Use of Nanoparticles as Antioxidant Agents to Combat Bacterial Infections and its Benefits to Intestinal Microbiota and Immune Response

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SUMMARY

Several symbiotic microbes remain in the gastrointestinal tract of humans and animals. These micro-organisms are beneficial because of their assisting role in digestion, preventing pathogens' entry, blocking harmful pathogens, and providing several functional molecules to the organisms. The irrational use of antimicrobial chemical drugs, increased consumption of junk food, and low-pH carbonated, alcoholic, or caffeinated energy drinks have led to the severe destruction of microflora. This destruction of microflora has made humans and animals susceptible to several pathogens which can kill the host. Management of this issue can be done by suitable alternatives of chemical medicine or at least control of its delivery to the target only so that normal microflora may not be disturbed. Among all the suggested methods, the nanoparticles have promising importance. Nanoparticles are nanometer-scale particles of metals and metallic compounds that can deliver the drug, nutraceuticals, or any other agent inside the body. They may act as carriers of themselves and can serve as active compounds to serve the body. Research suggests that their use can be beneficial for the improvement of microbiota because they target the specific target sites, easy elimination, maintaining controlled release of chemical antimicrobials, and enhancing immunity. Research is being done to manage their dosages and usages. This chapter highlights the importance of nanoparticles, the role of microbiota inside the body, and the potential of nanoparticles for the improvement of microbiota and enhancements in the immunity of the body.

INTRODUCTION

A variety of different microbiomes located in the digestive tract of humans and animals make the gut microbiota (Mondo et al., 2019). Gut microbiota harbour millions of microorganisms that start to multiply at birth age. The modification in the composition of gut microbiota depends mainly on genetic, nutritional, and environmental factors. This modification in gut microflora leads to a change in intestinal permeability and immune responses (Li et al., 2020). It is significantly vital in maintaining health by boosting the immune system, protecting against evil pathogens, vitamin synthesis, nutrient assimilation, and metabolic regulation. A minor change due to the pro-inflammatory state in the gut microbiota led to severe ailments, including gastrointestinal (inflammatory bowel disease, colorectal cancer, and liver diseases), immunological (allergic reaction), respiratory (asthma), neuropsychiatric, and metabolic diseases (Sitkin et al., 2022).

Most of the time, the frequent use of exogenous elements, such as drugs and food additives, including environmental toxicants, interact with the gut microbiota, thus influencing the health of the multicellular organism (Michalak et al., 2022). It is essential to come into knowledge about the toxicity mechanism of these exogenous substances and their interaction

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with the human metabolism. Therefore, it is necessary to discover new ingredients that interact with the gut microflora to improve its valuable belongings.

Nowadays, nanoparticles of various sizes and with good biochemical properties have been applied in the fields of biotechnology, microbiology, medicine, food, and agriculture (Salem, 2023). The beneficial effects of these nanoemulsions and nanoparticles on gut microflora have brought significant attention to their use to improve the health of humans and boost their immunity (Wei et al., 2022). For example, $TiO_{2\ is}$ used in the brewing and food industry to improve the taste, colour, and quality of the food, which automatically increases the uptake of food. Silver-based nanoparticles are used as antibacterials and are easily absorbed by the gastrointestinal tract (Blackadar et al., 2022). Similarly, different nanoparticles are being used as anthelmintic and antiparasitics. These nanoparticles not only improve the gut microbiota but also increase the digestibility and absorption of the food ingredients and are less toxic to the liver (Wang et al., 2023).

Finally, several research and review articles have been studied to compile the bioeffects of these nanoparticles and their effects on immunity (Xie et al., 2022b). This book chapter discusses several nanoparticles of metals gold (Au), zinc (Zn), silver (Ag), titanium (Ti), non-metal (carbon, liposomes, and silicon), and nanocomposite types with physicochemical properties, additionally, metal and non-metal-based nanoparticles and their effect on gut microbiota.

METAL-BASED NANOPARTICLES

Zinc and its combinations

Zinc belongs to transition elements and is found in trace amounts, but it is essential for the proper functioning of millions of enzymes in humans and animals. That's why Zn-based nanoparticles have significant importance by increasing the nutritional requirements of the body (Wang et al., 2022). Several bacteria present in the human digestive tract are hazardous to health, such as *Salmonella typhi* and *Streptococcus aureus* (Mak et al., 2022). Due to the increased resistance in these species when Zn oxide nanoparticles are given to the animals, a particular type of highly reactive oxygen species (ROS) from the surface of ZnO (zinc oxide) nanoparticles causes damage to the unusual creatures in the gut and blood of the microorganisms. These reactive oxygen species penetrate the cell wall, create pores, and cause leakage of cytoplasmic contents, leading to the shrinkage and, ultimately, death of the bacterial cell. These nanoparticles act on different gram-positive bacteria and gram-negative bacteria and act as bacteriostatic (ZnO released the Zn2+ that attack DNA and proteins) and bactericidal as they lysis the cell wall and cell membrane of certain species of bacteria (Ishida, 2020). The bacteriocidal activity of Zn nanoparticles depends upon size, concentrations, and method of synthesis. Zn-based nanoparticles, due to their broad-spectrum application, can kill those bacteria which have developed resistance against certain types of antibiotics (Leong et al., 2023). Due to bactericidal and bacteriostatic properties, they are used in dishwashers, food containers, milk packs, and refrigerators for the preservation of food. These Zn-based nanoparticles have also been helpful in drug delivery, personal care products, and cosmetics.

The effects of exposure to ZnO nanoparticles on the gut microbiota have been investigated in various animal models (Zhu et al., 2023b). For example, Feng et al. (2017) described the relationship between ZnO oxide nanoparticles and the gut microflora in the ilium of chickens. Various doses of Zn-based nanoparticles were prepared, mixed with feed, and fed to chickens for nine weeks. After treatment, the bacterial ecosystem of the intestine decreased, which showed the negative relationship of ZnO with the bacterial community. These nanoparticles not only reduced the number of bacteria but also altered the structure and chemistry of intestinal microflora (Zhu et al., 2023b). It was also seen that the organic compounds and vitamins associated with the improved microbiota were also increased. Consequently, ZnO nanoparticles can induce gut microbiota alterations and thus indirectly regulate blood metabolism. In a comparative study, Zhou et al. (2023) checked the effect of biosynthesized ZnO nanoparticles on attention-deficit hyperactivity disorder (ADHD) and healthy children. They concluded that the gut microbiota composition of ADHD children has been improved as compared to healthy children. This study may provide a new possibility to prevent ADHD using nanoparticles.

When ZnO nanoparticles were exposed to the gut microbiota, both harmful and beneficial effects were noted. The physicochemical characteristics of ZnO nanoparticles and their dynamic behaviour in bacteria must, therefore, be considered. The attraction of released Zn2+ to the surface of bacterial cell membranes and the disordered energy metabolism of bacteria caused by the internalization of ZnO nanoparticles are two potential sources of the harmful effects of ZnO nanoparticles (Ahmed et al., 2019). The beneficial effects of ZnO nanoparticles, on the other hand, may be connected to Zn2+ post-efflux mechanisms, which prevent effluxed Zn2+ from entering cells again through precipitation, complex formation, or protein attachment.

It is necessary to remember that while Zn-based nanoparticles are advantageous for gut flora and other bodily functions, they may also cause toxicity, increase inflammation, and cause neuropsychiatric problems (Liu et al., 2022). Eventually, it becomes clear that in contrast to TiO2 and silver nanoparticles, scientific research on ZnO nanoparticle-induced changes in the gut microbiota is uncommon. Further research is highly relevant, given the widespread use of zinc oxide nanoparticles in human beings. Therefore, research is required to ascertain how ZnO nanoparticles affect the microbiota in the intestines and the relationship between this influence and a variety of disorders.

Titanium (Ti) based nanoparticles

Titanium dioxide (TiO2) nanoparticles are frequently applied in many industries, including food items, cosmetics, paint, toothpaste, and medicinal tablets (Bevacqua et al., 2023). This is due to their excellent physicochemical features, such as a high refractive index and excellent brightness (Azab et al., 2022). To enhance the color, flavor, and quality of foods like candies, dairy products, custards, drinks, and sauces, TiO2 nanoparticles, for instance, have been employed as food additives for a long time. These uses significantly increase the amount of TiO2 nanoparticles that people consume, which has caught the attention of researchers and authorities everywhere. For example, when TiO2 is given to mice that are obese (due to a high-fat diet) and have a thick mucoid colon (Zhu et al., 2021). It ultimately reduced the Muc2 gene and inhibited further thickness. It not only blocks the thickness but repairs the injured mucosal layer. On the other hand, food-grade TiO2 NPs were tested for toxicity using a model intestinal bacterial population at a level comparable to what is seen in the human intestines after consuming 1-2 pieces of candy or gum (Baranowska-Wójcik et al., 2022). The study concluded that TiO2 NPs do not significantly alter the gut microbiota at low concentrations, finding only small reductions in *Bacteroides ovatus* and an increase in *Clostridium cocleatum*.

Furthermore, continuous use of Ti-based nanoparticles will induce oxidative stress and inflammatory processes. When TiO2 nanoparticles interact with gut microbiota, a variety of biological effects are observed. These include unusual oxidative stress, illness, and inflammatory responses, as well as an increased risk of hepatotoxicity metabolic syndrome, obesity, and colorectal cancer (Bruno et al., 2023). The catalytic capabilities of the TiO2 nanoparticles may be the primary cause of these adverse effects. The way that TiO2 nanoparticles poison bacteria involve the formation of ROS species that cause damage to biological components like the cell wall, cytoplasm, DNA, and proteins (Kamyab et al., 2023). Contrary to Zn-based nanoparticles, whose toxicity is mainly ascribed to the released cation Zn2+, TiO2 nanoparticles' bacterial toxicity is typically caused by harmful reactive oxide species (Rai et al., 2021). In summary, further studies are needed to promote the safe use of TiO2 nanoparticles in everyday life.

Silver-based nanoparticles

The unique properties of silver-based nanoparticles, such as antimicrobial, antifungal, and antiviral effects, make them widely used in many fields that are closely related to human life (Rai et al., 2021). According to the statistics, currently, more than 400 consumer products that contain Ag nanoparticles are inventoried as emerging nanotechnologies, including topical wound dressings, food-related products, biomedical devices, and dietary health supplements (Xie et al., 2022b). Consequently, it is necessary to explore the potential effects of Ag nanoparticles on the gut microbiota and the changes within the host.

Research trials demonstrated that Ag nanoparticles can alter the composition of the gut microbiota and induce colitis-like symptoms (Ghebretatios et al., 2021). Ag nanoparticles were orally administered to mice. After treatment, the *Firmicutes* and *Bacteroidetes* bacteria were reduced while the number of low-abundance families of bacteria was increased. Similar results have been found in other intestinal inflammatory diseases. Ag nanoparticles' harmful effects principally result from the release of Ag+. The discharged Ag+ can destroy DNA, disrupt cell walls, and derangement of membrane proteins. These findings suggest that Ag sulfidation, which lowers Ag+ release and lessens Ag nanoparticle effects on gut microbiota, arises from Ag nanoparticle aging in food (Nauroze et al., 2023). Different other questions regarding the impact of silver-based nanoparticles still need to be debated.

Copper-based nanoparticles

The body needs copper as a micronutrient. It serves as a cofactor for several enzymes involved in metabolic processes like melanin formation, the Kreb cycle for ATP production, and the metabolism of iron because of its capacity to receive and donate electrons (Kidd, 2005). Consequently, a Cu metabolic abnormality may increase the risk of developing metabolic and systematic diseases. Nanotechnology has encouraged the manufacturing of Cu on a nanoscale over the past ten years. Cu nanoparticles have been extensively probed for medicinal applications like cancer therapy and diagnostic imaging due to their unique characteristics (Musielak et al., 2021). The likelihood of ingesting copper nanoparticles in the body has grown because of these applications (Muhammad et al., 2022).

According to the research, the strains of probiotic bacteria and the species that were part of the normal flora of the birds, including *Enterococcus*, *Enterobacterium*, and *Lactobacillus*, remained unchanged when the nanoparticles were fed in small concentrations (Manzoor et al., 2022). The beneficial outcome was attributed to nanoparticles' low dissociation, which released physiologically active ions considerably more gradually. As a result, using modest amounts of Cu-based nanoparticles is safe for gut flora. Another study found that consuming Cu nanoparticles could reduce the generation of short-chain fatty acids when the enzymatic activity of gut microbiota is suppressed in the ceca of rats (Broom et al., 2021). As a result, bacterial cells secreted more glycoside hydrolases. Cu nanoparticles, on the other hand, had less excretion from urine and feces than Copper sulfide (CuS), were more easily absorbed by the intestine, and accumulated in brain tissue. Additionally, a greater dosage of Cu nanoparticles may cause liver necrosis further, how cooper silicate nanoparticles impact broilers' intestinal microbiota. Escherichia coli and total aerobe numbers were dramatically decreased by copper silicate nanoparticles, whereas *Lactobacillus* and total anaerobe numbers were significantly raised. This evidence suggests that Copper sulfate nanoparticles not only prevented the growth of harmful bacteria but also encouraged the growth of beneficial species (Bhattacharjee et al., 2022). As a result, these nanoparticles may have a beneficial impact on enhancing the state of the gut and defending the intestinal tract. These copper-based nanoparticles are associated with the production of reactive oxygen species, which causes the lysis of cell walls of certain types of bacteria, particularly *E. coli*, thus defending the host body from harmful pyrogens.

Gold-based nanoparticles

Gold (Au) has attracted much attention in biomedicine due to its therapeutic effect on a variety of illnesses, including autoimmune and neoplastic diseases (Zhu et al., 2023a). However, individuals frequently get adverse effects from them. Fortunately, scientists have discovered that Au-based nanoparticles are safer and more efficient than Au compound medications. As a result, there are now more opportunities for gastrointestinal tract exposure to gold-based nanoparticles, which have gained significant interest for medicinal purposes in recent years. Investigation of the interactions between gut microbiota and Au-based nanoparticles in this context is necessary (Mertens et al., 2023).

According to research, Au-based nanoparticles have effective anti-inflammatory and antibacterial properties (Pragathiswaran et al., 2020; Muniyappan et al., 2021). The question of whether gut flora will be harmed when Au-based nanoparticles are employed as antibiotics has thus been a focus of investigation. Additional research on the bioeffects of alterations in the gut flora caused by Au has frequently been disregarded. We still include studies on the impact of Au-based nanoparticles on gut microbiota, despite the lack of acceptable examples of the bio-effects, in the hopes that they may stimulate further research into associated biological activities and safety evaluations. For instance, experimental data investigated how mice's gut microbiota was affected dynamically by short-term exposure to gold nanoclusters (Li et al., 2021). Nanoparticles were repeatedly given to mice for seven days, and the alterations in the gut flora were examined. The diversity and population of the gut microbiota did not noticeably change after the first three days of exposure to the nanoparticles (Xue et al., 2012). After seven days, however, nanoparticles changed the bacterial makeup, causing an increase in the antibiotic-producing bacteria as well as changes at the genus level, including a drop in *Roseburia* and an increase in *Staphylococcus*. This study introduces a novel, promising methodology for the safety assessment of Au nanoparticles. Another study showed that oral delivery of nanoparticles of Au reduced the chances of colitis but resulted in dysbiosis of the gut microbiota (Zhu et al., 2018). There were positive anti-colitis benefits found. However, the gut microbiota was altered by the Au nanoparticles due to a decline in diversity, *Firmicutes*/*Bacteroidetes* ratio, and *Lactobacillus* concentrations. The gut flora may be negatively impacted by the Au nanoparticles following oral treatment, even though they show significant potential as anti-inflammatory drugs. Therefore, safety measures are required to mitigate this unfavorable effect in potential therapeutic uses (Aggarwal & Harikumar 2009). As anti-inflammatory drugs, Au nanoparticles represent a promising new paradigm overall, although vigilance is needed to prevent their negative impact on gut microbiota. However, it is anticipated that when Au-based nanoparticles are utilized as antibiotics to treat bacterial infections, they will not have a negative effect on gut microbes.

Iron-based nanoparticles

Iron-based nanoparticles' effects on the gut flora have been the subject of few investigations, although the information that is currently available points to their safety and non-toxicity (Shukla et al., 2017). It has been demonstrated that diets containing ferrous sulfate decreased *Bifidobacterium* and enhanced sulfate-reducing bacteria, both of which are undesirable results (Dordević et al., 2021). Nano-ferrate, on the other hand, was discovered to be a superior substitute with no detrimental effects on the gut microbiota (Xie et al., 2022a). The authors also found that using iron NPs reduced the amount of iron that the microbiota was exposed to compared to using iron salt. This indicates that the nano form has a restricted ability to dissolve in the gut, potentially resulting in fewer interactions with the microbiome (McClements & Xiao 2017). Similarly, another study found that iron nanoparticles improved the microbiota's diversification and health, as seen by a rise in *Lactobacillus*.

NON-METALLIC NANOPARTICLES

Silicon-based nanoparticles

These particles, however, appear to have some adverse effects on the gut flora, according to one study (Okeke et al., 2023). Researchers observed that the microbial population of mice exposed to human-relevant levels of SiO_2 NPs for a week was more diverse and more affluent (Chen et al., 2017). These nanoparticles increased the population of Firmicutes and Proteobacteria while decreasing the population of Bacteroidetes and *Lactobacillus*. The pace of absorption of precipitated or fumed (amorphous) silicate is noteworthy because it permits the substance to build up in the gut lumen, giving the gut microbiota more time to be harmed by toxicity (Chen et al., 2017). This suggests that fumed silicate may be more harmful than previously thought.

Carbon-based nanoparticles

Carbon nanomaterials and carbon-based nanoparticles are widely employed in a variety of industries, including agriculture, medical, food, and the textile sector (Zaytseva & Neumann 2016). They differ from other nanoparticles in that they have distinctive physiochemical properties. Scientists focus their attention on using them to improve gut microbiota by preventing bacterial infections because of their regular use in numerous fields (Liang et al., 2018). In a research experiment, it was revealed that carbon-based nanoparticles can alter the gut microbiota in mice to increase intestinal permeability and inflammation (Chen et al., 2016). Different carbon nanoparticle concentrations mixed with food were administered to the mice as a treatment. The pro-inflammatory bacteria Lachnospiraceae grew after therapy, but Firmicutes and Bacteroidetes declined (Wu et al., 2019). When fullerene nanoparticles are administered and create anti-hyperlipidemic effects, they also have good benefits in addition to unfavorable ones. After 7–28 days of therapy, it significantly boosted the number of butyrate-producing genes. When mice were given injections of carbon nanoparticles in a related study, the gut microbiota entirely changed, and the relative concentrations of *Bifidobacteriales*, *Lactobacillus*, *Enterobacteriales*, and *Bacillales* increased.

NANOPARTICLES AND IMMUNE RESPONSE

Nanoparticles can interact with immune cells when they enter the body and cause an inflammatory response. Cytokines and chemokines are secreted in response to inflammation, granting immune cells to respond (Bianchi et al., 2017). The inflammatory reaction of negatively charged nanoparticles often has a lower subversive potential than positively charged ones. This can be justified by the fact that granulocytes readily interact with positive ion chemicals due to the negative charge of sialic acid on their surface. Some types of receptors, such as Toll-like receptors (TLRs), when attached to the antigen, start a series of reactions that lead to the inflammatory response. In an in vitro study, when macrophages of humans are exposed to various concentrations of SiO_2 and TiO_2, the increased appearance of TLR receptors and production of inflammatory cytokines were observed. Silicon dioxide (SiO_2 and TiO_2 nanoparticles produced the inflammatory cytokines, interleukins 1 and 2, and caused anti-inflammatory IL-1RA. Another research described the release of interleukins, which caused cytotoxicity and inflammation in the brain cells of mice when treated with silver nanoparticles. CeO_2 and TiO_2 nanoparticles, in contrast, failed to produce a similar result. Various in vivo trials have also demonstrated the inflammatory processes of nanoparticles.

To determine the exact biochemical effects of the nanoparticles, it is essential to know their physicochemical properties. The functions of these nanoparticles depend upon size, delivery, surface area and responsiveness, crystallinity, combination in relevant medium, configuration, surface coating, synthesis method, and impurities. The effect may also depend upon the solubility of the nanoparticles. For example, ZnO and FeO are more toxic than cerium oxide (CeO_2) and TiO_2 (Hayati et al., 2022).

Numerous studies have shown that size considerably affects the biological effects of nanoparticles. The generation of reactive oxygen species and the solubility of hazardous ions are both increased as length decreases and relative surface area increases (Carlson et al., 2008). For biological effects, nanoparticle form is also crucial. For instance, although fullerenes and carbon nanotubes have identical chemical makeup, their varied conditions have an impact on their toxicological characteristics. Their surface characteristics influence nanoparticle behavior in suspensions and interactions with cell membranes. The ability of nanoparticles to penetrate biological barriers and aggregate in media are both correlated with their surface charge. Impurities, endotoxins, and by-products of nanoparticle manufacturing can all affect physical consequences (Garcés et al., 2021). Biological responses to nanoparticle exposure can be influenced by the properties of nanoparticles, which can alter physical environments such as the bloodstream or in vitro cell culture medium.

CONCLUSIONS

Nanoparticles have been extensively used in various departments, from medicine to food. Research findings demonstrated the positive and negative impact of nanoparticles on gut microbiota. All discussions in our nook chapter include the effect of metal and non-metal-based nanoparticles on the gut microbiota and their impact on the immune system. These nanoparticles reduced the number of pathogenic bacteria and increased the number of valuable bacteria, hence increasing the overall performance of the gut microbiota. Further systematic research must be done to fully determine the impact of chronic exposure to NPs with consideration for methodological variables that may be contributing to conflicting findings.

Further research must also be done to determine the exact mechanism of nanoparticles, the combination of nanoparticles, and the factors influencing their action.

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