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Corresponding Author:

Ayesha Muazzam

ashu2nice@gmail.com

Interactions between Gut Microbiota and Nanoparticles: Implications for Health and Disease

Uzma Bilal[1, a], Rabbya Rayan Shah[2, a], Bushra Bilal[3], Fatima hameed[4], Ambreen Talib[5], Amara Ijaz[6], Hafiza Arshi Saeed[7], Hafiza Rida Fatima[8], Maryam Zahra[9], Ayesha Muazzam[10*]

[1]Department of Zoology Muhammad Nawaz Shareef University of Agriculture Multan 25000, Pakistan

[2, 4, 5, 7, 8] Department of Pathobiology and Biomedical Sciences, Muhammad Nawaz Shareef University of Agriculture. Multan 25000, Pakistan

[3]National University of medicine sciences (NUMS), Rawalpindi, Pakistan

[6]Department of Poultry Science, Muhammad Nawaz Sharif, University of Agriculture, Multan, 25000, Pakistan.

[9]Department of Veterinary and Animal Sciences Muhammad Nawaz Shareef University of Agriculture. Multan 25000, Pakistan

[10]Department of Animal Science Gyeongsang National University 501, Jinju-daero, South Korea

[1]uzmabilal31@gmail.com, [2]rabbiyarayanshah@gmail.com, [3]bushrabilal550@gmail.com, [4]fatimahameed838@gmail.com, [5]ambreentalib212@gmail.com, [6]amaraijaz36@gmail.com, [7]arshisaeed111@gmail.com, [8]ridafatimabaloch01@gmail.com, [9]maryamzahra309@gmail.com, [10]ashu2nice@gmail.com

"a" sign denotes that both are equal (primary authors)

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Abstract:

Many bacteria share a healthy human body, generating natural flora. According to many predictions, bacterial genetic material is much more important in the human body than a certain amount of DNA. Any modification in the composition of this flora could result in a wide range of disorders, considering that it plays a crucial role in human health and illness. In many different sectors, nanoparticles are frequently used: industry, food, and platforms for the transportation of pharmaceutical products in the medical domain. Different industries, fields, and occupations, such as pharmaceutical products, cosmetics, and medicines, widely use nanoparticles. Nanoparticles could interact with the human body in multiple ways at various stages because of their many potential applications. Due to the shape, type, and concentration of nanoparticles, their interaction can cause the microbiota to become unstable, regenerate themselves, or show no harmful effects. Additionally, the microbiota can be controlled or some disorders can be treated with nanoparticles. Nanoparticles may also be used as a vehicle to regulate the microbiota or to treat some of its diseases.

Keywords:

Nanoparticles, microbiota, health, disease, interaction

Introduction:

About 400 years earlier, when Antony van Leeuwenhoek made the first optical microscopic observation of bacteria [1], shortly after observing the works of Koch, Pasteur, and Cohn in the middle of the nineteenth century, anaerobic microbiology and molecular biology emerging and growing in the last half of twentieth century and the first decade of the twenty-first century emerging of DNA sequencing technologies, microbe's researchers have traveled a journey full of diverse discoveries [2]. Improved bacterial community identification and differentiation were made possible by the development of metagenomic analyses of microbial communities. As a result, a remarkable observation emerged: various microbes inhabit various organs inside the healthy human body. These microbes are considered to number at least 100 trillion, classified into 1800 genera with approximately 40,000 species in contrast to 10 trillion eukaryotic human cells. [3, 4]. Microbiota is the collective term for these microorganisms [5]. Since its discovery, the human microbiota composition, distribution, and variation have made significant advancements in our understanding. The Human Microbe Project" is one of the largest studies on the human microbiota [6]. The aim is to identify the human microbiota to recognize inter-individual variances and additional variables that may impact it, collaborated research is being initiated in Europe, Asia, and the USA [7]. This large-scale study indicates the importance of this field of study across three

countries and demonstrates research efforts dedicated to human microbiota. Several studies have brought attention to the impact of external factors on the stability of the microbiota and the potential ramifications for human health given that it is an integral element of the human body [8]. Nowadays, a great number of compounds that may interact with human microbiota contain nanoparticles; airborne pollutants, where they may react with the respiratory tract microbiota; food, where they may interact with the gut microbiota; and pesticides, where they interact with the skin microbiota [9]. This overview describes the human microbiota including its components, functions, and effecting factors. Next, the discussion of the effects of various nanoparticle kinds influenced by different works is presented.

1. Gut Microbiota:

The human gastroenterological tract is home to over 1040 microorganisms, including approximately 104 kinds of bacteria. There are different types of bacteria depending on the Location of the gut, and the majority of them are Anaerobic. Bacteria proliferate from the stomach into the ileum, jejunum, and colon. Nutrition and age also have an impact on the bacterial floral makeup [10]. It has been established that the development of the gut immune system depends critically on the microbiota [11] and that the systematic immune system is also impacted by them [12]. The composition of the microbiota is also associated with various diseases.

1.1.Composition of Gut Microbiota:

Gut microbes are often not cultivable, making a detailed investigation of them difficult. [13]. The resolution of microbial biodiversity and the quantification of microbial species have been improved by the use of real-time PCR, microarray, and pyrosequencing techniques. [14]. DNA pyro-sequencing based on 16S rRNA genes is one of the gene-based techniques at present this approach is the most beneficial for the thorough comprehensive study of gut microbiota that produces precise measurements and high resolution [15].Using pyro-sequencing, examined the makeup of the intestinal microbiota by amplifying more than 40000 16S rRNA gene V4 regions. They discovered that the phylum Bacteroides was the most frequent kind of bacteria in 68% of the people under observation, with an average of 57% [16]. The phylum Firmicutes came in second with an average proportion of 40%. *Faecalibacteria*, *Actinobacteria*, and *Proteobacteria*, were

other species found. Individual variations in composition were observed, as well as variations based on age. The diversity of Bacteroides species was found higher in elderly people, but the diversity of Bacteroides was reported to be lower [17]. Even though different outcomes have been found [18].

1.2.Function of Gut Microbiota:

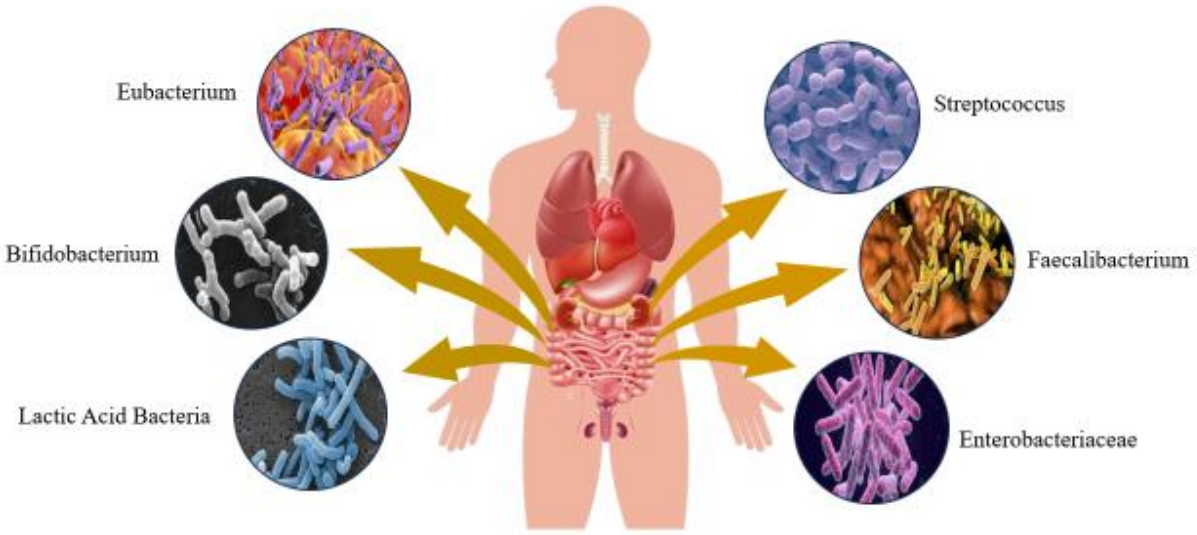

Figure 1 Composition of Gut Microbiota: There are billions of microbes in human gut

1.2.1. Digestion and metabolism:

It is widely recognized that plant polysaccharides and complex carbohydrates are indigestible by human enzymes [19]. Human enzymes are known to be unable to digest complex carbohydrates and plant polysaccharides. As an alternative, the nondigestible carbohydrates in the colon such as cellulose, resistant starch, and inulin, are fermented by gut microbiota to produce the energy for the growth of microorganisms and by-products such as short-chain fatty acids (SCFAs) [20]. The main organic fatty acids (SCFAs) are produced butyrate, propionate, and acetate. The intestinal epithelium uses butyrate as an energy substrate, while peripheral tissues use acetate and propionate

propionic acids and trigger the release of hormones [22], and the liver's regulations of fat and glucose metabolism [23]. Furthermore, it has been demonstrated that several SCAFs have anti-inflammatory and immunomodulatory properties [24, 25].

[21]. It has been demonstrated that cell division and proliferation are controlled by butyric and Bacterial makeup is generally constant and does not trigger inflammation, even though each person's stomach has approximately 104 different bacteria [26], currently maintaining the long-term flora can be achieved by procedures that are not completely understood. Since the range of microbiota, develops in the early stages of life after birth, when the immune system continuously develops and enables the complete elimination of intestinal microorganisms, the prevention of gut flora could depend on immunological tolerance to microbiota [27, 28].

By developing and enhancing the performance of Foxp3+ regulatory T cells (Tregs) through the production of polysaccharide A by the bacteria, Round et al [29] demonstrated that Bacteroides fragilis could develop immunological tolerance to the gut microbiota. Another investigation showed that the most successful species of Clostridium for producing the differentiation were those belonging to phylogenic groups IV and XIV but not Lactobacillus or Bacteroides [30]. For the formation and composition of gut microbiota, a significant role is played by CD1d molecules, which are Natural killer T (NKT) cells, a subset of T cells that recognize self-antigens and microbial lipids antigens that CD1d provides.

In contrast, associated gut microbiota regulates the growth and maturation of systemic NKT and mucosal cells [31] Furthermore, NKT cells play an important role in the pathophysiology of human inflammatory bowel disease and are presented with self-antigens and microbial lipid antigens by CD1d [32]. Hence intestinal inflammation and microbial homeostasis both are greatly impacted by the interaction between the microbiota and CDd1-restricted NKT cells.

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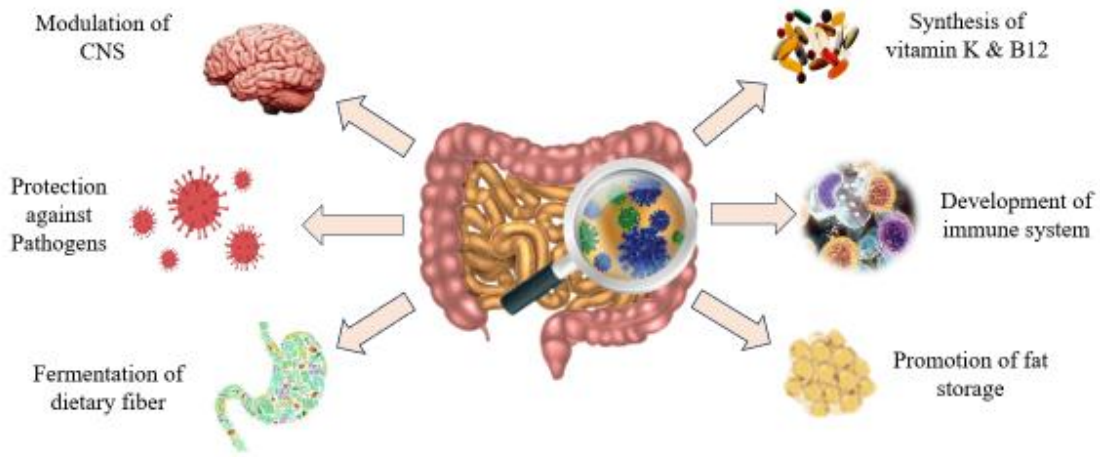
1.1.1. Role of gut microbiota in the maturation of the immune system:

Mice have been used to demonstrate the involvement of gut microbiota in the development of gut immune development, involving the quantity of intestinal CD4+ and CD8+ T-cells and dendritic cells [33]. The microbiome in the liver plays a crucial role in preserving liver well-being and overall metabolic equilibrium. It generates short-chain fatty acids (SCFAs) and other substances that impact metabolic functions like glucose production and lipid processing [34]. Short-chain fatty acids (SCFAs), for instance, act as a fuel for liver cells and possess anti-inflammatory characteristics. The liver and gut are linked via the portal vein, which carries substances from the intestines to the liver. This connection forms the gut-liver axis, facilitating ongoing communication between the gut microbiota and liver microbiota [35]. This interaction affects gut penetrability and microbiota makeup, thereby influencing overall health. An inequality in the liver microbiota, known as dysbiosis, is linked to various liver diseases [36]. An imbalance in gut bacteria can worsen liver fibrosis and inflammation, leading to more severe disease outcomes [37]. Moreover, an imbalance in microbial flora and ongoing inflammation are contributors to the development of hepatocellular carcinoma (HCC). Changes in the microbiota of the liver can facilitate the



development of cancer through different pathways, such as causing DNA damage and evading the immune system [38].

1. Nanoparticles:

A developing branch of science known as nanotechnology" explores the production and synthesis of nanomaterials. Over 4,500 years ago, applying natural asbestos-exposure nanofibers in the ceramic matrix favorable reinforcement introduced the concept of nanoparticles in human life [40]. Lead sulfide chemicals were man-made products used by ancient Egyptians, 4000 years ago, for hair dye [41]. They also created the first synthetic pigment in the third century B.C. utilizing the combination of quartz and glass nanoparticles [42]. Since then, without properly any scientific justification fabrication and formulation of nano-materials have been used in various everyday applications. Since then, nanomaterials have been used in different fields of daily life but without

Figure 2 Different functions of gut microbiota [39]

any scientific narration of the procedure of synthesis and formulation [43].

Finally, colloidal gold nanoparticle suspensions were first time scientifically and optically described by Michael Faraday in 1857 [44]. The procedure of synthesis of polymer nanoparticles, analysis of them, and loading them with labile proteins were all discussed in the first work describing the evaluation of neon particles in an in vitro model, which was published in 1976 by Birrenbach and Speiser [45]. Just before it, it was believed that it to be impossible to administrate intravenous suspension [46]. Throughout history, these materials have been described in different ways. The national nanotechnology initiative's definition, which describes nanoparticles as materials with sizes between 1 and 100 nm at least one dimension is the most recent and widely used one [47].

1.1.Synthesis of Nanoparticles:

Chemically and biologically nanoparticles can be prepared. Techniques of chemical preparation of nanoparticles are connected with challenging impacts because of various poisonous chemicals

noticed externally [48]. Biological manufacturing of nanoparticles involving plants or herbal extract, mold, enzymes, and plants is an ecologically sustainable replacement for chemical and physical processes [49].

1.2.Types of Nanoparticles:

Three different types of nanoparticles may be recognized depending on the ingredients utilized to prepare them, organic, inorganic, and metal-organic framework (MOF) nanoparticles [50]. Various nanoparticles may be characterized depending on their shapes, benefits, content use, and formulation methods, such as hybrid nanoparticles, lipid nanocapsules, polymer nanoparticles, liposomes, micelles, protein-based nanoparticles, biological nanoparticles, and metal-based nanoparticles [51,52]. These nanoparticles are also known as nanomedicines largely used in pharmaceutical sectors. Among its multiple advantages, its small size which helps to cross through biological obstructions like cell membranes is the most significant [53]. Their interface is changeable and adjustable to increase biodistribution and tissue uptake [54]. They can distribute medication, genetic materials, shield proteins, and encapsulation [55,56]. The delivery can be time-controlled or activated by a particular stimulus [57].

These benefits assist many other therapies and change many of other traditional limitations. Such as minimizing the therapeutic agent, and essential quantity to provide a biological impact that is better than before [58], while simultaneously lowering the active substances associated with toxicity [59].

1.3.Applications of Nanoparticles:

Several medical applications have been developed for nanoparticles, such as fluorescent biological labeling [60], pharmaceutical delivery systems [61,62], pathogens and protein detectors [63,64], tissue engineering probe DNA structure [65], biological tissue engineering [66,67], heating mediator for hyperthermia in cancer therapy [68]. They are also used in cleansing and separation of biological substances and cells [69], in MRI imaging [70], and in cell test mobility to determine how cancer cells metastasize [71].

The interaction of nanoparticles with the human body at daily usage should be further researched and considered to improve knowledge and quantity of the risks that the consumer may counter. Due to its various functions and various illnesses that may occur from its imbalance already described microbiota is now regarded as an organ of the human body [72].

The various interactions between nanoparticles and bacteria, as well as the various factors that may affect such interactions, are discussed in the next section of the review along with their implications for the human microbiota [73]. Various research that examined the interactions between nanoparticles and microbiota have been discussed in detail, providing an up-to-date picture of the field.

1.4.Mechanism of bacteria and nanoparticle interactions:

The quantity of bacteria that make up the human microbiota is ten times greater than that of human cells, but the potential interactions between nanoparticles and the healthy microbiota are far less explored and understood than those involving eukaryote cells [74].

1.4.1. Interactions between matter and chemicals:

Because of their huge surface area and nanoscale size, nanoparticles have special characteristics that make it easier for them to interact with microbial cells [75]. The adherence of nanoparticles to the surface of microbial cells is one of the main physical interactions. The nanoparticles' size, shape, charge, and surface chemistry all impact this adherence. For example, physical disturbances might result from metallic nanoparticles like gold and silver attaching to bacterial cell membranes. These alterations have the potential to enhance membrane permeability, trigger lysis of cells, and eventually lead to microbial demise [76]. Furthermore, because of their high reactivity, nanoparticles can produce reactive oxygen species (ROS), which can cause oxidative stress and harm biological components like proteins, DNA, and lipids [77]. The dynamics between

nanoparticles and bacteria are also heavily influenced by chemical interactions. Ions that have strong antibacterial properties, such as silver ions from silver nanoparticles, can be released by nanoparticles [78]. These ions can enter microbial cells and obstruct vital biological functions like DNA replication and enzyme activity [79].

In addition to sequestering vital nutrients and signaling chemicals, the adsorption of nanoparticles onto microbial surfaces can also interfere with microbial metabolism and communication [80]. Moreover, surface changes of nanoparticles, including polymer or biomolecule coating, can change how they interact with microorganisms. To decrease protein adsorption and increase circulation time in biological systems, for instance, polyethylene glycol (PEG)-coated nanoparticles may have different interactions with liver microorganisms [81].

1.4.2. The Impact of Nanoparticles on Biological Pathways:

Within microbial cells, nanoparticles can profoundly impact a variety of biological pathways [82]. The expression of genes is one of the main effects. Microbes exposed to nanoparticles may experience stress responses, which could result in the up-or-down-regulation of particular genes. For example, in response to ROS produced by nanoparticles, genes involved in oxidative stress defense, such as those encoding catalase and superoxide dismutase, may be activated. These variations in gene expression may have an impact on the growth, metabolism, and viability of microorganisms [83, 84].

Furthermore, quorum sensing—a communication mechanism that bacteria employ to coordinate group activities based on population density—can be interfered with by nanoparticles [85]. Quorum sensing controls processes like the development of biofilms, the synthesis of virulence factors, and the resistance to antibiotics. These coordinated activities can be hindered by nanoparticles that interfere with quorum-sensing signals, which can affect the structure and function of microbial communities [86]. The liver microbiota's ecological balance may be changed, pathogenic may be decreased, and biofilm formation may be prevented. Such relationships have major implications for the liver [87]. The portal vein transports a significant amount of blood from the stomach to the liver, which makes it the main location where

nanoparticles accumulate after oral or systemic exposure [88]. Liver bacteria can interact with

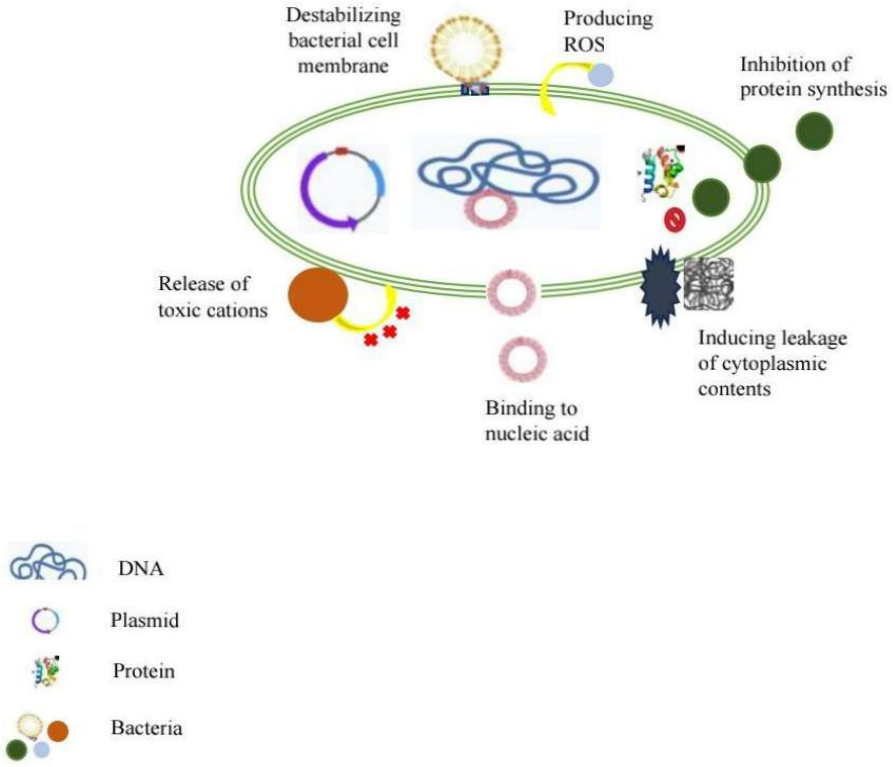


Figure 3 Mechanism of interaction of bacteria and nanoparticles

nanoparticles employed in medicine administration, diagnostics, or environmental toxins, changing their function and composition. For example, nanoparticles can alter the metabolic activity of hepatic microorganisms, which can impact the biotransformation of medications and other substances. Therapeutic drugs' toxicity and efficacy may change as a result of this modulation [89]. Furthermore, nanoparticles may affect the liver's immune response, potentially resulting in immunological tolerance or inflammation [90].

2. **Impact of Nanoparticles on Microbiota:**Based on recent research, the effects of certain nanoparticle interactions with various bacteria from the human healthy microbiota have been documented. **(table 1).**

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Nanoparticles	Species	Target Microbiota	Effects of Interactions	References
AgNPs	Avian species	Lactic acid bacteria (except *Lactobacillus*)	Promotes growth	[91]
Copper loaded chitosan NPs	Avian species	*Bifidobacterium*, *Lactobacillus* spp.; *E. coli*	Promotes growth; Antimicrobial effects	[92]
AgNPs	Humans (fecal material)	*Roseburia* spp. *E. coli*, *Bacteroides*, Bacterial isolates; increase in Firmicutes and decrease in Bacteriodetes	Promotes growth, antimicrobial effects; changes in numbers	[93]
SLN	Humans (fecal material)	Firmicutes, Bacteroides, Bacteriodetes; *Bifidobacterium* spp., *Lactobacillus* spp.	Antimicrobial effects; promotes growth	[94]
Zinc, TiO2, and cerium NPs	Humans (fecal material)	Firmicutes, Bacteroides, Bacteriodetes	Phenotypic changes	[95]
Selenium NPs	Animals (fecal material)	*E. ceconum*	*E. ceconum* Antimicrobial and prebiotic	[96]
AgNPs	Pigs	*E. coli,* Firmicutes	Antimicrobial	[97]
ZnO NPs	Pigs	Increase in *Lactobacillus* and *Streptococcus* in the ileum, decrease in *Lactobacillus*, *Provotella*, and *Oscillaspira* in the colon.	Changes in growth and diversity	[98]
AgNPs	Mice and rats	Firmicutes and *Lactobacillus*	Antimicrobial	[99]
TiO2 NPs	Mice and rats	Firmicutes, Bacteroides, Bacteriodetes	Alterations in gut microbiota during pregnancy and increase in blood glucose level in pregnancy	[100]
Silica and AgNPs	Mice and rats	Bacteroides, Firmicutes and Actinobacteria	Changes in number of population	[101]
AgNPs, TiO2 NPs and SiO2 NPs	Mice and rats	Lactobacillus decrease, a shift in Bacteriodetes and Firmicutes	Changes in numbers and groups	[102]

AgNPs and Copper loaded NPs	Fish	*Cobacterium somerae*	Antimicrobial	[103]
AgNPs	Male zebrafish	Bacteroides, Firmicutes, and Bacteriodetes	Dysbiosis	[104]

3. Biotransformation of Nanoparticles by Microbiota

3.1.*Metabolic Pathways Involved:*

By exploiting numerous metabolic pathways, liver microbes play a critical role in the biotransformation of nanoparticles by altering their structure and function [105]. In the detoxification and transformation of nanoparticles various microbial enzymes including oxidoreductase, hydrolases, and transferases are involved. These enzymes work by changing the surface chemistry of nanoparticles resulting in altering their stability, solubility, and reactivity [106]. For instance, some microbes reduce metal ions present in nanoparticles converting them into less toxic form. Moreover, these liver microbes modify the characteristics of nanoparticles by breaking their functional group or outer covering [107].

3.2.*Effect on Nanoparticle Properties and Toxicity:*

Liver microbes remarkably influence the properties and toxicity of nanoparticles through biotransformation [108]. Nanoparticles interact with the body system by modifying cellular uptake, excretion, and biodistribution. This is influenced by the change in size, surface charge, and aggregation state of nanoparticles caused by microbes. In particular, liver microbiota degrades the toxicity and antimicrobial activity of silver nanoparticles by depleting them [109]. Contrarily, during the biotransformation of nanoparticles, the formation of reactive metabolites can modify the cytotoxicity of certain nanoparticles [110]. The efficiency of nanoparticle-based drug delivery systems can be affected by this microbial moderation. This happens by changing drug-release

profiles and therapeutic outcomes [111]. In the medical and environmental implementation of nanoparticles, understanding the biotransformation process is crucial for forecasting their biological attitude and safety [112].

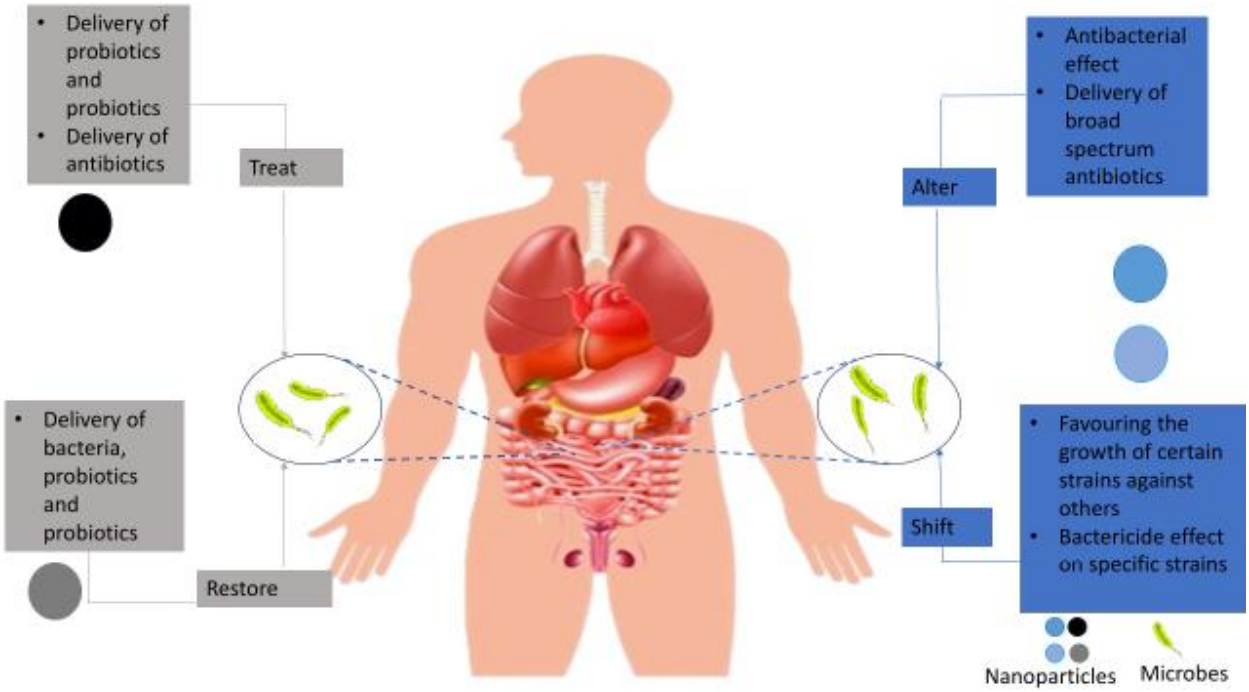

Figure 4 Effect of nanoparticles on human microbiota [113]

4. Implications for health and disease:

Significant effects on both health and disease are associated with the relationship between liver microbiota and nanoparticles. To evaluate the safety and effectiveness of nanoparticle-based systems for industrial and medical applications, these consequences must be understood [114].

4.1.*Healthy Advantages:*

By being used in the administration of medications, evaluations, and therapies, nanoparticles have demonstrated interest in boosting human health. Treatments for liver illnesses can be more

precisely and effectively administered if nanoparticles are designed to target particular microbial communities within the liver [115]. Furthermore, by encouraging the development of advantageous bacteria and preventing the growth of harmful ones, nanoparticles can be employed to modify the liver microbiota. By focusing on specific areas, this strategy can enhance liver function, preserve microbial balance, and fend off illnesses [116].

4.2.*Potential hazards and negative outcomes:*

The relationship between nanoparticles and the liver microbiota, however, may pose health risks [117]. Hepatocellular carcinoma (HCC), non-alcoholic fatty liver disease (NAFLD), and cirrhosis are all associated with dysbiosis, a microbial imbalance brought on by nanoparticle disturbance of the liver microbiota [118]. Moreover, nanoparticles can exacerbate hepatic damage and induce oxidative stress, inflammatory reactions, and immune responses [119]. In addition, liver bacteria can create reactive compounds when they bio-transform nanoparticles, increasing the toxicity of the particles and potentially harming human health [120].

4.3.*Regulatory and Safety Considerations:*

Considering the possible advantages and drawbacks, it is crucial to thoroughly assess the safety of nanoparticles before their application in clinical and industrial settings [121]. Regulatory frameworks need to include thorough evaluations of how nanoparticles interact with liver microbiota, taking into account variables like dosage, duration of exposure, and individual susceptibility [122]. Methods to minimize negative impacts involve improving nanoparticle design to lower toxicity and utilizing positive microbial interactions to improve therapeutic results. In conclusion, although nanoparticles hold considerable promise for enhancing liver health and treating diseases, managing their interactions with liver microbiota is crucial to avoid adverse effects and optimize health advantages [123].

5. Future Directions and Challenges:

Future studies should focus on the precise mechanisms by which nanoparticles interact with the liver microbiota as well as the effects of the particles' physicochemical characteristics on microbial responses [124]. To assess the long-term impacts of nanoparticle exposure on microbial diversity and liver health, a great deal of research is needed. Our understanding of these complex linkages can be enhanced by the combination of omics technologies and computational modeling [125]. Strong safety evaluations and standardization of experimental procedures are crucial for regulatory approval and reproducibility [126]. Developing targeted delivery vehicles with minimal off-target consequences is a major problem in the design of biocompatible nanoparticles. Although exploiting these interactions for therapeutic interventions in liver disorders shows promise, sustainable nanotechnology techniques necessitate an understanding of the environmental consequences of nanoparticle discharge [127, 128].

Conclusion:

This article elucidates the effects of nanoparticles on gut microbes. In this, we discussed the role of gut microbes which boost the gut and systemic immune system. As the analysis of gut microbes is difficult, various biotechnological techniques like real-time PCR, microarray, and pyro sequencing have ameliorated the genome analysis and quantification of microbes. Studies revealed that microbes including Bacteroides, Proteobacteria, Firmicutes, Actinobacteria, and Faecalibacteria are normally present in the gut. These microbes function as catalysts in the digestion of complex carbohydrates and polysaccharides. The connection between the gut and liver through the portal vein permits the interface between gut and liver microbes thus influencing systemic health. Nanoparticles provide protective delivery of proteins, drugs, and genes to targeted places. Also, it improves the oral drug delivery. This leads to overcoming problems related to other therapies. The presence of nanoparticles in different daily used products impels us to study their role in improving health and all related risks to the consumers. The small size along with the larger surface area of nanoparticles ease their interaction with microbes. Studies revealed that the antimicrobial effect of nanoparticles is due to their property to release ions. These ions, by

Penetrating microbial cells, interfere with biological processes like enzyme activity and DNA replication. Nanoparticles persuade stress response in microbes contributing to changes in gene expression. By interfering with quorum sensing, nanoparticles impact on microbial structure and function. Microbes in turn also have an impact on the biotransformation of nanoparticles microbial enzymes play a role in the detoxification and conversion of nanoparticles resulting in changes in their solubility, stability, and reactivity. By understanding the interrelationship between nanoparticles and microbes, we should focus on the impacts of nanoparticle exposure on microbes and guidelines for their safe use. Computational modeling and techniques can help us in understanding this interaction.

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