BENEFICENCE OF PROBIOTICS AND PREBIOTICS FOR HUMAN HEALTH: A REVIEW

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Abstract
Functional foods generally contain health-promoting components beyond traditional nutrients. It can be an unmodified natural food; a food in which a component has been enhanced through special growing conditions, breeding or biotechnological means or a food to which a component has been added to provide benefits. The health benefits imparted by probiotics and prebiotics have been the emerging area of research considering the prevailing lifestyle. These also facilitate smooth functions of the intestinal environment. Most commonly used probiotic strains are Bifidobacterium, Lactobacilli, Saccharomyces boulardiiand Bacillus coagulans. Probiotics play a beneficial role in a variety of medical conditions, including diarrhoea, gastroenteritis, irritable bowel syndrome, inflammatory intestinal and hepatic diseases, immune function, allergies, failure-to-thrive, hyperlipidaemia, Helicobacter pylori-based infections etc. Prebiotics fermented substrates that exclusively stimulates microflora growth in the gastrointestinal tract and therefore improve hosts' health. Fructo-oligosaccharides, inulin, oligo-fructose, lactulose and galacto-oligosaccharides, are commonly used together with probiotics to improve the viability of probiotics. Present review focuses on the roles of probiotics and prebiotics on human health.

Key words: gastritis, hepatic, hyperlipidaemia, irritable bowel syndrome, probiotic, prebiotic

Received: 16.02.2022 Reviewed: 30.03.2023 Accepted: 31.03.2022

INTRODUCTION

Elie Metchnikoff, also known as the Father of Probiotics, stated that themajorityof the diseases beginin the digestive tract whengood bacteriaare not able to get a control on the bad bacteria. The human gut microbiota constitutes a complexecosystem consisting of almost 1000species, 7000strains and gene that are more than 150 times than that of the human genome. Interaction between the microbial ecosystem and the host represents a long evolutionary symbiosis that is essential for optimal health throughoutlife. With the broad genetic and metabolic diversity of the resident microbiota, these microbes exert an effect on thehosts' metabolism, physiologyand immune systemdevelopment. For this reason, the microbiota is now recognized as a "virtualorgan". Every human surface which is exposed to the environment and every body part with an opening to the environment has a microbiome (Munoz-Garach et al. 2016). The Figure 1 and 2 shows the sites that harbor a normal flora and the distribution of gut microbiota in the human body respectively.

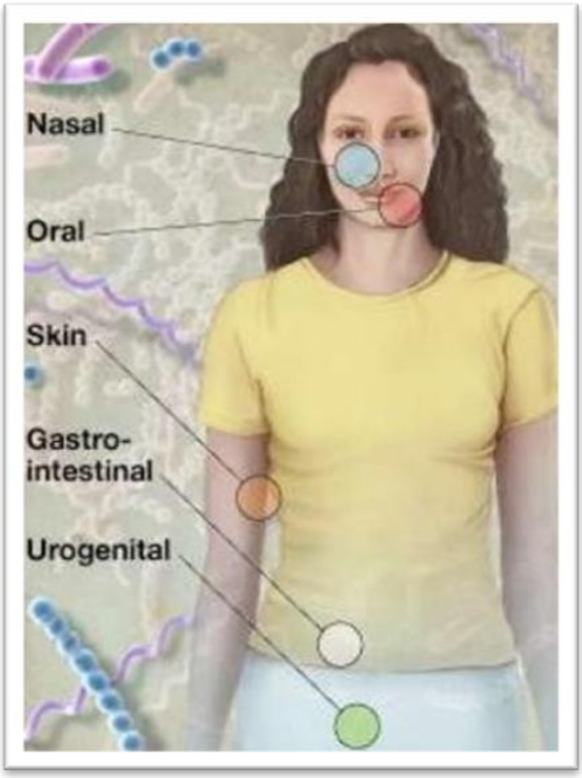

Figure 1. Sites harbouring microflora

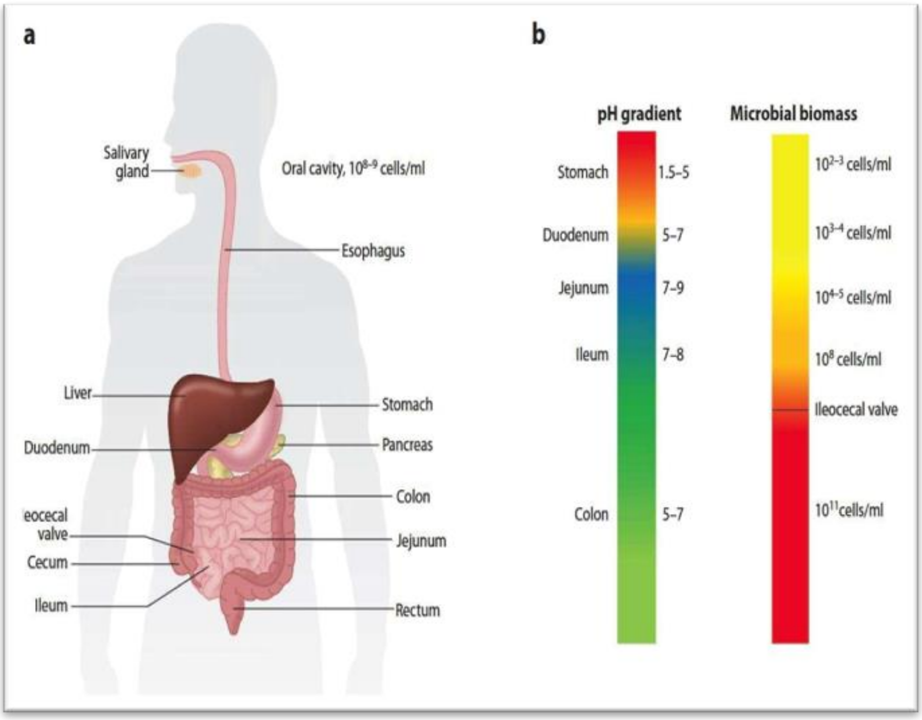

Figure 2. Distribution of Gut Microbiota

The human gastrointestinal tract is inhabited by a wide variety of microorganisms, comprising bacteria, archaea, viruses, fungus and protozoa. The activities and composition of these microbes (collectively known as gut microbiota, microbiome or intestinal microflora) can have an impact on human health and disease. Probiotics can populate the human gut mucosa in totally specific clusters based on the probiotic strain and the region of the gastrointestinal tract based on the baseline microbiota (Zmora et al.2018).

Non-specific, species-specific and strain-specific processes also have health consequences that are exerted by probiotics. Species or genera of predominantly used probiotic supplements are distinct in terms of non-specific mechanisms. These involve inhibiting growth of gastrointestinal pathogenic microorganisms (by fostering the resistance of invasion, enhancing intestinal transit or aiding to normalise discomposed microbiota), generating biologically active compounds (*e.g.*,SCFAs) and decreasing the colon luminous pH. Vitamin synthesis, strengthening of intestinal barrier, bile salt metabolism, enzyme activity and toxin neutralisation are included in the species-specific mechanisms. The strain specific pathways of cytokine generation, immune-modulation, and influence on the endocrine and neurological systems are unusual and used by just a few strains of a given species. Through all of these mechanisms, probiotics can have a significant impact on human health and disease (Hill et al. 2014).

Since probiotic effects may be unique to certain probiotic species and strains, clinical or research recommendations need to be species-specific and strain-specific (Sanders 2015).

Das et al. (2012) investigated the effects of probiotics on gut microbiota and found that probiotics reinstate the configuration of the gut microbiota and incorporate necessary functionality to the phenotypes of gut microbial or systemic disease, and also arrived at the conclusion that food and gut microorganisms' intestinal luminal conversion have a part in determining the form and composition of intestinal ailment. The different types of gut microbiota that are present in the gastro-intestinal tract are shown in the Figure 3.

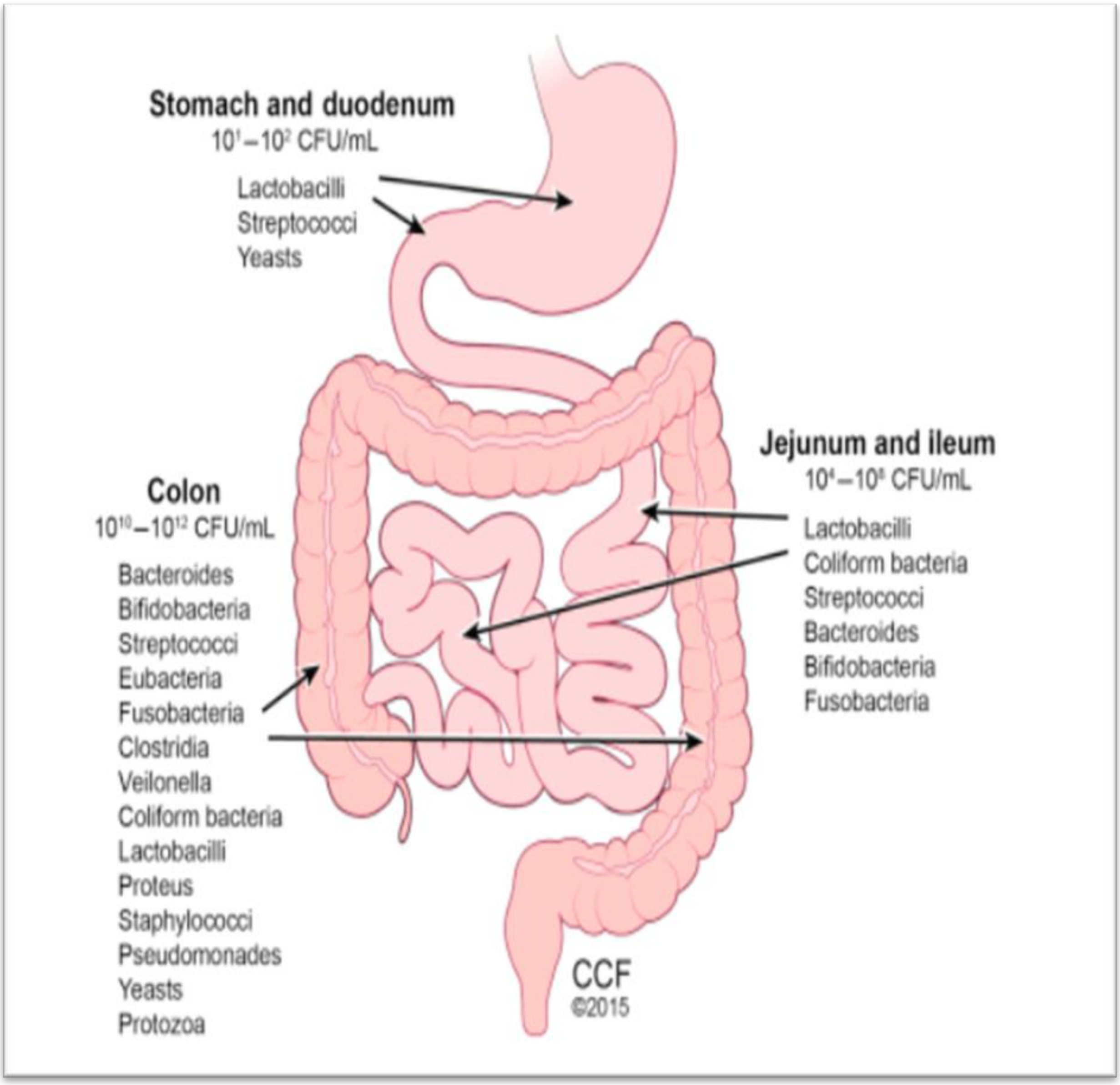

Figure 3. Types of Gut Microbiota (Cresci and Izzo 2019)

MATERIALS AND METHODS

1.1 Microbiome and Gut Dysbiosis

Dysbiosis is described as an "imbalance" due to the growth, loss or changes in the relative number of microbes in the gut microbial population. Gut microbiomes play an integral role in promoting food digestion, xenobiotic metabolism and control of innate and adaptive immunologic processes. Disease occurrence can be correlated with these roles (Messer and Chang 2018). Cell signalling and pathways are produced by proteins, peptides and metabolites released locally and in distant sites. The hosts' microbial homoeostasis is preserved by this intense crosstalk. Diet, ageing, stress and diseases can cause an increase or decrease in the relative abundance and variety of bacterial species in the GI and other body parts (Catinean et al. 2018). Animal model and human studies have shown that a chronic microbial gut imbalance contributes to inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), diabetes, obesity, cancer, cardiovascular and central nervous system disorders (Figure 4).

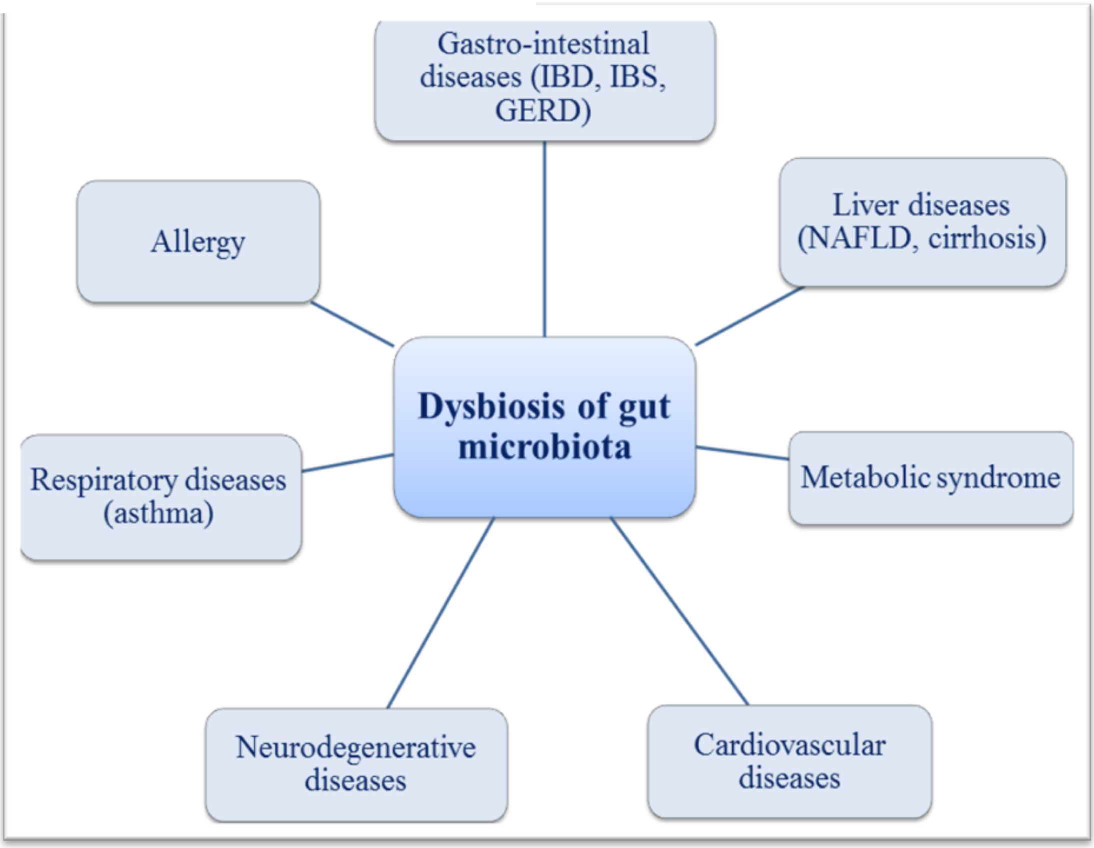

Figure 4 Gut Microbiota and associated health problems (Catinean et al. 2018)

Notably specific bacterial communities are promising clinical target to treat inflammatory and infectious diseases. In this context, intestinal microbiota transplantation (IMT) is one optional treatment for IBD, in particular to patients with recurrent Clostridium difficile-induced pseudo-membrane colitis.Whole gut microbiome dysbiosis is related to metabolic and inflammatory diseases and potential prophylactic and therapeutic applications of faecal and phage therapy, probiotic and prebiotic diets (Belizário and Faintuch 2018).

Diet is critical in ensuring this diverse microbiota since it comprises energy-supplying elements for the hosting microbiome. High-fat, high-sugar and low-fermentable-fiber diets can trigger dysbiosis, whereas low-fat, low-sugar and high-fermentable-fiber diets, particularly prebiotic fibre, can substantially support adequate energy homoeostasis and immunological responses, lowering the risk and maintaining optimum health. Dietary modification and synbiotic interventions can assist to maintain a healthy microbiota balance in a controlled environment, boosting energy and immunological homoeostasis. In a dysbiotic scenario, dietary modifications, probiotic and prebiotic therapy, and, in more serious situations, stool transplantation to restore the faecal microbiotamay help to respond to the disease (Tungland 2018).

2. CLINICAL SIGNIFICANCE OF PROBIOTICS

Health conditions including diseases of the gastrointestinal system, genitophytosis, asthma, urinary tract infections, bowel disease, immune disorders, *Helicobacter pylori* infections and cancer, *etc.* are strengthened *via* probiotics. Bacterial components or probiotic metabolites play a major role in the prevention of many diseases. Figure 5 displays the established characteristics of probiotics*i.e.*, pathogenicity, anti-diabetic behaviour, antiobesity, anti-inflammatory, anticancer and anti-allergy behaviour.

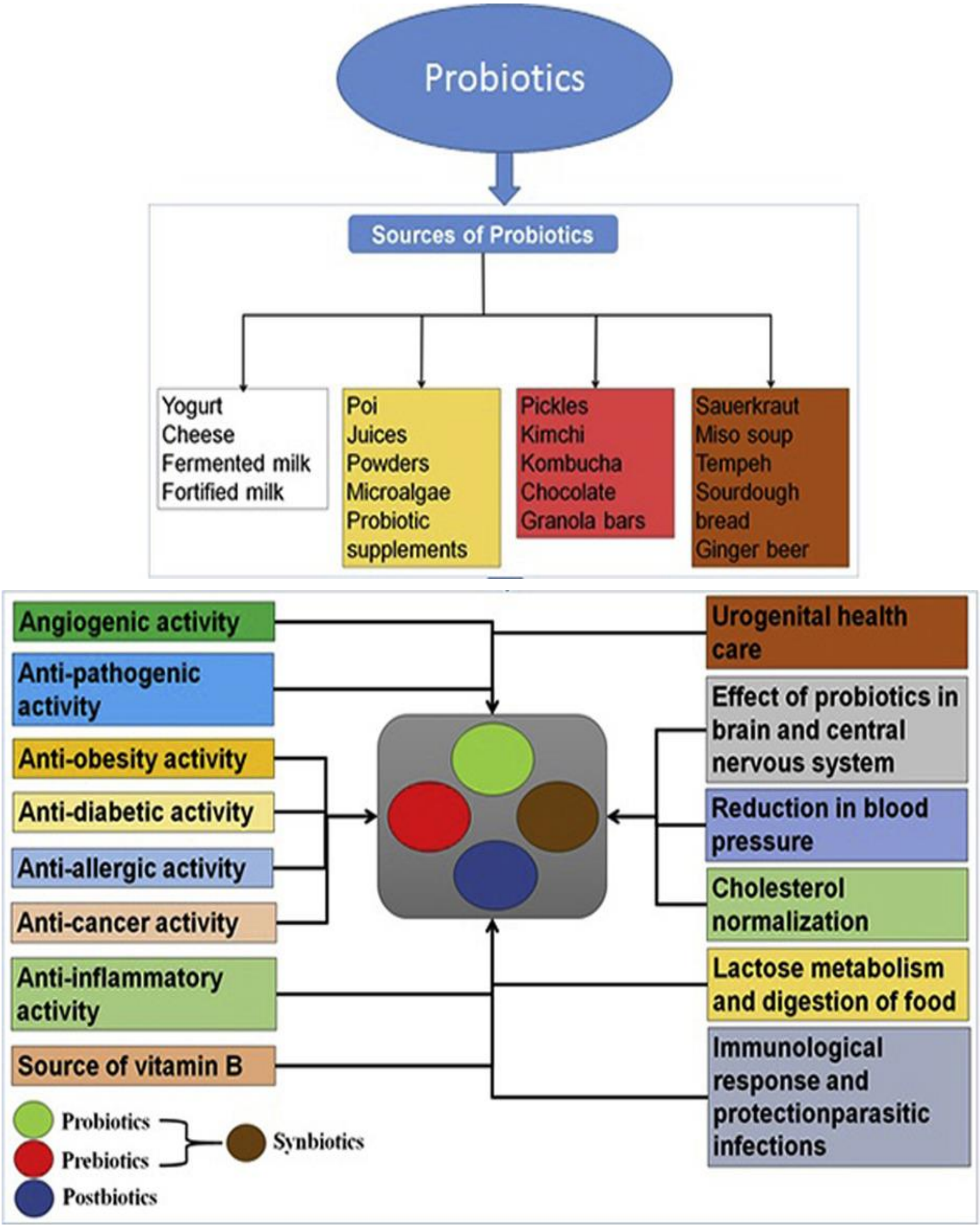

Figure 5. Health Benefits of Probiotics (Kerry et al. 2018)

2.1. Anti-pathogenic Activity of Probiotics

To mitigate infectious attempts by a pathogen, probiotic bacteria display several strategies. In combination with gut epithelium lining, probiotics act antagonistically and naturally inhabit beneficial microbes. A study conducted by Van Zyl et al.(2020) highlighted that the use of probiotic strains is focused on the premise at a given dosage; they alter the composition of the intestinal microbiota and counteract pathogens.

In an *in vitro* model, Oleskin and Shenderov (2019) analyzed the effect of probiotics on the survival of *Salmonella enterica, Serovar typhimurium* and *Clostridium difficile*. The results postulated that probiotics inhibit pathogenesis by producing short chain fatty acids (SCFAs), as acetic, propionic, butyric and lactic acids. SCFAs also help in maintaining an optimum pH in the colonic lumen.

Tomar et al. (2015) evaluated that pathogen inhibition and possible mechanisms of action are largely strain-specific, and the introduction of a new probiotic for its antimicrobial potential can also depend on its origin and place of isolation. The screening of anti-pathogenic activity of probiotics is typically based on the development of antimicrobial compounds verified by step-by-step in the initial *in vitro* studies and subsequent *in vivo* studies by animal models and final confirmatory confirmation by clinical studies seeking clear cyto-protection.

Anti-pathogenic action is considered to be one of the most beneficial results of probiotics, as disruption or alteration in the composition of the diverse gut microbiota community is prevented, unlike conventional antibiotics. Islam (2016) has recommended several anti-pathogenic compounds, such as acetaldehydes, bacteriocins, diacetyl, ethanol, hydrogen peroxide, organic acids and peptides, developed by various probiotics. In particular, bacteriocins and peptides increase membrane permeability between these target cell compounds, leading to an increase in the membrane depolarisation capacity. Another mechanism for showing the antipathogenic activity of probiotics is the competition between pathophageal binding and reception sites. The factors like nutrient availability and growth are responsible for showing the antipathogenic activity of probiotics.

Bacterial cultures, yoghurt starters and certain probiotic cultures was shown to be beneficial in improving the lactose digestion in lactose mal-digestors. The lactose-cleaving enzyme, β-galactosidase and bacteria from fermented or unfermented foods are very poor in the subjects suffering from lactoseintolerance. When consumption of fermented or unfermented food happens, the bacteria consumed releases β-galactosidase into the small gut, enabling lactose digestion (Li et al. 2012).

2.2. Probiotics and Urogenital Health Care

Non-sexually transmitted urogenital infections, such as bacterial vaginosis (BV), urinary tract infection (UTI) and many other yeast infections affect women worldwide, and the species usually linked to BV include *Gardnerella vaginalis, Ureaplasma urealyticum* and *Mycoplasma hominis.* Sexually transmitted infections, Gonorrhea and Chlamydia attributable to *Neisseria gonorrhoeae* and *Chlemydia trachomata*, respectively are also very common. The correlation of abnormal vaginal flora with a growing incidence of Urinary Tract Infection (UTI) is known and established (Hanson et al. 2016).

Chulani et al. (2019) documented that *Lactobacillus casei* administration increases insulin tolerance and preserves the Islets of Langerhans in Type-II diabetic mice. The underlying mechanism behind these results may be the PI3K/Akt signalling system and processes of SCFA/intestinal microbiota.

Ballini et al. (2018) stated that urogenital infections are a major medical problem around the world, affecting millions of women in response to various endogenous and exogenous factors due to drastic changes in bacterial composition and concentrations. A mutually beneficial relationship with their host is established by urogenital micro biota and has a significant effect on health and illness. There is now clear evidence that, while signs do not usually exist, a vaginal flora without

Lactobacilli corresponds with an infected condition (*e.g.*, BV). Such species as *Gardnerella vaginalis* have been shown to express factors of virulence that are thought to be responsible for causing a symptomatic disease.

2.3. Probiotics and Anti-diabetic Activities

In the control and maintenance of various physiological processes, the intestinal microflora has its significance. Once set, various internal or external variables can affect the gut microflora, which can alter its ecological structure. Type-II diabetes was studied to be correlated with compositional changes in intestinal microbiota with the slightly lower relative abundance of *Firmicutes*, while in diabetic patients the proportion of *Bacteroidetes* and *Proteobacteria* was higher compared to safety controls (Wang et al. 2020).

Wihansah et al. (2018) stated that antibiotics, prebiotics and probiotics are such influencers that can change different processes in the human body. Therefore, the gut microbiota is a main organ of the nutritional metabolism and may lead to obesity and diabetes. The use of probiotic products to enhance the beneficial microbiota is expected to be effective in neutralising the disorder.

Research by Sanchez et al. (2014) suggested that the administration of *Lactobacillus acidophilus, Lactobacillus gasseri* and *Lactobacillus rhamnosus*, can help in reducing the risk of Type-II diabetes mellitus and insulin resistance. A similar trend has been linked to the onset of auto-immune illnesses including Type-I diabetes(Hu et al. 2015). Microbiome modifications routinely encourage the infiltration of opportunistic diseases that are resistant to oxidative stress and can concurrently reduce sulphates while decreasing the rate of butyrate-producing bacteria (Hartstra 2015).

A research conducted by Iqbal et al. (2014) illustrated that the oral administration of probiotics containing *Lactobacillus acidophilus* and *Lactobacillus casei*can significantly delay the progression of high intolerance of fructose-induced glucose, especially *Lactobacillus casei* reduces the rate of plasma glucose.

The number of *Firmicutes* species have decreased significantly in patients with Type-II diabetes, thus raising the ratio of *Bacteroidetes* to *Firmicutes* which can be positively correlated with the level of plasma-glucose (Barrett et al. 2012).

2.4. Probiotics and Obesity

Obesity predisposes an increased chance of incidence of metabolic syndrome. A connection has been identified between obesity and certain gut microbiota which suggests that intestinal microbiota may be of critical importance in the development of obesity.

Latest systematic examination and meta-analysis of 15 random tests of 957 people who were overweight or obese have reported a decrease in the bodyweight (by 0.6 kg), body mass index (by 0.27 kg/m^2) and fat percentage (by 0.6 per cent) by the supplementation of various doses and strains of probiotic products for 3 to 12 weeks (Borgeraas 2018).

Lee et al. (2018) studiedanti-obesity activity of *Lactobacillus paracasei subsp.,Paracasei* NTU 101 and *Lactobacillus plantarum* NTU 102and their fermented products containing soy milkon insulin resistance and gut microbiota in Type-II diabetic mice and found that the administration of probiotics helps in reducing weight and managing diabetes.

The effectiveness of different probiotic and bacterial products used in milk-based products to prevent the development of obesity and enhance proven obesity management in mice fed a high fat diet has been investigated (Roselli et al. 2018).

A consistent analysis of 14 experiments in 1,067 overweight or obese individuals showed that the body weight and/or the body fat were considerably reduced in nine tests, with no results in three tests. And, a significant increase in body weight in two trials upon the administration of probiotics (mostly *Lactobacillus* administered at various doses for 3 weeks to 6 months) was also noted (Crovesy et al. 2017).

A link has been identified between obesity and certain microbiological intestinal microbiota, which shows that the bowel microbiota may play a significant role in obesity management. While there were several probiotic health benefits, the focus recently was on intestinal microbiotic manipulation, including lactic acid bacteria (LAB), which affected the growth of obesity (Tsai et al. 2014).

2.5. Probiotics and Anti-inflammatory Activity

The biologically active compounds were developed by probiotic species and beneficial microbes such as *Lactobacillus reuteri* that modulate the immunity of the hosts' mucosa. The anti-diabetic and anti-inflammatory properties of the probiotic *Lactobacillus fermentum* MCC3216 in high fructose Type-II diabetic rats was illustrated by Mahajan et al. (2019).Probiotics are considered to be beneficial microbes and provide medical benefits, if ingested in adequate quantities. Lactic acid bacteria are an essential category of probiotic bacteria used in human health care and treatment.

Ayyanna et al.(2018)investigated the potent antioxidant probiotic strains *Lactobacillus mucosae* and *Lactobacillus fermentum*. These strains were evaluated in Carrageenan(an additive used to thicken, emulsify, and preserve foods and drinks) in acute and full adjuvant-induced inflammation (chronic) models for their anti-inflammatory properties. Compared to the control and inflammation control tissues, the two probiotic strains displayed a low level of lipid peroxide production and greater anti-oxidant activity.

Gray et al. (2017) conducted a study and concluded that for the immune responses in the lungs, the presence of gut commensal bacteria is essential. Researchers have injected new-born mice with *Streptococcus albinicans, Escherchia coli* or *Candida albinicants*, from barrages which were either untreated or treated 5 days in advance with an antibiotic cocktail. This maternal antibiotic exposure did not only minimise the overall bacterial load on the pup's intestines but also raise *Streptococcus pneumonia* in the lungs. The oral inoculation of microbiota from antibiotically free mice to antibiotic-exposed mice restored the resistance to pneumonia to pups.

Lactobacillus reuteri, a part of the gut microbiome, converts a dietary component, L-histidine, into an immuno-regulatory signal, histamine, which suppresses the development of pro inflammatory TNF. The identification of the bioactive bacterial metabolites and their respective immunomodulation mechanisms can lead to improved anti-inflammatory strategies for chronic immune-mediated diseases (Thomas et al. 2012).

2.6. Probiotics and Cancer

The bacterial components or probiotic metabolites play an essential part in preventing many diseases. Cancer is one of the major risks to human health.

Saud and Adhikari (2018) studied that probiotic in the form of a single bacterial strain, or a combination of several, have demonstrated anticancer activity in humans through various mechanisms. *Lactobacillus acidophilus* LA102 and *Lactobacillus casei* LC232, two separate probiotic strains, have also been discovered to have considerable cytotoxic activity, with *in vitro* anti-proliferative interaction against two colorectal cancer cell lines (Caco-2 and HRT-18) (Awaisheh 2016). Probiotics also play a key role in cancer neutralisation, although research is confined to *in vitro* experiments. As a result, probiotics' anti-cancer potential must be demonstrated in *in vivo* models before moving on to animal and clinical trials.

In vitro investigations have reported that the probiotic strains *Lactobacillus fermentum* NCIMB-5221 and *Lactobacillus fermentum* NCIMB-8829 are exceptionally capable of inhibiting colorectal cancer cells and stimulating normal epithelial colon cellular proliferation by generating SCFAs (ferulic acid). This ability was compared to other probiotics, such as *Lactobacillus acidophilus ATCC 314* and *Lactobacillus rhamnosus* ATCC 51303, both of which have previously been identified as having antitumorigenic activity (Kahouli et al. 2015).

2.7. Probiotics and Allergies

It is considered that a genetic predisposition to allergy is of significance. Latest evidences

demonstrated the significantly positive effects of probiotics in treating and preventing allergies.In the prevention and treatment of various allergic reactions, Plaza-Diaz et al. (2019) tested the effectiveness of probiotics. The results have shown beneficial effects on the primary prevention of infant atopic eczema.
The free-radical scavenging behaviour of the *Lactobacillus plantarum* was studied by Giardina et al. (2014). In addition, *Lactobacillus plantarum* was also identified with beneficial effects such as an anti-carcinogen, anticoagulant, antivirus and immune modulator, anti-inflammatory agent, antidiabetes agent and an antioxidant (Sornplang and Piyadeatsoontorn 2016).
Dendritic cells appear to make a significant contribution in channelling the beneficial immune response to probiotic bacteria and in interpreting microbial signals from the intrinsic to the adaptive immune system, whereas regulatory T cells are emerging as pivotal signaling pathways of probiotic-mediated responses, particularly in the lessening of allergic inflammation (Forsythe2011).

2.8. Angiogenic activity of Probiotics

A critical and necessary phenomenon for the process of wound healing is angiogenesis. The angiogenic mechanism includes the intentionally conceived sequence of cytokines, matrix degrading enzymes and chemokins, in which new vessels are formed by existing vessels by facilitating the mobilisation of inflammatory cells and generating cytokines. Deregulated angiogenesis plays an important role in essential human conditions such as cancer, diabetic retinopathy and IBD, and also in ulcerative colitis and Crohn's disease (Komi et al. 2020).
Saccharomyces boulardii, non-pathogenic probiotic yeast, has been revealed with defensive abilities against intestinal injury and inflammation. In all respects, probiotics intercede on molecular pathways for such effects and appear to be too vague. Probiotics may have a possible mode of action in angiogenesis by altering and down regulating inflammatory cytokine profiles, decreased visceral hypersensitivity, activating regulatory mechanisms often referred to as the feedback system, improving the structure of the epithelial obstacle and decreased spinal afferent traffic and stress reaction (Smits et al. 2013).

2.9. Probiotics as Potential Antioxidants

Probiotics are noted for their positive health benefits and are produced as dietary adjuncts. For both humans and animals, Probiotics are common residents of the gastrointestinal tract and may contribute to the reduction in the oxidative stress bymonitoring the composition of intestinal microbiota and preventing the excessive proliferation of harmful bacteria. *Lactobacillus* and *Bifidobacterium*, the most common probiotic microbes containing lactic acid, acetic acid and propionic acid, can reduce intestinal pH and inhibit the growth of various pathogenic bacteria in order to maintain the equilibrium of the gut flora. The *Lactobacillus rhamnosus* GG, which secretes low molecular weight compounds, can inhibit many gram positive, gram negative and anaerobic bacteria. In addition, for a particular probiotic strain, the production of various organic acids, bacteriocins and bio surfactants is detrimental to pathogenic microorganisms. In non-intestinal tissues *e.g.,* the liver and adipose tissue, the cell metabolism can often be disrupted by the gut microbes, which can further modulate lipid and glucose homoeostasis and systemic inflammation in the hosts' tissues (Ayyanna et al. 2018). From the donor molecules, Folate accepts one-carbon unit and operates different metabolic forms. The efficiency of DNA replication, repair and methylation affects the supply of folate. The capacity to manufacture folate has been intensively studied in different probiotic strains from several sources due to its potential antioxidant applications (Wang et al. 2017).
Mishra et al. (2015) studied the antioxidant potential of probiotics and found out that reduction in the oxidative stress and modifications in the essential antioxidant enzyme activity in human cells can be the resultant of intake of probiotics alone or foods supplemented with probiotics. The methods used are variations of those used to assess the antioxidant properties of foods based on plants.

Probiotic treatment can be effectively used to regulate the amounts of hosts' antioxidant metabolites (Al-Maskari et al. 2012; Amaretti et al. 2013).

2.10. Probiotics for Bowel Diseases

In the pathogenesis of intestinal disorders such as Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS), and of extra-intestinal disorders including allergies, asthma, Type-I diabetes, cardiovascular disease, metabolic syndrome and obesity, the imbalance in the gut microbiota, , or dysbiosis, is considered to play a significant role (Carding et al 2015). The efficacy of probiotic treatment against a number of gastrointestinal and other conditions has been constantly investigated.

Differences have been seen in the microbiota between Non-Alcoholic Fatty Liver Disease (NAFLD) and healthy patients, also patients with NAFLD have an increased intestinal permeability. To alter the gut microbiome, Fecal microbiota transplantation (FMT) can be a useful strategy. Insulin Resistance (IR), hepatic Proton Density Fat Fraction (PDFF) and intestinal permeability can be addressed when FMT from a healthy donor is administered to individuals with NAFLD. In NAFLD patients, FMT can also contribute to decrease the permeability of the small intestine(Craven et al. 2020).The incidence and length of antibiotic-related diarrhoea were also shown to be reduced with the administration of probiotics, in both children and adults (Guo et al.2019).

The effects of probiotics on gut microbiota were investigated by Das et al. (2012) and the results showed that probiotics have the potential to reclaim the structure and composition of intestinal microbiomes. Furthermore, probiotics were also proved to display positive functions to the phenotypes of intestinal microbes or systemic diseases. The study also stated that diet and bowel luminosity are important for preserving the structure and function of intestine microbial communities *via* intestinal microbes.

Meta-analytical researchinvolving 82 Randomised Controlled Trials (RCT) and more than 10,000 patients studied the ability of probiotic products to avoid antibiotic-related diarrhoea and concluded that probiotic usage did have a positive effect in preventing diarrhoea (Hempel et al. 2012).

2.11. Effects of Probiotics on Brain and CNS

The brain is a pivotal organ that is involved in the regulation, organisation and coordination of the body's homeostasis. Mutual contact between brain and gut is known and the exchanging of information was carried out through multiple immune systems, neuroendocrine pathways, and enteric nervous systems. Brain function abnormalities or deficiencies are directly related to the occurrence of a significant neurological and emotional disability (Qureshi and Mehler 2013).

A study by Cryan et al. (2019) proved a substantial decline in the symptoms of stress-induced gastrointestinal disorders, like vomiting and stomach ache by probiotic supplementation, but not affecting the social, emotional, behavioural, neurological, physical and sleeping problems related to an irksome lifestyle. Probiotic supplements, especially multispecies formulation, can positively control the intestinal microbiota, the brain function and can help to maintain the natural host immune state. The diet, genetic make-up and commensal microbiological species of the host are closely related to the positive effects of probiotics.

Pärtty et al. (2015) conducted a longitudinal study on infants which were followed for thirteen years. The research contained the administration of *Lactobacillus rhamnosus vs.* placebo for the first six months of life. In the placebo group, 17.1 per cent of children showed a concentration deficiency/hyperactivity disorder, which was not seen in the group provided with probiotics.

The beneficial influence of *Bifidobacteria longum* 1714 on the modulation of cognitive processes in an anxious mouse strain was researched by Savignac et al. (2015), and the neuroprotective properties of *Clostridium butyricum in vivo* were shown by Sun et al, (2016).

Bacillus fragilis can enhance anxiety-like, stereotyped, sensorimotor and communication behaviours, as commented by Hsiao et al. (2013). Probiotics, such as *Bacillus animalis* subsp. *Lactis, L. lactis* subsp. *Lactis* aids in the regulation of brain activity through the metabolic, neuroendocrine and immune pathways of the Central Nervous System. Probiotics also contribute to the early development of normal social and cognitive behaviours(Tillisch2013; Liu et al. 2015).
Cognitive dysfunction occurs not only due to a reduced brain activity, but also because of changes in the immune system and the microbiome. Recent findings have revealed that the addition of probiotics to the conventional functional diets helps in improving the hosts' emotional health and cognitive performance (Selhub et al. 2014; Zheng et al. 2015).
Probiotic strains like *Streptococcus thermophilus, Lactobacillus reuteri, Bifidobacterium bifidum, Lactobacillus acidophilus* and *Lactobacillus casei* are proved to be beneficial in suppressing the incidence and progression of experimental autoimmune encephalomyelitis (Kwon et al. 2013).
The potential forms in which probiotics have benefitted the mental wellbeing are the secretion of neurotransmitter-like molecules and the production of helpfulcommensal bacteria.

3. CLINICAL SIGNIFICANCE OF PREBIOTICS

Prebiotics are the non-digestible food additives that selectively stimulate or induce the growth and/or functioning of one or only a few positive colon bacteria, thus, improving the health of the host. Some of the potential health benefits of prebiotics developed are as follows in preventing and treating various diseases.

3.1. Prebiotics and Gastrointestinal Disorder

The first defensive line for both the intestinal barrier and gut-associated lymphoid tissue (GALT) is the Innate immune reactions. GALT is a monolayer that helps to selectively allow bacteria, toxins or antigens against entering the intestinal epithelium. The selectivity of the barrier is mediated by the development of complex protein networks linking the neighbouring cells and blocking the intercellular space. Desmosomes, adherence joints and tight joints are the three components of these systems. Autoimmune and inflammatory diseases are triggered due to any damage happening to this blocking mechanism. Many studies have confirmed the functions of prebiotics on flourishing the gut microflora (Figure 6) and also proved that the consumption of prebiotics would lead to improvement in the metabolic functionality of the intestinal flora. The bulking capacity of inulin-type fructans showed benefits for metabolic bowel functions and also contributed to inhibit and treat constipation. Prebiotic therapy has also shown strengthening of the intestinal barrier. Prebiotics are considered safe, non-toxic and demonstrate a beneficial impact on the management and treatment of various gastrointestinal diseases (Akram et al. 2019).
Impact of prebiotics on Crohn's disease and Irritable Bowel Syndrome (IBS) has been suggested in many reports. In the absence of any organic origination, IBS is a gastrointestinal condition characterised by persistent abdominal discomfort and altered bowel patterns. Crohn's disease is a type of persistent, relapsing IBD that may spread from the mouth to the anus to any portion of the gastrointestinal tract. The *Bifidobacteria* and *Faecalibacterium prausnitzii* population and the Bacteroides to Firmicutes ratio have been reported to have decreased in both IBS and Crohn's disease (Wilson and Whelan2017).
Kleessen et al. (2017) investigated the effect of inulin and lactose intake on faecal microflora, microbial activity and bowel habits in elderly constipated individuals. The results concluded that *Bifidobacteria* were increased to a significant level by inulin, but inulin decreased the amount and the frequency of *Enterococci* bacteria. In the individuals who were consuming lactose,an increase in the faecal counts of *Enterococci* and decrease in bacterial count of *Lactobacilli* and *Clostridia* was observed, while the overall bacterial count remained unchanged. Inulin had a better

laxative effect than lactose in this study and decreased functional constipation with moderate discomfort.

Prebiotics has been reported to influence the role of the gut barrier by influencing the epithelial cells of the intestines. It is due to a compromised gut membrane that induces chronic inflammation of the *Escherichia coli* lipopolysaccharide (LPS) from the GI tract. The penetration of *Escherichia coli* lipopolysaccharide (LPS) from the GI tract into circulation is the result of a weakened intestinal membrane, which can result in chronic inflammation. This inflammation allows the body's nutrient intake to be smaller, especially in children (Quigley 2012).

3.2. Prebiotics and the Immune System

The immune system comprises a broad range of cells and biomolecules associated with pathogenic microorganisms for the purpose of protecting cells from attacks. The immune system have two classes of responses which are called as Innate (or non-specific) and Adaptive (specific) immune responses. The innate immune system accelerates the gap between the self and the non-self, and allows the adaptive immune system to be enabled against the microbial threats (Kabat et al. 2014).The use of prebiotics allows the population of protective microorganisms to improve the immune function. Both animal and human researches have shown that the population of dangerous bacteria can be decreased by prebiotics along with the probiotics like *Lactobacilli* and *Bifidobacteria* (Shoaei et al. 2015).

According to Guarner (2013) prebiotics can influence the immune system directly or indirectly through either by particular products obtained from carbohydrate fermentation, or by modifying the microbial composition of the intestinal microbiota. A rise in the number of certain microbial genes/cells, or a relative decrease in the number of other microorganisms, will change the reciprocal interaction of microbes with immune sensors and modify the equilibrium between the effector and the regulatory pathways.

3.3. Prebiotics and Skin

People are less aware of prebiotics - foods or supplements containing a non-digestible component that selectively promotes the production and/or operation of healthy indigenous bacteria. Prebiotics may be more relevant when it comes to skincare. Suh et al. (2019) performed cell and clinical studies to study the inhibitory effect of GOS on skin pigmentation. GOS effects were tested *in vitro* on the aggregation of melanin. In this study, the melanin and erythema indexes were also read following the intake of GOS.

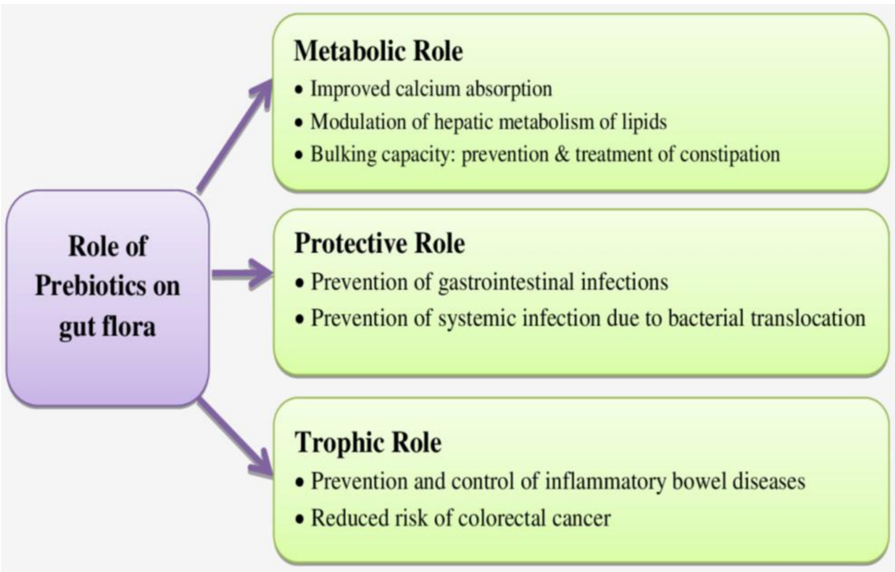

Figure 6. Role of Prebiotics on Gut Flora (Akram et al. 2019)

The results were indicative of inhibition in skin pigmentation, suggesting the implementation of this dietary approach in skin care. Hong et al. (2017) showed that GOS intake enhanced the moisture absorbing capacity of the skin and it also helps in the prevention of trans-epidermal water loss as compared to controls in UV-irradiated hairless mice.

Boyle et al. (2016) performed a randomised clinical trial for the prevention and management of eczema in high-risk children. The children were fed with a partly hydrolysed cow's milk formula enriched with inulin and positive results were achieved. Water, carbon sources (sugars, *e.g.*, mannose), nitrogen sources (amino acids) and oligo-elements are prebiotic agents that may help rebalance the skin microbiome. The efficacy of Galacto-Oligo Saccharides (GOS) in improving the water retention, reducing erythema and maintaining the skin health was also been reported.

3.4 Prebiotics and Cardiovascular System

A major health concern globally is the rising prevalence of cardiovascular diseases. Individuals with cardiovascular disease are also at risk or have other disorders, which combined may lead to metabolic syndromes and may raise the risk of morbidity and mortality. The microbial balance of the gut is increasingly recognized as a potential risk factor for cardiovascular disease. In several animal trials, the capacity of prebiotics to change/affect the serum lipid levels were illustrated. Therefore, prebiotic therapies can be used to combat obesity, which can further be closely linked to atherosclerosis, cardiovascular disease, and Type-II diabetes. Double-blind, randomised controlled trials of inulin, Fructo-Oligo Saccharides (FOS) and Galacto-Oligo Saccharides (GOS) were conducted on 12 humans by Černáková et al. (2019) and lower amounts of fecal acetate have been shown in the inulin and GOS therapy cycles.

Prebiotics, when fermented by the gut microbiota, yields SCFAs. de la Cuesta-Zuluaga et al. (2018) assessed the fecal microbiota of 441 adults and the SCFAs.Fecal concentrations were found to be inversely proportional to the diversity of the microbiota. Higher fecal SCFAs should be researchd upon for the development of obesity and cardiometabolic disregulation.

Mistry et al. (2018) stated that in a hypercholesterolemic rat model, probiotic supplementation decreases overall serum cholesterol. In this experiment, one of three diets supplemented with 0, 10, or 20 percent prebiotic fibre for 10 weeks was given to rats. Both prebiotic fibre doses decreased serum cholesterol levels by around 25 percent. This transition is also due to an improvement in caeca digestion and an increase in gene control concerned in the cholesterol biosynthesis and bile output. In comparison, obese rats with 10 percent prebiotic supplementation reported a drop in the concentration of triacylglycerol in the liver of around 40 percent.

3.5 Prebiotics and Bone Health

Driven by dietary prebiotic ingestion, intestinal atmosphere and tissue morphology are further strengthened by intestinal microbiota development. These improvements facilitate the generation of signaling molecules, immune cells and metabolites which beneficially influence the bone mineral uptake. Microbial signalling molecules will activate systemic neuroinflammatory responses that will eventually induce the release of hematopoietic and immune stem cells from the bone marrow which feed back to the intestinal tissue to influence intestinal microbial communities and tissue inflammation as shown in the Figure 7 (Whisner and Castillo 2018).

Prebiotics have shown that the calcium production in the lower intestine increases the bone mineral density and strength in humans as well as animals. Prebiotics enhance calcium absorption which is the secret for most processes and can create minerals for bone production. The prebiotic fermentation action to release short chain fatty acids contains templates to improve the absorption of calcium into prebiotics (SCFAs). Models for enhancing calcium absorption in prebiotics include prebiotic fermentation intervention to release the short chain fatty acids (SCFAs). Several prebiotic fibres, like acetate, propionate, butyrate, isobutyrates, valerates and isovalerates showed a consistent increase in the cecal SCFA (*i.e.*, soluble maize fibre or dextrin fibre, inulin, FOS, agave fructans). With regard to the relation between the bone metabolism and the prebiotic effects, some research findings have shown that prebioticscan adversely affect the functions of osteocytes and/or osteoclasts, depending on the situation and the type of prebiotics used (Davani-Davari et al. 2019).

Parallel studies conducted by Kruger et al. (2016) with FOS for 12 weeks (4gms/day) on premenopausal and postmenopausal women has concluded that the consumption of FOS reduced the bone resorption and improved the status of the vitamin D in both the cases.

Findings by McCabe et al. (2015) show that bone formation was improved and there was increase in the serum levels of osteocalcin in female mice after 6 weeks treatment with inulin and agave fructans.

The supportive impact of prebiotics on bone health were concluded by trials of prebiotic treatments using mixed prebiotics. For example, soy isoflavone was increased by FOS therapy in rats with the correct dosage of 10 µg/g/day of isoflavone (for 70 days). It also increased bone health at doses above 20 µg/g/day. The effect showed that bone resorption decreased rather than bone production was increased (García-Vieyra et al. 2014).

3.6 Prebiotics and Obesity

Gut microbiota helps to produce low level inflammation that impairs with the metabolism of glucose and absorption of fat. Such disturbances are distinguishing traits of obesity. Prebiotics strengthen the stability of the gastrointestinal barrier and decrease low-grade intestinal inflammation, thus enhancing metabolic changes and encouraging weight loss. Studies indicate that prebiotic fibre can assist in the digestion of intestinal fat and can thus be used as an efficient means to bring about weight loss. A risk factor for coronary disease, asthma, dyslipidemia, premature mortality, hepato-biliary disease, and many cancers is Obesity, which induces low-grade inflammation. Research performed by Maida et al. (2020) explored the correlation between body fat in obese children and prebiotic intake, and concluded that prebiotic foods like onions, garlic, asparagus, leeks, artichokes, bananas, *etc.* play a major role in body fat reduction.Another study conducted by Lenssen et al. (2018) claimed that prebiotic fibres impede caloric absorption into the bloodstream and hinder the gain of weight.

Obese persons seem to have a modified composition of the intestinal microbiota which indicates intestinal micro-biocenosis. This environmental component can lead to the development of obesity (Tamang et al. 2016).

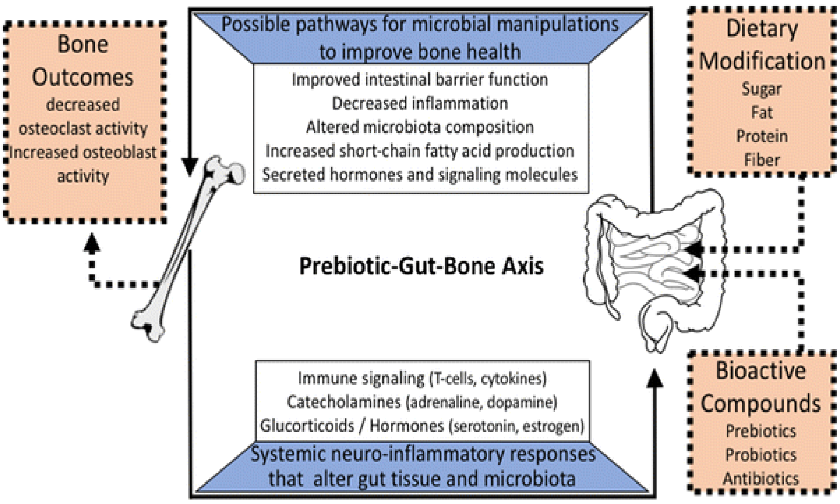

Figure7. Prebiotics, Bone and Mineral

CONCLUSION

Probiotic organisms are crucial for the maintenance of balance of human intestinal microbiota. Numerous scientific reports confirm the positive effect of probiotic son the host's health. Probiotic microorganisms are attributed to high therapeutic potential in, *e.g.*, obesity and diabetes. It has also been reported that probiotics are helpful in the treatment of irritable bowel syndrome, enteritis, bacterial infections and various gastrointestinal disorders. A positive effect of probiotics in the course of various neoplastic diseases and side effects associated with anti-cancer therapies is also worth noting. Prebiotics may be used as an alternative to probiotics, or as an additional support for them. It turns out that the development of bio-therapeutic formulas containing both appropriate microbial strains and synergistic prebiotics may lead to the enhancement of the probiotic effect in the small intestine and the colon. Those "enhanced" probiotic products may be even more effective, and their protective and stimulatory effect superior to their components administered separately.

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