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Bionanomaterials – an emerging field of nanotechnology

A.R. Shelin, S. Meenakshi*
Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Chennai, Tamil Nadu, India
* Corresponding e-mail address: srgmeenakshi@gmail.com
ORCID identifier: https://orcid.org/0000-0002-7944-5840 (S.M.)

ABSTRACT

Purpose: The science that involves nano-sized particles have been shown to have a huge impact on a variety of research fields, such as electronics, medicine, engineering, robotics and technology. The involvement of biological agents in nanoscience helped in the origin of bionanotechnology, which is deeply rooted in therapeutic and medical applications. This review provides an initiative to understand the combination of biological molecules and nanoparticles in delivering a great impression in the world of therapeutics.

Design/methodology/approach: Conjugation of nanoparticles with the biological molecules makes them more friendly for the living system by increasing biocompatibility and reducing toxicity.

Findings: Growing research in this area has revealed the identification and characterization of numerous biological agents of nano-sized that can serve as better carrier systems. They are exploited in the development of advanced nanoparticle-based targeted drug delivery systems. In general, either the combined form or the one in the derived form of nanoparticles from different biological organisms provides a valuable understanding of their specifications and importance in different therapeutic aspects.

Research limitations/implications: The combined form of biological molecules and nanoparticles is not yet well understood, and this might provide a baseline for prospects.

Originality/value: This review provides an understanding of biologically synthesized and conjugated nanoparticles and their potential as therapeutic norms and highlights their applications, especially in the clinical field.

Keywords: Nanomaterials, Bionanomaterials, Biosensor, Antimicrobial agent, Organic bionanomaterials

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BIOMEDICAL AND DENTAL MATERIALS AND ENGINEERING

1. Introduction

Nanotechnology is a unique technology that potentiates wider applications with the use of nanoparticles in the fields of science, physics, electronics, medicine, engineering, robotics and technology. It ensures their unique phenomena and their capabilities in diagnostics and clinical application. The interesting pros of nanotechnology are that they can acquire novelty in nanosized particles compared to the ones without nanoscaled size [1]. The history of nanotechnology dates back to 1925 when Richard Zsigmondy, a Nobel prize laureate, first suggested the term "nanometre" and was the first to initiate the understanding of gold colloidal particles using the microscope. In 1959, physicist and noble prize laureate Richard Feynman proposed a lecture titled "There's plenty of room at the bottom". This resulted in the evolutionary and imaginative concept of nanoparticles, which also led to understanding the Feymann hypothesis and further identification. After Quindecennial (15 years) in 1974, Norio Taniguchi, a Japanese scientist, coined the word "Nanotechnology," characterizing it as "the separation, consolidation, and deformation of materials by one atom or one molecule [2]. "Due to their good biocompatibility and lower toxicity, nanotechnology has been reinstated into the medical field. Although the description of nanoparticles is not new, their evolution has been quickened by the industrial crisis, which has involved them as unique particles in medicinal and therapeutic applications [3].

2. Nanoparticles

The word Nano defines the term "dwarf" or "small" particles with a diminutive size and stable spatial dimension between (1-100 nm) at a nanoscale level [3,4]. Nanoparticles are chemical materials derived synthetically by two methods: top-down and bottom-up synthesis from metals like gold, silver, selenium, iron oxide, etc. Milling, laser ablation, and spark ablation are examples of top-down processes in which bulk material is physically broken down to generate smaller molecules. In contrast, bottom-up synthesis employs a number of solvents and other chemicals and is generally referred to as the "wet" method. In order to stabilize their size, immediately after the synthesis, the particles are capped in solution. Therefore, the particles must be relocated or transferred from their solutions immediately after formation. These nanomaterials have the same composition but different physicochemical properties of known bulk materials [4].

NPs are derived in various structural forms, such as nanospheres, nanocapsules, nanotubes, etc., to employ their specific role in medical or molecular applications. The classification of various types of nanoparticles is described in Figure 1. The biodistribution of nanoparticles to the target cells depends on their size and shape. For example, cationic rod-shaped nanoparticles have been easier to approach the uptake by endosomes since they are distinguished as rod-shaped bacteria in the views of immune cells [4]. Like size and shape, the surface charge of nanoparticles is also essential for creating a unique and clear targeted delivery. NPs that are positively charged have gained importance as they exhibit elevated immune responses. Polymer-based (dendrimers, micelles, etc.) and lipid-based nanoparticles (liposomes, exosomes) are being mainly investigated for their application in clinical research [5]. Types and applications of nanoparticles are described in Table 1.

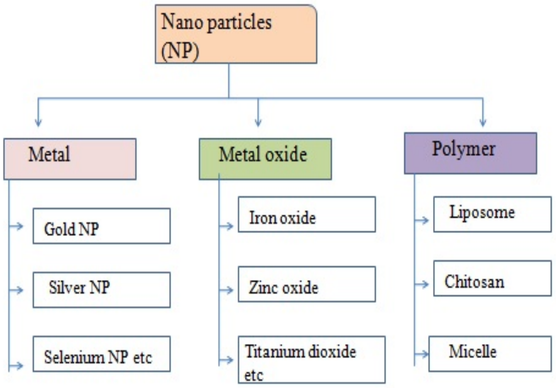

Fig. 1. Classification of nanoparticles [6]

2.1. Application

Antimicrobial agents

Antimicrobials have significantly reduced morbidity and mortality due to bacterial infectious diseases. The infections caused by multi-drug resistant (MDR) microbes are associated with an increased mortality rate compared to the ones led by susceptible bacteria, and they carry a severe healthcare burden [7]. First-line antibiotics deplete their activity against infections, and the pathogens have made themselves superior by increasing their resistant phenotype. Novel findings of new therapeutic agents have been inevitable as the evolution of resistant pathogens doubles the speed compared to the discovery of therapeutic agents and become a future hazard. Conjugation of small molecules such as antibiotics along with the nanoparticle has been a positive approach to overcome such difficulties [8]. Antimicrobial peptide (AMP), Phage therapy, and Nanomaterials have become significant strategies in controlling the evolution of drug-resistant pathogens.

Table 1.
Types of nanomaterials and their applications

Particle	Classification	Comment	Application	References
Liposomes	Polymer-based nanoparticles	• Biodegradable, versatile, and clinically approved, • Carrier.	Drug delivery	[9,10]
Dendrimers		• Biodegradable, • Substitute for injections and are slow in drug release.		[5]
Nanotubes		• Biodegradable, used in multifunctional application.		[4,5]
Quantum dots (Fluorescence imaging)		• Combined with antibodies and exhibit a broad spectrum, • Biosensing and bioimaging.	Tracking and imaging	[11,12]
Iron oxide particles (MRI)	Metal-based nanoparticle	• Able to kill tissue at targeted sites and are used in multifunctional application, • Used as biosensors.		[12,13]

The use of AMP is effective, and it functions through membrane disruption. However, identifying and characterising new AMPs are time-consuming, extravagant, challenging, and frequently using such synthetic peptides might once again result in the evolution of multidrug-resistant pathogens [14].

Meanwhile, the use of Phage therapy functions through a virus that lyses the infectious bacterial cells. This method is less effective as they exhibit target specificity and can bind only to a certain host range; thus their use is limited. Despite the potent ability, as the regulatory functions are limited, they cannot be used for broad-spectrum treatment [15].

On the other hand, nanoparticles have been used as carrier molecules to deliver drugs and, on the whole, as therapeutic agents. Increased research on nanoparticles explained their safety and effectiveness against infections. Metallic NPs (MNPs) have been widely studied in features of antimicrobial properties. Commonly used MNPs, like silver (Ag), gold (Au), etc., have been widely studied using antibiotics in bacterial infections [16]. Meanwhile, Selenium NP (SeNPs) exhibit certain applications in properties of antioxidant and anti-cancer effects and have been shown to have enhanced bioavailability. Huang *et al.* demonstrated the synthesis of SeNPs, by two approaches traditional and green synthesis methods. Traditional SeNPs have been produced by physical and chemical platforms or by combining them. He examined their antibacterial activity, and the result showed a maximal inhibitory effect towards Methicillin–susceptible *Staphylococcus aureus* (MSSA) and Methicillin-resistant *Staphylococcus aureus* [17]. Another work on silver NP has been made to bind with a combination along with the antibiotic tetracycline; this resulted in anti-bacterial activity against Salmonella species and concluded that a complex of silver-tetracycline NP enabled elevated drug activity; this combination enhanced the activity resulting in growth inhibition.

2.2. Perspectives in biomedical imaging

Medical imaging techniques play a stable role in diagnosis, early detection in response to infection, and proper assessment of clinical issues. Imaging modalities like X-ray, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), and positron emission tomography (PET) instruments help in the identification of lesions in tumour conditions. Contrast agents are used to figure out healthy tissue from other abnormalities. For classical imaging, small molecules of contrast agents have majorly used that exhibit accurate anatomical and physiological information. However, in these contrast agents, the resolution is limited in tumour detection build-up by imaging hardware; the enhanced contrast CT has been able to detect as small as 3mm in hypervascular hepatoma [13]. Presently NPs have been used to elevate biomedical imaging detection due to their unique targeting properties. These NPs uniformly distribute in tumour penetration during imaging and equal distribution in biological fluids and targeting. Due to their diminutive size, NPs provide unique passive and active targeting properties. NPs surfaces have been labelled with a specific ligand that targets specific receptors, which increases the image contrast in localized lesions. Gold NP has been coated onto the specific prostate membrane, resulting in high-resolution CT imaging of prostate cancer cells [18].

In contrast to traditional agents, nano agents resulted in high surface resolution and improved toxicity profile. Other pros of nanoparticles are the targeted imaging of angiogenesis and the functional display of biological processes. The size of nanoparticles optimizes the loading capability to meet clinical needs [11].

Another type of imaging that is rapidly emerging is molecular imaging which includes optical imaging and single-photon emission CT (SPECT). Traditional imaging techniques have specific intrinsic limitations, such as low spatial resolution in PET, and in fluorescent imaging, the penetrated depth is limited. The use of nanoparticles is encouraging in overcoming the limitations associated with classical imaging methods. Sustained release and target specificity make NPs a promising agent for clinical research, particularly imaging systems. In MRI, Iron oxide nanoparticles have been utilized as contrast agents, and Quantum dots are being used because of their quantum yield in the intensity of fluorescent probes. For NP to be such a powerful suitable ligand target should be conjugated on the surface of the molecule. Such targeting molecules like antibodies, and aptamers have been conjugated to exhibit higher affinity. Futuristic applications of nanomaterials research are based on multifunctional NPs, which may lead to multimodal imaging to visualize diseases and provide molecular information [12].

3. Bionanomaterials

Bionanotechnology is a sub-type of nanotechnology in which the biological environment serves as the source of the platform, and this combination perhaps results in a better final outcome [19]. It is a multi-disciplinary approach involving the concepts of biology, materials science, chemistry, immunology, physics, mathematics, and engineering. Accumulating evidence substantiates that bionanotechnology is emerging as a promising field of science with wider applications [20]. The word 'bio' defines term as naturally degradable materials derived from living microorganisms like microbes, crops, and even plants. Bionanomaterials are molecular materials made nearly wholly or partially from biological molecules, such as antibodies, proteins/enzymes, DNA, RNA, lipids, oligosaccharides, viruses, and secondary metabolites, resulting in molecular structures with nanoscale dimensions [21]. They have unique structural, chemical, physical, optical, functional, mechanical, and electrical features that distinguish them from the bulk matter due to their exceptionally small size. These distinguishing characteristics aid them in a variety of medicinal applications, including tissue engineering, medication, cancer treatment, neurological illnesses, inflammation and gene delivery. The application of bionanomaterials from biological sources is illustrated in Figure 2.

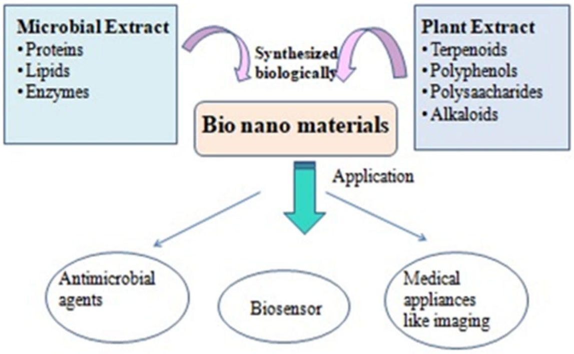

Fig. 2. Picture showing the sources of bionanomaterial and their applications [21]

Synthesis and characterization of bio-NPs

Bionanomaterials are generated via bio-reduction processes, which include the use of reducing sugar, proteins, enzymes, and phenolic chemicals. pH, concentrations, and the nature of source material have been reported to influence the synthesis process. After synthesis, they are analysed through Fourier transform infrared spectroscopy (FTIR), coupled plasma spectrometry (ICP), transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy, etc [22]. Bio-NPs are classified into categories:1) Organic 2) Biological, where organic particles are further characterized into.

4. Organic bio-NPs

4.1. Polymer-based

Bionanomaterials made of polymers have also emerged as a potential carrier for the controlled distribution of pharmaceuticals. It is widely applied in drug delivery mechanisms, as mentioned in Table 1. Biological nanoparticles have been mainly defined by the scope of overcoming the obstacles in drug delivery systems. Such organic polymers include chitosan, liposomes, dendrimers, micelle, etc.

Chitosan

Chitosan is a polysaccharide comprised of β-linked D-glucosamine and N-acetyl-D-glucosamine and is obtained from the hard outer skeleton of shellfish, including crab, lobster, and shrimp. It is also found in fungal cell walls, exoskeletons of insects, and the scales of fish [23]. Tiyabooncjai *et al.* described that the primary amine present at the C-2 position of the glucosamine residues in chitosan is indeed a unique property. The presence of high amines enhances chitosan's functional qualities.

Chitosan is a complex form of various elements like Carbon (44.11%), Hydrogen (6.84%), and Nitrogen (7.97%). The average molecular weight of chitosan is ~5.3X10 Daltons [23,24]. Chitosan's chemical functional groups can be altered to fulfil a specific aim, broadening its range in potential application. Chitosan NPsare widely developed to ensure distinct applications in size, stability, drug loading capacity, etc. The basic method to produce chitosan NPs is emulsification, precipitation, ionic or covalent cross-linking, or combinations. Alternatively, reverse micellar is also an effective method; this approach was utilized to encapsulate the doxorubicin-dextran conjugate with chitosan NPs [25].

Chitosan and other compounds

Chitosan-based nanoparticles can be utilized to deliver active substances like pharmaceuticals or natural products via diverse approaches, including oral and parenteral administration [26]. Chitosan has recently discovered its possibilities in bone formation therapies, such as developing chitosan nanomaterials-based scaffolds for tissue regeneration. It improved the growth of bone regeneration with the help of collagen. Other organic bionanomaterials like biopolymers such as PLGA (Poly lactic-co-glycolic acid) were generally used for their biocompatible nature in drug delivery. Some anti-cancer drugs like Cisplatin, paclitaxel, doxorubicin, etc., are reportedly integrated with PLGA-NPs [6].

Additionally, when PLGA was coupled with chitosan, nanostructures were formed that might be employed in wound repair properties in dentistry [27]. Del-Caprio and his colleagues used chitosan NPs instead of EDTA in root canal therapy. They demonstrated that chitosan NPs are a good nanomaterial for dental applications because of their antibacterial and chelating properties. Chitosan is also shown to be an antioxidant agent as it can donate hydrogen and result in the absorption of free radicals and metal ions chelation [28]. Besides, therapeutic application chitosan NPs are typically used in agriculture, holding a wider application in herbicide delivery, a fungicide treatment, and also delivering regulator that regulates the growth of the plant [29].

Liposomes

Liposomes are small spherical artificial vesicles generated from cholesterol and non-toxic phospholipids. Liposomes are promising drug delivery devices because of their size, hydrophobic and hydrophilic properties, along bio-compatibility. Encapsulation in a liposome enhances the stability of various nanoparticles. For systemic and non-systemic applications, liposomes are shown to be non-toxic, flexible, biocompatible, biodegradable, and non-immunogenic. The size of liposomes ranges from extremely small (0.025 µm) to large (2.5 µm) vesicles [9]. It is reported that when phospholipids are hydrated in aqueous solutions, they automatically form closed structures. Depending on the nature of the medications, such vesicles with one or more phospholipid bilayer membranes can carry aqueous or lipid drugs. The hydrophobic and hydrophilic properties of lipids help accumulate their hydrophobic sections into spherical bilayers. In order to ignore these disadvantages, liposome-mediated drug delivery is enhanced [10]. Recently, the Food and Drug Administration approved liposomal formulations of trans-retinoic acid and daunorubicin as first-line therapy for AIDS-related advanced Kaposi's sarcoma. [30]. Illustration of liposome-based cancer drug delivery system explained in Figure 3.

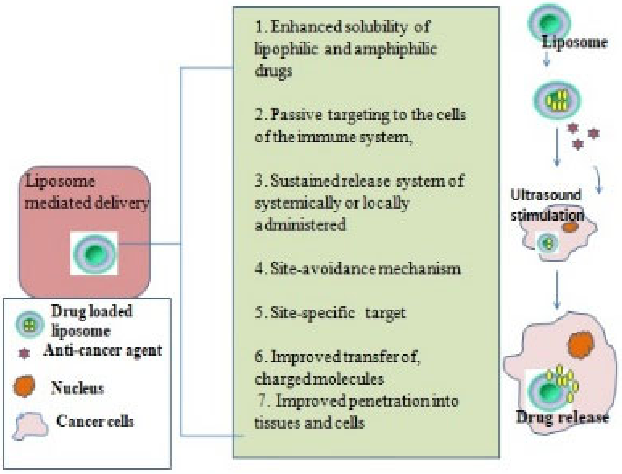

Fig. 3. Advantages associated with liposome-based drug delivery systems [10]

4.2. Biological-based bio-NPs

Biological bio-nano particles are categorized into two subtypes, namely green synthesized bio-NPs and naturally synthesized bio-NPs. Microorganisms like bacteria, archaea, and fungi are the most highly preferred systems because of their advantages, such as easy cultivation, flexibility in growth modulation depending upon the growth conditions, and ability to tolerate metallic environments. Fariq *et al*; demonstrated that the intracellular synthesis of NPs involves trapping the positively charged metals to the negatively charged cell wall, followed by the enzymatic process in which the NPs are clustered that diffuses through the cell wall. In contrast to intracellular, extracellular synthesis involves the reduction of metal ions into NPs by the cell-free supernatant [31,32]. Biological nanoparticles have been mainly defined by the scope of overcoming the obstacles in drug delivery systems. It has been developed in order to limit the use of liposomal approaches as the stability of these vehicles decreases as they enter the bloodstream [33]. Microbes like Lactobacillus, Corynebacterium, Aspergillus, etc., have been used to synthesize microbial-mediated bio-NPs [34]. The microbes often transform sulphate ions into sulfides via the reduction reaction to maintain environmental status. The large-scale sustainable manufacture of bacteria-based nanoparticles with low usage of harmful chemicals is a key advantage; nevertheless, there are certain drawbacks, such as tedious bacterial cultivation techniques and limited management over their size, shape, and dispersion.

5. Application

5.1. Anti-cancer activity

Cancer remains one of the deadly diseases affecting the world population. Cancer history shows nearly 57% of new cases in developing countries. It is assumed that it may increase by 44% by 2030. Several studies have been reported the biocompatibility and nontoxicity of biosynthesized metal NPs in normal cell lines but with an elevated toxic range, specifically in tumour cell lines. Metal bio nanoparticles have been reported to exert anti-cancer action in in-vitro against various cancer cell types. Du *et al.* demonstrated that plant-mediated synthesis of AgNPs reported anti-cancer activity against Hela and A549 in 1–5 µg/mL and showed no caustic impact in 10 µg/mL in normal HaCaT [35]. Suganya *et al.* reported the anti-cancer effect of biosynthesized SNPs in breast cancer cell lines [36]. Furthermore, Heydari *et al.* reported anti-tumour effects of bio-fabricated AgNPs against MCF-7 cell lines; however, it hasn't shown any significant cytotoxic effect in normal human mononuclear cells [37]. Illustration on the anti-cancer effect of bio-NPs in carcinoma cell lines explained in Figure 4.

5.2. Bionanoparticles as biosensors

A biosensor is a useful analytical device used to detect analytes by measuring their signals and displaying their electrochemical analysis; for instance, peptide nucleic acids (PNAs) replace DNA probes and show potential ability in the development of biosensors. It has various applications in molecular genetics, cytogenetics, and the diagnosis of various infectious and non-infectious diseases [38]. Bionanomaterials have become key components in bioanalytical tools because they clearly improve sensitivity. Among all the metal nanoparticles, gold nanoparticles (AuNPs) are the most often utilized noble nanoparticles for biosensor applications due to their biocompatibility, signal detection, or specific response to analytes that are especially in low concentration [39]. Horseradish peroxidase (HRP) is conjugated on these gold nanoparticles via a biotin-streptavidin linkage. Since it can form coloured, fluorescent or redox-active molecules, it is widely used in biosensing applications [40]. Besides AuNPs, iron oxide nanoparticles (magnetic nanoparticles) are also used to concentrate the possibilities before the detection event. Schematic representation in the application of nano biosensors is explained in Figure 5.

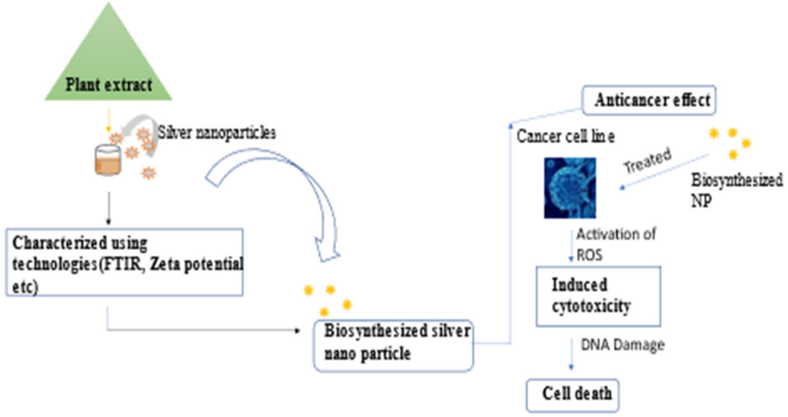

Fig. 4. Mechanism of biosynthesized NP on the effect of a cancer cell line [36]

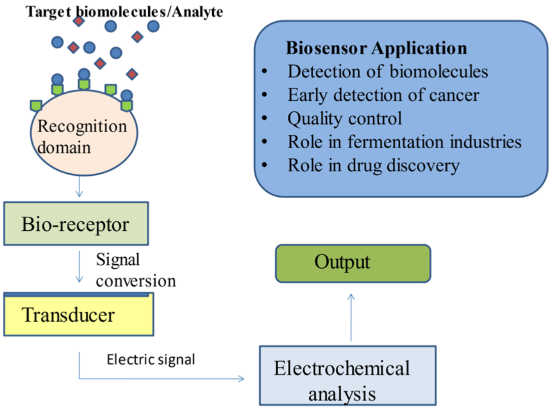

Fig. 5. Mechanism of action of nanobiosensor and their applications [39]

6. Conclusions

The rise of nanotechnology has gained enormous attention in the field of pharmaceutical and medical aspects. This emergence has brought even more popularity for the complex form of biologically synthesized nanoparticles and metallic nanoparticles in molecular imaging and medical diagnosis. The physical and chemical processes synthesize NPs, but alternative exploration has been done to administer and limit the problematic issues when it comes to the fabrication of NPs. The drawback of physical and chemical fabrication is the requirement of high energy and toxic substrates and less productivity [41]. Therefore, biological factories have been brought into sight to overcome these issues. Their intrinsic biocompatibility and low toxicity have elicited great interest among scientists to further investigate the bionanomaterials based on future diagnostic applications.

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Additional information

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