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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 offer distinctive opportunities for the targeted and regulated administration of medicinal medicines to specific areas 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. The Metabolites and inflammatory biomarkers, enabling rapid and accurate diagnosis of dysbiotic conditions, 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.

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 different characteristics and are more than 100 times the microbial genes present in the human body [1,2]. These microorganisms in our body are referred to as the microbiome, and those in our intestines are referred to as the gut microbiome. These microbiomes are more than just present in the intestine; they play a vital role. They digest our food, produce vitamins, and educate the immune system to kill pathogenic organisms. According to scientific studies, the modulation of the specific microbial community is accountable for the specific disease condition [2,3]. 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 through 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 fabrication of nanoparticles with appropriate sizes, morphologies, chemical compositions, and concentrations may circumvent this fundamental obstacle. The utilisation of nanoparticles as a delivery mechanism for gut microbiota affects both the pathway of biomarker detection and the interaction route of nanoparticles with target cells [4,5].

In recent studies on the microbiome and its impact on health is a topic of interest and the gut microbiome contributes to more than 90% part of the study. Trillions of microorganisms are present in our body, mainly located inside the gut. Majorly, there are two types of microbial communities present in our body, which are good and bad microorganisms. Good microorganisms are also called probiotic microorganisms [1,2]. Probiotics are live microorganisms when administered in an adequate amount, confer health benefits to the host [4,5]. Once established, these probiotic bacteria can exert their beneficial effect in many ways. Some reports showed the ability of probiotics that 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 [2,3].

An imbalance in the gut flora, also known as dysbiosis, is a 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. Probiotics are generally regarded as living drugs with immunomodulatory, anti-carcinogenic, anti-allergic, and anti-inflammatory effects [8]. Even though many reports are available on mechanisms to kill pathogens, the 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 science and has diverse applications [9]. The phrase "nanotechnology" was first coined by Japanese academic Norio Taniguchi [10]. A nanoparticle is a material with a diameter up to 100 nm 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 means "very small," is the basis of nanotechnology. Nanotechnology is an interdisciplinary field that encompasses biotechnology, biology, chemistry, physics, medicine, pharmacy, and engineering [12]. Nanotechnology intervention to modulate the gut microbiome, which may aid in alleviating dysbiosis. In this chapter, we focus on the nanotechnology intervention to alleviate microbiome issues and address various diseases.

Health benefits of the probiotic microbiome

The term “Probiotics” is derived from the Greek word, which means 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 between 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 for good microbiome health and clinical applications [15].

Disease-specific microbiome and the role of nanotechnology

Recent advancements have enhanced the comprehension of probiotics and their advantageous and suitable use 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]. Numerous studies have been undertaken regarding the correlation between the human microbiome and illnesses. According to one study, a consistent pattern of the microbiome was found in specific diseases, which can vary from disease to disease [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 of changes in eating habits, intake of abundant food and decrease in expenditure energy, high consumption of 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 came to know that microbial ecosystems in obese and lean people are different. When obese individuals lost weight, the microflora reversion 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 composition in the gut may be a novel method for the treatment of obesity. The gut microbiome significantly contributes to weight gain and insulin resistance, which may be linked to enhanced energy extraction, elevated blood LPS levels, and chronic 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 regulating glucose tolerance [23]. Regulating blood glucose and insulin resistance would be a possible way, and it also lowers the hypertensive condition, which is closely related to diabetes [24]. A recent study indicates that dietary polyphenols contribute to maintaining gut microbial health, stimulating a good microbiome that is very low in diabetic patients. Polyphenols may reduce postprandial glucose response by increasing gut microbial health [25].

Modulation of gut microbiome depicts many diseases have been hypothesized to be associated with modulation of the specific microbial community in the specific disease condition, including various diseases (Table 1), but there is a lack of understanding precisely how the microbial community and specific microbes within these communities contribute to disease [26].

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 1: List of reported disease-specific probiotics

Owing to the potential benefits, the nanotechnological intervention aims to develop more effective tools for the prevention of diseases [27]. This could also provide solutions to persistent ambiguity and a lack of therapeutic compound target specificity [28]. It has been demonstrated that designing NPs from natural sources and arranging them in a thorough drug delivery mechanism is beneficial for gastrointestinal microbiota. Curcumin and ginger-derived NPs enhance gastrointestinal microbiota absorption, allowing them to exert their respective effects. [29,30]. 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 regulating immune cells [29,30]. Extracellular vesicles from other natural sources, such as milk, altered intestinal short-chain fatty acids (SCFA) metabolites boosted gut immunity [31].

The ability to conceal NPs with natural cell membrane coating allows for their continued circulation and ultimate targeted administration. Titanium dioxide nanoparticles, which are typically found in daily necessities, also alter the morphology and metabolism of the gut microbiota [32,33]. The detailed description of 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 changes in human physiological conditions [34]. Lactobacillus GG has the potential to strengthen mucosal barrier mechanisms to overcome inflammatory conditions. Probiotics are known to increase phagocytosis and also help to increase anti-inflammatory cytokines like TNF [35]. Nanotechnology is proven for modulation of microbiome and induces the secretion of short-chain fatty acids such as butyrate, propionate, etc., which is reported to decrease inflammation [36].

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 [37].

Lactose intolerance

The ingestion of lactose by individuals deficient in lactase production in the small intestine may result in symptoms of lactose intolerance, including gas, cramps, nausea, diarrhoea, stomach pain, and flatulence. Lactose intolerance can be cured by administering probiotic bacteria. Probiotic microorganisms like *L. acidophilus* and *Bifidobacteria* have been reported to improve lactose digestion [38].

Vaginosis

The microbiota is crucial for sustaining vaginal health; vaginosis can be induced by many organisms in numerous instances. Lactobacilli are predominant in a healthy vagina, and a deficiency of lactic acid bacteria or normal flora may result in vaginosis. The Lactobacilli species and LAB can maintain the favorable pH in the vaginal tract and also produce bacteriocin, organic acid, hydrogen peroxide, and other antimicrobial compounds to maintain a healthy vaginal tract [39].

Diarrhoea

Probiotics are extensively utilised for the treatment of diarrhoeal disorders. Significant potential advantages include the prevention and treatment of acute viral and bacterial diarrhoea, along with the management of antibiotic-associated diarrhoea. Certain specific strains, such as *Lactobacillus* GG, *L. reuteri*, *Saccharomyces boulardii*, and *Bifidobacterium*, have been documented as beneficial against diarrhoea. Reported in vivo studies proved that *Saccharomyces boulardii* is effective against antibiotic-associated diarrhoea [40].

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 [41]. In the human body, cholesterol is important for various body functions. The body synthesizes and maintains the appropriate amount for smooth body function. However, cholesterol is considered a risk factor for heart and cardiovascular diseases [42]. Probiotics are well known for reducing excess cholesterol. Probiotics have considerable effects on lowering LDL and reducing cholesterol in the blood. Some studies reported that *Lactobacillus* and *Bifidobacterium* are effective in reducing cholesterol in blood serum [43]. The human microbiome significantly influences metabolism, immunity, and several disorders, including coronary artery disease (CAD).

However, the intervention of nanotechnology along with gut microbiome enables the high efficacy and precision in the therapeutic approach for CAD [44]

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 [45].

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 [46,47]. These abrupt changes might trigger in pro-inflammatory opportunistic pathogens that could ultimately lead to tumour formation [48]. Use of anti-carcinogenic probiotic bacteria such as several species of *Bifidobacterium* and *Lactobacillus*, have been reported [49]. Also, the approach of modulating and restoring microbiome through the use of prebiotics have also been reported [50]. These approaches for microbiome modulation, ultimately preventing or curing disease at a primary stage hence does not have the ability to interact with tumour-associated bacteria (TAB) [51,52]. Overall, the use of nanotechnology in microbiome modulation and anti-cancer applications is at a nascent stage and further studies will be fruitful for exploiting the technology against cancer [53]. The interaction between nanotechnology and the microbiome modifies microbial metabolites and can be engineered to release chemotherapeutic agents.

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 [54]. 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 [55]. Consumption of probiotic microorganisms which can maintain epithelial barrier and intestinal barrier function. 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 [36].

Increase adherence to the intestinal mucosa

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 [56] 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* [57]. Probiotics are bound to microbial binding sites and protect against invasion by pathogens.

Immunomodulatory Probiotics microbiome

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 [58] also by producing, bacteriocins contain antimicrobial proteins, peptides, antibiotic compounds etc., can be active against pathogenic microorganisms. After prebiotic consumption, such as Galactooligosaccharides (GOS) consumption induces 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. Despite the fact that ENMs do not appear to have negative effects on immunity or induce severe inflammation, it is unclear how these effects may manifest implicitly.

In this viewpoint, some supporting data shows a potential relationship between ENM exposure, gut microbiome, and host immunity. 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, 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 [59].

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 [60]. 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-CoV-2 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 regarding how SARS-CoV-2 affects the gut

[61]. The presence of SARS-CoV-2 for quick diagnosis and monitoring [62,63]. On the other hand, a healthy gut is also important in SARS-CoV-2 infections. Some studies point out the importance of good microbes in fighting this virus [64]. 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 [59,65]. These drugs and foods should target 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 [63]. 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

Currently, no direct link or study substantiates the efficacy of probiotics against SARS-CoV-2 infections; yet, numerous prior investigations on probiotics and viral infections may elucidate potential mechanisms and their implications. SARS-CoV and SARS-CoV-2 employed the same entrance mechanism by binding to the ACE2 receptor located on the surfaces of lung and intestinal epithelial cells. A report on SARS-CoV-2 infection indicated that a dysbiotic condition induced by Salmonella America, a member of the Enterobacteriaceae family, was prevalent; this condition elevated the quantity of ACE2 receptors in intestinal epithelial cells, rendering them more vulnerable to infection [81].

Probiotics are bacteria that serve as a potential barrier during viral attacks via immunomodulation, as previously outlined (Figure 1). It may function indirectly through competitive inhibition or directly through the interaction of immune cells via the generation of chemokines and cytokines, and it may also participate in additional immunologic pathways. This knowledge allows us to hypothesise about the potential role of these bacteria in avoiding or mitigating SARS-CoV-2 illness. A model illustrating the expected immunomodulatory impact of probiotics and prebiotics during the onset of SARS-CoV-2 infection has been shown.

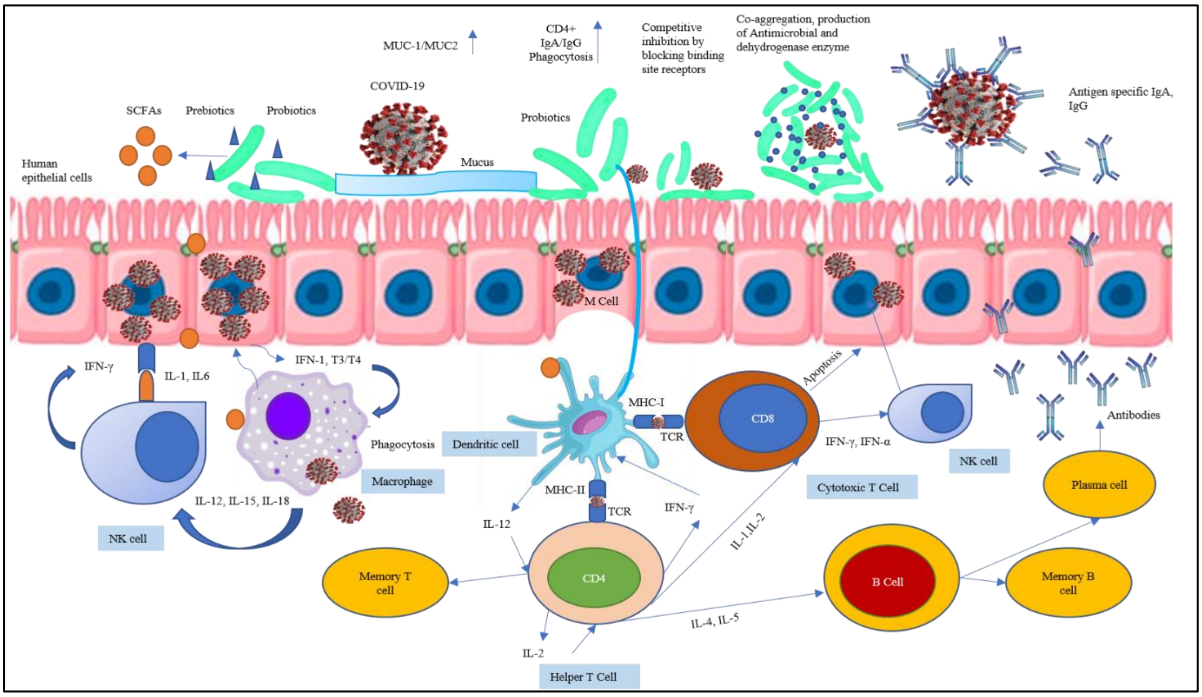

Figure. 1 Anticipation of the Role of probiotics in immunomodulatory [64].

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 the intervention of nanotechnology.

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