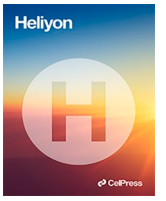
Heliyon 10 (2024) e31728

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Use of nanotechnology-based nanomaterial as a substitute for antibiotics in monogastric animals

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ARTICLE INFO

Keywords:
Nanotechnology
Nanoparticles
Antibiotics
Monogastric animals

ABSTRACT

Nanotechnology has emerged as a promising solution for tackling antibiotic resistance in monogastric animals, providing innovative methods to enhance animal health and well-being. This review explores the novel use of nanotechnology-based nanomaterials as substitutes for antibiotics in monogastric animals. With growing global concerns about antibiotic resistance and the need for sustainable practices in animal husbandry, nanotechnology offers a compelling avenue to address these challenges. The objectives of this review are to find out the potential of nanomaterials in improving animal health while reducing reliance on conventional antibiotics. We examine various forms of nanomaterials and their roles in promoting gut health and also emphasize fresh perspectives brought by integrating nanotechnology into animal healthcare. Additionally, we delve into the mechanisms underlying the antibacterial properties of nanomaterials and their effectiveness in combating microbial resistance. By shedding light on the transformative role of nanotechnology in animal production systems. This review contributes to our understanding of how nanotechnology can provide safer and more sustainable alternatives to antibiotics.

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https://doi.org/10.1016/j.heliyon.2024.e31728
Received 15 November 2023; Received in revised form 20 May 2024; Accepted 21 May 2024
Available online 22 May 2024
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1. Introduction

Biotechnology and nanotechnology are considered to be the 21st century's most emerging and advanced technologies [1]. Nanotechnology (from the Latin nanus, meaning the dwarf) can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale (~1–100 nm) or one billionth of a meter (10^9) [2]. Nanoparticles are attractive due to their compact size and large surface area, which leads to a higher ratio of surface atoms to interior atoms. Consequently, when larger materials are reduced to nanoscale dimensions, their surface chemistries gain prominence and cause changes in their physical properties [3].

Livestock producers want their herds and flocks to reach optimal slaughter weights as soon as possible to maximize profits. Antibiotics are currently used as feed additives to prevent and treat illnesses as well as to accelerate growth, thereby shortening animal production cycles [4]. While beneficial in terms of production, this widespread practice has resulted in the emergence of antibiotic-resistant bacteria strains, posing risks to livestock health and meat consumption [3]. Antibiotic usage data from various countries shows that agricultural applications outnumber human applications [5]. As a result, several countries have enacted legislation to limit antibiotic use in animal production (19). Nanoparticles offer a promising solution to fill the void left by these restrictions, providing a way to boost growth without increasing antibiotic resistance in microbial populations [3].

The shortening production cycles and the early weaning of livestock increase their sensitivity, concentrating physiological properties for increased growth while also making them more prone to environmental factors and pathogens. This approach will not always serve the increased vulnerability the animals have but can significantly reduce outputs. In livestock nutrition, the focus has shifted from merely meeting growth requirements to prioritizing health parameters, often achieved through the use of feed additives to optimize productivity alongside nutritional value [6]. However, it is unclear to some extent whether this response is linked to its impact on the gastrointestinal microbial environment [7], which affects the production and functions of pancreatic and intestinal digestive enzymes, as well as the maintenance of the intestinal mucosa morphology [8,9]. Over the last 30 years, significant efforts have been made to find alternatives to the use of antibiotic growth promoters in livestock nutrition. Organic acids [10], plant extracts [11], oligosaccharides [12], and probiotics [13] are some of the most commonly used products in pork and poultry production.

In recent years, phytogenic natural compounds have been extensively used in livestock feeding as antimicrobial growth promoters (AGPs) to substitute antibiotics in monogastric animals [14,15], poultry [16], and aquaculture [17]. The indiscriminate usage of antibiotics in livestock feed is known to favor the development of antibiotic-resistant strains of bacteria [16], and their buildup in edible tissues [18]. For animal disease resistance and growth promotion, researchers are putting much emphasis on the usage of natural growth promoters and non-antibiotic growth promoters (NGPs) in improving the gastrointestinal tract [19] via the integration of several feed additives. For instance, curcumin and its derivatives are known to possess antimicrobial, antioxidant, anti-inflammatory, appetite-increasing, immune-modulatory, and gastroprotective effects on the health of animals [16].

2. Nanomaterial applications

Nanotechnology has the potential to restore the use of hazardous medications using multifaceted structures that allow drugs to be carried to the pathogen while protecting host cells and exerting less toxicity [20]. Nanomaterials have been industrialized for use in medicine and a variety of devices. Antimicrobial, antiviral, and anti-parasitic properties have been demonstrated for nanoparticles (NPs) with specific physicochemical properties [21]. It is important to note that the most important and extensive field of science that utilizes nanobiotechnology in human medicine [22]. Nanobiotechnology is used to provide nanomaterials with a controlled drug delivery system for cancer remediation [23], nutrient utilization [24], hormonal controls, and gene therapy in humans [25]. In

Table 1
Toxic effects of nanomaterials.

Nanoparticles	Animal	Toxic effects	References
TiO_2NPs	Mammals	• Target mitochondria and cause mitochondrial dynamic imbalance. • It might alter the cell metabolism causing cell death ultimately.	[34]
Cadmium oxide NPs and silica NPs	Mice Zebra fish	•Cause injurious effects on the embryonic and reproductive system (cadmium oxide NPs in mice and silica NPs in zebra fish)	[35,36]
CuNMs	Rats	•Higher concentrations (about 50 μg/mL) encouraged the increase of prostaglandin E2. TNFa and ILb Extracellular levels were significantly high and the toxicity affected the blood–brain barrier finally	[37]
AgNMs	Rats	•Affects the blood–brain barrier, causing a pro-inflammatory reaction that developed later into a brain inflammation joined with neurotoxic effects.	[37]
AuNMs	Rats	• Cardiac hypertrophy caused by gold nanoparticles	[38]
TiO_2, CuO, and ZnONMs	Xenopuslaevis	• Induced teratogenic effects, especially on guts when concentrations are higher than 50 mg/L. ZnO-NMs caused the most damaging effects on the gut barrier which reached the connective tissue.	[39]
AgNPs	Carp fish	• The findings revealed that silver nanoparticle bioaccumulation resulted in histopathological changes such as damaged gill tissues leading to necrosis and severe alterations in the intestine, which mostly occurred at the highest concentration of silver NPs of 0.09 mg/L.	[40]
SnO_2, CeO_2 and Fe_3O_4 NMs	Sea urchin	• NMs were found in the sea urchins' immune cells. These cells have shown a decrease in cholinesterase activity, disturbances in stress protein regulation, and morphological alterations in ER lysosomes.	[41]

instances of animal welfare, this technology can be applied to improve growth [26], meat quality [16], reproductive performance [27], immunity enhancement [28], disease resistance [26], antioxidant activity [29], and intestinal functions [29], including food preservation [30].

Nanoparticles can easily enter pathogenic cells and interfere with cellular contents such as protein and DNA, causing programmed cell death due to their small particle size and charged surface [31]. The primary goal of treatment is to keep the patient as comfortable as possible. Therapy involving biotechnology has been evolving at a rapid pace for many years and with the introduction of nano-therapy healthcare, a new promise in medicine has emerged [32]. The use of nanomaterials as a new addition to enhance traditional therapeutic procedures can be extremely beneficial to livestock and humans [33]. We should however acknowledge that some of the nanomaterials have some toxic effects which are discussed further in Table 1.

3. Types of nanomaterials

Nanomaterials can be characterized into four main classes: metals, polymers, natural compounds, and nanostructured materials [33]. Metals are generally mineral nanoparticles such as gold [42], copper [43], selenium [44], and palladium [45]. However, the major challenge of utilizing metal nanomaterials is their non-biodegradability [3]. Some polymers of nanomaterials are pieces of nanometer-sized substances that are biodegradable, biocompatible, and can be efficiently utilized [46]. Biocompatibility is the greatest issue of concern in nanobiotechnology to have low or minimal toxic properties on an organism [47]. Nanoparticles that are derived from natural sources are referred to as natural compounds (natural polymers or proteins) which are extremely biodegradable, biocompatible, and distributable in the body of an animal [3]. Nanostructured materials are the pairings of lipids or proteins with nanoparticles for example phospholipid-based nanoparticles (curcumin nanospheres) or phosphoprotein-based nanoparticles (casein micelles). In animal nutrition, natural and nanostructured nanoparticles have more positives about nutrient delivery using encapsulation or adhesion of nanomaterials. In some instances, natural or nanostructured nanoparticles are considered toxic in elevated dosages if they are not properly regulated in an organism. In livestock nutrition, there is a huge debate on nanotechnology concerning the nature of food, its taste, texture, processing time, thermal susceptibility, stability, safety, and bioavailability of nutrients as well as safety for feeding livestock [48].

4. The role of nanotechnology in animal health care applications

Nanotechnology is important in a variety of animal healthcare applications. Here are a few of the most important roles of nanotechnology in animal health care.

4.1. Diagnosis of diseases

Animal diseases are allocated into categories based on their causative agents. Some causative agents of infectious diseases are prevalent in humans and animals and others are pathogenic only for non-humans or to specific species of animals. Infectious diseases manifest in the form of individual cases or assume a widespread distribution. In general, the traditional methods to identify the presence of pathogens have various limitations: (1) working with samples directly, (2) it is time-consuming, (3) some microorganisms cannot grow easily, and (4) significant limitations in the classification of viruses as a result of them being small in size [49]. Despite elevated sensitivity and precision in the detection of pathogens using advanced techniques like polymerase chain reaction (PCR) (a technique that is used to amplify specific DNA segments) and enzyme-linked immunosorbent assay (ELISA) (a test that detects and measures antibodies in the blood) [50].

Nanotechnology indicates vast opportunities to develop fast, accurate, and cost-effective materials for pathogen detection. In 2006, avian influenza viral diseases (H5N1) manifested into a global epidemic, increased mortality rate, and economic fatalities [51]. Research by Emami et al. (2012) tried to improve the capability of the Western blot technique to identify and classify small molecules of proteins or peptides [52]. Emami et al. (2012) used nanotechnology to build a sensitive and precise technique for detecting avian flu antibodies in poultry serum by coating the immobilizing-polyvinylidene difluoride membrane with gold nanoparticles (AuNPs) [52].

Bovine tuberculosis is a chronic bacterial disease of cattle that rarely affects other mammalian species and is known to cause enormous economic losses due to livestock deaths, low productivity, and trade restrictions. This ailment can be spread to humans using air or unpasteurized milk. In countries that are developed, control of these diseases in domestic livestock and humans has flourished through various methods such as milk pasteurization and thorough annihilation programs [53,54]. Nevertheless, challenges exist to exterminate diseases as a result of the unauthorized transportation of infected animals and uncontrolled herds, and the existence of wildlife reservoirs of the disease [55].

In 2012, Peled et al. described a new methodology for detecting *Mycobacterium bovis* infection in cattle grounded on identifying exceptional volatile organic compound profiles in the breath of cattle [56]. A tailor-designed nanotechnology-based array of sensors was implanted into a nano artificial nose (NA-NOSE) to sense the volatile organic compound forms linked with some disease conditions. "NA-NOSE is an artificial olfactory system built on an array of cross-reactive, nanomaterials-based, chemical gas sensors which can detect and distinct gaseous mixtures, even if their compound analytes are present at very low concentrations and their differences are very minimal" [56]. Their research strongly indicated that NA-NOSE effectively detected *Mycobacterium bovis* (*M. bovis*) infected cattle via breath analysis [56].

4.2. Veterinary medicines and vaccines

Nanomedicine is characterized by 'smart drug' distribution systems utilized in animals to distribute the drug to the target tissue while delivering a drug-release profile that would ensure that the drug is distributed as required [57]. Drug constituents entrapped by biodegradable nanoparticles can be protected against degradation by gastrointestinal fluids and for enhanced absorption of the drug across the intestinal mucosa [58]. More even drug absorption and minor hazards of local irritation could be accomplished through preparations founded on polymeric nanoparticles administered by oral delivery [59].

Pathogens are regarded as one of the most significant obstacles in the animal production sector as a result of them being relocated easily from infected individuals to healthy ones [51]. The most common treatment for eradicating diseases comprises the collective usage of vaccines and/or antibiotics. Despite all these benefits, the shortcomings of live vaccines are comprised of the instability and risk of relapsing the pathogenic strain back to its virulent form [60]. Additionally, the usage of antibiotics and chemicals has occasioned the appearance of resistant strains of pathogens, as well as the potential for amplifying environmental pollution and residual effects in eggs or meat. Additionally, a consideration in the food chain is the hazard of shifting antibiotic resistance from animal production to humans, which signifies a public health challenge [61].

Nanoparticles exhibited a possibility to provide novel substitutes to produce a new generation of drugs, comprising vaccines. The nanoparticles function as delivery carriers for vaccines and new adjuvants to boost the immune response because the antigen is a very weak immunogenic agent in many cases [62]. Recent investigations have exposed the higher effectiveness of nano-vaccines and nano-antibiotics. Biodegradable nanoparticles in vaccine formulations displayed advantages such as enhanced antigen firmness and immunogenicity, specific delivery, and slow release [63]. Consequently, nanomedicines are generally concluded to be very advantageous in disease prevention and treatment of animals. Also, the pathways of vaccine administration have been established from intravenous and muscular injection to oral, nasal, and transdermal nano distribution systems. Although some vaccines are effectively commercialized products through an oral route delivery system, such as the polio vaccine, the improvement in the commercialization of nanomedicine still faces technical difficulties associated with the mechanism of cellular access and toxicity for many nano-materials [64]. For instance, in humans, despite the absence of information on the method of action of nano-aluminum salt adjutants, vaccines containing aluminum salts have been exhibited to supply higher and longer-lasting antibody titers after a single immunization [60]. Even though there are biological and technical difficulties that are encountered by the nanomedicines, the nanoparticles may perhaps be very beneficial in supplying medicines effectively by all different pathways and in strengthening the efficacy of vaccines particularly during bird and animal epidemics such as avian flu.

4.3. Nano applications in animal feeding

Nutrition characterizes a key portion (≈60–65 %) of poultry and animal production systems inputs. Nanofeed constituents may perhaps aid in refining the feed effectiveness, reducing feed costs, and amplifying the yield and quality of animal products [65]. Regarding the superiority and safety of feedstuffs, nano biosensors could be used for the detection of the existence of toxin-producing insects or fungi inside bulk grain storage silos. Also, nanoparticles concocted to defend fats in ruminant diets to lessen fermentation interruption in the rumen and to shield crucial amino acids and make them more accessible for the host animal might be beneficial in the future [65]. In the current period, there are numerous effective and promising illustrations of the use of diverse nanomaterials in poultry and livestock feeding. It is anticipated that in the intensive production of poultry or ruminants, nano feed additives, and novel detoxifying nanomaterials may perhaps deliver additional benefits in feeding practices as a result of their positive result on motivating productivity and livability. In addition, ovo feeding may be considered a future safe nano application for the poultry industry [65]. A few of the examples of nanomaterials used in feed additives are presented in Table 2 below.

4.4. Poultry and animal shelter nano applications

Multiple studies confirmed that nanomaterials have a definite attribute that may facilitate them to be used in farm construction and equipment manufacture. It is recommended that nanomaterials be utilized as effective thermal insulation materials. Reduced pore sizes of 40 nm for air, specifically allow the nano insulation material (NIM) to have an initial state low thermal conductivity of less than

Table 2
List of some nanomaterials used as feed additives in animal feed.

Nanomaterial	Use	Animal	Action	Reference
Selenium	Feed additive	Chicken	Increasing productive and reproductive performance Enhancing immune response	[66]
Zinc	Feed additive	Chicken, Pig	Enhancing the immune response	[67]
Chromium	Feed additive	Pig	Anti-diarrheal, Enhancing antibody production	[68]
Nano Polystyrene with poly(ethylene glycol) linkers and mannose targeting biomolecules	Feed additive	All animals	Binding and removing food-borne pathogens in animal feed	[63]
Copper	Feed additive	Chicken	Strengthening immunological biocompatibility	[69]

4 mW/(mK). NIM is essentially a homogeneous material with a small nanopore structure that, in its initial state, is guaranteed to have a thermal conductivity of less than 4 mW/(mK), regardless of whether it is closed or open [70]. In the future, this might be valuable for large-scale poultry and animal production in tropical and sub-tropical areas. Other promising applications are paints that comprise a nano-photocatalyst e.g., TiO_2. These photocatalyst constituents can oxidize organic and inorganic substances and microorganisms under the stimulus of light [71]. Because of its cost-effectiveness, non-toxicity when consumed, and stability in water, TiO_2 is a good choice for water treatment applications. TiO_2 photocatalytic disinfection capabilities have been the subject of numerous studies, demonstrating the material's potential for drinking water filtration [72]. The decontamination role may be a future application for the provision of a solution to attain a microorganism-unrestricted environment, that conforms to high-standard hygiene parameters in a hatchery. AgNPs are a type of disinfectant that is used in animal husbandry, including the aquaculture, livestock, and poultry industries, for a variety of uses, including surface disinfection, water treatment, and therapeutic applications. They successfully stop the growth and reproduction of bacteria and fungi that cause sores, infections, unpleasant odors, and itching. These nanoparticles are very effective, take effect quickly, and have a deodorizing quality. They are also very effective against bacterial resistance because they are hydrophilic, non-toxic, non-irritating, and non-allergenic. Ag NPs are therefore used in animal husbandry as a disinfectant and disease prevention [73].

4.5. Nano applications in food processing

Processing is an indispensable fragment of both poultry and livestock production systems for the reason that processing adds value to the product and various products are produced to conform to consumer demands [63]. In food processing industries, the most common practices of nanotechnology comprise nano-empowered water treatment technologies, novel antimicrobial exteriors, and quality observations of food products in the form of nanosensors. Water is deemed to be a leading nutrient for all animal species and a very important commodity in food processing. Water purification utilizing nanofiltration is relatively recent and utilizes a filtration membrane which was designed to eliminate solids, bacteria, and parasites from the surface and fresh groundwater [63].

This innovation might be very beneficial in supplying high-quality water and recycling wastewater from processing plants, specifically in regions with limited water resources. Nanosensors can precisely spot the existence of antibiotic residues in meat [49]. This application is vital for protecting live birds and animals on the farms and manufacturing points from contamination from residues during several stages of processing that facilitate and ensure the safety and quality of products for consumers. Currently, engineered nanomaterials are incorporated in food packaging containing nanosilver, nano zinc oxide, and nano titanium dioxide due to their functional properties such as lighter weight with tougher packaging barriers [74].

Antimicrobial materials play a major position in preserving meats or poultry from pathogens by offering safe products and prolonging the shelf life. Many researchers recommended that nano-sized materials might give rise to new prospects in the fields of food preservation and packaging [74,75]. It was found that low and medium molecular weight chitosan possessed higher antimicrobial activity than ordinary chitosan on *Escherichia coli (E. coli)* (NCIMB 11943), *Staphylococcus aureus (S. aureus)* (NCIMB 13062), *Bacillus cereus (B. cereus)* (NCIMB 9373) and *Pseudomonas fluorescens* (*P. fluorescens*) (NCIMB 9046) isolated from raw chicken fillets. They recommended that nano-sized materials might result in novel applications in the areas of food preservation and packaging [75].

5. Uses of different nanoparticles as antibacterial agents

Nanoparticles have shown great promise as antibacterial agents due to their unique properties. The following are some examples of nanoparticles used as antibacterial agents.

5.1. Antibacterial activity of metal and metal oxide nanoparticles

The antibacterial action of metal and metal-oxide nanoparticles has been extensively reported and discussed by many researchers [76]. The magnitude of the particles and the large surface area compared to the volume of metal and metal oxide NPs allow close connections with microbial membranes, as well as surface function which assist in producing more effective antibacterial agents. Nanoparticles with antibacterial properties have the likelihood to diminish or eradicate the evolution of more resistant bacteria because nanoparticles target various species of bacteria at the same time, in that way preventing the development of resistant strains. Nanoparticles also can overcome drug resistance due to their multi-functionality because bacteria do not develop multiple gene mutations concurrently [77].

Over the past decade, there has existed an outstanding focus on conventional and biogenic metallic nanoparticles globally as ground-breaking tools for fighting the high rates of antimicrobial resistance [76]. In this case, nanomaterials have revealed promising outcomes owing to their exclusive physical and chemical qualities [78,79]. Numerous findings have singled out the antibacterial action of the metal nanoparticles [80–82].

5.2. Copper nanoparticles (CuNPs) as an anti-microbial agent in gut health

In recent years, several studies have described CuNPs as an encouraging substitute for antibacterial reagents and a growth enhancer. The usage of CuNPs has lately gained momentum because of their high electrical and melting points, low electrochemical migration characteristics high bioavailability, and relatively low cost of producing them [83]. As a result of the high physical reactivity of CuNPs, they can be utilized as a substitute for an effective health and growth supporter in minimal doses than bulk minerals in

livestock feed [69,84], and they can significantly reduce the elimination of these minerals into the environment. Furthermore, it has been described that the small size of the CuNPs can intensify its uptake from the gastrointestinal tract (GI tract), hence leading it to be more effective than the bulk Cu mineral, even at minor doses [85].

The inorganic copper salts utilized for the synthesis of nanoparticles greatly affect the antimicrobial properties of nanominerals. The crystalline CuNPs have robust antimicrobial action against both Gram-positive and Gram-negative bacteria [86]. The diverse shape, size, and strong antimicrobial action of CuNPs have a higher potential in the line of biomedical sciences and food packaging [87]. CuNPs are more effective antimicrobials as compared to organic and inorganic materials used in livestock health because them having a larger surface area [88]. It has been stated that CuNPs less than 100 nm in size can go into the bloodstream via the GI tract, and then enter several organs and tissues. In poultry, it has been linked to improving immunity by promoting gut microbiota [89].

The linoleic acid-capped CuNPs have massive bactericidal action for *S. aureus*, *E. coli,* and *Bacillus subtilis (B. subtilis)*, signifying that CuNPs can be utilized as a working growth inhibitor against several microorganisms making them applicable in increasing gut health in livestock [90]. In another study, it was proved that the chitosan implanted with CuNPs minimizes gut bacteria such as *E. coli*, *Enterococcus faecalis (E. faecalis)*, *S. Aureus,* and predominantly, *Lactobacillus fermentum (L. fermentum)*, which can be used to optimize unwanted levels of microbial populations [91]. The mechanism may be because of the dissipation of the cell membrane under the effect of nanoparticle buildup or the generation of reactive oxygen species (ROS) by highly concentrated $Cu2^{+}$ ions [92]. Ramyadevi et al. (2012) described that CuNP is more poisonous to bacteria than fungi as a result relations of CuNPs with the immune system are a vital issue to guide the future use of CuNPs in livestock feed and medicine [93].

5.3. Zinc nanoparticles (ZnONPs) as an anti-microbial agent in gut health

The importance of Zn in the animal system is thoroughly defined and documented. Nano-Zn as an alternative to conventional Zn sources can be a good substitute in livestock feeding. Apart from being exceedingly bioavailable, reports have signaled the growth-encouraging, antibacterial, immunomodulatory, and many other helpful effects of nano-Zn. Amongst metal nanoparticles, nano-zinc is the third highest internationally manufactured nano-metal after nano-SiO_2 and nano-TiO_2 [94]. The unexpected rise in the demand for ZnONPs is generally linked to their better antibacterial characteristics than conventional ZnO [95]. According to research findings, ZnONPs proved to have a wide variety of antimicrobial actions against several microorganisms [96]. Studies done so far have already demonstrated the dose-dependent effect of ZnONPs as an antimicrobial and immunomodulatory agent by minimizing the rate of diarrhea in piglets [97]. Piglets suffering from diarrhea after weaning are treated with ZnO, an inorganic compound that is highly effective and often used in the industry. ZnO as a whole and the zinc ions (Zn^{2+}) that are liberated from it are both antibacterial. Several investigations have proposed that ZnO's antibacterial properties stem from its rough surface, which encourages adherence to pathogens and causes cell disruption [98]. Available literature does not concisely agree on the precise mechanisms of cell disruption. Several studies have suggested various outcomes, such as disruption of the cell wall leading to intracellular leakage [99] inhibition of cellular metabolism, or damage to the cell membrane and interference with DNA ([100]). Furthermore, it has been demonstrated that ZnO produces ROS when exposed to light [101] and potentially via piezoelectricity [102]. Because ROS can compromise cellular integrity, ZnO can indirectly combat bacteria through this mechanism. ZnO has been reported by Ref. [103] to down-regulate oxidative stress-related genes, including kata and perR, which control peroxidase stress in bacteria. Because of this down-regulation, pathogens are more susceptible to ROS and oxidative stress. ZnO can also dissolve into Zn^{2+}, which has antibacterial properties. According to a related study, Zn^{2+} stimulates the production of ROS, which causes ion inflow and membrane leakage [104]. Another observation proved that the health condition and immunity of birds by adding nano-Zn to broiler diets at 0.06 mg/kg has enhanced significantly, as equated to the conventional dose of 15 mg/kg of organic and inorganic Zn with the basic diet [105]. Additionally, it has been described that by complementing basic diets with 400 mg/kg ZnONPs, the diarrhea rate decreased up to 49.1 % equated to 21.6 % upon supplementation of 3,000 mg/kg ZnO. Henceforth, this proves the fact that ZnONPs are a massively effective antibacterial agent even at extremely low concentrations, compared to the conventional ZnO [106].

5.4. Selenium nanoparticles (SeNPs) as an anti-microbial agent for gut health

SeNPs have been described to encompass effective antibacterial properties [107]. SeNPs when fed to broilers at a dose rate of 0.3 ppm and 0.5 ppm compared to both organic and inorganic selenium sources exhibited more effectiveness and higher performance in the treated group as compared to the control [108]. SeNPs move across the membrane barriers of the bacteria inflicting their anti-bacterial activities. Huang et al. (2016) reported that nano selenium particles have effective antibacterial and bactericidal activities, verifying that these are good antimicrobial substitutes to produce antimicrobial agents. Additionally, they also stated that acetyl-choline hybrids of SeNPs possess the capability to combine with the acetylcholine receptors on the bacteria cell membrane and intensify the permeability of cell membranes. This causes membrane interruptions and leads to the seepage of the cytoplasm, permitting nanoparticles to subsequently invade bacterial cells and interrupt the DNA structure [109].

Consequently, the acetylcholine-conjugated SeNPs have improved antibacterial activity. Quercetin and acetylcholine coupled with SeNPs greatly reduce the viability of *E. coli* and *S. aureus* cells over time. *E. coli* and *S. Aureus* when treated with SeNPs displayed a 60 % decrease in the capability of both Gram-positive and Gram-negative bacteria. These study findings revealed a complex potency of antibacterial activities of quercetin and acetylcholine coupled with SeNPs. Besides this, the latter exhibited a synergistically improved antibacterial reaction against the multi-drug resistant superbugs [109]. The elevated antibacterial activity of SeNPs is a result of compromised bacterial cell membranes' integrity, by increased intracellular production of ROS, and/or disturbance of the bacterial DNA structure upon passage into the cell. SeNPs also confine growth and biofilm establishment of *E. coli* and *S. aureus* [110].

5.5. Silver nanoparticles (AgNPs) as anti-microbials for gut health

Silver has a steady antimicrobial potential and has been utilized since ancient times. Silver in the arrangement of several compounds and Bahamas (ash obtained through incineration) has been used in Ayurveda to cure various bacterial infections since time immemorial. With time, as respective pathogenic bacteria are exhibiting antibiotic resistance, silver nanoparticles are the new hope to eliminate them. AgNPs have been extensively utilized as an efficient antimicrobial agent for fighting bacteria, fungi, and viruses [111]. Although the mode of action of AgNPs is still not very clear, AgNPs of minor diameter have a greater antimicrobial outcome than those of their colleagues with bigger diameter [111].

Silver ions are known to be positively charged and the physical properties of the Ag ion are vital for its antimicrobial activity by advantage of the electrostatic interaction between the negatively charged cell membrane of the microorganism and positively charged nanoparticles [112]. AgNPs intensify the membrane absorbency and incapacitate the respiratory system in Gram-negative bacteria like *E. coli* [113]. Choi et al. (2008) discovered that the Ag ion has an attraction for sulfur and nitrogen which impedes and/or interrupts protein assembly by attaching to thiol and amino groups [114]. Much previous research has additionally reported that silver nanomaterials are photocatalytic and can encourage the production of ROS [115]. Findings by Shahverdi et al. (2007) showed that AgNPs also possess synergistic antibacterial effects both on Gram-positive and Gram-negative bacteria after being dossed in combination with antibiotics [116].

In another study antibacterial activities displayed by AgNPs are to attach to the thiol clusters in enzymes, producing ROS, and unsettling the preserved bacterial respiratory chain in dissimilar types of bacteria. In addition, Agions can also interrelate with microbial DNA, thereby preventing growth by hindering DNA replication and cell division [117]. Fondevila et al. (2009) have reported widely on the antibacterial action of AgNPs in chickens and pigs [118]. Apart from demonstrating substantial antibacterial properties, it was proved that silver nanoparticles minimized the dangers of aflatoxin on the development and performance indices in broiler chickens suffering from experimental aflatoxicosis [119]. Table 3 shows nanominerals used as alternatives to antibiotics.

These days, there is a lot of interest in the possible application of silver nanoparticles in the animal production industry, especially as a toxicity analysis in place of antibiotics and chemotherapeutics. Silver (Ag) deposits were found in the brain, lung, liver, kidney, and testis of mice, according to Ref. [136]. In other, rat experiments, it is shown that the liver, kidneys, spleen, stomach, and small intestines all accumulated silver when 12 nm silver nanoparticles were administered once or more. Scholars concur that even in the absence of obvious pathomorphological abnormalities, nanosilver can be absorbed from the gastrointestinal tract into the bloodstream and cause organ toxicity and inflammatory reactions. Reports on the neurotoxicity of AgNPs are well documented in many research findings [137].

Researchers from Skaland associates examined the effects of administering AgNPs to rats over two weeks [138]. Their findings showed marked changes in the ultrastructure of the brain. They noticed a noticeable rise in the density of synaptic vesicles assembling in the middle of the presynaptic region as well as hazy synapse patterns.

6. Antibacterial nanomaterials and their mechanism of action

Metal and metal oxide nanoparticles have been shown to have a variety of antibacterial effects. Some proposed mechanisms include disruption of the cell wall and cytoplasmic membrane, production of ROS resulting in oxidative stress, enzymatic inhibition, changes in

Table 3
Nano minerals and their effects on microbes.

Metal nanoparticles	Microbes affected	Effect on microbes	Reference
Cu	*S. aureus*, *B. subtilis*, *E. coli*, *Micrococcus luteus*, *K. pneumoniae* and *Pseudomonas aeruginosa*	Inhibits the growth, DNA replication, induce membrane damage and generation of ROS	[93,120, 121]
Zn	*L. monocytogenes*	Inhibits the growth and is toxic to bacteria.	[122]
Zn	Salmonella	brane disruption and ROS production	[123]
Zn	*K. pneumonia*	Membrane disruption and ROS production	[124]
Zn	Streptococcus	Membrane disruption and ROS production	[125]
Zn	*E. Coli*	Growth inhibition, damage bacterial cell membrane, leakage of intracellular contents and eventually the death of bacterial cells	[126]
Zn	*S. aureus*	Higher antibacterial effects	[127]
Zn	*P. aeruginosa*	Generation of ROS, disruption of membrane permeability	[128]
Zn	*Bacillus subtilis*	Electrostatic interactions, morphological changes in the cell, increase in membrane permeability	[129]
Se	*E. coli* and *S. aureus*	Inhibition of growth, directly kills bacteria by changing cell permeability, attaches to the bacterial cell wall causing irreversible damage to the membrane	[109]
Se	*S. aureus*	Inhibition of growth	[130]
Ag	*S. aureus* and *Pseudomonas aeruginosa*	Generation of ROS, disrupting bacterial respiratory chain	[131,132]
Fe	*Pseudomonas aeruginosa*	Prevention of biofilm formation	[133]
Al	*E. coli*	Perforation and membrane disorganization, leading to cell death	[134]
Mg	*E. coli* and *S. aureus*	Prevents biofilm formation, inducing ROS, directly inhibiting essential enzymes of the bacteria	[135]

gene expression, and protein deactivation. One advantage of using NPs for antimicrobial applications is their multilevel mode of action, which makes bacterial resistance development much more difficult. Furthermore, NPs can act as drug carriers, delivering antibiotics directly to bacteria, and improving drug potency while limiting overall drug exposure [77].

Metal and metal oxide nanoparticles have been found to accumulate on the surface of bacterial cells, causing indentations or "pits" in the cell wall. This accumulation has the potential to penetrate the cell wall, causing structural damage to the membrane and, ultimately, cell death [139]. Bactericidal activity has been demonstrated for positively charged ions released by metal and metal oxide nanoparticles. The binding of positively charged ions with the negatively charged surface of bacteria, which typically contains carboxyl and phosphate groups, enhances this effect even more. This binding process is known as biosorption, and it can improve the NPs' bactericidal effect [77]. Aside from biosorption, electrostatic binding of metal and metal oxide nanoparticles to the bacterial cell wall can result in membrane depolarization, a change in membrane potential, and membrane integrity loss. This disrupts energy transduction and eventually leads to cell death [78]. Gram-positive bacteria, on the other hand, have a thick peptidoglycan layer that makes NP penetration into the cell more difficult. As a result, in these bacteria, NPs primarily interact with the bacterial surface [140].

By generating ROS with a strong positive redox potential, metal, and metal oxide nanoparticles can cause oxidative stress in bacteria. The ROS are produced either by the disruption of the respiratory chain or by the NPs themselves [141]. ROS can include hydrogen peroxide (H_2O_2), singlet oxygen (O_2), hydroxyl radical (OH), and superoxide radical (O_2). Different types of NPs produce different combinations of ROS. Silver (Ag) and copper (Cu) NPs, for example, can produce all types of ROS, whereas magnesium oxide (MgO) NPs only produce the superoxide radical, and zinc oxide (ZnO) NPs produce a combination of hydrogen peroxide and the hydroxyl radical [77].

ROS production, according to Malka et al. (2013), is a natural process caused by defects and vacancies in the crystal during the basic mechanism [142]. In a normal cell, there is a balance between the production and removal of ROS. When a cell is stressed, however, it produces an excess of ROS, which alters the permeability of the cell membrane and causes damage to bacteria [143,144]. ROS can be produced via a variety of mechanisms, including the photocatalytic hypothesis. When nanoparticles are exposed to energy greater than the band gap, electrons in the valence band are stimulated and transition to the conduction band, resulting in the formation of a hole in the valence band and the formation of highly reactive species on and within the material. ROS produced inside or outside the cell can disrupt the cell membrane via lipid oxidation, resulting in free radical production [145]. Gram-positive bacteria have a thick cell wall structure with a negatively charged surface, making oxygen radicals such as OH more difficult to penetrate. ROS can cause damage to macromolecules within the cell, resulting in lipid peroxidation, protein alterations, enzyme inhibition, and RNA or DNA damage. ROS production has antimicrobial properties, particularly in the case of silver (Ag) [146,147].

6.1. Silver NPs (AgNPs)

Although the precise mechanism of action is unknown, it makes understanding the interactions between bacterial cells and nanoparticles difficult. Nonetheless, current evidence suggests that AgNPs have diverse antibacterial mechanisms and attach to a wide range of targets. As a result, they disrupt multiple aspects of cell metabolism, making it difficult for bacteria to develop resistance to them [148,149]. AgNPs, act as a reservoir for silver ions released via oxidative dissolution [150,151].

The NPs then adhere to the negatively charged bacterial cell wall, resulting in pits or holes. This process causes the plasma membrane potential to depolarize and collapse, resulting in cytoplasmic leakage and increased cell membrane permeability. This facilitates NP entry and interaction with intercellular components, as described by Refs. [152,153]. This causes cytoplasmic contents to leak and the cell membrane to become more permeable. As a result, silver nanoparticles can enter cells and interact with intercellular components more easily [154–156]. A released Ag + ion can block the site where cytochrome 2 and b-cytochromes interact in the respiratory chain, inhibiting cellular respiration. Similarly, nanoparticles can disrupt cellular respiration by inhibiting cytochromes in the electron transport chain or by denaturing the 30-S ribosomal subunit, which prevents protein translation [109,143].

According to the second proposed mechanism, the production of ROS at the cell membrane can result in DNA replication damage, biomolecule destruction, and increased oxidative stress. AgNPs are also highly reactive to thiol, amino, and phosphate groups found in DNA, peptides, and enzymes. Nanoparticles can inhibit or damage DNA/RNA replication by inactivating enzymes, changing protein expression, and disrupting metabolic processes when they interact with these groups. Bacteria may eventually die because of irreversible damage. To summarise the interaction of silver nanoparticles with key biological components, AgNPs were proven to significantly harm bacterial cells [153,154,157,158]. The observed synergism is caused by the production of hydroxyl radicals and the degradation of protective factors, which results in a decrease in antibiotic concentration and a decrease in bacterial viability [159].

6.2. Gold nanoparticles (AuNPs)

The observed synergism is caused by the production of hydroxyl radicals and the degradation of protective factors, which results in a decrease in antibiotic concentration and a decrease in bacterial viability [160,161]. AuNPs are more potent against Gram-negative bacteria due to their easier incorporation into the bacteria [162,163]. Because gold nanoparticles may have a ROS-independent mechanism, they appear to be safer for mammalian cells [164].

6.3. Titanium dioxide NPs (TiO_2-NPs)

TiO_2NPs have photocatalytic properties that allow them to kill bacteria when exposed to UV light. This exposure produces ROS, which causes oxidative stress and damage to bacterial DNA, lipids, and proteins [165,166]. TiO_2NP nanoparticles have antibacterial

Table 4
Types of nanomaterials with their efficacy against bacteria.

Nanoparticles	Targeted Bacteria and Antibiotic Resistance	Antibacterial Mechanisms	References
Inorganic Nanoparticles			
Fe_2O_3-NP	• MRSA *K. pneumoniae* • MDR *E. coli* • MDR *Staphylococcus epidermidis* • MRSA *Pseudomonas aeruginosa* • Vancomycin resistant *Enterococcus* • *A. baumannii*, carbapenem resistant	• Disruption of cell walls through ROS • Lipid peroxidation • Intercalation between DNA bases • ROS generation • Inhibition of cell wall synthesis • Inhibition of cytochromes in the electron transport chain • Ribosome	[192,193]
AgNPs	• *P. aeruginosa* Carbapenem and polymyxin B-resistant • Carbapenem resistant • *Enterobacteriaceae* • *Klebsiella pneumoniae* • Extended spectrum beta-lactamase producing organisms	• Dissipation of proton gradient resulting in lysis • Increase in membrane permeability • Cell surface binding which causes lipid and protein deterioration • Bacterial membrane disintegration	[193,194]
ZnONPs	• *K. pneumoniae*, • *Enterobacter aerogenes*, • *ESBL*-producing *E. coli* • *MRSA* • *K. pneumonia* • *E. coli* • *Klebsiella oxytoca*	• Lipid and protein damage • Adsorption to cell surface • ROS production, disruption of membrane	[194]
CuNPs	• *A. baumannii* • MDR *E. coli*	• DNA degradation • ROS generation, • Cell membrane potential dissipation • Protein oxidation • Peroxidation of lipid	[194,195]
AuNPs	• *MRSA*	• The generation of cell wall apertures. • Loss of membrane potential • Decline in tRNA binding to ribosome subunit	[196]
TiO_2NPs	• *S. aureus* • *E. coli* • *Enterococcus faecium* • *P. aeruginosa*	• Adsorption to thecell surface • ROS generation	[192,194]
SiNPs	• MRSA	• Disruption of cell walls through ROS	[113]
MgONPs	• *S. aureus* • *E. coli*	• Alkaline effect • ROS generation • Electrostatic interaction • Lipid peroxidation	[192]
AlNPs	• *E. coli*	• Disruption of cell walls through ROS	[192,194]
SPIONS	• *S. aureus* • *E. coli*	• NO release • Production of ROS.	[197]
Organic Nanomaterials			
Poly-ε-lysine	• *S. cerevisiae* • *B. subtilis* • *B. stearothermophilus* • *B. coagulans* • *E. coli*	• Disrupt the cell wall and membrane integrity. •Destroy cell membranes or cell walls	[198]
Quaternary ammonium compounds	• *Pseudomonas* • *Pseudoalteromonas* • *Erwinia* • *Enterobacter*	• Interfere with the function of the cell membrane • Lysis, or destruction of the cell • Affects DNA • ROS release	[199]
N-halamine compounds	• *S. aureus* • *P. aeruginosa*	• Interfere with the function of the cell membrane • Complete inactivation of the bacteria	[92]
Quaternary bisphosphonium and ammonium	• *S.* aureus • *S.* epidermidis • *B. subtilis* • *E. coli*	• Inhibits the growth of bacteria • disruption of the cell division mechanisms	[200]
Fullerenes	• *E. coli* • *K. pneumoniae* • *E. faecalis* • *P. aeruginosa* • *S. aureus*	• Methicillin resistant • MDR	[201,202]
Composite-Based Nanomaterials			
Metal Matrix Nanocomposites	• *A. baumannii* • *S. aureus* • *E. coli*	• Inhibit the bacterial growth • Physical interaction	[203]

(*continued on next page*)

Table 4 (*continued*)

Nanoparticles	Targeted Bacteria and Antibiotic Resistance	Antibacterial Mechanisms	References
Polymer Matrix Nanocomposites	• *K. pneumonia* • *A. baumannii* • *S. aureus* • *E. coli* • *K. pneumonia* • MDR	• formation of irregular pores in the outer membrane of bacteria • Inhibit the bacterial growth • Physical interaction	[204]

properties in addition to photocatalytic properties, even when not exposed to UV light. In this case, the NPs adsorb on the bacterial cell surface and interact directly with the cell wall, causing membrane integrity to be compromised. The bacteria are eventually destroyed as a result of this disruption [167]. A mixture of TiO_2NPs with other metal nanoparticles can improve their antibacterial properties and combat bacterial infections [168–170].

6.4. Zinc oxide NPs (ZnONPs)

ZnONPs, like titanium dioxide nanoparticles, have strong photocatalytic properties. They produce ROS when exposed to UV light or even in the absence of UV light, which can inhibit DNA replication, cause protein denaturation, and disrupt cell membranes. As a result, the antibacterial effect is extremely potent [171,172]. Another mechanism of action for ZnONPs has been proposed, which involves the release of zinc ions, which then accumulate on the bacterial membrane via electrostatic forces. This buildup can disrupt transmembrane electron transport or prevent essential compounds from entering the cell, resulting in enzymatic inhibition, DNA damage, and mitochondrial damage. All of these effects inhibit bacterial growth and eventually lead to cell death [100,173,174].

A new mechanism of action for ZnONPs has been proposed, which involves altering energy metabolism within bacterial cells, resulting in an increase in pyrimidine biosynthesis, particularly uridine monophosphate biosynthesis, and carbohydrate metabolism, as well as a decrease in amino acid synthesis. This mechanism may explain why ZnONPs have greater antibacterial activity against *Staphylococcus aureus* than against *Escherichia coli* because *E. coli* does not require uridine for anaerobic growth [175,176].

6.5. Iron oxide NPs

Iron oxide nanoparticles (Fe_3O_4 NPs) have antibacterial properties because they dissolve metal ions, which then interact with bacterial cells. Metal ions can pass through the bacterial membrane and disrupt electron transfer, resulting in bacterial cell disruption. Furthermore, Fe_3O_4 NPs can produce ROS, which can damage bacterial DNA and proteins and cause cell death [77,177,178].

6.6. Platinum NPs

Platinum nanoparticles (Pt-NPs), like other metal nanoparticles, can diffuse through the bacterial cell wall and cytoplasmic membrane. Once inside the cell, they can cause the production of ROS, which causes DNA damage and cell accumulation during the S phase of the cell cycle. These effects eventually result in cell death [113,179].

6.7. Copper and copper oxide NPs

CuNPs and the ions they release can cause changes in shape and structure, as well as interact with the cellular membrane, reducing its electrochemical potential across the membrane. This change in potential can hurt membrane integrity and lead to cell death [180]. Furthermore, copper nanoparticles can produce ROS, which can cause mitochondrial damage, initiate lipid peroxidation, and damage DNA. The presence of Copper Oxide causes the formation of ROS, which can lead to DNA degradation or membrane disruption. These occurrences can impair essential enzymes, ultimately leading to cell death [181–183].; When Copper Oxide nanoparticles are present, the expression of critical proteins changes significantly, which has a significant impact on bacterial denitrification as well as other metabolic processes such as active transport and electron transfer [141,184].

6.8. Selenium NPs

The release of Selenium oxyanions from SeNPs can cause cell wall disruption or produce ROS that can react with thiol groups within the cell. These processes can produce superoxide radicals, which can lead to oxidative stress. Another possible mechanism for Selenium NP action is interference with intercellular adenosine triphosphate concentrations or depolarization/disruption of bacterial membranes. These events can hurt cell division and membrane transport, resulting in cytosolic content leakage [185].

6.9. Magnesium oxide NPs (MgONPs)

MgONP antibacterial activities are affected not only by particle size but also by the pH of the environment. High pH conditions can

damage the bacterial cell membrane, resulting in cell death [186–188]. MgONPs can also produce ROS on their surface, causing cell wall damage. This damage can cause intracellular contents to leak, eventually leading to cell death [189–191]. Table 4 elaborates details of some of the different types of nanomaterials and their efficacy.

7. Environmental impact of NPs

As noted by Ref. [205], a thorough grasp of the environmental harm that NPs cause requires a thorough understanding of their characteristics, including identification, physicochemical properties, emission pathways into the environment, and their impact on living organisms. One important factor influencing NPs' intrinsic toxicity is their ability to permeate different environmental media, including soil, water, and air. The number of NPs discharged into the biosphere is directly related to this effect. The hazards linked to the utilization of nanomaterials are contingent upon multiple mechanisms that govern their discharge into the surroundings, conveyance between sites and organisms, encompassing the food chain, and plausible metamorphoses they experience post-release [206]. Comprehensive studies covering the whole life cycle of nanomaterials are required to evaluate and quantify the amount released [207]. This study should start with the processes involved in producing nanomaterials and continue to include recycling and disposal strategies while considering how they are used and integrated into finished goods.

Depending on their nature, nanoparticles can be released as aerosols into the atmosphere, soil, and surface water. For example, particles dispersed into the atmosphere may eventually become incorporated into the soil. These nanoparticles can be aggregated, functionalized, bare, or embedded in a matrix. They can also be dispersed accidently or purposely throughout the environment, ending up in soil, water, and the atmosphere. These particles can be absorbed by living things or remain for long after they are released. Studies by Refs. [208,209] suggest that they may biodegrade, accumulate in the food chain, or present possible ecotoxicological hazards. The introduction of nanotoxicity in the natural environment occurs in several stages, such as the dispersal, emission, and influence on the aquatic life of nanosilver released from products. AgNPs may be harmful to human cell lines, according to research by AshaRani and colleagues, as shown by cytotoxicity, genotoxicity, and antiproliferative parameters [210]. This review delves into the ways that the environment alters the surface properties of AgNPs, including sulfidation, aggregation, and phase transformation, all of which increase their toxicity to aquatic life. Furthermore, another study revealed the detrimental effects of AgNPs on a variety of organisms, including terrestrial and aquatic life, plants, algae, fungi, vertebrates, and human cells like glioblastoma, lung fibroblast, and keratinocyte cells [211].

8. Biocides

A study revealed that AgNPs are detrimental to a variety of organisms, including plants, animals, algae, fungi, vertebrates, and human cells like lung fibroblast, keratinocyte, and glioblastoma [211]. Assessing environmental exposure necessitates several factors, including determining and measuring sources, assessing concentrations in the environment, examining potential bioaccumulation, and comprehending patterns of environmental release. According to their study, Colleset and colleagues found that antibacterial nanoparticles had a major effect on possible infections [212]. According to Kareem and colleagues' research, giving mice antibiotic nanoparticles topically or systemically had no negative effects. The use of tetracycline-chitosan nanoparticles effectively inhibited the growth of *E. coli* which was resistant to tetracycline. As noted by Ref. [3], it is noteworthy that nanoparticles derived from natural or organic materials and specifically engineered to target Gram-negative bacteria are highly preferred for feed applications. It is impossible to overestimate the significance of nanotechnology in the fight against foodborne illness; the scientific community uses it as one of its most important tools. Using hydrogels to stop germs from attaching to surfaces helps to eliminate pathogens and restrict their growth when added to animal feed in the form of nanoparticles. These hydrogels can also bind to viruses, which increases their ability to prevent disease.

It has been discovered that the molecular weight of the polymer and the polycation type influence the toxicity of cationic polymers. Mice were given unquaternized Poly[2-(Dimethylamino)ethyl Methacrylate (PDMAEMA) experienced hemolysis; therefore, it can only be used as an external biocide [212]. Furthermore, more investigation is required into the use of biocidal hydrogels and nano solutions for spreading across feed containers, pens, and thresholds [3].

9. Microbial resistance of nanomaterials

Antibiotic mechanisms of action are critical in determining the synergistic effects that may occur between different antibiotics and metal nanoparticles. Taking the information presented above into consideration, these mechanisms provide valuable insight into the potential enhancement of antibacterial activity. Combinations of antibiotics that cause cell membrane disruption, such as colistin, have been shown in studies to have enhanced antibacterial properties when combined with silver nanoparticles. NPs can boost colistin activity by disrupting the outer membrane and cell wall, allowing the antibiotic to penetrate and target the cytoplasmic membrane [213,214].

NPs have the potential to enhance the antibacterial effects of almost all antibiotics that disrupt cell wall synthesis (such as amoxicillin, ampicillin, cefotaxime, ceftazidime, meropenem, imipenem, and penicillin) and protein synthesis (such as amikacin, gentamicin, kanamycin, and neomycin). There were a few exceptions, such as amoxicillin, amikacin, and gentamicin, where not all combinations were evaluated in the same way by all authors. In general, bacterial resistance to antibiotics that inhibit cell membrane/protein/cell wall synthesis (such as beta-lactams) can be reversed when combined with AgNPs, even at lower concentrations [213,214].

AgNPs are thought to interact with porin channels and peptidoglycan on the surface of bacteria, causing cell wall disruption and penetration, allowing the antibiotic to be effective again. In the case of beta-lactam antibiotics, disruption of the cell wall and outer membrane may result in carbapenemase leaking out of the bacterial cell, decreasing its activity inside the periplasmic space and reversing the resistance mechanism. However, unlike antibiotics that act on cell membrane/protein/cell wall synthesis, glycopeptide antibiotics such as vancomycin could not be enhanced in all cases. This is because glycopeptide antibiotic resistance mechanisms frequently involve chemical changes at the target site, such as the conversion of D-alanyl-D-alanine to D-alanyl-D-lactate, which are difficult to overcome [213,214].

In cases where the mechanism of resistance is related to the cell wall, nanoparticles can aid antibiotic penetration by creating pits in the wall [215], This mechanism enables antibiotics to enter bacteria and bind to their normal binding sites. Antibiotics that inhibit folate acid synthesis (trimethoprim) and most cases tested with antibiotics that inhibit nucleic acid synthesis (ciprofloxacin) did not improve antibacterial activity. Nonetheless, some discrepancies in the results were discovered. Resistance to these antibiotics is typically caused by an irreversible chromosomal mutation that nanoparticles cannot easily reverse. The results for other nanomaterials, such as AuNPs and TiO_2NPs have not been tested as thoroughly as AgNPs [216]. Because only one bacterial strain was tested with a specific antibiotic, the results may be biased in some cases.

In general, gold nanoparticles have the potential to enhance the antibacterial properties of antibiotics that inhibit protein synthesis (gentamicin), nucleic acid synthesis (ciprofloxacin, levofloxacin, nalidixic acid, rifampicin), and cell wall synthesis (only glycopeptide antibiotics, vancomycin). Vancomycin and rifampicin's antibacterial properties were not enhanced in any of the bacterial strains tested. Amoxicillin, cefotaxime, and ceftriaxone were found to be more effective than methicillin, and the two tested bacteria for beta-lactam antibiotics that act on cell wall synthesis. Furthermore, the combination of titanium dioxide NPs with all tested antibiotics that act on cell wall/protein/nucleic acid synthesis, except nalidixic acid, overcame *S. aureus* bacterial resistance. It should be noted, however, that in these studies, only one author evaluated one bacterial strain [217]. Table 4 enlisted some of the nanoparticles used in multidrug resistance. In Table 5 some of the important nanoparticles acting against multidrug resistant pathogens are discussed.

10. Synergistic effects of nano antibiotics

Combining nanoparticles and antibiotics can have synergistic effects, increasing antibacterial activity and overcoming some of traditional antibiotic therapy's limitations. Here are some examples of synergistic effects observed when nanoparticles and antibiotics are combined.

10.1. Synergistic activity against antibiotic susceptible bacteria

It has been demonstrated that combining nanostructured materials with antibiotics improves their antibacterial effects at lower

Table 5
Nanoparticles against MDR (multi-drug resistance) pathogens and their mechanisms of action.

Types of nanoparticles	Targeted bacteria	Mechanisms of antibacterial actions	Reference
AgNPs	*E. coli*	• ROS generation	[218]
	E. faecalis, *S. epidermidis* (MRSE), *P. aeruginosa*, *S. aureus*	• Lipid peroxidation • Inhibition of cytochromes in the electron transport chain	[76]
	S. aureus, *P. aeruginosa*, *K. pneumoniae*, *B. cereus*, *S. typhimurium*	• Bacterial membrane disintegration • Inhibition of cell wall synthesis	[219]
	E. coli, *S. aureus* (MRSA), *S. Pneumoniae*	• Dissipation of proton gradient resulting in lysis • Adhesion to cell surface causing lipid and protein damage • Ribosome destabilization • Intercalation between DNA bases	[219]
AuNPs	*E. coli*, *K. pneumonia*	• Loss of membrane potential	[218]
	S. Bovis, *S. epidermidis*, *E. Aerogenes*	• Reduced ATPase activity • The decline in tRNA binding to ribosome subunit • Bacterial membrane disruption • Generation of holes in the cell wall • Evade multidrug efflux pumps • Disruption of the bacterial cell wall • DNA damage Disruption of the bacterial cell wall	[218]
ZnONPs	*E. coli*	• ROS generation and disruption of bacterial cell wall	[218]
	S. aureus, *P. aeruginosa*	• Enzyme inhibition • Lipid and protein damage	[220]
CuNPs	*E. coli*	• Reactive oxygen generation	[76,218]
	S. aureus, *S. epidermidis*	• Copper ions release and subsequently bind with DNA leading to the disorder of helical structure	[221]
	P. aeruginosa	• Dissipation of cell membrane potential	[76,218]
TiO_2NPs	*S. aureus*	• Release ions and react with the thiol group of proteins present on the bacteria surface • ROS generation and disruption of bacterial cell wall	[217]

concentrations of both NPs and antibiotics. Numerous scientific papers have reported on the synergistic effects of metal and metal oxide nanoparticles combined with antibiotics, which resulted in increased antibiotic activity and reduced nanoparticle toxicity to mammalian cells. Several times, the current state of knowledge regarding this synergistic activity has been summarized [141,177,186].

However, as reported in several reviews, the majority of studies reporting synergistic effects between metal and metal oxide NPs and antibiotics were conducted on antibiotic-sensitive bacteria. The disc diffusion or microdilution methods were typically used to assess synergistic effects. The microdilution method determines the fractional inhibitory concentration (FIC) index, which allows for the determination of whether the effect is synergistic, additive, indifferent, or antagonistic. The disc diffusion method, on the other hand, does not allow for the quantification of the synergistic effect, making it difficult to distinguish between synergistic and additive, indifferent, or antagonistic effects. Furthermore, silver NPs have been used in the majority of experiments investigating synergistic effects between antibiotics and metal and metal oxide NPs [222,223], and AuNPs [224,225].

The synergistic effects of metal and metal oxide NPs have been studied not only with silver, but also with other NPs with antibacterial properties, such as copper [226–228], titanium dioxide [139,217], and zinc oxide [140,229]. The interaction of silver nanoparticles with various antibiotics has been extensively studied, including antibiotics with various modes of action and chemical structures, such as those that inhibit protein synthesis (aminoglycosides), cell wall synthesis (beta-lactams and carbapenems), nucleic acid synthesis (quinolones), and those that disrupt the cytoplasmic membrane (polymyxins). AgNPs have been shown to have synergistic effects when combined with beta-lactams (ampicillin, methicillin, penicillin), glycopeptides (vancomycin), quinolones (ciprofloxacin), sulfonamides (trimethoprim), aminoglycosides (amikacin, gentamicin, kanamycin, streptomycin), macrolides (erythromycin), and tetracyclines [223,230], Synergistic effects of AgNPs and antibiotics have been shown in studies to be effective against a wide range of Gram-negative and Gram-positive bacteria. The use of AgNPs improves the antibacterial activity of antibiotics at very low concentrations, typically tens to hundreds of ppm. This is advantageous because it reduces the toxicity of the nanoparticles. After all, low concentrations of silver are not toxic to mammalian cells or humans. AuNPs have been shown in studies to have synergistic effects when combined with antibiotics against sensitive Gram-negative and Gram-positive bacteria. Several studies have shown that when combined with meropenem against *Acinetobacter baumannii* [224], and amoxicillin and streptomycin against *S. aureus* and *E. coli* [225], AuNPs have high synergistic effects. Bismuth NPs, on the other hand, have only been studied for synergistic effects in combination with antibiotics that inhibit nucleic acid synthesis (fluoroquinolones), and only ciprofloxacin combined with bismuth NPs enhanced antibacterial activity against *K. pneumoniae* [231]. CuNPs have been shown to improve antibiotic efficacy against a variety of bacteria, including *B. subtilis*, *E. coli*, and *S. typhimurium*. This synergistic effect was observed at concentrations of CuNPs ranging from 20 to 50 mg/L, depending on the antibiotic and bacterial strain used. Antibiotics like ampicillin, amoxicillin, ciprofloxacin, and gentamicin all performed better when combined with copper nanoparticles [226].

Fluoroquinolones norfloxacin and ofloxacin have been used in combination with ZnONPs at concentrations ranging from 30 to 80 mg/L [229], or β-lactams (cephalexin, ceftriaxone, cefotaxime) [232]. Tio_2NPs have been studied as a potential antibacterial agent in combination with streptomycin to improve efficacy against Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. The combination demonstrated improved antibacterial activity against *K. pneumoniae*, *S. typhimurium*, *E. coli*, and *S. aureus* [233].

Table 6
Examples of biocompatible nanomaterials for healthcare applications.

Nanomaterial	Respective Nanomedicine	Biomedical Applications	Properties	References
AuNPs	Verigene	In vitro studies	Genetic	[235]
	Nanogoldhn nm, mmv, or colloid Au NPs	Enhanced bioimaging. Loading and releasing agents for Drugs.	Optoelectronic features due to Controlled Surface and band positions.	[236]
	Aurimm une	Anticancer	Anticancer impacts	[237]
AIE-active fluorogen-loaded BSA NPs	Fluorogen, 2-(2,6,bis((E)-4-(phenyl(4-(1,2,2-triphenylvinyl)-[1,1 biphenyl]4-yl)amino)styryl)-4Hpyran-4-ylidene)malononitrite(TPE-TPA-DCM	advanced uptake tendency for cancer cells and in vitro and in vivo studies	Improved penetrability with good stability	[238]
Nano-shell	Auro-shell	Aeroshell Semiconductor	Neck and head targets	[239]
Quantum-dots	Qdots, EviTags	In vitro studies	Tumor-based cell studies	[240]
Semiconductor	Nanoco, CrystalPlex, cytodiagnostics	Enhanced Fluorescence study	Molecular sensing inside tissue cells	[77,241]
Self-assembled chitosan (CHI) and modified lecithin (ML)	Biosuitable and stable nanosystems	Several applications, such as reversible hemostatic activities in wounds, nanocarriers for drugs, etc.	Higher encapsulation performance with strong ionic nature, solubility, or lyophilized solid or rigorous colloidal system	[242]
Targeted polymer NPs loaded with (−) epigallocatechin 3-gallate (EGCG	Chemotherapeutic markers	Stronger anticancer for prostate cancer (PCa)	Marker for Prostate specific membrane antigen (PSMA	[243]

10.2. Synergistic activity against antibiotic-resistant bacteria

It is important to note that all the studies demonstrating strong synergistic effects of metal and metal oxide nanoparticles with antibiotics were conducted on antibiotic-resistant bacteria. While these experiments are important for demonstrating the ability of nanoparticles to enhance antibiotic antibacterial properties, they are relatively unnecessary and insignificant because antibiotics have already been shown to effectively combat bacteria. The true importance of improving and restoring antibiotic effects lies in the treatment of antibiotic-resistant bacteria, which pose a significant challenge in the treatment of bacterial infections and can lead to increased mortality rates. As a result, the focus of this review will be on investigating potential methods of overcoming bacterial resistance by investigating the synergistic effects and enhancement of antibiotic antibacterial activity when combined with nanomaterials against antibiotic-resistant bacteria. Furthermore, this discussion will delve into the links between antibiotic mechanisms of action, bacterial resistance mechanisms, and various types of nanostructured materials, as well as how they influence the resulting synergistic effects. We will specifically investigate how the antibacterial activity of several antibiotics is enhanced when they are combined with silver [213,214,230], gold [216,234], and TiO_2NPs [217].

Current research has only looked at the effectiveness of combining antibiotics with silver NPs against resistant Gram-positive and Gram-negative bacteria that are resistant to antibiotics primarily (naturally) or secondarily (via genetic mutations or gene transfer from other bacteria). Antibiotics-enhanced antibacterial activity when combined with silver nanoparticles has only been studied against resistant bacteria. When it comes to secondarily resistant bacteria, however, researchers have investigated the synergistic effects of antibiotics combined with silver, gold, and TiO_2-NPs [233]. Clinical Applications of various nanomaterials used in healthcare applications are tabulated in Table 6.

11. Future perspectives

While nanotechnology has shown promising results in the treatment of bacterial infections in monogastric animals, it should be noted that it is not yet a replacement for antibiotics. For decades, antibiotics have been the primary treatment for bacterial infections in animals, and their use has contributed to improved animal health and productivity. However, antibiotic overuse and misuse have resulted in the emergence of antibiotic-resistant bacteria, posing a significant threat to both animal and human health. As a result, there is an increasing demand for alternative strategies to combat bacterial infections in animals, and nanotechnology may provide a potential solution. Nanotechnology-based approaches may be used alongside antibiotics in the future to improve efficacy and reduce the risk of antibiotic resistance. The nanotechnology-based approaches may provide a long-term alternative to antibiotics, especially when antibiotics are ineffective or unavailable. Further research is needed, to design nanomaterials that deliver antimicrobial agents precisely to the site of infection or colonization within the animal's body. However, nanomaterials can be engineered to stimulate specific immune pathways or enhance the innate immune system's ability to combat pathogens. This will not only reduce the reliance on antibiotics but also promote the animals' overall health and resilience to infection. By leveraging the full understanding of nanotechnology's potential in treating bacterial infections in animals, including its safety, efficacy, and cost-effectiveness. Furthermore, to ensure safe and responsible use of nanotechnology in animal health, regulatory bodies must establish clear guidelines.

12. Conclusion

In conclusion, the use of nanomaterials-based approaches as a substitute for antibiotics holds promising results. These innovative approaches offer potential solutions to mitigate antibiotic resistance, improve targeted delivery, enhance treatment efficacy, they also raise concerns regarding safety, regulatory approval, cost-effectiveness, and the potential for unintended consequences such as nanotoxicity and resistance development. While moving forward, further research efforts are needed to comprehensively evaluate the efficacy, safety, and long-term impact of nanomaterials in animal health.

Funding

The authors also extend their appreciation to the Deanship of Scientific Research at King Khalid University (KKU) for funding this research through the Research Group Program Under Grant Number: (R.G.P.2/572/44) and Polyfunctional particles to reduce zinc and antibiotics in weaned piglets (QL24010214).

Ethics approval and consent to participate

Experiments on animals were not provided.

Consent for publication

We consent to the publication of the manuscript.

Data availability statement

Experimental data were not used in the study.

CRediT authorship contribution statement

Abdul Qadeer: Writing – original draft, Formal analysis. **Aamir Khan:** Writing – original draft, Resources. **Noor Muhammad Khan:** Writing – original draft, Conceptualization. **Abdul Wajid:** Visualization, Software, Resources. **Kaleem Ullah:** Writing – original draft, Validation. **Sylvie Skalickova:** Supervision. **Pompido Chilala:** Writing – original draft. **Petr Slama:** Supervision, Formal analysis. **Pavel Horky:** Supervision, Formal analysis. **Mohammed S. Alqahtani:** Writing – review & editing, Validation. **Maha Awjan Alreshidi:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Pavel Horky reports financial support was provided by Mendel University in Brno. Pavel Horky reports a relationship with Mendel University in Brno that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

Abbreviation

AGPs: Antimicrobial growth promoters, **Ag:** Silver, **AgNPs:** Silver nanoparticles, **AuNPs:** Gold Nanoparticles, **AlNPs:** Aluminum Nanoparticles, **β-lactams:** Beta-lactams**, *B. cereus:*** *Bacillus cereus,* **CeO_2:** Ceric Oxide, **CuO:** Copper oxide, **Cu:** Copper, **CuNPs:** Copper nanoparticles**, *E. coli:*** *Escherichia coli,* ***E. faecalis*****:** *Enterococcus faecalis*, **ELISA:** Enzyme-linked immunosorbent assay, **ESBL:** Extended Spectrum Beta-Lactamase, **Fe:** Iron, **FIC:** Fractional inhibitory concentration, **GIT:** Gastrointestinal tract, **H_2O_2:** Hydrogen peroxide, **H5N1:** Avian influenza viral diseases, ***K. pneumoniae:*** *Klebsiella pneumoniae,* ***L. fermentum:*** *Lactobacillus fermentum,* **MRSA:** Methicillin-resistant *Staphylococcus aureus*, **MDR:** Multi-drug resistant, **Mg:** Magnesium, **MgO:** Magnesium oxide, ***M. bovis*****:** *Mycobacterium bovis*, **NIM:** nano insulation material, **nm:** nanometer**, NMs:** Nanomaterials, **NA-NOSE:** nano artificial nose, **NPs:** Nanoparticles, **NGPs:** non-antibiotic growth promoters, ***P. fluorescens*****:** *Pseudomonas fluorescens,* **PCR:** Polymerase Chain Reaction, **O2:** Oxygen, **OH:** hydroxyl radical, O_2, superoxide radical, **PtNPs:** Platinum nanoparticles, **PLGA:** Poly lactic-*co*-glycolic acid, **ROS:** Reactive oxygen species, ***S. aureus:*** *Staphylococcus aureus***, SeNPs:** Selenium nanoparticles, **Se:** Selenium, **Ag:** Silver, **SnO_2:** Stannic Oxide, **TiO_2:** Titanium dioxide, **TiO_2NPs:** Titanium dioxide nanoparticles **Zn:** Zinc, **ZnONPs:** Zinc oxide nanoparticles.

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