiotics exert their beneficial effects generally by four mechanisms which include (1) antagonism through the production of substances which inhibit or kill the pathogen[94,100,101]; (2) competition with the pathogen for adhesion sites or nutritional sources[102,103,104,100]; (3) immunomodulation of the host[105,106,107] and (4) inhibition of the production or action of bacterial toxins[108,109]. The first three mechanisms are generally ascribed to lactic acid bacteria and *E. coli* whereas the later two are more specifically attributed to *Sac*. *boulardii.* Mead also suggested the first four of these to be the ways for such beneficial effects[110].

In vitro, the bacteriocins inhibit the growth of several pathogenic organisms, including *Staphylococcus, Enterococcus, Streptococcus, Listeria, Clostridium,* and *Bacillus*[111]. Ocana *et al.* isolated a bacteriocin from a *L. salivarius* strain that exerted inhibition of *Enterococcus* and *Staphylococcus.* The bacteriocin produced by *L. delbruekii* may confer an advantage during colonization by inhibiting other strains of *Lactobacillus* only[112]. Other isolates have also been reported to produce bacteriocins. *L. paracasei* ssp. *paracasei* strain M3 used as a starter for Bulgarian yellow cheese, produces a proteinaceous substance that has bactericidal and fungistatic activities[113]. Antagonistic compounds linked with lactic acid bacteria, including reuterin are produced by a strain isolated from goat's milk cheese, *L. coryniformis* strain CECT 5711[114].

Kabir *et al.* 2005[115] and Kabir, 2009[116], demonstrated the potential role of probiotics for controlling of *Salmonella* strains of poultry via the mechanisms of competitive exclusion.

Probiotic microorganisms evade the colonization by *Salmonella* spp. and *E. coli* strains by competing with pathogenic bacteria for epithelial binding sites[117,118]. Possible mechanisms by which *L. salivarius* eradicates *H. pylori* include the ability of the former to bind to gastric epithelial cells, high quantity of lactic acid, and rapid proliferation[119]. *L. salivarius*, a strain that produces a large amount of lactic acid and completely inhibits the growth of *H. pylori* in a mixed culture, suppressed *H. pylori*, and reduced the *H. pylori*-induced inflammatory response in infected gnotobiotic mice[119]. Oral treatment of conventional mice with the spent culture supernatant of the human *L. acidophilus* gave protection against *H. felis* infection by reduction in the urease activity of *H. felis* in the stomach, inhibition of colonization of the stomach, and abolishing the *H. pylori*-induced gastric histopathologica lesions[77].

Recent breakthroughs in the explanation of mechanism by which members of the intestinal microbiota influence intestinal functions have been reported by Midtvedt and coworkers[120] and Gordon and coworkers[121,122,123,124,125,126,127,128] by means of cross talk with the epithelial cells. For example, the intraluminal microbiota influences the release of biologically active gastrointestinal peptides and contributes to regulating gastrointestinal endocrine cells and the epithelial structure[120]. Moreover, the colonization of germ-free mice by commensal bacterium *Bacteroides thetaiotamicron*VPI-5482, has been shown to modulate expression of genes involved in several important intestinal functions, including nutrient absorption, mucosal barrier fortification, xenobiotic metabolism, angiogenesis, and postnatal intestinal maturation[126,127].

CONCLUSION AND FUTURE TRENDS

Probiotics have been extensively studied and explored commercially in many products/forms in various food matrices, dairy and non-dairy, throughout the world. Most of the studies have demonstrated beneficial effects of probiotics to human and animal health. Some of the identified probiotic strains exhibit beneficial anti-inflammatory, anti-allergic and other important properties; however, the other aspects viz. the potential for negative side effects from probiotics needs to be explored. Probiotics should be further investigated for their possible benefits to patients affected by certain medical conditions. Future research must be directed as to how the gut microflora interacts with the intestinal epithelium in healthy and diseased conditions so as to form a knowledge base for optimal probiotic strains. New technologies should be developed to enable high cell yield at large scale and ensure probiotic stability for a long period in food as the viability of probiotics is a key parameter for developing probiotic food products. With different technologies, such as microencapsulation, cell immobilization and continuous fermentation, the probiotics will become an important and viable ingredient in the functional food, expanding the probiotic application outside the pharmaceutical and supplement industries. Clearly, this exciting field is at a new beginning. If supported, research into"indigenous and probiotic microbes will form an important part of future research that would shed light on health, disease and a basic understanding of life itself.

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