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Improvement of Health by Probiotics: The Roles on Human Gut and Immune Modulation

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Authors' contributions

This work was carried out in collaboration with all authors. All authors contributed equally. Author AG managed literature searches, designed figures and wrote the first draft of the manuscript. Author AB managed literature searches and edited the manuscript. Author MP managed the final manuscript editing. All authors read and approved the final manuscript.

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ABSTRACT

The term probiotic refers to viable, non-pathogenic microorganisms when ingested in an adequate and controlled amount confer health benefits for the host. In present review, the beneficial effect of probiotics to human health is presented. Introduction section discuss details about backgrounds of probiotic, criteria associated with probiotic, mechanisms and beneficial effect on human gut and immune system and beneficial effects of probiotics on health. The review mainly focused on clinical studies with probiotics and different investigations are discussed in detail. On these regard many experimental studies have found that probiotics have specific effects for different diseases that have been studied are presented. This review also gives back ground on different strain of probiotics and introduces some harmful strains and there possible health related consequences.

Keywords: Probiotic; neutraceuticals; preservatives; GIT; immune modulation.

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1. INTRODUCTION

We are exposed daily to tens of thousands of potential bacterial pathogens, through dermal contact, ingestion and inhalation. The system of innate immunity prevents these pathogens, in small to modest doses, from colonizing and growing to a point where they can cause life threatening infections [1,2].

Most foods are unsterile and contaminated with pathogenic and saprophytic microorganism. Saprophytic microorganisms utilize substrates in food. The metabolites they produce are accumulated and causing microbial spoilage [3]. Human Pathogens that contaminate food cause food borne illness. This includes disorders, gastritis, enteritis, peptic ulcer, ulcerative colitis, and others when they enter the gastrointestinal tract. To ensure food safety and to protect public health, there is a trend for enrichment of food with *Lactobacilli*, *bifidobacteria*, propionic acid bacteria with high antimicrobial activity against pathogens that cause food toxic infections, toxemia and saprophytic microorganisms [4].

The term probiotic refers to viable, non-pathogenic microorganisms when ingested in an adequate and controlled amount confer health benefits for the host. They are commonly lactic acid producing and constitute a major part of the normal intestinal microflora in animals and humans [5]. These include a wide spectrum of species of *Lactobacillus*, *Bifidobacterium*, *Streptococcu*s, *Lactococcus*, some *Enterococcus* species and probiotic yeast *Saccharomyces boulardii* [3,6].

A number of health benefits have been claimed for probiotic bacteria and are also being recommended as a preventive approach to maintain the balance of intestinal microflora. Their beneficial effects on humans include stabilization of intestinal microflora [7], reduction of lactose intolerance [5], prevention of antibiotic-induced diarrhea, and stimulation of the immune system. In addition, probiotic have been found to produce antimicrobial products during fermentation which has been proposed for safe and long storing of foods [8]. They fight against pathogenic bacteria through blocking effects by producing bactericidal substances, competing with pathogens, toxins for adherence to the intestinal epithelium, regulation of the immune responses enhancing the innate immunity and stimulating protective responses [9,10]. The probiotic microorganisms have a characteristic tolerance to high acidity, bile and ability to adhere to intestinal surfaces to survive and colonize in gastro-intestinal tract of the host [11]. This review discusses the role of probiotics on treatment of GIT related illness such as diarrheal, Inflammation and *Helicobacter pylori* infection, oral cavity inflammation, Lactose intolerance, NEC, HIV, atopy and asthma, candida infection and IBS. The review also gives background on innate and adaptive immune modulation mechanism of probiotics and introduces different strains of probiotics found with an optimal number for complete coverage.

2. OVERVIEW OF PROBIOTIC BACTERIA

2.1 Criteria Associated with Probiotic Bacteria

Probiotic have constituted a major part of the natural microflora of human intestine and create a healthy equilibrium between beneficial and potentially harmful microflora in the gut [12]. For some positive effects on human health, a probiotic strain has to reach the large intestine. Microorganisms ingested with food begin their journey to the lower intestinal tract via the mouth and are exposed during their transit through the gastrointestinal tract to successive stress factors that influence their survival [11,12].

Probiotic bacteria must overcome physical and chemical barriers in the GI tract, especially acidic environment of the stomach, and then the activity of hydrolytic enzymes and bile salts in the small intestine. In a typical acid tolerance tests, the viability of potential probiotic organisms is determined by exposing them to low pH in a buffer solution or medium for a certain period of time, during which the number of surviving probiotic bacteria is determined [12]. For example, *Lactobacilli* are adhering to the intestinal mucosa during stationary phase than log phase [13] and auto-aggregation of probiotic strains appeared to be necessary for adhesion to intestinal epithelial cells. According to some literatures, co-aggregation abilities may form a barrier that prevents colonization by pathogenic microorganisms [13,14]. Antimicrobial compound produced by *Lactobacilli* provided this organism a competitive advantage over other microorganism [15].

2.2 Production and Development of Probiotic Foods

It is common that probiotic are incorporated in foods such as yoghurt, cheese, ice cream, infant formulas, breakfast cereals, sausages, luncheon

meats, chocolates, puddings, and also sold as capsules containing freeze-dried cell powders [16]. While adding probiotic to a food product, several factors must be considered that may influence the viability of the culture and its benefit in human intestine [16].

The major challenge in probiotic food preparation is the maintenance of viability of the cultures. Typical methods for preserving sensitive biological materials include freeze drying, cryopreservation, and spray drying. These techniques involve the use of extreme temperatures that may initiate structural damages to the cell membranes, protein denaturation, and/or DNA damage, and can lead to a decrease in cell viability [17]. In order to increase the resistance of probiotic bacteria against the detrimental food processing conditions, several approaches such as selection of acid- and bile-tolerant strains, microencapsulation, packaging in oxygen protected materials, double-step fermentations, pre adaptation to stress conditions.

Any new drug under investigation must be submitted and approved by FDA as safe and effective before an investigational or biological product can be administered to humans. Probiotic is intended for use as a drug, it must undergo the regulatory process as a drug, which is similar to that of any new therapeutic agent [16]. In an attempt to standardize the global requirements needed to make health claims regarding probiotic agents, the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics developed guidelines for evaluating probiotics in food that could lead to the substantiation of health claims. The recommended evaluation of probiotics for food use is shown in Fig. 1.

2.3 Neutraceuticals and Functional Foods

The term nutraceuticals was originated from nutrition and pharmaceutical. It is the food or part of a food that provides health benefits, including the prevention and treatment of a disease [18,19]. These products may range from dietary supplements, herbal products, functional foods such as yoghurt, cereals, fermented food and enriched foods to genetically engineered designer foods [20]. The word nutraceuticals in the food industry has no regulatory definition. Hence the terms nutraceuticals, functional or medical foods, or dietary supplements are often used interchangeably. For instance functional food is a term to emphasize foods that may have a beneficial effect on the health [20,21]. But, when a functional food is associated

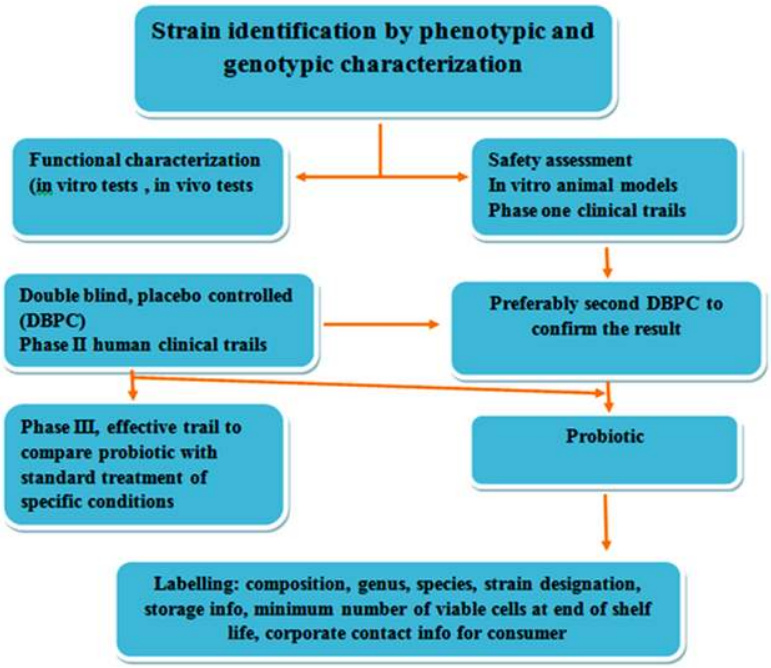

Fig. 1. FAO/WHO Guidelines for the evaluation of probiotics for food use

with the prevention and treatment of disease, it is called a nutraceuticals [22]. Since nutraceuticals provide nutrition and health benefits, can be considered as food used for the prevention, treatment, or cure of a disease and therefore can be considered as drugs. Functionally, nutraceuticals occupy a central area between food and drugs. Food is generally recognized as safe (GRAS). Whereas nutraceuticals, even though they contain natural substances they may not be GRAS simply because they have not gone through an approval process [23]. Probiotic produces various nutraceuticals such as B vitamins (mainly folate, riboflavin, and Cobalamin), low-calorie sugars (Mannitol, sorbitol) and L-alanine [24]. Bio yoghurts containing *L. acidophilus* and *bifidobacteria* and other specialist fermented products such as yakult, nestles (Providing *L. johnsonii*), and the culturelle (providing *Lactobacillus* GG) are leaders in Dairy industry sector [25].

2.4 Probiotic as Bio-Preservative

Bio preservation is the use of natural or added microbiota and/or their byproducts for extending the shelf life and enhanced food safety. Probiotic as bio-preservation organisms are of particular interest since they greatly influence the nutritional, sensory, and shelf-life characteristics of fermented food products [26]. They do so by production of organic acids, mainly lactic acid. In addition to this, their production of acetic acid, ethanol, aroma compounds, bacteriocines, exopolysaccharides, and several enzymes is of importance in health benefits.

Traditionally based on spontaneous fermentation or backs lopping, industrial food fermentation is nowadays performed by the addition of probiotic bacteria as starter cultures to the food medium. This has been a breakthrough in the processing of fermented foods, resulting in a high degree of control over the fermentation process and standardization of the end products. Recently, the use of functional starter cultures novel generations that offers functionalities beyond acidification are being explored [5,10]. For instance, probiotic bacteria capable of inhibiting various microorganisms (Table 1) in a food environment and display crucial antimicrobial properties with respect to food preservation and safety are in use. Moreover, certain strains of probiotic are further known to produce bioactive molecules such as ethanol, formic acid, fatty acids, hydrogen peroxide, diacetyl, reuterin and reutericyclin. One of the characteristics of these probiotic is the potential to combat gastrointestinal pathogenic bacteria such as *Helicobacter pylori*, *Escherichia coli*, and *Salmonella* by producing bacteriocines [23]. Moreover, bacteriocin produced by probiotics has important application on the human gastrointestinal health and food preservation.

3. PROBIOTIC AND HUMAN HEALTH

3.1 Diseases and Some Disorders Caused by Alterations in the Human Gut Microbiota

Probiotic plays an important role in human health. Most existing probiotics have been isolated from the human gut microbiota. Not only due to its participation in the digestion process, but also for the function it plays the development of the gut and the immune system [25]. The mechanism by which probiotics act is not completely understood. However, the general mechanism of actions include the following; 1) Adherence into gut and colonization, 2) Inhibition of the overall growth of pathogenic bacteria, 3) Production of antimicrobial compounds, 4) Improvement of intestinal barrier activities, 5) Prompt the mucosal and systemic host immunity, 6) Controlled transfer of dietary antigens [26] (Fig. 2).

The most important function of this intestinal microbiota is to act as a microbial barrier against pathogens, by so-called competitive exclusion mechanisms. But also influence the humoral and cellular mucosal immune responses during the neonatal phase of life, and thereafter to maintain a physiologically-normal steady-state condition throughout life [27]. Commensal probiotic bacteria supply the host with essential nutrients and defend the host against opportunistic pathogens. They are involved in the development of the intestinal architecture and immunomodulatory processes. On the other hand; the host provides the bacteria with nutrients and a stable environment. This function of the microflora is also known as the barrier effect [28].

Gastrointestinal (GI) tract is approximately 25 feet long and is responsible for digesting and absorbing the nutrients in the foods, while also helping to eliminate waste products from body. Beyond these important functions, GI tract, particularly the intestines, also performs very important immune functions in the body [29]. A healthy intestinal tract is critical for optimal

digestive function and immune system support. It is evident that prenatal maternal exposure influences postnatal microbial colonization [30] and this plays pivotal roles in gut-associated lymphoid tissue (GALT) development [31], specific aspects of immune system development [32,33].

Many studies have associated diseases such as diarrhea [34,35,11] and lactose intolerance [12] to alterations in the gut microbiome (Table 1). In many instances, there is an imbalance in the population densities of gut microbiota (dysbiosis) and this results in an overgrowth of pathogenic microbes. In obesity, the altered microbial population is associated with a shift in function of the cells, resulting in increased energy harvest from ingested food; unexpended excess energy is deposited as adipose tissue [36].

There are different strains of probiotic microorganisms isolated and characterized for human health benefit. As such, predominantly known strains are discussed in Table 1. Common strain of these probiotics has several health benefits of GIT associated problems and immune system modulation.

3.2 Immune System and Probiotic Bacteria

The practical application of bacterial-epithelial interation is the communication between colonizing bacteria and the germ-free neonatal gastrointestinal tract immediately after birth. The nature and composition of these colonizing bacteria are important contributors to the development of gastrointestinal host defenses against infection and allergic reaction in newly born children.

The innate and adaptive mechanisms are the two components of immune systems. The former includes, Neutrophils, Natural Killer (NK) cells and serum complement system and involved to protect the human system from pathogens. However, there are many agents that this system is unable to control the effect of the pathogens and/or their toxic byproduct. Hence, the adaptive system (B and T cells) should be involved and provide additional means of defense, while cells of the innate system modulate the beginning and subsequent direction of adaptive immune responses as described by many researchers [37]. Natural killer cells, including gamma/delta T cells, control the development of allergic airway disease, where the immune messengers like cytokine particularly the interleukins play an important role. Probiotic antigenic fragments (e.g., cell wall compounds) are able to cross the intestinal barrier via intestinal epithelial cells and mast cells. Then these cells process and present the pathogens for further action by the immune system and modulate even the innate and adaptive response [38]. The interaction of the immune system and the probiotic is shown in Fig. 3.

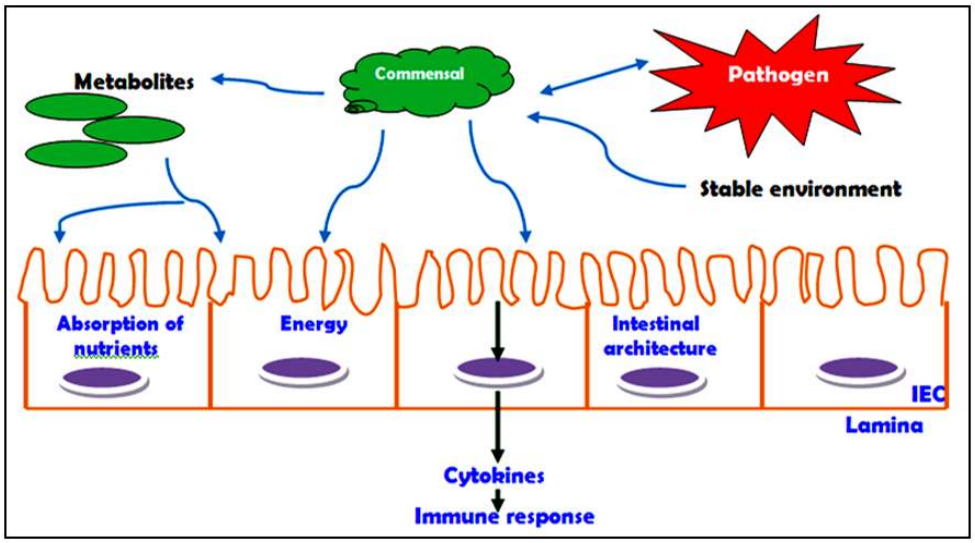

Fig. 2. The mechanism of probiotic prevention of intestinal tract infection

Table 1. The strains of probiotic and their role in treatment of different illness

Strains	Potential role of probiotics	Findings
Lactobacillus salivarius	Protects against cavities and gingivitis	The strain called as gingivitis-fighter has been shown to be useful in targeting peridontopathic bacteria [39,40].
Lactobacillus casei	Inhibits inflammatory responses Disturbances of the intestinal microbial flora Inflammation limited to the unattached gingiva and Affects all supporting tissues of the teeth	The strain has potential in anti-inflammatory role in the human intestine. Studies suggest it has also been shown to reduce inflammation in cells from individuals with Chrohn's disease [41,18]. Eradication of *Helicobacter pylori* infection of the gastric mucosa in humans. Inhibit the growth of *H. pylori* [42,43]. Inhibit the growth period of pathogens and play a role in the oral ecological balance [44,45].
Lactobacillus plantarum	Wound healing properties	This versatile type strain of probiotic is valuable in the treatment of first, second and third-degree burns. Similar studies suggest it accelerated healing and decreased inflammation in cutaneous (skin) wounds [46,47].
Bifidobacterium infants	Advances the immune system	Studies have found *Bifidobacterium Infants* strain of probiotic works to improve the immune response within the digestive system. Another study is showing this immune-boosting property actually extends to the entire body [48].
Bifidobacterium bifidum	Fights candida overgrowth Disrupt intestinal function Depletion of gut microbiota permits *Candida albicans* proliferation and infection Maintain changes in bacterial fermentation	A study conducted found that *Bifidobacterium bifidum* reduced candida in the digestive system. Supplementation with this probiotic would be useful for people on antibiotics, as they often cause yeast infections [49]. Other studies found that, the bacterium compete with viruses or pathogenic bacteria for binding sites on epithelial cells [34,35,11]. Study suggests probiotics maintain gut microbiome through antimicrobial activity [50]. Disturbances of mucosa-associated bacteria may be important in the pathogenesis of IBS symptoms [51].
Lactococcus lactis	Breaks down carbohydrates	*Lactococcus lactis* was found to break down the sugars lactose, galactose and glucose. Different investigations suggest that, it works to break down all carbohydrates in the digestive system, not just sugars [52,53].
Lactobacillus paracasei	Clinically proven relief	A study of children with atopic dermatitis treated with *Lactobacillus paracasei* showed clinical improvement in the children's dermatitis. Another study found

Strains	Potential role of probiotics	Findings
		the same effect in adults [54,55].
Streptococcus thermophilus	Fights respiratory infections	A study conducted in children with respiratory infections found that, supplementation with *Streptococcus thermophilus* reduced the toxic load in the body [56].
Lactobacillus acidophilus	Reduces blood pressure and cholesterol	This strain uses several mechanisms to minimize blood pressure and total cholesterol. Studies suggest it could be a helpful addition to traditional medications for these situations [57].
Bifidobacterium breve	Reduces gas and bowel irritations stomach intestine	This strain of probiotic improved gastric transit, the pathway of the food you ingest through the body. It also demonstrates “intestinal persistence,” meaning once it's in the gut, it's staying there [58].
Lactobacillus brevis	Protects against kidney stones	Manipulation of gastrointestinal flora with probiotics including *Lactobacillus brevis* was found to decrease the oxalate content in urine. Lower oxalate concentrations are likely to lead to fewer kidney stones [59].
Bifidobacterium lactis	Improves digestive comfort	Studies have shown that daily consumption of this probiotic improves digestive comfort in healthy people without digestive disorders. It has also been used in the treatment of irritable bowel syndrome (IBS.) [60].
Lactobacillus bulgaricus	Draws away toxins	This disease-fighter is capable of knocking out *E. coli* toxins, which can cause serious intestinal distress and even death. It has also been shown to kill c. difficile toxins, which can also be deadly to humans [61,53].
Bacillus animalis	Immature intestinal barrier	Study suggests protect from NEC illness through lower bacteria diversity in all preterm of infants [62].
Lactobacillus rhamnosus GG	Maintain gut microbiome	The strain maintains gut microbiome dysbiosis may be critical for pathogenesis. An important relationship exists between altered mucosal bacterial communities and intestinal inflammation during chronic HIV-1 infection [62,63].
Lactobacillus casei Shirota	Respiratory system organ	One study suggests the strain has potentials in atopy and asthma pre- and postnatal microbial exposures influence immune development [30].
Bacillus bifidum	Maintain ecological balance of oral cavity Maintain gut microbiome through antimicrobial activity	Inflammation limited to the unattached gingiva and affects all supporting tissues of the teeth. Inhibit the growth period of pathogens and play a role in the oral ecological balance [64,65]. The strain has potential in depletion of gut microbiota permits *Candida albicans* proliferation and infection [54].

Strains	Potential role of probiotics	Findings
Saccharomyces cerevisiae	Disrupt intestinal function	Several studies suggest the bacterium has a potential to compete with viruses or pathogenic bacteria for binding sites on epithelial cells [66,67,68].
B. breve	Antirotaviral effect in Mice	The study conducted using this strain showed it has a potential in antirotaviral activity by increasing production of IgA and anti-influenzal effect by increasing IgG [69].
Yogurt bacteria	Effect in HIV/AIDs infection	Study suggests yogurt bacteria have potential to increase CD4 count in blood and also reduce diarrhea incidence in HIV infected patients [70].
Saccharomyces boulardii	Rotavirus mediated gastroenteritis in children	One study suggested that *Saccharomyces boulardii* has a useful effect in antirotaviral therapy [71].
L. acidophilus	Hepatitis A, B vaccination	Study showed the potential of *L. acidophilus* strain as vaccination against Hepatitis A, B [72].
L. rhamnosus	Treatment of RTI in children	Study suggests the strain has significant reduction in infection [73].

3.3 Modulation of Innate Immunity

Non-specific or the innate immune response constitutes the first line of defense for the host as describe above. It is induced by different stimuli and it is quickly activated. The cell base of non-specific immunity is composed of mononuclear phagocytic cells (Monocytes, macrophages), polymorph nuclear leukocytes (mainly neutrophils) and NK cells Phagocytosis (Fig. 3) which initiates a series of intracellular reactions that continue with the production of reactive oxygen and nitrogen radicals, TNF-α and IL-1 [74].

The ability of specific strains of probiotic to enhance aspects of natural immunity in human subjects have been researched and reviewed by many researchers. Delcenserie et al. [14] reported enhanced phagocytic capacity of peripheral blood leucocytes in healthy human adults administered fermented milk supplemented with specific strains of probiotic (*Lactobacillus johnsonii* or *Bifidobacterium lactis*) for three weeks as a starter culture. The improvements in phagocytic activity was sustained for several weeks after cessation of probiotic consumption and granulocytes showed higher increases in phagocytic cell function compared with monocytes.

Lactobacilli had been found to be capable of translocation and surviving for many days in the spleen, liver, and lungs [75]. Immune modulation of blood leukocytes in humans by lactic acid bacteria had also been reported. The increase interferon production and increase in numbers of T lymphocytes, CD^+ cells and antibody-secreting cells, including those in the intestinal mucosa, and enhance lymphocyte proliferation, NK cell activity, IL-1, TNF and IFN- production, antibody production, phagocytic activity and the respiratory burst of macrophages [75,39]. All these showed that the probiotic are vital for modulation of the innate immune system to act against pathogens.

3.4 Modulation of the Adaptive Immune System

The specific (adaptive) immune response can be divided into two main categories: Humoral immunity and cellular immunity. Antibodies produced in plasma cells (mature B-lymphocytes) mediate humoral immunity. Cellular immunity is mediated by T-lymphocytes, which proliferate after contact with antigens processed in the innate immune system, produce specific cytokines, and influence the activity of other immunocompetent cells [36].

Many probiotic strains have the capability to stimulate the production of IgAs by B-cells [75]. Probiotic have been shown to stimulate rotavirus-specific IgA antibody responses in children significant in the prevention of re-infections by the said virus [74]. Probiotic can influence the production of cytokines by intestinal lymphocytic cells and, modulate the orientation of the adaptive response [76]. According to Wheeler et al. [77] the Th1 cytokines augment cellular immunity and Th2 cytokines augment humoral immunity. The balance of the two cell populations is believed to be important for the maintenance of homeostasis in the host (Fig. 3).

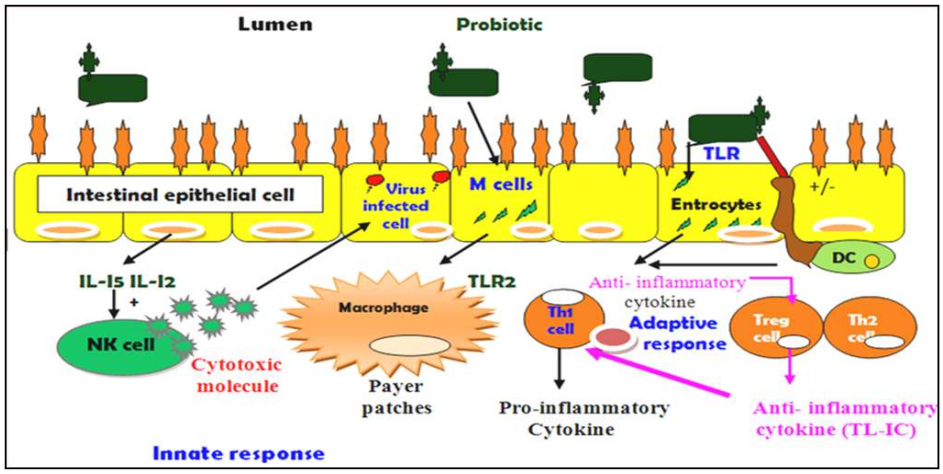

Fig. 3. Mechanism of probiotic effect on innate and adaptive immune response

Once this balance becomes disturbed, various immunological diseases, such as allergies and infections can occur through the evasion of host defense mechanisms. Probiotic have the potential to improve host immune system disorders via regulation of the Th1 and Th2 balance. It is time for researchers to focus more research on probiotic for the treatment of immune-mediated diseases, including allergies and other autoimmune diseases.

3.5 Risks Associated with the Use of Probiotics

Mostly considered as safe probiotics are *Lactococcus* and *Lactobacillus. Streptococcus, Lactobacillus* and *Enterococcus*, species contain some opportunistic infectious species [78]. In general, probiotics are grouped into two classes based on their risk to human health. The first groups are risk group one, which is known as (No risk) consists of *Lactobacillus* and *Bifidobacteria.* The second group termed as risk group two, this group characterized by the presence of small risk contains *L. rhamnosus* and *Bifidobacterium dentium* [77]. In addition to their harmful effect, probiotics generate resistant factor for antibiotics [78]. For example *Enterococci* have resistance against glycopeptides antibiotic (Vancomycin and teicoplanin) and can transmit this resistance to other bacteria. Vancomycin is a drug of choice in multi drug resistant pathogen. When there is resistance against vancomycin by *Enterococci* then it will be very difficult to treat them [78]. Studies suggest different strains of probiotics with potential adverse effects. Some of these are *Sacharomyces bulardi, Bifidobacteria* - Bacteraemia and Meningitis [77]; *Bifidobacteria, Lactobacillus* - Abdominal abscess [79]; *L. rhamnosus*- Liver abscess [80] and *L. casei* - Pneumonia and sepsis [81].

4. CONCLUSION

This review has illustrated the potential of probiotics in improvement of human health through treatment of gastrointestinal disorders. Probiotics have exhibited treatment potential for GIT related illness such as diarrhea, Inflammation and *Helicobacter pylori* infection, lactose intolerance, atopy and asthma, candida infection, HIV, NEC, IBS and Oral cavity infections. Probiotics boost human immune system through modulation of innate and adaptive immune mechanisms. These positive findings suggests the potential use of dietary alternatives such as probiotics, to alleviate the occurrence of different diseases and metabolic disorders via a less radical approach compared to drugs or hormone therapy, with milder, if not none, known side effects.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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