PROBIOTICS, PREBIOTICS & SYNBIOTICS – IMPACT ON HEALTH

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ABSTRACT:

Probiotics are live, nonpathogenic microorganisms that are given to patients to help with microbial balance, especially in the digestive system. They are controlled as dietary supplements and foods and are made of *Lactobacillus* and *Bifidobacterium* species or *Saccharomyces boulardii* yeast. Probiotics work to benefit the body through a number of processes, including as reducing intestinal pH, preventing the colonisation and invasion of the body by harmful organisms, and altering the host immune system. Benefits of probiotics linked to a particular species or strain may not apply to others. Probiotics may help prevent conditions such antibiotic-associated diarrhoea, travellers' diarrhoea, irritable bowel syndrome (IBS), ulcerative colitis, Crohn's disease and vulvovaginal infections, hypertension, mental illness although more research is required to fully understand this. A probiotic should normally contain several billion germs to improve the likelihood that proper gut colonisation will occur, but there is no agreement on the minimum quantity of microorganisms that must be consumed to have a positive effect. Probiotics are typically seen to be safe and well tolerated, with bloating and flatulence being the most common side effects. Since systemic infections can infrequently happen, they should be used cautiously in patients who are very ill, highly immunocompromised, or those who have central venous catheters. Probiotics made from bacteria should be taken at least two hours apart from antibiotics.

Keywords: Probiotics,Traveller's diarrhoea **,** irritable bowel syndrome (IBS),Hypertension .

Introduction

The word "probiotics" is a Greek word that means "for life" Probiotics were described by an expert panel FAO (Food and Agriculture Organisation) and WHO commissiond as "live micro-organisms" which, when provided in sufficient proportions, impart a health benefit on the host. The bacterial genera *Lactobacillus, Bifidobacterium, Escherichia, Enterococcus, Bacillus,* and *Streptococcus* are the most frequently employed in probiotic formulations. Additionally, some Saccharomyces-related fungal strains have been utilised. Eli Metchnikoff, the 1908 Nobel Prize laureate, proposed that the long life of Bulgarian peasants was due to their consumption of fermented milk products, which is when the idea of probiotics first emerged. Lilly and Stillwell

used the word "probiotic" in 1965 to refer to chemicals generated by one organism that promote the growth of another. They were described as "microbial preparations or components of microbial cells that have a beneficial effect on health and well-being". Despite being a relatively recent concept, the health benefits of some meals containing live bacteria have been understood for ages. However, the idea of probiotics did not emerge until the early 19th century when researchers postulated that the gut flora could be changed by replacing harmful germs with good bacteria. Probiotics are bacteria or yeast that are regulated as food additives and dietary supplements. They come in the form of capsules, tablets, packages, powders, or other forms and are found in a variety of fermented foods, most frequently yoghurt or dairy products. Products with probiotics may contain a single species of bacteria or a blend of several. Probiotics may also be effective for treating conditions that are not related to the gastrointestinal tract or gut microbiota, such as numerous urogenital issues (such as bacterial vaginosis, candidal vaginitis, and urinary tract infections). Additionally, probiotics have been investigated for their potential benefits in the treatment of upper respiratory infections (such as acute otitis media), lowering the risk of bladder and colon cancer, allergic disorders, and atopy, enhancing immunological function, and preventing dental caries. Commonly, but not always, probiotics are commensal bacteria. The definition of probiotics that is most commonly used asserts that they are live microorganisms that, when given to a host in sufficient quantities, offer health benefits. Microorganisms must satisfy the majority, if not all, of the listed requirements in order to be considered probiotics.

The requirements or criteria to be used as probiotics are

- Genus, species, and strain level identification.
- DNA-DNA hybridization is the gold standard for species identification; 16S rRNA sequence analysis is a suitable alternative, especially if phenotypic tests are used for confirmation. Pulsed-field gel electrophoresis should be used to type strains. Strains should be deposited in an international culture collection.
- Nonpathogenic, not damaging to the intestinal mucosa, not transferring antibiotic resistance genes, safe for food and therapeutic use failing to conjugate bile acids.
- Antibiotics are effective against.
- Able to withstand intestinal transit; tolerant of bile and acid.
- Being able to cling to mucosal surfaces.
- Able to (at least temporarily) colonise the human gut or vagina.
- Creating antibacterial agents.
- Able to combat harmful bacteria.
- Having medically verified and confirmed health effects.
- Independent confirmation of results by a different centre for at least one phase 2 trial
- Stable throughout processing and archiving.

Health Benefits of Probiotics

Inflammatory bowel disease

Ulcerative colitis and Crohn's disease are two examples of inflammatory bowel disease that traditionally depict various patterns of chronic GIT inflammation. Recent clinical and experimental findings point to an imbalance in the intestinal mucosa, with a relative prevalence of aggressive bacteria and a relative scarcity of protective bacteria, as well as the stimulation of proinflammatory immune systems. Probiotics appear to be effective in treating IBD patients, as evidenced by improved gut barrier functioning, increased immune response, and lower production of inflammatory markers ex vivo, according to a number of investigations. Probiotics may therefore be able to induce or sustain remissions in IBD.

Cancers

Lactobacilli has the ability to attach to carcinogenic substances in the colon and also inhibit the growth of bacteria that turn procarcinogens into carcinogens, they can prevent or postpone the formation of intestinal tumours. Based on *lactobacilli's* capacity to alter gut flora and lower levels of β -glucoronidase and other carcinogens, it has also been proposed that *lactobacilli* lower the risk of cancer.Studies suggest that taking probiotics like *L. casei Shirota* internally may reduce the risk of urinary bladder cancer recurrence, however this discovery has to be verified.

Infections of the genitalia

Vulvovaginal candidiasis (VVC) and other symptomatic infections may result from abnormal vulvar microbiota. In healthy premenopausal women, *lactobacilli*—particularly *Lactobacillus crispatus* and *Lactobacillus iners*—are the most common vaginal microbes. *Candida albicans* may overgrow when the natural vaginal microbiome is disturbed, such as when using broad-spectrum antibiotics, which might result in VVC. This vaginal infection might be treated by using lactobacilli to restore the normal flora.

IBS (Irritable Bowel Syndrome)

Abdominal pain, bloating, gas, and irregular bowel movements are symptoms of IBS. These signs and symptoms could be the result of an overgrowth of bacteria in the small intestine, which would enhance fermentation and gas generation. Probiotics may be helpful in lowering the bloating and gas linked to IBS, according to some research. IBS is most usually treated with probiotics such as *lactobacilli* and *bifidobacteria*.

Traveller's diarrhoea

It is a common health issue for people who are on the move. Depending on the destination, traveller's diarrhoea rates might range from five to fifty percent. On published randomised controlled clinical trials of travellers' diarrhoea cases, a meta-analysis was conducted. Probiotics are proven to greatly reduce the risk of traveler's

diarrhoea. Significant effectiveness was seen with *Saccharomyces boulardii* and a blend of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*.

Antimicrobial effects

Various studies conducted in vitro reveal that various probiotic compounds have a number of distinct anti-pathogen effects, including those against *Listeria monocytogenes, Salmonella typhimurium, E. coli, and H. pylori,* among other pathogens. Probiotic medications may therefore offer prototypical antimicrobial compounds that will aid pharmaceutical companies in the creation of novel antibiotics.

Using probiotics for allergic disorders

Patients with atopic eczema have good effect when they consume probiotics. The effects of probiotics on allergies to the respiratory system, such as asthma, have also been studied over several years. According to researches, some probiotic strains may affect the gut mucosa and perhaps affect how allergic reactions are triggered.

Mental illnesses

It is possible to use probiotic microorganisms to aid in the bidirectional connection of the intestine-brain axis. In the treatment of disorders brought on by stress, including as anxiety and depression.

Mechanism of action:

The activity of probiotics has been attributed to a number of processes. As a potential defence against some kinds of diarrhoea, partial lactose digestion and promotion of intestinal mucosal lactase activity have been proposed. Utilising active beta-galactosidase, the lactobacilli employed in the fermented milk business might reduce the lactose content of dairy products, potentially reducing the severity of osmotic diarrhoea brought on by rotavirus. The growth of food-borne pathogens in dairy products is inhibited by the metabolites that lactic acid bacteria create, such as fatty free acids, hydrogen peroxide, and bacteriocins, among others. Probiotics can alter toxin receptors and prevent toxin-mediated disease using enzymatic pathways as well. By inhibiting competition, probiotics also stop infections from colonising. Other proposed methods for how intestinal microflora is affected include reducing intestinal pH, releasing gut-protective metabolites, controlling intestinal motility, and producing mucus. The primary point of contact between the immune system and the outside world is the mucosa of the digestive tract. Antigen transfer increases whenever intestinal microbiota decreases, demonstrating that the healthy gut microflora supports gut defences. To initiate the immunological signals, the non-pathogenic probiotic bacteria contact with the gut epithelial cells and the immune cells. These bacteria must interact with gut epithelial cells, related immune cells, and M cells in Peyers patches. The production of immunoglobulins has been found to be modulated by probiotic microorganisms. Mucosal immunity benefits from secretory IgA, which helps to form a defence against harmful bacteria and viruses. The most notable effect that probiotic bacteria and fermented milk yoghurt had was an increase in the number

of IgA-producing cells. The stimulation with probiotic bacteria has also been reported to raise the profiles of certain cytokines (TNF- IFN, IL-10). In order to control immune responses and preserve intestinal homeostasis, cytokines are released. It is still unclear how probiotic microorganisms interact with GALT (Gut Associated Lymphoid Tissue), how they modulate the immune system, and how they have anti-inflammatory characteristics.

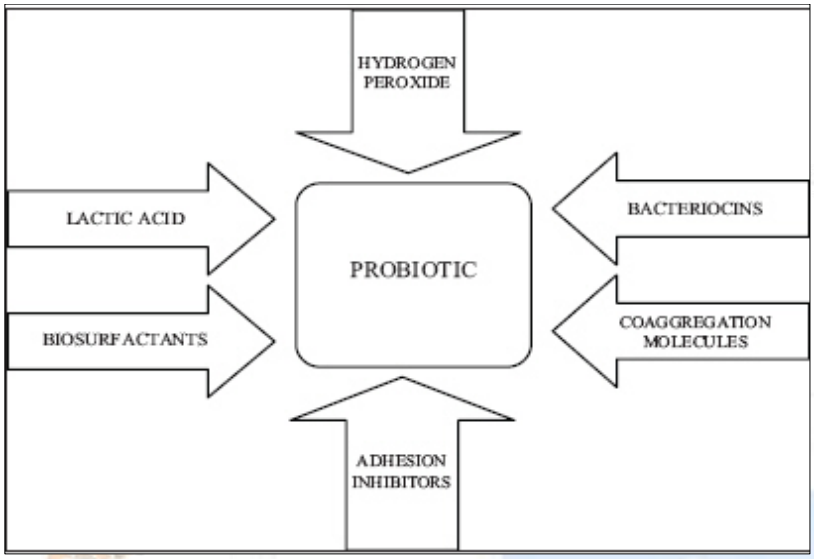

Figure 1 : Metabolic Products of Probiotics (Gupta *et al* ., 2009)

Role of Probiotics in Hypertension:

A risk factor for cardiovascular disease is hypertension. The control of hypertension frequently requires long-term therapy based on a cocktail of medications. However, antihypertensive medications might cause adverse effects in people. For example, beta-blockers have also been linked to depression. As a result, some novel techniques must be created in order to treat and prevent hypertension. The elements that directly influence the prevalence and progression of hypertension are environmental factors. Recent advances in sequencing technologies and the disappearance of microbial communities have prompted us to reconsider the billions of microorganisms that live in the human gut. The gut microbiota performs a wide range of metabolic and protective tasks for the health of the host, including the digesting of food, the breakdown of host-indigestible polysaccharides, and vitamin production. A growing area of research focuses on the connection between gut microbes and cardiovascular disorders. According to research there may be a connection between the incidence of hypertension and gut microbial dysbiosis.

Mechanism of Action:

Low microbial community richness has long been a risk factor that affects the symbiotic connections between hosts and microbes. Short-chain fatty acids are increased, colonisation and stability of the gut microbiota are encouraged, and the structure and function of the gut microbiota are affected. These effects help to control inflammation and influence host intestinal homeostasis. Probiotics control the balance of intestinal fora for a

number of reasons. The initial step is to create a variety of compounds, such as bacteriocins, to compete with harmful bacteria and subsequently prevent their development and reproduction in the intestine. Symbiosis with host cells is the second. The mucus layer of the gut lumen is home to the commensal microorganisms. Due to the splitting of mucin, the loose mucus expands in bulk, which enables bacterial penetration. According to recent research, colonic goblet cells MUC2 mucin exocytosis via VAMP8 preserves innate intestinal homeostasis. The third is that probiotics' metabolites, which include short-chain fatty acids, enzymes, and vitamins, boost the microbiota that is colonising the intestine. The decomposition of proteins produced peptides derived from dietary proteins, which had an antihypertensive effect. Casein and whey proteins can be hydrolyzed by probiotics into peptides that decrease the activity of ACE. By controlling the gut microbiota, preventing bacteriophages from producing nitrogen oxides, and other methods, probiotics and their fermented products may lower blood pressure. By controlling the gut microbiota, preventing bacteriophages from producing nitrogen oxides, lowering the formation of reactive oxygen species, and improving calcium absorption from food, probiotics and their fermented products may lower blood pressure. Probiotics and their fermented derivatives have also been shown to effectively lower cholesterol. Inflammation and hypercholesterolemia affect the renin-angiotensin system. With the expanding knowledge. A new approach to treating hypertension may involve using probiotics to control the gut microbiota or consuming fermented foods that contain antihypertensive peptides because of the probiotics ability to lower blood pressure. Blood pressure and the metabolic network linked to probiotics, gut microbes, and hosts are not completely understood yet.

Probiotic effects on hypertension via neuroimmune activation:

The metagenomic sequencing of host and symbiotic microorganisms helps us understand the intricate mechanisms of host-microbe symbiosis and the differences between healthy and ill people. In order to prevent the host from being killed by the immune system, symbiotic microorganisms direct their parasitic environment to activate bacterial metabolism in accordance with their survival needs. Animal studies have also demonstrated that certain chemicals derived from microorganisms can encourage particular symbiotic activities that are advantageous to the host and the microbes, while other compounds can cause the host's innate and acquired immune responses to be activated. Immune dysregulation and disease susceptibility arise in the body when the gut microbiota is altered. Experimental and clinical evidence is growing. Cells produce a lot of inflammatory cytokines when their BP is encouraged to rise which causes vascular endothelial dysfunction and vascular resistance to worsen. The link between elevated oxidative stress, inflamation, and autoimmune alterations and the onset of hypertension. In epithelial immunity, ACE2-mediated control of the gut microbiota is crucial. Masson discovered that SHR increased mean arterial pressure, heart rate, and vasomotor sympathetic activity in addition to increasing tumour necrosis factor (TNF), interleukin-6 (IL-6), and phosphorylation of human nuclear factor inhibitory protein (IKB-). The influence of brain-gut bone marrow connection on hypertension.

Prebiotics

Prebiotics are nondigestible food elements that, "beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon for improving the host health." A group of specialists from the International Scientific Association for Probiotics and Prebiotics (ISAPP) has examined the definition of prebiotic. The panel expanded the concept to include "a substrate that is utilised specifically by host microorganisms to confer a health benefit." This definition broadens the idea of prebiotics to potentially encompass substances that aren't carbohydrates, uses for body parts other than the gastrointestinal system, and several categories besides food. Typically, these are short-chain carbs.

Synbiotics

According to Markowiak and Liewska (2017), synbiotics are a combination of prebiotics and probiotics that are used to promote human or animal health. Probiotic bacteria use the prebiotics in synbiotic food products as a selective growth medium. A group of specialists from the International Scientific Association for Probiotics and Prebiotics has updated the synbiotics idea. They distinguish between complimentary and synergistic synbiotics. A probiotic and a prebiotic that are complementary synbiotics work together to provide one or more health advantages without requiring co-dependent processes. A synergistic synbiotic has a substrate that the co-administered microorganism(s) use specifically. These recommendations will be useful in the future for comprehending how pre- and probiotics interact and for creating synbiotic products with health and therapeutic uses.

COVID-19 and probiotics

Millions of people worldwide have been killed by the ongoing pandemic as a result of problems brought on by the coronavirus sickness. Unfortunately, the disease has been spreading despite the strict public health precautions that have been implemented globally, such as social distance, staff care, mask wearing, lockdowns, etc., leading to a rise in infections and fatalities everywhere. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which differs from other coronaviruses previously recognised, is the primary cause of this infection. As a result, antivirals currently on the market are not very effective. In these conditions, natural products like probiotics and their derivatives may be crucial in the prevention, management, and treatment of the continuing COVID19 pandemic, the post-pandemic, and other dangerous illnesses.

HIV infection and probiotics

Probiotics may specifically assist HIV-infected patients during therapy by enhancing the microbiota and lowering inflammation, according to recent research. While prebiotics have modulated gut microbiota reconstruction with reduction in lipopolysaccharides (LPS) and CD14 levels and activation of CD4+, T cells, and NK cells, few studies have demonstrated the use of prebiotics and probiotics in HIV therapy. Prebiotics are helpful in regulating the homeostasis of the resident gut and selectively increasing the growth of good

microorganisms with a concurrent decrease in pathogenic gut bacteria that cause opportunistic infections during HIV infection. Additionally, they have reduced clinical GI symptoms and CD4+ T cell counts. According to Dai *et al.* (2012), probiotics also control the intestinal epithelial barrier and lower the risk of contracting HIV.

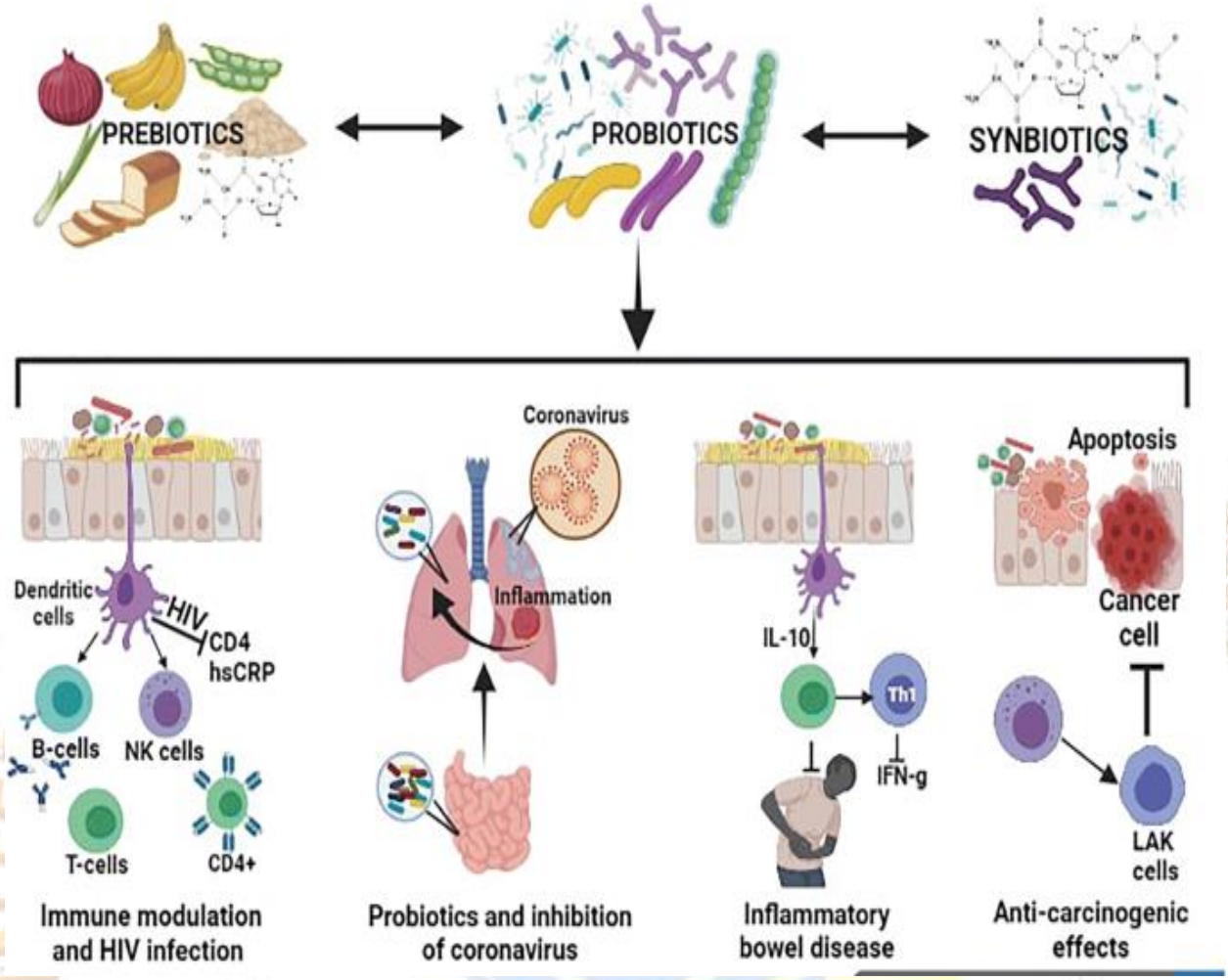

Fig. 1: A schematic diagram showing the potential roles of prebiotics, probiotics and synbiotics in immune modulation, inhibition of HIV and coronaviruses, inflammatory bowel diseases and cancer cells. HIV, human immunodeficiency virus; CD4, cluster of differentiation 4; hsCRP, high-sensitivity C-reactive protein; B cells, t-lymphocyte cells; NK cells, natural killer cells; T cell, t-lymphocytes; IL-10, interleukin-10; IFN-g, interferon gamma.

Safety Of using Probiotics

Due to their extensive history of usage in food fermentation, the majority of probiotics have been given the "generally recognised as safe" (GRAS) designation. However, there have been sporadic instances of bacteraemias and endocarditis linked to Lactobacillus, usually in those who are extremely immunocompromised. This led to the notion that probiotics should be the subject of some sort of surveillance. In their analysis of the safety information, Salminen & Donahue (1996) found no evidence that probiotics were connected to human illnesses. Epidemiological information on the safety of dairy products lends support to

this [3]. Probiotics are living microorganisms, hence it is possible that they could make the host sick. Probiotic strains come in a variety of safety characteristics. Although probiotic therapy is typically regarded as safe, the idea of voluntarily consuming living bacteria still seems a little strange. Bifidobacterium has rarely been linked to systemic infections, however *Lactobacillus rhamnosus* GG or Lactobacillus casei have been linked to sepsis in several cases. When Enterococcus spp. is used as a probiotic, the safety issue becomes more complicated. The potential for sepsis caused by more pathogenic bacteria and the morbidity of the illnesses for which probiotic bacteria are being employed as therapeutic agents should be compared against the danger and morbidity of sepsis caused by probiotic bacteria. Another study on dietetic goods for newborns recommends that probiotic therapies should be used with caution and that the use of organisms other than Lactobacillus should be encouraged. However, the conclusion based on several findings is that use of such products poses a minor danger to consumers, including immunocompromised hosts, and that the risk of infection with probiotics Lactobacilli or Bifidobacterium is equivalent to infection with commensal strains. However, FAO and WHO advise that probiotic strains be characterised at a minimum with a series of tests, such as antibiotic resistance patterns, metabolic activities, toxin production, hemolytic activities, infectivity in immunocompromised animal models, side effects in humans, and adverse outcome in consumers, in order to establish safety guidelines for probiotic organisms. In 2002, FAO/WHO created Operating Standards, which provided rules for all businesses manufacturing probiotic goods. The rules were:

1) Good manufacturing practises and the creation of high-quality products

2) Studies to determine the mechanism of action in vivo

3) Phase I, phase II, and phase III clinical trials to demonstrate health benefits that are equivalent to or superior to the recommended preventative measures or treatments for a specific condition or disease

4) Clear and informative labelling

5) The creation of probiotic organisms that can deliver vaccinations to their hosts and/or antiviral probiotics

6) The expansion of tested strains to benefit the mouth, nasopharynx, respiratory system, stomach, vagina, bladder, and skin as well as for cancer, allergies, and healing after surgery or injury.

7) Implementing the probiotics use guidelines is one of these recommendations.

Conclusion:

Probiotic microorganisms boost the immune system and suppress infections, which have a favourable impact on human health. There has been a lot of interest in probiotics and prebiotics in healthcare and consumer products because of their numerous health advantages. A thorough study's data, however, is only available for a few probiotics and prebiotics. The use of probiotics and prebiotics both separately and in conjunction (synbiotics) has been proven effective in the treatment and prevention of a wide range of life-threatening

conditions, including cancer, HIV infection, digestive disorders, and many more. Probiotics and their derivatives may also play a substantial role in the management of COVID19, according to sufficient data. Therefore, it is necessary to clinically validate more probiotics, prebiotics, and synbiotics for use in therapeutic and human health settings. For a complete knowledge of the structure and function of the microbiome with respect to probiotics and prebiotics, modern techniques based on molecular biology, genetic engineering, system biology, multiomics, nanotechnology, and immunology must be used.

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