**Title: Nanotechnology Intervention to Alleviate Disease-Specific Dysbiotic Microbiome**

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**Abstract**

Dysbiosis of the microbiome, characterized by an imbalance in the composition and functionality of microbial communities, has been linked to various diseases and disorders. The emerging field of nanotechnology offers promising strategies to address these dysbiotic conditions and restore microbial homeostasis. This abstract explores the application of nanotechnology interventions in alleviating disease-specific dysbiotic microbiomes. Nanoparticles in delivery systems provide unique opportunities for targeted and controlled delivery of therapeutic agents to the affected sites within the microbiome. Functionalized nanoparticles can be engineered to specifically interact with dysbiotic microbial populations, selectively delivering antimicrobial agents, probiotics, or prebiotics to restore a healthy microbial balance. Moreover, nanomaterials can be designed to enhance drug stability, solubility, and bioavailability, enabling precise modulation of microbial communities. Additionally, nanotechnology-based biosensors and diagnostic tools offer efficient and sensitive means for early detection and monitoring of dysbiosis. Miniaturized nanodevices can detect and quantify microbial markers, metabolites, and inflammatory biomarkers, enabling rapid and accurate diagnosis of dysbiotic conditions. These technologies can provide critical insights into disease progression, facilitate personalized treatment strategies, and monitor treatment efficacy. However, the translation of nanotechnology-based interventions for dysbiotic microbiomes into clinical applications requires addressing concerns related to safety, biocompatibility, and long-term effects. Comprehensive investigations of potential nanomaterial toxicity and environmental impacts are essential for ensuring the responsible development and deployment of nanotechnology in microbiome therapeutics. Further research and development efforts are necessary to advance these interventions benefiting patients suffering from dysbiotic microbiome-related conditions.

Keywords: Microbiome, Disease, Health, Probiotics, Immunomodulation.

**Introduction**

The human body contains approximately 100 trillion cells, while there are over one thousand trillion bacterial cells present, which is 10 times more than human cells. The thirty thousand human genes present in a body are responsible for the expression of 100 times more characteristics than microbial genes. These microorganisms in our body are referred to as the microbiome, and those in our intestines are referred to as the gut microbiome. These microorganisms are more than just present in our tissues; they play a vital role. They digest our food, produce vitamins, and educate the immune system to ward off pathogenic organisms. According to scientific studies, the modulation of the specific microbial community is accountable for the specific disease condition. Numerous investigations revealed a recurrent pattern of the microbiome that was unique to the condition; certain diseases were connected with over 50 genera, while others were found to have 10-15 genus-level modulations. Recent advancements in this field state that reverting to normal flora can overcome the disease by a therapeutic approach. The main problem is the lack of specificity in target-oriented modulation of the microbiota and metabolites. This limitation can be addressed using nanotechnology, as the usage of nanoparticles (NPs) in disease diagnosis and treatment has increased over the last few decades. Research on nanomedicine formulations for diagnostic and therapeutic purposes has produced a number of successful platforms, including those for integrated diagnosis, targeted drug delivery, and therapeutics. The development of nanoparticles with the proper sizes, morphologies, chemical compositions, and concentrations may be able to get around this fundamental barrier. Using nanoparticles as a delivery system for gut microbiota influences the route of biomarker detection and the route of the interaction of nanoparticles with target cells.

In recent studies on the microbiome and its impact on health is a topics of interest and the gut microbiome contributes to more than 90% part of the study. Trillions of microorganisms are present in our body majorly located inside the gut. Majorly there are two types of microbial community present in our body which is good and bad microorganisms. Good microorganisms are also called probiotic microorganisms [1,2]. Probiotics are live microorganisms when administrated in an adequate amount confers health benefits to the host [3,4]. Once established, these probiotic bacteria can exert their beneficial effect in many ways. Some reports showed the ability of probiotics that can produce vitamins, maintain gut pH, and modulate the host’s immune response. Moreover, they are well characterized for their ability to maintain the gut microflora, especially after an antibiotic course [2,5].

Imbalance in the gut flora, also known as dysbiosis is the decrease in the number of desirable microorganisms and an increase in the number of undesirable microorganisms in the gut [6]. Dysbiosis can lead to infections, poor nutrition, lack of nutrient absorption, etc. [7] as well as acute and chronic disorders such as Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Probiotics are generally regarded as living drugs with immunomodulatory, anti-carcinogenic, anti-allergic and anti-inflammatory effects [8]. Even though many reports are available regarding the inhibition of pathogenic microorganisms by probiotics, lack of specificity in target-oriented modulation of the microbiota and metabolites is the main problem. This limitation can be addressed using nanotechnology.

Nanotechnology is an applied scientific discipline and has diverse practical applications [9]. The term "nanotechnology" was initially used by the Japanese professor Norio Taniguchi [10]. A nanoparticle is a material with a diameter of 100 nm or less and is regarded as the fundamental unit of nanotechnology. Mycoplasma, the smallest microbe known to science, with a length of about 200 nm [11]. The Greek word "nano," which meaning "very small," is the basis of nanotechnology. Nanotechnology is a multidisciplinary science that combines several scientific fields including biotechnology, biology, chemistry, physics, medicine, pharmacy and engineering, etc. [12]. With nanotechnology intervention and interaction with microbiome to modulate hence alleviate dysbiosis. In this chapter we focus on the nanotechnology intervention to alleviate microbiome and addresses various diseases.

**Health benefits of probiotic microbiome**

The term “Probiotics” was derived from the Greek word for life [13]. Ellie Metchnikoff was the first researcher to propose the health benefits of probiotics, after observing the correlation between daily consumption of fermented food and health in Bulgarian populations. She explained that the microbiota present in fermented food plays a major role in maintaining a healthy gut environment. Recently, researchers have proven the ability of probiotics to control cholesterol in the blood as well as shown the link of probiotics in reducing heart disease, cancer and diabetes [14]. There is a proven link between the types of microflora present in the gut and the onset of disease. Evidence accumulated in the last decade clearly emphasizes probiotic intervention's importance for good microbiome health and clinical applications [15].

**Disease-specific microbiome and the role of nanotechnology**

Recent advances have been made in the understanding of probiotics and their beneficial and appropriate uses as therapeutic agents. It can be disease-specific probiotics which are stated by reported studies [16]. Change in the gut microbiome may be the centre point that can be responsible for various clinical conditions and maintaining the normal flora of the gut may be the best therapy to overcome [17]. Hundreds of studies are carried out on the association of the human microbiome and diseases and reported study states that the consistent pattern of the microbiome was found in specific diseases and can vary from disease to disease, some of the diseases associated with over 50 genera and some are 10-15 genus-level change [18].

According to WHO there are 35% of adults aged more than 20 and 400 million people were obese in 2008 and till 2015 it reaches 700 million found be obese research states that these changes are because by changes in eating habits, intake of abundant food and decrease in expenditure energy and because of high-fat sugar, and low fibre playing a key role in chronic diseases and metabolic syndrome such as obesity, diabetes, cardiovascular etc.

In a recent study, we come to know microbial ecosystems in obese and lean people are different, when obese lost weight then microflora revert back was observed [19]. Data also suggests that probiotics can modulate the markers of metabolic stress [20] and also help to decrease adiposity, fatty liver and glucose levels in different mice models. Manipulation of the microbial environment composition in the gut may be a novel method for the treatment of obesity. The gut microbiome plays important role in increasing body weight and insulin resistance which can be associated with increased energy harvest, increased blood LPS level and low-grade inflammation [21].

Modulation of gut microflora can be a potential target to treat obesity and diabetes, *Bifidobacterium* and *Lactobacillus* showed beneficial effects on obesity and diabetes. *Lactobacillus acidophilus* reported a decrease in insulin resistance and inflammatory markers [22]. The researcher found increased phyla Bacteroidetes as compared to Firmicutes in the diabetic condition which leads to decreased glucose tolerance which is a key problem of diabetes [23]. Lowering blood glucose by decreasing insulin resistance would be a possible way and it also lowers the hypertensive condition which is closely related to diabetes, Bifidobacterium was reported for levering insulin resistance [24]. A recent study indicates that dietary polyphenols contribute to maintaining gut microbial health stimulation of a good microbiome which is very low in diabetic patients polyphenols may reduce postprandial glucose response by increasing gut microbial health [25].

Changes in the gut microbiome depicted many diseases hypothesize associated with modulation of the specific microbial community in the specific disease condition, it includes metabolic disorders, inflammatory and autoimmune diseases, neurological conditions and cancer among others (Table. 1) but there is a lack of understanding precisely how microbial community and specific microbes with these community contribute to disease [26]. There are clinical indications for certain probiotic strains such as probiotics for necrotizing enterocolitis [27]. Antibiotic-associated diarrhoea and *H. pylori* infections defecation frequency infantile colic mild to moderate ulcerative colitis, IBS [28] Acute diarrhoea etc.

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| --- | --- |
| Probiotic culture | Effective against |
| *Lactobacillus acidophilus* | Maintain normal intestinal microbiota |
| *Lactobacillus paracasei* | Has antibacterial and anticandidal activity |
| *Lactobacillus rhamnosus* | Treat infectious diarrhoea |
| *Lactic acid bacillus* | Alleviates intestinal bowel disease symptoms |
| *Bifidobacterium lactis* | Eases ulcerative colitis |
| *Streptococcus faecalis* | Reduce typical symptoms of IBS |
| *Bacillus clausii spores* | Prevents side effects of *Helicobacter pylori* |
| *Saccharomyces boulardii* | Prevent antibiotic-associated diarrhoea |
| *Clostridium butyricum* | Effective against *Clostridium difficile* infection |
| *Bacillus mesentericus* | Decreases potentially pathogenic microorganisms |

Table no 1: List of reported disease-specific probiotics

Owing to the potential benefits, the nanotechnological intervention aims to develop more effective tools for the prevention and treatment of various diseases [29]. This could also offer solutions to long-lasting issues in medical research, such as poor drug solubility and a lack of target specificity for therapeutic compounds [30]. It has been shown that designing NPs with natural sources and lining them up into a methodical drug delivery mechanism is advantageous to gut microbiota. Curcumin and ginger-derived NPs are shown to improve absorption by gut microbiota, so that they can produce their respective effects [31,32]. Ginger NPs are made to contain microRNA that may help mice colitis, whereas studies have indicated that curcumin NPs inhibit the development of mouse colitis by increasing butyrate-producing bacteria and regulatory T cells (Tregs). Extracellular vesicles from other natural sources, such as milk, altered intestinal short chain fatty acids (SCFA) metabolites boosted gut immunity [33].

The ability to conceal NPs with natural cell membrane coating allows for their continued circulation and ultimate targeted administration. Red blood cell (RBC) membrane-coated NPs are one of the most extensively studied cell membrane-based nanocarriers for drug delivery to target cancer cells. Inorganic nanoparticles, in particular silver, titanium dioxide, silicon dioxide, and zinc oxide, have been shown to influence intestinal microbiota via their interaction with the immune system. This alteration in the gastrointestinal microbiota-immune axis is linked to numerous chronic diseases, including inflammatory bowel disease (IBD), diabetes, and colorectal cancer [34,35]. Due to their antimicrobial properties, silver nanoparticles (NPs) are used in hundreds of commercial products, and both intentional and incidental absorption of silver NPs, which may affect the gastrointestinal microbiome, are underestimated. Titanium dioxide nanoparticles, which are typically found in daily necessities, also alter the morphology and metabolism of the gut microbiota [36,37]. The detailed discerption for major diseases and the use of nanotechnology in targeted disease and gut microbiome is given below.

**Inflammation/Arthritis**

Probiotics are exhibit a direct effect on the gastrointestinal tract, these effects lead to an impact on immunity, via changes in inflammatory cytokines [38]. Inflammation associated with rheumatoid arthritis may be modulated by the use of probiotics. *Lactobacillus* GG has a potential character to reinforce mucosal barrier mechanisms in inflammation. Probiotics are known to increase phagocytosis and also help to increase anti-inflammatory cytokines like TNF [39]. Nanotechnology is proven for modulation of microbiome and induce the secretion of short chain fatty acids such as butyrate, propionate etc. which is reported to decrease inflammation [40].

Free radicals have been linked to a number of pathological diseases, including cancer, ageing, diabetes, atherosclerosis, Alzheimer's, cardiovascular diseases, and more. However, excessive free radical production causes oxidative damage, which in turn results in a number of chronic diseases. Because of their harmful toxicity in synthetic materials, the use of synthetic antioxidants is restricted. As a result, natural antioxidants are now the focus of research [41]. One of the key uses of the biologically created NPs is the search for green synthesised NPs for treating such free radical-related medical disorders.

**Lactose intolerance**

Lactose intolerance is the inability to digest milk sugar (lactose), or lactose digestive enzyme lactase. Consumption of lactose by those lacking lactase production in the small intestine can lead to lactose intolerance symptoms are gas, cramps, nausea, diarrhoea, abdominal pain and flatulence. Lactose intolerance can be cured by administrating probiotic bacteria. Probiotic microorganisms like *L. acidophilus* and *Bifidobacterial* reported improving lactose digestion [42].

**Vaginosis**

Microbiota is important to maintain vaginal health, vaginosis can cause by several different organisms, and in many cases. Lactobacilli predominate in the healthy vagina, and a lack of LAB or normal flora can lead to vaginosis. The Lactobacilli species and LAB can maintain the favourable pH in the vaginal tract and also produce bacteriocin, organic acid, hydrogen peroxide and other antimicrobial compounds to maintain healthy vaginal track Research suggests that Lactobacilli may help to control the incidence and duration of vaginal infections, but larger, controlled studies are needed [43].

**Diarrhoea**

Probiotics are widely used for diarrheal diseases. Major potential benefits are the prevention and treatment of acute viral and bacterial diarrhoea, as well as regulation of antibiotic-associated diarrhoea. Some particular strains, including *Lactobacillus GG, L. reuteri, Saccharomyces boulardii,* and *Bifidobacterium* these species are reported and effective against diarrhoea. Reported In vivo studies proved that saccharomyces boulardii is effective against antibiotic-associated diarrhoea [44].

**Elevated blood cholesterol**

Cholesterol is important to maintain body functions properly. Cholesterol plays an important role in the production of vitamins and hormones it acts as a precursor [45]. In the human body, cholesterol is important to various body functions and the body synthesizes and maintains the appropriate amount for smooth function. However, cholesterol considers a risk factor for heart and cardiovascular diseases [46]. Probiotics are well known for excess cholesterol reduction. Probiotics have considerable effects on lowering LDL and reducing cholesterol in the blood. Some studies reported that Lactobacillus and Bifidobacterium are effective to reduce cholesterol from blood serum [47]. The human microbiome plays important role in human metabolism, immunity and several diseases including coronary artery disease (CAD). However, intervention of nanotechnology along with gut microbiome enables the high efficacy and precision in therapeutic approach for CAD [48]

**Diabetes, gut microbiome and nanotechnology**

When dealing with a significant metabolic illness such as diabetes, maintaining a healthy microbiota composition in the gut is equally essential. Around the world, more than 380 million people are living with type 2 diabetes, and it is anticipated that this number will climb to more than 550 million by the year 2030 [49]. *Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia*, and *Roseburia* were found to be linked to type 2 diabetes in a bad way, while *Ruminococcus, Fusobacterium*, and *Blautia* were linked to type 2 diabetes in a good way [50]. Differences in the gut microbiome between people with and without type 2 diabetes may show how diet and other environmental factors affect insulin resistance and the development of type 2 diabetes. Multiple biological pathways by which gut bacteria contribute to metabolic illness and T2D have been addressed elsewhere in the recent past [51]. The gut microbiome can affect the host's insulin sensitivity, intestinal permeability, glucose and fat metabolism by interacting with food and habits [50]. The short chain fatty acids (SCFAs) work by activating the G proteins of the L-cells, which leads to the release of GLP-1 and peptide YY (PYY) to regulate glucose homeostasis. At the same time, the SCFAs also affect the intestinal barrier, up-regulate 5'-AMP-activated in muscle and liver tissues, and the protein kinase signalling pathway, all of which are linked to insulin resistance and inflammation [52].

Nanoparticles and protein bioconjugates have been studied for multiple biomedical applications. As per the study reported by Akib Nisar et al. (2022), The interaction and structural changes between bovine serum albumin (BSA) and iron oxide nanoparticles (IONPs). IONPs were green synthesised with E. crassipes leaf extract and characterised with transmission electron microscopy, energy dispersive X-ray analysis, and X-ray diffraction. Native PAGE, HPLC, and FTIR analyses revealed a differential behaviour of IONPs with native and glycated BSA; consequently, they could be utilised for treating diabetes [53].

**Cancer**

Cancer emerges as a result of chronic inflammation due to various factors including microbiota. There is a drastic microbial change as seen in cancer patients that displays low microbial diversity with significant increase of pathogenic Proteobacteria and decrease in butyrate producing microbes such as Firmicutes and Actinobacteria when compared to healthy individual microbial profile [54,55]. These abrupt changes might trigger in pro-inflammatory opportunistic pathogens that could ultimately lead to tumour formation [56]. Use of anti-carcinogenic probiotic bacteria such as several species of *Bifidobacterium* and *Lactobacillus* have been reported [57]. Also, the approach of modulating and restoring microbiome through the use of prebiotics have also been reported [58]. These approaches for microbiome modulation, ultimately preventing or curing disease at a primary stage lack specificity in achieving the targeted modulation i.e. they were not originally developed to target tumour cells and hence does not have the ability to interact with tumour associated bacteria (TAB) [59,60].

In this context, nanotechnology seems a fruitful approach as it can (i) navigate complex microenvironment including microbiome and tumour microenvironment; (ii) specifically interfere with molecular pathways; and (iii) be functional at sites beyond the primary tumour e.g. metastases [61]. Since, the microbiome is patient unique ecosystem that dynamically changes in response to diet, drugs and so on, nanotechnology is capable of performing their targeted delivery and microbiome modulating functions even regulating metabolites that are known for carcinogenesis. Overall, the use of nanotechnology in microbiome modulation and anti-cancer applications is at nascent stage and further studies will be fruitful for exploiting the technology against cancer [61].

Nanotechnology's interaction with the microbiome modifies microbial metabolites and can be engineered to release chemotherapeutic agents upon microbiome interaction. To enhance immunotherapy, nanotechnology was used to interrupt the chemical communication between microbial metabolites and the immune system. Also known for its use in facilitating the tumour-suppressing stimuli-responsive drug release of a chemotherapeutic from a nanoparticle [62]. Strategies to alter the microbiome composition towards protection from or treatment of cancer may include the addition of beneficial microbial species, the deletion of cancer-causing microbial species, or the modulation of the existing commensal population to promote the proliferation of beneficial anti-cancer microbial species, such as those that secrete the short-chain fatty acid [63].

**Antimicrobial probiotics and their mechanism of inhibition.**

There are many known antagonistic mechanisms of probiotic microorganisms, including alteration of the gut microbiota, competitive adhesion to the mucosa, epithelial reinforcement of the antimicrobial gut epithelial barrier, bacteriocins, adhesion, competitive exclusion, anti-inflammatory activity and immune system modulation to convey an advantage to the host [62]. Enhancement of epithelial barrier, Intestinal epithelial cells are in permanent contact with the diverse microbial community and epithelial integrity is essential to defend from pathogenic microorganisms [63]. Once the barrier function is disrupted bacterial food antigen can enter the submucosa and can induce an inflammatory response that leads to infectious diseases like IBD. Consumption of probiotic microorganisms which can maintain epithelial barrier and intestinal barrier function.

Increasing the expression of genes implicated in tight junction signalling has been shown to be a possible mechanism [66]. Lactobacillus can modulate the regulation of multiple genes and junction proteins, including E-cadherin and b-catenin [67]. Mucin glycoproteins (mucins) are important macromolecular components of epithelial mucus and have been used for a long time to treat health conditions and diseases. However, a number of issues are associated with the acquired resistance of to antibiotics. Therefore, researchers seek an alternative to antibiotics in order to reduce the danger of such infectious diseases proliferating [40]. Thus, the significant advancement in nanobiotechnology provides novel formulation tools for biologically derived NPs with antimicrobial potential [40].

Increase adherence to the intestinal mucosa

Adherence to the interaction between the probiotics and the host is also essential for the modulation of the immune system. Antagonism against pathogens intestinal epithelial cells (IECs) secretes mucin which is a complex glycoprotein mixture that can prevent the adhesion of pathogenic microorganisms because it presents lipids, free proteins, immunoglobulins and salt to prevent mucous gel adhesion [64] this interaction indicates possible competitive exclusion of pathogenic bacteria although mucous binding proteins (MBP) surface-associated proteins are present only on probiotic microorganisms. Probiotics such as *L. reuteri*, *L. fermentum*, *L. plantarum* are reported to induce MUC2 and MUC3 mucin to produce epithelial cells, which is responsible to inhibit adherence of enteropathogenic and *E.coli* [65]. Probiotics are bound to microbial binding sites and protect against invasion by pathogens. The establishment of a stable population or commercial microbiota will reduce nutrient availability for entering pathogenic micro-organisms and inhibit their colonization.

**Immunomodulatory Probiotics microbiome**

Probiotic microorganisms exert an immunomodulatory effect and interact with epithelial, dendritic cells (DCs) and with monocytes/macrophages and lymphocytes. It is studied that probiotics can interact with IECs and encounter DCs which have an important role in innate and adaptive immunity, through pattern recognition receptors (PPRs). Probiotics also improve the normal immune system by increasing the concentration of IgA producing plasma cells, improving phagocytosis as well as increasing the cell concentration of T-lymphocytes and natural killer cells. Some probiotics have been shown to increase phagocytosis or natural killer cell activity and interact directly with dendritic cells [66]. some are also upregulating the antibody secretion to improve defence against pathogenic microorganisms. Probiotics can increase the level of anti-inflammatory cytokines such as TNF [67].

In probiotics mainly LAB produces lactic acid and acetic acid as an end product of carbohydrate metabolism, and an increase in butyrate and other SCFA production [68] also by producing, bacteriocin contains antimicrobial proteins, peptides, antibiotic compounds etc. can be active against pathogenic microorganisms. After prebiotic consumption such as Galactooligosaccharides (GOS) consumption induce immunity by enhancing phagocytosis activity and natural killer cells and also maintaining Th1/Th2, although probiotics may show positive effects by enhancing non-specific (Innate) and antigen-specific (Adaptive) Immunity.

Engineered nanomaterials (ENMs) have been extensively used in a variety of industrial fields as well as in everyday life, raising questions about any potential negative effects. While ENMs do not typically appear to have negative effects on immunity or cause severe inflammation, it is less clear how these effects may manifest themselves indirectly. In particular, since the gut microbiota has been tightly associated with human health and immunity, it is possible that ingested ENMs could affect intestinal immunity indirectly by modulating the microbial community composition and functions [69].

In this viewpoint, some supporting data shows a potential relationship between ENM exposure, gut microbiota, and host immune response. According to some experimental studies, prolonged exposure to ENMs may alter the gut microbiota, which would affect the integrity of the intestinal epithelium and the degree of inflammation. Numerous microbiota-derived substances present in this microenvironment, including but not limited to SCFAs and lipopolysaccharide (LPS), may play a significant role in the ENM effect on intestinal immunity. As a result, upon ENM exposure, the gut microbiota is implicated as a critical regulator of the intestinal immunity. In order to evaluate ENM biocompatibility and immune-safety in the future, it is necessary to include gut microbiota analysis [69].

Nanoparticles, gut microbes and SARS-CoV2

In the past twenty years, nanotechnology has been developed into a topic that applies to many subfields of study and may be utilised to produce nanoscale materials using a variety of processes, including chemical and physical processes. Nanoparticles have dimensions ranging from 1 to 100 nm and possess features that can be controlled precisely. These qualities are distinct from what the particles appear to be on a larger scale. This enables them to be employed in novel contexts [70]. Nanoparticles are used in many biomedical applications because of their unique properties. These include diagnostics, medical imaging, treatments, and medication delivery, all of which are being increasingly utilised in the management of SARS-CoV2 in the modern era. Based on what has been said, nanotechnology may be very important for quickly diagnosing COVID-19, keeping track of it, and coming up with effective ways to treat it, especially about how SARS-CoV2 affects the gut [71]. With arrays of nanomaterials, non-invasive breath tests can identify the presence of volatile organic compounds with the signatures of modulated microbiota and, therefore, the presence of SARS-CoV2 for quick diagnosis and monitoring [72,73]. On the other hand, a healthy gut is also important in SARS-CoV2 infections. Some studies point out the importance of good microbes in fighting this virus [74]. Nanotechnology can be used effectively to design smart drugs or functional foods that can be delivered locally in the gut. It can also be used to design smart functional foods [69,75]. These drugs and foods should go after bacterial strains that cause problems in the GI tract and improve its health by making the gut more resistant to pathogens and inflammatory chemicals and by laying the groundwork for developing disruptive treatments based on microbiome engineering [73]. We may one day be able to watch, traverse, and interact with the intricate ecology of the gut if we have the assistance of technologies that can function at the nanoscale level. This may assist us in locating a therapy or cure for COVID-19 as well as in maintaining control over SARS-CoV-2.

Immunomodulation and Anti-COVID mechanisms

As of yet, no direct correlation or study exists to support the role of probiotics against SARS-CoV2 infections; however, many previous studies on probiotics and viral infections can be used to establish the possible mechanisms and their role. SARS-CoV and SARS-CoV2 utilised a common entry site by interacting with the ACE2 receptor present on the lung and intestine epithelial cell surfaces. In one report of SARS-CoV2 infection, a dysbiotic condition caused by Salmonella America, a member of the Enterobacteriaceae family, was found to be prevalent; this condition increased the number of ACE2 receptors in the epithelial cells of the intestine, making them more susceptible to infection [106]. The SARS-CoV2 virus must overcome the immunologic barrier of respiratory tract epithelial cells in order to invade cells via ACE2 receptors, whereas probiotic microbiota with commensal bacteria may assist the immune system in reducing or inhibiting this infection by immunomodulation.

Despite the absence of a direct effect, probiotics create an immunologic barrier by stimulating an immune response that supports the body's first line of defence [107]. In general, probiotics interact with lung and intestinal epithelial cells as well as specialised cells (M cells) for immunoregulation by interacting with macrophages and dendritic cells, which activates T and B lymphocytes. It may inhibit viral attachment by inhibiting competition for binding sites on the epithelial lining. Probiotics induce the upregulation of mucin-1 (MUC1) and mucin-2 (MUC2), which inhibit virus attachment to epithelial cells and inhibit viral replication. In addition, it generates antimicrobial peptides, dehydrogenase, and nuclease enzymes that can degrade viral nucleic acid, and the co-aggregation of probiotics with viral particles prevents the virus from attaching to the epithelial cell line [108]. Probiotics play an important role in the induction of type 1 T helper (Th1) cells, which are specific for antimicrobial/antiviral mediated immunity, whereas IFN, a glycoprotein, and IgA are antiviral agents. Short-chain SCFA is one of the essential molecules produced by probiotic MOs upon decomposition of the prebiotic compound. By activating tumour necrosis factor- (TNF-), it has an effect on the immune system and induces pattern recognition receptors (PRR). Specifically, probiotics such as Lactobacillus and Bifidobacterium modulate the immune system by modulating cytokines, thereby increasing IgA and IgG antibody production [109]. Specifically, Lactobacillus species such as *L. acidophilus, L. casei, L. rhamnosus, and L. helveticus* are effective to enhance phagocytosis and improve the secretion of cytokines, immunoglobulin, and plasma cells, according to a study. *L. casei and L. acidophilus* induced interleukin (IL) such as IL-10 and CD4+ regulatory T (Treg) cells. Furthermore, L. Plantarum and L. reuteri reduced inflammation, whereas L. rhamnosus and B. lactis increased IFN-, IL-4, IL-10, and IL-6 in bronchoalveolar lavage [84]. In addition, probiotics can increase the level of Bcl2 (B cell lymphoma 2), which is responsible for the activation of cellular and humoral immunity, cytokine production, and Th1/Th2 expression.

Depending on the contact-based mechanism, probiotics have also been investigated for their influence on immune-related gene expression and cytokine activation. A study suggested that probiotics such as Lactobacillus mediate the expression of TLR2, which stimulates TNF-, whereas Bifidobacterium longum mediates the expression of IL-10 and IL-12 through a contact-dependent mechanism, resulting in the modulation of T helper cell response in the gut and lung [110].

It is known that the oral administration of 109 CFU of probiotics is more efficacious and may exert a long-lasting homeostasis and immunomodulatory effect on the host. It has been demonstrated that oral administration of Bifidobacterium bifidum and B. breve increases humoral immune responses, such as IgA stimulation [111]. Therefore, probiotics have the potential to be utilised as an oral live vaccine. Moeini et al. (2011) employed live L. acidophilus as a vehicle for oral immunisation against chicken anaemia virus (CAV). The ACMA-binding domains on the surface of Lactococcus lactis were utilised to display the viral protein 1 (VP1) CAV on L. acidophilus in order to actively immunise specific-pathogen-free poultry. Immunisation elevated Th1 cytokines, including IL-2, IL-12, and IFN- [112]. Furthermore, some studies have demonstrated that probiotics administered via the nasal route can improve the outcome of influenza virus infection. The nasal administration of Lactobacillus rhamnosus strains CRL1505 and CRL1506 enhanced respiratory antiviral defences and modulated the immune response by activating TLR3 and PRR (RIG-I, a retinoic acid-inducible gene I) [113].

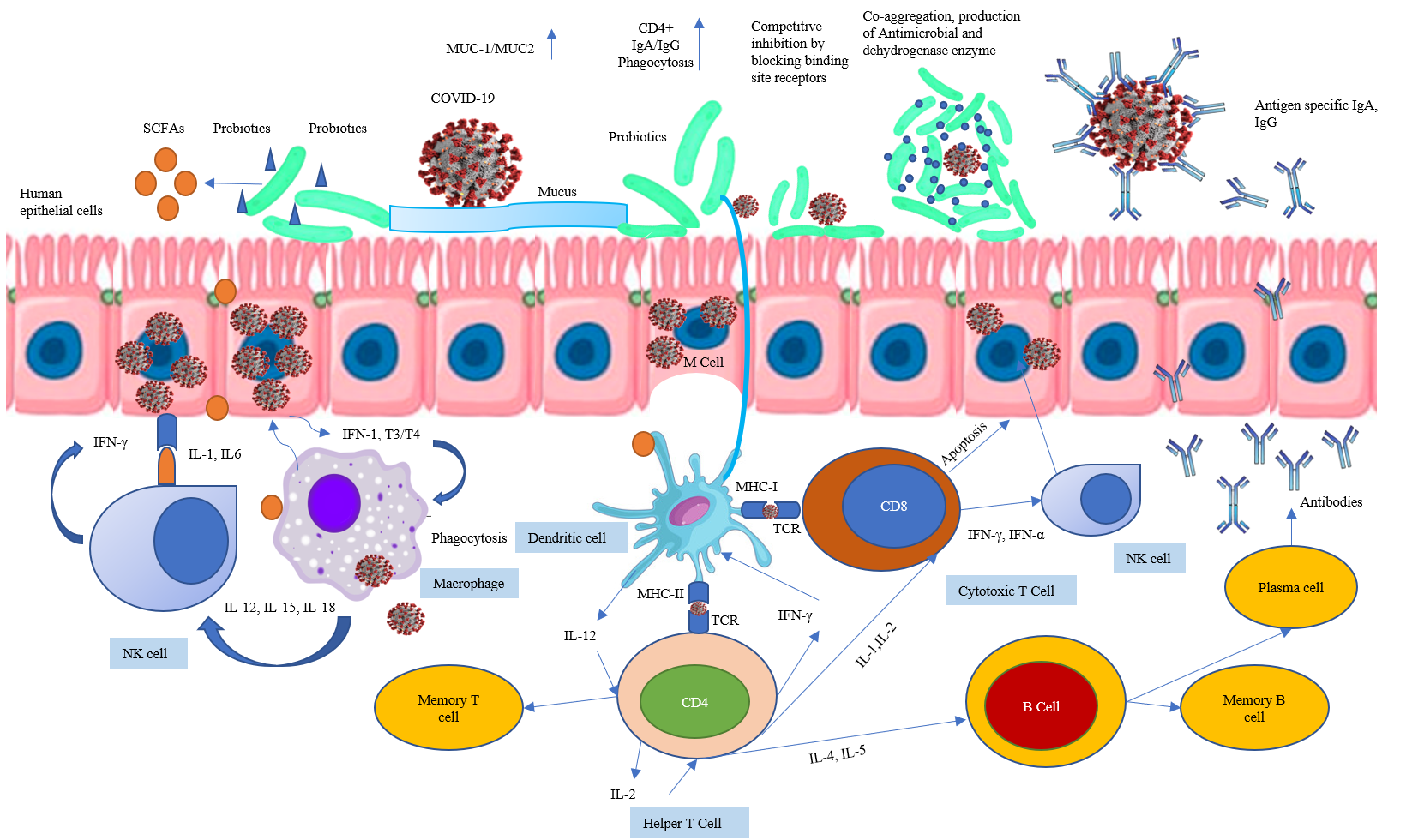
Probiotics are microbiota that function as a potential barrier in the event of a viral attack through immunomodulation, as described previously (Figure 1). It may act indirectly via competitive inhibition or directly via the interaction of immune cells through the production of chemokines and cytokines, and it may also be involved in other immunologic pathways. On the basis of this information, we can speculate about the potential function of these microorganisms in preventing or reducing SARS-CoV2 infection. In this context, a model depicting the anticipated immunomodulatory effect of probiotics and prebiotics at the commencement of SARS-CoV2 infection has been provided.

Figure no. 1 Anticipation of the Role of probiotics in immunomodulatory [76].

**Conclusion**

Role of gut microbiome in our body is extensively hot topic of research. These microorganisms are extremely important for production of enzymes, vitamins, biomolecules and modulation of metabolic pathways and immune system. The main problem is the lack of specificity in target-oriented modulation of the microbiota and metabolites. This limitation can be addressed using nanotechnology. Research on nanomedicine formulations for diagnostic and therapeutic purposes has produced a number of successful platforms, including those for integrated diagnosis, targeted drug delivery, and therapeutics. Using nanoparticles as a delivery system for gut microbiota influences the route of biomarker detection and the route of the interaction of nanoparticles with target cells. In this chapter we discussed how different diseases are correlated with gut microbial profile and reverting dysbiosis can solve the problem with intervention of nanotechnology.

References:

[1] Jernberg C, Löfmark S, Edlund C, Jansson JK. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. 2007; 1: 56–66.

[2] Kathade SA, Aswani MA, Anand PK, Jagtap S, Bipinraj NK. Isolation of Lactobacillus from donkey dung and its probiotic characterization 2020; 56: 160–69.

[3] Ganguly N, Bhattacharya S, Sesikeran B, Nair G, Ramakrishna B, Sachdev HPS, et al. ICMR-DBT Guidelines for Evaluation of Probiotics in Food 2011; 134: 22–25.

[4] Kathade SA, Aswani MA, Anand PK, Kunchiraman BN. Probiotic characterization and cholesterol assimilation ability of Pichia kudriavzevii isolated from the gut of the edible freshwater snail “ Pila globosa ”. disease . 2020; 24: 23–39.

[5] Aswani MA, Kathade SA, Anand PK, Kunchiraman BN, Dhumma PR, Jagtap SD. Probiotic Characterization of Cholesterol-Lowering Saccharomyces cerevisiae Isolated from Frass of Pyrrharctia isabella Caterpillars 2021; 8: 189–98.

[6] Dudek-Wicher RK, Junka A, Bartoszewicz M. The influence of antibiotics and dietary components on gut microbiota 2018; 13: 85–92.

[7] Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation 2011; 108: 4554–61.

[8] Hudson LE, McDermott CD, Stewart TP, Hudson WH, Rios D, Fasken MB, et al. Characterization of the probiotic yeast Saccharomyces boulardii in the healthy mucosal immune system 2016; 11: 1–21.

[9] Rastogi A, Singh P, Haraz FA BA. Biological synthesis of nanoparticles: an environmentally benign approach. In: Fundamentals of Nanoparticles. Elsevier Inc, Typeset by Thomson Digit. India.; 2018; pp. 571–604.

[10] Taniguchi N, Arakawa C KT. On the basic concept of ‘nano- technology’. In: Proceedings of the international conference on production engineering. Japan Soc. Precis. Eng. Tokyo.; 1974; pp. 18–23.

[11] KW G. An overview of green nanotechnology. In: Bio-nanotechnology: a revolution in food, biomedical and health sciences. Blackwell Publ. Ltd, Oxford.; 2013; pp. 311–54.

[12] Saini R, Saini S, Sharma S. Nanotechnology: The future medicine 2010; 3: 32.

[13] Gismondo MR, Drago L, Lombardi A. Review of probiotics available to modify gastrointestinal flora. 1999; 12: 287–92.

[14] Ma C, Zhang S, Lu J, Zhang C, Pang X, Lv J. Screening for Cholesterol-Lowering Probiotics from Lactic Acid Bacteria Isolated from Corn Silage Based on Three Hypothesized Pathways 2019; 20: 2073.

[15] Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic 2019; 16: 605–16.

[16] Mardini HE, Grigorian AY. Probiotic mix VSL#3 is effective adjunctive therapy for mild to moderately active ulcerative colitis: a meta-analysis. 2014; 20: 1562–67.

[17] Duvallet C, Gibbons SM, Gurry T, Irizarry RA, Alm EJ. Meta-analysis of gut microbiome studies identifies disease-specific and shared responses 2017; 8.

[18] Zhu L, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. 2013; 57: 601–9.

[19] An HM, Park SY, Lee DK, Kim JR, Cha MK, Lee SW, et al. Antiobesity and lipid-lowering effects of Bifidobacterium spp. in high fat diet-induced obese rats 2011; 10: 116.

[20] Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D, et al. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. 2009; 90: 1236–43.

[21] Aronsson L, Huang Y, Parini P, Korach-André M, Håkansson J, Gustafsson J-Å, et al. Decreased fat storage by Lactobacillus paracasei is associated with increased levels of angiopoietin-like 4 protein (ANGPTL4). 2010; 5.

[22] Larsen N, Vogensen FK, van den Berg FWJ, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. 2010; 5: e9085.

[23] Yadav H, Jain S, Sinha PR. Antidiabetic effect of probiotic dahi containing Lactobacillus acidophilus and Lactobacillus casei in high fructose fed rats. 2007; 23: 62–68.

[24] Vanamala JKP, Knight R, Spector TD. Can Your Microbiome Tell You What to Eat? 2015; 22: 960–61.

[25] Druart C, Neyrinck AM, Dewulf EM, De Backer FC, Possemiers S, Van de Wiele T, et al. Implication of fermentable carbohydrates targeting the gut microbiota on conjugated linoleic acid production in high-fat-fed mice. 2013; 110: 998–1011.

[26] Vanderhoof JA, Whitney DB, Antonson DL, Hanner TL, Lupo J V, Young RJ. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. 1999; 135: 564–68.

[27] Szajewska H, Albrecht P, Topczewska-Cabanek A. Randomized, double-blind, placebo-controlled trial: effect of lactobacillus GG supplementation on Helicobacter pylori eradication rates and side effects during treatment in children. 2009; 48: 431–36.

[28] Olbjørn C, Cvancarova Småstuen M, Thiis-Evensen E, Nakstad B, Vatn MH, Jahnsen J, et al. Fecal microbiota profiles in treatment-naïve pediatric inflammatory bowel disease - associations with disease phenotype, treatment, and outcome. 2019; 12: 37–49.

[29] Desai N. Challenges in development of nanoparticle-based therapeutics. 2012; 14: 282–95.

[30] Bawa R. Regulating nanomedicine - can the FDA handle it? 2011; 8: 227–34.

[31] Ohno M, Nishida A, Sugitani Y, Nishino K, Inatomi O, Sugimoto M, et al. Nanoparticle curcumin ameliorates experimental colitis via modulation of gut microbiota and induction of regulatory T cells. 2017; 12: e0185999.

[32] Teng Y, Ren Y, Sayed M, Hu X, Lei C, Kumar A, et al. Plant-Derived Exosomal MicroRNAs Shape the Gut Microbiota. 2018; 24: 637-652.e8.

[33] Tong L, Hao H, Zhang X, Zhang Z, Lv Y, Zhang L, et al. Oral Administration of Bovine Milk-Derived Extracellular Vesicles Alters the Gut Microbiota and Enhances Intestinal Immunity in Mice. 2020; 64: e1901251.

[34] Afonina IS, Zhong Z, Karin M, Beyaert R. Limiting inflammation—the negative regulation of NF-κB and the NLRP3 inflammasome 2017; 18: 861–69.

[35] Meijnikman AS, Gerdes VE, Nieuwdorp M, Herrema H. Evaluating Causality of Gut Microbiota in Obesity and Diabetes in Humans. 2018; 39: 133–53.

[36] Mao Z, Li Y, Dong T, Zhang L, Zhang Y, Li S, et al. Exposure to Titanium Dioxide Nanoparticles During Pregnancy Changed Maternal Gut Microbiota and Increased Blood Glucose of Rat 2019; 14.

[37] Chen Z, Han S, Zhou Di 周迪, Zhou S, Jia G. Effects of oral exposure to titanium dioxide nanoparticles on gut microbiota and gut-associated metabolism in vivo 2019; 11.

[38] Klaenhammer TR, Kleerebezem M, Kopp MV, Rescigno M. The impact of probiotics and prebiotics on the immune system. 2012; 12: 728–34.

[39] Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics--approaching a definition. 2001; 73: 361S-364S.

[40] Rizzello L, Cingolani R, Pompa PP. Nanotechnology tools for antibacterial materials. 2013; 8: 807–21.

[41] Kumar B, Smita K, Vizuete KS, Cumbal L. Aqueous phase lavender leaf mediated green synthesis of gold nanoparticles and evaluation of its antioxidant activity 2016; 8: 1–4.

[42] Lebeer S, Vanderleyden J, De Keersmaecker SCJ, Guarner F, Perdigon G, Corthier G, et al. Regulatory effects of bifidobacteria on the growth of other colonic bacteria 2010; 69: 412–20.

[43] Pelto L, Isolauri E, Lilius EM, Nuutila J, Salminen S. Probiotic bacteria down-regulate the milk-induced inflammatory response in milk-hypersensitive subjects but have an immunostimulatory effect in healthy subjects. 1998; 28: 1474–79.

[44] Usman, Hosono A. Bile tolerance, taurocholate deconjugation, and binding of cholesterol by Lactobacillus gasseri strains. 1999; 82: 243–48.

[45] Saikia D, Manhar AK, Deka B, Roy R, Gupta K, Namsa ND, et al. Hypocholesterolemic activity of indigenous probiotic isolate Saccharomyces cerevisiae ARDMC1 in a rat model 2018; 26: 154–62.

[46] Gagliardi A, Totino V, Cacciotti F, Iebba V, Neroni B, Bonfiglio G, et al. Rebuilding the Gut Microbiota Ecosystem. 2018; 15.

[47] PULUSANI SR, RAO DR. Whole Body, Liver and Plasma Cholesterol Levels in Rats Fed Thermophilus, Bulgaricus and Acidophilus Milks 1983; 48: 280–81.

[48] Hagemeyer C, Lisman T, Kwaan H. Nanomedicine in Thrombosis and Hemostasis: The Future of Nanotechnology in Thrombosis and Hemostasis Research and Clinical Applications 2020; 46: 521–23.

[49] Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes 2017; 389: 2239–51.

[50] Gurung M, Li Z, You H, Rodrigues R, Jump DB, Morgun A, et al. Role of gut microbiota in type 2 diabetes pathophysiology 2020; 51.

[51] Aw W, Fukuda S. Understanding the role of the gut ecosystem in diabetes mellitus. 2018; 9: 5–12.

[52] Kim HJ, Kim Y-S, Kim K-H, Choi J-P, Kim Y-K, Yun S, et al. The microbiome of the lung and its extracellular vesicles in nonsmokers, healthy smokers and COPD patients. 2017; 49: e316.

[53] Nisar A, Ajabia DK, Agrawal SB, Varma S, Chaudhari BP, Tupe RS. Mechanistic insight into differential interactions of iron oxide nanoparticles with native, glycated albumin and their effect on erythrocytes parameters 2022; 212: 232–47.

[54] Saffarian A, Mulet C, Regnault B, Amiot A, Tran-Van-Nhieu J, Ravel J, et al. Crypt- and mucosa-associated core microbiotas in humans and their alteration in colon cancer patients 2019; 10: 1–20.

[55] Sánchez-Alcoholado L, Ramos-Molina B, Otero A, Laborda-Illanes A, Ordóñez R, Medina JA, et al. The role of the gut microbiome in colorectal cancer development and therapy response 2020; 12: 1–29.

[56] Chan Y-Y, Li C-H, Shen Y-C, Wu T-S. Anti-inflammatory Principles from the Stem and Root Barks of *Citrus medica* 2010; 58: 61–65.

[57] Hendler R, Zhang Y. Probiotics in the Treatment of Colorectal Cancer 2018; 5: 101.

[58] Mahdavi M, Laforest-Lapointe I, Massé E. Preventing colorectal cancer through prebiotics 2021; 9: 1–16.

[59] Young V. Therapeutic Manipulation of the Microbiota: Past, Present and Considerations for the Future 2016; 22: 1–11.

[60] Vargason AM, Anselmo AC. Clinical translation of microbe-based therapies: Current clinical landscape and preclinical outlook 2018; 3: 124–37.

[61] Song W, Anselmo AC, Huang L. Nanotechnology intervention of the microbiome for cancer therapy 2019; 14: 1093–1103.

[62] Collado mc, gueimonde m salminen s. probiotics in adhesion of pathogens: mechanisms of action; in watson rr, preedy vr (eds) bioactive foods in promoting health, chennai, 2010; 23: 353–70.

[63] Ohland CL, Macnaughton WK. Probiotic bacteria and intestinal epithelial barrier function. 2010; 298: G807-19.

[64] neutra mr forstner jf. gastrointestinal mucus: synthesis, secretion and function; in johnson lr (ed): physiology of the gastrointestinal tract , ed 2 1987.

[65] Kim YS, Ho SB. Intestinal goblet cells and mucins in health and disease: recent insights and progress. 2010; 12: 319–30.

[66] Przemska-Kosicka A, Childs CE, Enani S, Maidens C, Dong H, Dayel I Bin, et al. Effect of a synbiotic on the response to seasonal influenza vaccination is strongly influenced by degree of immunosenescence 2016; 13: 6.

[67] Aoudia N, Rieu A, Briandet R, Deschamps J, Chluba J, Jego G, et al. Biofilms of Lactobacillus plantarum and Lactobacillus fermentum: Effect on stress responses, antagonistic effects on pathogen growth and immunomodulatory properties. 2016; 53: 51–59.

[68] Kathade SA, Aswani MA, Anand PK. Isolation , Characterization , and Diversity of Probiotic Microorganisms from Different Postpartum Milk of Various Animals 2022.

[69] Singh T, Shukla S, Kumar P, Wahla V, Bajpai VK, Rather IA. Application of Nanotechnology in Food Science: Perception and Overview 2017; 8.

[70] Omran B. Nanobiotechnology: A Multidisciplinary Field of Science. 2020.

[71] Kalantar-Zadeh K, Ward SA, Kalantar-Zadeh K, El-Omar EM. Considering the Effects of Microbiome and Diet on SARS-CoV-2 Infection: Nanotechnology Roles 2020; 14: 5179–82.

[72] Nakhleh MK, Amal H, Jeries R, Broza YY, Aboud M, Gharra A, et al. Diagnosis and Classification of 17 Diseases from 1404 Subjects via Pattern Analysis of Exhaled Molecules 2017; 11: 112–25.

[73] Biteen JS, Blainey PC, Cardon ZG, Chun M, Church GM, Dorrestein PC, et al. Tools for the Microbiome: Nano and Beyond 2016; 10: 6–37.

[74] Nisar A, Kathade SA, Aswani MA, Harsulkar AM, Jagtap, S. D Kunchiraman BN. Understanding the correlation of diet, Immunity, and probiotics: A credible implication in SARS-CoV2 infections 2022; 19 (2).

[75] Hua S, Marks E, Schneider JJ, Keely S. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: Selective targeting to diseased versus healthy tissue 2015; 11: 1117–32.

[76] Nisar AA, Kathade SA, Aswani MA, Madhukar A. Title : Understanding the Correlation of Diet , Immunity , and Probiotics : A Credible Implication in SARS-CoV-2 Infection n.d.: 9888.