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The Impact of Nanotechnology in Health:
A Review of Recent Studies and Products

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Highlights:
(1) Holistic Health Approach: "One Health" integrates humans, animals, ecosystems for collaborative solutions.
(2) Nanotech in Healthcare: Nano properties reshape diagnostics, therapy, devices, with potential and challenges.
(3) Untapped Potential: Article explores nano's roles in health, current and future applications.

ABSTRACT

Several people suffer from diseases and injuries and many of them die because of late diagnostic and/or inefficient treatment. Many of these diseases affect humans and animals, and animals can be vectors for humans. In this perspective, it is necessary works that integrate humans, animals, and ecosystems, thus, to arise One Health. Along with it, nanotechnology is a great alternative to improve health care, due to its revolutionary and complex properties. Although, how can nanomaterials be capable of working with or against cells, tissues, drugs, and medical devices? There are already many products in the market, but there are a lot of challenges to face and a whole new world to discover. This article are given the application of nanostructures in diagnostic, therapy, medical devices, tissue and implant engineering, human health and animal, and a future perspective.

Keywords: human health; tumor cells; drug delivery; nanostructures; animal health.

O IMPACTO DA NANOTECNOLOGIA NA SAÚDE: UMA REVISÃO DE ESTUDOS E PRODUTOS RECENTES

RESUMO

Muitas pessoas sofrem de doenças e lesões e muitas delas morrem devido a um diagnóstico tardio e/ou a um tratamento ineficaz. Muitas dessas doenças afetam seres humanos e animais. Além disso, os animais podem ser vetores para os seres humanos. Nesta perspectiva, são necessários trabalhos que integrem humanos, animais e ecossistemas, surgindo, assim, a One Health. Junto a isso, a nanotecnologia é uma ótima alternativa para melhorar os cuidados com a saúde em razão das suas propriedades revolucionárias e complexas. Como, porém, os nanomateriais podem ser capazes de trabalhar com ou contra células, tecidos, medicamentos e dispositivos médicos? Já existem vários produtos no mercado, mas há muitos desafios a enfrentar e todo um novo mundo a descobrir. Neste artigo são apresentadas as aplicações das nanoestruturas no diagnóstico, na terapia, nos dispositivos médicos, na engenharia de tecidos e implantes, na saúde humana e animal e numa perspectiva futura.

Palavras-chave: saúde humana; células tumorais; administração de medicamentos; nanoestruturas; saúde animal.

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INTRODUCTION

Health can be defined as a state of complete physical, mental, and social well-being, according to the World Health Organization (WHO), and not just for not having a disease. Nowadays, cardiovascular disease and cancer lead to the causes of death, followed by chronic diseases, such as diabetes, Alzheimer's, arthritis, dementia, multiple sclerosis, Parkinson's, and alcohol- and drug-related conditions, among others, which keep rising. Up to 50 % of the world's population has one or more of this chronic disease. Also, WHO reports the existence of vector-borne diseases, responsible for more than 17% of all infectious diseases, which causes more than one million deaths annually. It is important to note that vectors are organisms that can transmit infectious diseases between humans or from animals to humans (1).

It is hard to think of a world without disease, as there are vast ways of contamination, such as chemical materials, water, food, and air, and social and economic factors can cause many diseases and injuries (1). Over 45 % of all deaths in 2015 had serious health problems, the majority (80 % of whom) were in low- and middle-income countries (LMICs). This is related to precarious treatments without improvements and it calls for global policies to strengthen healthcare systems (2,3). Primary health care is estimated to require US$ 200-328 billion per year in the next decade, mainly for LMICs. The health system will need at least 1 more worker per 1000 population. Investments in this sector can avert around 60.1 million death and increase 3.7 years in average life expectancy (4).

In this context, to develop new technologies for health improvement, researches are extremely important for humans and animals. According to the Web of Science, the number of publications about "nanotechnology in health", has been rising since 1945, with a total of 2,768 works divided into many sectors, the most part in Nanoscience and Nanotechnology. Refining the research, just 62 publications are about "nanotechnology in veterinary", while there are 1,185 publications on "nanotechnology in human health". Also, 514 publications are about "nanotechnology in One Health". In 2004 the concept of One Health emerged because of the need for a multidisciplinary, interdisciplinary, and transdisciplinary approach to deal with the health of mankind, fauna, and ecosystem, once environmental factors cause 1.4 million deaths per year (5). The goal of One Health is to align human and veterinary medicine to improve the cooperation and capacity for response to current and upcoming health threats (6).

Aligned with the workforce, many technologies are in use to upgrade medicine. Health care has been computerized, through blockchain technology, improving the management of the supply chain, remote patient monitoring, and health data analytics, among others (7). Another new technology of care is digital health, used to get remote diagnostics and treatment, assistance by protocols, and better access to goods and services by delivery. Besides all challenges of this alternative, this is already helping people around the world (8). For example, currently, the health team worldwide is preparing for permanent changes in the concepts of face-to-face consultation. With the pandemic caused by Covid-19, there was a need to speed up the possibility of consultations via video or telephone, remotely (9).

Nanotechnology has infinite advantages in health, which make it a great alternative. Nanomedicine can identify a single ill cell and heal or kill it. Diagnostic imaging has been also improved with nanomedicine (10,11). For tissue engineering nanomaterials can improve cell responses and protein absorption, enhance osseointegration, bone-to-implant contact, biosensing, and bioimaging, and empower disease markers (12). All properties are possible due to the nanostructures' high surface area to volume ratio compared with the macromolecular structure. Also, mechanical, biological, and other properties are improved because of the different shapes and sizes.

This article aims to discuss the vast application of nanotechnology in human and animal health, covering new products and technologies in the global market with patents. With this multidisciplinary field, we expect to open the gates of science helping other researchers to have access to more recent data, being possible to innovate in their work having the best results.

DIAGNOSTIC AND THERAPY

Among all causes of death, cancer is one of the leaders, with around 7.6 million deaths every year, and mortality is expected to rise to 13.1 million by 2030. Many instances of cancer become a reckless lifestyle and could be avoided. Although cancer can develop a series of diseases, there are some vaccines against it and the use of nanotechnology can improve its efficiency (13,14).

The most common treatment of cancer is chemotherapy, which is an expensive treatment (15) and results in the development of multidrug resistance. Although chemotherapy increases the survival rates, oxidative stress of normal tissues (such as the heart, brain, and kidney) is a meaningful side effect and reduce the quality of life of patients. For instance, doxorubicin, an important component, kills cancer cells through DNA intercalation and inhibition of topoisomerase II. Many strategies have been applied to reduce their side effects (16,17). As stated by Whitaker (18), an early diagnosis can not only increase the chances of survival, but also can reduce the treatment morbidity, promote better experiences of care, and improved quality of life. However, one challenge is discovering the disease early, once many symptoms are presented with advanced disease (ie, stage IV).

Nanotechnology emerges in this context making it possible to diagnose and treat many diseases earlier. Nanoparticles (NPs) have a specific target for encountering damaged cells, having a great therapeutic efficacy with minimal toxic effects on normal cells (19–21). The use of nanotechnology makes it possible to create, stabilize and accurately deliver drugs to the target cells. Although, the entire understanding of the mechanisms, toxicity, and efficacy of this system needs a lot of studies (22,23). By extension, many nanoparticles have been used in the alternative development of treatments for cancer disease, honestly, iron oxide nanoparticles have been proven grateful result front of the way to diagnosis and therapy in the medicine area. The iron oxide (Fe3O4, Fe2O3, and others has been used for drug delivery due to its properties magnetic and biocompatibility (24,25). Wherefore, according to Rego et al (2019) made an innovation in therapeutic evaluation using iron oxide nanoparticles in the glioblastoma animal model used to be a big step in the studies of nanotechnology and medicine therapy (26). Also, other studies accomplish the acting of nanotechnology showed up the important authentic numbers of patents approved to use this nanomaterial (Table 1).

Nanosensors can enhance the detection of cancer biomarkers, improving diagnostic capability. It is composed of a bio-receptor, which recognizes molecules like enzymes and antibodies; immobilization and a transducer, transforming the biochemical response into the measurable signal, as conventional, optical, electrochemical, and microfluidics-based systems (27). Fiorani and Merino (2019) show the use of carbon nanomaterials, such as nanotubes, carbon dots, and graphene, to detect analytes as metal ions, cancer biomarkers, and cells, proving its efficiency to optimize the electrochemiluminescence signal of a biosensor (28).

Different nanoparticles (NPs) can be used for drug delivery. Saeedi and Eslamifar (2019) showed the advantage of using lipid and poly cyanoacrylate NPs, polymeric micelles, dendrimers, nanogels, and carbon nanotubes to transfer anticancer drugs to the central nervous system, it is controlled and extended drug release (reducing the dose required), non-toxic, biodegradable and biocompatible, physical and chemical stability in blood and non-invasive for the brain cells (29).

Some nanostructures can link the diagnostic and treatment and much more. As described by Solomon (2008), nanorobots can map the human body, find and mark pathogen cells, regulate the cardiovascular system, regulate insulin, delivery drugs to target cells, and destroy tumor cells by engulfing or rupturing them. The mechanism to destroy a cell often is accomplished through penetration of the cell membrane letting holes that allow the passage of liquids and ions which cause cell lysis (30).

Quantum Dots (inorganic semiconductor nanocrystals) have been used for locating tumor target cells with simple tests (31). Also, it can simultaneously detect and treat, as described by Iannazzo, Pistone (2019) with Graphene Quantum Dots, which are great as nanocarriers for drug delivery due to its low toxicity, water-solubility, chemical inertness, and biocompatibility (32).

As shown in Table 1, there are many patents about materials encapsulated in nanoparticles (NPs) to treat many diseases. Varan, Benito (2017), in your study with chitosan-coated, non-ionic, and polycationic paclitaxel-loaded cyclodextrin NPs to cancer therapy, state that the surface charge of nanomaterial can affect the drug release profile. Also, they found a longer-release profile with smaller nanoparticles (non-ionic) (33). Huang, Ma (2012) had a similar result using gold NPs, showing that smaller particles (2 and 6 nm) can penetrate, possibly by free diffusion, and localize within cancer cells, tumors in vivo, and multicellular spheroids, while larger particles obstructed the penetration (34).

Besides size, Banerjee, Qi (2016) show the role of NP shape and surface chemistry in oral drug delivery, testing many structures of polystyrene conjugated with targeting ligands. It was proved that rod-shaped particles have better efficiency than spherical particles, having a greater cellular uptake and transport on intestinal cells. But there is still a need to *in vivo* studies to validate these results (35).

However, as shown in Table 1, there are many patents about nanomaterials that are used not only to treat cancer. According to Rabanel, Perrotte (2019), among all neurodegenerative diseases (NDDs), Alzheimer's disease is the most frequent. These diseases cause physiopathology modifications, such as cerebral atrophy, and modulation of glucose and lactate and neurotransmitter concentration alteration. So, it is desirable to develop non-invasive sensors to detect these phenomena. The lack of early diagnostic tools leads to later treatments. The advance in nanotechnology can provide better NDDs diagnostics and monitoring (36).

Table 1 – Recent applications of nanomedicine in drug delivery

Patent number	Nanoplataform	Size (nm)	Type of administration	Property	Disease
WO2019135715A1(37)	Poly (glycolic-co-L,D-lactic acid) (PGLA)	75 to 300	Oral by tablet/ capsule Nutraceuticals Cosmeceuticals A nutritional agent	Biocompatible Does not cause adverse side-effects Can be degraded in vivo	Cancer Microbial infection
US10596124B2(38)	Cannabinoids encapsulated in the phospholipids NPs	50 to 150	Oral Sublingual Transdermal Intranasal	Decrease the cannabinoid dosages Less adverse effects (cardiovascular and disruption of short-term memory) Increase patient compliance and cost-effectiveness Safety	Physicological disease Alzheimer HIV Diabetes Fibromyalgia Epilepsy Hepatitis C
US10500244B1 (39)	Black eggplant skin NPs	1 to 200	Oral by pills, tablets, capsules, etc	Increase antibacterial Antioxidant capacity	Cancer Heart and neurodegenerative disease
US20190298682A1 (40)	Poly (alkyl cyanoacrylate) NPs	Less than 800	Intraperitoneal	Reduced toxicity Less adverse effects	Cancer

WO2020036501A1 (41)	Nanocapsule in form of water-in-oil-in-water double emulsion	180 to 600	Oral	More effective Enable protection	Cancer Diabetes
WO2019203459A1	Thermosponge NP-based hydrogel	50 to 100	Human body injectable	Biodegradable Biocompatible Sustained and controlled release	Tissue infections
DK2451284T3 (42)	Gold-based nanocrystals	Less than 50	Oral	Fewer side effects Less toxicity	Arthritis Multiple sclerosis Psoriasis, Eczema Uveitis Diabetes mellitus, HIV, HBV, HCV Tuberculosis Malaria
US20190030187A1(43)	Histidine-Lysine co-polymer siRNA NPs	150	Intranasal	Stable Soluble Inhibit infection by viruses	Middle-East Respiratory Syndrome Coronaviral Infection
US20160046936A1 (44)	Magnesium phosphate with aiRNA	2 to 200	Oral	Biocompatible Stable Biodegradable	Diabetes Cancer
US20170296661A1(45)	Atomic number (Z) of at least 25	80 to 105	Intravenous	Biocompatibility Biodistribution Cell uptake reasons	Cancer

Alzheimer's disease (AD) does not have known prevention or treatment and affects around 47 million patients in the world. The available therapies show a better efficiency when there are few amyloid plaques to detect, there is, at very early stages. Areas with a high presence of these plaques can accumulate ferritin. Magnetic nanoparticles have been used as a specific contrast agent for magnetic resonance imaging. Authors proposed a new nanoconjugate composed of iron oxide NPs bound to an anti-ferritin antibody, making possible an anticipated diagnostic (46).

Moody, Payne (2020) proved the efficiency of gold nanoparticles, due to its great stability and low toxicity, used in a rapid and non-invasive method for neurotransmitters through the skull, permitting an earlier diagnosis for AD. It happens because AuNP can interfere with the wavelength of Raman spectroscopy (47).

Parkinson's disease (PD) is the second most common NDDs, having as first symptoms depression, fatigue, and sleep disturbance, and in advanced disease, causing memory loss. The cause is not clear, but studies suggest that PD happens by a combination of factors, like inflammation, head trauma, and diabetes. Nanobiotechnology is a powerful tool to enhance the efficiency of drug delivery with reduced toxic effects on the central nervous system (48,49). An ultra-sensitive immunoassay was described by Yang, Chiu (2016) to discriminate patients with PD or Parkinson disease dementia. Fe_3O_4 nanoparticles (size around 55.5 nm) were used as a reagent for immunomagnetic reduction, being a potential biomarker (50).

Schisantherin A is an herb, isolated from the fruit of Schisandra Chinensis, capable to protect neurotoxic synthetic organic compounds and it is used for PD treatment. Although its limitation is lower water solubility and delivery to the brain, nanotechnology can improve this lack (51). Authors showed that nanocrystals, with a particle size of around 160 nm, can reverse the neuronal loss and locomotion deficiency.

Besides neurological disorders, nanotechnology has an extremely important role in cardiovascular diseases. Around 23.3 million people die, every year, because of atherosclerosis, which is a chronic inflammatory disease affecting all arteries (52). An encapsulation of annexin A1 (the protein responsible to regulate the inflammatory process) in a polymeric nanoparticle, along with a collagen IV, was used to prevent heart disease. This encapsulation could promote an anti-inflammatory process and target nano therapy against advanced atherosclerosis (53).

Medical devices

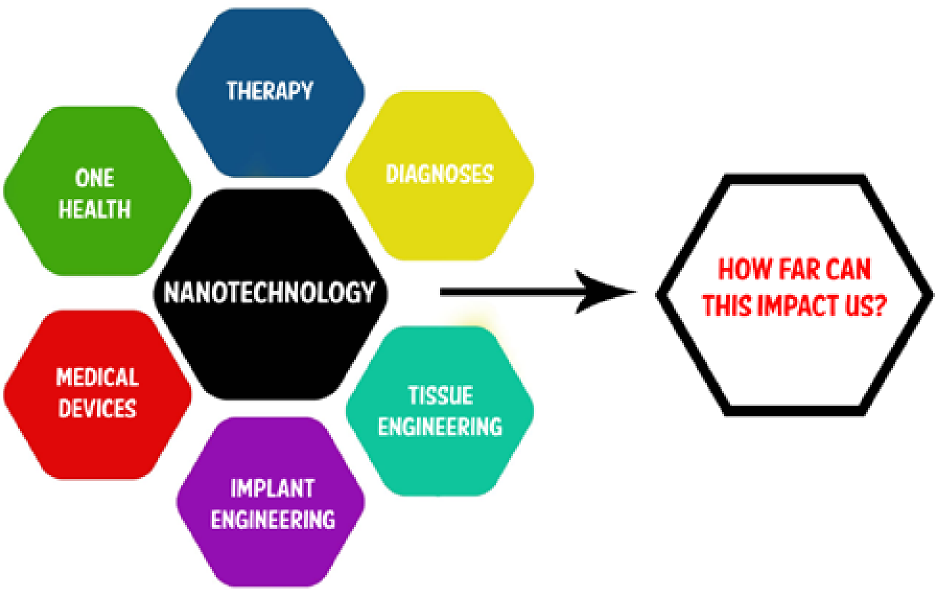
The medical device is any instrument, apparatus, or material used for diagnosis, prevention and/or therapy. Nanostructures are constantly being used in this sector to improve performance and/or increase biocompatibility (54,55).

According to Ramasamy and Lee (2016), many nanoparticle-based antibiofilm are being added to the surfaces of biomedical devices, such as contact lenses, oral implants, endotracheal tubes, heart valves and pacemakers, urinary catheters, prosthetic joints, wound dressings, nano tattoos, electronic devices, apparatus for disinfecting surfaces (56–58), and so forth (Image 1).

Other studies are using different nanostructures for medical devices. Ultrafine bubbles are often produced by hydrodynamic cavitation, having a size range of 100 – 200 nm in diameter (59), and can be used in medicine to prevent bone loss by inhibiting osteoclastogenesis (60) and as contrast agents in ultrasound imaging (61). Another kind of structure, a plant virus coated with gold, was used by Aljabali, Al Zoubi (2019) as a computed tomography contrast agent (62).

However, does not exist a regulatory framework homogenous for the world, authorizes and supports the use of nanoscale medical devices, mainly because: there are loads of materials in potential; the complexity of nano-bio interactions; and the lack of international consensus standards (50). Therefore, this restriction impacts the use of health devices containing nanotechnology. There are fewer patents for these products and some of them are shown in Table 2.

Figure 1 – How far can this impact us?



Legend: This graphic image reports many of chances and development of nanotechnology application

Table 2 – Devices applied in health using nanotechnology

Patent number	Nanotechnology	Size (nm)	Application	Property
US10583037B2 (63)	Nanofibers of thermoplastic polymer	1 - 500	Treatment of wound, infection, pain and injury. Prevent skin infections	Higher efficiency Lower waste of energy Improved recovery
EP3041787A1 (64)	Nanospikes	100 - 600	Biocidal surfaces for many sectors (food, equipment, tools, veterinary, utensils, etc)	Desirable flexibility More lethal to cells
US20070208243A1 (65)	Single- and multi-walled carbon nanotubes and nanowires	<100	Detection and measurement of biomolecules, such as blood glucose	Better conductivity Highly sensitive detection Reduced system calibration problems Reduced costs Improved reliability Greater convenience of use
KR20160117440A (66)	Silica-based nanoparticles	< 20	System for imaging diseases or cell malformations, e.g., for surgery and diagnostic	Images with higher resolution Easier manipulation to view the anatomical locations Improved in vivo imaging
US20170027660A1 (67)	Nanosphere with a metallic particle	500	Surgery imaging device and instruments	Better detection Highly amplified optic signal

Tissue engineering and implant engineering

Tissue engineering is a multidisciplinary field, as it connects material science, bioengineering, biology, medicine, and chemistry aiming to reproduce clinical needs and to cure disease, through new technologies and methods, as shown in Table 3 (68,69). Tissue engineering is also a crucial alternative to reduce animal testing with advances in downstream experiments such as drug testing and in the replacement of *in vivo* models.

Table 3 – Application of nanotechnology in tissue engineering and implants

Reference	Nanostructure	Technology	Property	Limitations
Popat, Leoni (2007) (70)	Titania nanotubular	Implants with controlled, guided and rapid healing	Support higher cell adhesion Proliferation and viability up to 7 days of culture Higher Alkaline Phosphatase activity Higher Calcium and Phosphorous concentration None adverse immune response Higher osteoblast activity	Authors suggest other researchers to evaluate molecular *in vitro* and *in vivo* responses to implant surface topography
Nishimura, Huang (2007) (71)	Hydroxyapatite NPs on titanium implant	Improved bone-implant material	Higher mechanical withstanding load Equivalent bone volume Better shear bonding strengths Fast early osseointegration process	HA nano has not been considered a osteoconductive material.

Karagkiozaki, Logothetidis (2009) (72)	Titanium nitride nanocoating	Biocompatible implants	Promotion of platelets adhesion and activation	Parameters of Atomic force microscopy to this coating were not found by authors
Aversa, Petrescu (2017) (73)	Nanodiamond hybrid material	Biomechanical active scaffolds for cartilage cells tissue engineering	Similar mechanical behaviour Biocompatibility Rigid and strength	Lack of toxicity
Tavassoli, Javadpour (2018) (74)	Nano alumina incorporated in Hydroxyapatite	Filler, implant and scaffold material for ear, bone and gingival	Best mechanical behavior Enhanced bioactivity Superior hardness values Higher attachment and proliferation	Chemically inherent low degradability

The biggest challenge to developing a biological system having the same physiologic activity is to make it suitable and repeatable. However, nanotechnology is already a reality to face this challenge, developing an artificial cell or organ. For instance, scaffolds hold a great number of cells for a long time and matrices with different materials (75,76).

Important knowledge in this sector is to understand the cell behavior and so that, there are several studies about the cell size, geometry, integrin-binding, structure, etc, as well as, techniques, for example, nanolithography (77,78), hydrolytic etching (there are not patents using nanotechnology published up to now), microcontact printing (there are few patents published recently) (79), among others. Table 4 brings patents about new published techniques as mentioned above.

Table 4 – Different techniques to develop structures for tissue and implant engineering

Patent number	Technique	Nanotechnology	Description	Application
US20170145169A1 (80)	Lithography	Nano-sized hydrogels	Methods to produce particles with controlled size	Cell encapsulation Drug delivery Tissue scaffolding
CN106366615B (81)	Lithography	Nano-cellulose	Method to produce photocurable resin material	Platforms for biomimetic tissue engineering, as cartilage
US20170020402A1 (82)	Photolithography	Silicon nanomembranes	Production of implantable and bioresorbable sensor	Implantation into skull
US7371400B2 (83)	Plasma etching	-	Fabrication of polymer scaffold having a pattern of microchannels inside	Vascularized organs
US9994812B2 (84)	Microcontact printing	Nanotextured platform	Production of the platform and in-vitro tests	Muscle cells, such as cardiomyocytes

According to Saji, Choe (2010), depending on the topography of a nanostructure, it can affect the cellular response through some mechanisms such as protein deposition, controlling cell growth, and increasing osteoblast adhesion and proliferation. Also, the authors report that nanostructures can affect the topography of a surface or can release nanoscale chemical molecules on a surface (12).

There are many methods to produce systems to affect the topography. As well as photolithography, soft lithography, dip photolithography, and inkjet printing, colloidal lithography is a technique for patterning hydrogel colloidal particles. The last one is based on the production of three-dimensional particle crystal multilayer film. Comparing cells cultured on flat surfaces, cells grown on nanotubular surfaces are more able to adhere, proliferate and show higher alkaline phosphatase activity and bone matrix deposition (12).

Many products capable of releasing compounds are already in clinical trials, such as medical sutures and bioactive brackets (85,86). Silver nanoparticles are commonly used in medicine due to its antimicrobial activity, being used in wound coating with a therapeutic effect (87), an antibacterial sanitary napkin to protect women's health, and in bone material (nanosilver incorporated in hydroxyapatite (HA) surface) (88).

Researchers also have an interest in nanotubes, because it has some great properties, such as low density, synergy with metal and organic/inorganic materials, biocompatible, and capability of connecting biomolecules (89). Because of those characteristics, Huang et al (2019) used halloysite nanotubes enhancing its efficiency as a platform for promoting bone regeneration (90). Hydrogels with nanofiber structures were used as potential cell carriers for cell delivery and tissue engineering (91).

The principal materials for implant devices are polyglycolide, polylactide, and poly (glycolide-co-lactide). These polymers have to have high strength and be biodegradable. To select the right polymer is important to consider the porous size, degradation rate, and surface morphology, for scaffold applications. A bone tissue engineering scaffold (nano-HA-degradable polymer) developed should simulate the macro- and microstructure of natural bone, replacing the natural extracellular matrix momentarily (92,93).

There are several methods for fabricating HA-based nanocoatings on implants, such as sol-gel, electrolytic and electrophoretic deposition, pulsed laser deposition, high-velocity oxy-fuel process, electrohydrodynamic spray deposition and RF magnetron sputtering (12).

Therefore, an ideal biomaterial scaffold integrated has to provide mechanical support to an injured site assisting tissue growth without causing an inflammatory response (94). So, nanotechnology has been providing excellent products and techniques in tissue engineering and regenerative medicine and there are still many types of research in the study, mainly involving biopolymeric matrices due to its similarities with native tissues, good biological performance, and specific degradation rates (95–98).

Animal Health

Over 60 % of all human pathogens are due to zoonoses. The vaccine is an active immunization method to prevent infections and diseases. Although, there are some dilemmas some vaccines require an adjuvant, must be administrated by needle and the patient need more doses to induce a sufficient immune response. Because of that, the administration of nanoparticle vaccines via nasal or inhalation is extremely interesting (99,100).

Animal health is an important sector of society and according to the veterinarian, Feneque, nanotechnology has a huge potential to update veterinary medicine (101). This sector is rising and improving nutrition, therapeutic, vaccine production, animal breeding, and methods of reproduction and diagnosis, even before its clinical manifestation. Also, it can provide better tools to manipulate biological samples such as DNA, protein, and cells (102). Another advantage of nanotechnology is to minimize the drug residues in milk and meat (103). Table 5 is presented many applications of this sector.

Scott (2005) showed the use of nanoshells containing target agents to map an animal's bloodstream and attach to the surface receptors of tumor cells. With infrared light, the temperature of those cells increases, which kills it (101).

Although veterinary health care is a common concern, the higher costs and increasing pet population requires urgent innovative solutions. Also, the effective delivery of therapeutic molecules, especially for cancer treatment, has certain limitations due to toxicity, cell impermeability, and poor aqueous solubility. Despite this, nanotechnology has shown promise in replacing conventional methods of diagnosis and treatment for having the potential to get around these challenges (104,105).

Table 5 – Different applications of nanotechnology in animal health

Sector	Nanotechnology	Size (nm)	Improvements	Reason	Patent number
Diagnostic and treatment	Suspension of Oxfendazole nanocrystals	50-950	Solubility Dissolution speed Oral adsorption Without organic solvent No irritation Little toxic and side effect	Preventing and treating parasitic diseases of cattle, sheep, horses, pigs, chickens, and pets caused by worms	CN110693830A (106)
	Thimerosal with nano-Ag	5-15	Disinfection effect Longer retention time No irritating odor Green non-pollution	Antiseptic	CN109362801A (107)
	Snail sirna-loaded mesoporous silica nanoparticles	< 40	Specificity	Ovarian cancer	WO2020028562A1 (108)
	Enrofloxacin nano-self-microemulsion	Uninformed	Solubility Antioxidant Suitable for spray delivery Long-time stability	Antibacterial drug	CN109431999A (109)
Nano-vaccine and nano-adjuvants	Nanocarrier incorporating T- and B-cell antigen	60-250	Long-lasting immune responses Do not cause disease Increased stability, uniformity, and viscosity	Pharmaceutical preparations and kits for the prophylaxis and treatment	US9526702B2 (110)
	Poly (lactide-co-glycolide) NPs	200-600	Efficacy Better virus clearance Higher levels of IFN-γ and IL-12 Better immunization	Treating or preventing Porcine reproductive and respiratory syndrome infection	US9457074B2 (111)
	Nanoemulsion adjuvant comprising a cationic lipid, non-ionic surfactant, and an organic solvent	300-600	Antimicrobial property Adjuvant activity Reduced tissue toxicity Higher efficiency	Treatment and prevention of infectious disease, cancer, and allergy	WO2017196979A1 (112)
Food and nutrition	Nano-zinc oxide nutrient in Trionyx	< 1000	Can diffuse by passive transport The zinc absorption rate is improved Mouldy feed defense capability	Turtle breeding feed	CN102511672B (112)
	Nanocrystalline cellulose, polymers, and plastics	5-10	Better mechanical properties, such as elastic, strength, and barrier	Packaging Beverage containers Food additive	CA2898513A1 (113)
Animal reproduction	Single-walled carbon nanotubes	900-1600	Improved timing of insemination	Tracking estrus, particularly in cows and pigs To monitor pregnancy	US8765488B2 (114)

One Health

More than just unite multiple disciplines, the Food and Agriculture Organization of the United Nations (115) endorses the One Health concept of "…unifying force to safeguard human and animal health, to reduce disease threats and to ensure a safe food supply through effective and responsible management of natural resources." It is also stated that crowded and unhealthy conditions cause disease in animals and humans in the same way, such as HIV, pandemics H1N1 influenza in 2009, and severe acute respiratory syndrome (SARS), mainly Covid-19 in 2019 (130). SARS-CoV-2, which causes Covid-19, is likely a bat-origin coronavirus and the human infection is not so clear. The virus could have been transmitted to humans through spillover from bats or an intermediate animal host like swine, bovine, avian, etc. Therefore, the application of One Health approaches is important to reduce the threats of emerging viruses (116).

Human health is strongly linked to animal and environmental health. Zoonoses control programs are extremely important to avoid pandemics and to give a great lifestyle for everybody. As stated before, nanotechnology has the potential to mitigate these health problems. Also, nanotechnology is immersed in the One Health concept making it achieve its high performance (117). Several studies about nanotechnology have been using the concept of One Health and, as stated before, the number of publications about this topic has been rising every year, according to the Web of Science, but there is still a long road to explore.

For instance, Benelli, et al (2018) show the use of green-fabricated (plant-based) nano pesticides against mosquito vectors of malaria, dengue, chikungunya, Zika virus, and West Nile (117). It is a great alternative to replace synthetic insecticides and repellents, which could be a health hazard to humans and animals and some populations of mosquitoes develop resistance, reducing its efficacy.

Nanostructures have different comportments as they change the environment and these transformations are not entirely understood. Thus, a transdisciplinary approach and larger studies, including human, animal, and environmental nanosafety, underpinned by the One Health concept, are needed for a life better (118).

Prospects and Challenges

The application of nanotechnology in health has been in constant growth over many years. Although it is the target of investments from the public and private sectors, there are some challenges to face. Permission to use drug delivery systems takes a long and costly process. There is no consensus about the number of medications using nanotechnology. According to Saxena, et al (2020), in the last few years, only 30 new medications were approved by the US FDA every year, and the list has just a few medications with nanotech-based (31). On the other hand, von Roemeling, et al (2017) show that there are already several nanomedicines in clinical use for cancer therapy (119), and confirming this, Kumari, et al (2020) mentioned that only 20 nanoparticle therapeutics are in clinical use (120). Therefore, there is a need to study in-depth these nano medications and the exact safety outline of nanostructures through toxicity assays. They must develop technologies that do not put in risk human and animal health, and the environment (121).

Some technologies are still being developed using nanotechnology. Caracciolo, et al (2019) state that early cancer diagnosis will be established with the exploration of the biomolecular corona of nanomaterials *in vivo*, by blood tests, having high sensitivity and specificity and allowing the detection of small changes in plasma proteins (122). Currently, many *in vitro* diagnostic tests are done with benchtops laboratories. Therefore, nanotechnology will be combined with microfluidics to develop the next-generation *in vitro* diagnostic tests, allowing sample preparation and handling with minimal human interference, improving sensitivity and efficiency (123).

The challenge in oncology is killing the tumor cells without causing any damage to healthy cells. Photo Dynamic Therapy utilizing nanotechnology-based medication will be a great alternative to chemotherapy and radiotherapy, but it still needs detailed studies of cytotoxicity. It will be essential to understand and mitigate unintended damage to the commensal microbiota caused by nanotechnology (124). Besides toxicity, complex manufacturing processes and stability issues are other concerns associated with nanostructures (125).

Smart dressings and bandages are expected to promote therapeutic activities, reduction of healthcare costs, and provide information about the patient's clinical situation, which is obtained and transmitted, at the site or distance (through Wi-Fi transmission), by sensors within dressings. Also, identifying the type of microorganism present in a wound that causes the disease will be a reality due to nanosensors (126).

A new class of multifunctional electronic devices will emerge with sensing functionalities embedded in the same platform, such as low cost, porosity, versatile, and robust properties. It will open numerous applications such as flexible thermal management, temperature sensing and stabilization, and flexible/wearable devices for healthcare. However, these systems require complex fabrication processes and very little progress has been recently achieved (127).

Carbon nanotube wire is inert, soft, and lightweight and has the potential to be used as medical devices, such as millirobots increasingly smaller and implantable electronic devices and sensors. Although it has perfect properties (good conductivity, good strength, and small size) for *in vivo* applications, long-term safety needs to be studied (128).

Soon, cyborgs, made of nanomaterials and coated with human tissues will revolutionize surgeries such as transplantation and implanting. Paraplegic patients, blind or in the queue of organ transplants will have the opportunity to reestablish lost functions with the advance of "biotechnological tissues" (127).

According to Yadid, et al (2019), gold nanoparticle-integrated scaffolds has superior potential for tissue engineering and regenerative medicine, but a study about its toxicity is needed. These structures could be used as many kinds of tools, enhance tissue formation and act as nanosensors. So, it can also allow controlled drug delivery (129).

The use of artificial intelligence (AI) can improve some methods of producing and analyzing systems of tissue engineering based on previous data. An object that needs more study is the design of smart materials able to adhere, proliferate and promote tissue morphogenesis. Allied with that, is important to have faster fabrication that impacts less the environment (130) and has fewer side effects (131). So, it is extremely important to understand the biological machinery, once developing a system with all the wanted properties and being biocompatible can be challenging.

The advance of nanotechnology keeps rising and nano-supplements will be used to fortify livestock feed. However, biosecurity in animal production is a relevant area of caution, once nanostructures need to be tested in vivo to fully replace antibiotics in feed. A description of each feed additive and its mechanism of action, efficiency, and advantages and disadvantages of use must be exposed (132,133). Recent research has directed studies toward the use of inorganic NPs (gold, nickel oxide, cobalt-zinc ferrite, cadmium selenide QD) to the detection of the Leishmania parasite, but a lot still has to be explored (134).

One of the most important contaminants in food and feed is mycotoxins and its early and fast diagnostic reduces damage to human and animal health. Most conventional methods have certain limitations. Although nano-based technology has a huge potential for locating mycotoxins, there is a necessity for extensive studies about it (135). The association research platform of Mycotoxins and

Toxigenic Fungi (MYTOX) highlights the importance of multidisciplinary efforts to lighten mycotoxin contamination in the food chain, following the One Health concept (136).

Many barriers are preventing One Health from reaching its full potential. The first action is the reduction of disciplinary divisions and sharing of knowledge between stakeholders, such as scientists, farmers, industry, NGOs, and consumers. It is important to have someone to help with decision-making about nanostructures' use and regulation. So, there are five crucial steps to break these challenges: (a) integrate, cooperate, and communicate between the sectors of human and environmental toxicology; (b) standardize protocols and collect consistent datasets about human and environmental toxicology; (c) encourage studies; (d) engage stakeholders in research and innovation; (e) bringing together regulators to develop a transdisciplinary framework for nanotechnology (118).

We expect that future advances in the areas mentioned above can develop much more products for fast diagnostic and easy therapy, medical devices more accurate, biocompatible implants, and so forth, being able to end human and animal suffering and bring a new model of care.

CONCLUSION

Nanotechnology is a powerful tool to develop a wide number of products to upgrade some processes and overcome some limitations of traditional medicine. In this way, nanotechnology has the potential to guarantee biological safety in human and animal healthcare, improving their quality of life in many aspects. The use of nanomedicine leads to earlier and faster diagnostics, increasing survival chances; more efficient treatments without or with minimal side effects, controlled drug delivery; and less invasive surgeries, with safety devices and real-time monitoring.

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