Chapter 10

Green Nanoparticles; Sustainable Approaches and Applications in Veterinary Medicine

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ABSTRACT

Nanoscience and nanotechnology has gain massive attention in several research areas, including nano-medicine, biotechnology, biomedical sciences and veterinary medicine. A relatively new branch of research called "green nanotechnology" focuses on using biological processes to produce nanoparticles from live cells. The biological routes need application of either plants or microorganisms (bacteria, fungus, yeast, and algae, etc.) for synthesis. Using microorganisms poses higher risk due to pathogenicity and large-scale culture management. Nanoparticles have several applications in medicine, drug and gene transport, cell imaging, bio sensing, wound healing, dental care, x-ray imaging, and activation of antibacterial, antifungal, anti-inflammatory, anticancer, and antifouling properties. Use of green technology in animal husbandry and veterinary care is relatively novel. Recently veterinary medicine has gain remarkable advancements in health care technologies. Animal production and growth are being improved with the application of current state and advances in nanotechnology. Therefore, nanoparticles are alternative antimicrobial agent for identification of pathogenic bacteria and to counteract the misuse of antibiotic. Additionally, nanoparticles are utilized as drug delivery agents to create new drug and vaccine candidates with enhanced properties and performance, as well as for diagnostic and therapeutic purposes.

KEYWORDS		
Nanotechnology, Nanoparticle, Green technology, Antibacterial, Veterinary medicine	Received: 23-May-2024 Revised: 19-Jul-2024 Accepted: 16-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Presently, nanotechnology has gained a lot of attention as one of the vital disciplines due to its technological advancement in several fields of science including physics, biology, chemistry, medicine, pharmacy, material science and environment (Nicolas et al., 2013). Nanotechnology refer towards investigation and manipulation of materials with an objective of achieving a dimension falling within range of 1–100 nm (Ahmad et al., 2017). A Professor Norio Taniguchi of Tokyo Science University first used the word "nanotechnology" in 1974 to refer the precise process of creating materials (Taniguchi, 1974). The word "nano" is derived from Greek word "nanos" meaning dwarf and "nanometer" (10^{-9}) meaning the length of three atoms aligned in a single pattern, or one billionth of a meter (Thakkar et al., 2010).

Importance of Nanotechnology

Nanotechnology plays an imperative role in several technical domains owing to its pre-established superstructures. This field pertains towards the manipulation of atoms or molecules in order to create structures with desired shape and characteristics. Its health and environmental applications involve efficient drug delivery and solar energy harvesting. Additionally, it contributes towards reduction of industrial chemical use and creation of better, healthier, and more livable environment. Moreover, it contain applications in water filtration, cancer treatment, and food packaging (Khan et al., 2019). Nanomaterials (NMs) possess numerous unique properties because of their greater surface area to volume ratio, specific size, composition, shape and concentration of individual constituents. These properties also makes possible the application of particles in different fields as catalysts, drug/gene delivery system, nano-magnets, quantum dots for electronic devices, water disinfectants and pollutant remediating agents (Khin et al., 2012; Tang et al., 2014; Gong et al., 2018).

Nanoparticles

Nanoparticles (NPs) are solid particles with size of few nanometers, created at molecular or atomic level containing unique or superior physical properties that are not possible for bulk solids. These NPs exhibit the properties of unified cohesive entity (Sharma et al., 2019). Because of their unique characteristics over their bulk counterparts, NPs are created in variety of sizes and shapes. Nanoscale materials possessing high surface to volume ratios vary significantly because of their mechanical properties, biological activity, light absorption, thermal conductivity, melting points and catalytic properties (Mandhata et al., 2022).

Classification of Nanomaterials

Numerous classifications of nanomaterials have been established, based on following factors:

(I) **The structure:** Dendrimers carbon tubes, liposomes, nanoclusters, nanotubes, micelles and fibers (Abdullaeva, 2017).

(II) **The dimension:** The size of NPs ranges from 1 to 100 nm; smaller particles containing larger surfaces, affects both toxicity and functioning (Saleh, 2020; Lang et al., 2021).

(III) **The morphology:** NPs might be manufactured in a variety of shapes, including cubes, triangles, wires, helices, stars, hooks, plates and spheres (Buzea and Pacheco, 2017).

(IV) **The application:** NPs can be used in nutritional, medicinal, diagnostic, theranostic and vaccine manufacturing purposes.

(V) **The surface modifications:** It refers to surface functionalization of NPs by adding thiols, fatty acids, anionic chemicals, or by carboxylation, PEGylation, or amination linking to functional groups. It also refers to adjustment of surface charge, either negative or positive (Saleh, 2020).

(VI) **The composition:** In order to overcome limitations of single-component NPs, improve their properties, and accomplish multiple functionalities. A NMs can be synthesized using a single material or composite of at least two different NPs (Buzea and Pacheco, 2017; Ma, 2019; Du and Yuan, 2020).

(VII) **The nature:** NPs can be divided into three categories: carbon, organic and inorganic (Ealia et al., 2017). Metals or metal oxides make up inorganic NPs. Gold, silver (Ag), copper, cadmium, iron, aluminium, cobalt and zinc are materials used to make metal NPs (Reverberi et al., 2016). Because iron (Fe) NPs are very reactive and quickly oxidize to Fe_2O_3 in the presence of oxygen at ambient temperature, coating FeNPs is recommended to maintain them stable and to stop aggregation (Ali et al., 2016). Because of their higher reactivity and efficiency, metal-oxide NPs are mostly produced (Tai et al., 2007). Carbon-based NPs should be categorized into, black carbon, fullerenes, carbon nanofibers, carbon nanotubes and graphene (Bhaviripudi et al., 2007). Proteins, liposomes, and peptide-based NPs are examples of organic NPs (Osama et al., 2020). They are biodegradable, biocompatible and non-toxic. Nano-capsules, as liposomes and micelles, are an excellent alternative for sustained release and drug administration due to their outside shell and empty internal portion (Abd El-Ghany et al., 2021).

Green Nanotechnology

NPs produced using environmentally friendly techniques are often devoid of harmful substances and compatible with living organisms due to absence of reducing agents or external coatings in their synthesis methods. That’s why they are less harmful than nanoparticles synthesized chemically (Porzani et al., 2021). Biologically produced nanoparticles have provided a modern approach for developing an alternative technology (Ebrahimzadeh et al., 2020). The advantages of biological synthesis compared to traditional physiochemical techniques are its cost-efficiency and eco-friendliness (Duran et al., 2016).

In addition, biological engineering enables creation of nanoparticles with exact dimensions and shape by controlling several factors, including pH, temperature, incubation time, as well as concentration and developmental settings of biological agent used (Gericke and Pinches, 2006a; Gericke and Pinches, 2006b). Green synthesis of several nanoparticles from different plants, including *Solanum nigrum*, *Ocimum basilicum*, *Azadirachta*, *Camellia sinensis*, *Mangiferaindica* and green tea have been reported recently (Majidi et al., 2016).

Green Nanoparticles Production Methods

Green nanoparticles (GNPs) are synthesized using various components and bio-chemicals derived from plants acting as stabilizing and reducing agents. Green synthesized technologies are more durable, economical, non-toxic, and eco-friendly compared to other physical, biological, and chemical techniques (Mustapha et al., 2022). The procedure of synthesizing NPs from plant extract is cost effective and yields higher products since, extract contains large amount of phytochemical components that can be used as stabilizing and reducing agents to transform metal ions into metal NPs (Venkataraman, 2022).

Variations in Green Synthesis of Nanoparticles

Diverse factors, as temperature, pH, reaction time, and reactant concentration, might be adjusted according to requirements of environmentally friendly production of NPs for their morphological analysis. These features primarily recognize the impact of extrinsic variables on synthesis of NPs, and they might have pivotal part in improving the efficiency of producing metallic NPs (Zhang et al., 2020).

Biological Methods

Biological techniques are acquiring ubiquity due to their reduced impairment, ease of application, eco-friendliness, and effectiveness compared to traditional treatments. This method employs microorganisms (as bacteria, viruses, and fungi) or extracts from plants or algae as direct substitutes for chemical and physical procedures (Eszenyi et al., 2011; Abdelnour et al., 2021). The extracts include polyphenols, terpenoids, sugars, proteins, and other components that function as reducers to maintain minerals in reduced state throughout production (Marappan et al., 2017). Biological techniques have several limits when it comes to retrieving NPs, as time required to manufacture them and need to maintain culture medium and conditions (Abdelnour et al., 2021).

Synthesis using Plant Extract

Numerous phytochemical substances with oxidation-reduction properties, as flavonoids, phenolics, terpenoids and polysaccharides are found in plants. Therefore, they are ideally used in eco-friendly synthesis of NPs (Widatalla et al., 2022). The synthetic GNPs have an impact on several components of plants, including roots, stems, leaves, seeds, and fruits, due to availability of important phytochemicals (Parmar and Sanyal, 2022). Various techniques for synthesizing plant-mediated NPs include: (i) employing specific phytochemicals (Ivask et al., 2014), (ii) using plant extracts externally (extracellularly), and (iii) using plant extracts internally (intracellularly). Several plants contain the capacity to accumulate metals and subsequently convert them into NPs within their cells. Numerous key biomolecules present in plants, as proteins, polysaccharides, alkaloids, phenolics, aldehydes, ketones, terpenoids, saponins, tannins, flavones, and vitamins, play a crucial role in reducing metals (Nath and Banerjee, 2013). Fig. 1 indicate green fabrication process of metal NPs mediated by plants.

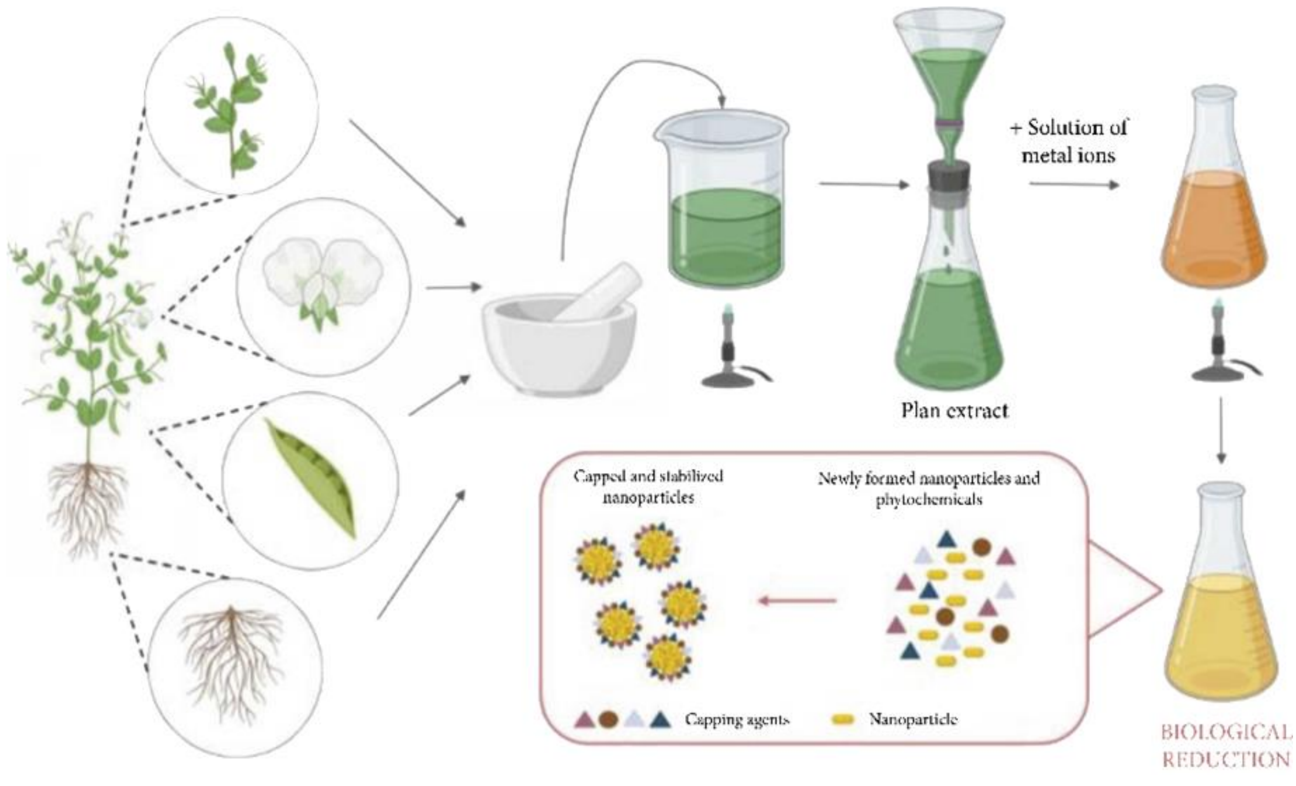

Fig. 1: The typical process of plant-mediated green synthesis of metal nanoparticles Copyright © 2021 (Ronavari et al., 2021).

Biosynthesis using Microorganisms

Microorganisms like bacteria, fungi, and yeast are showing huge interest for synthesis of NPs however, lack of control over NP size, extensive procedures, and culture contamination pose threats to the method. Microbial-derived NPs can often be categorized into several types based on the particular environment within which they are synthesized (Li et al., 2011).

Bacteria

Bacterial species have been extensively used in several commercial biotechnological applications, as genetic engineering, bioremediation and bioleaching (Gericke and Pinches, 2006). Bacteria are vital prospects for NPs manufacturing due to their ability to reduce metal ions (Iravani, 2014). Numerous bacterial species are employed in synthesis of metallic and other new NPs. Actinomycetes and prokaryotic bacteria are often used in the production of metal/metal oxide NPs (Singh et al., 2018).

Fungi

Fungi that synthesize metal/metal oxide NPs provide very effective method for producing well-dispersed NPs with distinct morphologies due to their diverse intracellular enzymes. They are highly efficient in producing metal and metal oxide NPs (Chen et al., 2009). Proficient fungus have higher NPs production rates than bacteria (Mohanpuria et al., 2008).

Viruses

Viruses, which are not regarded as entire living beings, are also utilized in process of producing nanomaterials. Plant virus capsids in particular are helpful bio-template for synthesis of NPs (Young et al, 2008; Banik and Sharma, 2011; Love et al., 2014). A few plant viruses, including red clover necrotic mosaic virus, cowpea mosaic virus, and tobacco mosaic virus, have been utilized to create Fe–Pt, Co–Pt, Co–Fe, and Cd–Se alloy NPs (Tsukamoto et al., 2007; Loo et al., 2007; Shah et al., 2009).

Yeast

The single-celled microorganisms known as yeasts are found in eukaryotic cells containing about 1500 known species (Yurkov et al., 2011). Yeast strains have various advantages over bacteria, including the ability to synthesize several enzymes, rapid development using inexpensive resources, efficient mass production, and easy regulation in laboratory settings (Kumar et al., 2011).

Comparison of Plant-based Green Synthesis over Microorganism-based Methods

Reaction rates in synthesis methods based on plant extracts are relatively high. Depending on kind and number of plants involved, this process may take a few minutes to many hours. In microorganism-based techniques, microbe cultivation requires significant amount of time, sometimes several days. This indicates time-consuming nature of this approach. Some of bacteria in addition to these are highly dangerous and could threaten human health. However, *Pseudomonas*, *Fusarium* and *Escherichia coli* are safest and most benign bacteria to produce nanoparticles. In nature, there are numerous plants especially evergreens, which are almost constantly present. In contrast to microbes, herbal extracts usually produce metal nanoparticles at ambient temperature without heating the reaction mixture or culture medium. Broadly, plant extracts are more suitable for industrial scale synthesis than microbes (Noruzi, 2015).

Applications of Green Nanoparticles

i. **Agriculture;** GNPs made from different plants, decrease harmful emissions of nitrous oxide, carbon dioxide and methane. This is an important idea of employing green nanotechnology in agriculture to reduce detrimental environmental consequences and high cost of fertilizers. GNPs have potential to alleviate health problems among farmers while simultaneously increasing agricultural output (Raja et al., 2022).
ii. **Detoxifying agent;** Plants naturally contain wide variety of phytochemical constituents which, are affordable and environmentally beneficial. Green synthesized NPs are subjected to substantial significance and detoxification of environmental heavy metal. Because heavy metals contaminate soil and water in large quantities, green nanoparticles can help reduce metallic toxicity in the environment (Jadoun et al., 2022).
iii. **Energy;** The energy sector is core area where green nanotechnology offer opportunities as addition of NMs to solar cells can increase their ability to absorb light and convert it into electricity, creating cleaner and more effective energy sources (Cuong et al., 2022).
iv. **Biosensor;** The visual characteristics of gold NPs produced by algae have demonstrated exceptional performance and might be valuable in biological sensing applications as determining kind and quantity of hormones present in human body, particularly in cancer diagnosis. Algal-produced Au-Ag demonstrated exceptional electro-catalytic activity against 2-butanone at room temperature, and might be used as substrate to create biosensors for cancer detection and to identify presence of malignant cells (Anvar et al., 2023). A new and practical method for creating nano-biosensing instruments to target environmental contaminants is use of biosynthesized Ag-NPs. The Ag-NPs produced from *Anacardium occidentale* leaf extract have been utilized as a sensing probe to find Cr (VI) in tap water (Balavigneswaran et al., 2014). Green-synthesized NPs, including Ag-NPs, CuO-NPs, ZnO-NPs and NiO-NPs, show antibacterial activity through several mechanisms. Ag-NPs possess ability to rupture bacterial cells by creating holes in their membrane (Annamalai and Nallamuthu, 2016), resulting disruption in DNA replication, ATP production, protein denaturation and loss of proton motive force (Shao et al., 2018; Jemilugba et al., 2019). NPs contain ability to damage polymer components of cell membranes found in both pathogenic and non-pathogenic microorganisms, including peptidoglycan in cell walls. Increasing the concentration of NPs can increase permeability of membrane and cause cell wall rupture (Dakal et al., 2016).

The primary characteristic of NPs with small sizes that may lead to cell wall damage is their large surface area (Janthima et al., 2018).

v. **Antifungal agent;** Numerous medical applications of green synthesized NPs are presented in Fig. 2. The development of effective, new and potent antifungal medicines is very promising, as fungal infections have become a critical public health concern due to drug resistance and restricted access to antifungal treatment. Fantastic antifungal efficacy is demonstrated by NPs, which may offer a novel treatment option for fungal illnesses. The most potent antifungals that can be produced through green methods are silver nanoparticles. For example mechanism involved in biocidal effects of *Nostoc* Bahar_and *Desertifilum* sp. IPPAS B-1220 against *Candida albicans* attributed to their capacity to interfere along with fungal cell structures and stimulate oxidative stress, assisting them to be utilized as robust antimycotic agent (Hamida et al., 2021).

vi. **Anti-inflammatory agent;** Anti-inflammatory mechanism of various NPs may be applicable for targeting, drug designing, in food and cosmetic industry , as well as offers feasible solution for treatment of several types of inflammations with minimal side-effects (Agarwal et al., 2019). Selenium (Se) an crucial trace element that perform critical role in counteracts chronic inflammation and immune functions by regulating signal-transduction pathways and inflammatory gene expression in triggered macrophages (Narayan et al., 2015). The roles of Se in immunity and inflammation have been recognized, and can reduces risk of cardiovascular diseases and rheumatoid arthritis (Huang et al., 2012). It has been reported that silver NPs demonstrate anti-gastric ulcer properties (Sreelakshmy et al., 2016) and solid lipid NPs (Sun et al., 2017) and anti-peptic ulcer assets of chitosan NPs (Goncalves et al., 2014).

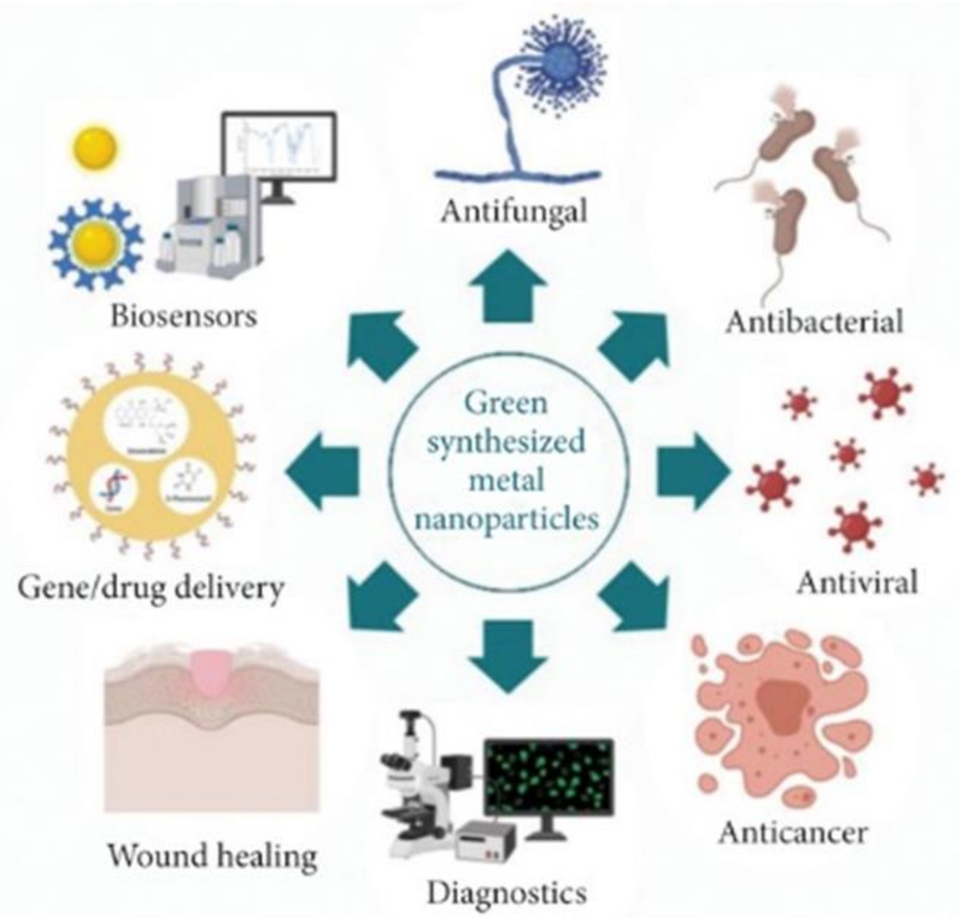

Fig. 2: Green-synthesized metal nanoparticles' medical applications Copyright © 2021 (Ronavari et al., 2021).

vii. **Anticancer;** Synthesized silver NPs derived from several plants, such as *Ficus religiosa* (Antony et al., 2013) and microorganisms such as *Deinococcus radioduran* (Kulkarni et al., 2015), *Streptomyces rochei* MHM13 (Abd-Elnaby et al., 2016) have demonstrated *in-vitro* anticancer actions towards different cancer cell lines. The synthesized silver NPs from *Indigofera tinctoria* leaf extract revealed cytotoxicity against lung cancer cell line A549. It was discovered that the cytotoxic effects of silver NPs were dose-dependent and more distinct than those of leaf extract administered as a placebo (Vijayan et al., 2018).

Application of Nanotechnology in Veterinary Medicine

❖ NMs are very beneficial in biomedical applications because of their small size, which makes them compatible with a wide range of biological organisms as shown in Fig. 3. Nanotechnology contain significant potential for resolving wide range of issues in veterinary medicine and veterinary-sanitary inspection (Patil et al., 2009). Many applications, such as medicine administration, gene transfer, imaging, parasitology, tissue engineering and pest control, might be revolutionized by nano-biotechnologies (Rai et al., 2009; Heng et al., 2013; Amerasan et al., 2016). Recently, garlic oil nano-emulsion has emerged as promising technique that may be greatest antibiotic substitute in chicken farms. Because application of garlic nano-emulsion greatly decreases gene expression levels of multi drug resistant (MDR) *P. aeruginosa* in broiler farms, it is great choice for therapy as an alternative to antibiotics (El-Oksh et al., 2022). In the animal model of atopic dermatitis (AD), nano-sized zinc oxide significantly decreased pro-inflammatory cytokines, exhibiting stronger anti-inflammatory effects than bZnO (IL-10, IL-13, IFN-, and Th2 cytokines) (Yousaf et al., 2024).

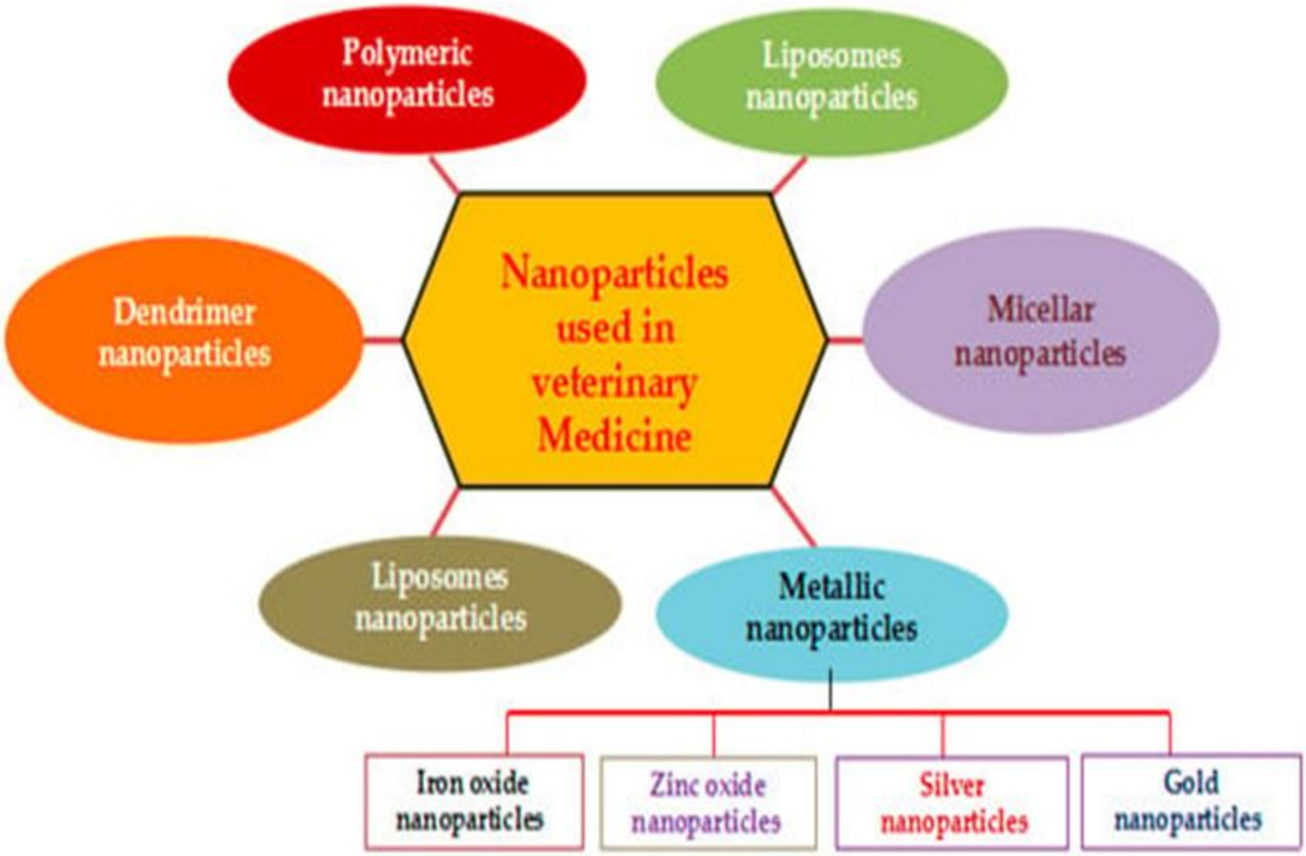

Fig. 3: Type of nanoparticles used in application of veterinary medicine and animal production (Bai et al., 2018).

❖ The hydrogel of silver NPs made from *Arnebia nobilis* root extract demonstrated effective wound healing activity in an animal excision model. The antibacterial qualities of biosynthesized silver NPs are correlated with their therapeutic effects in wound treatment (Garg et al., 2014).

❖ A substance termed timicosin contain semisynthetic characteristics. Broiler chicks were given three different kinds of micellar NPs as lipid-core nanocapsules, solid lipid NPs, and nanostructured lipid carriers-pills. Improved medication bioavailability and pharmacokinetics were the goals of their utilization. The pharmacokinetic properties and bioavailability of the medication were improved in three separate batches of lipid NPs administered to broiler chickens (Al-Qushawi et al., 2016).

Diagnostics

Bio-imaging plays vital role in disease diagnosis, particularly in identification of cancer and tumors, as well as in recognition of forms, structures and pathways inside organisms. Gold, iron-based NPs and quantum dots are being used in various biomedical imaging techniques as magnetic resonance imaging (MRI), photo-acoustic (PA) imaging, computed tomography (CT), contrast-enhanced dual-energy mammography (DEM), high-order multiphoton luminescence (HOMPL) microscopy for cancer and tumor detection (Nune et al., 2009; Chou et al., 2016).

Certain NMs (e.g., magnetic, fluorescent and catalytic) can be used as probes for various imaging and diagnostic applications because of their essential physicochemical qualities and biocompatibility. Biochips for early diagnosis of animal illnesses have been developed and effectively implemented. These chips are made from silicon pools that have hundreds or thousands of small recombinant Deoxyribonucleic acid (DNA) strands grafted on them (Hanafy, 2018). Molecular diagnostic methods are becoming more common in diagnostic laboratories these days. Immune diagnostic probe integration with NMs significantly increase the specificity and sensitivity of antibody-based immunodiagnostic techniques and provide strong impetus for their development. More biocompatible, stable, and sensitive to target antigens are the antibodies conjugated to NPs (Vrublevskaya et al., 2017).

Therapeutic usage of Green Nanotechnology

Drug Delivery

Higher binding affinity for biomolecules, decreased oxidative stress and inflammation in tissues have demonstrated by nano-medicines. Thousands of unique nano-medicines have been created over time, each with different use for handling of different diseases. Many more are in the clinical testing phase and very few have been authorized for use in clinical settings. Different kinds of NPs were found based on therapeutic need as shown in Fig. 4, depending on their origin and use. Iron oxide NPs, polymeric proteins, liposomes and metal-based materials have all become highly effective (Dikshit et al., 2021). They have notable advantages in terms of improving drug stability inside the body as well as bioavailability, pharmacological activity, toxicity protection, distribution, solubility and resistance to degradation from both physical and chemical sources (Zoroddu et al., 2014).

It offers a platform for development of therapeutic NMs or nano-medicines. Numerous opportunities in medical sciences, particularly in area of drug delivery systems, have been made possible by development of nano-medicines. Because of their structural qualities, they have great way to target particular locations and enter cells or sick areas quickly (Luque-Michel et al., 2017). Nano-medicines have shown greater ability to cooperate with biomolecules and to lower oxidative stress and inflammation in tissues (Dikshit et al., 2021).

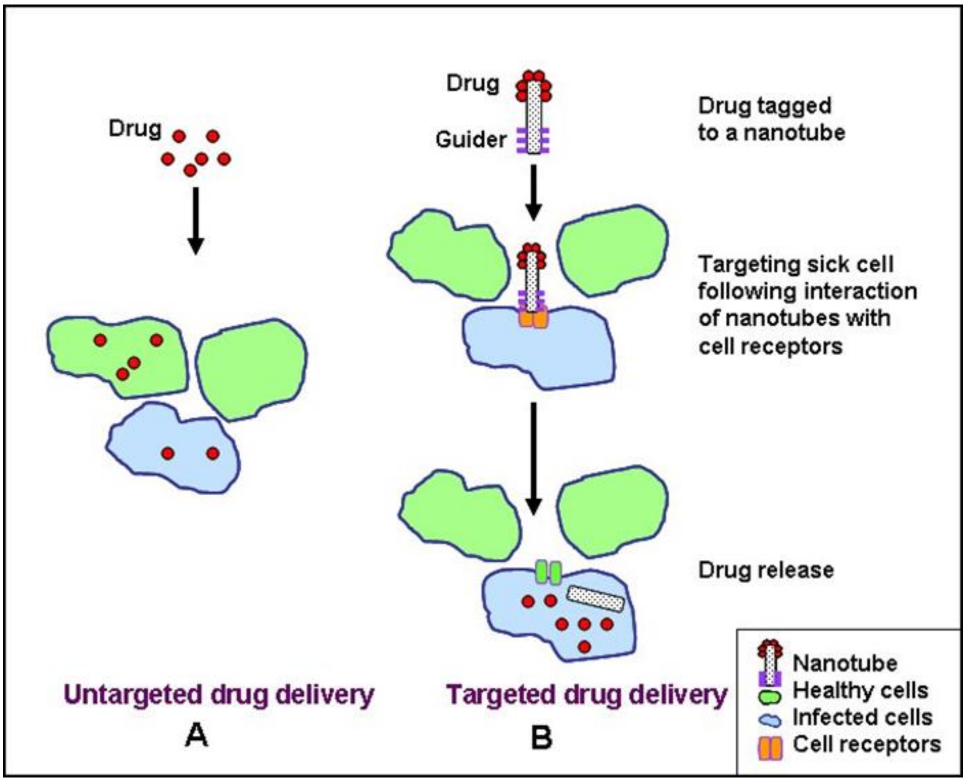

Fig. 4: Targeted drug delivery of nanotubes (Suri et al., 2007).

Future Perspectives

The development of innovative nano-drugs and delivery systems using non-toxic nanoparticles such dendrimers, polymeric nanoparticles, liposomes, and metal nanoparticles is now more possible because to recent developments in nanotechnology. The unique characteristics of each form of nanoparticle are employed to improve the therapeutic indices of the integrated pharmaceuticals in a number of ways as prolonged release, bioavailability, retention time, and protection of the entrapped agent from the internal body environment. Additional metallic nanoparticles are being thoroughly investigated for a range of biomedical uses as "nanotheranostics." In addition to being widely used as diagnostic, therapeutic, imaging, and nanocarrier agents in veterinary medicine, metallic nanoparticles serve as artificial platforms for multimodal imaging approach to the detection and treatment of degenerative illnesses, including cancer in humans. For veterinary illnesses, targeted drug delivery via various metallic nanoparticles holds out a lot of potential for both immediate and long-term therapy plans (Bai et al., 2018).

While, taking into account their manufacturing capabilities and enhancing their size, stability and lifespans, it is crucial to guarantee the quality and safety criteria of green NPs. Despite a vast extent of research, only a little amount of NP-based drugs are in use nowadays, and the bulk are still in the experimental stage. In order to enable functional nanotechnology design, further study is required to comprehend toxicity, cellular and physiological factors that affects distribution of medications via NPs, improved permeability and retention impact and pharmacokinetic mechanisms in human body (Hosseingholian et al., 2023).

Crucially, to utilize all of the tools derived from a variety of nanomaterials towards being beneficial instruments for different diseases and therapies in veterinary animals, like humans, further in-depth pre-clinical investigations are urgently needed to realize the bright future of veterinary medicine. Predicting future risks to biological systems and the environment therefore necessitates ongoing, thorough research into the short- and long-term impacts of such materials in vivo as well as a thorough grasp of molecular mechanisms. Utilizing nanoparticle-mediated drug delivery broadly is crucial in veterinary medicine as it holds great promise for more effective medication delivery to specific target sites and for overcoming biological obstacles (Bai et al., 2018).

Conclusion

The most significant application of nanotechnology in tissue engineering is regenerative medicine, which has potential to revolutionize the design of scaffolds and transplants with tissue-regenerative qualities. Creating perfect nanomaterials that can communicate with damaged or sick cells and tissues to start regeneration process is still difficult. Similar to this, as regenerative medicine is still in its early stages of development, there is great deal of concern regarding safety of using nanomaterials on animals. Ultimately, strong collaboration between scientists and veterinary physicians is critical to comprehending underlying principles of cell-biomaterial interactions at nanoscale level and being able to convert findings from bench to bedside. Additionally, research is crucial to the animal production sector, especially in identifying gaps in applications and knowledge.

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