
















Nanotechnology in veterinary medicine: a review

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ABSTRACT: *The purpose of this review was to address the applicability of nanotechnology in veterinary medicine, with an emphasis on research in Brazil from 2013 to 2020. Firstly, we introduced to the general aspects of applicability of nanotechnology in veterinary medicine, and lately we pointed the research involving nanoscience performed in Brazil, in the studied period. Nanotechnology is the field of science that has the capacity to organize matter in nanoscale structures (1 to 100 nm), enabling innovations in different areas including biotechnology, agriculture, disease diagnosis, food and clothing industry, electronics, and pharmacological therapies. In veterinary medicine, several studies are being carried out in the world, mainly in the areas that involve search of new treatment options and the development of immunotherapy, as well as in the diagnosis of diseases. In Brazil, it is clear that the use of nanotechnology in veterinary medicine is still incipient, but it can be considered a growing area. In addition, several points have to be reflected and researched, including some adverse effects and implications to validate the safe use of nanotechnology in veterinary medicine. Therefore, this review highlighted the nanotechnology as a promise alternative in the current context of Brazilian technological innovation involving animal health, as well as a possible diagnostic tool and highlighting its potential therapeutic use in disease control in veterinary medicine. Regarding future perspectives, we believed that greater investment in science and technology could contribute to the advancement and strengthening of nanotechnology in Brazil.*

Key words: nanoscience, technological innovation, animal health, diagnostic, treatment.

Nanotecnologia em medicina veterinária: uma revisão

RESUMO: *O objetivo desta revisão foi abordar a aplicabilidade da nanotecnologia na medicina veterinária, com ênfase nas pesquisas no Brasil de 2013 a 2020. Primeiramente, apresentam-se os aspectos gerais da aplicabilidade da nanotecnologia em medicina veterinária e, posteriormente, apontam-se as pesquisas envolvendo nanociência realizadas no Brasil, no período estudado. A nanotecnologia é o campo da ciência capaz de organizar a matéria em estruturas de nanoescala (1 a 100 nm), permitindo inovações em diferentes áreas, incluindo biotecnologia, agricultura, diagnóstico de doenças, indústria de alimentos e vestuário, eletrônica e terapias farmacológicas. Na medicina veterinária, diversos estudos estão sendo realizados no mundo, principalmente nas áreas que envolvem a busca de novas opções de tratamento e o desenvolvimento de imunoterapia, bem como no diagnóstico de doenças. No Brasil, está claro que o uso da nanotecnologia na medicina veterinária ainda é incipiente, mas pode ser considerada uma área em crescimento. Além disso, vários pontos devem ser refletidos e pesquisados, incluindo alguns efeitos adversos e implicações para validar o uso seguro da nanotecnologia na medicina veterinária. Nesta revisão, destaca-se a nanotecnologia como uma alternativa promissora no atual contexto de inovação tecnológica brasileira, envolvendo saúde animal, o diagnóstico e o potencial uso terapêutico no controle de doenças em medicina veterinária. Em relação às perspectivas futuras, acredita-se que maiores investimentos em ciência e tecnologia são fatores fundamentais a contribuir para o avanço e fortalecimento da nanotecnologia no Brasil.*

Palavras-chave: nanociência, inovação tecnológica, saúde animal, diagnóstico, tratamento.

INTRODUCTION

Nanotechnology refers to the manipulation of the structure of materials, substances, or elements

at the nanometer scale, producing structures between 1.0 nm and 100 nm (ROCO, 2011; PELAZ et al., 2017). In 1959, Richard Feynman first mentioned the concept of nanotechnology in the lecture *Plenty of*

Room at the Bottom in Nobel Prize, proposing that mounting a material atom by atom would never be possible (FEYNMAN, 1960). With the discovery of fullerenes (KROTO et al., 1985) and the synthesis of carbon nanotubes (IJIMA, 1991), nanoscience and nanotechnology – once viewed as fiction – was considered a viable technology (FERREIRA et al., 2009). In 1991, a processing method involving the molecular manipulation of atoms was proposed (FERREIRA et al., 2009). Later, different areas of activity contributed to nanotechnology. These included, among others, chemistry, biology, molecular physics, material science, computer science, and electrical and mechanical engineering (ROCO, 2011).

The increased interest in the applications of nanotechnology in medicine has led to the emergence of a new field called nanomedicine (PROW et al., 2004; FREITAS JR., 2005; PELAZ et al., 2017).

Research on nanoparticles is promising in the areas of disease diagnosis, control, and treatment. In addition, it is promising in the development of strategies for improving animal fertility and reducing contaminants in industry (VON SAMSON-HIMMELSTJERNA et al., 2005; SMITH et al., 2013; ALI et al., 2014; CHAO et al., 2016; KING et al., 2018; SHAKIR et al., 2018; FEUGANG et al., 2019). Nanotechnology has been identified as a high impact technology in the 21st century, particularly in the livestock industry (FEUGANG et al., 2019).

Scientifically validated nanoparticle products have been incorporated into marketable products for veterinary medicine (UNDERWOOD et al., 2012). This highlights the growth of research involving nanotechnology as a science applicable to veterinary medicine.

The aim of this narrative review is to address the applicability of nanotechnology in veterinary medicine with emphasis on research in Brazil from 2013 to 2020. This narrative review has the following structure: the reader is first introduced to the general aspects of applicability of nanotechnology in veterinary medicine, while later describing the research involving nanoscience performed in Brazil in the mentioned period.

Therapeutic applications

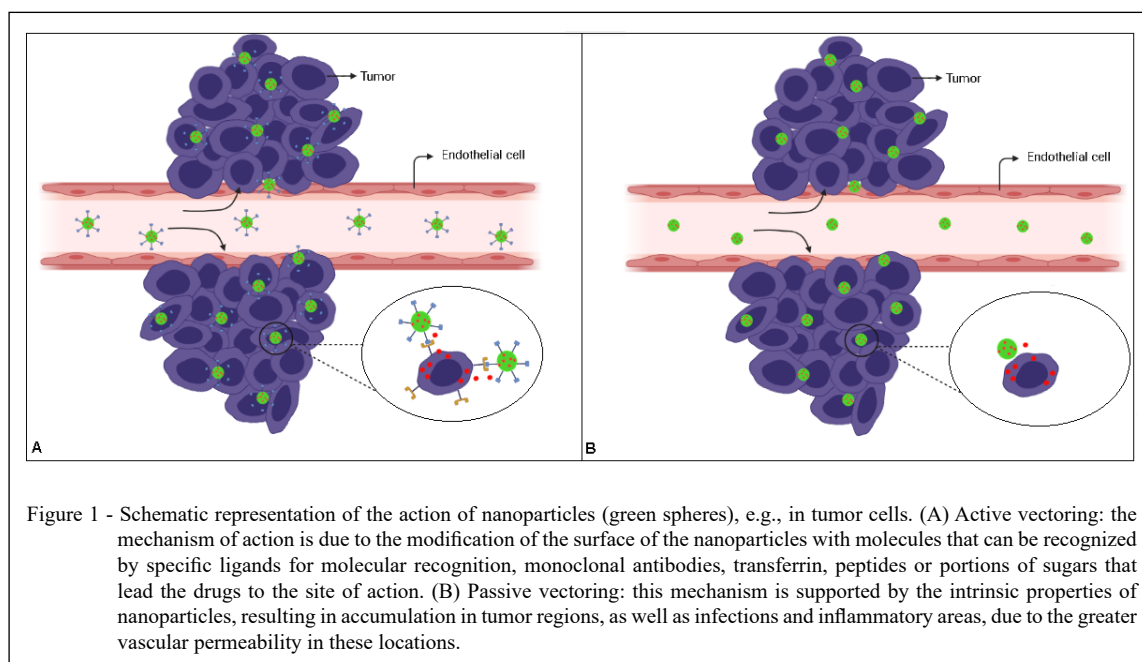
Drug delivery systems using nanoparticles are their most widespread applications (PROW et al., 2005). The following advantages were obtained using this technology; assistance in the delivery of unstable and insoluble drugs, maintenance of active principle concentration at the expected site of action, and low systemic toxicity and reduced clearance

compared to that of the original drug (SAHOO et al., 2003; BAKKER-WOUDENBERG et al., 2005; FAHMY et al., 2005; PARVEEN et al., 2012). Thus, nanoparticle formulations require lower therapeutic doses than conventional drugs. This feature is very important in veterinary medicine as it allows lower doses of drugs and favors the reduction in residual levels of pharmaceuticals, particularly antimicrobials in carcasses and other animal products, as well as reduction in the cost of treatment (UNDERWOOD et al., 2012).

Various drug delivery systems with nanoparticles have been developed. These include antineoplastic drugs (HOFHEINZ et al., 2005), antimicrobials (CORDEIRO et al., 2000), analgesics (ROSE et al., 2005), and anti-inflammatory drugs (METSELAAR et al., 2003). In veterinary medicine, nanoparticles of various substances have been tested for antibacterial (OLIVEIRA et al., 2013; SAGAVE et al., 2015; JAGUEZESKI et al., 2019; ACOSTA et al., 2020), antiviral (GREENWOOD et al., 2008; ZHAO et al., 2016; ZHAO et al., 2018), anthelmintic (KHAN et al., 2015; TOMAR et al., 2017; REHMAN et al., 2019), antiprotozoal (KROUBI et al., 2010; HASSAN et al., 2019), antifungal (BANSOD et al., 2015), antioomycetes (VALENTE et al., 2016; VALENTE et al., 2019; VALENTE et al., 2020), anti-algae (JAGIELSKI et al., 2018; ELY et al., 2020), and antineoplastic (ROCHA et al., 2019) activities.

The passage of nanoparticles to specific locations can occur passively or actively through vectorization. In active vectorization, the mechanism of action is due to the coupling of a targeting portion. These include specific binders for molecular recognition, monoclonal antibodies, transferrin, peptides, or portions of sugars that lead drugs to the site of action (Figure 1-A). The passive form is supported by the intrinsic properties of the nanostructured molecule and occurs through the retention and increased permeability effect. This is based on the ability of the nanoparticles to spill blood vessels to other tissues, resulting in accumulation at sites of increased vascular permeability (tumors, infections, and inflammatory areas) (Figure 1-B) (ISHIHARA et al., 2010; MAEDA, 2010; PARVEEN et al., 2012). The combination of passive vectorization with active vectorization can potentiate the nanocarrier effect thereby increasing the effectiveness of treatment (CHEN et al., 2010; DANHIER et al., 2010; LEE et al., 2012).

COUVREUR (1993) and LIU et al. (2007) reported that the standard mechanisms involved in the release of drugs include enzymatic degradation or disintegration and fusion with the cell membrane surface, releasing the contents into



the cell and/or endocytosis. These mechanisms can be triggered by external factors such as changes in temperature, pH and magnetic field. To avoid such influences, nanostructured systems (polymeric or lipid nanoparticles, nanoemulsions, and liposomes) appeared to be a great option with several advantages. These include the improvement in efficacy and bioavailability of drugs, reduction of side effects, increased stability, and reduced drug delivery rate (SCHAFFAZICK et al., 2003; PADMAVATHY et al., 2008; MISHRA et al., 2011).

The term nanoparticles includes nanocapsules and nanospheres, which differ in composition and structural organization. Nanocapsules are formed by a polymeric shell disposed around an oily core; the drug may be dissolved in the core and/or adsorbed to the polymeric wall. Moreover, nanospheres, which have no oil in their composition, are formed by a polymeric matrix in which the drug can be entrapped or adsorbed (ALLEMANN et al., 1993).

Nanoemulsions are droplets dispersed in the size range of nanoparticles, which provide stability for preventing sedimentation or creaming (SOLANS, 2005). These characteristics allow some water-soluble substances to remain permanently stable in the aqueous phase (VANDAMME et al., 2010). The formulations are suitable for therapeutic use due to their inability to cause cell damage and possible application to the skin and/or mucous

membranes. Nanoemulsion formulations may also be used to transport insoluble drugs in aqueous media, carry antigens to generate mucosal immunity, and in anticancer therapies (THAKUR et al., 2012).

Liposomes are microscopic vesicles composed of one or more concentric lipid bilayers separated by an aqueous medium. These structures have the ability to encapsulate hydrophilic and/or lipophilic substances where the first stand in the aqueous compartment and the lipophilic substance is inserted or adsorbed into the membrane. Liposomes are biodegradable, biocompatible, and non-immunogenic and are highly versatile for research, therapeutic, and analytical applications (EDWARDS et al., 2006).

Industry

Nanomaterials have been used in different industries, offering potential applications in providing solutions through green chemistry approaches for advancing food security (KING et al., 2018). Titanium dioxide nanoparticles are the most commonly used metal oxide nanoparticles in various industrial and commercial products, including food (WEIR et al., 2012). Silver nanoparticles and nanocomposites are the most widely used antimicrobial nanomaterials in the food industry due to their biocidal activity against a broad range of Gram-positive and Gram-negative microorganisms, yeast, molds, and viruses (HE et al., 2016; PETERS et al., 2016). Nanoparticles were used

in animal feed supplements, equipment disinfectants, refrigerators and cutting boards, nano-clothes, air and water filters, packing, and monitoring of biological contaminants (KING et al., 2018). Problems with the use of nanotechnology for the animal food chain include the costs and potential adverse effects of nanomaterials on mammalian health and the environment (BRADLEY et al., 2011; KING et al., 2018).

Diagnostic applications

Nanoparticles may contain gold dots, perfluorocarbons, and liposomes as imaging agents to detect specific cell types (MATTEUCCI et al., 2000; BENTOLILA et al., 2009). In imaging-based diagnosis, nanoparticles increase the resolution of images, thus enhancing the sensitivity and rapidity of detection of lesions. Further, they are specific biomarkers of pathogens (SMITH et al., 2012). When infectious animal diseases caused by pathogenic microorganisms threaten public health, pathogen detection is an important step in the diagnosis as it enables the successful treatment of these diseases (VIDIC et al., 2017).

New diagnostic assays have been developed for ligand functional nanoparticles with biological molecules such as antibodies, peptides, proteins, and nucleic acids (DRISKELL et al., 2005; LUCHINI et al., 2010; CHAO et al., 2016). In spectroscopy, flow cytometry, and histological methods, nanotechnology enhances the sensitivity of the test by providing an appropriate tool for diagnosis. Moreover, this technology allows the mapping of molecular profiles associated with diseases (HALFPENNY et al., 2010).

Nanosensors have great potential in animal production areas and inspection of products of animal origin due to their ability to measure and distinguish a substance from an organic material or tissue. This has enabled the detection of microbial agents, organophosphate compounds, and antibiotics in the β -lactam group (MACHADO et al., 2014; HANAFY, 2018). Nanoshells, which are examples of nanosensors, can be made from optically tunable nanoparticles manufactured from a dielectric center covered with an ultrathin metallic layer. This makes them potential candidates for use in the expeditious diagnosis and detection of tumors. Their mechanism results from their infusion into the animal's circulation system with focused operators connected, to search for and append to the surface receptors of tumor cells. This illuminates the body with infrared light, thereby increasing the cell temperature and demolishing the tumor (HANAFY, 2018).

In addition, diagnostic methods in veterinary medicine using nanoparticles validated

for the detection of pathogens have been reported. These include viral agents such as Newcastle disease, poxvirus goat (YUAN et al., 2009), avian influenza, foot-and-mouth disease, bovine respiratory syncytial viruses, and bluetongue and epizootic hemorrhagic (VIDIC et al., 2017), bacterial agents such as *Mycobacterium avium* subsp. *paratuberculosis* in fecal samples (KUMANAN et al., 2009), *Escherichia coli*, *Salmonella* spp., *Clostridium perfringens*, *Campylobacter* spp., *Mycoplasma* spp., other bovine mastitis pathogens, and protozoans such as *Eimeria* spp. (VIDIC et al., 2017).

An example of a rapid, sensitive, and inexpensive test available in veterinary medicine is the diagnostic method for *Mycobacterium bovis*, which is based on an electronic nose (NA-NOSE) that is capable of distinguishing between positive and negative animals in serum samples (FEND et al., 2005).

Reproduction

Nanotechnology is an important tool that could benefit the livestock industry, particularly through post-collection manipulation of semen, routinely used for artificial insemination. It could potentially revolutionize the global livestock breeding industry (FEUGANG et al., 2019). In reproductive biology, nanoparticles have been reported to increase the longevity of spermatozoa, improve male fertility, and select the best spermatozoa for insemination and semen purification (FALCHI et al., 2016; DURFEY et al., 2017; FEUGANG et al., 2019). A nanotube embedded under the skin can provide constant estimation of changes in the blood estradiol level (O'CONNELL et al., 2002), thus detecting estrus by close infrared fluorescence (O'CONNELL et al., 2002; HANAFY, 2018). In the future, it will be possible to distinguish the best reproducers and detect hereditary diseases using nanotechnology (HANAFY, 2018).

Vaccine

Compared to conventional vaccines, formulations containing nanoparticles may reduce the frequency of vaccine doses and restrict the handling of domestic and wild animals (AUCOUTURIER et al., 2001; NORDLY et al., 2009).

The immunostimulatory activity of nanoscale materials has been attributed to antigen presentation at the depot effect, stability, conformational integrity, slow release, and prolonged exposure to antigens. Additional mechanisms are associated with enhancement of the innate immune response and release of soluble mediators (cytokines,

chemokines, and immunomodulatory molecules) that regulate the immune response (LOOK et al., 2010).

Nanoparticles, nanoemulsions, and nanotubes can be very useful in vaccinology as entrainment mechanism antigens, adjuvants, and immunomodulators of the immune system (SMITH et al., 2012). In veterinary medicine, cost, stability, facility of administration, bioavailability, and biodegradability are some essential characteristics for applicability and possible implementation of nanotechnology, including as immunobiological agents (AUCOUTURIER et al., 2001; DURAN et al., 2010).

Implications of nanostructures

Careful assessment of the use of nanostructures for animals, people, and the environment is essential for the development and safe use of nanostructured compounds (QUINA, 2004; O'BRIEN et al., 2010). Thus, as the biological and physicochemical properties of nanostructures vary, their toxicity may be affected by different factors, including the chemical composition, electrical charge, size, and shape of the material used for the development of nanostructures, among others (CARD et al., 2011).

The evaluation of nanostructure formulation security requires a combination of *in vitro* and *in vivo* research. A preliminary step is to evaluate *in vitro* cytotoxicity, genotoxicity, influence of nanostructures on cell signaling, and other cellular functions using cell culture models and analysis of gene expression in cells (SCHRAND et al., 2010). When internalized in cells, nanomaterials can originate reactive oxygen species, surpassing the ability of antioxidant enzymes to maintain the balance of intracellular oxidation-reduction reactions, causing oxidative stress, one of the main factors of cytotoxicity caused by these nanoparticles (WELLS et al., 2009; PASCHOALINO et al., 2010). Therefore, the absorption, distribution, metabolism, and excretion of each nanostructure formulation should be defined by pharmacokinetic, pharmacodynamic, and toxicokinetic studies (CHEN et al., 2006; JI et al., 2007; SZEBENI et al., 2007; HO et al., 2013).

Non-biodegradable nanostructures, particularly inorganic ones, may be associated with side effects. Further, they have greater potential for tissue accumulation than biodegradable nanostructures. However, biodegradable nanostructures may exhibit toxicity due to biodegradation of the product or their metabolites (DURÁN et al., 2010). Thus, the toxicity of nanostructured compounds needs to be further evaluated, particularly the implications for the environment. In this sense, ecotoxicity is considered one of the main

challenges to be addressed in an interdisciplinary way to understand the behavior of nanomaterials in the environment (BOTTERO et al., 2015).

Nanotechnology in veterinary medicine in Brazil

As presented, nanotechnological innovations have been used in veterinary medicine with different applications and have been reported by several researchers (IRACHE et al., 2011; UNDERWOOD et al., 2012; EGUCHI et al., 2013).

In Brazil, one of the world's agricultural commodity powerhouses, livestock plays an important economic, environmental and social role (FERRAZ et al., 2010; VICENSOTTI et al., 2019). Since 2009, with the support of the Ministry of Science, Technology, Innovations and Communications, the Nanotechnology Laboratory for Agribusiness (LNNA) at the Empresa Brasileira de Pesquisa Agropecuária (EMBRAPA), located in São Carlos city, in São Paulo State, is performing research in collaboration with EMBRAPA and other public research institutions and private companies. LNNA is a reference center that enables the development of research projects of interest to agribusiness. However, in veterinary medicine, the research topics include biosensors for the diagnosis of animal diseases, veterinary drugs, and functional food packaging (EMPRAPA, 2012).

Nanotechnology applied in veterinary medicine helps impart greater safety and speed in diagnoses, improves treatment efficiency using lower doses of medication, and thus reduces costs. It also contributes to the reduction in residual drug levels, mainly in products of animal origin (UNDERWOOD et al., 2012; VIDIC et al., 2017). However, this technology can improve the competitiveness and sustainability of Brazilian agribusiness, seeking to improve the quality of products and processes, and the development of new uses for agricultural products (MATTOSO et al., 2005; EMBRAPA, 2012).

Since, the nanotechnology market has shown to be highly promising, new products and applications are launched in practically all sectors and at an increasing speed. According to information obtained from the StatNano website database, 231 agricultural technological products are currently available on the world market, these being compounds for food supplementation, disinfectants for birds, livestock and aquaculture, vaccines and pharmacological treatment, made available by 75 companies, distributed in 26 countries (STATNANO, 2021). Brazil, together with India, Germany, the United Kingdom, the United States of America (USA), Vietnam, Taiwan, China, Malaysia, and the

Netherlands are the countries most active in promoting nanotechnology for the prosperity of agriculture. However, the USA is the country that most invests in this new technology, offering 3,056 products, varying in 433 sectors and 695 companies involved, 22 of which are agricultural products, involving 12 companies. In comparison, Brazil has 186 products, varying in 58

sectors and 90 companies, of these, nine products are from the agricultural sector, which involve eight companies active in this sector (STATNANO, 2021).

However, basic and applied research in the field of veterinary medicine is growing, and we list the main nanotechnology studies related to this sector in Brazil (Table 1). Although, still incipient,

Table 1 - Different applications of nanotechnology in veterinary medicine in Brazil during the period 2013 to 2020.

Application	Description	Nanostructure	References	
Anesthesiology	Use of propofol	Nanoemulsion	GALL et al., 2013	
Surgery	Bone application	Nanostructure	COSTA et al., 2015	
Diagnostic	<i>Leishmania infantum</i>	Nanoparticle	ROSA et al., 2013	
	<i>Actinobacillus pleuropneumoniae</i>	Nanoparticle	BRANDÃO et al., 2014	
	<i>In vitro</i> sensitivity of <i>Staphylococcus</i> spp. causing mastitis in goats	Nanoparticle	OLIVEIRA et al., 2013	
	<i>In vitro</i> susceptibility of <i>Rhodococcus equi</i>	Nanocapsules and nanoemulsions	SAGAVE et al., 2015	
	<i>In vitro</i> susceptibility of <i>Pythium insidiosum</i>	Nanoemulsion Nanoparticle	VALENTE et al., 2016 VALENTE et al., 2019	
	Experimental pythiosis	Nanoparticle	VALENTE et al., 2020	
	Effect of curcumin on treatment and energetic metabolism of gerbils infected by <i>Listeria monocytogenes</i>	Nanocapsules	JAGUEZESKI et al., 2019	
	Nematicidal activity of silver nanoparticles from the fungus <i>Duddingtonia flagrans</i>	Nanoparticle	BARBOSA et al., 2019	
	<i>In vitro</i> antimicrobial efficacy of nanopropolis for mastitis treatment	Nanoparticle	TRONCARELLI et al., 2014	
	Treatment subclinical mastitis of sheep	Nanoparticle	SANTANA et al., 2016	
	Pharmacology/ Therapeutics	<i>In vitro</i> sensitivity of <i>Staphylococcus aureus</i> causing mastitis in cows and goats	Nanoparticle	ACOSTA et al., 2020
		<i>In vitro</i> sensitivity of <i>Prototheca</i> spp. causing mastitis in cows	Nanoparticle	ELY et al., 2020
<i>In vitro</i> susceptibility of <i>Aeromonas hydrophila</i> , <i>Edwardsiella tarda</i> and <i>Streptococcus iniae</i>		Nanoparticle	LUIS, 2017	
Gastrointestinal nematodes		Nanocapsules	RIBEIRO et al., 2014	
<i>Trypanosoma evansi</i> treatment		Nanocapsules	DO CARMO et al., 2015	
Photodynamic therapy of cutaneous hemangiosarcoma in dogs		Nanoemulsion	ROCHA et al., 2019	
<i>In vitro</i> and <i>vivo</i> trypanocidal effect of (-)- α -bisabolol		Solid lipid nanoparticles	BALDISSERA et al., 2016	
Suppress hepatic cellular damage and impaired bioenergetics caused by nerolidol in <i>Oreochromis niloticus</i>		Nanospheres	BALDISSERA et al., 2020b	
Improves therapeutic efficacy of <i>Melaleuca alternifolia</i> in experimentally infected <i>Rhamdia quelen</i> with <i>Pseudomonas aeruginosa</i>		Nanocapsules	SOUZA et al., 2017	
Dietary supplementation		Digestibility of nutrients	Nanoparticles	MOSS et al., 2017; FIGUEIREDO et al., 2019
	Nerolidol improves growth, antioxidant status and fillet fatty acid profiles in <i>Oreochromis niloticus</i>	Nanospheres	BALDISSERA et al., 2020	
	Diphenyl diselenide in silver catfish feed enhance growth, improve muscle antioxidant/oxidant status and increase selenium deposition	Nanocapsules	BALDISSERA et al., 2020a	

nanotechnology in veterinary medicine in Brazil has evolved gradually in the last seven years, mainly in the development of therapeutic products for the treatment of infections caused by different pathogens. Additionally, it is observed that most studies are related to research and technological innovation projects developed in educational institutions.

CONCLUSION

Nanotechnology has several benefits to different fields of industry and science, including human, animal and environmental areas. In veterinary medicine, the use of nanostructures in the pharmacological and immunological areas is promising. In Brazil, the use of nanotechnology in veterinary medicine; although incipient, has demonstrated many possibilities for basic and applied research and numerous advances in animal production and health, especially in the area of pharmacological therapies, which has provided promising treatments for diseases with an unfavorable prognosis.

We emphasized that nanotechnology is a recent and promising science that has been breaking many paradigms, and still needs studies to validate its safe use in veterinary medicine. Therefore, aspects related to ecotoxicity, as well as bioaccumulation of nanoparticles in animal and plant tissues must be evaluated in order to guarantee the safety of nanostructured substances. Regarding future perspectives, we believed that greater investment in science and technology could contribute to the advancement and strengthening of nanotechnology in Brazil.

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DECLARATION OF CONFLICT OF INTEREST

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to the manuscript.

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