J. Res. Technol. Eng. 3 (3), 2022, 32-54

Journal Of Research Technology & Engineering
www.jrte.org

Nanotechnology Applications in Biomaterials; A review

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Received:02 July 2022; Revised: 08 July 2022; Accepted: 24 July 2022; Available online: 25 July 2022

Abstract: Development of nanobiomaterials has become essential in the field of biomaterials engineering, specifically in bone replacement, tissue regeneration, drug delivery, and cardiovascular treatment. In general, ceramics, metals, polymers, and their advanced composites and hybrids have been used as the matrix owing to their excellent biocompatibility and mechanical durability. However, there have been continued efforts to improve the properties of such matrix materials to minimize toxicity while introducing various smart characteristics resulting in a new generation of novel biomaterials with unexpected properties. Nanotechnology has provided a template for developing a plethora of new biomaterials whose ultimate properties are derived from the synergistic effects arising from the nanomaterial and the matrix. Nanofibers, nanoparticles, nanotubes, and 2-D structural materials have received the highest priority in such advanced applications. This review focuses on a survey of the nanomaterials used in bio-materials/bio-composites, their historical evolution, how their structural characteristics enhance the properties of biomaterials, and evaluation of their potential in revolutionizing the field of biomaterials.

Index Terms: biomaterials, nano biomaterials, nanotubes, nanoparticles

1. INTRODUCTION

Nanotechnology is an interdisciplinary subject that spans its implications across different fields such as biology, physics, chemistry, and engineering. The designing, synthesizing, reforming, characterizing, and manufacturing of the materials, devices and systems on the scale of 1-100 nm is considered as nanotechnology [1]. Owing to their very high surface to volume ratio, the physical and chemical properties such as melting point, electrical conductivity, thermal conductivity, magnetism, and catalytic activity of nanomaterials are different compared to their bulk material. The size effect describes the physical properties of the nanomaterials, and the chemical properties of the nanomaterials cause the surface effect. For example, when the size of a material is decreased, the surface area is increased, leading to enhanced reactivity [2]. Therefore, it is imperative that coating, doping, or compositing nanomaterials [3] with the biomaterials can revolutionize the properties of engineered biomaterials to enhance their properties such as biocompatibility and non-toxicity and durability [4].

Biomaterials are defined as "*engineered to interact with biological systems for medical purposes*". These biomaterials can be natural or synthetic and are used to support, enhance, or replace damaged tissue or a biological function [4]. In ancient times, commonly used biomaterials were animal tissues. However, synthetic and advanced biomaterials are synthesized in modern applications with interdisciplinary contributions from diverse fields such as biology, physics, chemistry, computational chemistry, and materials engineering [5].

Conventionally, ceramics [6], metals [7], polymers [8], glass [9], and other composite materials [10] were commonly used as the main components for producing bio-engineered materials. Even today, these materials are widely used for medical implants [11], healing and regeneration of human tissues [12], cancer imaging and therapy [13], biosensors [14], and drug delivery systems [15].

Biocompatibility, mechanical continuity with the surrounding bone tissue, the non-toxicity of biomaterials, and their by-products during degradation are the most critical factors that have to be considered when fabricating biomaterials and bio-composites [16]. Among the many focused methods of developing novel and advanced biomaterials, nanotechnology has undoubtedly provided a smarter template.

Existing reviews are based on some specific areas such as nanotechnology for orthopedic medical applications [17], nanofilm biomaterials[18], nanotechnology for treatment and repair of soft tissues in wound healing [19], nanotechnology applications in tissue engineering [20], [21], and Polymeric biomaterials for cancer nanotechnology [22]. This review focuses on sources of biomaterials and nanomaterials used in biomaterials/biocomposites.

2. SOURCES OF BIOMATERIALS

Conventionally, biomaterials have been produced by various natural sources such as animals, minerals, and metals.

2.1. Biomaterials from animals

Spider silk, egg shells, fish bones, and corals are some primary animal resources used to produce biomaterials because of their favorable bio-compatible and mechanical properties. Tissue engineering, neurology, and dentistry are the key applications of biomaterials [16].

Spider silk is used as a common source of biomaterial because of its high strength, elasticity, and biocompatibility. Spider silk contains various amino acids (glycine and polyalanine), which form into secondary structures by which the mechanical properties of the fibers can be enhanced. Drug delivery systems, implant coatings, and tissue engineering processes are some common applications of spider silk-based biomaterials [17].

Eggshells, a common waste in the food industry, is another commonly used material to produce biomaterials. The major component of eggshells is calcite ($CaCO_3$). The eggshells are mainly used as a source of calcium for the synthesis of hydroxyapatite and which is applied in tissue engineering [16], [24].

Fish bones are another material that is used for biomedical applications. Importantly, it contains porous structures of calcium carbonate ($CaCO_3$) and calcium phosphate $Ca_3(PO_4)_2$, which are the elements that are naturally present in the bone. Due to this similarity in chemical composition, crystallinity, and pore size of fish bone with that of human beings, they are often used to recover bone damages [19].

The coral materials such as coral hydroxyapatite, coral granules, natural coral fragments, and coral calcium are taken to produce biomaterials. The high stability and the ease of decalcification are the main reasons for using corals to form biomaterials. Orthopedic, craniofacial, and dental applications are the major applications of coral-based biomaterials [20].

2.2. Ceramic biomaterials

Ceramic is a material that is brittle, hard, and with corrosion-resistant and heat-resistant properties. Because of the above properties, ceramics include a wide variety of applications, including the field of biomaterials too. Basically, ceramic biomaterials are divided into two groups, namely bioinert and bioactive [27].

Bioinert ceramics are the ones that do not interact with the body's environment. Alumina (Al_2O_3) and zirconia ceramics (ZrO_2) are commonly used as bioinert ceramics [27]. Due to their excellent biocompatibility and higher compressing and bending strength than stainless steel or other alloys. In addition, they show wear-resistant properties when their surface is polished [28]. Most frequently, these bio-inert materials are applied in hip replacements and other clinical surgeries [29].

In contrast, bioactive ceramics directly bind to human tissues without having fibrillar connective tissues [30]. Calcium phosphate ceramics, bioactive glasses and glass-ceramics are some bioactive ceramic types widely used in the biomaterials industry. Calcium phosphates ceramics are synthesized by mixing calcium and phosphate solution under acid or alkaline conditions. These types of ceramics are commonly applied in bone replacement applications because of their chemical compatibility with the inorganic component of human bone and teeth [27].

Bio glass is a series of specially designed glasses consisting of a Na_2O-CaO-SiO_2 glass with the addition of P_2O_5, B_2O_3, and CaF_2[31]. A hydroxy-carbonate apatite layer is formed on the surface of bioactive glasses, and this layer is chemically and structurally equivalent to the mineral phase of bone so that it provides direct bonding by bridging the host tissue with implants [27].

2.3. Metallic biomaterials

Metallic biomaterials are designed to provide internal support to biological tissues, and they are usually used in joint replacements[32], dental implants[33], and orthopedic fixations[34]. Permanent and bio-degradable metallic implants are the two main categories of metallic biomaterials [35].

2.3.1. Permanent metallic implants.

Permanent metallic implants are the synthetic connections implanted in the human body to remain permanent in the body. Typically, the permanent metallic implants contain metals such as stainless steel, titanium, and cobalt.

Stainless steel is a corrosion-resistive material used to get long-term medical outcomes with fewer post-surgery complications. Mixtures of high chromium content with nickel and molybdenum are used to prepare stainless steel with high corrosion resistance [35]. The typical applications of stainless steel-based permanent implants include precision stainless steel tubing, bone fixation, artificial heart valves, and curettes [36].

Titanium (Ti) is a very light material with a density of 4.5 g/cm^3. Pure Ti is an allotropic metal that has a hexagonal alpha phase below 882 ºC. It transforms to a cubic beta phase over that temperature [37]. This material has good biocompatibility due to the formation of an oxide film (TiO_2) over its surface. The oxide layer provides corrosion resistance by acting as a stable layer surrounding this material, which grows spontaneously in contact with air and prevents the diffusion of oxygen from the environment into the biomaterial [37]. The applications of titanium as a permanent metallic implant include dental implants [38], orthodontic replacements [39], joint replacements such as in hip and knee [40], bone fixation materials [41], artificial heart valves [42], and surgical instruments [43].

Having a higher wear resistance compared to Ti alloys, Cobalt (Co) is another metal used in permanent implants, such as in hip joints [41]. The Co-Cr alloy is also used in dental, orthopedic, and cardiovascular implants and devices [44] due to its corrosion and wear resistance.

2.3.2. Biodegradable metallic implant

In contrast, biodegradable metallic implants will be temporary scaffolds serving their particular function as a biomaterial within the human body and will be degraded upon completion of the target benefit.

Magnesium (Mg) and its alloys differ from other biomaterials by having compatible mechanical and physical properties with human bone. Their densities and elastic modulus are relatively close, removing elastic mismatches between implants and the bone [45]. Usually, metallic implants remain after the healing process, and a second operation has to be done to remove those metallic implants, but the biodegradation of magnesium eliminates the need for a second operation to remove the implant after the healing process is completed, thereby reducing the cost and pain of patients [46].

Zinc (Zn) plays a significant role in the structure and function of proteins, being essential to catalytic functions in more than 300 enzymes, inducing folding and stabilizing of protein subdomains[35]. The pure Zn is not that mechanically strong enough, but by alloying Zn with other metals, the mechanical properties of Zn can be increased. These Zn alloys are commonly applied in orthopedic devices and cardiovascular stents (alloying with Mg and Sr) [47].

3. NANOBIOMATERIALS

Nanobiomaterials (NBMs) can be generally defined as particles and devices in the nano-size regime (1-100 nm) which are fabricated to use in biological and/or biomedical applications. The main types of nanobiomaterials, based on the material composition, include metallic NBMs, semiconductor-based NBMs, silica-based NBMs, polymeric NBMs, and carbon-based NBMs [48]. On the other hand, based on the structural properties, they could be classified as tube structures and other complex NBMs.

3.1. Nanotubes for biomaterials.

Nanotubes are cylindrical or tube shaped materials, which are categorized under 1D nanomaterials, of which the diameters are in the nanoscale (1-100 nm). Nanotubes can be made from several materials such as carbon, titanium dioxide, silica, boron, and organic nanotubes. Fig.1 summarizes the nanotubes from different origins and their applications in the field of biomaterials engineering.

Fig.1**.** Nanotubes in Biomaterials

3.1.1. Carbon Nanotubes (CNTs) in biomaterials.

Carbon nanotubes are tubular structures with a diameter between 1 nm to 100 nm and can reach up to several micrometers. Carbon nanotubes consist of carbon shells that are closely related to honeycomb arrangement [49]. Basically, it divides into two categories, such as single-walled (SWCNT) (with a diameter of less than 1 nanometer) [50] and multi-walled (MWCNT) (consisting of several concentrically interlinked nanotubes) [50].

Due to the mechanical and electronic properties of both SWCNT and MWCNT, they act as actuators that can be used to develop artificial muscles [51], [52]. Further, CNTs are also used to develop artificial neurons because of their excellent electrical properties [53]. The growth of neurons on CNTs shows in Fig. 2 (a). Moreover, CNTs, and CNTs based nanocomposites are used to increase the efficiency of nano-robots for drug delivery and cancer treatments because the miniaturized size of CNTs allows the penetration of carriers drugs into the membrane of the sicken cells [52], [54] the drug-loaded MWCNTs are shown in Fig. 2 (b).

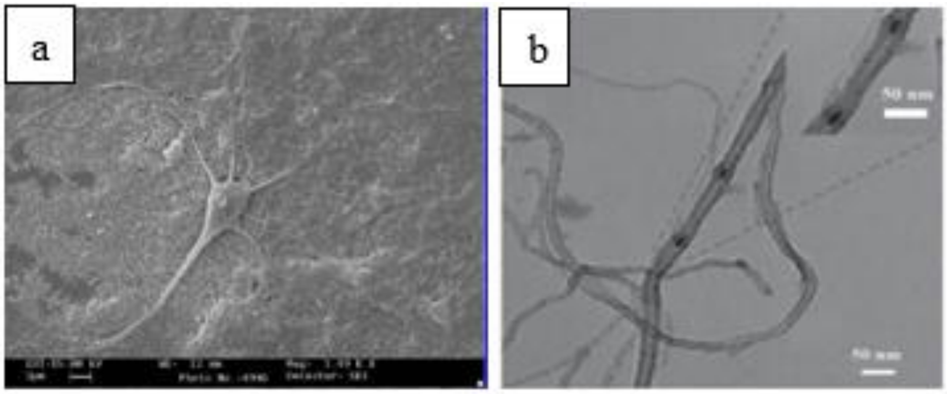

Fig. 2. (a) SEM image of neuron growth on SWCNTs [55]. (b) TEM image of drug-loaded MWCNTs [56].

3.1.2. Titanium Oxide (TiO_2) nanotubes in biomaterials.
TiO_2 nanotubes have a unique 3D nanostructure and are commonly used in orthopedic implantations [57] and bone regeneration applications [58]. TiO_2 nanotubes are conventionally produced by electrochemical anodization, and their nanometer thickness increases the surface area and porosity of the material. Those properties help to accelerate cell adhesion and bone growth capabilities[59].

The high surface area and the bioactivity of TiO_2 nanotubes, their coatings rectify the current problems of ceramic coatings applied for orthopedic implants [60], [61]. Titanium dioxide nanotubes can be filled with enzymes and some other chemicals. In addition, titanium dioxide nanotubes can be filled with enzymes and some other chemicals and, therefore can be applied in drug delivery and drug release systems [62].

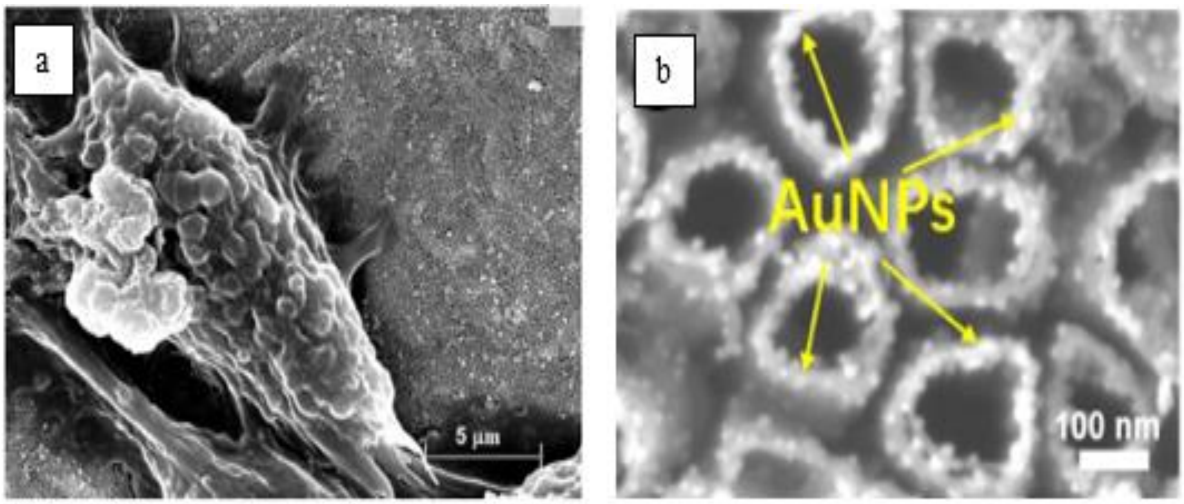

Fig. 3. (a) SEM image of human osteoblast cell attachment on TiO_2 nanoporous surface [63]. (b) SEM image of TiO_2 nanotubes with Au nanoparticles for controllable drug release [64].

3.1.3. Silicon nanotube in biomaterials.
Silicon and silicon-based materials are used in biomedical applications mainly because of their mesoporous structures. *In vivo* silicon is not toxic to the human body and hence is considered a bio-compatible material [65]. Silicon nanotubes are fabricated using a sacrificial ZnO nanowires template [66]. Some clinical studies have used porous silicon as a brachytherapy device for cancer treatments [67].

Further, as a semiconducting material, silicon nanotubes have a unique capability of loading superparamagnetic iron oxide nanocrystals into these nanotubes for long-term magnetic assisted drug delivery systems [68] (shown in Fig. 4).

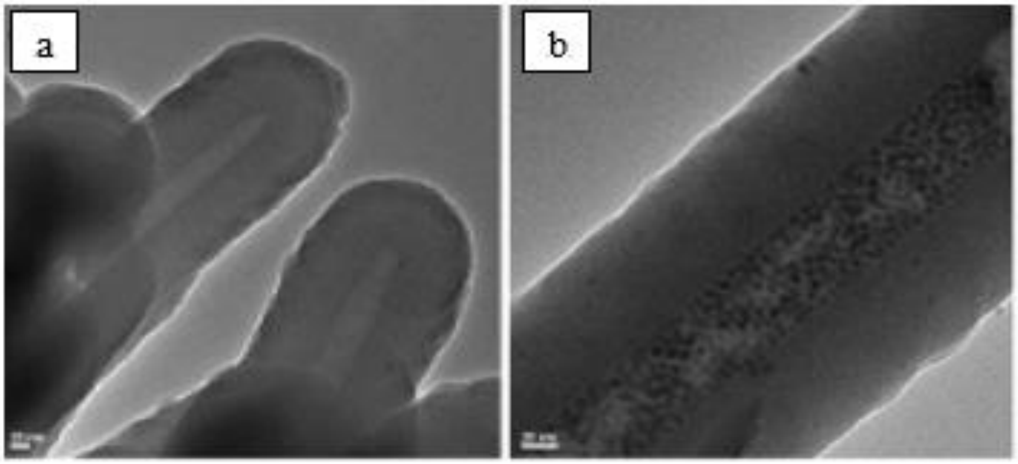

Fig. 4. (a) TEM images of empty silicon nanotubes with 70-nm wall thickness and (b) Silicon nanotube of 70-nm wall thickness filled with 4-nm Fe_3O_4 nanoparticles for magnetic assisted drug delivery [68].

3.2. Nanoparticles in biomaterials.

Nanoparticles are defined as aggregated but unbound particles that are at the dimensions of 1-100 nm[69]. Decreasing microparticle diameter to tens of nanometers increases the specific surface area up to 5 times more and which results in a larger amount of surface area per unit mass [70]. As particle size approaches smaller to a level of only a few nanometers, the edge, and vertex surface atoms which are lower-coordinated and hence are highly reactive, make up a significant fraction of the surface [70]. Fig. 5 summarizes the nanoparticles and their applications in biomaterials-related industries.

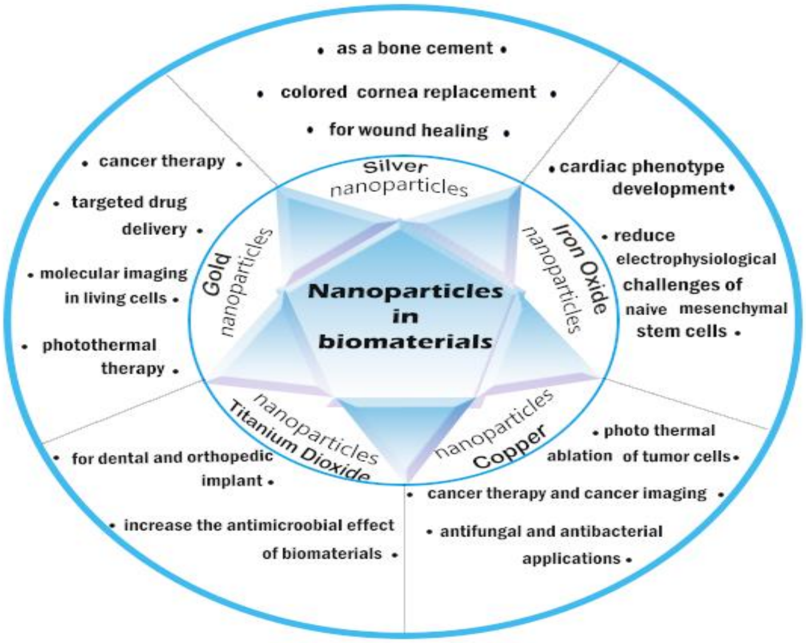

Fig. 5. Nanoparticles in biomaterials

3.2.1. Silver nanoparticle (Ag NP) in biomaterials

Silver nanoparticles can be easily synthesized by using silver nitrate ($AgNO_3$) as a precursor material [71]. Ag NPs are used to improve the surface functionalities of biomaterial and its anti-bacterial properties. Metallic silver is inert, but reacts with moisture in the skin or wound and then gets ionized. That ionized silver is highly reactive, and can destroy bacteria by disrupting the cell wall and nuclear membrane [72]. The large surface area of silver nanoparticles provides better contact with microorganisms, and those are attached to the cell membrane of the microorganisms as well as penetrate inside the cells of microbes. When silver nanoparticles enter the bacterial cell, it forms a low molecular weight. Then the bacteria conglomerates to protect the DNA from the silver ions, and the nanoparticles preferably attack the respiratory chain, cell division of the bacteria, and it leads to death of the bacterial cell [73] (Figure 6). Hence, silver acts as an anti-bacterial agent. The application of Ag NPs in the biomaterials industry spans a wide range, such as in wound dressing, bone replacements, and cornea replacements.

Colored cornea replacement: The bio-engineered cornea or contact lenses with the drawback of getting yellow coloration [74]. Ag NP has been used in fabricating contact lenses with different colors as a solution. The color changes originated from the different sizes and shapes of Ag NPs that give better compatibility for this fabrication and replacement [74].

As a bone cement: Bone cement is biomaterials used in hip and knee replacement surgeries. The infection rate of these replacements is 1% to 4%. Anti-biotic-based bone cement has reduced that rate from 0.8% to 1.4%. However, due to the anti-bacterial properties and high biocompatibility of Ag NPs, they have been suggested to mix with bone cement [75].

For wound healing: Ag-containing wound dressings are currently used for clinical treatments. These wound dressings consist of two layers of polyethylene mesh, forming a sandwich around a layer of polyester gauze with a 900nm silver nanoparticle layer, of which the particle size is 10–15 nm [76]. The antimicrobial property of silver nanoparticles can stop the growth of microorganisms in the injured areas and also helps the cell growth in that area. Ag NPs contained in wound dressings can be specially used to treat thermal injuries [77].

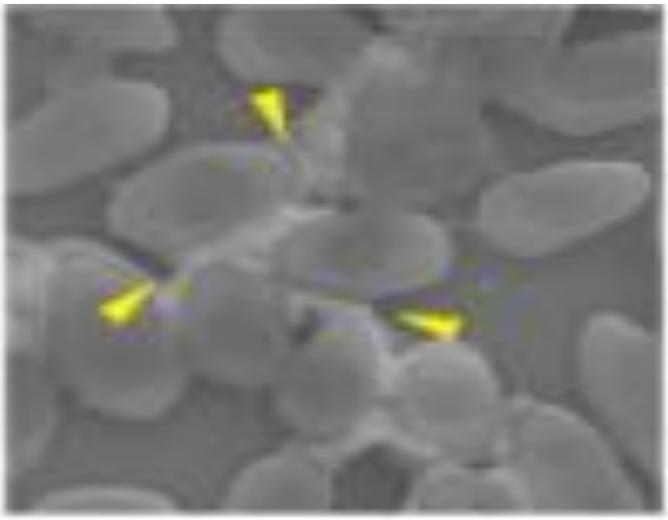

Fig. 6. SEM image of bacterial cells under 6 μg/ml of Ag NP concentration (yellow arrows show the distinct of extracellular polymeric substances formations of bacterial cells) [78].

3.2.2. Iron oxide nanoparticle (IO NP) in biomaterials

Iron oxide nanoparticles are of great interest in applications for biomaterials due to their non-toxic role in biological systems. These nanoparticles have both magnetic behavior and semiconductor properties, leading to multifunctional biomedical applications [79]. Iron oxide nanoparticles are used in biomedical fields such as anti-bacterial, antifungal [80], and anti-cancer [81].

Plumbagin-functionalized magnetite nanoparticles (PFMNPs) are hybrid drug molecules that can be applied to several fields such as theranostics. The extraction of plumbagin from the roots of *Plumbago indica L.* and ferrous ammonium sulfate, ferric ammonium sulfate, ammonium hydroxide (NH_4OH), and calcium hydroxide ($Ca(OH)_2$) have been used to prepare the magnetite nanoparticles. The photo and thermal stability of plumbagin are very low, but magnetite functionalization has improved the photo-thermal stability as well as displaying slow-release behavior of plumbagin and antimicrobial activity [82].

Mesenchymal stem cells (MSCs) are some adult stem cells that produce more than one type of specialized body cells like skeletal tissues, cartilage, bone, and fat [83]. MSCs cultured with magnetic IO NPs show enhanced therapeutic properties, and they can be applied in cardiac phenotype development and to reduce electrophysiological challenges of naive MSCs [84].

Specially IO NPs play an important role in magnetic resonance imaging (MRI) as a contrast agent because the cells should be magnetically tagged for MR imaging[85], [86]. Heat treatment is one of the standard treatments used to destroy cancer cells as cancer cells are destroyed at 43 °C, whereas normal cells can survive at this temperature [85]. The heat required for these therapies can be generated by applying a magnetic field to iron oxide nanoparticles to destroy the cancer cells [85][87].

3.2.3. Gold nanoparticles (Au NPs) in biomaterials.

AuNPs provide a powerful platform for solving health problems due to their unique physical and chemical properties. The visual and electrical properties of AuNPs can be modified by changing their size, shape, surface chemistry, and aggregation state [88].

Due to their shape and size, Au NPs are divided into nanospheres, nanoshells, nanocages, and nanorods. Surface plasmon absorption gives optical properties to Au NPs, which are applied for imaging, labeling, and sensing [89].

Some other applications of Au NPs include their use in targeted drug delivery [90] (Fig. 7), as a contrast agent in medical imaging [91], in antimicrobial treatments [92], in photo-thermal therapy [93], to treat tumors by hyperthermic effects [94], as biosensors [95], as biocatalysts [96], target intracellular free copper ions for selective copper detoxification (to treat the copper overload-related diseases and disorders) [97] as well as biomarkers [98].

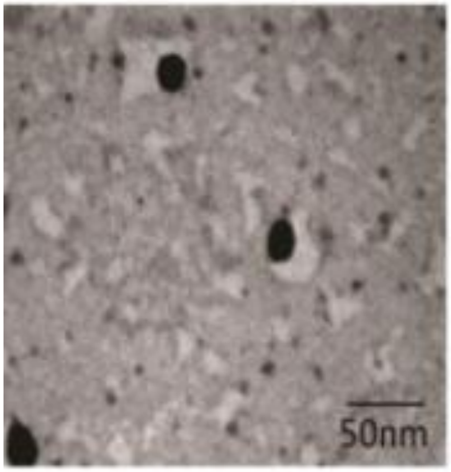

Fig. 7. TEM image of PEG-6000 coated Au NPs for drug delivery for cancer treatments (black color Au NPs, white color PEG-6000) [99].

3.2.4. Copper nanoparticles (Cu NPs)

High melting point, low electrochemical migration, and high electrical conductivity are some properties of Cu NPs [100] that are important for their applications in the biomedical field. Biogenic nanoparticles, including copper, copper sulfides [101], and copper oxides [100], are applied for biomedical applications such as molecular imaging [102], antifungal and anti-bacterial applications [103], photo-thermal ablation of tumor cells [104], cancer therapy and cancer imaging [105].

Due to their suitable band gap, copper oxide (CuO) nanoparticles have a higher electron transfer rate on the electrode surface. Hence, it provides a platform for glucose electro-oxidation and can be used to fabricate efficient non-enzymatic glucose sensors [106]. CuO nanoparticles are also used in cancer treatments. When the CuO nanoparticles enter the cells, they react with cell components and cause damage to DNA, mutations, alternation of gene expression, and mitochondrial localization [107].

3.2.5. Titanium dioxide (TiO_2) nanoparticles

TiO_2 exists in many natural forms, such as limonite, rutile, anatase, and brookite, where the ability to block UV light and antimicrobial activity are the significant properties of titanium dioxide. Stability, biocompatibility, non-toxicity, sensitivity, and selectivity are other properties of TiO_2 that make it a prominent candidate in biomedical applications such as drug delivery [108] and biosensing [109] to avoid blood clotting [110] and also in photodynamic therapy [111].

Suitable band gap, high surface area, and high oxidative power of TiO_2 help to photo-oxidate a wide range of microorganisms like viruses, bacteria, algae, and fungi [112], [113]. On the other hand, the excellent mechanical properties such as low density and high biocompatibility of titanium and its alloys are the key to their applications in dental [114] and orthopedic implants [115], [116].

3.3. Fullerene

Fullerene is an allotrope of carbon that consists of carbon atoms connected by single and double bonds and which has spheres, ellipsoids, tubes, or many other shapes and sizes [117]. One of the main characteristics of fullerene is free radical scavenging ability, which originated from several double bonds in the fullerene cage, which helps protect biological systems against cell damage and tissue abnormalities [118]. Fullerenes are used in cancer treatment; some are based on photodynamic therapy (non-invasive and nonsurgical treatment for some types of tumors and some non-malignant diseases) and photo-thermal therapy. Moreover, fullerene exhibits great potential in drug delivery systems because of its biocompatibility. Fullerene can be used for targeted drug delivery to deliver the drug to the targeted areas while having controlled drug release [119].

4. APPLICATIONS OF NANOBIOMATERIALS

Nanotechnology has revolutionized the field of biomaterials engineering by offering better efficiencies in the targeted applications, improving selectivity on the targeted site of action, spanning the range of applications, and sometimes even achieving better cost efficiencies. Consequently, numerous medical, dental, pharmaceutical and cosmetic industries have been widely using the engineered nanobiomaterials discussed in detail in this section. Fig.8 shows the application areas of nanobiomaterials.

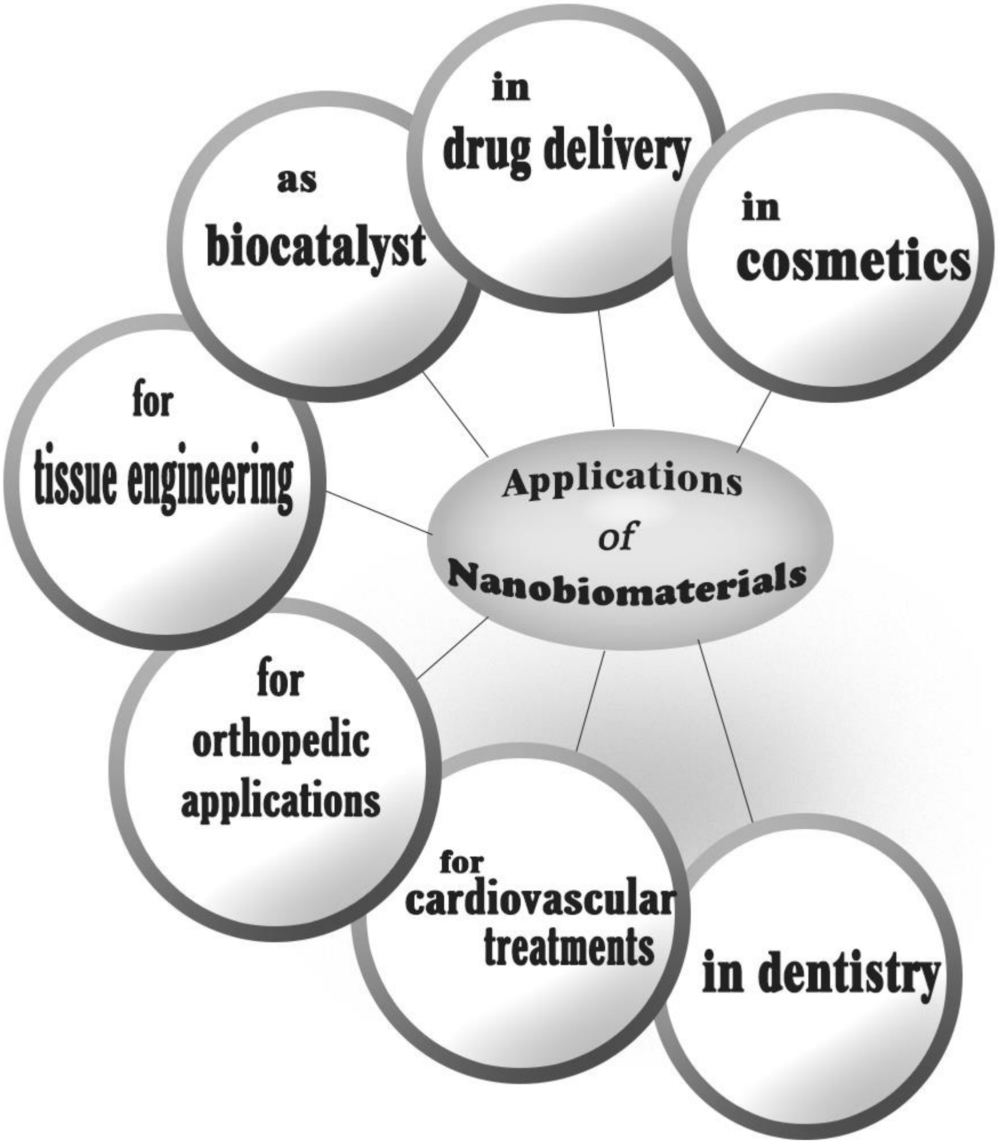

Fig. 8. Applications of nanobiomaterials

4.1. Nanobiomaterials in dentistry.

In order to increase oral health, nanotechnology has been used to develop strategies for preventing tooth decay and increasing anticavity [120]. Tooth decays are caused primarily by acid-producing bacteria. As a solution to this, nano composited layers can be applied on top of the enamel, and this layer blocks the bacteria from entering the enamel. Interestingly, researchers have found that the bacteria on the top of the nano-composited layers can even be removed by the shear forces in the mouth [120].

Acrylic teeth are coated with graphene because of their cost-effectiveness, fracture resistance, and low-density property [121]. Hydroxy apatite NPs are also widely used in dentistry as they have a similar composition to teeth and bone make, hence being highly biocompatible and holding the main composition of mineralized tissues of the human body. These hydroxyl apatite NPs can be firmly bound with enamel and hence can be used to fill even small cavities [122].

Nanoparticles loaded with triclosan have been developed to treat periodontal diseases. These nanoparticles are prepared by using Poly(D,L-lactide-co-glycolide), poly(D,L-lactide), and cellulose phthalate. The antimicrobial ability of triclosan and nanoparticles are proven to reduce inflammations [123].

Titanium and silica nanocomposites are used for dental implantations because titanium has better mechanical properties for load-bearing applications. Silica's bioactivity gives better hardness and growth in the micro and macro pore sizes present on the teeth surface [124].

4.2. Nanobiomaterials for cardiovascular diseases.

The heart is the tireless organ in the human body that circulates blood across the entire human body while pumping blood into itself through the coronary arteries. If the coronary arteries get narrower, it disturbs the efficient transportation of blood into the heart, which is the leading cause of heart diseases [125]. Nanoparticles and nanofibers are used to develop the treatment for cardiovascular diseases by the vascular stents, which are conventionally employed to ensure the efficient circulation of the bloodstreams, have been made from stainless steel and developed by using bioabsorbable lactic-co-glycolic acid (PLGA) or polycaprolactone (PCL) nanoparticles and coated with chitosan. [126], [127].

Nanofibers are also used as a stent surface coating for treating coronary artery diseases (CAD). These surface-coated nanofibers are produced by using electrospinning technique and the mixtures of hexafluoro-2-propanol (HFIP), PLGA, and polylactic acid (PLA) as the nanofiber base as well as incorporated with β-Estradiol [128].

Nanoparticles provide a platform for targeted drug delivery because of theirmulti-functionality, and these drug delivery abilities can be approached to treat cardiovascular diseases. The combination of super magnetic Fe-hydroxyapatite nanoparticles and the dose of a drug can be targeted the heart by facilitating electromagnetic devices. The drug release is managed by a helmholtz coils-based electromagnetic device that generates low frequency magnetic stimulation to release the the drug [129].

The development of synthetic heart valve leaflets can be done by using nanocomposite polymers with a soft polycarbonate segment and polyhedral oligomeric silsesquioxanes nanoparticles. Due to superior biocompatibility, biostability against oxidation, hydrolysis, and enzymatic attack of those nanoparticles have helped to develop synthetic heart valve leaflets [130].

4.3. Nanomaterial for orthopedic applications

Orthopedic devices have been designed to replace bones, joints, or cartilages of the body which are not properly functioning due to damage or deformity. Metals, polymers, and ceramics are the most common materials that are used to produce orthopedic devices. By applying nanomaterials in the above materials, the efficiency of those materials is enhanced [131].

Silver (Ag) doped nanocrystalline hydroxyapatite nanocomposites have demonstrated cell adhesion and cell proliferation properties which caused the synthesis of bone-related proteins and calcium deposition. Hence, this material is successfully used for surface modifications in orthopedic applications [131], [132].

Graphene oxide (GO) is also used for bone regeneration to increase the biocompatibility because of its high oxygen density and the richness of other functional groups such as epoxy, carboxyl, and hydroxyl groups [133].

Titanium dioxide (TiO_2) is used to increase the surface properties such as microhardness, biocompatibility, and corrosion resistance. So, TiO_2 nano coatings are applied in orthopedic bio-implants to develop the anticorrosion and anti-bacterial abilities of the surfaces [118].

SWCNTs are considered to be the ideal materials for artificial bone and also promote bone growth of bone. Further, it is reported that SWCNTs influence the growth of hydroxyapatite in the bone because the negatively charged functional groups of SWCNTs can attract the calcium cations, lead to self-assembly and increase the thickness of hydroxyapatite layers [135].

4.4. Nanomaterials for tissue engineering.

Biomaterials can be engineered to mimic local tissues, such as nanometer-sized extracellular fluid, bone, and heart tissue [136], another vast area of applying nanotechnology in biomaterials. Nanofibers and controlled release nanoparticles are used for tissue engineering because of their physical properties such as size, shape, surface chemistry and charge, porosity, mechanical strength, solubility, and degradation. High biocompatibility, low cytotoxicity, higher permeation and retention effect, ability to deliver poorly soluble drugs, and sustained release of them are other properties of nanomaterials that can be used for tissue engineering[137].

Nanomaterials with electroconductive abilities such as gold nanoparticles (Au NP) and carbon-based nanomaterials are used for cardiovascular treatments, neural tissue engineering, bone tissue engineering, muscle tissue engineering etc. [138]. Further, some studies have shown that gold nanomaterials, such as gold nanowires, can be used to fill cardiac patches. Damaged heart tissues are repaired using biological polymers, but the conductivity of these polymers is low. Hence, composite biological polymers with gold nanowires have been used to increase the electrical signal propagation throughout the cells [139]. Especially gold nanoparticles are applied for tissue engineering because they can be designed to minimize toxicity [140].

The piezoelectric effects of nanomaterials differ from bulk materials because of small-scale effects [141]. Piezoelectric materials generate surface charge when applying pressure on them or occur a deformation when applying an external electric field [142]. So that Piezoelectric nanomaterials have been suggested for some applications like drug delivery [143], bone and cartilage regeneration [141], [144], neural regeneration [145], ligament and tendon regeneration [146], skeletal muscle regeneration [147] and cardiovascular regeneration [148], [149].

4.5. Nanobiocatalysis

Nanobiocatalysis is a technique where enzymes are included in a nanostructured material to act as a biocatalyst. Infusing the enzymes into the nanomaterials is called nanoentrapment [150]. Nanoporous materials, nanoparticles, and nanofibers (nanotubes) can be used to entrap enzymes [151]. For example, lipase entrapped magnetic nanoparticles show good resistance to proteolytic digestion. The advantages of nanobiocatalysis systems include high enzyme loading capacity, improved enzyme activity, better rates of electron transfer, and the possibility of magnetic separation [150].

The enzymes are coated on top of the nanomaterials, such as nanofibers [152] and nanoparticles [153]. These enzyme-carried nanomaterials are applied to develop bioactive materials, biochips, biosensors [150], and drug modifications [154].

4.6. Nanomaterials in drug delivery.

Nano drug delivery systems are sub-systems of advanced drug delivery systems. Liposomes, fullerenes, carbon nanotubes, and inorganic nanoparticles are some examples of nano-drug delivery materials [119].

Several advantages can be identified in nano drug delivery materials, such as improving the solubility of poorly water-soluble drugs, improving the bioavailability, reducing the drug metabolism, and simultaneous delivery of two or more drugs [2].

Liposomes are some nanoscale spheres consisting of lipid layers around the drugs, and liposomes are used to form anti-cancer drugs. Micelles are also a spherical nanoparticles containing a hydrophilic head and hydrophobic tail. These micelles are also used in the sustained release of drugs and for *in vivo* imaging. Nanoscaled capsules are used to transport drugs through biological barriers like blood-brain barriers [155].

Targeted drug delivery systems reduce the side effects of drugs. To deliver the drugs to the targeted cells, the biodegradable nanoparticles can be used as well as these biodegradable nanoparticles can be designed to neutralize the drugs when they are expired. Therefore they will help reduce the side effects of drugs [2].

4.7. Nanobiomaterials in cosmetics.

Makeup, hair care products, moisturizers, and sunscreen products are among the cosmetics that use nanotechnology for their developments. Some nanoparticles like silver, carbon, gold, titanium, silica, and zinc are commonly used in cosmetics as active ingredients. On the other hand, the effective delivery of cosmetic ingredients to the skin is increased by nanocrystals, nanocrystals, nanospheres, nanocapsules, and liposomes [156].

Titanium dioxide and zinc oxide are most commonly used as UV protective sunscreen materials due to their photostability, high UV absorption property, and ability to re-emit the absorbed UV radiation as visible fluorescence or heat [157]. Liposomes are used in cosmetics to increase the concentration of active agents such as vitamin A and vitamin E [158], as well as solid lipid nanoparticles and nanostructured lipid carriers provide a control release profile for cosmetic agents [159]. Fullerene has also become suitable in skin rejuvenation cosmetic formulations [160].

5. FUTURE TRENDS OF NANOTECHNOLOGY IN BIOMATERIALS.

Nanotechnology has invaded the field of biomaterials during the last few decades by offering novel materials, better efficiencies in applications, higher selectivities, and cost-effectiveness. Newly developed biomaterials with nanotechnology show novel characteristics and functionalities [161]. Among the wide variety of nanomaterials, only a few types are used in the field of biomaterials due to some reasons such as safety and toxicity [162]. When applying nanomaterials into biomaterials, toxicity and response of the immune system are vital factors to be considered. In most cases, nanomaterials' toxicity depends on surface properties, size, and dosage [163]. So, future investigation of the environmental and toxicological impact of the nanobiomaterial is necessary.

Some nanomaterials can respond to properties like temperature, magnetism, light, electricity, and sound. By using the above functions, smart and automated nanobiomaterials can be invented in the future. Instead of designing nanobiomaterials for one function, multifunctional nanobiomaterials can be designed. For example, designing nanobiomaterials for both bone and tissue regeneration while minimizing immune response will be smart applications yet to be invented. By developing nanobiomaterials with electronic devices like nanoelectrochemical systems, nanobioelectronic devices can be further invented [162]. The characterization techniques and models will be developed to identify the characteristics of nanobiomaterials for future nanotechnology applications in biomaterials [163].

6. CONCLUSION

In summary, biomaterials are a group of materials that have features such as biocompatibility, mechanical continuity, and non-toxicity. In recent years, spider silk, egg shells, fish bones, and corals have been used as biomaterials because of their favorable biocompatibility, and metals and ceramics are also used as biomaterials. Nowadays, the involvement of nanotechnology has been given an excellent implementation to develop biomaterials. Nanoparticles and nanotubes such as gold NP, silver NP, iron oxide NP, fullerene, carbon nanotubes, silicon nanotubes, and titanium dioxide nanotubes are major nanomaterials that are used to develop biomaterials. Dentistry, tissue engineering, cardiovascular treatments, bone regeneration, and drug delivery are the main applications of nanobiomaterials. Designing of multifunctional and smart nanobiomaterials will be the future trend, and consider about toxicity, biocompatibility, and response to the immune system are the major factors to be considered when applying nanotechnology in developing advanced biomaterials.

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