R-2620
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REVIEW ARTICLE Agricultural Reviews

Nanotechnology for Animal Sciences-New Insights and Pitfalls: A Review

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10.18805/ag.R-2620

ABSTRACT

Nanotechnology applications are increasingly recognized as potential tools in animal sciences, veterinary medicine, drug delivery, disease diagnosis and vaccine development. The nanoparticles and their therapeutic trends provide a realistic glimpse of current and future trends in veterinary diagnosis and medicine. Nanotechnology is ascribed to provide new horizons for applications in molecular biology and biotechnology by revolutionizing almost every field of veterinary or animal sciences by offering novel nano-scale tools and materials which can benefit society in all walks of life. The nanoparticles have been employed in diverse biological and non-biological functions. Nanomaterials can contribute to the farm animals for long-term sustainability by increasing the quality and quantity of safe, healthy and functional animal products. Although there are advantages while using nanoparticles to enhance performance and heal diseases in livestock, it is universally recognized that some nanoparticles can cause toxic and adverse effects on living creatures. Apart from that, the promise of nanoscience in veterinary medicine and livestock reproduction is yet to be explored. A few studies have been made on the uses of nanoparticles in veterinary medicine, livestock health and reproduction. Awareness is needed about the possible toxic effects and hazards, which could harm the living world. To improve the efficient and accurate diagnosis and treatment of animal diseases, more sophisticated research on nanomaterials and nanomedicines is required.

Key words: Antimicrobial, Drug delivery, Nanotechnology, Nanotoxicity, Steroidogenesis.

Nanotechnology is the fastest-growing field of science that involves the study of structures and materials on ultra-small or atomic scale molecules which represents one billionth of a meter (10^{-9} m) (Shi *et al*., 2010). The concept of nanotechnology was described by eminent physicist and Nobel Laureate Richard Feynman in 1959 in his talk entitled “There’s plenty of room at the bottom”. During this talk, he illustrated that the modification of atoms is a key feature for a possible way of synthesis (Sahoo *et al*., 2007; Singh *et al*., 2011 and National Nanotechnology Initiative, 2021). After fifteen years in 1974, Professor Norio Taniguchi coined the term “Nanotechnology”. The ‘Nano’ word comes from the Greek prefix that means “dwarf” (Bayda *et al*., 2020; Kreuter, 2007). The National Nanotechnology Initiatives Council of the United States of America (2004), describes nanotechnology as “The understanding and control of matter at the scale of nanometre approximately 1 to 100nm range” (Jeevanandam *et al*., 2018; Jiang *et al*., 2008) (Fig 1). At this scale, the physical, chemical and biological properties of materials behave often unexpectedly from the adjacent bulk materials (Rai and Ingle, 2012; McNeil, 2005). Nanotechnologies have the potential to make enormous revolutionary changes in the agriculture and livestock sectors. Moreover, reforming almost every discipline of science, including chemistry, molecular biology, biotechnology, computer science, veterinary science and animal reproduction (Patil *et al*., 2009; Buzea *et al*., 2007). In recent years, nanotechnologies have been applied in various fields of science with promising results. It offers various diagnostic tools that are less expensive, faster and more sensitive than others. Nanoparticles have innovative physicochemical properties that are superior to bulk materials due to their huge surface-to-volume ratio, higher reactivity, stability, functionality, bioavailability, controlled drug arrival and drug delivery at the specific target site (Mohanraj and Chen, 2006; Num and Useh, 2013). Nanomaterials are now widely used in imaging and biomedical research screening and, earlier diagnosis of diseases (Tripp *et al*., 2007). Nanoparticles can penetrate cells, tissues and organs more than macroparticles and they have the potential to overcome poor bio-accessibility and high toxicity (Underwood and Van Eps, 2012; Prasad *et al*., 2021).

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How to cite this article: Kumar, P., Singh, P., Chauhan, S., Swaroop, M.N., Bhardwaj, A., Datta, T.K. and Nayan, V. (2023). Nanotechnology for Animal Sciences-New Insights and Pitfalls: A Review. Agricultural Reviews. doi: 10.18805/ag.R-2620.

Submitted: 18-01-2023 **Accepted:** 21-02-2023 **Online:** 27-03-2023

Types of nanoparticles

Nanoparticles are broadly classified into various types based on their origin, size, shape and chemical properties with a diameter of fewer than 1,000 nm (Brigger *et al*., 2012; Jeevanandam *et al*., 2018; Mahmoudi *et al*., 2011). Nanoparticles such as polymers, carbon nanotubes, dendrimers, silicon oxides, inorganic materials, quantum dots and liposomes have been discovered during the last few decades using a variety of components and a growing number of revolutionary novel nanomaterials (Baptista, 2009). Some of the common nanoparticles are described below in (Fig 2). These nanomaterials may be:

Organic nanoparticles

Organic nanoparticles are colloidal materials with unique size-dependent physicochemical properties such as optical, magnetic, catalytic and electrochemical. The most common types of organic nanoparticles are polymeric nanoparticles, liposomes, micelles and dendrimers (Fig 2).

Inorganic nanoparticles

This category includes various nanomaterials, such as quantum dots, carbon nanotubes, buckyballs, nanoshells, silver and iron oxide (Fig 2). They are generally safe and nontoxic, with unique optical and electrical properties that can be modified during the development process.

Applications of nanotechnology in animal sciences

Nanotechnology in farm animals

Nanoparticles are available in the market and as technology progresses, their properties would become more sophisticated for a broader variety of uses. Many developing countries are rapidly growing market demand for livestock products. The growing field has tremendous use of nanomaterials in our daily life. These NPs uptake mechanisms can be either intentional or accidental. These nanoscale particles can enter the body through skin pores, fragile tissues, infusions, the respiratory system and the intestinal gut. Their entry and accumulation into the cells might cause adverse health effects. Recently, the use of nanomaterials is quite common in the livestock, agriculture as well as poultry sector to enhance the shelf life and freshness of food products (Bai *et al*., 2018). They are also used to enhance animal immunity, oxidation resistance and output while reducing antibiotic use in livestock (Huang *et al*., 2015). According to recent research, the utilization coefficient of inorganic trace elements was found to be approximately 30%, while nanoparticles were close to 100%. Selenium nanoparticles have the potential to improve the health of livestock, poultry and fish, as well as promote growth and enhance feed conversion rate, among various aspects (Cai, 2012) (Fig 3).

Assisted reproductive technology

Assisted reproductive techniques (ART) have allowed breeders to generate progeny with desirable characteristics in farm animals that were previously thought to be infertile using traditional breeding methods. The productivity and profitability of livestock farming systems are strongly influenced by farm animals' reproductive performance. Nanotechnology has come to the forefront in the area of reproduction, fertility and optimal reproductive management is based on applying various precise strategies which also take into account cost and environmental implications (Olynk and Wolf, 2008; Smith *et al*., 2018). Traditional processes of *in vitro* fertilization (IVF) and *in vitro* embryo production, microfluidic and nanofluidic. It might be a beneficial tool in farm animal breeding and reproduction. Recent, research has shown that microfluidics may be used to isolate motile sperm without centrifugation with the development of this technology, oocyte modification *in vitro* may also become

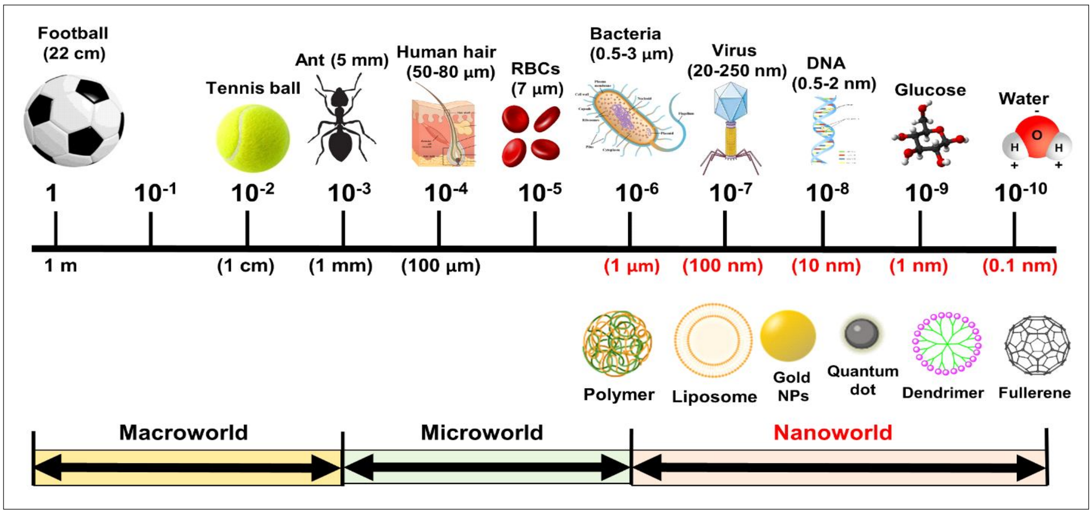

Fig 1: Represents the length of the relative size of nanomaterials in comparison to naturally occurring things. Some examples of nanoparticles are shown at the bottom of the right corner of the figure: fullerene, dendrimer, quantum dot, gold nanoshell, liposome and polymer nanoparticles (Irache *et al*., 2011).

feasible (Schuster *et al*., 2003; Suh *et al*., 2006). An *in vitro* study shows the effect of selenium nanoparticles on buffalo oocyte maturation. They have found that supplementation of selenium in large-size or nano-particle forms improved buffalo oocytes maturation and the size of nanoparticles has an impact on this improvement. Furthermore, when compared to bulk-form selenium nanoparticles (40 nm) stimulate greater antioxidant gene expression (El-Naby *et al*., 2020). Nanopurification could be used to separate damaged sperm from intact and healthy sperm. The protein-based elimination method is to bind magnetic nanoparticles with specific antibodies targeting ubiquitin or lectin a surface membrane marker of abnormal sperm. Nanopurified bull (*Bos taurus*) sperms produced pregnancy rates comparable to impurified sperm about half of the dose and without any adverse effects on inseminated cattle. Resulting, a single diluted nano-purified sperm sample can inseminate more females (Odhiambo *et al*., 2014; Petruska *et al*., 2014).

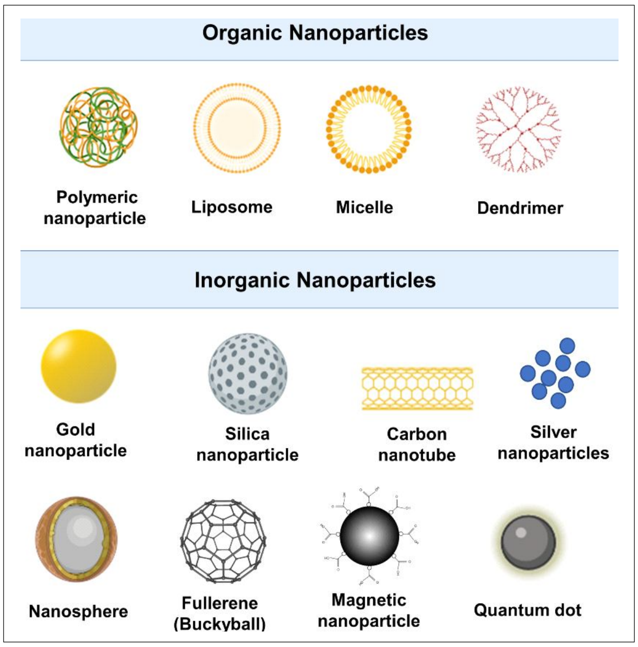

Fig 2: The schematic representation of various types of nanoparticles (Silva *et al*., 2019).

The purpose of these nanotechnology-based studies on animal reproduction is to characterize the nanoscale properties of gametic cells (sperm or oocyte) using atomic force microscopy (AFM) and similar scanning probe microscopy (SPM) methods. Development of nano biosensors for investigation of the physiological status of reproductive health. Production and development of metal-based nanoparticles used in fertility control applications developing nanodevices for reliable cryopreservation of gametes, embryos and sustainable release of small molecules such as hormones, vitamins, antibiotics, antioxidants and nucleic acids, among others (Saragusty and Arav, 2011). The purpose of these novel approaches is to characterize and modify matter at the nanoscale to generate products with value-added economics, social and environmental value and focus on animal reproductive

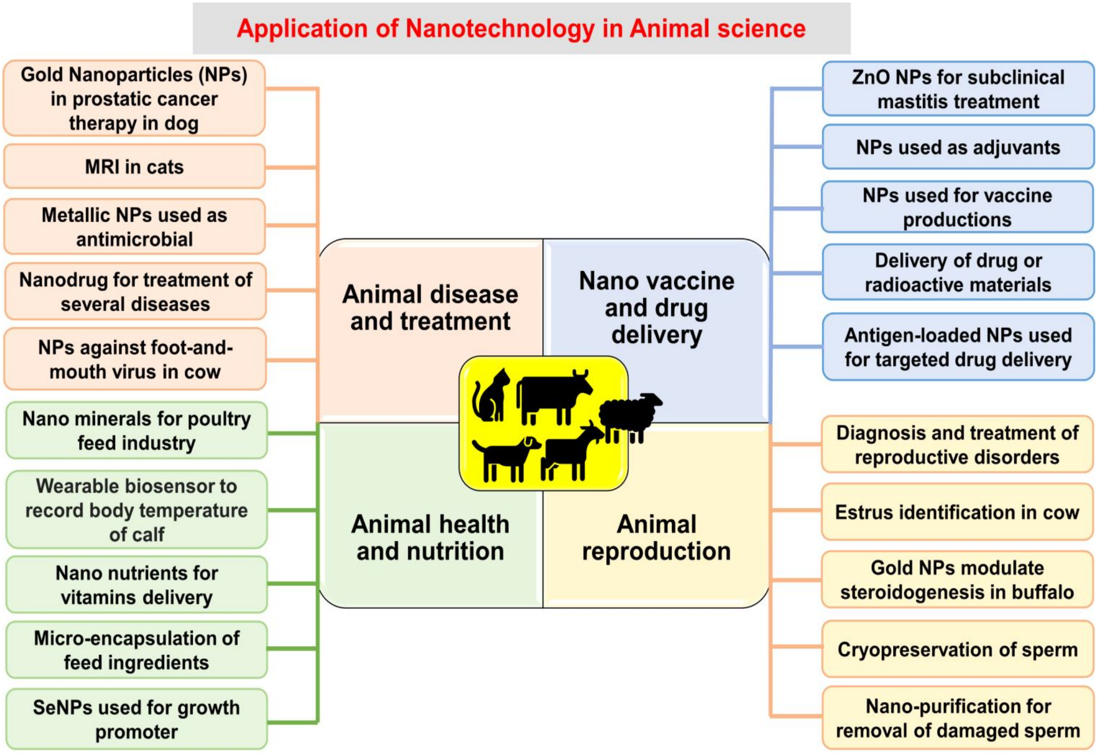

Fig 3: The schematic diagram represents applications of nanotechnology in animal science.

challenges (Scott, 2007). It is noteworthy, that nanotechnology has started to flourish in the field of reproduction and fertility (Chen and Yada, 2011; Verma *et al*., 2012).

Nano-biosensor for animal health and management

Researchers have developed nano biosensors for the diagnosis of pathogens, diseases, estrus, hormone level and physiological changes in the reproductive tract of animals (Monerris *et al*., 2012). Wearable biosensors are innovative technologies nowadays becoming increasingly important for animal health and management. Biosensors and wearable technology can be deployed on animals to detect their sweat composition and analyze the sodium content present at a particular time (Glennon *et al*., 2016). Respiratory disease in livestock is quite common and may cause infantile death. The efficient way to early diagnose respiratory infections is to measure the rectal temperature of a calf by using a thermometer. However, this method is time-consuming and required lots of effort from farmers during group feeding. The author has developed a wearable wireless biosensor device to record the body temperature of the calf automatically and save time and effort for the farmers (Nogami *et al*., 2014).

Veterinary medicine and diagnosis

Nanotechnology has potential applications in biosensing, bioimaging and veterinary medicine including disease diagnosis, treatment, pathogen detection and targeted drug delivery (Chakravarthi and Balaji, 2010). The varieties of nanomaterials used in diverse applications like nanoshells are used to destroy cancer cells by using Infrared Radiation (IR) carbon nanotubes for sensors and drug delivery, gold nanoparticles for disease diagnosis, nanocrystalline silver acts as an antimicrobial agent and iron oxide nanoparticles used for improved magnetic resonance imaging (MRI) (Meena *et al*., 2018). The nanoparticle-based medicine preparations have opened up new opportunities for the diagnosis and treatment of severe diseases. The area of veterinary medicine requires new innovative solutions to overcome from current challenges of antibiotic resistance. Nowadays antibiotics are frequently used to treat infectious diseases. High prices for medication and treatment services continue to require a novel solution in the veterinary sector. The nano-based systems have been developed to carry cargo including antibodies, vaccines, drugs and hormones at a specific target site. The effectiveness and safety of the administered drugs are very high when compared to the traditional drug delivery system (Cerbu *et al*., 2021). Nanoparticles, nanoemulsion, nanogels and nanocapsules are among the most frequent form of nanomaterial-based nano-carrier used as a controlled drug released into a specific location. The nanocarrier protects delivered steroid hormones and vitamins from deactivation and degradation by oxidation (Joanitti and Silva, 2014). The liposome is a spherical phospholipid nanoscale vesicle that can be easily formulated, highly flexible and administrable into the target site of the animal (Sadozai and Saeidi, 2013). The development of numerous pheromone-based protocols for biological control of reproductive events, including the male effect, estrous detection, postpartum anoestrous, adolescence, pregnancy diagnosis, male sexual activity and mother-offspring behaviour is a possible way to the rapid development of aerosol nano-drug delivery technology (Kekan *et al*., 2017; Archunan, 2020).

Nanoparticles as drug delivery systems

Precise nano-sized drug delivery systems are substantially smaller than their targets. It is highly anticipated that these nanoscale drug delivery methods are a reality through advancements in nanotechnology. Nanoparticles are rapidly being recognized as an excellent choice for efficiently transporting therapeutic agents into a particular area inside of an organ, tissue, or cells. The combination of nanomaterials, such as nanoparticles with therapeutic drugs has now created entirely new therapeutic opportunities for the treatment of mild and severe diseases in farm animals (Table 1). The usage and effectiveness of several presently available pharmaceutical drugs have low bioavailability and undesirable side effects. About 95% of all therapeutic drugs have poor bioavailability and pharmacokinetics (Scott, 2007). In numerous studies, nanoparticles have shown significant efficiency in the delivery of antineoplastic compounds (Patil *et al*., 2009), antimicrobial (O'connell *et al*., 2002) and anti-inflammatory compounds (Manikkaraja *et al*., 2020). Recently, nanotechnology-based drug delivery methods have been developed to enhance the biological activity of medications, including hormones. The effectiveness of the ovsynch estrous synchronization protocols improves ovarian response, in goats where GnRH and PGF2á are administered using a nano-based drug delivery system which helps to induce greater ovulation synchronization and improved luteal function in synchronized goats. This procedure is frequently employed in farm animals since it helps with herd management and is not dependent on the detection of estrus (Hashem *et al*., 2022). Furthermore, Bhardwaj *et al*., (2019) have developed a reliable method for total antioxidant capacity (TAC) and ferric reducing ability of plasma (FRAP) assay were used to identify the potential of antioxidants in Indian Halari donkey milk and French Poitu donkey milk.

Vaccine delivery

Nano-vaccines and nano-adjuvants have been widely used in the development of animal vaccinations due to their high capacity to boost immune responses. Nano-vaccines are more effective than traditional vaccination they enhance antigen-antibody interaction to stimulate antigen-presenting cells to prevent infections and diseases from spreading. Furthermore, they can be used as an adjuvant to slow down the release of antigens, which will improve vaccine efficacy (Awate *et al*., 2013; Torres-Sangiao *et al*., 2016). Antigen-loaded NPs can target lymph nodes improving vaccination efficacy (Moyer *et al*., 2016). This novel vaccine contributes to improving efficacy and safety performance in both pets and livestock (Akagi *et al*., 2011). Liposomal vaccines can be prepared by conjugation of bacteria, soluble antigens and cytokines with liposomes. Liposomes as vaccine adjuvants have firmly been recognized as immunoadjuvants (immunological response boosters) capable of enhancing both cell-mediated and humoral immune systems. These immune adjuvants act by slowly liberating encapsulated antigenic peptides on intramuscular injection in lymph nodes. Vaccination against the foot-and-mouth disease virus (FMDV) is a major issue since present vaccinations made it difficult to distinguish between infected and immunized animals (Gregoriadis, 1995). Furthermore, the novel nanoparticle-based adjuvants are suitable for mucosal routes. Another biological important rationale for using mucosal vaccines is that the majority of infections originated on the mucosal surface and protection at this point of entry is required (gastrointestinal, respiratory and urinary tracts). The mucosal vaccination with antigens-loaded particles promises a strong scientific rationale for protecting antigens from extreme conditions of pH, bile and pancreatic secretions (Desai *et al*., 1996; Arbos *et al*., 2003). Although, they provide a slow release of antigens (depot effect) for sustainable stimulation of the immune system (Storni *et al*., 2005).

Detection and removal of pathogens

The use of nanotechnology-based sensors gained tremendous popularity for the detection of foodborne pathogens. Nanomaterials are not only used to detect but also to bind and remove foodborne pathogens from poultry and could have great benefits in reducing the risk of food-borne disease (Kuzma *et al*., 2008). The nanoparticles have the potential to bind pathogens in the gut of animals to prevent colonization and growth and are removed through the waste. The nanoparticles could replace traditional sub-therapeutic uses of antibiotics such as penicillin, tetracycline, lincomycin and macrolides are also used in veterinary patients and assist them to prevent the spread of antibiotic-resistant bacteria (Taylor *et al*., 2004). Bhardwaj *et al*., (2019) have developed a standardized protocol for the production of recombinant pregnant mare serum equine chorionic gonadotropin (PMSG-eCG) based on immunoassay with great diagnosis efficiency. Nowadays, ticks (parasitic insects) are the major problems that cause huge economic losses in the dairy and livestock production sector worldwide (Zaheer *et al*., 2022). In addition, researchers investigated the potential of nanotechnology in the eradication of tuberculosis worldwide in livestock (Bharti *et al*., 2022). Recently, Dhoolappa *et al*., (2022) reported that the novel nano-bioscaffolds have excellent wound-healing properties in animals.

Table 1: Nanoparticles and their application in veterinary medicine.

Nanoparticles	Size (nm)	Applications	Animal species	Reference
Magnetic NPs	50-200	Anti-tumor effects	Cats	(Sincai *et al*., 2005).
Dendrimers	<10	Microbicide	Pigs	(Underwood and van Eps, 2012).
		Vaccine delivery and chemotherapy	Mice	(Malik *et al*., 2000; Kukowska-Latallo *et al*., 2005).
Nano-emulsion	10-1000	Drug delivery	Dogs, Cats and therapeutics	(Underwood and van Eps, 2012).
Micelle	<100	Therapeutics	Sheep, birds, horse	(Underwood and van Eps, 2012).
Liposome	50-100	Therapeutics, vaccine delivery, sarcomas therapy and antibacterial activity	Cattle, dogs, horses, cats, birds, sheep and mice	(Underwood and van Eps, 2012; Matteucci *et al*., 2000; Wang *et al*., 2015).
Nanosphere	1-1000	Vaccine delivery	Horse	(Underwood and van Eps, 2012).
Quantum dot	2-10	Drug delivery and bio-imaging	Mice	(Michalet *et al*., 2005; Bentolila *et al*., 2009).
Gold nanoparticles	5-400	Cancer therapy	Dog and Cats	(Zabielska-Koczyw¹s *et al*., 2017)
Polymeric NPs	10-1000	Cancer therapy, solid tumors therapy, antifungal treatment and tuberculosis	Mice, poultry and guinea pig	(Redhead *et al*., 2001; Rapoport *et al*., 2003; Yu *et al*., 1998; Vargas *et al*., 2004; Franklin *et al*., 2003; Kaur, *et al*., 2020; Sharma *et al*., 2004).
Metallic nanoparticles	<50	Treatment of canine distemper	Dog	(Bogdanchikova *et al*., 2016).
		In vitro effects against foot-and-mouth disease virus (FMDV)	Razi Bovine kidney (RBK) cell line	(Rafiei *et al*., 2015).

Diagnosis of mastitis and its prevention

Bovine mastitis is the most destructive disease in dairy cows around the world, caused by a variety of bacteria (*Staphylococcus aureus)*. The most severe infection, especially in the bovine, is the biggest threat to dairy production (Monistero *et al*., 2018). The failure of mastitis therapy is due to the rapid emergence of multidrug resistance. Therefore, it's an immediate need to overcome these traditional antibiotics. Recently, nano-drug have been used to solve these multidrug-resistant problems. Therefore, increasing the development of nanoparticles including liposomes, nano-gels, solid lipid nanoparticles (SLNs) and metal nanoparticles increases the enormous attraction for addressing the treatment challenges associated with mastitis (Le Ray, 2005; Franci *et al*., 2015; Wang and Shao, 2017; Zhou *et al*., 2018; Algharib *et al*., 2020). ZnO nanoparticles have been shown to promote growth rate and immunological response in livestock. It has the potential to treat subclinical mastitis in dairy cattle. ZnO can reduce antibiotic resistance and improve ciprofloxacin's antimicrobial activities against microorganisms by interacting with several proteins involved in antibiotic resistance (Num and Useh, 2013).

Estrus detection

Nanosensors are nanoscale devices that are highly sensitive to mobile sensing biomolecules. The application of nanosensors in livestock is to diagnose reproductive tract infections, metabolic and endocrine disorders as well as in estrus detection (Saragusty and Arav, 2011). Management of livestock breeding is costly and time-consuming for dairy farmers. Therefore, nanotubes are placed under the skin during the estrus of animals to measure the estradiol concentration in the blood at a particular time. The nanotubes have a binding affinity towards the estradiol antibody during the estrus phase and transmit the fluorescence signal towards the signal receiver central computer. Recently, a new approach based on a colorimetric assay to determine odorant chemical compounds (pheromones) for diagnosis of estrus in bovine by using capped L-tyrosine silver nanoparticles (L-TyrAgNPs). They have found that sex pheromones like acetic acid or propionic acid change color from yellow to reddish-brown which might have great potential to apply in colorimetric sensors for the identification of the accurate time of estrus (Manikkaraja *et al*., 2020). The main constraints in breeding animals are the accurate time of heat identification. Recently, Bhatia *et al*., (2021) developed a non-invasive method for estrus identification in buffaloes based on seed germination inhibition test.

Ovarian steroidogenesis

Granulosa cells are associated with steroidogenesis in the ovary of mammals. Recent studies have suggested that the buffalo granulosa cells co-incubated with AuNPs with two different concentrations (2×10^{9} and 2×10^{10} AuNPs/ml) for 24 h. In the buffalo ovarian granulosa cells, the gold nanoparticles did not show oxidative stress. AuNPs can regulate the endocrine system by modulating the steroidogenic and apoptotic pathways (Lyngdoh *et al*., 2020). Similarly, *in vivo* experiments showed that AgNPs modulated steroidogenic pathway mRNA genes (HSD3β, CYP17A1 and CYP19A1) expression in ovarian follicles in laying chickens (Katarzyñska-Banasik *et al*., 2021). *In vitro* effect of silver nanoparticles (SNPs) on the maturation of the rabbit's oocytes co-culture with granulosa cells. The reduction of granulosa cell viability was confirmed by the release of calcium and lactate dehydrogenase in the culture medium. The non-toxic effect of silver nanoparticles on rabbit oocytes is also observed due to the presence of zona pellucida (Syrvatka *et al*., 2015). Recent, studies have shown that inhaled, ingested, or dermally absorbed nanoparticles can translocate through the circulatory system and accumulate in different reproductive organs and even can enter into ovarian theca and granule cells. Which can modulate their normal function, especially in hormone secretion. *In vitro* studies revealed that certain NPs may enter into granulosa cells, causing an alteration in the hormone's secretion and dysplasia of the ovum (Stelzer and Hutz, 2009).

Nanotoxicity and safety issues

Nanotechnology and nanomaterials play an important role in reducing risk in animal husbandry and food systems. Nanotechnologies can be employed in a wide range of fields, while many positive outcomes have been achieved, they also have several negative effects or possible risks for humans, animals, plants and the environment. The toxic effects of nanoparticles are dose-dependent which affects cellular pathways including apoptosis, necrosis and autophagy causing cell death as described in Fig 4. There are various challenges associated with nanomaterials such as digestion and metabolism within the animal's body. Despite several impressive effects of nanomaterials such as targeted vaccine delivery, immune response, growth, antimicrobial and bioavailability. Therefore, authorities also must consider the economic, legal and ethical concerns regarding the use of nanomaterials. Government and regulatory authorities, environmental, health and safety councils and private and scientific organizations, around the world are recognizing the importance of risk assessment of nanotechnology (Mason, 2009; Hansen *et al*., 2013).

The current challenges and future perspective

While the process of introducing a new drug to market is costly and complicated, veterinary drugs and medicine must be cost-effective and affordable, human medicine is subsidized by the national health department in most countries and animal owners must pay the full price of prescription drugs for the treatment of their animals. Furthermore, the market for veterinary animals is less than that for human health medicine. In addition to that species-specific drug formulation and delivery methods are required for livestock. In the future, nanotechnology will reform veterinary science and technology and increase livestock production to fill knowledge gaps for the welfare of livestock.

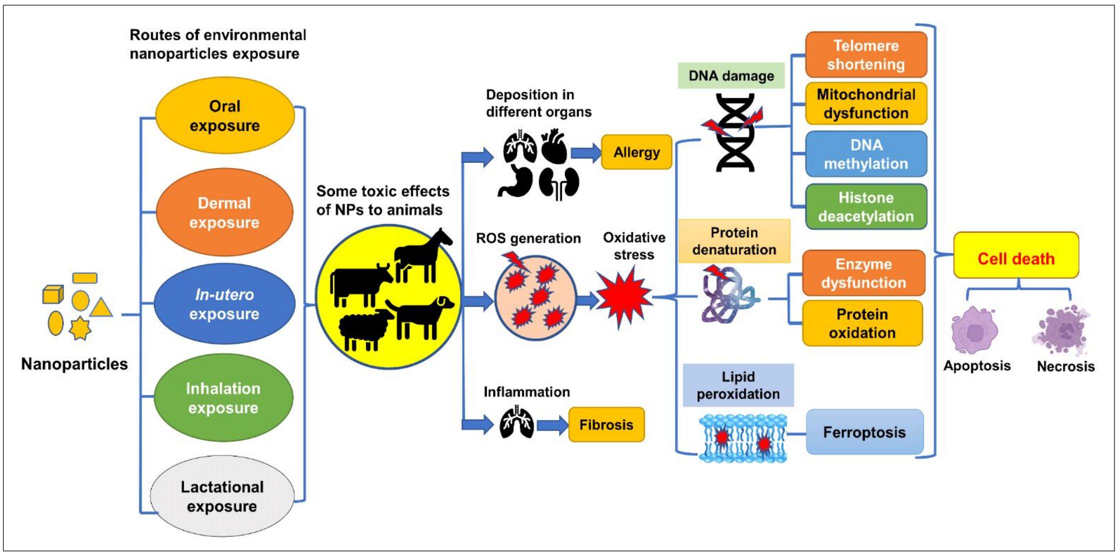

Fig 4: Environmental nanoparticles exposure to animals and its cytotoxic effects. The major routes of exposure to these nanoparticles in animals are oral, In utero, lactational, dermal and inhalation. Apart from those toxic effects of nanoparticles including reactive oxygen species (ROS) generation causes oxidative stress and deposition in various organs causing inflammation and allergy. The damage to DNA, proteins and lipids causes cell death via apoptosis, ferroptosis and necrosis (Sengul and Asmatulu, 2020).

Despite tremendous applications, nanotechnology also has some limitations in drug delivery systems, diagnosis, bioimaging and food safety concerns because it requires highly sensitive, degradable, affordable, cost-effective devices and less toxic nanoparticles. However, more research is needed to confirm the toxicity of nanoparticles.

CONCLUSION

Nanotechnology has emerged as a novel paradigm in almost every field of science. It has the potential to provide accurate and precise drug delivery systems, early diagnosis of diseases, therapeutic application, nanomedicine, breeding, reproduction and value addition to livestock products. Although, nanotechnology is considered one of the greatest advances in application in veterinary medicine is still in its beginning compared to other related disciplines. Nanotechnology also plays an important role in livestock foods such as meat and milk and will strengthen the quality and safety of animal-origin food products. Therefore, future research involving nanomaterials should be performed to assess their productivity, health, safety and toxicity issues.

Author's contributions

Prashant Kumar, Pushpanjali Singh, Shipra Chauhan, MNS, AB, TKD and VN has written the manuscript; PK, PS, SC and M.N. Swaroop, contributed to the literature search and Prashant Kumar, Varij Nayan, Anuradha Bhardwaj and T.K. Datta critically analyzed the manuscript. All the authors have read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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