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Literature review

Applications of metallic nanoparticles in veterinary science

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ABSTRACT

Nanoparticles (NPs) are generally less than 100 nm in size and originate either naturally or through human activities. According to their constituent elements, NPs exhibit unique and specific functions. In veterinary science, metallic NPs are considered revolutionary and an innovative tool that ushered in a new era in the transformation of drug and vaccine vehicles, diagnosis and treatment of infectious and degenerative diseases, improvement of the zootechnical aspects of animal breeding and reproduction, and innovations in the tools involved in safety monitoring of food products from animal origin. In this review, we focused on studies that highlighted the applications of metallic NPs in veterinary science, thereby providing the current holistic view on the scope and limitations of nanotechnology in different areas of veterinary science.

Keywords: Food safety; nanobiotechnology; nanomaterials; animal health (*Sources: FAO, USDA*).

RESUMEN

Las nanopartículas son materiales que se encuentran a una escala nanométrica menor a 100 nm, se originan de forma natural o por la intervención del hombre y de acuerdo con los elementos que las constituyen adquieren funciones únicas y específicas. En las ciencias veterinarias las nanopartículas metálicas son consideradas una herramienta revolucionaria e innovadora, que permiten entrar a una nueva era en la transformación de los vehículos de medicamentos y vacunas, en el diagnóstico y tratamiento de enfermedades infecciosas y degenerativas, además de mejorar los aspectos zootécnicos de crianza y reproducción de los animales e innovar las herramientas en la vigilancia de la inocuidad de los alimentos de origen animal. En esta revisión se analizaron estudios enfocados en las aplicaciones de las nanopartículas metálicas en las ciencias veterinarias, lo cual brinda un panorama actual de los alcances y limitaciones en el uso de estas herramientas nanotecnológicas en las diferentes áreas del conocimiento veterinario.

Palabras clave: Inocuidad alimentaria; nanobiotecnología; nanomateriales; salud animal (*Fuentes: FAO, USDA*).

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INTRODUCTION

Nanotechnology deals with the study of nanomaterials (1) and bionanotechnology studies the effects of interactions between nanomaterials and living beings. Bionanomedicine, on the other hand, is oriented toward the use of these nanomaterials in biomedical aspects (2,3).

Generally, the size of the nanoparticles (NPs) ranges between 1 and 100 nm in the nanometric scale; however, some authors have reported NPs of sizes up to 1,000 nm (1, 4). Materials at the nanometric scale acquire unique physicochemical properties compared to those of the original material (5). The properties of the nanomaterials depends on their constituting elements (4).

The differences in properties between the nanomaterials and their corresponding original materials may stem from two effects. First is the surface effect, attributed to the fact that the atoms of nanomaterials are less stable; hence, they require less energy to bind than the atoms in the source material. Second is the quantum effect; when nanomaterials reach a nanometric scale, their behavior is similar to the properties of an individual atom (6).

According to their origins, NPs are classified as naturally occurring NPs, which originate from organic, mineral, and anthropogenic NPs, produced by human activity during some industrial processes (7).

NPs can be also classified according to their composition. Carbon-based NPs are the most predominant types of NPs. Metal-based NPs made of different heavy metals (7) can be further grouped into four sub-categories, namely, metal NPs (0D), metal wires and rods (1D), metal sheets and plates (2D), and metal nanostructures (3D) (8). Dendrimer-based NPs are formed by synthetic polymer macromolecules (peptides, lipids, polysaccharides). Furthermore, composite NPs are combinations between similar NPs or NPs with different sizes (7).

Metal NPs have different mechanisms of action on eukaryotic and prokaryotic cells. They cause damage to the cell wall and membrane surface and induce cytotoxicity by generating reactive oxygen species (ROS) and the release of free radicals, which damage the intracellular structures (mitochondria, vacuoles, ribosomes) and biomolecules (proteins, lipids, carbohydrates, DNA). In addition, they interfere with cell division and modulate the signal transduction pathways involved in microbial growth and cell activity. Although the various mechanisms of action of metallic NPs may be beneficial in combating pathogens, they also pose a considerable risk to the host (7,9).

Currently, in veterinary science, several nanomaterials are being evaluated as vehicles for medicines and/or vaccines in the development of diagnostic techniques and treatments for various diseases. Their applications in the improvement of livestock productivity and reproduction and in innovations related to safety, which confer added value to food products obtained from animal origin are also being tested (10). The commonly studied nanomaterials in veterinary science are metallic NPs, such as silver NPs (AgNPs) (11), gold NPs (AuNPs) (12), platinum NPs (PtNPs), copper NPs (CuNPs) (13), selenium NPs (SeNPs) (14), iron oxide NPs (Fe_2O_3NPs and Fe_3O_4NPs) (15), titanium dioxide NPs (TiO_2NPs) (16), and zinc oxide NPs (ZnONPs) (17).

Metallic NPs have numerous advantages; they can be synthesized and modified with appropriate functional groups that allow them to bind to drugs, antibodies, ligands and active substances (18). Given the multiple beneficial characteristics of NPs they are considered important in the biomedical field (19), although a number of them also demonstrate potential risks to the health of animals and environment. Therefore, the objective of this review was to analyze the scientific advantages and limitations in the use of metallic NPs in different areas of veterinary science.

Applications in veterinary medicine

A wide range of metallic NPs have been evaluated in veterinary medicine for the treatment of bacterial, fungal (15), parasitic (20), and viral (21) infectious diseases and non-infectious diseases, such as neoplasms (22). In addition, research on metallic NPs focuses on improving the anti-inflammatory responses and healing processes (23), vaccine development, drug release, innovation in the diagnostic methods for detection of biomolecules (DNA, lipids, proteins, metabolites), and for identification of pathogens and adulterants in food products (Figure 1) (24, 25).

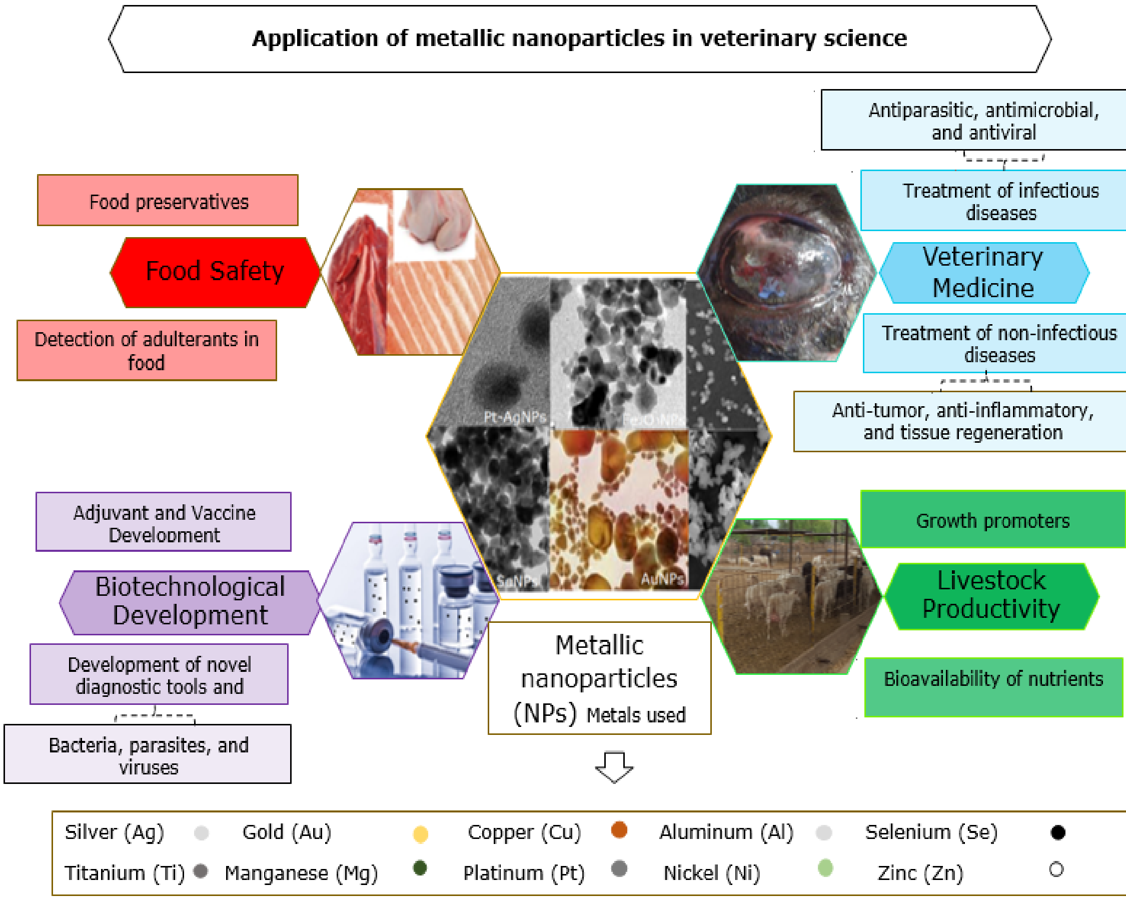

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Figure 1. Applications of metallic nanoparticles in different areas of veterinary science.

Antiparasitic properties of metallic nanoparticles

Various metallic NPs have been produced, characterized, and evaluated against endoparasites and ectoparasites causing disease in both terrestrial and aquatic animals (26-34). AgNPs (15-25 nm in size and spherical shape) synthesized with *Azadirachta indica* were evaluated *in vitro* against the larvae and adult forms of *Haemonchus contortus*, a common parasite of sheep and goats. AgNPs at a concentration of 1 µg/mL inhibited the hatching of *H. contortus larvae* and induced death of adult parasite at a concentration of 7.89 µg/mL. These findings demonstrated the anthelmintic properties of AgNPs (26).

The antiparasitic and cytotoxic effects of AuNPs (11-14 nm in size and spherical shape) were studied against the endoparasite *Heterosporis saurida,* which infects aquatic animals, such as lizard fish (*Saurida undosquamis*). AuNPs exhibited sporicidal activity but lacked cytotoxic effect, when tested on eel kidney epithelial cell line (EK-1). These findings suggested that AuNPs could be effective antimicrosporidial agents (27). A similar study that evaluated two types of AgNPs obtained using different synthesis methods (ARGOVIT with size of 35 nm and UTSA with size of 1-3 nm) against the egg and adult phases of *Cichlidogyrus* spp. Although both the AgNPs were reported to be effective against the parasite, AgNPs of UTSA were more effective, with 100% ovicidal and adulticidal effects at a concentration of 36 µg/L (28). The two studies mentioned above laid the foundations for further research on the use of metallic NPs for managing parasitic infections in fishes.

With regards to ectoparasites in fish, *in vitro* and *in vivo* studies involving various metallic NPs (AgNPs, AuNPs, and ZnONPs) have shown that the NPs exhibit protozoacidal effect against *Ichthyophthirius multifiliis, in vitro,* and AgNPs and ZnONPs were more effective than AuNPs.

Furthermore, *in vivo* studies on rainbow trout (*Oncorhynchus mykiss*) revealed AgNPs to be most effective against *Ichthyophthirius multifiliis* (29).

New ways are currently being sought to control ectoparasites that affects livestock productivity (20,30) and are responsible for transmitting various diseases to both humans and animals (31). ZnONPs (20-65 nm in size with spherical and hexagonal forms) synthesized with *Lobelia leschenaultiana* were evaluated *in vitro* against *Rhipicephalus microplus,* a tick, which affects cattle. The NPs exhibited 100% tick killing effect at a concentration of 8 µg/mL (20). AgNPs (25-60 nm in size and spherical in shape) synthesized with *Mimosa pudica* were also tested against *R. microplus* larvae; tick killing effect was reported at a concentration of 8.98 mg/L (32).

In another study, different concentration of AuNPs, AgNPs, CuNPs, NiNPs, ZnONPs, and TiO_2NPs were evaluated to control the different stages of the life cycle of mosquitoes belonging to the order Diptera, such as *Aedes aegypti*, *Anopheles stephensi*, and *Culex quinquefasciatus*. These mosquitoes are important vectors in human and animal diseases. Results revealed all the NPs to exhibit biocidal effect (ovicidal, pupicidal, larvicidal, and adulticidal) in every mosquito species (31). To prevent myiasis in cattle, ZnONPs synthesized with *Lobelia leschnaultiana* have been evaluated *in vitro* against the larvae of *Lucilia sericata.* ZnONPs showed a larvicidal effect at a concentration of 0.78 mg/L (33). TiO_2NPs (25-110 nm in size and irregular shape) synthesized with *Catharanthus roseus* have also been tested against *Hippobosca maculate,* a blood sucking fly. TiO_2NPs demonstrated larvicidal and adulticidal effects at a concentration of 7.09 mg/L (16).

For the treatment of pediculosis in humans and sheep, *in vitro* trials conducted using AgNPs (59.52 nm size and spherical shape) synthesized with *Lawsonia inermis* revealed its biocidal effects against *Pediculus humanus capitis* and *Bovicola ovis* at concentrations of 1.33 mg/L and 1.41 mg/L, respectively (34). Furthermore, TiO_2NPs showed the same effect against *B. ovis* at a concentration of 6.56 mg/L (16).

Although previous studies have proposed metallic NPs as an alternative for managing parasitic infections in aquatic and terrestrial animals, they also demonstrated the cytotoxic and genotoxic risks associated with the use of NPs owing to the induction of apoptosis and tissue necrosis by the NP-induced ROS. The cellular damage induced by NPs depend on several factors, such as the efficacy of antioxidant mechanisms, efficiency of the DNA repair systems, apoptotic propensity, cellular resistance, and the characteristics of the NPs themselves, namely size, shape, surface charge, surface coating, solubility, concentration, mode of entry, and stability (16, 21, 26,27,28,29,30,31,32,33,34).

Antimicrobial and antifungal properties of metallic nanoparticles

One of the alternatives that could be used to avoid the indiscriminate use of antimicrobials is Fe_2O_3NPs (80 nm in size) obtained by biological synthesis with *Candida albicans*. These NPs demonstrated antimicrobial effects against *Trichophyton verrucosum*, *T. mentagrophyte,* and *Dermatophilus congolensis,* which cause dermatological diseases in cattle (15). Furthermore, ZnONPs (60 nm in size and hexagonal shape) have also shown antimicrobial and antifungal effects against *T. mentagrophyte*, *Microsporum canis*, *C. albicans*, and *Aspergillus fumigatus* (35).

AuNPs, AgNPs, CuNPs, and PtNPs have been tested *in vitro* against the microorganisms causing bovine mastitis. The results of these studies revealed AgNPs and CuNPs to be effective against *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus uberis, C. albicans,* and *C. krusei* (13). In a similar study that focused on the causal agents of mastitis in goats, it was determined that AgNPs (1-21 nm in size) possess antimicrobial activity against multi-resistant strains of *S. aureus* and *Pseudomonas aeruginosa*. These effects are produced by the generation of ROS and malondialdehyde (MDA), causing the loss of proteins and structural sugars that make up the cytoplasm and cell membrane (36).

AgNPs (10 nm in size and spherical shape) used in the treatment of endometritis and metritis in dairy cows associated with multi-drug resistant strains of *Prevotella melaninogenica* and *Arcanobacterium pyogenes,* demonstrated inhibition of bacterial development and biofilm formation; therefore, they could constitute an alternative treatment for diseases affecting the reproductive tract of dairy herds (37). *In vitro* studies have shown that AuNPs (25 nm in size and spherical shape) combined with laser exhibit an inhibitory effect on *Corynebacterium pseudotuberculosis,* which causes caseous lymphadenitis in sheep and goats (38). AgNPs (≤100 nm in size) inhibited the development of multi-drug resistant *Moraxella ovis* obtained from clinical cases of sheep keratoconjunctivitis at a concentration of 10.87 μg/L (39). AgNPs (15-35 nm in size) synthesized with *A. indica* and functionalized using vegetable oils were bactericidal against *E. coli* and *S. aureus* and fungicidal against *A. fumigatus* and *Aspergillus niger.* all these pathogens are of clinical interest in humans and animals (40). The antimicrobial activities of AgNPs and silver nanowires (Ag NWs) synthesized with *Camellia sinensis* were also evaluated against *E*. coli and *S. aureus*. The results of these studies suggested that Ag NWs have a high inhibitory capacity against *S. aureus,* and Ag NWs were effective against *E. coli* at a concentration of 25.8 mg/mL (41).

AgNPs (18 nm in size) inhibited the growth of bacterial pathogens affecting fish, such as *Streptococcus iniae*, *Lactococcus garvieae*, *Yersinia ruckeri*, *and Aeromonas hydrophila* (42). In a similar study, commercial (C)-ZnONPs and C-AgNPs (size 100 nm), and AgNPs (11-39 nm in size and spherical shape) were evaluated against *A. hydrophila*, *Aeromonas salmonicida* subsp. *salmonicida*, *Edwardsiella ictaluri*, *Edwardsiella tarda*, *Francisella noatunensis* subsp. *orientalis*, *Yersinia ruckeri,* and *Aphanomyces invadans*. Results of these studies revealed that all NPs demonstrated antimicrobial activity. However, ZnONPs were the only ones to inhibit *Y. ruckeri*. Furthermore, in this study, AgNPs showed less cytotoxic effects on the cell lines used (43).

Antiviral properties of metallic nanoparticles

AgNPs (≤100 nm in size) stabilized with polyvinylpyrrolidone (PVP) diminished sequelae in dogs with canine distemper, with or without neurological signs. No signs of treatment toxicity was reported (21). Another study evaluated the *in vitro* effects of MgONPs (≤ 50 nm in size) against foot-and-mouth disease virus (FMDV). Inhibitory effects of the nanoparticles were reported at the adhesion and cellular penetration stages of the virus (44).

Anti-tumor properties of metallic nanoparticles

From an epidemiological point of view, the rising frequency of neoplastic diseases has resulted in an increase in mortality of livestock. Hence, *in vitro* and *in vivo* studies are being conducted to evaluate the effects of AuNPs with glutathione (Au-GHS) and in combination with doxorubicin Au-GHS-Dox in the treatment of feline fibrosarcoma. These NPs exhibited an apoptotic effect on three (FFS1WAW, FFS1, and FFS3) of the four tumor cell lines evaluated (23,45). An *in vivo* study on felines showed tumor size reduction with minimal bioaccumulation in the liver, spleen, kidney, and heart. Furthermore, normal functions or blood concentrations of blood urea nitrogen (BUN), aspartate aminotransferase (AST), or alanine aminotransferase (ALT) were unaltered (46).

Fe_3O_4NPs direct inoculated for the treatment of mammary gland adenocarcinoma in felines reduced the size of the tumor mass. Cytological studies revealed that the tumor cells massively endocytosed the magnetic NPs eventually causing cell death (47). It was also observed that reduced graphite-silver oxide (rGO-Ag) NPs synthesized with *Tilia amurensis* lysed the ovarian cancer cell line A2780 (48).

Anti-inflammatory properties and healing processes

The regeneration and healing effects of AgNPs synthesized with *A. indica* and functionalized using vegetable oils have been evaluated in rabbit ears. Results revealed a faster healing with AgNPs than with conventional antibiotic and anti-inflammatory treatments (40). The direct application of 90 μM AgNPs solution (14.5 ±1.2 nm in size) in the peritoneal cavity before surgical closure of the abdomen in mice reduced the peritoneal adhesion and controlled the inflammatory process. Furthermore, immunohistochemistry revealed a decrease in the expression of interferon gamma (IFN-γ) in the peritoneal tissue samples. In addition, these NPs also decreased the expression of tumor necrosis factor alpha (TNF-ɑ), an important pro-inflammatory cytokine, in the macrophage cell lines of mice, RAW264.7 and J774.1 (23).

Zootechnical aspects and food safety

Application of metal NPs in livestock productivity and food safety focus on improving different aspects of animal nutrition (from food intake to nutrient uptake and utilization), reproduction, traceability of animal products, and food biosafety (49). For detecting various compounds that alter food safety, such as aflatoxin, mycotoxins; bacteria that cause foodborne illness (ADI) (*Salmonella*, *E. coli* 0157:H7, *Campylobacter jenuni);* bacterial toxins, such as choleric toxin; chemical adulterants (melamine, oxalates, benzoic acid); and antibiotic residues (chloramphenicol and penicillin) (50).

AgNPs used as an antimicrobial additive in drinking water to promote growth in fattening poultry, showed no effect on growth, metabolic changes, or in the composition of the intestinal microbiota (51). In contrast, inoculation of AgNPs alone and in combination with essential amino acids, such as threonine, and non-essential amino acids, such as cysteine, in the air sac of the egg during the embryonic development of chickens, improved their immune status without altering their development (52).

SeNPs used for the treatment of selenium deficiency in small ruminants improved the availability and absorption of this mineral in the abomasum and duodenum (53). In addition, the implications of SeNPs in iron homeostasis were evaluated through the expression of transferrin and transferrin-binding proteins, which allow the uptake of iron and determine the plasma iron concentration (14).

Currently, new alternatives are being sought to improve or replace some of the existing food preservatives. In this regard, studies were carried out to compare the antibacterial properties of zinc oxide (ZnO) and ZnONPs. Results of these studies revealed that ZnONPs were effective against *Salmonella typhimurium*, *S. aureus,* and *E. coli*, suggesting that these NPs could be used as preservatives. However, studies are warranted to evaluate the nanotoxicological risks of these NPs (54). A similar study evaluating the antifungal effects of Fe_2O_3NPs (45 nm in size) and Fe_3O_4NPs (9 nm in size) against *Aspergillus flavus,* isolated from poultry feed*,* revealed Fe_2O_3NPs to exhibit greater inhibitory effect than Fe_3O_4NPs (55).

The electrocatalytic properties of AuNPs were used to develop a system for the detection of *E. coli* O157:H7 in ground meat and tap water samples. Magnetic beads conjugated with an antibody against *E. coli* O157:H7 (MBs-pECAb) and double marking with a secondary antibody (AuNPs-sECAb) using the electrocatalytic properties of AuNPs were used in the chronoamperometry system for the detection and quantification of *E. coli*. The system detected a low bacterial concentration of 10^2-10^5 colony forming units (CFU)/mL in 91.3% and 94.8% of meat and tap water samples. The speed and simplicity of the technique, indicates the potential of the system for application in other food and water sources (56).

In order to develop new methods for detecting adulterant compounds in food, studies are being carried out with AuNP probes (10, 40 and 80 nm in size) stabilized using trisodium citrate for the detection of melanin in raw milk (57)exploiting the selective binding of gold nanoparticles (AuNPs. Furthermore, for the detection and recovery of mycotoxins in food, such as aflatoxin B1 (AFB1) and zearalenone (ZEN), magnetic Fe_2O_3NPs (100 and 200 nm in size) functionalized using amine groups and monoclonal antibodies are being used. This new system allows recovery of about 90-92% of AFB1 and 81-88% of ZEN in corn products and other food products (58).

Development of adjuvants and vaccines

In the course of developing new vaccines and adjuvants that stimulate cellular immune response against intracellular microorganisms and tumor cells, AuNPs supported by ultra-spheres of graphene oxide and shielded with ovalbumin (UsGO-Au@OVA) have been tested. These NPs stimulate the cellular immune response through the secretion of TNF-α and IFN-γ in the macrophage cell lines of mice, RAW264.7 (59). Another *in vitro* and *in vivo* study evaluating AgNPs synthesized with *Eucalyptus* as an adjuvant in rabies vaccine showed favorable results with minimal adverse effects on L929 cell line and in murine and canine models compared to the conventional vaccine with the aluminum adjuvant (60). SeNPs and AuNPs conjugated with the viral antigen from the causal agent of porcine transmissible gastroenteritis (TGS) produced an immunogen that generates good humoral and cellular immune responses in guinea pigs and increases the plasma concentrations of INF-γ, interleukin-1β (IL-1β), and IL-6, which leads to the activation of macrophages and lymphoid cells, promoting the expression of antigenic viral peptides on the surface of antigen-presenting cells, thereby contributing to their effective presentation to CD4 and CD8 T-lymphocytes (61).

Diagnosis of viral and bacterial diseases

New diagnostic technique for FMDV involves the use of AuNPs as biosensors, capable of specifically identifying the three serotypes of the virus (O, A, and SAT2). This technique may be considered as a tool for the diagnosis of this FMDV in endemic areas (12). Furthermore, for the detection of classical swine fever virus (CSFV), nanoflare probes have been designed using AuNPs conjugated with specific sequences of the virus, which can recognize and detect low concentrations of the virus (50 pg/μL) in the tissues (62).

A new diagnostic method for the detection of porcine reproductive and respiratory syndrome virus (PRRSV) uses optical and nanophotonic biosensors consisting of two biomolecule architectures: the first is a specific antibody against PRRSV marked with a fluorophore and attached to a protein marked with a quantum dot and the second architecture is marked with AuNPs. These biosensors could detect up to three PRRSV particles suspended in a sample (63).

Rapid, sensitive, and specific diagnostic techniques have been developed for bacterial diseases. Examples include nano polymerase chain reaction (PCR) using AuNP probes to detect the *IS711* region of *Brucella* spp. Bacterial DNA can be identified at a NP concentration of 1.09 pg/L (64). For the diagnosis of some diseases affecting fish, specific immunoassays have been developed. AuNPs coated with polyclonal antibodies allowed the detection of *Aeromonas salmonicida* at a concentration of 110^4 CFU/mL from the spleen or kidney of fish showing clinical signs of furunculosis (65).

In conclusion recent scientific advances and the development of new technologies have allowed the implementation of nanotechnology in different fields of science, including veterinary science. Currently, there exist hundreds of publications concerning the synthesis and evaluation of various metallic NPs that have determined their unique properties and proposed their use in different disciplines because of their advantages. In veterinary science, the properties of NPs allow them to be considered as candidates for immunogens and drugs to establish novel strategies for the prevention and control of infectious and degenerative diseases for short-, medium-, and long-term.

Despite the advantages of metallic NPs, some *in vitro* and *in vivo* studies have shown a bioaccumulation effect of metallic NPs in animal cells and tissues, which may cause damage to the eukaryotic cells. Furthermore, in order to achieve a cytotoxic effect in living organisms, high concentrations of metallic NPs are required over a long period of time compared to the concentrations of the source materials. Additional applications of metallic NPs include development of diagnostic methods for the detection of various pathogens and as complementary diagnostic tools for food safety monitoring. The development of these diagnostic tools would facilitate faster generation of results, achieve higher sensitivity and specificity of tests, and provide easy access to professionals in the field. Applications of nanotechnology in veterinary science is still in its early stages, and further research is required to determine their potential adverse effects and understand their mechanisms of action to predict their risks to humans, animals, and environment.

Conflict of interest

The authors declare no conflicts of interest.

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