Nanobiotechnology for Plant Protection

Silver Nanomaterials for Agri-Food Applications

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Edited by

Kamel A. Abd-Elsalam

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CHAPTER

27

Potential of silver nanoparticles for veterinary applications in livestock performance and health

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27.1 Introduction

The use of nanoparticles in human lives and activities is increasing each day. The concept of nanoparticles has been applied in food packaging, equipment manufacturing, and health care and could extend their applications in diverse fields as more discoveries unfold. Agriculture is currently facing challenges and backlashes on its present way of practice and the effect of its previous activities. Many practices have been banned or limited because of their relative effects on human health due to resistance, environmental pollution, and residues in food production. Because of these complications, farmers, academics, and researchers are dealing with implications to combat various health-related issues, thereby reducing morbidity and mortality of livestock. Several options have been explored, especially on the use of materials of phytogenic origins for animal health. Although anecdotal, several successful cases

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were reported as evidenced by the ethnoveterinary practices among rural and nomadic farmers. However, the modern-day intensive system of livestock farming faces increased pressure of meeting the demand for animal products. To meet this demand, the antimicrobial feed additives or drugs are essential for either curative or preventive purposes. Epidemic outbreaks of zoonotic or animal-related diseases usually have devastating effects on livestock production activities in nations, with many farmers being unable to recover economically from the shock. For instance, the outbreak of Avian influenza in Nigeria and African swine fever in Asian countries in 2006 and 2019 caused the loss of millions of birds and pigs, which has economic and protein security implications. Other challenges in animal agriculture include the prevention of environmental pollution, disease outbreak, re-emergence of infectious diseases, antimicrobial resistance of strains to established drugs, and the emergence of resistance against newly developed antibiotics. The problems demand the use of potential alternatives in veterinary medicine and animal health.

Nanotechnology holds some potential for use in the activities related to animal production, health, and veterinary medicine (Meena et al., 2018). This technique uses biogenic, organic, and inorganic minute-sized (usually between 1 and 100 nm) materials for various applications (Adegbeye et al., 2019). The term nanoparticles refers to their small sizes. These nanoparticles have a high surface area, charges, catalytic activity, and adsorption activity (Khurana et al., 2019). Furthermore, they could provide alternatives for developing new drugs, delivery of vaccines, adjuvants to improve immune responses, antigen stability, and immunogenicity (Sekhon, 2014; Zhao et al., 2014; Hill and Li, 2017; El-Sabry et al., 2018) and has high potential for use in veterinary medicine. As the field of nanotechnology continues to gather attention, its use in animal agriculture will be more expansive (Hill and Li, 2017) and could contribute to the development of nanovaccines, nanoantibiotics, and nanoantibiotics-hybrids with various diagnostic and therapeutic applications.

Several nanoparticles such as silver, gold, calcium, iron, selenium, silicon, titanium, and zinc-based particles have been used in various agricultural and environmental applications. Of these nanoparticles, silver nanoparticles have distinguished themselves as strong antimicrobial agents by causing death and inhibiting pathogenic organisms (bacterial, fungal, and viral origin). The objective of this chapter is to explore various ways by which silver nanoparticles could have veterinary applications in livestock farming. Also, this chapter explored some negative impacts of silver nanoparticles on livestock performance and health.

27.2 Brief on silver nanoparticle synthesis

The increased applications of silver nanoparticles in health, cosmetics, electrochemistry, material science, food, and agriculture result from their distinctive physicochemical properties and varying methods of synthesis. These methods include chemical, physical, and biological (microbial and plant-based); however, due to concerns about the hazardous byproducts, expensive, low yield, and labor-intensive from chemical (requires additional reducing and stabilizing/capping agent) and physical method, green synthesis of silver nanoparticles methods are being used (Ledwith et al., 2007). The green (biological) method of synthesis is a sustainable approach that involves controllable design and processes of cost-effective and less/no toxic nanoparticle substances (Ahmad et al., 2019; Tripathi et al., 2019). For a sustainable livestock agricultural management, the use of green synthesis approach is an interesting area because of its economic, biocompatible, and eco-friendly benefits over chemical and physical methods. These methods include pest and disease control, disinfection of livestock, home, and utensils, and as feasible alternative to antibiotics (Huang et al., 2014).

Silver nanoparticles have been synthesized from plant extracts such as *Cleome viscose*, Alfalfa sprouts, *Elaeagnus latifolia*, Geranium, *Ganoderma neojaponicum*, *Glycyrrhiza glabra*, *Feronia elephantum*, *Amphipterygium adstringens*, *Aloe vera*, neem, and bamboo (Gardea-Torresdey et al., 2003; Yasin et al., 2013; Rodríguez-Luis et al., 2016; Lakshmanan et al., 2018; Eze et al., 2019). Bacteria and fungi are major sources for microbial-based synthesis of silver nanoparticles. The bacteria (*Pseudomonas stutzeri*, *Bacillus* spp., *Escherichia coli*, *Xanthomonas* spp., *Staphylococcus* spp., *Deinococcus radiodurans*, and lactic acid bacteria) and fungi (*Aspergillus* spp., *Arthroderma fulvum*, *Trametes ljubarskyi*, *Fusarium oxysporum*, and *Ganoderma enigmaticum*) are known for their great potential in the biosynthesis of silver nanoparticles with controllable uniformity and stability (Bhainsa and D'Souza, 2006; Gudikandula et al., 2017; Javaid et al., 2017). Subsequent studies demonstrated other cell-mediated silver nanoparticles synthesis with macro- and microalgae such as *Caulerpa racemosa*, *Sargassum muticum*, *Chlorella vulgaris*, *Spirulina platensis*, *Chaetoceros calcitrans*, *Padina pavonia*, *Isochrysis galbana*, and *Tetraselmis gracilis* because of their high silver metal uptake potential (Azizi et al., 2013; Kathiraven et al., 2015; Annamalai and Nallamuthu, 2016; Abdel-Raouf et al., 2019; Khanna et al., 2019). Biosynthesis of silver nanoparticles involves either intracellular or extracellular reduction of Ag^+ to Ag^0 (Fig. 27.1) facilitated by active compounds such as alkaloids, terpenes, fatty acids, and amino acids in biological extracts for stabilization (Khanna et al., 2019). These processes including dimension and morphology of the nanoparticles are influenced by factors such as temperature, pH, extract concentration, exposure/reaction time, interactions, and biochemical activities (Pathak et al., 2019). The potential delivery methods of silver nanoparticles have been extensively discussed by Hill and Li (2017) and Fahimirad et al. (2019).

27.3 Potential routes of administration

Silver nanoparticles are efficient materials for therapeutics and drug delivery in veterinary practices. The minute-sized particles provide potentiality in bypassing many-body barriers such as placenta and blood–brain barriers. Silver nanoparticles could be applied through several means such as topical, oral, intranasal, intravenous,

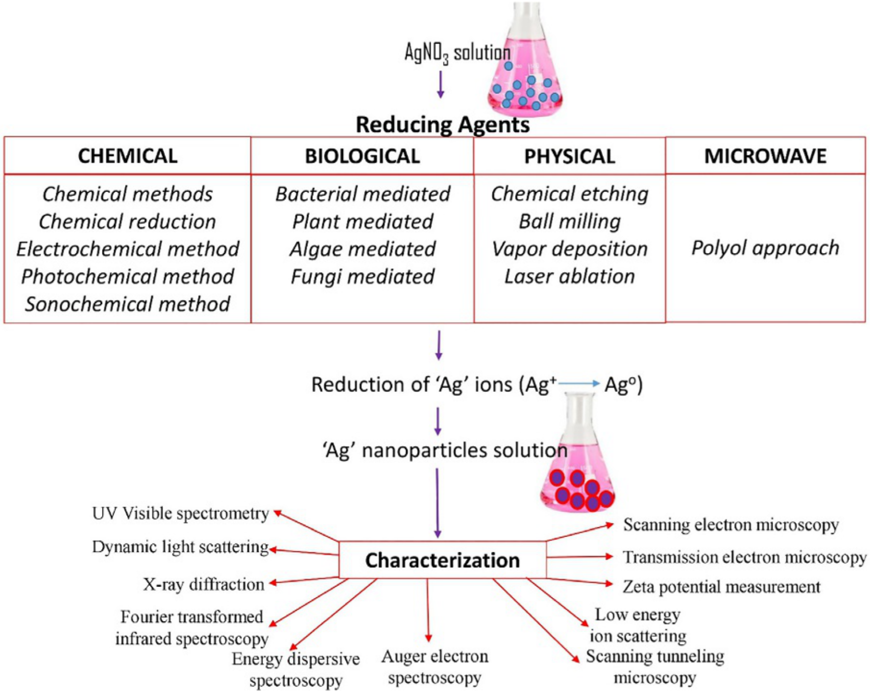

FIG. 27.1

Synthesis and characterization techniques of silver nanoparticles.

muscular, and transdermal nanodelivery systems (Sekhon, 2014). Other means include *in ovo*, intravenous (Lee et al., 2018; Mathur et al., 2018), intragastric (Melnik et al., 2013), intraperitoneal (Doudi and Sertoki, 2014), and subcutaneous (Tang et al., 2007; Mathur et al., 2018) injections. Administering silver nanoparticles through inhalation for 6 h/day for 90 days revealed no genotoxicity with a reduced lung burden of 24 h postexposure (Kim et al., 2011).

27.4 Potential for nanoveterinary application of silver nanoparticles

Nanomedicine refers to the procedure of applying nanoparticles in diagnosis, prognosis, and treatment, while nanopharmacy and nanotherapy relate to their utilization in drug-making-related applications and animal rehabilitation, respectively. It involves the "smart" delivery of a drug to the target tissue with a profile that drugs are delivered as needed (Scott, 2005). These drugs could be packed with biodegradable nanoparticles so that they would be delivered to the intestine for absorption (Simon et al., 2016) and reach other target sites within the body. Further, the use of silver nanoparticles could be extended to treat the ailments caused by various diseases, parasites, open injuries, and other microbial infections. This section is meant to discuss the various applications of silver nanoparticles in livestock health and well-being.

27.5 Endoparasites (helminths)

Helminthiasis is a major challenge in extensive livestock management systems involving grazing animals for a significant period. The mortality and morbidity rates will be higher with a parasitic disease burden, which ultimately decreases the flock's production performance. To overcome the helminths, conventional anthelminthic like albendazole and some herbs such as neem and pineapple leaves are generally used. However, the chemical antihelminth is expensive and could be unaffordable to many farmers in developing countries. Often, the standard dosage of active ingredients on the label differs from the actual dosage of the active ingredient. In regions where standards are upheld, these helminthic parasites have evolved resistance to various anthelmintic, such as benzimidazole, imidazothiazole, and ivermectin (Waller, 2003), which is a major concern worldwide. Also, despite the presence of many herbs with potent anthelminthic activity, the nonuniversality of these herbs and possibility of low financial gain from the economy led to low or limited adoption by global farming companies. Among these helminths, *Haemonchus contortus* is a gastrointestinal nematode that affects small ruminants in tropical, subtropical, and temperate regions. Tomar and Preet (2017) and Avinash et al. (2017a) have shown that neem-mediated nanoparticle is more effective than the individual neem or albendazole drug against helminth. Furthermore, the IC_{50} and IC_{90} values of neem mediated AgNp were 99.5% and 97.2% lower than albendazole (Avinash et al., 2017a). This implies that neem-mediated AgNp is more lethal than albendazole. Another study showed that 1–25 μg/mL of neem-mediated AgNp resulted in 15%–85% motility of adult *H. contortus*, whereas 200–1200 μg/mL of neem was required to do same, and the IC_{50} for the adult mortality was 7.89 μg/mL (Tomar and Preet, 2017). In another study by Preet and Tomar (2017), the LC_{50} of *Ziziphus jujuba* leaf extract biofabricated AgNp was 98.37% lower than the individual leaf extract in raw form. The authors reported that the nanoparticle worked by altering the egg morphology and depleting the nutrients (glycogen, lipid, and protein) of adult worms in a range of 5.69%–21.81%. The low concentration required by herbal conjugated AgNp suggests the importance of silver nanoparticles in potentiating the lethal effects of herbal extracts against pathogens and the development of "nanoherbal medicines."

Fascioliasis, an infectious parasitic disease caused by liver fluke, tops all zoonotic helminths globally. The infestation affects various ruminants and pseudoruminants, including sheep, goats, cattle, buffalo, horses, donkeys, camels, and rabbits. Its prevalence could be up to 90% in some zones causing huge animal losses (Farag, 1998). Triclabendazole is a safe and effective drug of choice against the fluke. However, there are reports from Australia and Ireland about the inconsistencies in the obtained results, presumably due to antiparasitic drug resistance (Alvarez-Sanchez et al., 2006). Despite the resistance, developing a new drug or breaking the resistance mechanism of the fluke is essential. In this regard, the efficiency of the established drug could be improved by employing nanotechnology. Due to the minute-size conjugation of silver nanoparticle with triclabendazole, this could allow the particle to serve as a carrier of the drug into the cell membrane, thereby increasing the efficiency. An in vitro report (Gherbawy et al., 2013) showed that the conjugation of triclabendazole drug with *Trichoderma harzianum* biosynthesized silver nanoparticle inhibited the egg hatchability by 89.67% compared to the 69.67% of those hatched under triclabendazole drug control group. The increased inhibitory activity was due to a pit-like perforation on the egg surface, which was not observed in the drug alone and untreated group. This study shows that the silver nanoparticle could be combined with a drug to aid its quick delivery and enhance efficiency at the target site.

Cystic hydatid disease is a helminth infection and a major neglected cyclozoonotic disease caused by *Echinococcus granulosus* in many countries globally (Adibpour et al., 1998). It is an infection that causes economic and animal protein losses such as decreased meat, milk, fiber, and mortality of offspring. An invasive method is practiced to treat this disease, but there are setbacks such as anaphylactic shock, mortality, and even potential for reoccurrence (Rouhani et al., 2013). Other noninvasive methods such as hypertonic saline, mannitol, chlorhexidine gluconate, *Allium sativum*, *Sambucus ebulus*, and fungal chitosan have been used, but their usage is not recommended because of low efficacy, high toxicity, and undesirable effects (Rahimi et al., 2015). Discovering a noninvasive and nontoxic treatment for hydatid cysts is essential. An in vitro exposure of protoscolices eggs to 0.1–0.15 mg/mL Ag-Nps for 60 and 120 min caused a 79%–80% and 83%–90% mortality, respectively (Rahimi et al., 2015). The liver contains a high residue of nanoparticles after administration of nanotechnology-based medication. Since liver is the organ that the disease attack, silver nanoparticles has a great possibility of treating the liver-related ailment. This suggests that silver nanoparticle could be used against the disease without resorting to an invasive method. Indeed, the Ag-NPs decreased protoscolices by 40% in 10 min, even at a lower concentration. Because of the Ag-NPs' strong scolicidal activity, they could be projected as an ideal and economical scolicidal agents against the disease without resorting to an invasive method.

27.6 Ectoparasites (ticks)

Grazing animals, both under semi-intensive and nomadic systems, are infested by various ectoparasites, which affect their productive efficiency by competing for nutrients with the host (Adegbeye et al., 2018). Ticks serve as vectors to various infections such as anaplasmosis, babesiosis, borreliosis, and ehrlichiosis. Because of the resistance phenomenon, the effectiveness of acaricidal products against several tick species of tropical and subtropical countries is declining. The residues in meat and milk are another major concern and discovering new acaricidal product is cost-intensive (National Research Centre, 1986; Perez-Cogollo et al., 2010; Benelli et al., 2017). Hence, there is a need to find acaricidal and repellent products to mitigate tick resistance. Silver nanoparticles could help in reducing difficulties and expenses related to manufacturing new acaricidal against ticks (such as *Rhipicephalus* (Boophilus) *microplus*, *Haemaphysalis bispinosa*, and *Hyalomma anatolicum*). Further, silver nanoparticles could be projected as a novel strategy against acaricide resistance. Another study proved that the neem-coated silver nanoparticles are toxic to larvae and adult *Rhipicephalus microplus* ticks (Avinash et al., 2017b). Additionally, 10 and 25 μg/mL of silver nanoparticles had 100% mortality against the larvae of *Rhipicephalus* (Boophilus) *microplus* and *Haemaphysalis bispinosa* adults, respectively (Santhoshkumar et al., 2012; Rajakumar and Rahuman, 2012; Zahir and Rahuman, 2012), whereas the silver nanoparticles at 50 mg/L of silver nanoparticle killed 40% (*Rhipicephalus* (Boophilus) *microplus*) adults (Johari, 2016).

The resistance against deltamethrin, the most common chemical agent used against ticks, is widespread and making vector control programs vulnerable. Hybridizing this drug with silver nanoparticles could provide a synergistic effect on tick. In this view, Avinash et al. (2017a, b) reported that 50 ppm of deltamethrin neem-coated silver nanoparticles killed *Rhiphicelus microplus* larvae, while 360 ppm of deltamethrin was required for 100% ticks' mortality. Furthermore, the deltamethrin neem-coated silver nanoparticles killed 93.33% of the adults and had 99.16% oviposition inhibitory activity. In addition, the LC_{99} and IC_{99} against both larvae and adults of *R. microplus* and for oviposition inhibitory activity were lower than deltamethrin alone. The tick activity could be controlled using conjugated AgNP-coated deltamethrin as topical agents by immersion in dip or pour-on sprays.

27.7 Potential application in poultry and hatcheries

The major constraints in livestock production are due to the use of antibiotic feed additives, mortality, morbidity, environmental challenges, and vaccine failures. Because of the lesser contribution of poultry to greenhouse gases, environmentalists endorse chicken as nonvegetarian protein source compared to beef, carabeef, and pork. Since the recent past, global warming potential of diet is an alarming concept, and hence, the poultry market has a great potential for expansion soon. Vaccination is done in poultry hatcheries and farms to prevent the devastating effects of pathogenic diseases caused by both bacteria and viruses. Failure of immunization programs due to improper vaccinations may cause huge losses to poultry farmers. Commercial poultry birds are periodically vaccinated *in ovo*, orally, or through the wing web against diseases such as infectious bursal disease, fowl pox, Newcastle, Marek's disease, avian influenzas, and infectious bronchitis.

Most recently, researchers are developing nanoparticles to challenge viruses by delivering enzymes that prevent the replication of the virus in the blood system of humans or livestock (Meena et al., 2018). Infectious bursa disease or gumboro is caused by a virus and can spread by contact, feces, or contaminated feed. Silver nanoparticles at a concentration of 20 ppm were found to act as both preventive and therapeutic agents by decreasing the growth of IBD virus in embryonated eggs (Pangestika et al., 2017). The preventive technique was developed by mixing silver nanoparticle and IBD virus 2 h before inoculation, while therapeutic techniques were developed by inoculating virus first and then injecting silver nanoparticles 48 h postinfection. In the preventive methods, the silver nanoparticle prevented the penetration of the virus into the host cell, while the therapeutic methods inhibited the interaction between liver nanoparticle and the DNA, consequently hindering the replication of the virus (Galdiero et al., 2011). Silver nanoparticles could be employed with these methods to build the immunity in chicks against IBD virus before hatching. Thus, the preventive and therapeutic application of silver nanoparticles on IBDV may be a novel strategy to prevent virus replication at an early stage. In addition, Kordestani et al. (2015) reported SilvoSept® at 4 ppm had anti-H1N1 influenza A virus activity reducing optical absorption by 99%. Hence, silver nanoparticles could be applied to improve the biosecurity of poultry ventures (farms and hatchery) to prevent the spread of diseases. In addition, silver nanoparticles could be used to develop vaccines as adjuvant or in other capacities for these deadly poultry diseases.

Embryonic development is important in the poultry industry as the finishing age of the commercial broiler is reducing (Goel et al., 2017) due to improved nutrition, genetic, and consumers demand tender meat. *In ovo* injection with silver nanoparticles could improve the bird's growth and immunocompetence of the late-term embryo or post-hatch chicks. Toll-like receptors (TLR-2) and TLR-4 play a key role in innate adaptive immune systems and recognize the invading pathogens by a series of pathogen-associated molecular patterns (Beutler, 2004; He et al., 2006). Silver nanoparticles enhance the vulnerability of macrophages to inflammatory stimulation by activating the specific ligands on the toll-like receptor (Castillo et al., 2008). Injecting the AgNPs at 12.5, 25, or 50 μg into egg increased the bursal weight, spleen weight, and hatchability, along with immune parameters such as foot web index and expression of TLR2 and TLR 4 genes (Goel et al., 2017). Bursa and spleen play important roles in imparting immunity and elicit cellular and humoral immune response in chicks. The increased response indicates a better immunological health status *in ovo*-injected birds. This improvement in immunity could be through enhanced early maturation of the immune system and higher phagocytic activity producingmore antibodies against invading pathogens (Goel et al., 2017). Therefore, if the *in ovo* silver nanoparticle application can boost the embryo's immune system, it can enhance the body's first line of defense such that there is a reduction in the use of antibiotics for preventive or therapeutic purposes.

Because of the faster growth rate, leg paralysis is one of the main challenges in broiler production. Adding nano-Ag to the chicken embryo at 0.25 μg Ag/g egg improved the calcium, iron, and copper content in the embryo skeleton by 3%, 12%, and 9%, respectively (Sikorska et al., 2010). Furthermore, about 8% of silver nano was settled in the thigh bone. This shows that silver nanoparticles improve mineralization in chicken. Moreover, the ability of the silver nanoparticle in penetrating and settling in the embryo reveals that the silver nanoparticle could be a potential carrier of drugs and minerals. Further, the increased copper, iron, and calcium after AgNano use suggest that the silver nanoparticle can mitigate rickets and brittleness of chickens' bone by stimulating the hydroxylapatite formation. A silver nanoparticle can also improve the hatchability of eggs. Another study reported that injecting silver nano at 10, 20, or 30 μL/mL into allontoic cavity of eggs increased hatchability by 69%, 75%, and 81%, respectively (Kathiresan et al., 2019).

In hatcheries, formaldehyde is used to fumigate the hatchable eggs before incubation to eliminate pathogenic microbes. However, Chmielowiec-Korzeniowska et al. (2015) revealed the toxic and carcinogenic nature of formaldehyde. The same authors attempted to find an alternative to formaldehyde for fumigation and revealed that silver nanoparticles in spray form decreased the pathogenic load and lowered the residues in visceral organs such as the liver, GIT, and eggshell. Because of the established antimicrobial activity, silver nanoparticles could be useful to disinfect hatchers and eggshell instead of formaldehyde. Silver nanoparticles could protect the chicken embryo from pathogenic infection as well as support the growth of a healthy embryo.

27.8 Immunity

The immune system comprises innate (first line of defense) and adaptive responses. The former is present and mobilized rapidly during infections (Marquardt and Li, 2018). The nuclear factor κB (NF-κB) is a transcriptional factor that plays a key role in the defense of the organism. The defense mechanisms inlcude proinflammatory pathways and could be activated or stimulated by pathogenic bacteria or their products (LPS and endotoxins), viruses, and reactive oxygen species (Sawosz et al., 2010). The phosphorylation of IκB activates NF-κB and releases of P50 and P65 subunit, which binds to genes involved in immune defense activities (D'Acquisto et al., 2002). Preinjection of 0.3 mL colloidal Ag nano *in ovo* at 50 ppm concentration in eggs challenged with *Escherichia coli* strain 0111:B4 LPS (0.4 mg/egg) showed improvement in chicks body weight by 6.5% besides limiting the expression of proinflammatory NF-κB mRNA (Sawosz et al., 2010). The silver nanoparticles, in colloidal form, could be used to improve the immune system of chicks so that the chicks could manage the intestinal microbial imbalance and immune disorders. In stressed animals, the oxidation stress-led ROS can trigger the translocation of Nrf2, leading to the production of various antioxidant genes (e.g., *sod1*, *sod2*, *cat*, *gclc*, *gstD*, and *gstE*) (Nguyen et al., 2009). A study by Mao et al. (2018) found that the use of AgNPs at lethal and sublethal doses (50 μg/mL) caused damages to the DNA of the brain and salivary gland and gut apart from the activation of Nrf2-dependent antioxidant pathway, consequently triggering autophagy. Usually, autophagy is induced by activating Nrf2/antioxidant response element-dependent antioxidant system during cellular stress or homeostasis or removing misfolded protein and damaged organelles) (Kraft et al., 2010). As such, AgNPs may trigger the body Nrf2-dependent antioxidant pathway in a time-dependent manner to help an animal when they are stressed cellularly. Furthermore, caution is advised to limit the high doses, leading to chronic cumulative effects on the host.

Injecting Ag-NPs (5 and 10 mg/L) at 2.87 and 12.25 mg/bird stimulated the production of B lymphocytes, ultimately producing IgA and Ig A immunoglobulins at 95% and 37%, respectively. The study showed exertion of proinflammatory effects by elevating IL-6 by 125% and increased ESR by 97% (Kulak et al., 2017). This suggests that AgNPs exert an immunotropic effect on livestock if applied appropriately at right doses and appropriate administration methods. The importance of neutrophils in regulating immune networks and innate defense stresses the impact of silver nanoparticles on immunoregulation (Fraser et al., 2018). Besides, the phagocytic activity of circulating neutrophils is an indispensable defense mechanism of the immune system. They also play an important role in releasing cytokines and chemokines, which contribute to modulation of the immune network and responses (Scapini et al., 2000; Pelletier et al., 2010). Exposing to 20 µg AgNPs/10^5 cells for 20 h triggered the activation and maturation of circulating neutrophils, thereby increasing the key cytokine release including, IL-8, IL-16, and IL-27. However, the increased cytokine levels did not cause proinflammatory or damaging effects (Fraser et al., 2018). The above-mentioned effects of silver nanoparticles on immune system suggest their usage in the veterinary sector to strengthen the immune system and avoid invading pathogens. However, appropriate dosage and period of contact have to be established to prevent inflammatory pathogenesis because of inappropriately recruited or activation of neutrophils (Jorch and Kubes, 2017) (Fig. 27.2).

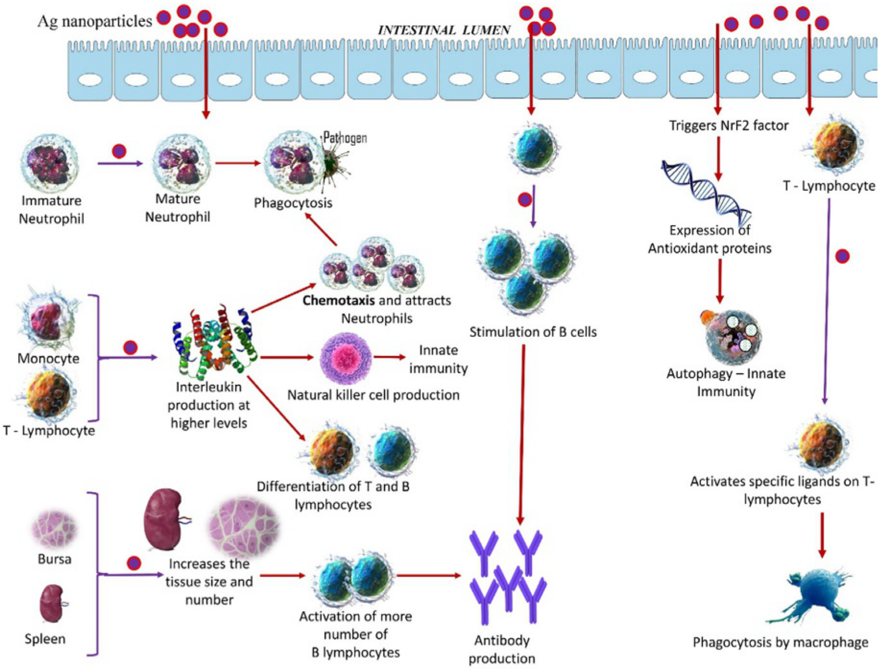

FIG. 27.2

Immunomodulatory effects of silver nanoparticles.

27.9 Wound and burn healing

In nations with a transition economy, the usage of animals for carting or ploughing purpose is common, causing open injuries, sunburns, and other stress-related problems. Although farmers use herbal extracts or gentian violet to improve the healing process, those topical medicines could not heal the wounds at a faster rate. Several swine breeds such as large white, Yorkshire, and Poland China are susceptible to sunburn, causing an open wound, which may take a long time to heal. Kitsyuk and Zvyagintseva (2018) found a quick restoration of the normal structure of the epidermis, density index fibroblasts, and reduction in the thickness of the epidermis in guinea pigs exposed to ultraviolet irradiation and Ag Np-tiotriazolin ointment. In contrast, untreated groups had a thick epidermal layer, dystrophic changes in epidermocytes and dyskeratosis, increased thickness of fibroblasts and dermis collagenization, changes in the content and structure of elastic fibers, and uneven derma fibrosis along with sclerotic changes. In the future, climate change could increase the pronocity for sunburn, as such, silver nanoparticle could be applied for quick healing of the wounds. Salih et al. (2016) showed that olive leaves extract-based silver nanoparticles promoted the healing of burned wounds. The silver nanoparticles improved in the formation of a thin epithelial layer in 14 days and reduced the burn diameter by 94.23%. Similarly, silver nanoparticle was shown to prevent and treat burn infection wounds faster than established drug-silver sulfadiazine, which is used globally. Ag Np-aloevera combination (containing 7 cc nanosilver, 0.2 g *Aloe vera*, and other materials) increased rate of epidermis re-epithelialization and decreased the total body surface area affected by burns faster than silver sulfadiazine (Mousavi et al., 2019). The superiority of silver nanoparticles in healing process compared implies that the herbal–nanoparticle formulation could be promoted as an alternative to the conventional treatments in livestock. The silver nanoparticles could also be used to treat certain surgical infectious diseases such as caseous lymphadenitis, a chronic and potentially zoonotic disease caused by *Corynebacterium pseudotuberculosis* bacterium in ruminants small ruminants (Santos et al., 2019).

Surgery is often carried out on animals depending on the disease and discomfort. Draining and cauterizing the lesions with 10% iodine solution could consume more time to heal. Hence, other alternatives to hasten the healing process are necessary. In this regard, Santos et al. (2019) used an ointment formulation based on biogenic AgNPs mixed with natural waxes and oils. The healing rates of surgical wounds of goat and sheep treated with silver nanoparticles were 5 and 8 days faster than those treated with iodine. Further, the wounds treated with silver nanoparticles had less purulent discharge and lower leukocyte counts and anti-C pseudotuberculosis antibody titers. Therefore, it could be concluded that postsurgical treatment of wounds with AgNP-based ointment may be a promising tool to enhance the healing rate of surgical wounds. Similarly, Kordestani et al. (2015) showed that rinsing the wound with SilvoSept® was effective against a wide spectrum of microorganisms and could be used to rinse wounds as an alternative to iodine-based ointments. The wound healing activity of AgNPs could be related to the antimicrobial properties and autoinflammatory effects, which are implicated in wound-healing responses. Furthermore, silver could modulate the cytokines involved in tissue repair (Tian et al., 2007; Vasile et al., 2020). These nanoparticles could be applied as ointment, spraying, cream, and powder.

27.10 Antimicrobial activity and synergy of silver nanoparticles

Antimicrobial resistance to medical and veterinary drugs worldwide is a cause for concern and one of the greatest threats to human health (Marquardt and Li, 2018). Also, resistance poses a threat to animal-derived protein security. Affordability, excessive use, and adulteration of antibiotics has led to increased resistance of pathogenic gram-positive and gram-negative bacteria to drugs. In addition, accumulation of antibiotic residues in animal products has resulted in the resistance of transmissible food pathogens to antibiotics in humans (World Health Organisation (WHO), 2017). Moreover, the rate at which these microbes generate resistance outcompetes new antibiotics (Vazquez-Muñoz et al., 2019) and biofilm is one of the modes whereby microorganisms build resistance to antibiotics. Therefore, there is a need for developing new antibiotics and finding a way to break the resistance of the microbes. Kathiresan et al. (2019) reported that silver nanoparticles (10–30 μL/mL) were able to inhibit the biofilm formation of pathogenic microbes.

Nonjudicious utilization of antimicrobial agents causes the spread of resistance, consequently reducing their efficacy. According to the collected literature, several pathogens such as *Escherichia coli*, *Salmonella* spp., *Pasteurella multocida*, and *Actinobacillus* spp. have shown antimicrobial resistance at different levels. As the threat of antimicrobial resistance continues to grow globally, the impact of drug resistance could be mitigated by employing combination therapy of different antibiotics or antibiotics with nonantibiotic agents such as silver nanoparticles. Smekalova et al. (2015) revealed that silver nanoparticles are able to act in synergy with amoxycillin, Penicillin G, gentamicin, and colistin against some resistant microbes like *Staphylococcus aureus*, *Actinobacillus pleuropneumoniae*, *Streptococcus uberis*, and *Pasteurella multocida.* Besides, Tetracycline-conjugated *Oscillatoria limnetica* synthesized-silver nanoparticles and cefaxone-conjugated *Oscillatoria limnetica*-silver nanoparticles showed higher inhibition zone diameter (26 and 24 mm, respectively) than 19 and 18 mm for cefaxone and tetracycline against *E. coli* and *B. aureus* (Hamouda et al., 2019).

In Nigeria, antibiotics such as tetracycline, penicillin, and gentamycin are used as either feed additives or injectables in livestock. However, few authors have reported resistance of pathogenic microbes to antibiotics used in Nigerian livestock sector (Oluwasile et al., 2014; Nsofor et al., 2013). Despite the antimicrobial properties of silver nanoparticle, few reports of resistance were observed in some gram-positive and gram-negative bacteria (Panacek et al., 2018; Jose et al., 2019; Mohammed and Aziz, 2019). As such, formulating antibiotics to overcome the resistance challenge is essential. The gram-negative resistance was due to the production of flagellin, a flagellum protein, while the same from gram-positive was due to the role of efflux pump on the cell wall. In a recent study, Khatoon et al. (2019) tested the efficacy of a nanoformulation involving ampicillin antibiotic (AMP), silver nanoparticles (Ag-NPs), and a combination of silver nanoparticles and ampicillin antibiotic (AMP-Ag-NPs). They revealed that the MIC_{90} of AMP-silver nanoparticles against the bacterial strains was 3–28 μg/mL lower than the AMP (12–720 μg/mL) and synthesized silver nanoparticles (280–640 μg/mL). Further, the authors revealed no evidence of resistance mechanism on testing the AMP-silver nanoparticles against bacterial strains in 15 repeated cycles. Hence, hybridizing silver nanoparticle antibiotics could be done in livestock industries to mitigate the resistance of pathogenic microbes, thus reducing the morbidity and mortality of livestock suffering from antibiotic-resistant infections.

Besides, the localized surface plasmon resonance properties of silver nanoparticles make them attractive against antimicrobial-resistant bacterial strains with excellent antimicrobial activities at lower concentrations (Jose et al., 2019). The peptidoglycans on the cell wall of gram-positive microbes may play a pivotal role in preventing the cytoplasmic entry of nanoparticles protecting them from cell death. The coevolution of microbes against antibiotics is of greatest concern over the excessive use of silver nanoparticles. As such, the overuse of silver nanoparticles could also lead to an evolution in bacteria to make themselves resistant to it. More recently, Jose et al. (2019) found high toxicity levels of silver-silica nanoparticles to *Bacillus subtilis* and *Escherichia coli* at low concentration (20 μg/mL); however, *S. aureus*, a gram-positive bacterium was resistant with only 20% mortality even at 100 μg/mL concentration. It was observed that gram-positive *Bacillus subtilis* and *S. aureus* maintained 60% and 80% of their respective cell walls within the exposure period. The authors found that the resistance was due to the role of efflux pump; hence, inhibiting the efflux pump with calcium channel blockers such as verapamil may facilitate the entry of silver–silica nanoparticles into the cell, ultimately causing DNA damage and cell death. Therefore, when treating gram-positive bacteria, an antimicrobial formulation of silver nanoparticle could be administered along with efflux pump inhibitors to breach the cell wall of gram-positive microbes. Furthermore, the sensible use of silver nanoparticles is essential to prevent the possibility of antimicrobial resistance. The combination of antimicrobial agents with silver nanoparticles could be a promising way to decrease the number of antibiotics used in livestock and enhance the efficiency of injectable antibiotics at a lower quantity.

27.11 Infectious diseases

27.11.1 Mastitis

In practice, many farmers and veterinarians administer antibiotics and drugs to overcome mastitis-related illness and death based on previous experience or recommendation rather than scientifically informed drug prescription. Bovine mastitis is an important economic disease that affects cost of milk production and cows performance, which greatly decreases milk production. The excessive use of antibiotics in cattle leads to antibiotic-resistance of mastitis-causing bacteria. Mastitis is primarily caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Corynebacterium bovis*, and *Bacillus cereus* (Yuan et al., 2017). Mastitis is a critical threat to the dairy industry because of its devastating effects on animal health, milk production, and the cost of milk production. Indiscriminate antibiotic usage against mastitis is common in developing nations such as India; hence, the disease is heavily related to the antibiotic-resistance. As *Staphylococcus aureus* is a major pathogen of mastitis prevalence in dairy herds, the resistance of the bacteria against antimicrobial agents is well-documented. Silver nanoparticles had MIC values ranging from 1.25 to 10 μg/mL, which inhibited 50% and 90% of *S. aureus* by 7 min contact time at a concentration of 5 and 10 μg/mL of silver nanoparticle, respectively (Dehkordi et al., 2011). Furthermore, 11 nm-sized spherical silver nanoparticles had a MIC of 1 and 2 μg/mL against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, respectively (Yuan et al., 2017).

27.11.2 Tuberculosis

Mycobacterium bovis, the causative agent of bovine tuberculosis, can be responsible for human tuberculosis, thus having zoonotic importance (Allix-Be'guec et al., 2009). Both *M. tuberculosis* and *M. bovis* cause serious tuberculosis infection in both human beings and animals and have high mortality than any infectious disease. Large cattle population reported to be infected with bovine tuberculosis worldwide (WHO, 2010; Selim et al., 2018). Often *M. bovis* infected cattle are sold even in local markets, which could be purchased unnoticeably. Consumption of beef with white sphere-like structures predisposes humans to tuberculosis infection. The antimycobacterial activity of silver nanoparticles against *M. bovis*, *M. tuberculosis* H37Rv, and multidrug-resistant *M. tuberculosis* inhibited them at MIC of 1, 4, and 16 μg/mL, respectively (Selim et al., 2018).

27.12 Contaminated/infected water

Contaminated drinking water is another concern for livestock disease burden. For instance, *Cryptosporidium parvum*, a major coccidian in contaminated drinking water, causes a significant losses in farms due to the higher mortality rate of preruminant calves, especially those below one month age (Thomson, 2015). Surprisingly, the oocysts have low infection doses and even resist chlorinated water treatment (Rose et al., 2002). Silver nanoparticles at 500 μg/mL resulted in 33% excystation far lower compared to 83% in control, while 5–500 μg/mL of silver nanoparticles caused 60%–93% decrease in sporozoite or shell ratio. The excystation process includes the rupture of oocyst releasing sporozoites that initiate infection in the host cell. Therefore, it could be assumed that silver nanoparticle prevents infection in host cells. The impact of silver nanoparticles was due to the ability of Ag ions in breaking the cell wall and entering into the oocyst wall, ultimately destroying the sporozoites (Cameron et al., 2016; Bravo-Guerra et al., 2020). In typical farms of developing nations, the freshwater sources and the disposed of wastewater from agriculture and human activities get mixed up through percolation to the groundwater, resulting in a high pathogenic bacterial population, which indirectly affects livestock production. A study conducted in India found that 15 nm-sized silver nanoparticles had a MIC for *E. coli* from farm water at 50 mg/L. Adding 15 nm-sized silver nanoparticles to the poultry diets improved feed intake and body weight, decreased mortality (4.92% vs 14.13% in the control group), and the meat was fit for consumption (Kumar and Bhattacharya, 2019). Therefore, AgNPs can be used as water disinfectant, surface disinfectant, and therapeutic material in livestock; and aquatic industry (Deshmukh et al., 2019; Prosposito et al., 2020).

27.13 Biosecurity/disinfection

The ability of silver nanoparticles against many bacteria shows that it could be used as an antimicrobial agent against many aerosol microbes such that it could be sprayed as foam and hung between buildings to reduce the exchange of infected air. These particles could also be used on-farm to minimize the spread of disease as an aid of biosecurity measures such as spraying and dipping. Combining antimicrobial agents with silver nanoparticles is a promising way to decrease antibiotic usage in the extensive livestock production systems. Furthermore, silver nanoparticles can play an essential role in agriculture and animal production by using sterilization tools and equipment in animal buildings.

The endospores of *Bacillus* and *Clostridium* species are means of transmitting spore-mediated diseases like anthrax, gas gangrene, botulism, tetanus, food poisoning, and pseudomembranous colitis, which are resistant to heat, chemical, and UV radiation treatment (Nicholson et al., 2000; Aminianfar et al., 2019). A study showed that 90% of the *Bacillus* and *Clostridium* endospores were inhibited with chemicals such as glutaraldehyde (20 mg/mL), sodium hypochlorite (0.25 mg/mL), and formaldehyde (5 mg/mL) in 25, 20.6, and 11.8 min, respectively (Gopinath et al., 2016). However, biogenic nanosilver (75 µg/mL) inhibited more than 90% of the *Streptomyces* sp. in 20 min. This inhibitory effect of nanosilver at lower concentration compared to chemical methods could be useful in disinfection of farms during hazardous spores' epidemic attack or outbreak. Furthermore, silver nanoparticles proved to be an effective disinfectant by sterilizing cages co-contaminated with opportunistic pathogens—*B. cereus* and *C. difficile* at 1×10^6 spores. The animals in cages void of AgNPs had infected lungs, inflammation, submucosa edema, ulceration, and hyperplasia of the GIT, deformation of hepatic parenchyma, and lympho-monocytic infiltration around portal vein (Gopinath et al., 2016), whereas no signs of pathological lesions were observed in the rats maintained in nanosilver sterilized cages. This suggests that sterilizing the cages and livestock houses regularly with nanosilver could improve their biosecurity and enhance animal safety against endospore infections. Therefore, nanosilver could be applied as a surface disinfectant against environmental spores as well as for several theragnostic applications. The nanosilver adhere to the spore's coat, leading to pitting formation by denaturing the proteins and glycosidic bonds of the peptidoglycan *N*-acetylglucosamine and *N*-acetylmuramic acid (Mirzajani et al., 2011; Gopinath et al., 2016; Ismail et al., 2019).

27.14 Mechanism of action

Silver nanoparticles exhibit an array of mechanisms of action involving antimicrobial activity against bacteria, fungi, and viruses, as antioxidants, nutraceuticals, drug delivery systems and immunological responses (Hill and Li, 2017). The silver nanoparticle has various means of action against microbes. The antimicrobial mechanisms include inactivation of enzymes, change of protein expression, damaged respiratory chain, production of reactive oxygen species, and increasing the membrane permeability resulting in cytoplasmic leakages and disruption of the cell membrane (Choi and Hu, 2008; Jin et al., 2010; Hartemann et al., 2015; Wu et al., 2016; Bondarenko et al., 2018). Besides, there are reports of a compromise of notable organelles in bacteria causing interruption of transmembrane electron transport (Potbhare et al., 2019; Eze et al., 2019). Due to the hydrophobic nature of silver nanoparticles, the nanoparticles interact and alter membrane permeability through cell penetration. They inactivate and inhibit the lactate dehydrogenase activity leading to increased leakage of proteins, sugars, and DNA, structural damage, severe disturbance to cell function, and cell death (Prabhu and Poulose, 2012; Yuan et al., 2017). This mechanism can also be attributed to silver cations, which specifically bind to thiol (–SH) groups of bacterial proteins by displacing the hydrogen atom to form –S–Ag, thereby suppressing the enzymatic function of affected protein leading to cell death (Kim et al., 2011). Most antibiotics are ineffective to inhibit multidrug-resistant (MDR) bacterial strains. However, silver nanoparticles can eliminate MDR bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Arcanobacterium pyogenes* responsible for mastitis, metritis, gastrointestinal, and respiratory infections in livestock (cattle, sheep, goats, pigs, and horses) by inhibiting the respiratory chain dehydrogenases and generating reactive oxygen species, thereby affecting ATP synthesis and cellular metabolic process (Gurunathan et al., 2018). Other means include the variation in the zeta potential on the surface of AgNP and microbes, synergistic ability of silver nanoparticles with β-lactam antibiotics in inhibiting hydrolytic β-lactamases, and biofilm disruption by inhibiting exopolysaccharide production (Kalishwaralal et al., 2010; Hwang et al., 2012).

In other words, there are electrostatic forces between the positively charged surface of NP and negatively charged surface of parasites allowing closer attraction and interaction for its scolicidal activity (Franci et al., 2015; Rahimi et al., 2015). Silver nanoparticles act in synergy with β-lactam antibiotics by inhibiting the hydrolytic β-lactamases produced by bacteria, disrupting the biofilm, consequently penetrating the cell and altering the cellular function (Hwang et al., 2012). The hydrophobic nature of AgNPs makes it easier for them to pass through cellular membranes and act as a carrier for hydrophilic antibiotics (Jamaran and Zarif, 2016). Reports have shown the ability of silver nanoparticles to exert bactericidal activity through a Trojan-horse mechanism, a mechanism involved in the cellular uptake of nanoparticles leading to cellular respiration impairment and release of intracellular metallic toxic silver ion (Hsiao et al., 2015). The antifasciolasis activity of AgNp when working in synergy with the established drug is by causing a pit-like structure on egg surface, leading to penetration of drug and cytoplasmic leakage causing death (Gherbawy et al., 2013). The antifungal activity of silver nanoparticles occurs by transcriptional inhibition of many aflatoxin genes, especially the two key regulatory genes for secondary metabolism, viz., laeA and veA and an associated decrease in total reactive oxygen species (ROS) (Mitra et al., 2017). The probable mechanism during healing is the increased blood flow to the wound area and decreased inflammatory response caused by silver nanoparticles (Li et al., 2006).

Drug solubility and bioavailability are major challenges in medical sector those need to be solved. Because of the properties, such as small size and the ability to withstand gastric enzyme and pH, nanoparticles have been used for encapsulation and targeted delivery of drugs and bioactive (hydrophobic and hydrophilic) compounds. Depending on silver nanoparticles composition and surface modification, these nanoparticles have been evaluated for their ability to enhance cellular and humoral immunity by increasing the production of lymphocytes, monocytes and neutrophils (Al-Rhman et al., 2016). The mechanism of silver nanoparticles in initiation and regulation of the immune response is not clearly understood, though it is suggested to be attributed to its interaction with macrophages which stimulates upregulation of proinflammatory genes (interleukin-IL1 and IL6), cytokine release, and leukocyte recruitment (Shin et al., 2007; Greulich et al., 2009) (Fig. 27.3).

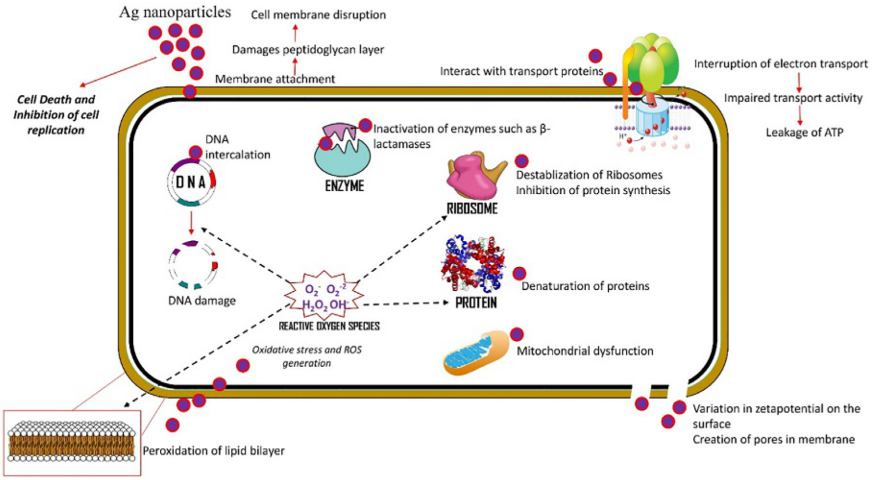

FIG. 27.3

Mechanism of antimicrobial activity of silver nanoparticles.

27.14.1 Nutrient deliveries for fetuses/neonates

Diarrhea is a major cause of loss in neonatal and preweaned livestock. This loss has economic implications. Administering nanoparticles either orally or intragastrically in pregnant and lactating mothers, respectively, can lead to accumulation in fetuses (Lee et al., 2012, 2018; Melnik et al., 2013). These reports indicate the possibility of nanoparticles to cross natural biological barriers like placenta or blood–brain barrier and pass from mother to offspring. During the transition from weaning to solid food in calves or lambs, certain gut microbial profile changes cause an influx of some pathogenic bacteria leading to diarrhea. The correct application of silver nanoparticles as a carrier of drugs or additives in the dam could be used as a medium of stabilizing the gut microbial community, thereby preventing disruption or gut microbial imbalance through breast milk. Pregnancy is important to all livestock operations as it represents the next generation of milk and meat-producing animals. At this stage, the cellular and hormonal system of offspring will be established and maternal nutrition can have an indelible influence on the lifetime productivity and health of progeny, which could enhance or limit productivity and efficiency (Greenwood et al., 2017). During mid to late pregnancy, the dam undergoes physiological changes to help maintain the increase in metabolic demand (Lemley, 2017). Abnormality at this stage can increase the risk of morbidity and mortality during the early neonatal stage (Sawalha et al., 2007) and other lifelong complications and developmental disabilities (Reynolds et al., 2013). The placenta helps in transporting nutrients between the mother and fetus, and this transfer is vital specifically in the growth and development of the fetus during the last half of gestation (Redmer et al., 2004). Size and nutrient transporter abundance are important factors affecting placental nutrient transfer capacity (Fowden et al., 2006). Due to its size and ability to cross the barrier, nanosilver can be designed to transport therapeutic supplements that could improve fetal growth, increase the average body weight at birth, and improve the chance of survival of offspring. Producers can use nanoparticle features as a specific strategy to improve reproductive efficiency of livestock (Lemley, 2017). Particularly, nanoparticles could be used to deliver drugs or vaccines to a fetus during growing epidemic regions.

27.14.2 Potential side effects

Many drugs used in both human beings and animals show some side effects, either mild or severe. For example, application of 50 ppm AgNP through drinking water reduced the growth and modulated the immune functions (Vadalasetty et al., 2018). Injecting nanosilver particles could cause lesions in liver and lungs by damaging the tissue (Doudi and Sertoki, 2014; Loghman et al., 2012). Application of nanosilver through drinking water reduced the yolk weight and hen-day egg production of Japanese quail layers (Farzinpour and Karashi, 2013).

Furthermore, oral subchronic exposure to silver nanoparticles for 13 days decreased the expression of immunomodulatory genes and altered microflora of ileal mucosa shifting the population towards gram-negative microbes, i.e., lowered *Firmicutes* phyla and *Lactobacillus* genus (Williams et al., 2015). Oral administration of silver nanoparticles at 0.5, 1.0, and 1.5 mg/kg BW showed a dose-dependent reduction in absorption of minerals such as K and Fe (Ognik et al., 2017). Intravenous administration of silver nanoparticles at 0.6 mg/kg BW reduced the sperm concentration in the first 21 days and had a similar effect to the control for the later 126 days period. However, the nanoparticles reduced sperm motility and sperm speed while increasing the sperm anomalies (Castellini et al., 2014). The aforementioned phenomena imply that silver nanoparticle has several negative effects on functions related to reproduction, mineral absorption, and metabolism.

The antimicrobial resistance phenomenon necessitates the precise use of nanoparticles according to the purpose. Further, we suggest investigation into other route of administration of nanoparticles that ensure minimal negative effects.

27.15 Conclusion

The use of silver nanoparticles as antimicrobial compounds possesses great potentiality in the animal husbandry sector. Despite the beneficial antimicrobial activity, silver nanoparticles pose negative effects on the environment due to the chemicals involved in the synthesis. Hence, green synthesis methods are most commonly encouraged nowadays. A silver nanoparticle can help overcome the resistance of disease-causing organisms by working in synergy with these established drugs and reducing the cost of developing a new drug. Nanoparticles could be used in fetal programing as delivery agents to immunity enhancement or delivery of mineral to a growing fetus. The wound healing properties of AgNp is outstanding as it aids quick healing of surgery wound and could be applied for healing of sunburn. The immunomodulatory function through the maturation of neutrophils and increased cytokine production is well evidenced. Overall, the diverse roles of silver nanoparticles in animal husbandry sector include, but not limited to, wound healing agents, health promoters, vaccine carriers, growth promoters, immunostimulants, synergic agents, and microbial-resistance preventive agents. However, projecting the silver nanoparticles as complete feed additives for livestock need extensive research, which is lacking at present. Similarly, the selecting appropriate dosages needs to be further studied by conducting a meta-analysis of all the data available on the usage of silver nanoparticles. Thus, the silver nanoparticle has excellent potentials for various veterinary applications.

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