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IOP Publishing | Songshan Lake Materials Laboratory

MATERIALS FUTURES

Mater. Futures 4 (2025) 012302 (31pp) https://doi.org/10.1088/2752-5724/ada62b

Topical Review

Tuning gut microbiota by advanced nanotechnology

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Received 16 November 2024, revised 21 December 2024
Accepted for publication 30 December 2024
Published 23 January 2025

Abstract

Gut microbiota reveals fundamental mechanisms of health and disease, and its modulation has important applications in biomedicine. Traditional modulation methods (*e.g.* diet, antibiotics, and probiotics) suffer from drug resistance, poor targeting, and low efficiency. Nanotechnology has become an attractive option for the precise modulation of gut microbiota due to its targeting and controllability. This review will focus on research progress in nanotechnology to modulate gut microbiota, including the direct use of nanomaterials as antimicrobials, nano-drug delivery systems, and stimulus-responsive nanotechnology. In addition, the applications of nanotechnology to modulate gut microbiota are summarized in terms of healthcare, animal protection, and agricultural development. Finally, the challenges and corresponding solution strategies for nanotechnology modulation are reviewed, and the future development prospects for nanotechnology modulation are summarized. This review provides an important theoretical basis and practical reference for the development of gut microbiota modulation, and promotes the research and application of more precise and efficient microbiota community intervention strategies.

Keywords: nanotechnology, gut microbiota, modulation, drug delivery

Abbreviation Index

FMT	fecal microbiota transplants
SCFAs	short-chain fatty acids
BBB	blood-brain barrier
NAFLD	non-alcoholic fatty liver disease
IBD	inflammatory bowel disease
miRNAs	small endogenous non-coding RNAs
ROS	reactive oxygen species
TGN-Res@SeNPs	resveratrol-selenium-peptide nanocomposite
CAgNCs	chitosan silver nanocomposites
EcN	*E. coli* Nissle 1917
NO	nitric oxide

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1. Introduction

Gut microbiota is an important part of host microbes and is closely related to host health, nutrient absorption, and nervous system. After a long period of evolution with the host, the bacteria, archaea, and eukaryotes colonizing the gastrointestinal tract have formed intricate and mutually beneficial relationships that together constitute the gut microbiota [1]. It is estimated that the human gut microbiota consists of about 100 trillion microbiota (most of which are bacteria), far more than the rest of the microbial community on the surface of the body combined [2]. As an important research object in microbiology, gut microbiota has become a current research hotspot due to its wide range of applications. Gut microbiota dysbiosis can lead to disruption of host function, including poor digestion, impaired immune system function, metabolic disorders, circadian rhythm imbalances, and may even increase the risk of chronic disease [3]. Behavioral disorders and neurological disorders are also thought to be closely related to gut microbiota imbalances [4]. Due to the complexity and individual specificity of the gut microbiota, traditional one-size-fits-all approaches are often ineffective. Therefore, precise modulation of gut microbiota is the key to achieving personalized health management. By targeting and modulating specific microbiota or functions, it is possible to effectively restore and maintain a balanced gut microbiota. This approach can lead to enhanced immunity, improved metabolic function, and a reduction in the risk of diseases.

Different approaches have been used for gut microbiota modulation. Common methods of gut microbiota modulation can be divided into chemical (antibiotics, bioactive compounds) and biological (probiotics, FMT, phages, bacterial modification, biomolecules) based on the principle of modulation [5, 6]. Chemical modulation methods (*e.g.* antibiotics, bioactive compounds) can impact gut microbiota by directly inhibiting harmful microbiota and promoting probiotics [7, 8]. In biological modulatory approaches, probiotics can replenish beneficial microbiota in the gut and restore and maintain gut microbiota homeostasis [9]. FMT allows fecal microbiota from a healthy donor into the patient, restoring the gut microbiota in the patient's gut [10]. Phages can target pathogenic bacteria and modulate gut microbiota without affecting beneficial microbiota [11]. Bacterial modification can affect gut microbiota by using gene editing tools to modify microbiota into engineered bacteria with specific functions [12]. Some biomolecules can play a modulatory role by specifically recognizing gut microbiota. Although these classical methods have shown some effects in modulating gut microbiota, such as antibiotics can inhibit harmful microbiota and probiotics can improve and increase beneficial microbiota. The traditional methods have limitations in terms of broadness of action and non-specificity, and may even induce antibiotic resistance or other side effects. Therefore, the development of new technologies that can realize precise and specific modulation of gut microbiota has become a key direction in the field of gut microbiota modulation.

With advances in nanotechnology and a better understanding of gut microbiota, nanotechnology has been proposed as a new approach to modulating gut microbiota. Nanotechnology is characterized by specificity, controllability and multifunctionality, and through precise delivery and targeting, it is able to reduce side effects, enhance therapeutic effects, and provide brand new possibilities for precision medicine and the treatment of complex diseases. It has been demonstrated that nanomaterials can be used as antimicrobial agents to inhibit the growth of gut pathogenic bacteria. Common nanomaterials used as bacteriostatic agents include metal nanoparticles, carbon-based nanoparticles, lipid nanoparticles, and polymer nanoparticles [13]. The unique size and physical properties of nanomaterials allow them to target biofilms and avoid antibiotic-induced resistance [14]. Several nanoparticles are used as drug delivery carriers, such as metal nanoparticles, mesoporous silica, liposomes, hydrogels, and dendritic polymers. The drugs that can be delivered by nanotechnology include chemical drugs, natural products, and biomolecules. Nano-drug delivery enables precise release and targeted delivery of drugs to improve therapeutic effectiveness and reduce adverse effects [15]. The exploration of nanotechnology for the modulation of gut microbiota is rapidly increasing, but it is focused on *in vitro* and experimental and animal trials, and more research is still needed for clinical translation. Nanotechnology as a new means of gut microbiota modulation has a broad application prospect.

Although nanotechnology shows great potential as one of the modulatory strategies for gut microbiota, with the complex environment of the gut and the diverse composition of gut microbiota, it seems that it is still difficult for existing nanotechnology to achieve precise modulation of specific microbiota. At the same time, the safety of nanoparticles must be taken into account when using nanotechnology as a means of gut microbiota modulation. To improve the safety and efficacy of nanotechnology to modulate gut microbiota, researchers are focusing on developing biocompatible, smart-responsive nanotechnology [16]. Smart responsive nanotechnology is capable of responding to specific stimuli at targeted sites to maximize accurate modulation of gut microbiota. The researchers tried to improve the controllability of the nanotechnology using different stimuli or even combined stimuli. To advance the modulation of gut microbiota through nanotechnology, more in-depth studies will explore how nanotechnology achieves targeted and efficient modulation of gut microbiota.

This review focuses on the research progress and application of nanotechnology to modulate gut microbiota. Existing approaches to modulate gut microbiota and their research progress are briefly described. Next, an overview of how nanotechnology can modulate gut microbiota is highlighted, including nanomaterials that can directly modulate microbiota, nano-drug delivery systems that modulate gut microbiota, and stimulus-responsive release nanotechnology for targeted release. With the development of nanotechnology, nanotechnology modulation of gut microbiota can be applied in

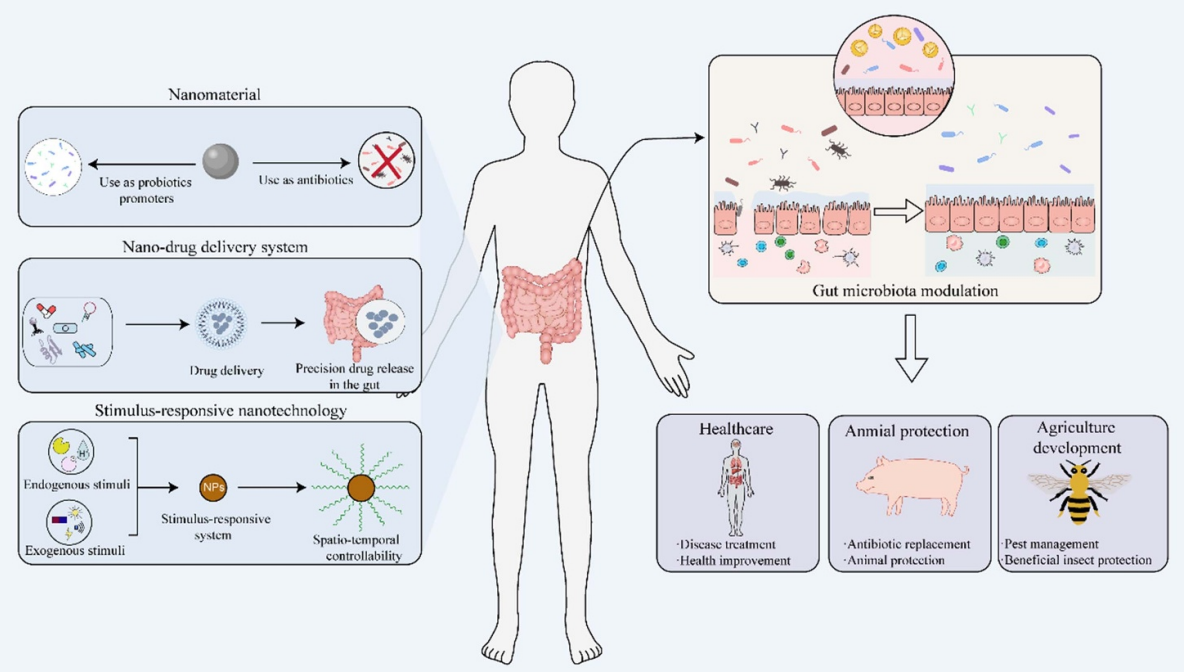

Figure 1. Schematic diagram of nanotechnology modulation of gut microbiota. Nanotechnology can play a role in healthcare, animal protection, and agricultural development by using nanomaterials as antibiotics, nano-drug delivery systems, and stimulus-responsive nanotechnology to modulate gut microbiota.

many fields, including healthcare, animal protection, and agricultural development. Finally, the challenges of nanotechnology to modulate gut microbiota are discussed, and future directions and application scenarios are proposed. This review provides a new reference approach to nanotechnology as a novel approach to gut microbiota modulation (figure 1).

2. Necessity of gut microbiota modulation

2.1. Critical gut microbiota composition to health

The composition of healthy gut microbiota is an important foundation for maintaining gut health and overall wellness. Healthy gut microbiota consists primarily of the phylum *Firmicutes* and *Bacteroidetes*, which account for more than 90% of the total gut microbiota, followed by *Actinobacteria, Proteobacteria, Fusobacteria, Verrucomicrobia* [17]. In addition to bacteria, fungi (mainly yeasts), viruses (mainly phages), and archaea (mainly *Methanobrevibacter smithii*) are also important components of the gut microbiota [18]. The main composition of gut microbiota remains constant at the phylum level but shows differences in distribution at the genus level and beyond. Gut microbiota is specific in humans, and the composition of gut microbiota varies considerably in healthy individuals. Even in twins, there are differences in gut microbiota as they age and their environment changes [19]. Gut microbiota is not static and is also influenced by a variety of factors, including geographic location [20], lifestyle [21], diet [22], and age [23]. Despite the impact that external factors may have on gut microbiota, gut microbiota is resilient and can quickly return to a stable state [24]. Modulating the composition of gut microbiota can maintain the balance of the gut microbial community, thus achieving the goal of promoting health.

2.2. Gut microbiota involved in multiple host functions

As an important component of the host ecosystem, gut microbiota has a profound impact on host health and physiological function. Studies have shown that gut microbiota has many significant functions, including synthesizing various metabolites, colonizing mucosal surfaces, creating antimicrobial substances to enhance the immune system, influencing the brain-gut communication and associating with other body organs to affect health [25]. Therefore, maintaining the balance and stability of gut microbiota is essential for health.

Gut microbiota plays an important role in host metabolism. Gut microbiota expresses carbohydrate-active enzymes that metabolize indigestible carbohydrates, such as cellulose, hemicellulose, starch, pectin, oligosaccharides, and lignin into SCFAs such as acetate, propionate, and butyrate. These SCFAs regulate cellular gene expression, differentiation, proliferation, and apoptosis, as well as participate in carbohydrate metabolism and lipid metabolism and regulate glucose homeostasis [26–28]. Undigested proteins can be broken down into amino acids and peptides by extracellular proteases and peptidases secreted by gut microbiota, which can be digested and utilized as substrates for microbiota metabolites [29]. SCFAs, bile acids, and lipopolysaccharides produced by gut microbiota can regulate lipid metabolism [30]. Gut microbiota also has a significant impact on protein metabolism. Gut

microbiota has been shown to synthesize vitamins in humans, particularly vitamin C, vitamin K, and vitamin B, including riboflavin, biotin, niacin, pantothenate, pyridoxine, and thiamine [31, 32].

The gut microbiota has a protective effect, preventing the invasion of pathogenic microbiota. Healthy gut microbiota can prevent the invasion of pathogenic microbiota by competitively competing for nutrients, producing antimicrobial substances, and regulating the host immune system [33]. Gut microbiota enhances host immunity by enhancing mucosal integrity, inducing antimicrobial peptide production, modulating immune cells, and promoting IgA synthesis [34, 35]. The protective role of gut microbiota maintains gut health and overall immune function.

Gut microbiota can have an effect on neurological function. The bidirectional communication between the gut and the brain is known as the gut-brain axis. The gut is connected to the brain through the enteric nervous system, involving the sympathetic nervous system, parasympathetic nerves, and the hypothalamic-pituitary-adrenal axis [36]. Currently, more and more studies are proposing mechanisms by which gut microbiota affects the brain. Gut microbiota is capable of synthesizing neurotransmitters that affect the central nervous system, such as glutamate, gamma-aminobutyric acid, serotonin, and dopamine. Dysfunction of these chemicals has been linked to many neurological disorders such as epilepsy, Parkinson's disease, and Alzheimer's disease [37]. The BBB is a diffusion barrier between the circulatory system and the central nervous system that limits the entry of undesirable metabolites into brain tissue [38]. Gut microbiota metabolites such as SCFAs and lipopolysaccharides can affect BBB integrity [39, 40]. Through the gut-brain axis, gut microbiota can have an impact on the nervous system by influencing brain function, regulating mood, and improving cognition.

In addition to the brain-gut axis, gut microbiota can impact health through important pathways such as the liver-gut, kidney-gut, and lung-gut axes, which are closely linked to other major organs in the body. An enterohepatic axis is formed between the intestine and the liver through the portal vein. Through the portal vein, the liver secretes bile acids, antibodies, and antimicrobial molecules into the gut, while metabolites of gut microbiota can reach the liver and affect liver physiology [41, 42]. The liver-gut axis is associated with a range of liver diseases, such as alcohol-associated liver disease, NAFLD, cirrhosis, and hepatocellular carcinoma [42]. Gut microbiota is connected to the kidneys via the gut-kidney axis. Normally, the kidneys can excrete potentially toxic metabolites such as urea to maintain gut microbiota balance [43]. When gut microbiota is out of balance, excessive accumulation of toxic metabolites and activated immune cells can pass through the gut-kidney axis and trigger kidney disease [44]. The link between gut microbiota and the lungs is known as the gut-lung axis. Interactions between the lungs and gut can occur through circulating inflammatory cells and mediators [45]. When gut microbiota is imbalanced, the immune response is altered, leading to the development of chronic inflammatory disease in the lungs [46]. In addition to this, the gut bone axis can influence bone density through gut microbiota metabolites, intestinal mucosal barrier function, and immune modulation [47]. In the gut-muscle axis, gut microbiota can alter muscle mass and function by influencing protein synthesis, lipid and glucose metabolism, neuromuscular junction, and mitochondrial function [48]. Gut microbiota works together to maintain homeostasis in the host body through coordinated communication with other body organs.

2.3. Gut microbiota dysbiosis related to disruption of host functions

Gut microbiota dysbiosis can adversely affect host function and even lead to a range of diseases. Gut microbiota dysbiosis is an abnormal change in the composition and function of gut microbiota, resulting in an increase in harmful bacteria or a decrease in beneficial bacteria [49]. Gut microbiota dysbiosis may lead to a range of diseases. Gut microbiota is associated with digestion, absorption, and metabolism of nutrients. There is substantial evidence that gut microbiota dysbiosis results in diarrhea, constipation, irritable bowel syndrome, and IBD [50]. Gut microbiota is important in the maturation of the immune system, so gut microbiota dysbiosis may lead to deterioration of immunological tolerance and autoimmune diseases [51]. Dysbiosis of gut microbiota can also cause viral susceptibility [52]. The gut-brain axis is critical to human health, and gut microbiota dysbiosis is thought to be associated with neurological and psychiatric disorders. Many neurological disorders, including anxiety, depression, neurodevelopmental disorders such as autism, and neurodegenerative disorders such as Alzheimer's disease, have been linked to alterations in gut microbiota [53, 54]. Gut microbiota dysbiosis may also affect metabolic health. Some studies have pointed out that gut microbiota dysbiosis is closely related to developing metabolic diseases such as obesity, diabetes, and dyslipidemia [55]. An imbalanced microbiota may affect energy metabolism and fat regulation in the body, leading to metabolic diseases [56]. Gut microbiota dysbiosis can seriously impair the normal life activities of the host, so it is important to improve gut microbiota disorders and maintain the homeostasis of gut microbiota.

2.4. Significance of gut microbiota modulation

There is growing evidence that gut microbiota is critical to the host. Firstly, gut microbiota is closely related to the normal growth of the host. Gut microbiota can directly participate in host metabolism, and influence host immune responses and inflammatory processes. Immune function can be enhanced by modulating the gut microbial community to promote healthy host growth. Secondly, gut microbiota plays a key role in developing many diseases, including obesity, diabetes, IBD, and even cancer. The modulation of gut microbiota offers a new avenue for treating disease, particularly targeting specific gut microbiota associated with disease. In addition, gut microbiota is intimately connected to the organs of the body through the gut-*X* axis, and has a broad and far-reaching impact on the

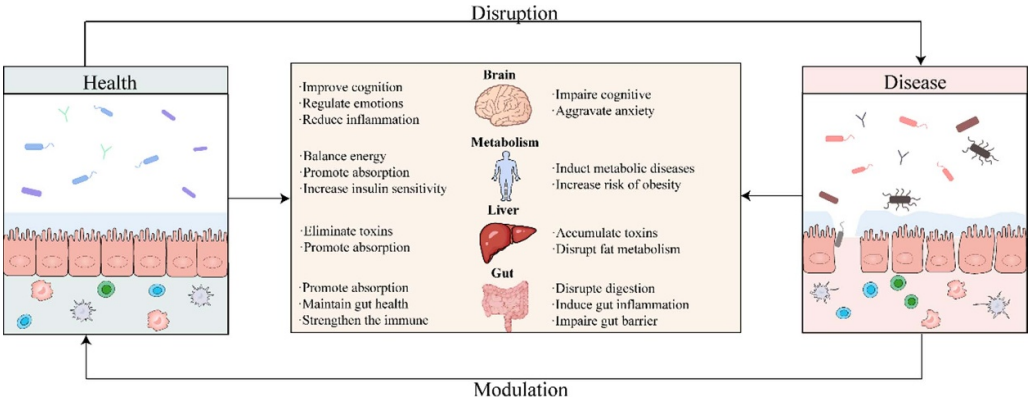

Figure 2. Gut microbiota and health. Gut microbiota is closely related to health, and gut microbiota imbalances can trigger several health problems. Health can be improved by modulating gut microbiota.

host. Modulation of gut microbiota can have various effects through the gut *X*-axis, including improving various body organs and even regulating the nervous system. Therefore, precise and personalized gut microbiota modulation has a wide range of applications and has received extensive attention in the fields of disease treatment and animal protection (figure 2).

3. Typical methods of modulating gut microbiota

Different research strategies have been developed to modulate gut microbiota to treat diseases and promote health. Common therapeutic approaches include diet, antibiotics, natural products, probiotics, bacterial modification, FMT, phage, and biomolecule, which are able to restore or maintain gut microbiota homeostasis (figure 3).

3.1. Antibiotic

Antibiotics are a common way to modulate gut microbiota. Antibiotics can alter gut microbiota composition by depleting harmful microbiota and reversing gut ecological dysbiosis. When antibiotics are discontinued, gut microbiota shows some resilience and partially returns to initial microbiota levels. Using antibiotics to modulate gut microbiota has been explored in the clinic, and a series of studies have now confirmed the effects of antibiotics on gut microbiota. Some antibiotics with multiple bacterial antimicrobial properties, such as macrolides, penicillin, clindamycin, and vancomycin, have been used in improving gut microbiota [57]. In recent years, some non-absorbed antibiotics, such as rifaximin, have also been used to balance the gut microbiota [58]. Antibiotics are one of the most effective means of modulating gut microbiota for a wide range of diseases, such as cancer, alcoholic liver disease, and Parkinson's disease [59–61]. Although antibiotic modulation can be effective in eliminating pathogenic or harmful bacteria, the non-selective antimicrobial effects of antibiotics can also affect beneficial bacteria in the gut. In recent years, there has been strong evidence that antibiotic misuse may lead to further dysbiosis of gut microbiota, thereby inducing disease [62]. Meanwhile, antibiotic modulation may result in the enhancement of bacterial resistance. Antibiotics have been shown to enrich phage-encoded genes for drug resistance [63]. Despite the significant effects of antibiotics in modulating the gut microbiota, their potential adverse effects limit their widespread use, and there is a need to explore safer modulation methods.

3.2. Natural products

In recent years, there has been a gradual increase in the understanding of nutrition. As a result, natural products of dietary origin have become an option. These natural products can affect the composition of gut microbiota through a variety of mechanisms, including inhibiting the pathogenic bacteria, promoting the beneficial microbiota, regulating gene expression, and producing beneficial metabolites [8, 64]. In recent years, a fairly well-documented body of research has explored the modulatory effects of natural products on gut microbiota in animal and clinical trials [65–67]. Common natural products such as polysaccharides, polyphenols, and peptides can ameliorate diseases, such as metabolic syndrome, neurological disorders, and alcoholic liver disease, by modulating the gut microbiota. Natural products are mostly of food origin, and therefore, natural products have a higher safety profile. Natural products also have a regulatory effect on other organs, and they can be broken down by gut microbiota into metabolites such as SCFAs and bile acids, which can achieve wider health benefits through a variety of pathways [68]. Due to the complexity of the gut environment, natural products face a number of challenges during delivery, including low delivery efficiency and poor stability. In order to improve the efficiency of natural product compounds in modulating the gut microbiota, more delivery vehicles will be developed to ensure the stability of natural products.

3.3. Probiotic

Advances in biotechnology have facilitated the screening, cultivation, and application of probiotics, making it possible to use probiotics to modulate gut microbiota. Probiotics are safe,

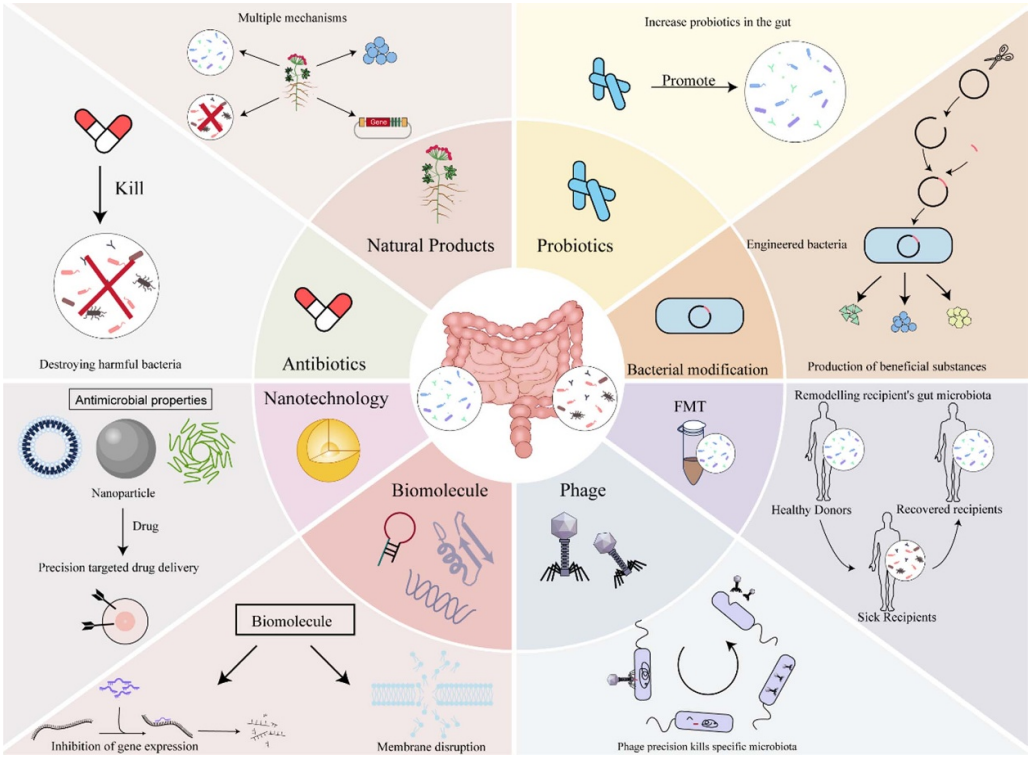

Figure 3. Methods of gut microbiota modulation. Modulatory approaches include antibiotics, natural products, probiotics, bacterial modification, FMT, phages, biomolecules, and nanotechnology, which can restore balance to the gut microbiota.

live microbiota that can provide health benefits to their hosts [69]. Probiotics can colonize and multiply in the gut, increasing the number of beneficial microbiota in the gut. The mechanisms by which probiotics modulate gut microbiota include competitive inhibition of the growth of pathogenic microbiota, production of antimicrobial substances, and modulation of the host immune system [70, 71]. Common probiotics include *Lactobacillus, Bifidobacterium, Enterococcus, Streptococcus*, and *S. cerevisiae* [72]. Recently, ample research has been conducted to confirm the modulatory effects of probiotics on gut microbiota in animal models and human trials [73–75]. Probiotics have been shown to relieve diarrhea, allergic rhinitis, IBD, enteritis, and more [71]. Probiotics have been used in functional foods and dietary supplements. Compared to antibiotic modulation, probiotics are mostly derived from human gut microbiota or food. So probiotics are safer and can modulate gut microbiota in the long term. However, a serious problem facing probiotic modulation is the challenge of oral delivery. The strongly acidic environment of the gastrointestinal tract, digestive enzymes, and bile salts significantly reduce probiotic viability, thus affecting probiotic colonization and reproduction in the gut [76]. Although probiotic modulation of the gut microbiota is a safe and effective method, the stability of probiotic delivery remains one of the concerns.

3.4. Bacterial modification

The development of synthetic biology has made it possible to modify bacteria to achieve gut microbiota modulation by means of gene synthesis, editing, and regulation. Through genetic engineering, bacteria are able to target the secretion and expression of therapeutic factors, such as metabolites, enzymes, and nucleic acids, to achieve stable colonization while continuously delivering the drug. This type of modified bacteria is known as engineered bacteria [77]. *Escherichia coli* (*E. coli*), as a common model laboratory microbiota, already has a large selection of gene editing systems available. To better facilitate host and gut microbiota interactions, researchers have focused on beneficial gut bacteria such as *Bacteroides, Lactobacillus*, and *Bifidobacteria* [78]. Enteric engineered bacteria can be categorized as diagnostic and therapeutic. As a non-invasive diagnostic method, diagnostic gut-engineered bacteria can detect transient molecules in the gut, greatly enhancing disease surveillance [79]. Therapeutic enteric engineered bacteria are mainly used for disease treatment by targeting the lesion and metabolizing the toxin factors into non-toxic products in the engineered bacteria. Currently, the main applications of using engineered bacteria to treat diseases are IBD, phenylketonuria, diabetes mellitus, and Parkinson's disease [80]. Despite the advantages, such as targeted drug delivery and flexible operation, there are some challenges for engineered bacteria to modulate gut microbiota. Safety issues such as possible genetic contamination and how to remove the engineered bacteria after they have achieved therapeutic effect also need to be taken seriously and considered. Bacterial modification of modulatory microbiota is an advanced technology with significant potential for the future along the lines of precision design of targeted and safe gut-engineered bacteria.

3.5. FMT

With the increasing understanding of the relationship between gut microbiota and disease, FMT has emerged as a promising approach to gut microbiota modulation. FMT consists of two types: heterologous FMT (h-FMT) and autologous FMT (a-FMT). h-FMT involves the transplantation of gut microbiota from a healthy subject into a recipient in order to fully reconstitute the recipient's gut microbiota. Ideally, reconstructed gut microbiota can restore microbiota functions, including provision of colonization resistance, production of beneficial metabolites, and restoration of immune functions [81]. h- FMT has been used for many years and has been approved by the Food and Drug Administration [82]. h-FMT has been well documented in treating *Clostridium difficile* infection and has been reported in cancer, metabolic diseases, and neurological disorders [81, 83, 84]. h-FMT restores the microbiota balance in the gut without disrupting the gut ecological balance as antibiotic therapy does, it is considered a safe treatment. However, h-FMT is still a riskier and more costly modulation method than strategies such as probiotics. For example, the transplantation process may lead to the spread of disease-causing genes and the transfer of pathogens [85]. Some studies have confirmed pathogen transmission events resulting from h-FMT, including *E. coli* [86], norovirus [87], and cytomegalovirus [88]. h-FMT may also lead to complications such as abdominal cramps, diarrhea, and bacteremia [89]. a-FMT is an extended form of h-FMT by reintroducing the patient's own gut microbiota, preserved during periods of health, to restore gut microbiota balance. Compared to h-FMT, a-FMT is a promising treatment that can more effectively rebuild a patient's microbiota while reducing the risk of immune rejection and infection [90]. There is still insufficient research on a-FMT. Currently, some studies point out that a-FMT is effective in the treatment of IBD, obesity, diabetes, and other diseases [91, 92]. However, further development of both h-FMT and a-FMT needs to overcome multiple technical, ethical, and regulatory challenges to ensure their safety and efficacy.

3.6. Phage

With a deeper understanding of gut microbiota, phages are considered an emerging approach to modulating gut microbiota with great potential for application. Phage modulation of gut microbiota is achieved through the interaction of bacteria and phages. As natural killers of bacteria, phages can inject genetic material into bacteria, which ultimately leads to the death of the bacteria through a replication cycle or a lysogenic cycle [5, 93]. Phages can specifically adsorb to bacterial surface receptors in this way, making phages a powerful tool for precisely killing microbiota [94]. Recently, antibiotic resistance has made phages to modulate microbiota a hot topic. Currently, there have been studies using phages to modulate gut microbiota, especially targeting antibiotic-resistant bacteria [95]. Using phages to modulate gut microbiota can treat enteritis, alcoholic hepatitis, and more [93, 96]. In addition, through genetic engineering techniques, researchers have been able to modify phages to improve their specificity and bactericidal effect [97]. The specificity of phage modulation makes it less likely to affect other microbiota. However, phages are not stable enough and are susceptible to harsh conditions such as low pH and digestive enzymes during delivery [5]. Phages have the advantage of precision, but phage stability severely limits their role in the gut. Exploring how to maintain phage stability and viability during transport is an important step in expanding phage applications.

3.7. Biomolecule

Some biomolecules, such as antimicrobial peptides and RNA, can also be used to modulate gut microbiota. Antimicrobial peptides can cause microbiota death by causing a rupture of the microbiota cell membrane or interfering with microbiota intracellular functions [98]. Researchers have demonstrated that antimicrobial peptides can inhibit harmful microbiota, such as *C. difficile, L. monocytogenes*, and *Bacillus cereus*, with the potential to serve as new alternatives to antibiotics [99]. miRNAs are transcription repressors of relevant genes, thus modulating microbiota composition [100]. Some studies have shown that miRNAs can modulate gut microbiota and ameliorate inflammation, with potential applications in treating diseases such as enteritis, systemic lupus erythematosus, and neurological disorders [100–102]. Biomolecules usually have high biological activity and are able to target specific microbiota. Antimicrobial peptides can be produced by bacteria, and miRNAs interact with target genes, making them safer and less susceptible to bacterial resistance. However, biomolecules are still limited to the laboratory stage due to the ease of degradation and the cost of production. Biomolecules have significant potential to modulate gut microbiota and will be more fully investigated in the future to improve delivery efficiency and reduce production costs.

3.8. Nanotechnology

Nanotechnology, as a novel technology, is emerging as one of the promising strategies to modulate gut microbiota. Some nanoparticles have antimicrobial properties that specifically kill pathogenic bacteria but retain beneficial bacteria. Therefore, they can be used as one of the drugs for gut microbiota modulation. Nanoparticles can also be used as drug delivery systems, where loaded drugs reach the gut and are released to modulate gut microbiota. In addition to being loaded with conventional drugs, nanoparticles can also be loaded with biomolecules such as DNA, RNA, proteins, *etc*. Different modification strategies (including surface modification, encapsulation, and modification of physical properties) can be used to enhance the delivery of nanotechnology-delivered drugs [103]. Nanotechnology can be externally controlled or internally stimulated by the environment to achieve a responsive release, increasing the bioavailability of the drug. The use of nanotechnology to modulate gut microbiota is still in its infancy, but some progress has been made in current research. Tissue targeting, co-delivery, and

stimulus-responsive functions of nanoparticles are used in microbiota modulatory processes. In contrast to other modulatory techniques, nanotechnology can connect microbiota to the gut across molecular and macroscopic scales, thus allowing adaptation to complex microenvironments and specific interference with relevant molecular pathways [104]. With further research, nanotechnology promises to be a precise, efficient, and safe method of gut microbiota modulation.

4. Direct use of nanomaterials as drugs

With the development of nanotechnology, nanomaterials are widely used in our daily lives, including food, daily necessities, and cosmetics. The effect of nanomaterials on gut microbiota has also received much attention (figure 4). Some nanomaterials have antimicrobial properties and can be used as broad-spectrum antibiotics to effectively modulate gut microbiota, known as 'nano-antibiotics'. There are several advantages to using nanomaterials as antibiotics: (1) compared to conventional antibiotics, nanomaterials are more stable and have a longer shelf life; (2) due to the smaller size of the nanomaterials, they have a larger surface area and can interact better with microbiota; (3) nanomaterials inhibit the growth of microbiota through a variety of mechanisms, so the drug resistance is reduced [105]. Research has confirmed the antimicrobial properties of nanomaterials *in vivo* and *in vitro* [106]. Nanomaterials are divided into three main categories: metal nanomaterials, nonmetal nanomaterials, and nanocomposites. Different nanomaterials have different effects on gut microbiota. Although there has been a great deal of research on nanomaterials affecting gut microbiota, more research is needed on how to precisely modulate gut microbiota using nanomaterials.

4.1. Metal nanomaterials

Metal nanomaterials, including titanium-based, silver-based, zinc-based, copper-based, and gold-based nanoparticles, have good bacteriostatic activity. Metal nanomaterials can inhibit the growth of microbiota through different pathways, including inducing the production of ROS, releasing metal ions to cause metabolic dysfunction, damaging cell membranes through electrostatic effects, causing protein and enzyme dysfunction, and inhibiting intracellular signal transduction [112]. Metal nanomaterials have been shown to inhibit pathogenic microbiota such as *E. coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus*, and *B. cereus* [13, 113, 114]. Studies have used metal nanomaterials to inhibit gut pathogenic bacteria for gut microbiota modulation. For example, silver nanoparticles, a widely recognized antimicrobial nanomaterial, have strong antibacterial activity against a wide range of bacteria. Silver nanoparticles can inhibit *Helicobacter pylori, Fusobacterium nucleatum, an*d others [115, 116]. In addition to being used alone, silver nanoparticles can also be used synergistically with other antibiotics, such as penicillin G, amoxicillin, erythromycin, clindamycin, and vancomycin, can greatly enhance their bacteriostatic activity against *S. aureus* and *E. coli* [117]. There have also been studies using Ag nanomaterials to optimize gut microbiota composition. Silver ions were cross-linked with hyaluronic acid to obtain hydrogel microspheres, which increased the beneficial bacteria *Lactobacillaceae* and *Bifidobacteriaceae* and decreased *Enterobacteriaceae* in the gut of colitis mice [118]. Li *et al* used 4,6-diamino-2-pyrimidinethiol-coated Au nanoparticles to treat bacterial infections induced by *E. coli*, and found that the nanoparticles were effective in curing bacterial infections, and could reduce the number of *E. coli*-infected mice intestinal *E. coli* from 1.21×10^7 CFU g^{-1} to 3.76×10^5 CFU g^{-1}, which is more efficient than levofloxacin [108]. Although some metal nanomaterials have a good inhibitory effect on gut pathogens, it has also been suggested that metal nanomaterials may sometimes lead to inflammation in the gut. Titanium dioxide, for example, may cause abnormal oxidative stress and may even lead to the disease [119]. The effects of nanomaterials may be related to the timing and dose of ingestion of metallic nanomaterials, and more detailed studies will be conducted to determine this. As metal nanomaterials have been widely used in food additives, dietary supplements, and biomedicine, the effects of metal nanomaterials on gut microbiota should be further investigated in future studies.

4.2. Nonmetal nanomaterials

The effects of non-metallic nanomaterials on gut microbiota have also attracted the interest of researchers. Nonmetal nanomaterials, including silicon-based, carbon-based, polymer, and liposome nanoparticles. Antimicrobial mechanisms of nonmetal nanomaterials include mechanical damage, oxidative stress, photothermal effects, and targeting cell membrane composition [13, 120]. Many studies have been conducted to confirm the modulatory effects of nonmetal nanomaterials on gut microbiota. Chen *et al* found that the richness and diversity of gut microbiota increased in mice after ingestion of SiO_2, with a significant increase in the genus *Lactobacillus* [121]. Carbon nanomaterials, as one of the most influential nanomaterials in the world, have a broad application prospect in the field of gut microbiota modulation. It has been found that carbon nanotubes with different diameters, lengths, and surface modifications can have bacteriostatic effects on common microbiota in the gut (*e.g. Lactobacillus acidophilus, Bifidobacterium adolescentis, E. coli, Enterococcus faecalis*, and *S. aureus*) in a concentration-dependent manner, single-walled carbon nanotubes at 100 ppm can inhibit some microbiota by more than 50% [122]. Researchers found that fullerenol nanoparticles improved the overall structure of mouse gut microbiota, significantly increasing the number of bacteria producing SCFAs [123]. This finding was further confirmed in high-fat diet-induced hyperlipidaemic mice, and graphene oxide increased the relative abundance of SCFAs-producing bacteria without affecting the total number of gut microbiota [124]. Lipid nanoparticles have a better specific inhibitory effect on *H. pylori. In vitro* and mouse experiments demonstrated that liposomes containing linolenic acid

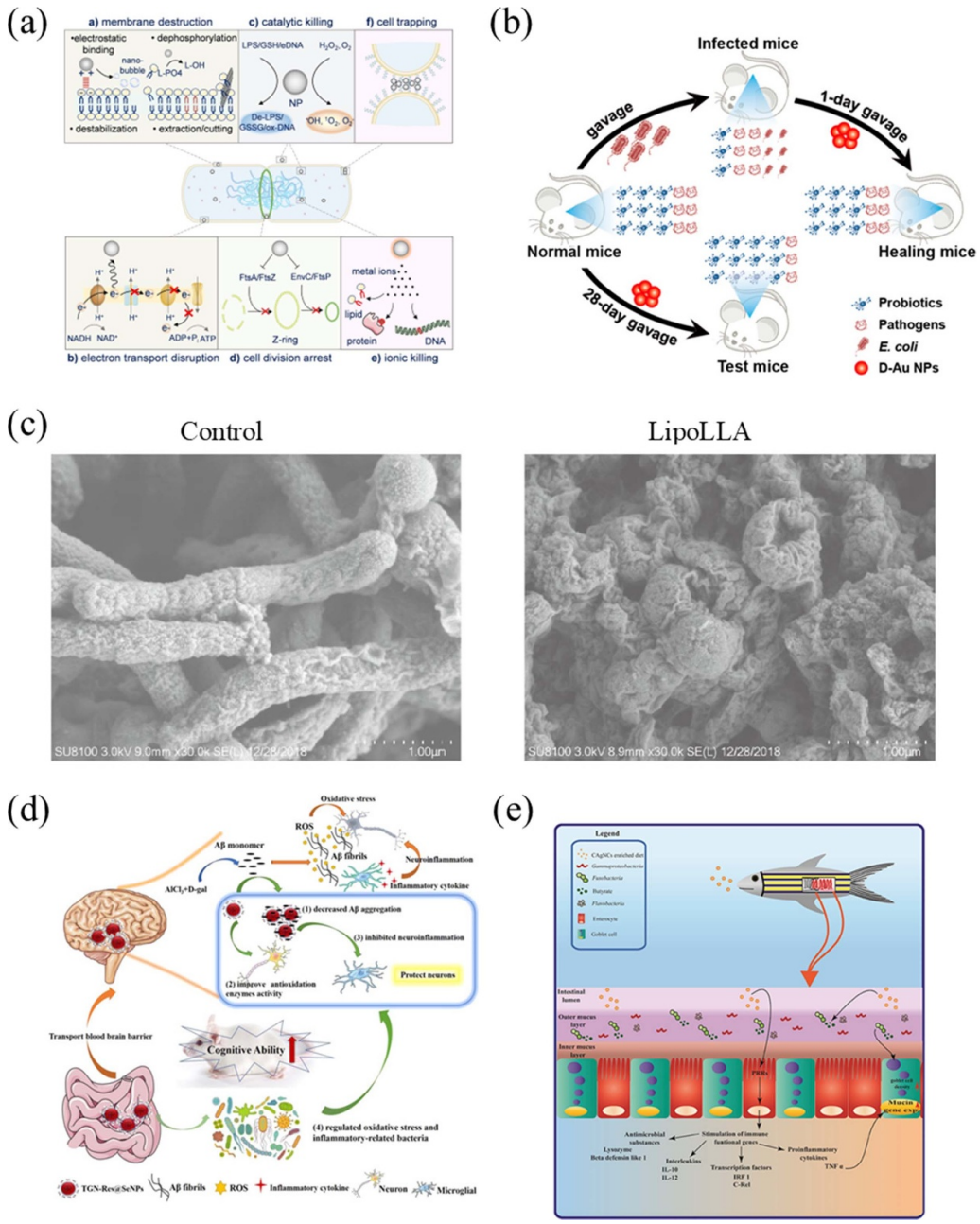

Figure 4. Effect of nanomaterials on gut microbiota. (a) Killing mechanism of antimicrobial nanomaterials. [107] John Wiley & Sons. © 2023 Wiley-VCH GmbH. (b) Schematic representation of 4,6-diamino-2-pyrimidinethiol -encapsulated gold nanoparticles for treating bacterial infections induced by *E. coli* in the gut. Reprinted with permission from [108]. Copyright (2019) American Chemical Society. (c) Liposomal linolenic acid can disrupt the cellular structure of *H. pylori.* Reproduced from [109]. CC BY 4.0. (d) Schematic diagram of chitosan-silver nanocomposites modulating zebrafish gut microbiota. Reprinted from [110], © 2017 Elsevier Ltd. All rights reserved. (e) Effect of resveratrol-selenium-peptide nanocomposites on specific gut microbiota composition in Alzheimer's disease mice. Reprinted with permission from [111]. Copyright (2021) American Chemical Society.

or docosahexaenoic acid could inhibit *H. pylori* while remaining largely unaffected by gut microbiota [109, 125, 126]. Despite the higher biodegradability of nonmetal nanomaterials, the safety of nonmetal nanomaterials is also a concern, with some studies suggesting that nonmetal nanomaterials, such as carbon nanotubes, may lead to altered gut permeability and inflammation [127]. The rational application of nonmetal nanomaterials to modulate gut microbiota is a promising approach as they have great potential in modulating gut microbiota.

4.3. Nanocomposites

Nanocomposites are a combination of two or more nanomaterials, offering greater advantages in modulating gut microbiota. Nanocomposites integrate each material's physical,

chemical, and biological properties and can modulate gut microbiota through various principles. Li *et al* developed a TGN-Res@SeNPs that was found to alleviate the imbalance of the gut microbiota caused by Alzheimer's disease. TGN-Res@SeNPs modulate oxidative stress and inflammation-associated bacteria, such as reducing *Alistipes, Helicobacter*, and *Rikenella* and increasing *Desulfovibrio* and *Faecalibaculum* [111]. The study was conducted with CAgNCs, which found that CAgNCs enhanced the abundance of *Fusobacteria* and *Bacteroidetes* in the zebrafish and improved gut immunity [128]. Nanocomposites made of half-fin anchovy hydrolysate and zinc oxide nanoparticles increase the abundance of gut probiotics such as *Lactobacillus* and *Bifidobacterium* as well as SCFAs-producing bacteria in female mice [129]. Rhamnolipid/fullerene nanocomposites are highly biocompatible and have been shown to reduce inflammation in mice with colitis and restore diseased mice gut microbiota composition. The content of *Lactobacillus, Bifidobacterium*, and *Akkermansia* was increased and was close to the level of gut microbiota in healthy mice [130]. Although it has been shown that nanocomposites can improve gut microbiota, there are fewer studies on the modulation of gut microbiota by nanocomposites. The effects and safety of nanocomposites in modulating gut microbiota still need to be further verified by a large number of experiments. As a current research hotspot, the effect of nanocomposites on the gut microbiota will be further investigated for precision, safety, and controllability.

5. Nano-drug delivery system

Nanoparticle-based drug delivery has been extensively studied over the past decade. Pharmacological treatments have a certain degree of effectiveness in modulating gut microbiota, but many limitations remain. These include the inability of traditional drugs to be accurately targeted, drug resistance caused by long-term use, and the poor stability of bioactive compounds in the gut [131, 132]. In order to improve the efficiency and accuracy of drug delivery, researchers have made various attempts, among which nano-engineered drug delivery systems have emerged as a potential new strategy for effective drug delivery. Nano drug delivery system is a technology that utilizes nanotechnology to design and fabricate nanocarriers to deliver drugs precisely to the target site. Nanomaterials are excellent carriers for carrying drugs due to their unique physical and chemical properties (small and controllable size, high surface area-to-mass ratio, structures that can be modified) [133]. Nano-engineered drug systems offer a variety of advantages, including targeted delivery, sustained drug release, uniform distribution in targeted tissues, fewer side effects, *etc*. Due to the inherent antimicrobial properties of the nanomaterials, nano-engineered drug delivery systems are a highly promising modality to modulate gut microbiota [134–136]. Researchers have recently developed several types of nano-drug delivery vehicles using different matrices to encapsulate drugs and improve delivery efficiency (figure 5). Common nanocarriers include liposomes, exosomes, metal nanoparticles, mesoporous silica, polymer micelles, and dendritic polymers. Nanocarriers have been shown to have the potential to overcome the harsh environment of the gut to deliver drugs efficiently.

5.1. Lipid-based nanomaterials

Lipid nanocarriers are one of the most widely used drug delivery carriers. They mainly include solid lipid nanoparticles, lipid nanocapsules, liposomes, exosomes, *etc* [141]. The similarity of lipid nanocarriers to biological membranes makes it easy to deliver drug molecules into cells [142, 143]. Lipid nanocarriers have great advantages in drug delivery and are now widely used in clinical practice. In the field of gut microbiota modulation, the most used application is liposomes. Liposomes are closed spherical vesicles consisting of one or more lipid bilayer structures that encapsulate drugs and protect drugs from environmental degradation. A bile acid liposome was developed that uses amphipathic bile acid-tauroursodeoxycholic acid to replace cholesterol in conventional liposomes. Studies have shown that bile acid liposomes protect emodin from the hostile gut environment so that it can reach the colon to do its job, with a cumulative release of up to 67.97% over 72 h. Increased overall abundance and diversity of gut microbiota and decreased abundance of *Enterobacter* and *Escherichia* in mice with colitis [137]. Liposome-loaded silibinin, a natural product used in treating liver disease, increases the relative bioavailability of silymarin by 9.45-fold, may achieve amelioration of NAFLD by restoring gut microbiota disorders [138]. Liposome encapsulation of essential oils improves the gut health of broilers by inhibiting the number of pathogenic bacteria *Clostridium* and *Escherichia* in their gut [144]. Despite the multiple advantages of lipid nanomaterials, hepatic aggregation is a significant impediment to developing effective lipid nanomaterials [145]. Lipid nanocarriers, as a widely used drug delivery vehicle, have excellent applications in delivering drugs to modulate the gut microbiota.

5.2. Inorganic nanomaterials

Inorganic nanoparticles are also one of the important carriers for drug delivery. Inorganic nanocarriers are widely used as carriers for drugs due to their unique physical and chemical properties and easier control of size, morphology, and surface functionality [146]. Inorganic nanocarriers include metal nanocarriers, mesoporous silica, and carbon-based nanomaterials. Metal nanoparticles are particles of metal oxides or metal compositions that can disperse or encapsulate a drug within a polymer shell. Fe_3O_4 nanoparticles coupled with ginsenosides Rg3 increase the abundance of *Bacteroidetes* and *Verrucomicrobia*, reduce *Firmicutes*, and inhibit the development of hepatocellular carcinoma [147]. Metal nanoparticles have unique physical and chemical properties that can improve drug treatment efficacy and reduce drug resistance through

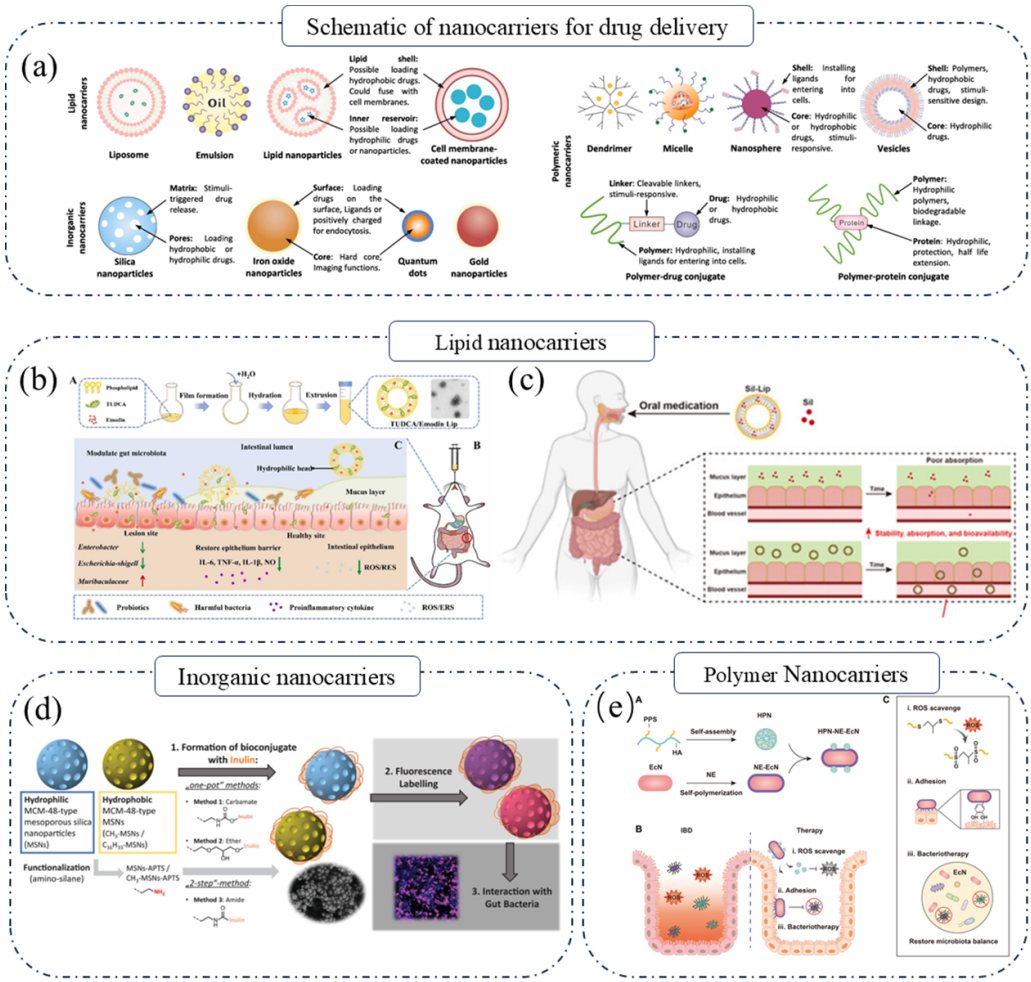

Figure 5. Nano-drug delivery system delivering drugs to modulate gut microbiota. (a) Schematic representation of nanocarriers developed for intracellular drug delivery. Reprinted from [110], © 2024 Elsevier B.V. All rights reserved. (b) Liposomal delivery of rhodopsin modulates gut microbiota in colitis mice. Reprinted from [137], © 2024 Elsevier B.V. All rights reserved. (c) Ameliorative effects on NAFLD can be achieved by restoring gut microbial dysbiosis using bile acid-containing liposome-loaded silymarin. Reprinted with permission from [138]. Copyright (2023) American Chemical Society. (d) Inulin-conjugated mesoporous silica nanoparticles target gut microbiota. Reproduced with permission from [139]. CC BY-NC 4.0. (e) Schematic representation of hyaluronic acid-polypropylene sulfide polymer delivers EcN and its mechanism for treating IBD. Reproduced with permission from [140]. Copyright © 2022 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC).

site specificity. However, the delivery of drugs by metal nanoparticles is still controversial, and detailed studies of the effects of nanoparticles on tissues are needed to reduce the adverse effects caused by long-term exposure [148, 149].

Mesoporous silica is a combination of surfactant micellar aggregates and active silica precursors. It is an excellent carrier for delivery due to its unique physicochemical properties, such as easily adjustable pore size, high specific surface area, and good biocompatibility [150, 151]. It has been demonstrated that silica can target gut microbiota by conjugating to inulin and has the potential to load antibiotics [139]. Mesoporous silica nanospheres immobilized on the surface of *Bifidobacterium* can be delivered intranasally into the gut to increase the proportion of anti-inflammatory microbiota and ameliorate cognitive impairment in Alzheimer's disease [152]. Although silica is considered to have low toxicity, the toxicity has been demonstrated in rodent models, and more long-term studies are still needed to confirm its biosafety [153]. Carbon family nanomaterials such as graphene, fullerenes, and carbon nanotubes have been used for drug delivery. Compared to mesoporous silica, carbonaceous nanomaterials also have desirable photothermal conversion capabilities and supramolecular π–π stacking structures [154]. However, carbon nanomaterials are still in the developmental phase in the field of drug delivery, and there have been no studies on the use of carbon nanomaterials as carriers to deliver drugs to modulate gut microbiota. Inorganic nanomaterials, as one of the important carriers for drug delivery, have great potential for application in modulating gut microbiota.

5.3. Polymer nanomaterials

In recent years, a number of biodegradable polymer nanomaterials have been extensively studied in the field of drug delivery. Common polymeric materials for drug delivery include polymer nanoparticles, hydrogels, and dendritic polymers. Polymeric nanomaterials offer a variety of advantages, including structural diversity and controllability, ease of drug loading and release, and good ability to absorb and swell water [155]. Positively charged cationic glucosylated nanoparticles encapsulated with antibiotics can enhance the absorption of antibiotics in the small intestine by binding to glucose transporter proteins, and their bioavailability is increased by 4-fold compared to free antibiotics, which reduces adverse effects on gut microbiota [156]. Chitosan nanoparticles loaded with amoxicillin can effectively eliminate *H. pylori* while reducing bacterial resistance and maintaining the balance of the gut microbiota [157]. Liu *et al* prepared torularhodin electrospinning nano-microspheres by electrostatic spinning technique and found that it can be released slowly in the colon to increase the diversity of the gut microbiota, such as *Phascolarctobacterium, Prevotella*, and *Faecalibacterium* [158]. Encapsulation of epigallocatechin gallate in nanoparticles assembled with chitosan and casein phosphopeptide ameliorated gut microbiota imbalance in high-fat diet-induced obese mice, increasing the growth of *Bifidobacterium* and *Lactobacillus-Enterococcus* spp., inhibiting *Bacteroides-Prevotella* and *Clostridium-histolyticum* [159]. A hyaluronic acid-polypropylene sulfide polymer that delivers modified EcN, not only protecting EcN, but also significantly prolonging its residence time in the gut. The amount of EcN encapsulated with the polymer after 48 h of residence in the gut was three times higher than that of unencapsulated EcN. This method increased the abundance and diversity of gut microbiota in mice with enteritis and alleviates IBD [140]. Despite the multiple advantages of polymer nanomaterials in drug delivery, some monomers of synthetic polymers may be cytotoxic, and some natural polymers are prone to degradation, limiting further applications of polymer nanomaterials [160]. With future research, polymeric nanomaterial-based drug delivery could have greater applications in the area of modulating gut microbiota.

6. Stimulus-responsive nanotechnology

Traditional drug delivery systems have been widely studied and applied in laboratories and clinics. However, as the demand for drug delivery increases, there are still problems, such as unstable drug release and insufficient drug release, which limit their further application [161]. Stimulus-responsive nanotechnology refers to technologies that trigger controlled changes in the properties or functions of nanomaterials in response to a specific stimulus (*e.g.* pH, temperature, light, magnetic field, or enzyme). Stimulus-responsive nanotechnology enables the precise release of drugs in the target area by designing stimulus-responsive systems [162]. Stimulus-responsive nanotechnology for drug delivery can reach specific gut locations and improve drug delivery ability. The rapid development of nanotechnology over the past two decades has led to extensive research and application of stimulus-responsive nanotechnology. It has been demonstrated that stimuli-responsive nanotechnology can optimize the efficacy of targeted drugs, modulating gut microbiota while avoiding side effects caused by early drug leakage (figure 6). Stimulus-responsive nanoscale drug delivery systems include endogenous (*e.g.* pH, specific enzymes, redox concentration), exogenous (*e.g.* temperature, light, magnet, ultrasound, and electronic), and multi-stimulus responsive systems (consisting of two or more stimulus-responsive factors) [163]. The development of stimulus-responsive nanotechnology has greatly expanded the application of nanotechnology in modulating gut microbiota, opening up new pathways for future medical technology innovations and disease treatments.

6.1. Endogenous stimulus-responsive nano-drug delivery system

Endogenous stimulus-response systems can be sensitive to organism-specific endogenous stimuli to achieve drug release. Oral administration usually requires passage through the stomach to reach the gut. The stomach usually has a low pH (about 1–3), while the gut has a high pH (about 6–8) [168, 169]. The change from acidic to basic may adversely affect the activity of the delivered drug, but provides the basis for a pH-stimulus responsive delivery system. The pH stimulus-responsive delivery systems consist of two main categories: one is the conformational changes of nanocarriers at different pH, and the other is the breakage of the acid-sensitive group of nanocarriers caused by the change of pH [163]. Yang *et al* prepared composite liposome nanocarriers consisting of liposomes and chitosan to deliver bioactive compounds, and found that the composite liposomes could release 80% to the small intestine within 20 min at pH 7.0, which has good potential for drug delivery [170]. Enzymes can also act as endogenous stimuli. Enzymes in the gut consist of two main components: those encoded by the genome and those encoded by the gut microbiota. Enzyme stimulus-responsive delivery systems can be developed for different parts of the gut that have different enzyme compositions and activity [171]. Enzyme-stimulated responsive delivery systems are already available for applications such as wound excipients and cancer therapy [172, 173]. Some polysaccharides, such as chitosan, pectin, inulin, *etc*, have the potential to be developed as enzyme stimulus-responsive delivery systems because they can be degraded by colonic enzymes [169]. A number of redox delivery systems have been developed to target redox substances in the gut, such as reactive oxygen, reactive nitrogen, and the antioxidant glutathione [174]. NO is an endogenous active substance and gaseous signaling molecule associated with oxidative stress in the gut [175, 176]. A technology based on droplet microfluidics can embed lactic acid bacteria in microcapsules of poly-γ-glutamic acid hydrogel, which showed high viability in the stomach (89.67%) and intestine (93.67%). The

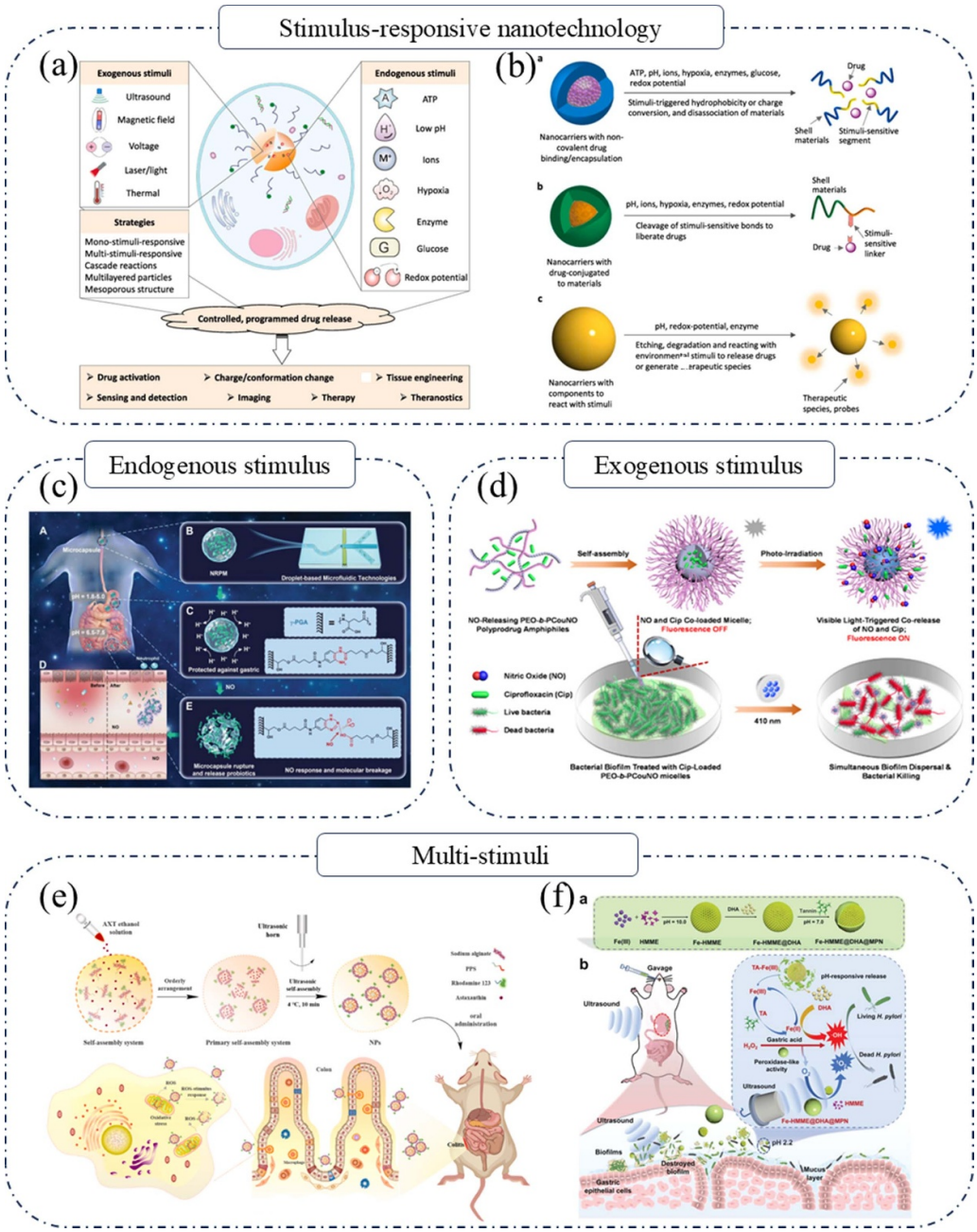

Figure 6. Stimulus-responsive nanotechnology regulates gut microbiota. (a) Mechanisms for controlling drug release using different types of nanocarriers. Reprinted from [110], © 2024 Elsevier B.V. All rights reserved. (b) Nanocarriers for stimulation-triggered drug release. Reprinted from [110], © 2024 Elsevier B.V. All rights reserved. (c) Schematic of the production process and design concept of NO-responsive poly-γ-glutamic acid hydrogel microcapsules. Reprinted from [164], © 2022 Wiley-VCH GmbH. (d) Micellar nanoparticles release NO and antibiotics under visible light to disperse *P. aeruginosa* biofilm and kill bacteria. Reprinted with permission from [165]. Copyright (2019) American Chemical Society. (e) Modulation of gut microbiota structure in response to drug administration. Reprinted from [166], © 2022 Elsevier Ltd. All rights reserved. (f) Gastric acid-responsive ROS nanogenerator effectively treats *H. pylori* infection. Reproduced from [167]. CC BY 4.0.

microcapsules could rapidly release lactic acid bacteria in response to NO molecules, modulating gut microbiota, ultimately slowing down colitis [164]. The endogenous stimulus-responsive systems allow for the design of nanocarriers based on gut-specific conditions, significantly increasing the drug's therapeutic efficacy and reducing systemic toxicity. However, the effectiveness of endogenous stimulus-responsive systems is difficult to ensure due to differences in endogenous biological factors in the individual gut [177]. In the future, endogenous stimulus-responsive systems will evolve toward greater stability and reproducibility based on gut pH, enzyme activity, and redox levels.

6.2. Exogenous stimulus-responsive nano-drug delivery systems

In order to overcome the factor of individual gut variability, several exogenously stimulated-responsive systems have been applied, which they can directly control. Common exogenous stimuli include temperature, light, magnet, ultrasound, and electricity. Temperature change is a convenient and gentle stimulus that has been widely used in stimulus-responsive delivery systems. Common temperature-responsive materials include liposomes and thermo-responsive polymers. The delivery system remains stable at body temperature, and when the ambient temperature is higher than the critical temperature of the delivery vehicle, the delivery vehicle structure collapses, and the drug is released [178]. Despite significant advances in thermal responsive systems, temperature-corresponding specificity is one of the important limitations, and components that are more sensitive to temperature changes will be developed for precise drug release. Light is a commonly used exogenous stimulus with the advantages of remote controllability, spatiotemporal selectivity, and noninvasiveness [16]. Under a specific wavelength of exogenous light, the structure of the light-responsive nanomaterials is disrupted to achieve drug release. Many UV-sensitive light-responsive moieties, such as azobenzene and o-nitrobenzyl ester, have been used in light-responsive delivery systems [179]. Shen *et al* synthesized amphiphilic polymers containing N-nitrosamine-based NO donors that release NO under visible light, which can disperse *Pseudomonas aeruginosa* biofilms and have the potential to load antibiotics [165]. However, due to the poor penetration of visible light, phototoxicity of UV light, and low efficiency of near-infrared light, appropriate light-responsive wavelength selection is important. In addition, the toxicity of light-responsive materials is an important factor limiting the application of light-responsive systems. Magnetic responsive nanocarriers are usually realized by doping magnetic materials (*e.g.* iron, cobalt, and nickel) into nanomaterials. Such carriers have better tissue permeability and biocompatibility, and can precisely control the location and rate of drug delivery under the action of an applied magnetic field [180, 181]. Magnetic-responsive nanocarriers can effectively achieve targeted drug delivery, improve therapeutic efficiency, and reduce drug dosage. Magnetic responsive system of drugs in polymers and silica has been achieved [182, 183]. The strength of the magnetic response is dependent on the setting of the external magnetic field, and the magnetic response system can only work in the gut if the magnetic field is strong enough and able to penetrate deeply into the tissue. Ultrasound has been widely used in diagnostic and therapeutic applications due to its safety, tissue penetration, and non-invasive [184]. The sound may lead to disruption of the structure of the nanocarriers for drug delivery. Electrical stimulation systems have also been applied to stimulus-responsive nanotechnology. Conductive polymers such as polyaniline, polythiophene, polypyrrole, and their various derivatives with good processing properties and electroactivity can be applied to delivery systems [185]. The interaction of ultrasound with biological tissues may limit its clinical application, and future optimization of ultrasound parameters is needed to maximize delivery efficiency while minimizing adverse effects on tissues. Electric fields can be used to achieve drug release through wireless dermal or implantable electronic delivery devices in response to external electric fields of varying intensities [186]. Exogenous stimulus-responsive systems have better spatiotemporal control by releasing drugs into the gut in response to external stimuli. However, implantable electronic delivery devices usually require invasive procedures and are not yet used in clinical practice [187, 188]. Meanwhile, the low penetration depth and voltage of the electric field may lead to undesirable tissue damage limiting the further application of electric field corresponding systems [162]. More future studies will focus on the implantability and long-term stability of electric field devices. With the continuous progress of nanotechnology and a deeper understanding of the exogenous stimulus-responsive mechanism, the exogenous stimulus-responsive system will have a broader application space.

6.3. Multi-stimuli responsive nano-drug delivery systems

In addition to single-stimulus delivery systems, researchers have developed two or more stimulus-responsive systems. The multi-stimulus responsive systems can further improve delivery accuracy, efficiency, and stability, and even realize the continuous release of drugs through corresponding different stimuli [189]. Currently, multi-stimulus responsive systems include temperature and ultrasound dual responsive delivery systems, pH and redox dual responsive delivery systems, enzyme and pH dual responsive delivery systems, and light and temperature dual responsive delivery systems [163]. Zhang *et al* constructed nanocarriers for astaxanthin delivery based on ultrasound-assisted self-assembly with dual redox and pH-stimulated responses. It showed that the alkaline environment and ROS stimulation in the colon could promote astaxanthin release, enhance the richness and uniformity of gut microbiota, increase the ratio of the *Firmicutes/Bacteroidota*, and alleviate colitis [190]. A pH-responsive reactive ROS nanogenerator kills 99% multidrug-resistant *H. pylori* and removes biofilm without impacting gut microbiota [167]. A nanoparticle composed of chitosan and pectin loaded with berberine reaches the colon and releases 92.9% berberine stimulated by pH and enzymes produced by bacteria. This restores the imbalance of the gut microbiota caused by a high-fat diet, increases *Bacteroidetes*, decreases *Firmicutes*, and ameliorates metabolic disorders [166]. Despite the higher delivery efficiency of multi-stimulus nano-responsive delivery systems, multi-stimulus responsive nano-systems often involve material design for multiple mechanisms, which is challenging and may be difficult to commercialize on a large scale. More research will be conducted to address these challenges and improve the accuracy of multi-stimulus responsive systems for drug delivery.

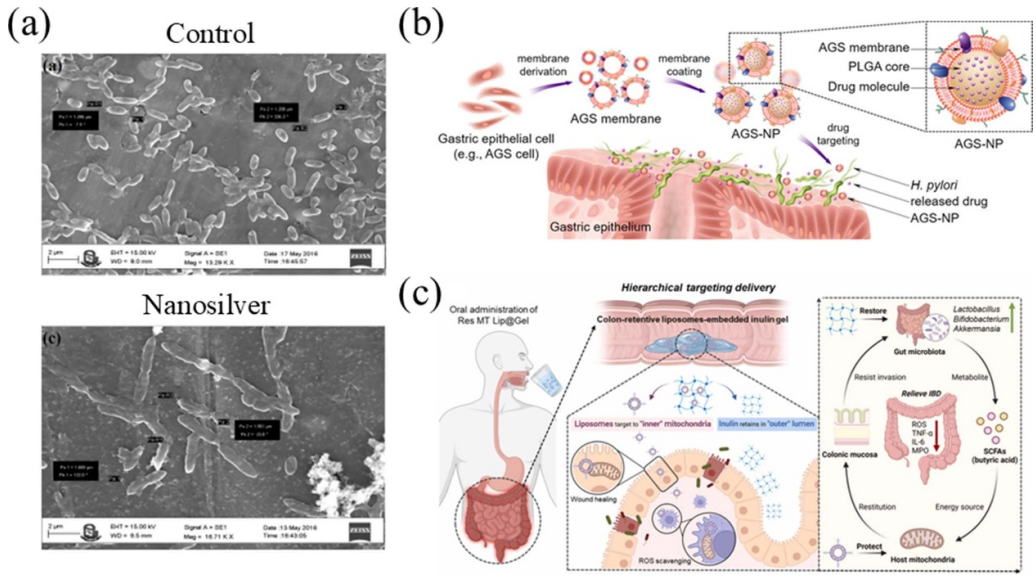

Figure 7. Nanotechnology modulation of gut microbes for healthcare applications. (a) SEM images of *E. coli* cells affected by nanosilver. Reprinted from [191], © 2019 Elsevier Inc. All rights reserved. (b) Schematic representation of gastric epithelial cell membrane-encapsulated nanoparticles for targeted antibiotic delivery to treat *H. pylori* infection. [192] John Wiley & Sons. © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (c) After oral administration, resveratrol-loaded mitochondria-targeted liposomal inulin gels modulates the microbiota and enriches probiotics to alleviate IBD through a hierarchical targeting approach. Reprinted from [193], © 2024 Elsevier Ltd. All rights reserved.

7. Applications of nanotechnology in gut microbiota modulation

The use of nanotechnology to modulate gut microbiota has become a hot research topic of great interest. Precise modulation of gut microbiota can play a significant role not only in healthcare, but also bring great economic and environmental benefits in animal protection and agriculture. Advances in nanotechnology have propelled nanotechnology as a promising means of microbiota control. Through continued research and innovation, nanotechnology is expected to play a greater role in healthcare, animal protection, and agriculture, driving development and progress in these areas.

7.1. Healthcare

Gut microbiota is closely related to human health, and imbalances in host gut microbiota are associated with a wide range of diseases. Modulation of gut microbiota has become a new way to treat diseases and improve health. As a whole, gut microbiota is interconnected and maintains a dynamic balance. Therefore, modulating gut microbiota to treat diseases requires precise targeting to achieve optimal therapeutic effects, and nanotechnology provides a strong foundation for this (figure 7).

Antibiotic abuse is one of the serious problems that global health faces at present. The development of nanotechnology provides new ideas and methods to solve this problem. Nanomaterials are considered one of the possible alternatives to antibiotics with broad-spectrum antibacterial capabilities. Nanoparticles with antimicrobial activity have been applied to kill gut pathogenic microbiota, such as metal oxide nanoparticles, and possible mechanisms include oxidative stress, release of metal ions, and photothermal effects [194]. Nanosilver can inhibit the growth of *E. coli* by disrupting the activity of the barrier efflux pump and altering the integrity of cell membrane [191]. Nano-drug delivery systems enable precise delivery of antibiotics at targeted locations, optimizing efficacy while reducing their interference with the rest of the gut microbiota. Encapsulation of antibiotics in positively charged glucosylated nanoparticles enhances antibiotic uptake in the proximal small intestine using binding of glucose and glucose transporter proteins, reduces their impact on microbiota in the large intestine, and decreases the accumulation of antibiotic resistance genes [156]. Probiotics can also be used in place of antibiotics to inhibit the growth of pathogenic microbiota. Phthalic anhydride coupled with dextran to form phthalyl dextran nanoparticles, which act as a prebiotic to promote the growth of probiotic bacteria, reducing the number of pathogenic *E. coli* O157:H7 in the gut of mice [195]. Nanotechnology, as one of the effective substitutes to antibiotics, shows great potential in the field of solving the problem of antibiotic abuse and modulating the gut microbiota.

Gut microbiota plays an important role in the development of cancer, and modulation of gut microbiota can improve cancer outcomes. It has been well established that nanotechnology can be used to modulate gut microbiota and improve anti-cancer effects. Through targeted delivery and surface modification of nanomaterials, it is possible to eliminate cancer-causing bacteria while retaining beneficial microbiota. Meanwhile, metal nanomaterials produce ROS that can synergize with antibiotics to kill cancer-related bacteria [103].

Nanotechnology can be loaded with antibiotics or antitumor drugs to inhibit the growth of cancer-associated pathogens, including the colorectal cancer-promoting bacterium *Fusobacterium* [196], and the gastric cancer-causing bacterium *H. pylori* [192]. Glucose nanoparticles loaded with irinotecan, covalently linked to phage, could inhibit the growth of colorectal cancer bacterium *Fusobacterium* while promoting the *Clostridium butyricum* and increasing the content of colonic SFCAs [196]. Nanotechnology can also deliver probiotics and prebiotics to promote the colonization of beneficial gut microbiota [197]. Combined with stimulus-responsive release mechanisms (*e.g.* pH, temperature), drugs or probiotics can be delivered to specific ecological sites in the gut. One study loaded probiotic *Lactobacillus fermentum* in magnetic and gold nanoparticles, which utilized heat generated by a magnetic field and near-infrared light to allow the probiotics to reach the gut [198]. The nanotechnology to modulate gut microbiota can be one of the effective strategies for adjuvant cancer therapy and has great potential for application.

Gut diseases are thought to be closely related to gut microbiota dysbiosis. Some redox nanoparticles have been shown to alleviate IBD by improving gut microbiota, including ZnO nanoparticles, amyloid-polyphenol hybrid nanofilaments, and oxidation-responsive nanoparticles. These nanoparticles are used to alleviate the symptoms of IBD by decreasing the number of harmful bacteria, such as *Aestuariispira, Escherichia*, and *Shigella*, and increasing the number of beneficial bacteria, such as *Lactobacillu, Bifidobacterium*, and SFCAs-producing microbiota [199–201]. Dietary supplementation with biogenic selenium nanoparticles prevents oxidative stress-induced intestinal barrier dysfunction by optimizing gut microbiota [202]. Nano-drug delivery, especially inulin gel, has also been applied to modulate gut microbiota and treat colitis. An olsalazine nanoneedle-embedded inulin hydrogel relieves colitis by increasing the diversity of gut microbiota and decreasing the abundance of pathogenic bacteria such as *Proteobacteria* [203]. Another inulin gel loaded with resveratrol can alleviate colitis by enriching probiotics [193]. Nanotechnology to modulate gut microbiota has been shown to be an effective strategy for treating gut diseases.

The use of nanotechnology to modulate gut microbiota has been applied in bacterial drug resistance, cancer, and gut diseases, and to a lesser extent in the treatment of other diseases. In fact, nanotechnology modulation of gut microbiota can also be used to treat other metabolic and psychiatric disorders associated with gut microbiota imbalance, including obesity, diabetes, and Alzheimer's disease. Using nanotechnology to modulate gut microbiota is expected to be an important component of personalized medicine, providing new ways to achieve individualized management and treatment of health. Toxicological factors of nanotechnology are one of the important reasons limiting the application of nanomedicine. Since nanoparticles can reach the whole body through the body circulation and lymphatic circulation, the problem of long-term toxicity should be taken seriously [204]. Further *in vivo* clinical trials are needed to better utilize nanotechnology to modulate gut microbiota for the purpose of improving host health and treating disease. With the development of nanotechnology, nanotechnology is expected to be a new way of modulating gut microbiota.

7.2. Animal protection

Gut microbiota is critical in the growth and development of animals. Similar to humans, gut microbiota in animals is acquired primarily after birth and can be influenced by factors such as breed, age, disease, and food [205, 206]. Gut microbiota is crucial in the growth and development of animals and has multiple functions such as regulating the immune system, improving digestion, and preventing pathogen colonization [207]. Therefore, modulating gut microbiota is an effective way to improve animal health. Using nanotechnology to modulate gut microbiota has been used in animal protection, including antibiotic replacement, disease treatment, and animal nutrition (figure 8).

Nanotechnology is a promising alternative to antibiotics. The major pathogenic bacteria in livestock and poultry include*S. aureus, E. coli*, and *Salmonella*, which pose a great threat to the growth of livestock and poultry. In the past, it was a common phenomenon to use antibiotics to promote livestock growth and modulate gut microbiota [211]. However, antibiotic accumulation has been banned in Europe and elsewhere due to its potential harm to animal and human health, and livestock scientists are actively seeking other strategies [212]. Nanomaterials have attracted the attention of researchers due to their antimicrobial ability to inhibit the growth of gut pathogenic microbiota. Selenium nanoparticles reduce *Enterococcus cecorum in vitro* [213]. Chemical nanoselenium reduces the number of gut pathogens such as *E. coli, Enterococcus* spp., and *Salmonella* spp. and increases lactic acid bacteria in the gut of quail [214]. Drug delivery using nanocarriers has also been applied to modulate the gut microbiota of livestock and poultry. Studies confirmed that chitosan nanoparticles encapsulating mint, thyme and cinnamon essential oils reduced *E. coli* and increased *Lactobacillus* in broilers, which can be used as a new way to add natural products to feed [215, 216]. Nanoparticle delivery of phage, oligodeoxynucleotides has also been studied for the treatment of *E. coli* and *Campylobacter jejuni* infection in broilers [217, 218]. Modulation of the gut microbiota of livestock and poultry through nanotechnology is still in its early stages. Further work is needed to explore the bacterial inhibitory ability of various nanomaterials at different doses, different nanocarriers for drug delivery, and different stimulus-responsive methods. It is believed that in the future the development of nanotechnology can effectively reduce antibiotics in animal husbandry.

Nanotechnology-modulated gut microbiota can also be used in the treatment of diseases in animals. Similar to humans, animal diseases are often associated with gut microbiota disorders. It has been shown that selenium nanoparticles can restore the α-diversity and β-diversity of the gut microbiota, optimize the structure and abundance of the gut microbiota, and thereby attenuate decabromodiphenyl ether-induced intestinal damage [209]. In addition, selenium nanoparticles were able to alleviate ochratoxin A-induced jejunum and liver

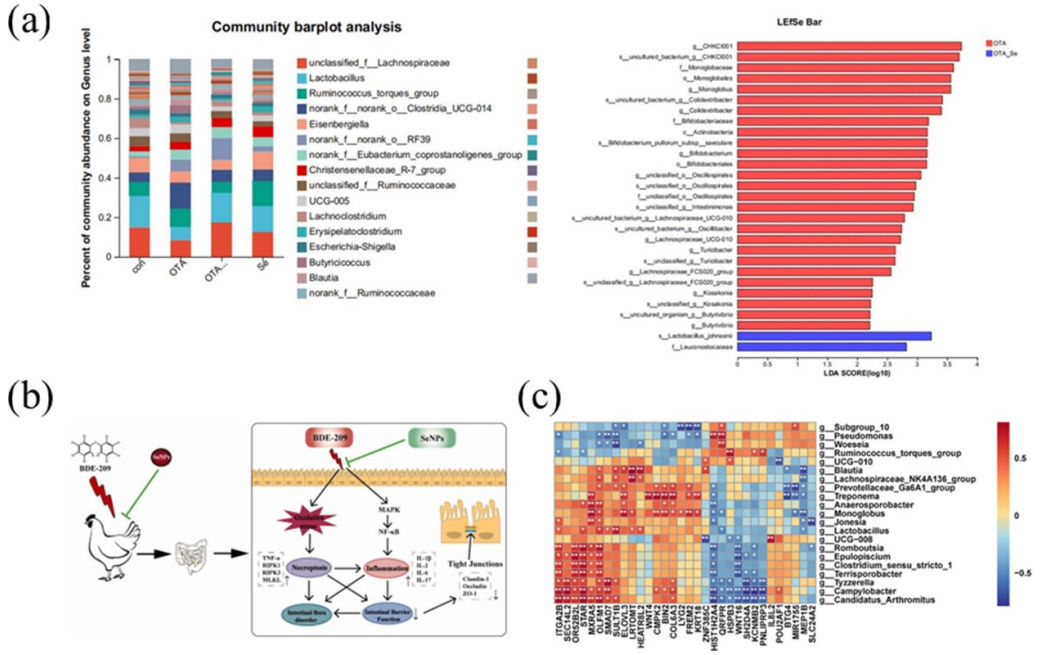

Figure 8. Nanotechnology modulation of gut microbiota in animals. (a) Effect of selenium nanoparticles on the microbial community of the cecum of ochratoxin A-attacked chickens. Reproduced from [208]. CC BY 4.0. (b) Schematic diagram of SeNPs attenuating intestinal damage by affecting necrotic apoptosis, inflammation, intestinal barrier, and intestinal flora in laying hens. Reprinted from [209], © 2023 The Authors. Published by Elsevier Inc. (c) Effect of dietary selenium dose on the cecum microbiota of breeder chickens. Reprinted from [210], © 2023 American Society for Nutrition. Published by Elsevier Inc. All rights reserved.

pathological injuries by modulating the gut microbiota [208]. Nanotechnology can also be used to modulate the gut microbiota of animals by delivering drugs or probiotics that can lead to the treatment of diseases. A polymeric micelle that can be loaded with halofuginone hydrobromide to alleviate coccidiosis in chickens by restoring the composition of the gut microbiota [219]. In conclusion, nanotechnology modulation of the gut microbiota has potential in the treatment of animal diseases. By designing nanomaterials and delivering drugs, nanotechnology can effectively modulate microbiota, improve animal health and treat a wide range of diseases.

Modulating gut microbiota through nanotechnology can also improve animal health and promote growth. Some inorganic nanomaterials are used as antimicrobial agents while supplementing trace elements and regulating animal immunity and fertility of animals [220]. Zinc oxide nanoparticles, a type of nanoparticles used in animal feeds, have been shown to modulate the gut microbiota of farmed animals, including piglets [221], beef cattle [222], and broilers [223]. Selenium nanoparticles improve reproductive health in roosters, which may be related to their modulation of gut microbiota homeostasis [210]. Copper-loaded chitosan nanoparticles have also been used in animal feed to reduce the number of *E. coli* and increase the number of beneficial microbiota in the gut, such as *Bifidobacterium* and *Lactobacillus* [224, 225]. Hydrocolloidal silver nanoparticles increase the number of lactic acid bacteria in quail [226]. Nanotechnology to modulate the gut microbiota to improve animal health is now more widely used. In the future, as research progresses, more in-depth and extensive studies will advance nanotechnology to modulate gut microbiota as a new way to improve animal health.

In the field of animal protection, nanotechnology has significant potential to modulate gut microbiota. Nanotechnology can be used as a substitute for antibiotics in animal husbandry to inhibit the growth of enteric pathogenic bacteria. Nanotechnology can also be used to treat animal diseases and improve health by modulating gut microbiota. Current applications of using nanotechnology to modulate gut microbiota are mostly focused on animal husbandry, with few applications in other animals. The safety of nanotechnology still needs to be evaluated in further studies. As nanotechnology continues to advance, its potential to improve animal health will be more widely applied, not limited to animal husbandry, but may also be extended to pet health, wildlife protection, and aquaculture, thus improving animal health and productivity.

7.3. Agricultural development

Nanotechnology can also be used in agriculture. There is a close relationship between agriculture and insects. Beneficial insects, such as pollinating insects, can pollinate crops, natural enemy insects can control pests, and pest insects can directly damage crops. Insect gut microbiota is important in several aspects of insect growth, including nutrient metabolism, host development, protection, immunity, pathogen resistance, *etc* [227]. Some insects can use gut microbiota to degrade toxic compounds and even plastic degradation [228]. Thus, modulating insect gut microbiota can protect beneficial insects as well as inhibit pest growth (figure 9).

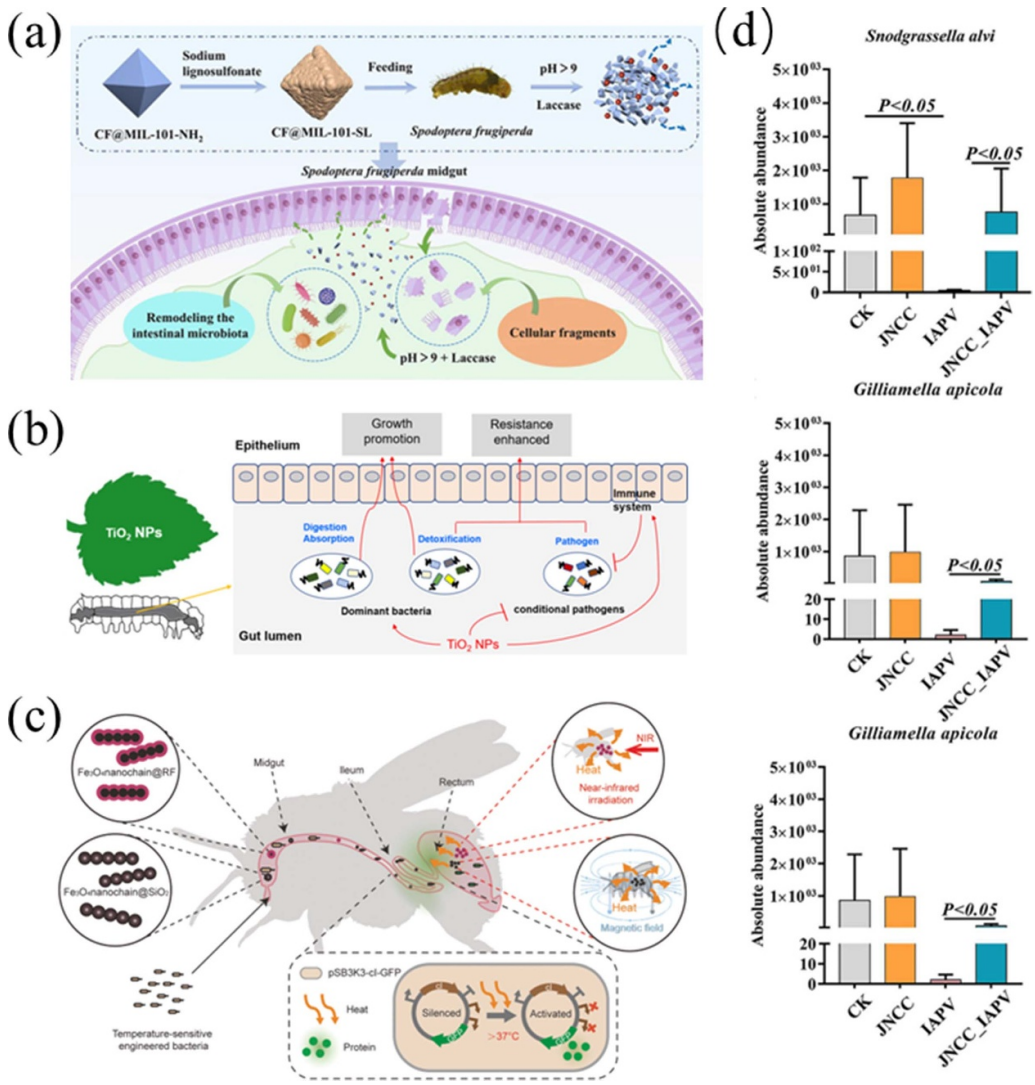

Figure 9. Nanotechnology modulation of gut microbiota in agriculture. (a) Iron-based metal-organic framework nanoparticles loaded with chlorfenapyr enhance the insecticidal activity of chlorfenapyr by altering the gut microbiota of *Spodoptera frugiperda.* Reprinted with permission from [229]. Copyright (2023) American Chemical Society. (b) TiO_2 NPs could alter the composition of the gut microbiota of *Bombyx mori*, and thus promote its growth and development, regulate its immune functions, and enhance its resistance to insecticide. Reprinted from [230], © 2019 Elsevier B.V. All rights reserved. (c) Schematic representation of heat-controlled engineered bacteria in the gut of bumblebees. [231] John Wiley & Sons. © 2023 Wiley-VCH GmbH. (d) Effect of natural plant nanocrystalline cellulose on the gut microbiota of honeybees after Israeli acute paralysis virus. Reprinted with permission from [232]. Copyright (2023) American Chemical Society.

Using nanotechnology to disrupt gut microbiota could be a new approach to pest control. Insecticides are a common method of controlling pests that kill or inhibit them. However, as pest resistance increases, insecticides can cause harm to the environment and other organisms, making it necessary to limit their use. The disruption of gut microbiota can impact the normal growth of insects, which allows some nanomaterials to be used as green pesticides to control pests. Nanomaterials are easily ingested by insects because of their smaller size and greater penetration. Nanomaterials that enter the body can disrupt insect gut microbiota due to their antimicrobial effects. For example, silver nanoparticles synthesized from pomegranate peel extract prevented the development of *Spodoptera litura* and reduced several microbiota in the gut [233]. Iron-based metal-organic framework nanocarriers loaded with chlorfenapyr affect nutrient and energy availability by altering the gut microbiota of the *Spodoptera frugiperda*, enhancing host damage by chlorfenapyr [229]. With the development of nanotechnology and genomics, researchers have analyzed the relationship between insect gut microbiota and insecticides. Nanotechnology to alter insect gut microbiota may be one of the choices to replace pesticides [234]. In the future, nanotechnology could replace insecticides or improve their effectiveness by modulating insect gut microbiota.

Nanotechnology modulation of gut microbiota could provide health benefits for insects. Insecticides can negatively affect the gut microbiota of insects and may even cause insects behavioral impairments [235]. Using nanotechnology to modulate gut microbiota may be able to mitigate the

negative effects of pesticides. It has been demonstrated that low doses of TiO_2 nanoparticles can alter the gut microbiota composition of *Bombyx mori*, thereby promoting their growth and development, and enhancing resistance to insecticides [230]. In addition to mitigating the negative effects of pesticides, some nanomaterials can also modulate insect gut microbiota and suppress pests and diseases. Natural plant nanocrystalline cellulose reduces the proliferation of Israeli acute paralysis virus in honeybees by enhancing the abundance of the core microbiota *Snodgrassella alvi* and *Lactobacillus* Firm-4 in honeybees [232]. Stimulus-responsive nanotechnology also has the potential to be applied to modulate insect gut microbiota. A temperature-controlled nanotransducer has been shown to precisely modulate the expression of engineered bacteria in the gut of bumblebees under the control of magnetic fields and near-infrared light, laying the groundwork for the future use of nanotechnology to modulate bee gut microbiota [231]. Nanotechnology can protect beneficial insects by modulating their gut microbiota.

Nanotechnology modulation of gut microbiota can positively impact agricultural development by protecting beneficial insects and suppressing pests. Nanotechnology modulation of gut microbiota is a novel technology, which is important for improving the efficiency of agricultural production, improving the quality of agricultural products, and protecting the ecological environment. However, the effects and potential hazards of nanotechnology have not been fully elucidated. Using nanotechnology to modulate insect gut microbiota should take into account its impact on agricultural plant production and the environment. In the future, with the development of nanotechnology, more insect microbiota will be modulated to promote agriculture.

8. Challenges of nanotechnology in gut microbiota modulation

With the development of technology and the increasing demand for modulating gut microbiota, nanotechnology has received widespread recognition for its precision, efficiency, and safety. Despite the great potential of nanotechnology in modulating gut microbiota, there are still some challenges to the widespread use of nanotechnology.

8.1. Technical challenges in nanotechnology

Nanotechnology enables communication at molecular and macroscopic scales for gut microbiota-gut interactions. However, there are also technical challenges, such as targeting efficiency, biocompatibility, biodistribution, and stability, many of which are governed by nanoparticle design (*e.g.* material selection and payload) and their morphology (*e.g.* size, shape, surface charge). In order to better utilize nanotechnology to modulate gut microbiota, associated technical challenges need to be overcome.

The stability of nanotechnology is one of the major constraints to its application. Gut has complex physiological features, such as intestinal mucosal barriers, digestive enzymes, and gut microbiota. These may affect the stability and functionality of nanotechnology. Nanotechnology wants to reach the gut, and before that, it will enter the stomach. The stomach acid causes an extremely low environmental pH, with pepsin and lipase present. After passing through the stomach, it reaches the gut, where bile salts and digestive enzymes are present [236]. Therefore, nanotechnology must overcome the above factors to work in the gut. To ensure that nanotechnology can work in the gut, nanomaterials need to be designed with good stability to withstand the harsh environment of the gut. Selection and modification of materials may be required to enhance the structural stability of nanomaterials.

How to improve the targeting of nanotechnology is also one of the factors hindering its further application. Precise delivery of nanotechnology enables precise modulation of gut microbiota, maximizing therapeutic efficacy and minimizing side effects. Stimulus-responsive nano-drug delivery systems can further optimize the ability to target microbiota and enable the modulation of specific microbiota. Stimulus sources for stimulus-responsive nano-drug delivery systems include endogenous and exogenous stimuli. Endogenous stimuli involve enzymes, pH, and redox within the gut. Accuracy and sensitivity are difficult to ensure. Exogenous stimuli also suffer from limited penetration, poor positional control, and injury to non-specific cells in the surrounding tissue [237]. Due to the complex physiological environment in the gut, single stimulus-responsive nanotechnology may not be able to achieve the desired results. Nano-drug delivery systems with multi-stimulus responsiveness are expected to enhance responsiveness, targeting, and precision. However, the complex preparation process is one of the reasons limiting the further application of multi-stimulus responsive delivery systems [238]. In the future, more research is still needed to explore how to improve the targeting of nanotechnology.

Although nanotechnology has shown great promise in the field of modulating gut microbiota, its clinical translation remains low. Factors limiting the clinical translation of nanotechnology, in addition to the technical issues mentioned above, the differences in gut microbiota between human and animal models are one of the important factors [239]. Despite the important reference value of animal models in initial experiments, there are still some differences between their gut microbiota composition and that of humans. These differences may lead to different outcomes of nanotechnology in animals than in humans, thus affecting the outcome of nanotechnology modulation of human gut microbiota. Animal models also fail to fully simulate the complex peristaltic patterns, neural control, and immune responses of the human gut, further increasing the difficulty of translating nanotechnology into clinical therapeutics [240]. Most nanotechnologies are developed and designed in a laboratory environment, often involving tedious steps and complex processes. Subtle differences in raw materials or conditions may lead to changes in the properties of nanotechnology, making the scaled-up production of

nanotechnology challenging. At the same time, the high cost of industrialized production also limits the practical application of nanotechnology, which restricts the clinical translation of nanotechnology. In addition, the current global regulatory standards for the clinical translation of nanotechnology are still imperfect. The lack of effective modulation to assess the safety and therapeutic efficacy of nanotechnology has largely hindered the application of nanotechnology in the field of gut microbiota modulation.

Nanotechnology faces many technical challenges in modulating gut microbiota. Overcoming these challenges requires interdisciplinary cooperation and innovation involving a wide range of fields, such as materials science, biology, and medicine. Only by overcoming these challenges will be able to better realize its potential in gut microbiota modulation and bring greater benefits to humans.

8.2. Safety of nanotechnology

Advances in nanotechnology have made it possible to utilize precise modulation of gut microbiota, along with increasing risks. Nanotechnology can come into direct contact with the human gut, which could lead to the riskiness of nanotechnology. There have been studies evaluating the potential hazards that nanotechnology may have, but further research is needed to analyze the safety of nanotechnology.

Nanotechnology may have adverse effects on the host, especially nanomaterials used as carriers. The extremely small size of nanomaterials allows for faster penetration within the host and can be transferred to various tissues or organs of the host [241]. Nanomaterials entering the gut first interact with the mucus layer, then pass through gut microbiota and intestinal epithelial cells, and then enter the intestinal-associated lymphoid tissues, and are subsequently absorbed by the intestinal epithelium into the blood circulation [242]. Nanomaterials can lead to effects on allergic diseases such as dermal hypersensitivity and asthma, with possible mechanisms including altered B-cell distribution, elevated IgE and IgG levels, and splenic toxicity. Some metal nanomaterials with antimicrobial properties may release metal ions when they enter the body, increasing intracellular ROS levels, which can be toxic to cells when accumulated over time [243]. Nanomaterials may have adverse effects on the gut. Nanomaterials can cause the mucin composition of the mucus layer to be altered [244], damaging the tight junction and microvilli of the intestinal epithelial barrier [245], triggering inflammatory and immune responses, and impacting the central nervous system through the gut-brain axis [246]. Nanoparticles can accumulate in the host for long periods of time, thereby producing adverse effects. The potential toxicity of some nanomaterials for reproduction has been demonstrated, with silica and titanium dioxide nanoparticles crossing the placental barrier of pregnant mice, being present in the fetal liver and brain, and causing neurotoxicity in their offspring [247]. However, it has also been noted that gold nanoparticles and silver nanoparticles did not significantly affect the offspring [248, 249]. The safety of nanotechnology is usually related to its distribution and accumulation concentration in the body.

Nanotechnology applications are promising, but their safety and toxicity must be carefully evaluated. Nanotechnology safety needs to be improved through comprehensive studies of its biocompatibility, metabolic pathways, and long-term effects. Only if it is safe can nanotechnology realize its wide range of applications in fields such as medicine, agriculture, and environmental science.

8.3. Environmental impacts of nanotechnology

As a cutting-edge technology, nanotechnology has great potential for application. However, nanotechnology is used in a large number of applications, and it may have a negative impact on the environment. The unique nature of nanocarriers makes them potentially risky in the environment, with possible adverse effects on ecosystems and biological health.

The widespread use of nanotechnology may lead to nanowaste entering the environment. Nanowaste can enter the environment through water, soil, air, *etc,* and have a negative impact on the environment. Nanowaste that enters the environment can be toxic to soil organisms, negatively affecting soil microbiota, plant root growth, and crop yields [250]. There have been studies evaluating the effects of long-term effects of nanomaterials on soils and crops. Long-term (98 d) exposure to Ag nanoparticles reduces peanut yield and quality and accumulates in the root system and pods, posing a threat to food safety [251]. Schlich *et al* demonstrated the long-term effects of Ag nanoparticles in soil over a period of 25 months, including entry into wheat and oilseed rape roots and inhibition of soil microbiota communities [252]. Nanowaste can also have toxic effects on aquatic organisms, including phytoplankton, fish, shellfish, *etc* [253, 254]. Exposure of *Daphnia pulex* to typical environmental nanoplastic concentrations (1 μg l^{-1}) for three generations affects reproductive, developmental, and antioxidant genes, which may have implications for multiple generations of *Daphnia pulex* [255]. Silver nanoparticles (0.09 mg l^{-1}) can accumulate in different organs of fish, including livers, intestine, gills, and muscles, and lead to histopathological alterations with effects on aquatic organisms [256]. Nanoparticles that enter the environment may alter their properties through various reaction processes such as adsorption, sedimentation, degradation, dissolution, *etc* [250]. Nanoparticles can interact with other pollutants to form mixtures when they enter the environment [257]. Nanowaste in the environment can persist for long periods of time and gradually accumulate through the food chain into higher organisms and even into the human body, leading to unknown health risks [258]. Some studies have exposed the environmental impacts of nanoparticles, but the concentration of nanoparticles in the environment is very low. The potential ecosystem impacts of longer-term exposure to low concentrations of nanomaterials are largely underexplored.

Although nanotechnology can play a positive role in a number of fields by modulating gut microbiota, its impact on the environment must be brought to the consideration of researchers. Minimize the negative environmental impacts of nanotechnology through more research and effective regulation to achieve sustainable development.

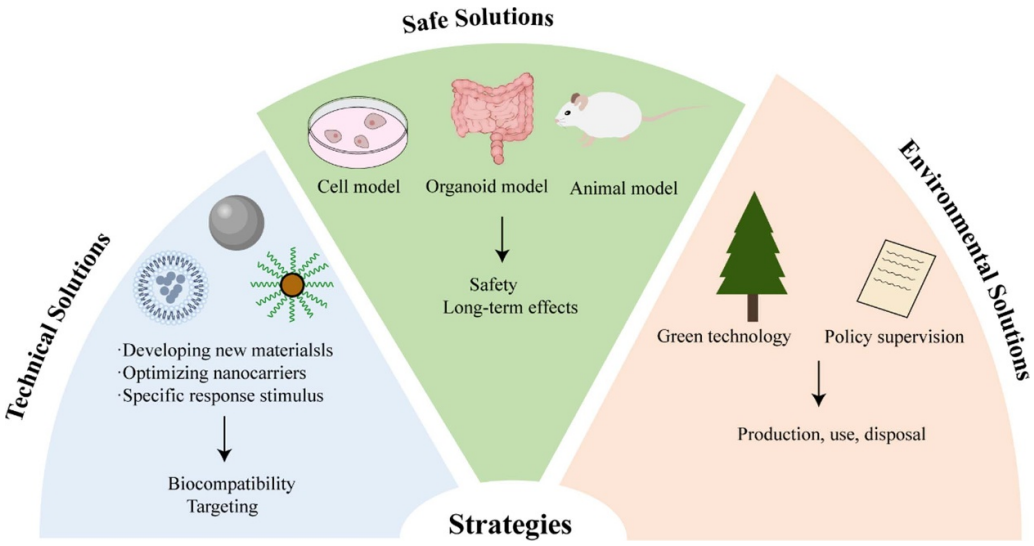

Figure 10. Future research directions of nanotechnology in the field of gut microbiota regulation include key steps such as nanomaterial development, nanocarrier optimization, precision regulation, safety assessment, environmental impact assessment and green technology development, and the development of a sound regulatory framework.

9. Prospects

The rapid development of nanotechnology has made it possible to use nanotechnology to modulate gut microbiota. In the future, with the deepening of the research, nanotechnology will make more progress and promote the innovation of gut microbiota modulation technology. This will bring new application prospects in the fields of healthcare, animal protection, and agricultural development (figure 10).

9.1. Solutions to the challenges of nanotechnological modulation of gut microbiota

The application of nanotechnology in the modulation of gut microbiota still faces several challenges that limit its practical application and clinical translation. In order to break through current bottlenecks and advance the clinical translation of nanotechnology, future research should focus on technical challenges, safety challenges, and negative impacts on the environment. Researchers will focus more on developing nanomaterials with higher biocompatibility and functionality that are better stabilized within the complex gut environment. Optimization of nanocarriers is also a hot topic for researchers. Precise drug release is achieved by specifically responding to endogenous or exogenous stimuli and even controlling the rate and stoichiometry of drug release according to changes in the gut environment. Precision medicine is also a focus of research on how to precisely modulate the composition of microbiota communities through nanotechnology. In particular, how to customize the modulation for specific hosts, specific pathogens or specific functional needs during disease treatment. In addition, the safety and degradability of nanomaterials are important directions for future research. Currently, different models, such as monolayer or co-culture cell models, animal models, and intestinal organoid models, have been used to evaluate the safety and compatibility of nanomaterials. Promote clinical trials of nanotechnology through more systematic studies to assess the safety, stability, and potential toxicity of nanomaterials, and ultimately validate their efficacy and safety in the treatment of disease. Furthermore, it is recommended to carry out environmental impact assessments, especially to develop green processes in all aspects of production, use and waste disposal of nanomaterials in order to minimize their threats to the environment. At the same time, better regulatory policies need to be developed and implemented to strengthen the management of nanowaste disposal. This will ensure that the development of nanotechnology is in line with the principle of sustainable development. The above strategies can provide a clear direction for cracking the current technical bottlenecks and challenges, and promote the clinical translation and practical application of nanotechnology in intestinal microbial regulation and related fields.

9.2. Cross-fertilization of nanotechnology with other technologies

Nanotechnology can be cross-fertilized with other advanced technologies to advance gut microbiota modulation. This convergence could not only broaden the scope of nanotechnology applications, but also bring new research methods and tools for the modulation of gut microbiota. The combination of nanotechnology and synthetic biology is bringing a whole new dimension to gut microbiota modulation. Synthetic biology allows for the construction of synthetic microbiota with specific functions for the modulation of gut microbiota through gene editing techniques. Nanotechnology can deliver gene editing tools (*e.g.* the CRISPR-Case system) into the gut. The rapid development of artificial intelligence provides strong technical support for the application of nanotechnology in gut microbiota modulation. Next-generation sequencing

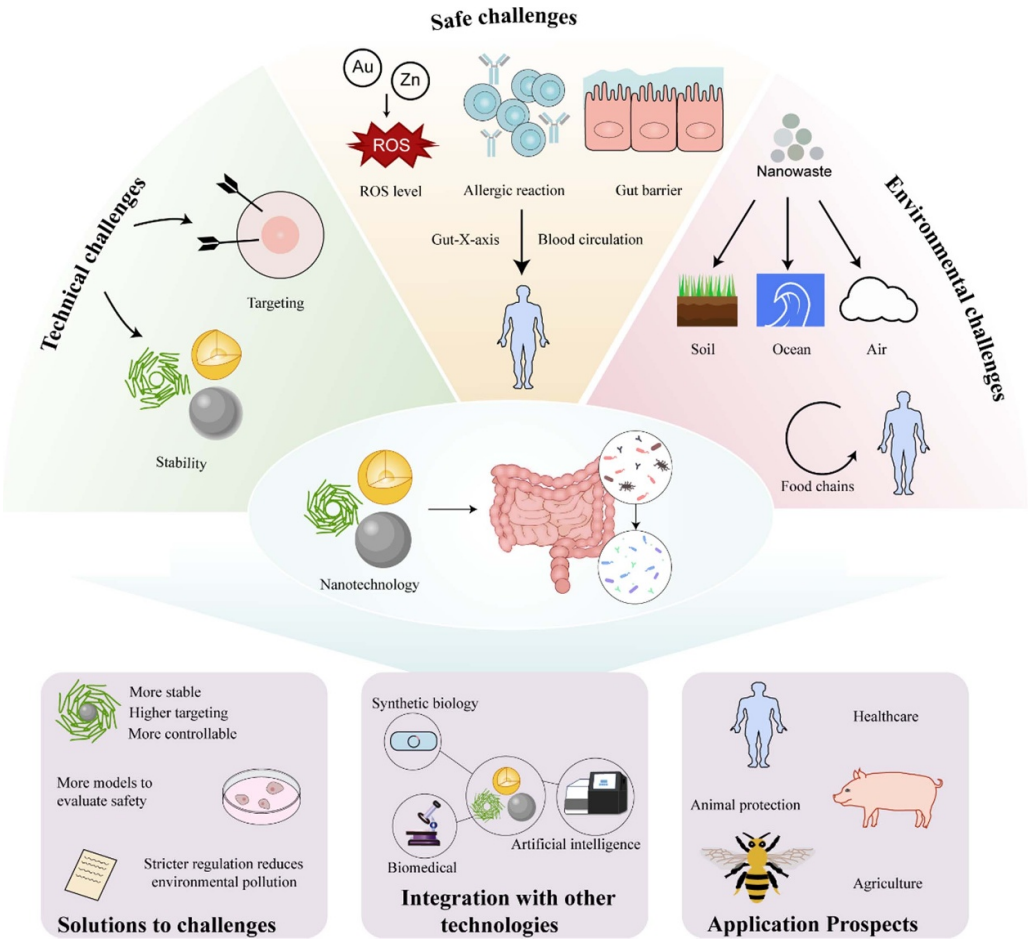

Figure 11. Challenges and application prospects of nanotechnology in modulating gut microbiota. The application of nanotechnology to gut microbiota modulation needs to address the technical, safety, and environmental challenges faced. The future focuses on the safety, dissolvability, and targeting of nanotechnology, integrating it with other cutting-edge technologies for broader applications in healthcare, animal protection, and agricultural development.

can analyze the composition of gut microbiota comprehensively and screen for specific pathogenic or probiotic bacteria, providing a theoretical basis for the modulation of nanotechnology. Meanwhile, artificial intelligence technology can analyze changes in the gut microenvironment, predict the delivery location and release conditions of nanotechnology, and optimize the design and application of nanocarriers. The combination of nanotechnology and biomedical engineering could lead to the development of novel diagnostic, therapeutic, and preventive methods for gut microbiota-related diseases. In the future, with the continuous progress and integration of various technologies, the application of nanotechnology in the modulation of gut microbiota will be more extensive and in-depth.

9.3. Prospects for the application of nanotechnology to modulate gut microbiota

Nanotechnology modulation of gut microbiota has multiple applications, including healthcare, animal protection, and agriculture. Nanotechnology is utilized to develop therapeutic and preventive approaches for diseases associated with gut microbiota dysbiosis (*e.g.* enteritis, irritable bowel syndrome). By modulating the composition and function of gut microbiota, it is possible to improve the symptoms and prognosis of diseases and enhance therapeutic efficacy. Traditional drugs that modulate gut microbiota *(e.g.* antibiotics, natural products, probiotics) face problems of resistance, stability, and targeting in the gut. By designing and preparing stimuli-responsive nanocarriers, targeted release of drugs can be achieved, improving drug bioavailability and reducing the development of drug resistance. In the future, researchers will focus more on how to achieve effective encapsulation and precise delivery of drugs, which is related to the design of nanocarriers. The composition of gut microbiota varies significantly depending on the genetic background, lifestyle and environmental factors of individuals, not only in terms of species and numbers, but also in terms of functional diversity. The complexity of gut microbiota composition makes it difficult to apply a 'one-size-fits-all' modulatory approach, which may be different for different populations. Therefore, personalized gut microbiota modulation is a hot topic for future research. With the development of

precision medicine, nanotechnology can be creatively applied to modulate an individual's gut microbiota for personalized microbiome therapy. Nanoparticles targeting specific microbiota imbalances or functional deficiencies are designed by combining advanced sequencing technologies, bioinformatics analysis and multi-omics data to analyze the microbiota composition of individuals. Although personalized approaches can improve the specificity and effectiveness of interventions, the implementation of personalized medicine requires high costs, complex technical support, and in-depth clinical studies, which poses higher requirements for future research and applications. As the study of gut microbiota in animals and insects intensifies, using nanotechnology to modulate gut microbiota can also be applied in animal protection and agriculture. For example, replacing antibiotics to improve the health and productivity of farm animals. Nanotechnology has great potential for agricultural development. It can provide innovative solutions for crop protection, improving the quality of agricultural products and reducing chemical pesticides. In the future, as technology advances, nanotechnology is expected to play an important role in broader gut modulation (figure 11).

10. Conclusion

This review describes the progress and application of nanotechnology to modulate gut microbiota. Nanotechnology can modulate gut microbiota through nanomaterials, nanomedicine delivery, and stimulus-responsive nanotechnology. Nanotechnology-based modulation of gut microbiota is presented for applications in healthcare, animal protection, and agriculture. Finally, the challenges faced by nanotechnology in modulating gut microbiota are summarized, and research gaps that have not been addressed in the current research are revealed, including technical challenges of nanotechnology, safety issues, and their impact on the environment. The solutions and future directions are proposed for future research, which provide an important reference for future research.

As one of the methods to modulate gut microbiota, nanotechnology has several advantages. However, multiple challenges remain, including stability, targeting, safety, and environmental impact. There is still a lack of systematic research on how to achieve precise targeted modulation of specific pathogenic or probiotic bacteria, as well as the long-term stability and safety of nanomaterials in complex gut environments. In addition, current supportive data for their clinical applications are limited, especially regarding in-depth validation of long-term efficacy and potential environmental impacts. To address these challenges, future research will focus more on developing nanomaterials with good biocompatibility and controlled release properties. This will be combined with internal and external gut stimulation to achieve precise, dynamic, and safe gut microbiota modulation. In addition, multidisciplinary cross-fertilization, such as the combination of artificial intelligence and synthetic biology, provides new solutions for applying nanotechnology in gut microbiota modulation.

Nanotechnology is still in its infancy in the modulation of the gut microbiota, but there has been a lot of pioneering work confirming its great potential, especially in the field of treatment of diseases related to gut disorders. It is believed that with in-depth research in nanotechnology, there will be significant progress in the field of gut microbiota modulation. The expanded application of nanotechnology will lead gut microbiota modulation into a new era.

11. Future perspective

Nanotechnology is able to directionally change the composition of gut microbiota through precise drug delivery and targeted modulation, showing great potential in gut microbiota modulation. It provides a novel approach to maintaining gut ecological balance and enabling precise disease treatment through controlled release, targeted action, and the ability to cross biological barriers. However, its widespread application still faces many challenges, including the stability and long-term safety of nanomaterials, the complexity and cost control in large-scale production, and the impact of nanotechnology on the environment. Future research needs to be conducted in the following areas to advance the application of nanotechnology.

First, there is a need to focus on the development of nanomaterials with higher biocompatibility, which can be modified through molecular design and multifunctionalization to enable them to precisely respond to endogenous or exogenous stimuli in the complex gut environment. By optimizing the structure and function of nanomaterials, targeted delivery and controlled release of drugs can be achieved, thus improving the precision and efficacy of treatment. In addition, exploring novel nanocomposites, especially their long-term stability and degradability in the gut environment, will greatly enhance their safety and reliability in practical applications.

Second, synergistic studies of *in vitro* models, animal models, and clinical trials should be strengthened. The complex environment of the human gut should be simulated through advanced models, such as organoids, to assess the stability, toxicity, drug release behavior, and other key factors of nanotechnology under different conditions of nanotechnology. In addition, combining long-term experimental data from animal models with feedback from clinical trials will further validate the feasibility and potential of nanotechnology in clinical translation, thereby advancing its practical application in the field of gut microbiota modulation.

Furthermore, as the application of nanotechnology expands, it is particularly important to assess its long-term impact on the environment and human health. There is a need to develop a sustainable green nanotechnology strategy that improves the biodegradability of materials and reduces the production of hazardous substances, thereby reducing the potential harm to the environment. At the same time, a comprehensive global regulatory framework should be established to define clear standards and guidelines for the production, application, and disposal of nanomaterials.

Finally, multidisciplinary cross-fertilization will be an important trend for future development. As nanotechnology continues to mature, combining it with synthetic biology, artificial intelligence, bioinformatics, and other cutting-edge technologies can provide a new perspective and means for personalized gut microbiota modulation. Through the deep integration of these technologies, the personalized process of gut microbiota modulation technology can be promoted, thus providing more innovative solutions for precision medicine and disease treatment and helping to address increasingly complex health challenges.

With the continuous progress of nanotechnology, especially the breakthroughs in material design, biocompatibility, targeting, and functionalization, its application in gut microbiota modulation has become more promising. In the future, nanotechnology is expected to provide more precise microbiota modulation methods, overcome the limitations of traditional methods in terms of specificity, long-term effects, and side effects, and show a wide range of application potential in multiple fields.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (32170495, 22278241) and a grant from the Institute Guo Qiang, Tsinghua University (2021GQG1016).

Conflict of interest

There are no conflicts to declare.

Author contributions

Conceptualization: H Z and Y L; Funding acquisition: Y L; Project administration: X W, H Z and Y L; Resources: Y Q and Y W; Visualization: Y Q; Writing—original draft: Y Q; Writing—review & editing: X W, H Z and Y L. All authors have approved the final version of the manuscript.

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