

# Fermented food in Asia as a source of potential probiotics: Properties and beneficial effects

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## Abstract

Consumption of probiotic food is known to strengthen the human natural microbiome, thereby providing health benefits to the host. Fermented food products are found to be natural sources of probiotics, also known as 'good' bacteria. Fermentation and pickling of food have long been carried out as a means of preservation and long-term storage. They have been associated with human nutrition and social aspects. In this paper, a compilation of some of the staple fermented foods found in the Asian region has been provided. The mode of action of probiotics and the benefits they bring to the host such as production of antimicrobial agents, blocking the adhesion of pathogens and toxins and modulation of immune responses have been outlined. Consumption of probiotics on a regular basis is known to benefit the overall well-being of the host.

*Index Terms:* Probiotics, immune response, *L. acidophilus*, *Bifidobacterium*, fermented food, belacan

## 1. Introduction

Probiotics are microorganisms which, when consumed, generally confer a health benefit on humans and this concept of probiotics was introduced by Russian scientist, Elie Metchnikoff 1907, also known as father of probiotics.<sup>1</sup> According to Snyderman, probiotics in many different forms are consumed across the world for the health benefits they offer and some of these are shown to be useful in the treatment of certain medical conditions.<sup>2</sup> Most commonly found probiotic bacteria in fermented products are *Lactobacillus acidophilus* and *Bifidobacterium* sp.<sup>3</sup> Other bacteria may also be used as probiotics as well as several species of yeasts such as *Saccharomyces boulardii*. Furthermore, some of the staple fermented foods used in the Asian families are known to be excellent natural sources of probiotics as shown in **Table 1**.

Diverse groups of both aerobic and anaerobic microbiota are found in the human body. These microbes, predominantly bacteria regulate the gut's epithelial development and function; a disruption of such interactions may result in

disease conditions.<sup>4</sup> The colonization of the gastrointestinal tract depends on the ability of the bacteria to tolerate acidic pH of the stomach and bile before it reaches the intestine. Desirable properties in potential probiotics include antimicrobial activity, triggering immune response and good adhesion ability of bacteria to intestinal cells and mucus. Probiotic bacteria can secrete antimicrobial chemicals thereby forming a physical barrier against the invasion of other pathogenic bacteria and yeasts.<sup>5</sup>

*L. acidophilus* has been largely proposed as the bacterium used for dietary use. The optimum temperature for this organism for growth is 35-40°C. The bacterium grows at an acidic pH of 6.4-4.5 but ceases to grow when pH 4.0-3.6 is reached. In a study reported by Shah, the acid tolerance of this organism with optimum pH at 5.5-6.0 changed from 0.3% to 1.9% titratable acidity.<sup>3</sup> Low concentrations of peptides and free amino acids in milk results in slow growth of *L. acidophilus*.<sup>3</sup> On the other hand, *Bifidobacteria* normally inhabit the gastrointestinal tract of human beings. This group of bacteria has good

Table 1. Asian food that contain probiotics

Name of food	Country	Composition/ constituents	Probiotic/microorganisms present	References
Balao-balao	Philippines	Traditional food generally consumed as a sauce after sautéing with onions and garlic in vegetable oil	<i>Leuconostoc mesenteroides</i> , <i>Edioccocus cerevisiae</i> and <i>Actobacillus plantarum</i>	[8]
Belacan	Brunei and Malaysia	Fermented food made from shrimp ( <i>Acetes</i> species).	<i>Bacillus</i> spp., <i>Straphylococcus</i> spp. and <i>Pediococcus</i> spp.	[9]
Belutak	Brunei	Made up of salted minced meat stuffed into casings of cow's or buffalo's small intestines.	<i>Lactobacillus</i> , <i>Bacillus</i> , <i>Alcaligenes</i> , <i>Pseudomonas</i> and <i>Staphylococci</i>	[10]
Budu Kupang	Brunei	Mussel and salt.	<i>Lactobacillus</i> , <i>Bacillus</i> , <i>Corynebacterium</i> and <i>Staphylococci</i> .	[10]
Dosa	India	Prepared with rice and black gram and commonly consumed as part of breakfast.	<i>Leuconostoc mesenteroides</i> , <i>Streptococcus faecalis</i> , <i>Torulopsis candidia</i> and <i>Trichosporon pullulans</i> .	[11]
Dua Muoi	Vietnam	Sour fermented fruit- or vegetable-derived foods.	<i>Lb. fermentum</i> , <i>Lb. pentosus</i> , <i>Lb. lantarum</i> , <i>Lb. paracasei</i> , <i>Lb. pantheris</i> , <i>P. pentosaceus</i> and <i>P. acidilactici</i> .	[12]
Douchi	China	Salt fermented soybean food.	<i>Lactobacillus plantarum</i> , <i>L. brevis</i> , <i>L. fermentum</i> , <i>L. alimentarius</i> , <i>Weissella confuse</i> , <i>W. paramesenteroides</i> , <i>W. cibaria</i> , <i>Pediococcus cidilactici</i> , <i>P. pentosaceus</i> , <i>Enterococcus faecalis</i> , <i>Straphylococcus simulans</i> and <i>S. capitis</i> .	[13]
Idli	India	Steamed cake made from a combination of rice and lentils that have been soaked, ground and fermented into smooth dough.	<i>L. fermentum</i> , <i>L. delbrueckii</i> , <i>L. lactis</i> , <i>Leuconostoc mesenteroides</i> , <i>Lactobacillus coryneformis</i> , <i>Streptococcus faecalis</i> , and <i>Pediococcus cerevisiae</i> .	[14]
Khalpi	Nepal	Fermented cucumber product.	<i>L. plantarum</i> <i>L. brevis</i> <i>Leuconostoc fallax</i>	[15]
Kimchi	Korea	The product of fermentation of over a hundred different types of vegetables and many species of <i>Lactobacillus</i> are involved in the fermentation of kimchi.	<i>Lactobacillus casei</i> spp., <i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus lactis</i> spp., <i>Lactobacillus curvatus</i> , <i>Lactobacillus debrueckii</i> spp., <i>Lactobacillus fermentum</i> , <i>Lactococcus lactis</i> spp., <i>Lactobacillus brevis</i> , <i>Weissella paramesenteroides</i> and <i>Lactobacillus sakei</i> .	[16]
Koumiss	China	A fermented milk drink.	<i>Lactobacillus plantarum</i> , <i>Lactobacillus helveticus</i> , <i>Lactobacillus casei</i> , and <i>Lactobacillus kefir</i> .	[17]
Miso	Japan	Prepared from fermented rice, rye, beans or barley in hot water.	<i>Lactobacilli</i> spp. <i>Bifidobacterium</i> spp.	[18]

Table 1. (cont.) Asian food that contain probiotics

Name of food	Country	Composition/ constituents	Probiotic/microorganisms present	References
Natto	Japan	Fermented soybean and rich in menaquinone-7.	<i>Bacillus subtilis</i> and <i>Bifidobacterium</i> spp.	[19]
Puto	Philippines	Steamed bread made from rice.	<i>L. mesenteroides</i> , <i>S. faecalis</i> and <i>Saccharomyces cerevisiae</i>	[20]
Sayur asin	Indonesia	A fermented mustard cabbage leaf product.	<i>Leuconostoc mesenteroides</i> , <i>Lactobacillus confuses</i> , <i>Lactobacillus curvatus</i> , <i>Pediococcus pentosaceus</i> and <i>Lactobacillus plantarum</i>	[15]
Tofu	Taiwan	A traditional fermented chinese snack, also known as stinky soybean curd.	<i>Lactobacillus</i> , <i>Enterococcus</i> , <i>Lactococcus</i> , <i>Streptococcus</i> , <i>Pediococcus</i> , <i>Leuconostoc</i> and <i>Weissella</i>	[17]
Suan tsai	China	Prepared from cabbage or mustard and has a sour flavor.	<i>Lactobacillus</i> , <i>Leuconostoc</i> , <i>Pediococcus</i> , <i>Pediococcus pentosaceus</i> and <i>Tetragenococcus halophilus</i>	[17]
Tapai	Brunei and Malaysia	Steamed non-waxy rice with ginger and sugar put into the rice alternatively with pulverized laru.	<i>Amylomyces rouxii</i> <i>Hansenula</i> spp., <i>Rhizopus</i> spp. and <i>Saccharomycopsis</i> spp.	[21]
Tempeh	Indonesia	Soybean dish, also made using other substrates e.g. legumes, cereals and soy-blends, non-leguminous seeds and presscake.	<i>Lactobacillus fermentum</i> , <i>R. oligosporus</i> , <i>Lactobacillus reuteri</i> , <i>Lactobacillus plantarum</i> and <i>Lactococcus lactis</i>	[22]
Tempoyak	Brunei and Malaysia	Fermented condiment prepared from durian pulp ( <i>Durio zibethinus</i> ).	<i>L. brevis</i> , <i>L. mesenteroides</i> , <i>Lactobacillus mali</i> , and <i>L. fermentum</i>	[15], [23]
Thua nao	Thailand	Fermented soybeans.	<i>B. licheniformis</i> , <i>Lactobacilli</i> spp., <i>B. cereus</i> , <i>B. megaterium</i> , <i>B. subtilis</i> and <i>B. pumilus</i>	[24]

effects on the gut microbiota and some select strains are known to survive the gastrointestinal transit to reach the colon in abundant number. The optimum pH of growth of *Bifidobacterium* is reported to be 6.0-7.0 and the optimum growth occurs at a temperature of 37-41°C. Nowadays, several different strains of bacteria and yeast are found to have probiotic properties which are more pH stable and thus have beneficial effects on human body for example *L. rhamnosus* GG, *L. casei* Shirota and *Saccharomyces cerevisiae* Bouldarii.<sup>3</sup>

Prebiotics, on the other hand are known as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth of certain specific bacteria in the colon.<sup>6</sup> Prebiotics essentially serve as 'food' for probiotics. The term synbiotic is used when a product contains both prebiotic and probiotic example: a product containing oligofructose and probiotic *Bifidobacteria* content is a synbiotic.<sup>7</sup>

## 2. Mechanism of action of probiotics

### 2.1 Production of antimicrobial agents

Several probiotic microbial strains produce at least one antimicrobial substance which includes organic acids, hydrogen peroxide, diacetyl, carbon dioxide, bacteriocins and related molecules.<sup>25,26</sup> However, none of the above listed substances are known to be the vital constituents in *in vivo* maintenance of health.<sup>26</sup> It has been observed that when some probiotics are consumed, the faecal pH is reduced.<sup>25,26</sup> The anti-infective effects of lactic acid bacterial culture supernatants in humans studies suggests that some of these substances are likely to be produced *in vivo*.<sup>27</sup> Further investigations are required to establish the effect of probiotic bacteria on the production of angiogenin, a potent stimulator of new blood vessels and defensin, the defense peptides active against bacteria, fungi and viruses in the host.<sup>26</sup>

### 2.2 Blocking the adhesion of pathogens

Probiotic bacteria are known to inhibit adhesion of some particular pathogens *in vitro*, for example *Escherichia coli*, *Salmonella enterica*, *Vibrio*, *Shigella*, *Campylobacter* and *Clostridium* sp. to epithelial cells in the gut. The attachment of pathogenic microbes to the cells and the host's mucosal surfaces are the main causes of the majority of infections.<sup>28</sup> A mucus layer of gel-like composition, constituting glycoproteins (mucin) can be found in the gut epithelium. When neurogenic factors are triggered along with the changes in the gut's environment, mucin is produced from the goblet cells and factors including the indigenous flora and microbe-causing infections. The glycoprotein, mucin, plays a role by acting as a barrier to adherence and intrusion of pathogens and toxin, by separating the epithelium from contact directly with the luminal contents. The mucus layer shields the surfaces on the gut against the enteropathogenic bacteria which involve in forming a covering blanket over the epithelial cells, binding competitively through carbohydrate component with pathogens and thereby releasing mucus inside the gastrointestinal tract which might subsequently draw away the contents of the lumen from epithelial cells.<sup>28</sup>

*Bifidobacteria* are reported to provide dose-dependent inhibition to the adherence of enteropathogenic *E. coli* and *S. typhimurium* *in vitro* to CaCO-2 cells.<sup>28,29</sup> Additionally, it has also been demonstrated that *Lactobacilli* can inhibit the adhesion and intrusion of epithelial cells by the enteropathogens - *Yersinia paratuberculosis*, *E.coli* and *Salmonella typhimurium*. The mode of action of this inhibition is not clearly understood, although competitive binding to receptors have been determined.<sup>30,31</sup> Similarly, prebiotic oligosaccharides present in the lumen are reported likely to block receptor sites for gut pathogens.<sup>26</sup> It has not yet been clearly understood how the antibacterial molecules such as bacteriocins are secreted or the secretion of defensin, the antimicrobial substances by the gut cells, are stimulated.<sup>28</sup>

### 2.3 Modulation of immune response

Oral administration of probiotic strains is found to illicit immune responses, both specific and non-specific to the host in both healthy and unhealthy conditions, including the improvement of phagocytic activity of leukocytes and natural killer cells.<sup>32</sup> Lipoteichoic acids in gram-positive bacteria such as *Bifidobacterium* have a high binding affinity for epithelial cell membranes; they are also reported to serve as carriers for other antigens thus provoking the immune reaction.<sup>33,34</sup> In this section, the two categories of the modulation of immune response are discussed.

#### 2.3.1 Effect on innate immunity

The natural killer cell activity is an example of immune response in the body. Natural killer cells are produced from the bone marrow, which are large granular lymphocytes. It is well known that natural killer cells have a role as cytolytic effector cells.<sup>35</sup> The immune system not only fights against the pathogens by providing first line of defense but also guides the adaptive immune system to bring out an innate immune response by sending biological signals to the targeted area.<sup>36</sup>

The specialized phagocytic cells, macrophages and the dendritic cells are responsible for initiating the innate immune responses that engulf the materials of foreign bodies and also defend against

infection. The pattern recognition receptors, which are developed by the phagocytes, are capable of identifying the specific molecular patterns of a pathogen that is present on the surface and the activation of these receptors happens only by pathogenic microorganisms.<sup>37</sup> The pattern recognition receptors like the Toll-like receptor (TLR) family are studied in-depth. When the pathogenic material exists in the gut, the purpose of the Toll-like receptors is to alert antigen-presenting cells to 'watch-out' for the harmful foreign body.<sup>38</sup>

*L. johnsonii* LJ-1 and *L. salivarius* UCC 118 stimulated a mucosal IgA response and increased phagocytic activity.<sup>39</sup> The enhancement of the circulating IgA antibody secreting cell response was observed in infants supplemented with a strain of *L. casei* responsible for prevention of diarrhea in the study group compared to the control (placebo). Furthermore, there was an increase in the non-specific immune phagocytic activity of granulocyte populations in the blood of human volunteers after consumption of *L. acidophilus* and *B. bifidum* because phagocytic activity is associated with natural immunity and phagocytes are involved in antibody immune responses as antigen-presenting cells.<sup>40</sup>

### 2.3.2 Effect on cellular immunity

According to Matsuzaki and Chin, two sections of murine T helper cells are classified depending on the pattern of cytokine production shown: It is reported that Interferon (IFN- $\gamma$ ), interleukin (IL-2), tumour necrosis factor (TNF- $\beta$ ) are produced by type 1 T helper cells while IL-4, IL-5, IL-6 and IL-10 are produced by type 2 T helper cells. In addition, the two types of helper T cells are categorized into two different kind of immunity: the type 1 cytokines contribute to the cellular immunity and type 2 cytokines to humoral immunity.<sup>35,41</sup> Several diseases caused by weak immune system, such as allergies and infections, can appear when the balance of the cell population are interrupted, since cell-balance is vital for the maintenance of homeostasis in each individual.<sup>35</sup>

Exerting an inhibition on the IgE production could be a helpful effect of probiosis on allergic

responses.<sup>42</sup> However, the inhibition of IgE production in vivo by the probiotics that are taken in orally through food, are still unsure. The consumption of probiotics by individuals with immune-inflammatory disorders such as atopy and Crohn's disease including those individuals with HIV and immunosuppression has been suggested in few reports.<sup>43,44,45</sup>

### 3. The benefits of probiotics

Probiotics are known to provide health benefits to humans. However, extensive research needs to be undertaken to provide substantial evidence and account for any side effects. Probiotics contain different strains of bacteria which have different functions in the body, for instance *L. Rhamnosus* GG, which stimulates most of the IgA production whereas *L. acidophilus* contributes in decreasing the amount of enzymes causing cancer.<sup>3</sup> Nevertheless, some of probiotics also provide the same benefit in the body for example *L. helveticus* and *S. cerevisiae Bouldarii* are able to suppress blood pressure.<sup>3,46</sup> The benefits of probiotic strains are summarized in **Table 2**. The main therapeutic and health benefits of probiotics are: (3.1) Treating acute gastroenteritis/diarrhoea (3.2) improvement of lactose digestion (3.3) prevention of allergy (3.4) Anti-mutagenic (3.5) Anti-carcinogenic (3.6) improvement of vitamin B profile (3.7) reduction of blood pressure (3.8) Decrease cholesterol consumption (3.9) Treatment or prevention of urogenital disease (3.10) reduce the amount of *Helicobacter pylori* in stomach (3.11) Treating inflammatory bowel disease.

#### 3.1 Treating acute gastroenteritis /diarrhea

Diarrhoea caused by *Clostridium difficile* (*C. difficile*) are commonly found in people who consume antibiotic such as metronidazole and vancomycin. This is because *C. difficile* are found in the healthy intestine in small number but there is a distortion of flora that is indigenous, due to antibiotic doses leading to an increased count of *C. difficile* and hence, toxin production.<sup>47</sup> Probiotics are reported to provide a prophylactic regimen with antibiotic-induced diarrhea. Studies have proof that *Lactobacillus* GG and *S. cerevisiae Bouldarii* are very effective in

Table 2. Type of probiotics and their beneficial effects

Type of probiotic strains	Beneficial Effects	References
<i>Bifidobacteria</i>	Decrease the amount of genotoxin from certain compound. Eradication of <i>H. pylori</i> . Increase phagocytic activity.	[46], [58], [91]
<i>L. acidophilus</i>	Decrease the level of enzyme that can cause cancer. Produce short fatty acids to inhibit the generation of carcinogenic products. Reduce the total cholesterol concentration by deconjugation of bile acid into free acids. Eradication of <i>H. pylori</i> . Increase phagocytic activity.	[3], [40], [72], [92]
<i>L. casei shirota</i>	Enhancement of the circulating IgA antibody secreting cell.	[3], [46]
<i>L. helveticus</i>	Suppress blood pressure.	[76], [81]
<i>L. Johnsonii</i> LJ-1 <i>L. salivarius</i>	Stimulate mucosal IgA-response. Increase phagocytic activity.	[39], [40],
<i>L. reuteri</i> CRL 1098	Produce vitamin B	[79], [80]
<i>L. Rhamnosus</i> GG	Effective in termination of diarrhea. Enhance the secretion of IgA-specific antibody. Inhibit the growth and adhesion of enteropathogens. Hydrolyse complex casein to smaller peptides and amino acids.	[40], [48], [49], [62]
<i>L. sporogenes</i>	Reduce the amount of bad cholesterol in the body.	[59], [85]
<i>S. cerevisiae bouldarii</i>	Effective in treatment of diarrhea. Suppress blood pressure. Increase secretory IgA levels in gut.	[3], [48], [81], [82], [95]

*cerevisiae* Bouldarii are very effective in termination of diarrhea.<sup>3,48</sup>

Diarrhoea caused by rotavirus is a common acute type diarrhea seen in children worldwide. This virus causes the gut permeability of epithelial cell to increase intact protein. Probiotics are claimed to shorten the time span of acute diarrhea as *Lactobacillus Rhamnosus* GG, which is present in yogurt enhancing the secretion of IgA-specific antibody to rotavirus.<sup>49</sup> Moreover, *Lactobacillus Rhamnosus* GG are reported to shorten the duration of rotavirus diarrhoea by inhibiting the adhesion of enteropathogens.<sup>3,50</sup>

Research has been carried out in acute gastroenteritis patients, to note the differences between children receiving yogurt and children consuming placebo (milk formula); duration of

hospitalization was shorter in children consuming yogurt and total weight gain also high in these children compared to children receiving placebo (milk formula).<sup>51</sup>

### 3.2 Improvement of lactose digestion

Lactose malabsorption is a condition where lactose (component of carbohydrate) cannot be hydrolyzed completely to glucose and galactose as a result of deficiency of enzyme  $\beta$ -galactosidase. People with lactose intolerance are often found to experience gastric distress on consumption of unfermented milk or milk products; this is reported to be due to microbial action on undigested lactose forming hydrogen gas in the gut.<sup>3,52</sup> The intolerance symptoms are developed depending on transit rate of lactose in to the large intestine and the ability to ferment lactose by colon microbiota.<sup>46,53</sup>

Yogurt with probiotic bacteria can improve the lactose digestion by fermenting lactose and thereby reducing lactose intolerance.<sup>54</sup> Moreover, microbial lactase from the starter culture also helps the intestine in lactose digestion as microbial lactase can survive in the stomach but will be destroyed in the small intestine by digestive enzymes due to difference in pH.<sup>55</sup> The survival and multiplication of beneficial bacteria in the gastrointestinal tract helps in breaking down the lactose in longer period for example *S. thermophilus* contain more lactase than *lactobacilli* or *bifidobacteria* strains.<sup>56,57</sup> It has been proposed that increase in viscosity of the fermented product could prolong the transit time through the gastrointestinal tract as it slows down gastric evacuation.<sup>46</sup>

### 3.3 Prevention of allergy

It has been reported that the milk protein casein can trigger the first allergic reaction in some milk-fed infants. There is a higher frequency of allergic diseases especially in western societies over the last 40 years.<sup>58,59</sup> Probiotic are known to be beneficial in lowering inflammation associated with hypersensitivity reactions in patients with food allergy.<sup>59,60,61</sup>

*Lactobacillus* GG along with other *lactobacilli* are claimed to hydrolyse complex structure of casein to smaller fragments of peptides and amino acids thereby decreasing the production of mitogen-induced human lymphocytes.<sup>40,62</sup> Bacterial host interaction is studied to likely induce the expansion of regulatory T-cells along with the expression of interleukin (IL)-10 and transforming growth factor (TGF- $\beta$ ) which belong to the group of immunomodulatory cytokines.<sup>63</sup> It has been proposed that probiotics might improve barrier mechanisms of the gut, providing a valuable tool for countering food allergic reactions and inflammation of the intestine.<sup>59,64,65</sup>

A study has been demonstrated in a double blind to find the potential of probiotics in atopic disease. Children with high risk of atopic disease were given probiotics and others were given a placebo for a study period of six months. The results show that the children receiving probiotics had reduced

occurrence of atopic eczema as compared to children who were given placebo.<sup>66,67</sup>

### 3.4 Anti-mutagenic

Mutagens are frequently formed due to stress, viral or bacterial infection and phagocytosis.<sup>68</sup> Endogenous DNA damage can be caused by age related degenerative processes in the body. The defense mechanism through leukocytes release several compounds for example NO, O<sub>2</sub><sup>-</sup> and H<sub>2</sub>O<sub>2</sub> to defend the individual from infection by bacteria and virus however, this mechanism can cause mutation and DNA damage. Anti-mutagenicity developed when the mutation process is stopped or suppressed.<sup>46,68,69</sup>

A study shows that *Lactobacilli* and *Bifidobacteria* decrease the amount of genotoxic from certain compounds. Probiotic organisms are claimed to bind mutagens into the cell surface and thereby reduce the activities of faecal enzymes involved in mutagen activation including nitroreductase, azoreductase and  $\beta$ -glucuronidase.<sup>3</sup> Dead cells shows a low rate in preventing mutation than live bacterial cells suggesting that live bacterial cells are involved in anti-mutagenic metabolism.<sup>46,70</sup>

Neosugar (fructo-oligosaccharide) with probiotics are given to healthy volunteers in chewable form increased *Bifidobacteria* in the intestines and also reduced the faecal enzymatic activities of genotoxic metabolites. This shows the potential of probiotics in prevention of mutation.<sup>33</sup>

### 3.5 Anti-carcinogenic

Genotoxic compounds such as heterocyclic amines, nitrosamine, ammonia and phenolic compounds are reported to be causative agents for colorectal cancer.<sup>3</sup> Enzymes such as azoreductase,  $\beta$ -glucuronidase and nitroreductase have the potential to convert procarcinogens into carcinogens.<sup>71</sup>

Certain strains of *L. acidophilus* and *Bifidobacterium* spp. contribute to decrease the level of enzyme that can cause cancer such as  $\beta$ -glucuronidase, azoreductase and nitroreductase thereby reducing the risk of tumour

development.<sup>3,72</sup> Furthermore, short fatty acids produced by *L. acidophilus* and *bifidobacteria* are known to inhibit the formation of carcinogenic products and hinder the continuation of cellular growth causing cancer.<sup>73</sup> Other probiotic bacteria also help in balancing the intestinal microbiota and subsequently preventing the absorption of toxins.<sup>3,74</sup> Probiotics can also decrease the inflammatory immune response to inhibit tumour development and enhancing the production of IgA-secreting cells and CD4<sup>+</sup> T-lymphocytes found in the lamina propria of the large intestine.<sup>75,76</sup>

### 3.6 Improvement of vitamin B profile

The action of microorganisms in the intestine can improve the digestibility and absorption of dietary nutrients.<sup>77</sup> The most common vitamin B produced by microbes are riboflavin (Vitamin B<sub>2</sub>) and cobalamin (vitamin B<sub>12</sub>). Riboflavin is the originator of the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are carriers of hydrogen in cellular reactions. Riboflavin is synthesized through the microbial route from the precursor's guanosine triphosphate (GTP) and D-ribose 5-phosphate through several enzymatic cascade mechanisms. The only vitamin that is reported to be produced exclusively by microorganisms, mostly anaerobes is cobalamin, a type of cobalt corrinoid. Human, animal and fungi cannot produce cobalamin.<sup>78,79</sup>

Probiotics improve vitamin nutrition by absorption of bacterial synthesized vitamin. Differences in processing technologies and the action of microorganisms can vary the concentration of riboflavin in food products. *Lactobacillus reuteri* CRL 1098 was found to be the first strain that is able to produce a cobalamin like-compound.<sup>79,80</sup>

### 3.7 Reduce blood pressure

Probiotic bacteria also play a role in blood pressure control as documented by animal and clinical studies.<sup>59</sup> The proteolytic action of some probiotic bacteria on the milk protein, casein results in the generation of bioactive peptides; these peptides such as valine-proline-proline and

isoleucine-proline-proline, isolated from yogurt fermentation by *Saccharomyces cerevisiae* and *Lactobacillus helveticus* are found to suppress blood pressure. These tripeptides are seen to function on the lines of angiotensin-I-converting enzyme inhibitors thereby reducing blood pressure.<sup>81,82</sup>

### 3.8 Decrease cholesterol consumption

Cholesterol, a component of cell membranes and nerve cells, is essential for several vital functions in the human body. It acts as a precursor to certain vitamins and hormones in the body. However, increased levels of blood cholesterol are considered risk factors for developing coronary heart disease.<sup>59</sup>

People who consumed probiotics were seen to excrete higher levels of cholesterol in faeces as compared to non-consumers suggesting the influence of probiotics on cholesterol levels. Changes in serum cholesterol have been hypothesized to be caused by alterations in cholesterol synthesis, absorption, conversion into bile acids and also synthesis and degradation of lipoproteins.<sup>82,83</sup> Cholesterol, being a precursor of bile acids converts its molecules to bile acids replacing those lost during excretion leading to a reduction in serum cholesterol. *Lactobacilli* and *Bifidobacteria* have the ability to deconjugate bile acids into free acids more rapidly from the intestinal tract than conjugated bile acids and increasing their rates of excretion.<sup>84</sup>

Results from previous studies demonstrate that probiotic bacteria may have a positive influence on blood cholesterol levels. A study conducted in hyperlipidaemic patients who were given *Lactobacillus sporogenes* reported a mean reduction of 32% in total cholesterol level and a reduction of 35% in low-density lipid over a study period of three months.<sup>82,85</sup> Furthermore, cholesterol levels in one of the studies showed significant decreases within 7 days of consuming yogurt and rose gradually to baseline levels within 4 weeks of resuming a normal diet.<sup>86</sup>



### 3.9 Treatment or prevention of urogenital infection

Intestinal tract is found to be the major source of pathogenic microbes for urinary tract infections in women. *Trichomonas*, *Candida*, *Gardnerella vaginalis* and *Mycoplasma hominis* are the examples of pathogenic microbes associated with vaginal infections, whereas urinary tract infections are reported to be caused by anaerobic microbes like *Chlamydia*, *E. coli* and *Candida*.<sup>82,87</sup>

High populations of *Lactobacilli* in the vaginal tract are found to be sign of good health. *Lactobacilli* reduce infections by replacing the population of other harmful bacteria in the intestine by interfering with the adhesion mechanisms of urinary pathogens. Reduction of *E. coli* colonization by healthy *Lactobacilli* has been proposed to result in lower UTI-associated morbidities. *Lactobacilli* are known to contribute to lower pH levels and thereby inhibiting the growth of *Gardnerella* and other related bacteria.<sup>82,88,89</sup> This shows the usefulness of using oral probiotics in disease management.

In a study done by Sanders, thirty-three women were studied to understand the effect of consuming yogurt on *Candida Vaginitis*. A decrease in *Candida* infection during yogurt consumption was observed compared to subjects who did not receive yogurt. Moreover, thirty-eight other women underwent the study on vaginal *Lactobacilli* present in the yogurt; results show that vaginal *Lactobacilli* contribute significantly to lowering the risk of urinary tract infections.<sup>82</sup>

### 3.10 Reduce amount of *Helicobacter pylori* in the stomach

*Helicobacter pylori* is a gram-negative, spiral bacterium that is reported to survive in acidic environment of the stomach and colonize the lining antrum of the epithelial cells. *H. pylori* is a pathogenic microorganism and increased densities of this bacterium reportedly causes chronic gastritis and peptic ulcer disease.<sup>90,91</sup>

The use of probiotics has been proposed for countering *H. pylori* infection by exhibiting an inhibitory effect on the pathogen attachment to the gastric epithelial lines.<sup>59</sup> Yogurt containing

*Lactobacillus* and *Bifidobacterium* are studied to not only improve the rate of eradication of *H. pylori* substantially but also restore the depleted levels of *Bifidobacterium* in stools. Increase in *Bifidobacteria* is also reported to lower the production of hydrogen gas which commonly produced by *Escherichia coli* and *Clostridium perfringens* which also increased the stomach's colonization by *H. pylori*.<sup>91,92</sup>

In an experiment conducted by Vasiljevic and Shah, intake of yogurt containing *Lactobacillus johnsonii* Lal for three weeks decreased the density of *H. pylori* in humans. Additionally, a decrease in antral inflammation was also observed.<sup>46</sup>

### 3.11 Treating inflammatory bowel disease

The overlapping phenotypes of Crohn's disease and ulcerative colitis typically characterize inflammatory bowel disease. People with inflammatory bowel disease reportedly have lower numbers of *Lactobacillus* and *Bifidobacterium* in their intestine whereas coccoids and anaerobic bacteria are higher.<sup>3</sup> Boosting the composition of normal microbiota is found to offer immunity against the disease.<sup>67,93,94</sup>

Improvement of intestinal mobility and constipation relief are found to be beneficial effects of lactic acid bacteria through a reduction in gut pH and offering protection against adhesion of pathogenic microbes.<sup>94</sup> *Sacchromyces bouldarii* in patient with Crohn's disease is claimed to reduce relapse rates and extend remission time. *Sacchromyces bouldarii* and *Lactobacillus* GG have been reported to contribute of higher levels of secretory IgA levels in the gut by down regulating TNF- $\alpha$ -induced IL-8 production.<sup>95,96</sup>

In a study conducted by Vasiljevic and Shah, four children with Crohn's disease were investigated for the effect of *Lactobacillus* GG supplementation. The study showed improvement in the clinical outcome of three children who received oral *Lactobacillus* GG. Moreover, additional study has been carried out using large samples in order to support the claim. Forty patients with chronic relapsing pouchitis were

involved in this study and were given a mixture of four species of *Lactobacilli* and three species of *Bifidobacteria* and *S. thermophiles*. After the study period of four months, fewer relapses were observed in the patients receiving probiotics as compared to the control group.<sup>46</sup>

#### 4. Concerns of probiotics

Some potential concerns have been raised with regards to the consumption of probiotics in humans.<sup>2,97,98</sup> Probiotics, according to Salminen and von Wright, can be responsible for four types of side effects: (4.1) systemic infections, (4.2) risk of metabolic disorders, (4.3) risk of adjuvant side effects, (4.4) risk of gene transfer. In addition, (4.5) minor gastrointestinal symptoms have also been reported, as stated by Salminen and von Wright.<sup>99</sup>

##### 4.1 Systematic infections

Probiotics are non-pathogens. Therefore, the risk of infection, if any, should be minimum. However, one of the potential concerns is that some probiotics mainly in commercial products, have been designed or selected to have good adherence to the gastrointestinal lining. According to Boyle et al. (2006), adherence to intestinal mucosa may contribute to bacterial translocation and virulence. Bacterial translocation is a phenomenon caused by a diminished intestinal barrier, which leads to the passage of bacteria across the epithelium and mucous membrane.<sup>100,101</sup>

Bacterial translocation may result in immunodeficiency in the host, intestinal mucosal injury and an abnormal intestinal bacterial flora.<sup>102</sup> The bacteria may be transported through the tunica propria to the mesenteric lymph nodes (MLN) and other organs which is a precursor to bacteremia with the potential to progress into septicemia.<sup>103,104,105</sup>

Reports from cases describe episodes of infection caused by organisms coherent with probiotic strains in patients consuming probiotics. Eight cases of bacteremia associated with *Lactobacilli* including *Lactobacillus acidophilus*, *Lactobacillus casei* and *Lactobacillus GG* have been reported.<sup>106,107,108</sup> Nine cases of overt sepsis

have also been observed, associated with *S. boulardii [cerevisiae]*, *Lactobacillus GG*, *Bacillus subtilis*, *Bifidobacterium breve* or combination probiotics.<sup>108,109,110</sup> Furthermore, endocarditis events caused by both *Lactobacillus* and *Streptococcus* probiotics have been documented.<sup>111,112</sup>

##### 4.2. Risk of metabolic disorders

The intestinal microbiota play an essential role in numerous metabolic activities, including carbohydrate and lipid metabolism and glucose homeostasis.<sup>[100,113]</sup> Thus, there is a potential risk of adverse metabolic effects. However, incidence of significant adverse effects appears to be lower.<sup>[100,114]</sup>

###### 4.2.1 Excessive degradation of intestinal mucus

It has been documented that some endogenous bacteria including numerous bacteroides species and some *lactobacilli*, as well as some strains of *Bifidobacteria* have the capability to degrade human intestinal mucus.<sup>99</sup> In order to study these effects, Ruseler-van Embden, van Lieshout, Gosselink, and Marteau, have examined the mucus degrading properties of three commonly used probiotic strains such as *L. acidophilus*, *Bifidobacterium* spp. and *L. rhamnosus GG* that were administered in fermented milk. Nevertheless, no mucus degradation was observed in vitro or in gnotobiotic rats mono-associated with the test strains and thus the strains were considered safe for the mucus.<sup>115</sup>

###### 4.2.2 Excessive deconjugation of bile salts

Secondary bile acids are produced by intestinal bacterial actions and can exhibit carcinogenicity by acting on the mucous-secreting cells and stimulating their proliferation. They can also act as promoters of carcinogenesis.<sup>116</sup> A study on hypothetical risk of excessive deconjugation of bile salts in the small bowel by probiotics was carried out in healthy humans, which showed how *L. acidophilus* and *Bifidobacterium* spp. contained in fermented milk could convert conjugated primary bile salts into toxic free secondary bile salts.<sup>99</sup> However, more studies are required to conclusively establish the side effects.

#### 4.3. Risk of adjuvant side effects

Studies on the role of intestinal microbiota in immune development suggest that manipulations caused by probiotics could lead to immunomodulatory effects. Boyle et al., reported that a medium to long-term alteration of the microbiota might be attained in neonatal probiotic supplementation.<sup>100</sup> However, it is difficult to predict the long-term effect of these manipulations on the host. Nevertheless, the consumption of probiotics during pregnancy, in neonates and in children has not been associated with any adverse immunological effects.<sup>2</sup>

According to O'Brien, Crittenden, Ouwenhand and Salminen, probiotic cell wall and cytoplasmic material have the potential to trigger the immune effects.<sup>117</sup> Studies have shown that cell wall fragments from *Lactobacilli* can induce arthritis in rats. As stated by Salminen and von Wright, immunological side effects have been observed in rats with systemic uptake of cell wall polymers from the intestinal lumen via colonic injury and during small bowel bacterial overgrowth.<sup>99,118 119</sup> Furthermore, the cell walls from *Bifidobacteria* have the potential to be arthritogenic.<sup>120</sup> Nonetheless, there have been no immunological side effects caused by oral-administered probiotic reported in humans.

#### 4.4. Risk of gene transfer

A major area of concern as stated Salyers et al. and Mathur and Singh has been the potential of transfer of antibiotic-resistance genes in the gastrointestinal tract between probiotic and pathogenic bacteria.<sup>121,122</sup> According to Lin, Fung, Wu, and Chung, in lactic acid bacteria, one can observe the presence of plasmids with antibiotic-resistance genes, including genes exhibiting resistance to a range of antibiotics such as tetracycline, erythromycin, chloramphenicol, lincosamide, macrolide, streptomycin and streptogramin.<sup>123</sup>

Morelli, Sarra, and Bottazzi reported that several attempts have been done to transfer antibiotic resistance with a broad-host-range plasmid pAMB. Morelli, Sarra and Botazzi also observed that merely one strain each of *L. brevis* and *L.*

*helveticus* accepted the plasmid with low efficiency ( $10^{-7}$ ), out of 14 strains of *Lactobacillus delbrueckii*, 44 strains of *L. acidophilus*, one strain of *Lactobacillus brevis*, one strain of *Lactobacillus helveticus*, 6 strains of *L. casei rhamnosis*, one strain of *L. fermentum* and 5 strains of *L. plantarum*.<sup>124</sup> Mathur and Singh and Soedings, Kleinschmidt, Teuber and Neve have reported that 7 of 14 strains were capable of transferring resistance from *Lactobacillus* to *Enterococcus* at  $10^{-4}$ – $10^{-7}$  of frequencies. Whereas, two of 14 strains could transfer to *L. lactis* but were not capable to transfer to *Staphylococcus aureus*.<sup>121,125</sup>

There have been molecular identification attempts of vancomycin-resistance genes in lactobacilli where one strain of *L. rhamnosis* and five strains of *L. reuteri* were probed for vanA, vanB, and vanC genes and none were found in the observation according to Klein, Hallmann, Casas, Abad, Louwers, and Reuter.<sup>126</sup> Doron and Snyderman reported that *Lactobacillus* GG has been examined precisely and no plasmids have been discovered; there is no verification of vanA, vanB, vanH, vanX, vanZ, vanY, and vanS, by hybridization or polymerase chain reaction products.<sup>108,126,127</sup>

As specified by Doron and Snyderman, in spite of the theoretical likelihood of lateral gene transfer between probiotic and other pathogenic microorganisms in sites such as in the gut, there has been no clinical evidence for the transfer of antimicrobial resistance seen.<sup>108</sup>

#### 4.5. Gastrointestinal side effects

Studies have reported minor gastrointestinal symptoms occurring in subjects receiving probiotics, for example abdominal cramping, flatulence, soft stools and taste disturbance. Gastrointestinal side effects happen when the gastrointestinal tract is colonised with a large number of bacteria. The organisms present in high numbers can induce intestinal inflammation mainly through deconjugation and dehydroxylation of bile salts.<sup>128</sup>

## 5. Conclusion

Probiotic bacteria such as *Lactobacillus* species and *Bifidobacteria*, widely occur in fermented products including local foods in various geographic locations. The bacteria present in the probiotic food products are essentially similar to the gut microbiota. Administration of these probiotic bacteria can provide health benefits to an individual by increasing the amount of good bacteria in the body and also provide therapy for certain diseases. Although, some of the mechanisms of blocking or inhibition of adhesion of pathogenic bacteria remains unclear, probiotic bacteria are well known of their benefits as they can increase the immunity of the host by strengthening the gut microbiota.

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