ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 11, pp.75341-75352, November, 2018

DOI: https://doi.org/10.24941/ijcr.33164.11.2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

PROBIOTICS AND PREBIOTICS

Athraa Saad Mtasher, *Ali Jabbar Abdulhussein and Shihab Hattab Mutlag

Department of Pharmacology, College of Pharmacy, University of Baghdad, Iraq

ARTICLE INFO

Article History:
Received 09th August, 2018
Received in revised form
12th September, 2018
Accepted 16th October, 2018
Published online 30th November, 2018

Key Words:

Probiotics, Prebiotics,
Normal flora, Gastric diseases.

ABSTRACT

The human GIT has normal flora of bacteria which play important role in homeostasis of human gut. The imbalance of gut flora is induced by traditional treatment such as antibiotics which causes increased prevalence of disorders and diseases. This disruption of host microbial can be manipulated by using probiotics and prebiotics. Probiotic is microorganisms that produce metabolic by-product which exerts beneficial effects on biological functions and modulate the immunity of the host. While, prebiotic is a fermented component or non-digested food which though to stimulate or activate the microorganisms in the human gut. In conclusion, probiotics and prebiotics can be used to treat gut disorders due to imbalance of normal flora which is reported to cause many gastric diseases.

Citation: ***Athraa Saad Mtasher, Ali Jabbar Abdulhussein and Shihab Hattab Mutlag*, 2018.** "Probiotics and prebiotics", *International Journal of Current Research*, 10, (11), 75341-75352.

INTRODUCTION

Understanding the anatomy and physiology of gastrointestinal system is an important step for accurately assessing patients with gastrointestinal disorders (Scanlon, 2014). The gastrointestinal tract is a tube that started from the mouth to the anus in which the movement of muscles and release of different enzyme to digest food. moreover, it been called alimentary canal, digestive tract and GI tract. There is hollow portion of tube known as the lumen, a muscular layer in the middle, and layer of epithelial cells in the outer surface. These layers are responsible for keeping the mucosal integrity alongside the GIT (Preston, 2013). The parts of GIT include the mouth (for mastication), esophagus, stomach and small intestine, large intestine, rectum, anus and accessory organs liver, gall bladder and pancreas. The average adult digestive tract is about thirty feet (30') long while in the digestive tract the food is passing through the body rather than being in the body (Agans, 2011). Importantly, the GIT's functions are firstly ingestion whichis taking of food into the alimentary tract, i.e. eating and drinking and moves the contents along the alimentary tract, digestion process consists of mechanical breakdown of food by, e.g. mastication (chewing) and chemical digestion of food into small molecules by enzymes which are produced by glands and accessory organs of the digestive system.

Corresponding author: **Ali Jabbar Abdulhussein**
Department of Pharmacology, College of Pharmacy, University of Baghdad, Iraq

Secondly, absorption this is the process by which digested food substances pass through the walls of some organs of the alimentary and use by body tissues and finally the elimination steps that food has been eaten but cannot be digested and absorbed are excreted from the alimentary canal as faces by the process of defecation (Waugh, 2010). The human intestinal tract has a various and complex microbe which plays a central role in human health. Know areas of the body with normal flora (GIT, Urogenital tract, and skin) and most common types of organism in these areas and relation to pathogenicity of these organism (Zhang, 2015). Owing to the increased prevalence of diseases and disorders associated with gut flora imbalances and the fact that traditional treatments such as antibiotic administration appear to have the potential for long-term disruption, microbial manipulation of the host microbiome to treat chronic diseases has become the focus of recent renewed interest. Manipulation may be elicited through probiotics and prebiotics.

Normal flora: The gut mucosa of humanincludesthe epithelial cells, lamina propria, and the muscularis mucosae, which is colonized by 1014 microbes includes not just bacteria, but also other microbes such as fungi, archaea, viruses, and protozoans (Zhang, 2015 and Sekirov, 2010). The mainbacteria in the human gut are Firmicutes, Bacteroidete, Actinobacteria, Proteobacteria, Verrucomicrobia and Fusobacteria. Firmicutes are gram-positive bacteria with a low G +, including the large class of Clostridia and the lactic acid bacteria, while Actinobacteria are gram-positive bacteria with a high G +, including Colinsella and Bifidobacterium spp. Lactic acid

bacteria and Bifidobacteria are two important types of gut bacteria, acquired from digested food. Lactobacillus and Leuconostoc spp. are the major lactic acid bacteria existed in the human intestine. Bifidobacterium spp. is the predominant bacteria found in GIT of newbornsand present at a low level in adults (Zhang, 2015).

The major functions of the normal gut

Nutrient metabolism: The gut flora mainly derives their nutrients from carbohydrates in diet. Fermentation of the carbohydrates byorganisms such as Bacteroides, Enterobacteria, Bifidobacterium, Fecalibacterium, and Roseburia result in the synthesis of short chain fatty acids (SCFA) such as butyrate, acetate, and propionate which are rich sources of energy. The oxalate that is produced in the intestine as a result of carbohydrate fermentation and bacterial metabolism is used by organisms such as Oxalobacterformigenes, Bifidobacterium species and Lactobacillus species, which is reducing the risk of formation of oxalate renal stones (Magwira. 2012). Thenormal flora in the human gut has also been reported to impart a positive effect on lipid metabolism by blocking the inhibition of lipoprotein lipase activity in adipocytes. Moreover, synthesis of vitamin K and vitamin B is another major metabolic function of the normal flora. The gut flora, particularly Bacteroides intestinalis, and to a certain extent Bacteroides fragilis and E. coli, also has the ability to deconjugate and dehydrate the primary bile acids and convert them into the secondary bile acids deoxycholic and lithocolic acids in the colon. The normal gut flora has also been shown to exert a healthy metabolome in the serum by increasing of, citric acid, fumaric acid,pyruvic acid and malic acid, all of which are markers of energy metabolism [8]. Recent studies have discussed that gut flora is also involved in breakdown of several polyphenols (phenolic compounds) which are consumed by human in the food. More in the same point, polyphenolic secondary metabolites are found in a various of plants, fruits (Marín, 2015).

Antimicrobial protection: The healthy gut flora for normal homeostasis makes the gut mucosal immune system in a challenging because it needs to be tolerant to the beneficial microbes and prevent overgrowth of the pathogens. The easiest mechanism of antimicrobial protection is the presence of the two-tiered mucus layer that maintains luminal microbes away from epithelial contact, predominantly in the large intestine. Mucus consists of a several mucin glycoproteins that are produced by the intestinal cells (Kim, 2010). The inner layer is denser and does not contain any organism, while the outer layer is more dynamic and produces glycan as a source of nutrition and energy for the microbes (Johansson, 2011).

Immunomodulation: The gut flora contributes to immunomodulation of gut in both the innate and adaptive immune systems. The components and the cell types Peyer's patches and isolated lymphoid follicles that are marked by the abundance of IgE+ B cells instead of from the immune system that contribute in the immunomodulatory mechanism includes the gut associated lymphoid tissues (GALT), effector andresident macrophages, IgA producing B (plasma) cells, regulatory T cells and dendritic cells in the lamina propria. The role of gut flora in forming a normal gut associated lymphoid tissues (GALT) is implied by the inhibited development of the normally seen IgA+ B cells (Jandhyala, 2015).

Xenobiotic and drug metabolism

The capability of the gut microbes to metabolize drugsand xenobiotics was discoveredbefore 40 years. An evidence has now provided reliable insights on the function of the normal flora on xenobiotic metabolism, which could have profound effect on treatmentofseveral diseases in future. Recent studies have demonstrated that a gut microbial metabolite p-cresol can decrease the capacity of the hepatocytes to metabolize acetaminophen due to competitive inhibition of hepatic sulfotransferases. Furthermore, cardiac glycosides like digoxin have been recently reported to increase a cytochrome containing operon in the common organism Eggerthellalenta from the Actinobacteria phyla thatleadsto inactivation of digoxin. Anotherexample, microbes that are induced drug metabolism is the microbial β-glucoronidasethat caused deconjugation of the anticancer drug which can contribute to its toxicities such as diarrhea, anorexia and inflammation (Marín, 2015).

Factors affecting variations in the normal gut

Age: It is widely believed that the GIT gets colonized by microbes immediately after birth, there is emerging evidence that the infant GIT could colonized by organisms even in utero [12]. The intestines of infants born vaginally the infant's gut flora after primary inoculation appears unsettled and devoid of but with time it stabilizes, diversifies, and acquires 40%60% similarity with the adult flora by the age of 3 years (Yatsunenko, 2012). On the contrary, studies have shown that young children and adolescents could demonstrate significant differences in proportions of Bacteroides and Bifidobacterium compared to adults (Ringel-Kulka, 2013). Few of the functional impacts of the temporal alteration in the normal gut flora include a reduced capability to synthesize vitamin B12, reduced activities of microbial reductases, increased propensity for DNA alterations, increase stress response, and immune dysfunction. Although the initially developing flora is largely effectedby the type of feed (breast milk or formula feeds) after primary inoculation, the temporal alteration is affected by dietary patterns, lifestyle, life events, and environmental factors including antibiotic use (Lan, 2013). In pre-term infants, bacteria that colonize the gut include Bifidobacterium and Lactobacillus and basically, these differ depending on the type of feeding habits. Breast milk contains indigestible glycans termed as human milk oligosaccharides (HMO) which are easily broken down by these bacteria. Preterm microbiota is said to maintain the gut associate lymphoid tissue (GALT), and is involved in generate in the innate immunity during development. Therefore, abnormal colonization of the gut flora may result in pediatric diseases because of poor immunity (Groer, 2014).

Diet: The earliest effect on the gut flora, after the mode of delivery, is the early infant diet, i.e., breast milk a formula feed. Several studies have shown substantial differences in the gut microbial component between breast-fed and formula-fed infants. It is important to understand the effect of breast milk and formula feeds on the GIT flora since there has been an increasing trend of moving away from breast-feeding by modern day mothers. Besides meeting the nutritional and physiological needs of the infant, breast milk also contains several bioactive compounds that are not available in formula-feeds. These compounds have a significant role in nutrient digestion and absorption, immune protection and anti-

microbial defense (Albenberg, 2014). Diet continues to be the most important determinant in shaping the composition, diversity and richness even throughout adulthood. In general, intake of diet rich in fruits, vegetables and fibers is associated with a higher richness and diversity of the gut flora (Walker, 2011). Several human and rat studies have demonstrated a significant shift in the gut flora upon the use of seaweeds as a food supplement. In humans, supplementation of Gelidium seaweed has significantly increased the expression of Bifidobacterium genera, without any change in the others (Ramnani, 2012).

Antibiotics: Even though study on antibiotics in general have centered around their bactericidal and bacteriostatic activities against pathogens. A strong body of evidence has now clearly demonstrated that use of antibiotics does have several short and long-term implications in the ecology of the normal gut flora. One of the major properties of the healthy gut flora against pathogen is the capability to cause competitive exclusion. It was demonstrated around four decades ago that antibiotics could result in disturbance of the competitive exclusion machinery that resulted in Salmonella infection immediately after antibiotic therapy. One of the possible mechanisms of this kind of event could be a loss of the wide network of interactions within the flora that increase the multitude of host-derived sialic acid which is growth promoting for pathogens such as Salmonella typhimurium and Clostridium difficile. Major changes in the gut flora in response to antibiotics include diminished taxonomic diversity and insistence of the changes in a substantial proportion of individuals. It has been shown that the effect of even short-term use (7 d) of broad-spectrum antibiotics with predominant anaerobic coverage (e.g., Clindamycin) could last up to 2 year, with a persistent non-recovery of the diversity of Bacteroides. Similarly, a short course H. pylori eradication with clarithromycin containing triple therapy resulted in a reduction in the diversity of Actinobacteria. The effect of ciprofloxacin, which has predominantly Gram-positive coverage, is relatively short-lived with abrupt reduction of Ruminococcussps (Ng, 2013).

Disease and disorders due to alteration of gut flora

Abnormality in gut flora associated with a number of diseases and disorders including allergic disease development, colon cancer and even progression and severity of HIV. Disruption of the gut microbiome, termed dysbiosis, is frequently accompanied by overgrowth of pathogenic bacteria orfungi, in conjunction with significant loss of microbial diversity or key functional groups and an inflammatory response by the host, which lead to disease development. Dysbacteriosis has been associated with an imbalance between populations of inflammation mediating T-helper cells (Th1, Th2 andTh17) and anti-inflammatory cells. Prolonged overproduction of Th1- and Th17-associated cytokines has been linked with Inflammatory Bowel Disease (IBD) (overproduction of Th1 for Crohn's disease) and Th17 for both CDand ulcerative colitis (Zhang, 2015).

Probiotics

History: Looking back through history, however one has forgotten the concept of using live bacteria called probiotics, beneficial to health has been resurrected and has now come under intensive research using modern study designs and methods [21]. The most common problem predominant in the field of medicine is the development of resistance to a range of antibiotics by some important pathogens. The illegal and heady use of antibiotics has led to the emergence of multi-resistant strains of bacteria. This unfortunate development has led scientists to shift the sample of treatment from specific bacteria elimination to altering bacterial ecology by use of probiotics (Vishnu, 2012). There is a long history of health claims concerning living microorganisms in food, particularly lactic acid bacteria. In 76 BC, the Roman historian Plinius recommended the administration of fermented milk products for treating gastroenteritis. In 1908 Elie Metchnikoff was perhaps the first researcher to propose that fermented dairy products have beneficial properties (Reddy, 2017). Which contain of rod-shaped bacteria (Lactobacillus spp). Therefore, these bacteria affect the gut microflora positively and reduction the microbial toxic activity in intestine (Hamasalim, 2016). Elie Metchnikoff proposed that the regular exhaustion of lactic acid bacteria in fermented dairy products, such as yogurt, was associated with enhanced health and longevity in Bulgarian peasant populations (Reddy, 2017). The expression “probiotic” comes from the Greek word “pro bios” which means “for life” as different to “antibiotics” which means “against life”. The history of probiotic began with the consumption of fermented diets by Greek and Romans (Hamasalim, 2015). Probiotic is defined as mono or mixed cultures of “live microorganisms which, when administered in sufficient amounts confer a health benefit on the host” (Sekhon, 2010). A new description by the American Academy of Pediatric Committee on Nutrition states that probiotic is “microorganisms that generate small molecular metabolic by-products that made beneficial regulatory effect on host biological functions and may function as immunomodulators” (Hickey, 2012). Probiotics as a term was first used by Lilly and Stillwell (1965) to describe the ‘substances secreted by one microorganism that stimulate the growth of another’. Parker (1974), proposed that Probiotics are ‘organisms and substances which contribute to intestinal microbial balance’. Later on, Fuller (1989) wanted to assure on the microbial nature of probiotics. He redefined the word as "dietary supplement of live microbes that beneficially affect the host by improving its intestinal balance".

A similar definition was given by Havenaar and Huis Int Veld (1992), who however redefined probiotics as "live cultures, consisting of one or more microbes which, when administered to animals or humans, are beneficially affecting the host by improving the properties of the intestinal flora". A few years later, in 1998, probiotics have been described by Guarner and Shaafsma as " live microorganisms, which when consumed in sufficient quantities, produce beneficial effects on the host beyond those of basic nutrition". Moreover, in the next year, ILSI (International Life Sciences Institute) Europe Working Group defined it as "A live microbial food ingredient that is beneficial to health". After that, the definition proposed by Schrezenmeit and de Vrese (2001) sets out that "probiotics are a preparation of microorganisms or a product that contains live, defined microorganisms, which positively alter the composition of the microflora by implantation or colonization in a host's residence, after repeated periodical reintroduction, thus exerting beneficial effects on health" (Αλεξοπούλου,?). Food and Agriculture Organization of the United Nations/ World Health Organization (FAO/WHO, 2001), defined Probiotics as "Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (Amara, 2015).

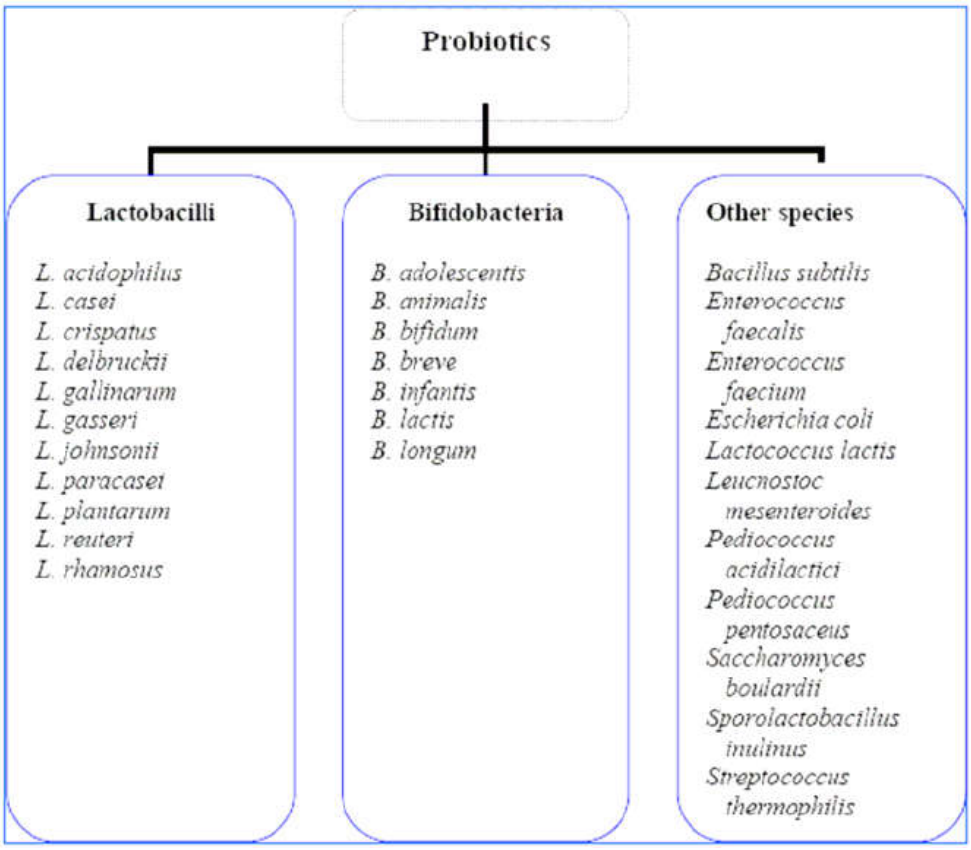

Figure 1. Microorganisms are used in probiotics (Anandharaj, 2014)

The definition was maintained by the International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2013 (Hill, 2014). laterGrigorov demonstrated how healthy bacteria in yogurt helped digestion and improved the immune system. He confirmed that some of the bacterial organisms present in the large intestine were a source of toxicants (toxic substances that contributed to illness and ageing). He suggested that "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes". To test the hypothesis on the health benefit of consuming lactic acid bacteria, Metchnikoff drank sour milk every day until his death at the ripe age of 71 in 1916. The concept of probiotics was thus born and a new field of microbiology was opened (Vishnu, 2012).

Microorganisms used in probiotics

The microbes used as Probiotics represent different types such as yeast, bacteria,or mold. However, there are more common species of each such as: 1- Bacteria: (i) Lactobacillus:

plantarum, rhamnosus,acidophilus delbrueckii, reuteri, brevis, casei, paracasei, gasseri, crispatus. (ii) Bifidobacterium: bifidum, infantis, adolescentis, longum, breve, lactis, animalis. (iii) Streptococcus: lactis, cremoris, alivarius, intermedius, thermophilis, diacetylactis. (iv) Leuconostocmesenteroide (v) Pediococcus. (vi) Propionibacterium. (vii) Bacillus; (viii) Enterococcus. (ix) Enterococcus faecium. 2-Yeast and molds: Saccharomyces cerevisiae, Saccharomyces bourlardii, Aspergillus niger, Sacaromycesboulardii. The type of the microbes used as Probiotics increased due to the increase in the research concerning the subject as well as by the increase of the newly discovered and identified microbes, which could be used as Probiotics.

One should update his microbial flora from time to time and follow the research and the published data about Probiotics to gain more knowledge and ideas [31]. Probiotic may play a beneficial role in several health conditions and performance, includingtherapeutic effects Intestinal microbial composition, metabolic effects and immunomodulation (Anandharaj, 2014).

Following are the requirements which have been identified for a microorganism to be defined as an effective probiotic:

- The probiotic should give positive effects on GIT of the host. It should be acid resistant, bile resistant.
- The adhesive capability of probiotics must be firm and faster.
- The probiotic should possess high survival rate & multiply faster.
- Exclude or reduce pathogenic adherence.
- Safe, noninvasive, non-carcinogenic and non-pathogenic to the host Produce acids, peroxide and bacteriocins, antagonistic for the growth of pathogens.
- Coaggregate to form a normal balanced flora.
- Probiotics should be durable enough to withstand the duress of commercial manufacturing, processing, packing and distribution so it can be delivered alive to the intestine (Behnsen, 2013).

Sources of probiotics

The most common source of probiotics is Yogurt. Yogurt consists of milk (usually from the cow, goat or sheep) fermented by bacteria that modify lactose into lactic acid. Lactic acid is responsible for giving yogurt its characteristics (sharp taste usually changed into good taste by using sweeteners and flavoring) and also denatures and precipitates casein, resulting in a semisolid consistency. ‘‘Bioyoghurts’’

are produced in a similar way, but bacteria used for fermentation are of different strains, usually L. acidophilus. Fermented milk and fortified fruit juice are common sources of probiotics (Iqbal, 2014).

Mechanism of action of probiotics: Probiotic bacteria have various effects on the host cells for example the prevention and treatment of a wide range of disorders. The main mode of probiotic actions Include: 1) enhancement of the epithelial barrier 2) increased adhesion to intestinal mucosa and simultaneous inhibition of pathogen adhesion 3) production of anti-microbial substances 4) competitive exclusion of pathogenic microorganisms 5) modulation of the immune system. Recent data exhibit the effect of probiotics in interference with quorum sensing.

Enhancement of the Epithelial Barrier: The intestinal barrier is a major defense mechanism used to maintain epithelial integrity and to protect the organism from the environment. Defenses of the intestinal barrier consist of the antimicrobial peptides mucous layer, secretory IgA and the epithelial cells that form tight junctions (Ohland, 2010). Disruption of epithelial barrier has been reported in several clinical conditions such as GIT infection, celiac diseases and infection bowel disease. Importantly, Consumption of probiotic bacteria can contribute to increasing intestinal barrier function. The process of enhancement of the epithelial barrier is accomplished by the enterocytes produce thick mucus secreted by goblet cells which are dispersed in the luminal epithelium of the intestines. The probiotic bacteria have been reported to increase the secretion of mucus by excite of inflammation in the enterocytes of the intestines (Anderson, 2010). Many studies have indicated that enhancing the expression of genes involved in tight junction signaling is a possible mechanism to reinforce intestinal barrier integrity. Some of the probiotics are able to induce signaling pathway involved in tight junction. For instance, lactobacilli modulate the regulation of E-cadherin and β-catenin, in a T84 cell (Hummel, 2012). Alteration in levels of pro-inflammatory cytokines can lead to intestinal permeability in intestinal disease such as IBD. Consumption of probiotic bacteria prevents cytokine-induced epithelial damage by inhibiting tumor necrosis factor (TNF) (Liu, 2015).

Increased Adhesion to Intestinal: Probiotic bacteria are able to adhere to epithelial cells, thereby, can block adherence of pathogens. The anti-adhesive effect may result of competition between probiotic strains and pathogens for the same receptor or the induction of mucin production by probiotics which is a complex glycoprotein mixture that is thecomponent of mucous, thereby preventing the adhesion of pathogenic bacteria. Several studies exhibited that different lactobacilli proteins promote mucous adhesions and bacterial surface adhesions mediate attachment to the mucous layer (González-Rodríguez, 2012).

Competitive exclusion of pathogenic microorganisms: Competition for space to adhere between indigenous bacteria and exogenous pathogens result in the competitive exclusion of pathogenic bacteria. Lactobacilli and bifidobacteria have been shown to inhibit a broad range of pathogens, including E. coli, Salmonella, Helicobacter pylori, Listeria monocytogenes and Rotavirus (Chenoll, 2011). Exclusion is the result of different mechanisms and properties of probiotics to inhibit pathogen adhesion, including physical blocking of pathogenic bacteria colonization by probiotic bacteria from their favorite site such as intestinal villus, goblet cells and colonic crypts. The probiotic bacteria can alter the physical environment of the intestines in such a way that pathogenic bacteria cannot survive. Probiotic bacteria exclude the opportunistic bacteria in two ways. First, the probiotic bacteria compete with pathogenic bacteria for nutrients and energy source thus, preventing them from acquiring energy required for growth and proliferation of pathogenic bacteria in the gut environment. Second, probiotics produce several organic acid and volatile fatty acids (VFA) as a result of their metabolism and fermentation. Consequently, the PH of the gut is lowered below that essential for survival of pathogenic bacteria such as E. coli and salmonella. Probiotic bacteria also eject the colonization of pathogenic bacteria by attaching themselves to the surface of the gut thus preventing the adhesion of the pathogenic bacteria to gastrointestinal epithelium. Probiotic bacteria such as lactobacillus induces the excretion of the mucins from the goblet cells, thereby inhibits the adherence of pathogenic such as E. coli to the intestinal wall (Brown, 2011).

Production of anti-microbial substances: Antimicrobial substances produced by probiotics can lead to inhibition of pathogen replication. These components are almost always low-molecular-weight (LMW) compounds such as short chain fatty acids (SCFA), antimicrobial peptides (AMPs) organic acids, and deconjugated bile acids. Importantly, these LMW compounds are short chain fatty acids. Short chain fatty acids (SCFA), which include acetate, propionate and butyrate are produced by bacteria in the gut during fermentation of insoluble fiber from dietary plant matter. Organic acids, in particular acetic acid and lactic acid, have a strong inhibitory effect against Gram-negative bacteria, and they have been considered the main antimicrobial compounds responsible for the inhibitory activity of probiotics against pathogens. The undissociated form of the organic acid enters the bacterial cell and dissociates inside its cytoplasm. The death of pathogen can result from eventual lowering of the intracellular pH or the intracellular accumulation of the ionized form of the organic acid (Bermudez-Brito, 2012). Many LAB produce antibacterial peptides, including bacteriocins, small AMPs defensins and cathelicidins. Bacteriocins produced by Gram-positive bacteria (usually LAB, including lactacin B from L. acidophilus, plantaricin from L. plantarum and nisin from Lactococcus lactis) have a narrow activity spectrum and act only against closely related bacteria, but some bacteriocins are also active against food-borne pathogens [43]. The most common mechanisms of bacteriocin-mediated killing include the destruction of target cells by pore formation and/or inhibition of cell wall synthesis. Intestinal bacteria also produce a diverse array of health-promoting fatty acids. Indeed, certain strains of intestinal bifidobacteria and lactobacilli have been shown to produce conjugated linoleic acid (CLA), a potent anticarcinogenic agent. Probiotic bacteria are able to produce so-called de-conjugated bile acids, which are derivatives of bile salts. De-conjugated bile acids show a stronger antimicrobial activity compared to that of the bile salts synthesized by the host organism. It is well known that metabolites of some strains of probiotics can inhibit the growth of fungi and other species of bacteria such asmethyl hydantoin benzoic acid, and short-chain fatty acids (Hassan, 2012).

Probiotics and the immune system: Probiotic bacteria can affect on numerous cell types involved in the innate and adaptive immune responses such as epithelial cells, monocytes/

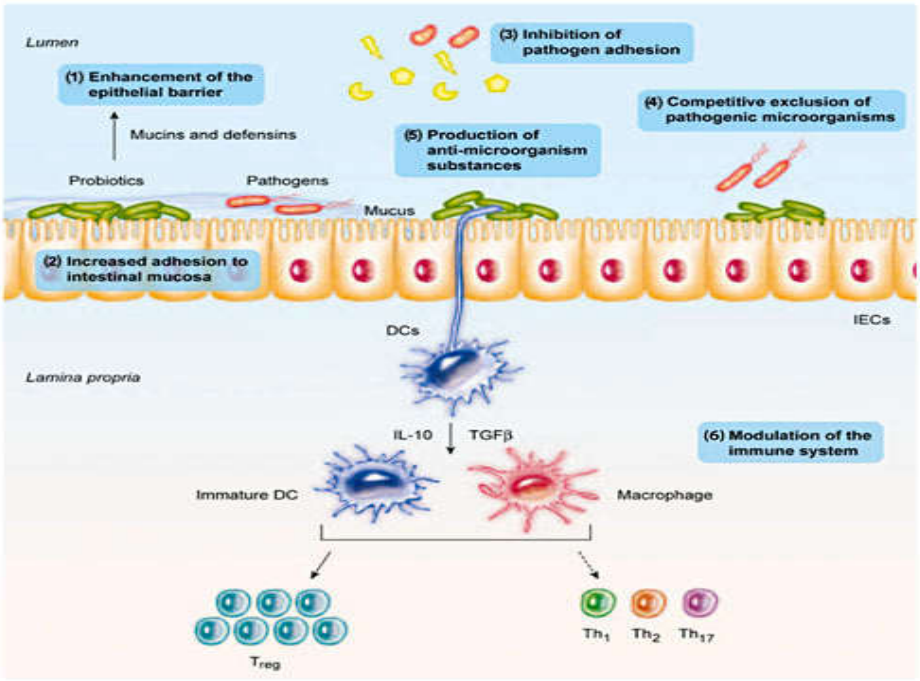

Figure 2. Mechanism of action of probiotics (Bermudez-Brito, 2012)

macrophages, dendritic cells, B cells, T cells, regulatory T cells and NK cells epithelial cells, dendritic cells, monocytes/ macrophages and thereby exert their immunomodulatory effect. Probiotic bacteria can reduce Th1 response and suppress the production of pro-inflammatory cytokines, IL-12, TNF-α, andIFN-γ by dendritic cells (DC). Administration of L. rhamnosus GG to children with acute gastroenteritis increased a nonspecific humoral immune response by an enhancement in IgG, IgA, and IgM secretion from circulating lymphocytes (Gómez-Llorente, 2010).

Interference with signaling factor of quorum sensing

Through chemical signals molecules called (auto-inducer), bacteria can communicate with each other and their surrounding environment through chemical signaling molecules. This phenomenon is known as quorum sensing (QS) that can measure the population density, nutrient concentration and other ecological characteristics. In addition to,(QS) can control the gene expression of the entire community in response to changes in cell number. Probiotic bacteria such as *Lactobacillus*, *Bifidobacterium* and *B. cereus* strains can produce autoinducers that can control virulence gene expression in numerous microorganisms. Lactobacillus acidophilus secretes a compound that reduces the production of auto-induced by E. coli and through it, leads to significant reduction in the transcription of genes involved in colonization (Vilà, 2010).

Role of probiotics in health and diseases

Oral Health

The use of probiotics to manage the oral microflora appears to be an effective method to control oral conditions because, The human mouth harbors diverse microbiomes in the human body such as viruses, fungi, protozoa and bacteria. The bacteria cause two common diseases namely dental caries (tooth decay) and the periodontal (gum) diseases.

The balance of all these microorganisms can easily be disturbed and a prevalence of pathogenic organisms can lead to different oral health problems such as dental caries, periodontitis, and halitosis. Species such as Streptococcus uberis and Streptococcus oralis also suppress periodontal pathogens. Probiotics was effective on halitosis and prevented the production of volatile sulfur compounds (VSC) by gram negative and gram-positive anaerobes residing in periodontal pockets and on the dorsal surface of tongue. A decrease in gum bleeding and reduced gingivitis has been observed with the application of L. reuteri (Anilkumar, 2012).

Diarrhea

Some probiotics have been revealed that they can treat a variety of gastroenteritis Diarrhea is the major world health problem which has its impact on several million deaths each year. They might decrease both the frequency of stools and the duration of illness. Antibiotic-Associated Diarrhea (AAD) occur after antibiotic therapy that mean an imbalance in the colonic microbiota. Alteration of microbiota changes carbohydrate metabolism with reduced short-chain fatty acid absorption. As a result, an osmotic diarrhea is occurred. Alsoantibiotic therapy leading to diarrhea is overgrowth of pathogenic organisms such as Clostridium difficile. For instance, Lactobacillus rhamnosus, Lactobacillus bulgaricus and yeast Saccharomyces boulardii may decrease the risk of AAD. Probiotics have been studied in prevention, and treatment of Clostridium difficile infections (CDI) and recurrent CDI. Lactobacillus rhamnosus GG (LGG) has shown to increase the expression of mucins and decrease the bacterial adherence (Cho, 2009). Probiotics supplementation of infant formulas has been aimed both at the prevention of rotavirus infections and the treatment of established disease. Several potential mechanisms have been proposed for how lactobacilli reduce the duration of rotavirus diarrhea. Treatment with L.rhamnosus was associated with an enhancement of IgA specific antibody secreting cells to rotavirus and of serum IgA antibody level during convalescence (Allen, 2010).

Lactose intolerance: The most common type of carbohydrate malabsorption is lactose intolerance (LI) also called lactose malabsorption. Due to low levels of lactase or β-galactosidase enzyme activity in patients, they are not able to digest lactose into glucose and galactose. Lactases produced by L. acidophillis and Lactobacillisdelbrlleckii ssp. are able to hydrolyze and ease absorption of lactose. The production of hydrogen in breath is an indicator of bacterial metabolism of lactose in the colon.

Irritable bowel syndrome: Irritable bowel syndrome (IBS) is a multifactorial disorder characterized by flatulence, diarrhea, constipation, and abdominal discomfort and pain. Intestinal gas can produce by gut flora but they also consume gas and probiotics might reduce gas accumulation and improve the balance within the bowel. There are many studies, and a number of reviews to demonstrate the mechanisms by which probiotics exert their beneficial effects on the host, suggested mechanisms of probiotics are as follows: The influence of intestinal luminal environment, the maintenance of epithelial and mucosal barrier function and the modulation of mucosal or systemic immune system including both innate and adaptive immune systems (Goudarzi, 2014).

Inflammatory bowel disease (IBD): Crohn's disease (CD) and ulcerative colitis (UC) are the chronic, relapsing or remitting diseases of GIT with more or less common symptoms. Both are collectively called inflammatory bowel disease (IBD). Probiotics are used in the treatment of inflammatory bowel disease likely decrease disease activity and increase remission through decreasing pathogenic bacterial growth byenhancing barrier function to prevent the invasion of tight junctions,lowering gut pH, and stimulating nonspecific and specific immune responses (Tiwari, 2012).

Lowering of cholesterol: There have been several mechanisms for the cholesterol lowering effects of probiotics, including deconjugation of bile acids by bile-salt hydrolase enzymes of probiotics, co-precipitation of cholesterol with deconjugated bile, assimilation of cholesterol by probiotics cholesterol binding to cell walls of probiotics, incorporation of cholesterol into the cellular membranes of probiotics during growth, conversion of cholesterol into coprostanol and production of short-chain fatty acids upon fermentation by probiotics in the presence of prebiotics.

Urogenital and vaginal health: The dominant microflora in a healthy woman vagina is a variety of Lactobacillus species which play essential roles in protecting women from genital infections. Any alteration in the population of lactobacilli can result in microbial imbalance in the vagina. Lactobacilli inhibit pathogen adhesion to the cells by produce biosurfactants and collagen-binding proteins. This may account for why the vaginal mucosa is dominated by lactobacilli making it less receptive to pathogens. Cell to cell communication could also be a mechanism by which probiotics stimulate mucus production which serves as a barrier to pathogens and also signaling the antiinflammatory cytokine production. In addition, L. acidophilus produces hydrogen peroxide and hypothiocyanate which inhibits the growth of C. albicans (Daliri, 2015).

Food and skin allergy: Small peptides and amino acids produced by some bacteria are able to made allergic reactions. Several research have shown that imbalance between bifidobacteria and clostridia can lead to allergies. Enzymes derived from L. casei GG degrade Small peptides and amino acids, in result it will produce molecules with inhibitory effects on lymphocyte reproduction. Mechanisms of antiallergic probiotic bacteria includemodulation of the immune system through the production of inflammatory cytokines, increasing intestinal barrier integrity, or enhancement of specific IgA responses and degradation of food antigens by means of productive enzymes of probiotics (Tiwari, 2012).

Anticancer effects

There are demand for anti-cancer activity of probiotics. Lactobacillus, Bifidobacteria and E. coli strains have anti-mutagenic activities due to ability to metabolize and inactivate compounds of mutagen. Probiotics have anticancer effect due to several mechanisms such as inhibition of procarcinogen transformation to active carcinogens, inactivation of mutagenic compounds, production of anti-mutagenic compounds, suppression of the growth of procarcinogenic bacteria, reduction of the absorption of mutagens from the intestine and reinforcement of immune system function (Soccol, 2010).

Production of vitamins: Vitamins are involved in many essential functions of the body like cell metabolism, synthesis of nucleic acids and antioxidant activities. Most of the vitamins cannot be synthesis by humans and animals, several species of bacteria may serve to produce folic acid, vitamin B12 or cobalamine, vitamin K2, riboflavin, thiamine, biotin and other essential vitamins (Lee, 2009).

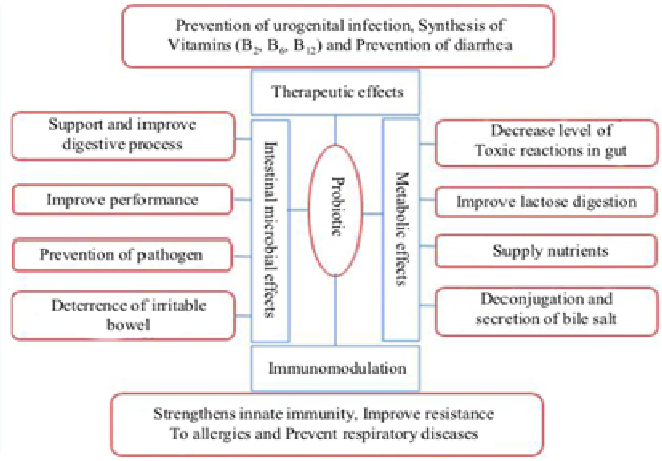

Figure 3. Role of probiotics in health and diseases (Hamasalim, 2016)

Prebiotics

History: In 1995, prebiotics were defined by Gibson and Roberfroid as non-digested food components that, through the stimulation of growth and/or activity of a single type or a limited number of microorganisms residing in the gastrointestinal tract, improve the health condition of a host (Tymczyszyn, 2014 and Liu, 2015). In 2004, the definition was updated and prebiotics were defined as selectively fermented components allowing specific changes in the composition and/or activity of microorganisms in the gastrointestinal tract, beneficial for host's health and wellbeing (Slavin, 2013). Finally, in 2007, FAO/WHO experts described prebiotics as a nonviable food component that confers a health benefit on the host associated with modulation of the microbiota

(Markowiak, 2017). Prebiotics may be used as an alternative to probiotics or as an additional support for them. However different prebiotics will stimulate the growth of different indigenous gut bacteria. Prebiotics have enormous potential for modifying the gut microbiota, but these modifications occur at the level of individual strains and species and are not easily predicted a prior. There are many reports on the beneficial effects of prebiotics on human health (Chung, 2016).

Types of prebiotics: Most identified type of prebiotics are carbohydrate found naturally in such fruit and vegetables tomatoes, as oatmeal, bananas, wheat , greens ,flaxseed, asparagus, barley, berries, garlic, wheat, onion and chicory, and legumes. Also, there are wide diversity of molecular structures. Importantly, these carbohydrates share numbers of physiological traits important to their beneficial effects (Ghouri, 2014). The largest number of reported studies and the most consistent evidence accumulated for prebiotic effects have been for several non-digestible oligosaccharides (NDOs) like fructooligosaccharides (FOS). The others include polyols (xylitol, sorbitol, mannitol), disaccharides (lactulose, lactilol), oligosaccharides (raffinose, soybean), oligofructose, other non-digestible oligosaccharides (palatimose, isomaltose, lactosucrose) and polysaccharides (inulin, resistant starch) (Calafiore, 2012). Inulin is resists digestion in upper gastrointestinal tract and fermented in the colon to produce short chain fatty acids, such as acetate, buty rate and propionate, which have positive effects on colonic cell growth and stability (Pradeep, 2012). Indeed, it appears that a wide range of non-digestible oligosaccharides (NDOs) can stimulate the growth of bifidobacteria and new potential prebiotics continue to emerge. There are evidence that some polysaccharide dietary fibers, such as resistant starch and plant gum have prebiotic potential is accumulating, but to date remains limited largely in vitro and animal studies (Śliżewska, 2012). It well established that lactulose, short-chain oligosaccharides, inulin, resistant starch and dietary fiber are not toxic, even at high doses (Slavin, 2013). Prebiotic is not broken down by gastric enzymes, but pass unchanged into the large intestine, where they are then selectively fermented, creating beneficial effects (Williams, 2010). The synergistic action of combinations of both pro and prebiotics are called Synbiotics as this approach includes a food or food supplement having both live cells of the beneficial bacteria and the selective substrate and the beneficial bacterial cells grow faster and competitively because of the presence of selective substrate and establish their predominance (Reddy, 2011).

Characteristics of ideal prebiotics

- Selectively enrich for or a limited number of beneficial bacteria.
- Neither hydrolyzed nor absorbed by mammalian enzymes or tissues.
- Beneficially alter the intestinal micro flora and their activities.
- Beneficially alter luminal or systemic aspects of the host defense system (Nazir, ?).

Sources of Prebiotics: Dietary sources of prebiotics include soybeans, inulin sources (such as Jerusalem artichoke, jicama, and chicory root), raw oats, unrefined wheat, unrefined barley, and yacon. Some of the oligosaccharides that naturally occur in breast milk play an important role in the development of a healthy immune system in infants. The breast-feeding infants have flora controlled by Lactobacilli and Bifidobacteria, which are part of the baby's defense against pathogens, which is an important primer for the immune system. These floras are nurtured by the oligosaccharides of breast milk, which is considered to be the original prebiotic. While some peptides, proteins, and certain lipids are potential prebiotics, nondigestible carbohydrates, in particular nondigestible oligosaccharides, have received the most attention (Anandharaj, 2014).

Mechanism of action of prebiotic

Modulation of the Gut Microbiota: Evidence from human feeding trials has shown that prebiotics affect the composition of the gut microbiota, leading to an increase in health-promoting organisms such as bifidobacteria and lactobacilli. These bacteria are generallysafe because they mainly ferment carbohydrates, are not pathogenic and are non-toxigenic, while they have a role in colonization resistance and frequently manifest immunomodulatory properties in the host. Some species are also able to ferment prebiotics to SCFA such as acetate and butyrate, which are important sources of energy for the host. While bifidobacteria do not produce butyrate, they have been shown to stimulate butyrate producing bacterial species such as eubacteria in the gut. SCFA also play a role in regulating growth and cellular differentiation, colonic epithelial cell transport processes, and hepatic control of lipid and carbohydrate metabolism (Sun, 2013). One advantage that prebiotics have over probiotics is that the target bacteria are already present in the host; however, it should be noted that if the organisms required to promote health are not already present in the gut, due to disease, for example, the prebiotic might manifest no useful effects. In certain cases, Studies with prebiotics have shown that they are able to reduce the numbers of some groups of bacteria in the gut, such as clostridia, bacteroides, enterococci and enterobacteria, some members of which may have a detrimental role in host health. Some of these organisms, particularly the clostridia, are directly toxigenic and are able to breakdown proteins, and ferment their component amino acids, resulting in the production of toxic metabolites such as indoles, phenols, ammonia, thiols, H2S and amines which may be involved in colorectal cancer. The sugar composition, and degree of polymerization of the prebiotic, together with the availability of other carbohydrates, all affect the way in which bifidobacteria (and other saccharolytic species) are able to grow on these substances (Cho, 2009).

Immune System: Evidencesuggests that prebiotics can have significant effects on the immune system. unknown if these are direct or indirect effects resulting from stimulation by immunomodulatory bacteria, or production of SCFA, which are known to have immunomodulatory properties, and can bind to SCFA G protein coupled receptors on immune cells within gut-associated lymphoid tissues (GALT). Addition of FOS and lactulose to the diet has been shown to increase mucosal immunoglobulin production, mesenteric lymph nodes, Peyer's patches and altered cytokine formation in the spleen and intestinal mucosa. Investigations on the effects of prebiotics on the immune system require careful assessments of the choice of markers, which will vary, and be dependent on the condition under study (Lee, 2009).

Anti-pathogenic activity: Prebiotics in diet protect the GIT from infection and inflammation by inhibiting attachment and/or invasion of pathogenic bacteria or their toxins to

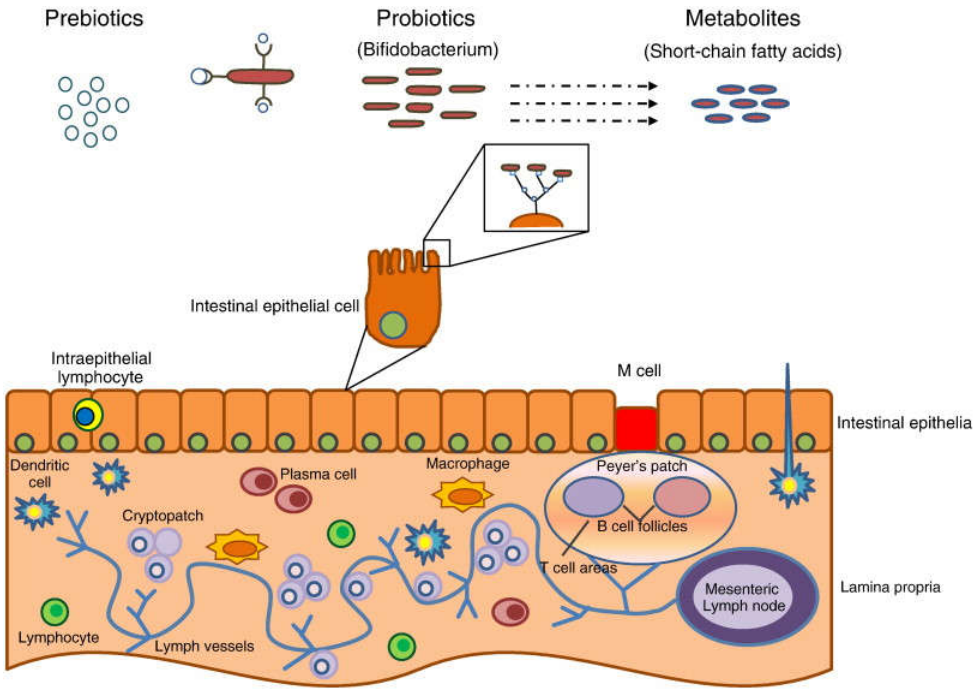

Figure 4. Mechanism of action of prebiotics (Tomar, ?)

colonic epithelium in various studies. This attachment is mediated by glycol conjugation glycoproteins and lipids present on the microvillus membrane. Prebiotic especially GOS contain structures similar to those found on microvillus membrane that interfere with the bacterial receptor by binding them and thus prevent bacterial attachment to colonic epithelium. Prebiotics, present in human milk are known to have antiadhesive properties and be capable of toxin neutralization (Tomar, ?).

Mineral Absorption: The ability to improve calcium, magnesium, iron and zinc absorption, and the attendant enhancement of bone mineralization is the most significant health effects of prebiotics on mammalian physiology and the attendant enhancement of bone mineralization. several mechanisms have been proposed for prebiotic action in mineral absorption. Although human studies have been limited and small in scale, this could be beneficial in preventing osteoporosis, a common and often painful disease, also in avoiding diet-related anemia and enhancing micronutrient absorption to avoid states of malnutrition. In humans, calcium is mostly absorbed in the small intestine, and prebiotic feeding studies have failed to show increased calcium absorption, suggesting that prebiotics were affecting these processes in the large intestine. Many investigations have confirmed findings suggesting that some calcium is absorbed from the colon, and prebiotic metabolism is thought to increase large intestinal calcium uptake. There are a number of mechanisms whereby this could occur. Fermentation of prebiotics, acts to lower intraluminal pH in the large bowel, thereby enhancing calcium solubility and bioavailability for absorption. Magnesium absorption has been specifically linked to the lactate pool in the gut, and low pH, but not the presence of SCFA. Lactic acid is more acidic than SCFA, implying that the mechanism is the act of lowering the pH directly absorption (Jain, 2014).

Health effects and applications of prebiotics

Laxatives: Lactulose is widely used as a pharmaceutical to treat constipation. Lactulose has an osmotic effect, trapping fluid, accelerating transit in the small bowel, and increasing ileocecal flow. Its rapid fermentation to SCFA and hydrogen also contributes to this effect and induces peristalsis by increased bowel content. A number of other NDOs, such as inulin has been shown to mildly improve stool frequency and consistency in adults although their applications are targeted towards functional foods rather than pharmaceutical applications.

Hepatic Encephalopathy: Lactulose are also front-line therapeutic agents for the treatment of hepatic encephalopathy (HE). This neuropsychiatric condition results from liver dysfunction. A dysfunctional liver is unable to clear ammonia from the blood stream, which then accumulates to levels toxic to the central nervous system. The ammonia is produced by the intestinal microbiota as an end product of protein metabolism. Lactulose act by limiting both ammonia production by the microbiota and the absorption of ammonia from the intestinal lumen. Inhibition of urease positive and deaminating bacteria (implicated in intestinal ammonia production) and importantly leads to the protonation of ammonia to ammonium ions in the intestinal lumen occur byacidification of the colonic lumen resulting from SCFA (Lee, 2009).

Amelioration of Inflammatory Bowel Disease: The microbiota is the likely source of the inflammatory stimulus, modification of the intestinal microbiota using antibiotics, probiotics, and prebiotics have all been proposed and trialed as approaches to treat IBD. Elimination of specific bacterial antigens, immunomodulation, and trophic effects of SCFA on the intestinal epithelium have all been proposed as mechanisms by which prebiotics could alleviate IBD. A healthy microbiota is predominantly saccharolytic, and contains a high concentration of bifidobacteria and lactobacilli. Treatment with prebiotics can alter the saccharolytic activity of the gut, as well as elevate the number of beneficial bacterial strains present in the microbiota. Studies in both animal models and human subjects have shown that prebiotic-induced stimulation of Bifidobacterium numbers has been associated with downregulation of inflammatory markers in intestinal mucosa

and evidence of increased immune regulation (Charalampopoulos, 2009).

Prevention of Colorectal Cancer: Prebiotics can be protective against the development of cancer. Secretion of carcinogens and tumor promoters by some species of bacteria of the colon can occur through the metabolism of certain types food; proteolysis in the colon is recognized as a mechanism for production of potentially malignant end products. Prebiotics modify the microflora by increasing the numbers of lactobacilli and/or bifidobacteria in the colon. The roles of short chain fatty acids, for example, acetate, propionate and butyric acid are being extensively studied because they have shown to inhibit the growth of colon tumor cells, encourage cell turnover and support normal gene expression (Jain, 2014).

Blood glucose: Evidence suggests prebiotics can favorably influence serum glucose and insulin levels in a variety of ways. Digestion resistant oligosaccharides, for example, inulin type fructans, galactooligosaccharides, lactulose and other prebiotics can reduce the amount of glucose available for absorption into bloodstream. Prebiotic also prevent excessive blood glucose elevations after a meal by delaying gastric emptying and/or shortening small intestine transit time. Bacterial fermentation making short chain fatty acids is another mechanism whereby prebiotics can modulate glycemia and insulinemia. The gut acts like an endocrine organ, producing a range of hormones that are devoted to the regulation of behavioral and metabolic function, by sending signals to the brain or other key target organs (eg. liver and pancreas).

Hypolipidaemic effect: First mechanism is the modification of glucose or insulin concentrations. Nondigestible carbohydrates reduce peak levels of blood glucose after a meal and consequently the inducation of lipogenic enzymes via an increased gene transcription. The second is the production of SCFA in the colon. The ratio of acetate to propionate reaching the liver is a putative intermediate marker predicting the potential lipid lowering properties of prebiotics. The third mechanism that serum cholesterol is reduced because of precipitation and excretion of bile acids to the intestine, which requires the liver to utilize cholesterol for further bile acid synthesis (Taiseer, ?).

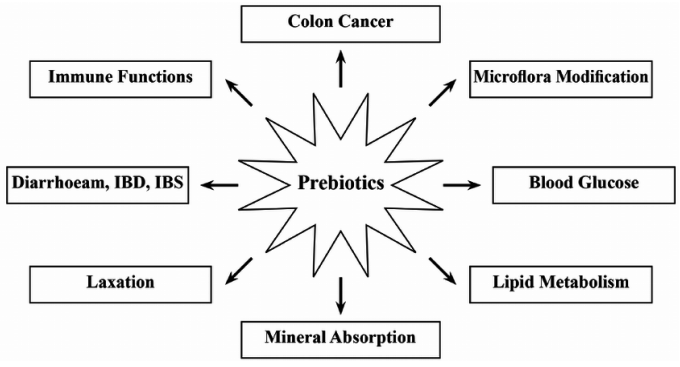

Figure 5. Health benefit of prebiotics (Taiseer, ?)

Conclusion

The intestinal microbiota forms a diverse and complex ecosystem. There is much variability in bacterial numbers and populations between the stomach, small intestine and colon. Human colon is an extremely- populated microbial ecosystem in comparison with other regions of GIT. This gastrointestinal microflora are important elements in the health of host animal. Moreover, environmental factors,medication anddiet, stress can all adversely affect the composition and/or activity of the GIT flora. The deficiencies created can be repaired either by added viable organisms (probiotics) or by stimulating specific components (e.g. Bifidobacteria) of the flora with chemical supplements (prebiotics). Probiotics and prebiotics are gaining popularity because of the innumerable benefits, e.g. treating lactose intolerance, hyperchloesterol problems. Also,Probiotic microbiota can have a significant influence on the treatment and prevention of various diseases. Prebiotics have similarities with dietary fiber functionality in that microbial fermentation of carbohydrate occurs. At present, a number of oligosaccharides have been used in foods and beverages such as candies, fruit juices, viscosity increasing agent and stabilizer of proteins, flavors and colors. Food supplemented with NDOs can have a potential to improve wellbeing and/or reduce the disease risk.

Author contributions

Athraa Saad Mtasher drafted the manuscript. Ali Jabbar Abdulhussein guided the review's composition and revised it. Shihab HattabMutlag did the proof reading and finalized it.

Acknowledgment: No acknowledgment.

Competing financial interests: No conflict of interest.

REFERENCES

Agans R, Rigsbee L, Kenche H, Michail S, Khamis HJ, Paliy O. Distal gut microbiota of adolescent children is different from that of adults. *FEMS microbiology ecology.* 2011 Jun 1;77(2):404-12.

Agarwal E, Bajaj P, Guruprasad CN, Naik S, Pradeep AR. Probiotics: A novel step towards oral health. Aosr. 2011;1(2):108-5.

Albenberg LG, Wu GD. Diet and the intestinal microbiome: associations, functions, and implications for health and disease. Gastroenterology. 2014 May 1;146(6):1564-72.

Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. *The Cochrane Library.* 2010 Jan 1.

Amara AA, Shibl A. Role of Probiotics in health improvement, infection control and disease treatment and management. *Saudi pharmaceutical journal.* 2015 Apr 1;23(2):107-14.

Amara AA. Toward healthy genes Ed. Amro Amara. 2012.

Anandharaj M, Sivasankari B, Parveen Rani R. Effects of probiotics, prebiotics, and synbiotics on hypercholesterolemia: a review. *Chinese Journal of Biology.* 2014;2014.

Anandharaj M, Sivasankari B, Parveen Rani R. Effects of probiotics, prebiotics, and synbiotics on hypercholesterolemia: a review. *Chinese Journal of Biology.* 2014;2014.

Anderson RC, Cookson AL, McNabb WC, Park Z, McCann MJ, Kelly WJ, Roy NC. Lactobacillus plantarum MB452 enhances the function of the intestinal barrier by increasing the expression levels of genes involved in tight junction formation. *BMC microbiology.* 2010 Dec;10(1):316.

Anilkumar K, Monisha AL. Role of friendly bacteria in oral health-a short review. *Oral health & preventive dentistry.* 2012 Jan 1;10(1).

Behnsen J, Deriu E, Sassone-Corsi M, Raffatellu M. Probiotics: properties, examples, and specific applications. *Cold Spring Harbor perspectives in medicine.* 2013 Mar 1;3(3):a010074.

Bermudez-Brito M, Plaza-Díaz J, Muñoz-Quezada S, Gómez-Llorente C, Gil A. Probiotic mechanisms of action. *Annals of Nutrition and Metabolism.* 2012;61(2):160-74.

Brown M. Modes of action of probiotics: recent developments. *Journal of animal and veterinary advances*. 2011 Jan 1;10(14):1895-900.

Calafiore A, Gionchetti P, Calabrese C, Tambasco R, Spuri-Fornarini G, Liguori G, Riso D, Campieri M, Rizzello F. Probiotics, prebiotics and antibiotics in the treatment of inflammatory bowel disease. *Journal of Gastroenterology and Hepatology Research.* 2012 Jul 21;1(6):97-106.

Charalampopoulos D, Rastall RA, editors. Prebiotics and probiotics science and technology. New York: Springer; 2009 Aug 12.

Chenoll E, Casinos B, Bataller E, Astals P, Echevarría J, Iglesias JR, Balbarie P, Ramón D, Genovés S. Novel probiotic Bifidobacterium bifidum CECT 7366 strain active against the pathogenic bacterium Helicobacter pylori. *Applied and environmental microbiology*. 2011 Feb 15;77(4):1335-43.

Cho SS, Finocchiaro T, editors. Handbook of prebiotics and probiotics ingredients: health benefits and food applications. CRC Press; 2009 Nov 19.

Chung WS, Walker AW, Louis P, Parkhill J, Vermeiren J, Bosscher D, Duncan SH, Flint HJ. Modulation of the human gut microbiota by dietary fibres occurs at the species level. *BMC biology.* 2016 Dec;14(1):3.

Daliri EB, Lee BH. New perspectives on probiotics in health and disease. *Food Science and Human Wellness*. 2015 Jun 1;4(2):56-65.

Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences.* 2010 Jun 29;107(26):11971-5.

Ghouri YA, Richards DM, Rahimi EF, Krill JT, Jelinek KA, DuPont AW. Systematic review of randomized controlled trials of probiotics, prebiotics, and synbiotics in inflammatory bowel disease. *Clinical and experimental gastroenterology.* 2014;7:473.

Gómez-Llorente C, Munoz S, Gil A. Role of Toll-like receptors in the development of immunotolerance mediated by probiotics. *Proceedings of the Nutrition Society.* 2010 Aug;69(3):381-9.

González-Rodríguez I, Sánchez B, Ruiz L, Turroni F, Ventura M, Ruas-Madiedo P, Gueimonde M, Margolles A. Role of extracellular transaldolase from Bifidobacterium bifidum in mucin adhesion and aggregation. *Applied and environmental microbiology.* 2012 Jun 1;78(11):3992-8.

Goudarzi M, Goudarzi H, Rashidan M. Probiotics: an update on mechanisms of action and clinical applications. *Novelty in Biomedicine.* 2014 Apr 28;2(1):22-30.

Groer MW, Luciano AA, Dishaw LJ, Ashmeade TL, Miller E, Gilbert JA. Development of the preterm infant gut microbiome: a research priority. *Microbiome.* 2014 Dec;2(1):38.

Hamasalim HJ. Synbiotic as feed additives relating to animal health and performance. *Advances in Microbiology.* 2016 Apr 7;6(04):288.

Hamasalim HJ. The Impact of Some Widely Probiotic (Iraqi Probiotic) on Health and Performance. *Journal of Biosciences and Medicines.* 2015 Aug 5;3(08):25.

Hassan M, Kjos M, Nes IF, Diep DB, Lotfipour F. Natural antimicrobial peptides from bacteria: characteristics and potential applications to fight against antibiotic resistance. *Journal of applied microbiology.* 2012 Oct 1;113(4):723-36.

Hickey L, Jacobs SE, Garland SM. Probiotics in neonatology. *Journal of paediatrics and child health*. 2012 Sep 1;48(9):777-83.

Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology and Hepatology.* 2014 Aug;11(8):506.

Hummel S, Veltman K, Cichon C, Sonnenborn U, Schmidt MA. Differential targeting of the E-cadherin/β-catenin complex by Gram-positive probiotic lactobacilli improves epithelial barrier function. *Applied and environmental microbiology.* 2012 Feb 15;78(4):1140-7.

Iqbal MZ, Qadir MI, Hussain T, Janbaz KH, Khan YH, Ahmad B. probiotics and their beneficial effects against various diseases. *Pakistan journal of pharmaceutical sciences*. 2014 Mar 1;27(2).

Jain M, Gupta K, Jain P. Significance of probiotics and prebiotics in health and nutrition. *Malaya Journal of Biosciences.* 2014;1(3):181-95.

Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Reddy DN. Role of the normal gut microbiota. *World journal of gastroenterology:* WJG. 2015 Aug 7;21(29):8787.

Johansson ME, Larsson JM, Hansson GC. The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host–microbial interactions. *Proceedings of the national academy of sciences.* 2011 Mar 15;108(Supplement 1):4659-65.

Kim YS, Ho SB. Intestinal goblet cells and mucins in health and disease: recent insights and progress. *Current gastroenterology reports.* 2010 Oct 1;12(5):319-30.

Lan Y, Kriete A, Rosen GL. Selecting age-related functional characteristics in the human gut microbiome. *Microbiome.* 2013 Dec;1(1):2.

Lee YK, Salminen S. Handbook of probiotics and prebiotics. John Wiley & Sons; 2009 Feb 17.

Liu HY, Roos S, Jonsson H, Ahl D, Dicksved J, Lindberg JE, Lundh T. Effects of Lactobacillus johnsonii and Lactobacillus reuteri on gut barrier function. *Physiological reports.* 2015 Apr 1;3(4).

Liu Y, Gibson GR, Walton GE. Impact of high fat diets, prebiotics and probiotics on gut microbiota and immune function, with relevance to elderly populations. *Nutrition and Aging.* 2015 Jan 1;3(2-4):171-92.

Magwira CA, Kullin B, Lewandowski S, Rodgers A, Reid SJ, Abratt VR. Diversity of faecal oxalate-degrading bacteria in black and white South African study groups: insights into understanding the rarity of urolithiasis in the black group. *Journal of applied microbiology.* 2012 Aug 1;113(2):418-28.

Marín L, Miguélez EM, Villar CJ, Lombó F. Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties. *BioMed research international*. 2015;2015.

Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients.* 2017 Sep 15;9(9):1021.

Nazir F, Salim R, Nissar J. Introduction to Prebiotics.

Ng KM, Ferreyra JA, Higginbottom SK, Lynch JB, Kashyap PC, Gopinath S, Naidu N, Choudhury B, Weimer BC, Monack DM, Sonnenburg JL. Microbiota-liberated host sugars facilitate post-antibiotic expansion of enteric pathogens. Nature. 2013 Oct;502(7469):96.

Nielsen DS, Cho GS, Hanak A, Huch M, Franz CM, Arneborg N. The effect of bacteriocin-producing Lactobacillus plantarum strains on the intracellular pH of sessile and planktonic Listeria monocytogenes single cells. *International journal of food microbiology.* 2010 Jul 31;141:S53-9.

Ohland CL, MacNaughton WK. Probiotic bacteria and intestinal epithelial barrier function. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2010 Mar 18;298(6):G807-19.

Pradeep K, Kuttappa MA, Prasana KR. Probiotics and oral health: an update: clinical review. *South African Dental Journal.* 2014 Feb 1;69(1):20-4.

Preston RR, Wilson TE. Lippincott's Illustrated Reviews: Physiology. Lippincott Williams & Wilkins; 2013.

Ramnani P, Chitarrari R, Tuohy K, Grant J, Hotchkiss S, Philp K, Campbell R, Gill C, Rowland I. In vitro fermentation and prebiotic potential of novel low molecular weight polysaccharides derived from agar and alginate seaweeds. Anaerobe. 2012 Feb 1;18(1):1-6.

Reddy JJ, Sampathkumar N, Aradhya S. Probiotics in dentistry: review of the current status. *Archives of Oral Research.* 2017 Nov 29;6(3).

Reddy P, Srivastava R. Probiotics the next savior in oral diseases. *International Journal of Dental Clinics.* 2011 Apr 28;3(2).

Ringel-Kulka T, Cheng J, Ringel Y, Salojärvi J, Carroll I, Palva A, de Vos WM, Satokari R. Intestinal microbiota in healthy US young children and adults—a high throughput microarray analysis. PLoS one. 2013 May 23;8(5):e64315.

Scanlon VC, Sanders T. Essentials of anatomy and physiology. FA Davis; 2014 Nov 25.

Sekhon BS, Jairath S. Prebiotics, probiotics and synbiotics: an overview. Journal of pharmaceutical education and research. 2010 Dec 1;1(2):13.

Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. *Physiological reviews*. 2010 Jul;90(3):859-904.

Slavin J. Fiber and prebiotics: mechanisms and health benefits. Nutrients. 2013 Apr 22;5(4):1417-35.

Śliżewska K, Kapuśniak J, Barczyńska R, Jochym K. Resistant dextrins as prebiotic. InCarbohydrates-Comprehensive Studies on Glycobiology and Glycotechnology 2012. InTech.

Soccol CR, de Souza Vandenberghe LP, Spier MR, Medeiros AB, Yamaguishi CT, De Dea Lindner J, Pandey A, Thomaz-Soccol V. The potential of probiotics: a review. *Food Technology and Biotechnology.* 2010 Oct 1;48(4):413-34.

Sun Y, O'Riordan MX. Regulation of bacterial pathogenesis by intestinal short-chain fatty acids. InAdvances in applied microbiology 2013 Jan 1 (Vol. 85, pp. 93-118). Academic Press.

Taiseer M, Youssef MM, Moharrm HA. Analysis, Health Benefits and Applications of prebiotics: A Review.

Tiwari G, Tiwari R, Pandey S, Pandey P. Promising future of probiotics for human health: Current scenario. *Chronicles of Young Scientists.* 2012 Jan 1;3(1):17-.

Tomar SK, Anand S, Sharma P, Sangwan V, Mandal S. Role of probiotics, prebiotics, synbiotics and postbiotics in inhibition of pathogens.

Tymczyszyn EE, Santos MI, Costa MD, Illanes A, Gomez-Zavaglia A. History, synthesis, properties, applications and regulatory issues of prebiotic oligosaccharides. *Carbohydrates Applications in Medicine*. 2014.

Vilà B, Esteve-Garcia E, Brufau J. Probiotic micro-organisms: 100 years of innovation and efficacy; modes of action. *World's Poultry Science Journal.* 2010 Sep;66(3):369-80.

Vishnu HP. Probiotics and oral health. InOral health care-pediatric, research, epidemiology and clinical practices 2012. InTech.

Walker AW, Ince J, Duncan SH, Webster LM, Holtrop G, Ze X, Brown D, Stares MD, Scott P, Bergerat A, Louis P. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *The ISME journal*. 2011 Feb;5(2):220.

Waugh A, Grant A. Ross & Wilson Anatomy and Physiology in Health and Illness E-Book. *Elsevier Health Sciences*; 2010 May 7.

Williams NT. Probiotics. *American Journal of Health-System Pharmacy.* 2010 Mar 15;67(6):449-58.

Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, Heath AC. Human gut microbiome viewed across age and geography. nature. 2012 Jun;486(7402):222.

Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, Li HB. Impacts of gut bacteria on human health and diseases. *International journal of molecular sciences.* 2015 Apr 2;16(4):7493-519.

Αλεξοπούλου Α. Probiotics and prebiotics in human health and animal welfare.

****