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Application of Nanotechnology for Animal Health and Production Improvement: A Review

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Abstract: Nanotechnology is an exciting and rapidly emerging technology allowing us to work at the atomic, molecular and macromolecular levels to create, manipulate and use tools, materials and functional structures that have nanometer dimensions. The concept of nanotechnology was created in 1959 for the first time. However, the basic idea of definition and popularization was explored in much more in 1980s. Nanotechnology has opened up new panoramas for applications in molecular biology, biotechnology in revolutionizing almost all the disciplines of veterinary and animal sciences by providing new, small scale tools and materials that are beneficial for living organisms. The variety of nanomaterials that are used for disease diagnosis, treatment, drug delivery, animal nutrition, animal breeding, reproduction and value addition to animal products; these are metallic nanoparticles, quantum dots, carbon nanotubes, magnetic nanoparticles, fullerenes, liposomes and dendrimers. Also nanoparticles play a great role in food industries to improve hygiene, extend the shelf life of products and prevent food-borne illnesses and contamination by chemicals. Even though nanotechnology is one of the major innovations which have already been applied in different area, it is still in the early stages of its development and also considered as it has a negative effect on environment and people health like intoxication. There for, scientists, engineers and biologists should work at the cellular and molecular levels for significant benefits and there should be public awareness about the potential risks.

Key words: Dendrimers · Fullerenes · Nanoparticles · Liposomes and Quantum Dots

INTRODUCTION

Nano is a Latin word which means 'Dwarf ' and the thought of nanotechnology was first time given by Nobel laureature physics Richard Fenman in the south California in 1952 [1, 2]. In real sense term nanotechnology was popularized by Eric Drexlerin 1980s. Nanotechnology is a technology of experimenting and manipulating with particles, called nanoparticles that are demonstrated in the scale of nanometers by the exploitation of the concept of nano-technology one can manufacture the structures materials, decades and machines by using nano-particles with programmed precision [3]. It is considered as a potential technology to revolutionize veterinary medicine, animal health and other areas of animal production [4]. By the use of emerging technology one can alter the form of production, processing, packaging and even mode of products ultimate use. Nanotechnology may also be useful to develop nanoscale materials, controlled delivery systems, contaminant detection and to form nano devices for molecular and cellular biology [5]. According to the United State (US) Government's National Nanotechnology Initiative, nanotechnology is defined as Research and technology development at the atomic, molecular and macromolecular levels at the scale of approximately 1-100 nanometer range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices and systems that have novel properties and functions because of their small and/or intermediate size [6].

Diseases of livestock such as helminthiasis, trypanosomiasis, tick and tick-borne diseases, influenza, clostridial infections, just to mention a few have made news headlines all over the world, because of their devastating effects on livestock population and the potential for some of these to be transmitted to human beings [7]. Several decades, to distinguish animal and human pathogens that caused similar diseases, because of unavailability of sensitive diagnostic tools and

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protocols [8]. Nanostructures developed by rational approaches are among the most impressive manmade materials and exhibit unique chemical, physical and /or biological features [9]. These features allow the nanostructures to be used for an unprecedented number of applications ranging from electronics and agriculture to medical and health care [10].

Nanotechnology has the potential to have great impact on diagnosis and treatment of humans and animals. Unique size dependent properties of nanoparticles have numerous diagnostic applications such as diagnostic biosensors, imaging nano probes for magnetic resonance imaging contrast agents [11]. It holds a major promise for animal health, veterinary medicine and other areas of animal production and has also a key role in treatment of diseases by the development of smart drug delivery systems which provides time controlled spatially targeted, self-regulated, pre-programmed and effective dosage of drugs to the site of disease. One particular application of nanotechnology in medicine currently being developed involves employing nanoparticles to deliver drugs, heat, light or other substances to specific types of cells (such as cancer cells). Particles are engineered so that they are attracted to diseased cells that allow direct treatment of those cells [12]. The development of such technique reduces damage to healthy cells in the body and allows for earlier detection of disease. However, nanoparticle does not actually destroy virus molecules but delivers an enzyme that prevents the reproduction of virus molecules in the patient's blood stream [13].

Nano probes are other promising area in healthcare that could actually be programmed to repair specific diseased cells, functioning in a similar way to antibodies in our natural healing processes. There are varieties of nanomaterials that are probed nowadays for their probable use in diverse applications examples, buckyballs (trapping free radicals generated during allergic reactions), nano shells (to destroy cancer cells using Infrared radiations), alum inosilicate nanoparticles (to reduce bleeding), carbon nanotubes (sensors and drug delivery), gold nanoparticles (diagnosis, labeling agents), nano-crystalline silver (antimicrobial agent), nano probes (individual cell repair) [14]. Therefore, the objective of this paper is to review the application of nanotechnology and highlight the types of nanoparticles and their roles on animal health and production improvement.

Nanotechnology and Medical Applications: Development of newer drug delivery systems based on nanotechnology methods is being tried for conditions like cancer, diabetes, fungal infections and viral infections and in gene therapy. The main advantages of this modality of treatment are targeting of the drug and enhanced safety profile. Nanotechnology has also found its use in diagnostic medicine as contrast agents, fluorescent dyes and magnetic nanoparticles [15].

Liposomes: Liposomes discovered in mid 1960s were the original models of nanoscaled drug delivery devices. They are spherical nanoparticles made of lipid bilayer membranes with an aqueous interior but can be unilamellar with a single lamella of membrane or multilamellar with multiple membranes. They can be used as effective drug delivery systems. Cancer chemotherapeutic drugs and other toxic drugs like amphotericin and hamycin, when used as liposomal drugs produce much better efficacy and safety as compared to conventional preparations [16].

Fullerenes: Fullerenes, a carbon allotrope, also called as "bucky balls" were discovered in 1985 [17]. Fullerenes are being investigated for drug transport of antiviral drugs, antibiotics and anti-cancer agents and used as free radical scavengers due to presence of high number of conjugated double bonds in the core structure [18]. Fullerenes have the potential to stimulate host immune response and production of fullerene specific antibodies. Animal studies with C60 fullerene conjugated with thyroglobulin have produced a C60 specific immunological response which can be detected by ELISA with IgG specific antibodies [19].

Nanotubes: Carbon nanotubes discovered in 1991 are tubular structures like a sheet of graphite rolled into a cylinder capped at one or both ends by a Bucky ball. Nanotubes can be single walled carbon nanotube (SWCNT) or multiwalled carbon nanotube (MWCNT) in concentric fashion. It can be made more soluble by incorporation of carboxylic or ammonium groups to their structure and can be used for the transport of peptides, nucleic acids and other drug molecules. Entry of nanotubes into the cell may be mediated by endocytosis or by insertion through the cell membrane [20, 21].

Quantum Dots (QD): Quantum dots are nanocrystals measuring around 2-10 nm which can be made to fluorescence when stimulated by light. Their structure consists of an inorganic core, the size of which determines the color emitted an inorganic shell and an aqueous organic coating to which biomolecules are conjugated.

It can be used for biomedical purposes as a diagnostic as well as therapeutic tool and can also be used for imaging of sentinel node in cancer patients for tumors staging and planning of therapy. This method can be adopted for various malignancies like melanoma, breast, lung and gastrointestinal tumors [22].

Dendrimers: Dendrimers are nano molecules with regular branching structures. The number of branching determines the size of the dendrimer which can be controlled [23]. It used for gene therapy where these can replace conventional viral vectors and their major stress in the treatment of cancer as these nano metric particles passively accumulate at the site of tumors, they enter the cells by endocytosis and the DNA gets transported into nucleus for transcription of the applied gene [24]. The recent research indicates that dendrimers might be considered as potential drug carriers for treatment of diseases with the capability to provide a sustained release along with reduced side effects [25].

Chemical Composition of Nanoparticles (Nps): A range of nano particular systems, which include functionalized fullerenes and carbon nanotubes, liposomes, iron oxide NPs, polymeric micelles, dendrimers, nanoshells, polymeric nanospheres, nanobins, quantum dots and polymer-coated nanocrystals, among others are being applied to improve human and animal disease outcomes, antimicrobials are being placed into polymer-coated crystalline nanoparticles, homogenized particulate suspensions, cholesterol-conjugated amphiphilic peptide self-assembled particles, composite hydrogel/glass particles, liposomes, polylactic -co- glycolic acid (PLGA), cationic and pDNA (photographer deoxyribonucleic acid) coated gold nanoparticles. Liposome-based therapeutics has been approved by the FDA (Food and Drug Administration) for indications including fungal infections, for example, liposomal amphotericin B [26]. These nanostructures have shown excellent results, especially in life-threatening diseases such as staph infections and tuberculosis [27].

Nanostructures can be equipped with smart components to allow their delivery beyond certain biological barriers, such as skin, eye, brain, placenta, mucus, blood, extracellular matrix, cellular and subcellular organelles. “Smart’ delivery systems can have multifunctional characteristics to successful targeting and they may also be time controlled; spatially targeted; self-regulated; remotely regulated; pre-programmed [28]. Monofunctional NPs provide a single function a liposome can transport drugs but does not have the inherent property to distinguish between healthy and unhealthy cells or tissues multifunctional nanoparticles combine different functionalities in a single stable construct [29].

Use of Antimicrobial Nanoparticles in Livestock Animals: The main safety and efficacy studies of nanoparticles in Veterinary Medicine are being done in livestock animals. Examples of potential applications of nanotechnology in the science and engineering of agriculture and food systems include disease treatment delivery systems, new tools for molecular and cellular biology, the security of agricultural and food systems, new materials for pathogen detection and protection of the environment [28]. Scientists are engaged to develop new antimicrobial products, using conventional or natural

Table 1: Chemical composition, characteristics and functions of nano particles

Chemical composition	Characteristics	Functions
Fullerenes and Carbon Nanotubes	Lack of water solubility	Vehicles for nano drugs delivery; Contrast agents; Photo thermal cancer ablation
Liposomes	Vesicles composed of a lipid bilayer surrounding a hollow core, they can be composed of natural phospholipids or other surfactants	Drugs or other molecules can be loaded for delivery to tumors or other disease sites; Liposomes can carry both hydrophobic and hydrophilic drugs and molecules to a target site
Dendrimers	Large, complex molecules with a well defined branched chemical structure;Monodisperse ,highly symmetric, highly branched, and generally spherical	Allow carriage of drugs or molecules for imaging; Dendrimer-based conventionalnanocomposites are been studied as possible antimicrobial agents against Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli
Nanoshells	Spherical particles consisting of adielectric core suded by a thin metallic shell, most commonly gold	Biomedical imaging and cancer treatment
Quantum Dots (QD)	Semiconductors with spatially confined excitons that afford them unique optical and electrical properties	Their distinct fluorescenceSpectra make them valuable tools for biomedical imaging.

Source: [30]

actives, in order to improve the therapeutic success, especially in chronic infections caused by intracellular microorganisms or pathogens which are hard to eliminate, like *Brucella, Mycobacterium bovis, Streptococcus aureus, Rhodococcus equi,* etc. On the other hand, researchers are also very concerned about tissue distribution of nanoparticles in animals and respective antimicrobial residues in food and environment and it is toxicity [31].

Nanotechnology Applications in Veterinary Diagnostics and Therapeutics: It is believed that in the near future, nanotechnology will play a leading role in global veterinary practice [28, 32]. The use of nanotechnology devices for diagnosis of animal diseases or as animal models for the diagnosis of human diseases is great achievement in the one health initiative. Reports suggest the use of quantum dots (QD) for in vivo imaging in small animal models [33]. Functionalized NPs conjugated to monoclonal antibodies have been used to rapidly and specifically detect respiratory syncytial virus in vitro and in vivo. It can provide direct, rapid and sensitive detection of viruses and there by bridge the gap between current cumbersome virus detection assays and the need for more rapid and sensitive detection of viral agents [34].

Nanotechnology is currently employed in the treatment of African animal trypanosomiasis [35]. It enabled the development of a new drug delivery system against diaminazene (DMZ) a trypanocidal drug registered for veterinary use. The porous cationic nanoparticles used improved the potential targeting of trypanosomes. Similarly, mice pre-treated with protein cage nanoparticles (PCN) independent of any specific viral antigens, were protected against both sub-lethal and lethal doses of two different influenza viruses, a mouse-adapted SARS-coronavirus, or mouse pneumovirus. Treatment with PCN significantly increased survival and was marked by enhanced viral clearance, accelerated induction of viral-specific antibody production and significant decreases in morbidity and lung damage [36].

Nanobiotix technology and its role in cancer therapy is a novel innovation that is already gaining acceptability in diagnoses and therapeutics. It is based on the novel idea of nano therapeutics, using NPs with control diameter less than 70 nm with a therapeutic core that can be remotely activated by an external energy supply. The NPs are injected into the patient intravenously or intratumoral and target tumor tissues and take 20-48 hours to accumulate selectively in them. Once the particles have been internalized by the cancer cells, an external energy field is applied to activate the NPs and a local physical or chemical effect then destroys the tumor cell [37].

The immunological properties of a novel nano-bead adjuvant in a sheep model were investigated [38]. In contrast to alum, antigen covalently coupled to nano-beads induced substantial cell mediated responses along with moderate humoral responses. No adverse reactions were seen at the site of immunization in the sheep. Vaccination against foot-and-mouth disease virus (FMDV) is a major problem, as current vaccines do not allow easy differentiation between infected and vaccinated animals. Furthermore, large scale production of inactivated virus poses significant risks and the feasibility of using inert nano-beads that target antigen to dendritic cells (DCs) to induce immune responses against FMDV specific synthetic peptides in sheep [39].

The Role of Nanotechnology in Animal Reproductive Biotechnologies: Nanotechnology has begun to blossom in the field of reproduction and fertility [40, 41]. In this way, the aims of these nanotechnology-based investigations related to animal reproduction are characterize the nanoscale features of gamete cells using atomic force microscopy and related scanning probe microscopy techniques [42]; develop nano biosensors for detection of physiological or altered (pathogens and diseases) reproductive status [43]; develop chemical approaches for production of metal nanoparticles for fertility control applications [44]; develop nanodevices for secure cryopreservation of gametes and embryos [45]; and develop sustained release systems of molecules, including hormones, vitamins, antibiotics, antioxidants, nucleic acids, among others. The goal of all these innovative efforts is not just to be able to characterize and manipulate the matter on nanoscale, but also develop products and processes with economic, social and environmental value added with emphasis on the development of solutions to animal reproduction challenges [46].

Nanobiosensors for the Detection of Reproductive Status/Stages: Nanobiosensors are very sensitive devices equipped with immobilized probe biomolecules and which are made up of nanomaterials, such as nanoparticles, nanotubes, nanowires, nanofiber and others. They are mainly applied in environmental monitoring and clinical diagnostics [47]. The development

and validation of nanobiosensors for the detection of diseases, pathogens, oestrus, hormone levels and metabolites profile provide to such systems the status of an important and promising tool for reproductive management [43].

Sustained Release Nanosystems for the Delivery of Reproductive Hormones: The development of nanostructured systems facing the delivery and sustained release of molecules towards specific targets represents a frontier area of nanoscience and nanotechnology, with the possibility of contributing substantially to advances in animal reproduction. Nanoparticles, nanoemulsions, nanogels, nanocapsules and liposomes are among the most common forms of administration of bioactive molecules based on nanobiotechnology [48]. Currently, nanostructured delivery systems have been intensively developed and evaluated due to several advantages shown in biological applications [49].

Nanostructures for the Sterilization of Animals: Despite the advantages associated with the use of nanoparticulate systems in order to optimizing the reproductive performance, it is largely accepted that some nanoparticles (e.g. metal nanoparticles) can elicit toxic and deleterious side effects towards living organisms [50]. However, this toxicity may also be used for reproduction technologies on the basis of contraceptive approaches [44]. Since several metals, including cadmium, at low to moderate concentrations may lead to sterility in a dose-dependent fashion, the delivery of metals as Nps to reproductive organs remains as a wide field to be explored by researchers and can be actively driven to reproductive and related organs (e.g. pituitary) by targeting molecules (e.g. antibodies) or using some physical characteristic (e.g. magnetic field-based delivery of magnetic nanoparticles) and thus avoiding or at least minimizing the systemic toxicity [51].

Nanosystems for Cryopreservation of Gametes and Embryos: Cryopreservation of gonadal tissues, sperm, oocytes and embryos has brought about novel and exciting research field in animal reproduction [52]. The use of biocompatible metal nanoparticles for cryopreservation of cells and tissues may become the next step of cryopreservation technologies to achieve ultra-fast cooling rates and also allow rapid and homogeneous rewarming of the biological materials under near physiological conditions. However, there are an incipient number of studies carrying out the use of nanoparticles for cryopreservation of cells and tissues [45].

Nanotechnology and Livestock Products: Nanotechnology is quite competent in new products and new processes development with the objective of enhancing the performance of the products, extending the product shelf life and freshness as well as in getting better the safety and quality of food [53]. It can also reduce the time of production of eggs and meat. Thus, consumers can get faster eggs and meat [54]. The quality of fermented livestock products are now well proven for health benefits which can easily to be obtained by this vital technology [55].

Potential Applications of Nanotechnology in Meat and Meat Products: Applications of nanomaterial are currently used for meat and food generally, include the use of NPs and nanomaterials as food ingredients/additives which are placed directly into food, or as a part of food packaging [56]. Microencapsulating process can improve dispersing ability of fat-soluble additives in food products, enhance taste and reduce the use of fat, salt, sugar and preservatives. Reducing the salt level is especially important and presents a great challenge for meat industry because in spite of advantages, use of salt has shortcomings since it is linked to hypertension and consequently increased risk of cardiovascular disease [57].

One of the functions of nano-carrier systems is to protect nutrients and supplements from degradation during processing. For example, carriers enable nutritive substances to be resistant to proteases and other denaturing compounds, improve their stability to pH value and temperature changes and increase their ability to be transferred across intestinal membranes into the blood and controlled release and better dispersion in aqueous systems for water-insoluble food ingredients and additives [58]. Nanotechnology can be utilized to improve the stability of such micronutrients not only during processing but storage and distribution, as well [19].

Nanomeat production*:* Nanotechnology can make poultry and meat products cost-effective with the natural properties and the differentiation in qualities of the products can easily to be made by nanotechnology based techniques [59]. One of the futuristic applications of nanotechnology lies in the production of “interactive”

poultry meat that changes, color, flavor or nutrients depending on the diner's taste or health. Many of the molecular structures that determine these characteristics are in the nanometer range and information on the source can play an important role in the poultry meat design, the purpose is to master over the characteristic of meat components in an intelligent manner by manipulating atoms individually and place them exactly where they are needed to produce the desire flavor and texture [3].

Nano-packaging: Packaging materials that have improved temperature performance can be used for hot fill operations. Very thin films that can offer the advantages of flexibility and functionalities like being anti-counterfeit, anti-tamper and anti-microbial should be made. Self-heating feature can also be incorporated in the packaging material [60].

Polymer nanocomposites (PNCs) are the latest materials aimed at solving these problems and Improvement of many other characteristics, such as gas and water vapor barrier properties, mechanical strength, thermal stability and chemical stability, recyclability, biodegradability, dimensional stability, heat resistance and optical clarity. This packaging supports the preservation of fresh foods, extending their shelf life and reducing the packaging waste associated with processed foods at the same time [61]. Nanoparticles can be applied as reactive particles incorporated into packaging in a form of nano sensors which provides quality, safety control of products and also to detect the presence of gasses, chemical contaminants or respond to changes in environmental conditions.

Nano milk production

Nanotechnology is new technological tool or in modern raw milk production and pasteurization, ongoing advancing in biomedical technology may assist in advancing our understanding if disease prevention and health promotion, as well as medical diagnostic and therapeutic [62]. These new emerging technologies such as micro array technology and nanotechnology have the potential to advance nutrition and health science in many aspects of relevance for modern milk production [63].

Impact of Nanotechnology on Human Health: Nanoparticles can enter the body by dermal contact, inhalation or ingestion [64]. In the food industry, the inhalation and the introduction by dermal contact and through skin penetration is almost exclusively related to workers in the nanomaterials producing factories which is why use of protective equipment is required, but main exposure of concern for final consumer occurs by ingestion [58]. Nanoparticles which are ingested with meat may come directly from meat if they are used as e ncapsulated additives, from accumulation in plants and animals used in food production or by migration from nano packaging. After entering through the gastrointestinal tract into circulation the liver and the spleen are the two major organs for distribution The effect of nanomaterials on human body or organism depends not only on the method of their introduction, but also on their properties.

The circulation time increases drastically when the NPs are hydrophilic and their surface is positively charged [65, 66] have suggested that nanomaterials can be classified based on solubility, digestibility and potential bio persistence. According to them, areas of least concern present food products containing natural food nanostructures, which are either digested or solubilized in the gastrointestinal tract and which are not bio persistent. Nanoparticles from last category may affect adsorption, distribution, metabolism and elimination and have potential toxicological effects, which depends mainly on chemical composition and diameter of nanoparticles Some studies have shown that migration of silver ions from packaging is necessary to exhibit antimicrobial effect [67] and exposure to high doses of nanocomposite packaging materials based on silver nanoparticles (AgNPs) is related to liver damage in rats.

CONCLUSIONS

Nanotechnology in animal health and reproduction is a growing and flourishing field that plays a great role in diagnostics and therapeutics of animal diseases and also it is intensified for improving livestock production and reproduction. Nanomaterials offer a vast number of breakthroughs like cost effective, lower risk to consumers and faster approach that will further advance the clinical aspect of veterinary sciences in future and conceived that bacterial infections can be eliminated in the patient within minutes, instead of using treatment with antibiotics over a period of weeks. Nanotechnology has found its way into the food industry to improve food shelf life, safety and quality control. In spite of all benefits and opportunities which use of nanotechnology offers, it is still in the early stages of its development and not applied throughout the world. Also, there are little concerns about impact of nanoparticles on human health and environment.

Based on the above conclusion the following recommendations are forwarded:

- Scientists, engineers and biologists should work in wider range
- Risk assessment should be done before field application
- Public awareness should be done about the effect of nanoparticles
- Peoples exposed to the nanoparticles should use personal protective equipments
- Excessive exposure to nanoparticles should be avoided

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