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POTENTIAL BIOMEDICAL APPLICATIONS OF METALLIC NANOBIOMATERIALS: A REVIEW

B. Shivaramakrishnan [*1], B. Gurumurthy [2] and A. Balasubramanian [3]

Department of Pharmacology [1], JSS College of Pharmacy, Udhagamandalam, Tamil Nadu, India.
Department of Radio Diagnosis [2], JJM Medical College, Davanagere, Karnataka, India.
Department of Earth Sciences [3], University of Mysore, Mysore, Karnataka, India.

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Correspondence to Author:
B. Shivaramakrishnan

Lecturer,
Department of Pharmacology, JSS College of Pharmacy, 'Rocklands', PB no-20, Udhagamandalam - 643001, Tamilnadu, India.

E-mail: shivaram14@jsscpooty.org

ABSTRACT: Nanobiomaterials are very effective components for several biomedical and pharmaceutical studies. Among the metallic, organic, ceramic and polymeric nanomaterials, metallic nanomaterials have shown certain prominent biomedical applications. Enormous works have been done to synthesize, analyse and administer the metallic nanoparticles for various kinds of medical and therapeutic applications, during the last forty years. In these analyses, the prominent biomedical applications of ten metallic nanobiomaterials have been reviewed from various sources and works. It has been found that almost nine of them are used in a very wide spectrum of medical and theranostic applications.

INTRODUCTION: Most of the earth's natural and synthetic materials are characterised by their diagnostic physical, chemical, thermal, magnetic, electrical, mechanical, optical and catalytic properties. They are classified into coarse (macro), fine and nanomaterials based on their sizes. Materials which range in size from 1 nm to100 nm (One nanometer is equal to 10^{-9} meter) are classified as Nanoscale materials, which are also termed as nanoparticles. Nanoscale materials exhibit very peculiar characteristics when compared to their micro/ macro or bulk-sized counterparts. Continuous size reduction in most of the solids may reach the atomic structure containing repeated arrangement of unit cells.

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The subject of materials science deals with the structure, properties and applications of crystalline and amorphous solids. The basic concept of nanomaterials was first brought to the surface in 1959 by the renowned physicist Richard Feynman in his talk "There's Plenty of Room at the Bottom", described the possibility of synthesis of materials through direct manipulation of atoms. Richard Feynmann highlighted the importance of controlling and manipulating materials at nano scale which has made a new raodmap in the field of science and technology [1]. Today, elaborate details of nanomaterials are available in the literature, for basic understanding and advanced applications [2].

The subject of Nanotechnology refers to the materials design, characterisation, production and application of structures, devices and systems, by controlling their shape and size at nano level. Nanoscience has beome an upcoming discipline. It is concerned with the understanding of the effects and influence on the inherent properties of the materials, at Nano scale [3].

There are certain principal factors which cause the properties of nanomaterials to differ much significantly from the other bulk materials. The dominant ones are the increased relative surface area, and the quantum effects. These factors can change or enhance the properties including reactivity, strength and electrical characteristics. Nanotechnologies aim at exploiting these effects to create structures, devices and systems, with novel properties and functions due to their reduction in size [4]. Today, nanoscience and nanotechnologies are very widely seen as vital sectors having huge potential to bring a lot of benefits, in the areas as diverse as drug development, water decontamination, information and communication technologies, and the production of stronger, lighter, durable and useful consumer and life saving materials. Nanomaterials are also called as nanoparticles (NPs). Based on the application potential, new subjects of studies are also emerging continuously [5].

The most widely used nanomaterials are categorised into metal-based nanomaterials, non-metallic nanomaterials, carbon-based nanomaterials, semiconductor nanomaterials, polymer- based nanomaterials and nanocomposites [6]. This study is aimed at identifying the potential applications of metallic nanoparticles in medical fields.

1.1 Nanotechnology and Medicine: The application of nanotechnology to medicine is termed as 'nanomedicine'. This emerging discipline has the potential to transform our earlier approaches to human health and disease, in a different way with a lot of improvements in disease prevention, diagnosis, treatment and control[7]. Advancement in nanoscale systems, particularly the use of nanoparticles, has shown profound impacts on molecular sensing, imaging, disease diagnosis, treatment and monitoring [8].

Some of the nanomaterials are synthesized, tuned and characterised in such a way, so that, they are suitable for various biological and biomedical applications such as, drug delivery, biosensors, bio-imaging, tissue engineering, bio-electronics, bone regeneration, drug and gene delivery [9-12]. Due their prominent applications in biology, these nanomaterials are termed as Nanobiomaterials. Almost all categories of nanomaterials are found to be useful in nanomedicine. The prominent applications of metallic nanobiomaterials are identified and discussed, in this work.

2.0 Nanobiomaterials (NBM) and their categories: Nano biotechnology, bio nanotechnology, and nanobiology are the terminologies used refer to the intersection of nanotechnology and biology [13]. Nanomedicine is the medical application of nanotechnology combining the two major disciplines [14-15]. The diversified fields of nanomedicines have a lot of challenges and perspectives [16-17]. Engineering of nanoscale biomaterials, for various biological applications, is an emerging field in nanotechnology [18]. The experts converging to produce and analyse the nanobiomaterials are chemists, electronic engineers, microbiologists, radiologists, biochemists, material scientists, electrical engineers, environmental toxicologists, pharmacologists and molecular biologists [19]. Quite a lot of studies have been carried out in the field of materials sciences and nanotechnology during the last three to four decades.

A substantial amount of work has been carried out in the field of understanding nanobiomaterials[20]. There are some specific areas in which the innovative contributions have been continuously made by the researchers. They are broadly confined to the: a) synthesis, b) characterisation and c) applications of nanomateials [21]. The types of nanobiomaterials synthesized, produced and used are very highly heterogeneous with reference to their physical, chemical, biological and engineering properties. They pose not only many challenges in their design and development, but also provide ample opportunities to use them in several of the modern applications. Voluminous collections of literature collections are available on the first two areas [22]. The applications part alone is considered, in this work. Nanobiomaterials include a wide range of nanoscale fine particles and devices that are fabricated with a focus on biological and biomedical applications including drug delivery [23-24], nanopharmaceutics [25-26] and several therapeutic applications [27-28]. The potential applications of nanomaterials are verywide and varied [29].

In general, nanobiomaterials are prominently used as biocatalysts [30], nanobots and nanocarriers [31-32], biomarkers for diagnostic purposes and as biosensors [33], in bioimaging [34], for Molecular imaging [36], preclinical diagnosis [37], contrast agents in MRI and CT scanning [38-39], gene and drug delivery [40-42], targeted drug delivery and cancer therapy [42-44]. Multifunctional nanomaterials are also designed to enhance a drug's therapeutic effect [45-48]. They are also used as nanocarriers. The typical examples include liposomes that are well known as nanocarriers in drug delivery [49]. In addition to these, nanobiomaterials are also used for antimicrobial activities [50-52]. The emerging applications are found in cancer diagnosis and therapy [53-58], for detecting and treating tumors [59], photodynamic therapy [60-61], tuberculosis [62] and dental implants [63]. Nanobiomaterials are suitable tags for cellular detections, in cell and molecular biology [64-65].

Based on the application potential and the nature of nanomaterials used for various biological applications, nanobiomaterials are grouped into various categories as shown in **Fig. 1**.

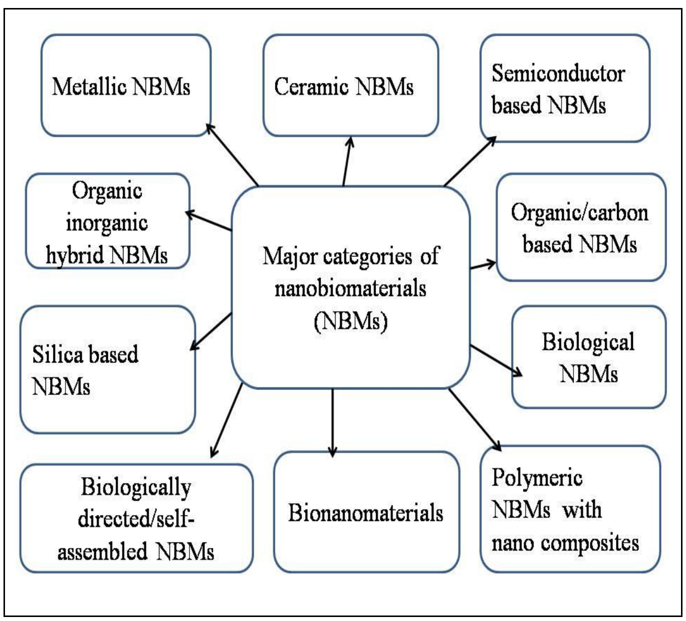

FIG. 1: MAJOR CATEGORIES OF NANOBIOMATERIALS

Literature sources on almost all the categories of nanobiomaterials are available along with their usage [66]. It is also very difficult to present most of those details in this article. However, an attempt has been made to enlist only the potential biomedical applications of metallic nanobiomaterials.

It has been found that there is a wide spectrum of utility areas that are on the growing path, especially on the use of metallic nanobiomaterials, in health, medicine, theranostics and pharmaceutical applications.

3.0 Metallic Nanoparticles: Metallic nanoparticles are nanosized metals with at least one of the dimensions restricted 1 to 100 nm. The metallic nanomaterials are broadly classified in to four major categories as metallic nanoparticles (0D), metallic nanowires, nanotubes and nanorods (1D), nanolayers, sheets and platelets (2D) and nanoshells and other nanostructures (3D), including nanoporous materials. The earliest application of metallic nanoparticles was probably their use in the manufacturing of stain glass at the medieval era. It was originally used to decorate cathedral windows and porcelainware. The first reported scientific exploration of metallic particles with small sizes was made by Michel Faraday in 1857, who investigated the stability parameters of these particles.

Metallic nanoparticles have attracted a large proportion of scientists to carry out many novel methods in synthesizing them, characterise them and also to find out their prominent applications, in a sustainable environment. This interest was shown primarily due to the number of useful properties that these materials have got for commercial production and essential requirement. Among the industrial sectors, the field of biomedical engineering is heavily focussing its thrust on the application of metallic and other nanomaterials, at present [67]. The most widely used metallic nanoparticles in biological and biomedical applications are, gold(Au), silver(Ag), copper (Cu), iron oxide ($Fe^2 O_3$), zinc oxide (ZnO), titanium oxide(TiO_2), platinum(Pt), selenium (Se), gadolinium(Gd) and palladium(Pd), as shown in **Fig. 2**. Among these, the most extensively explored metallic nanoparticles are from gold, silver, iron and copper [68].

Nanomaterials can be synthesized and modified with appropriate functional groups that would allow them to bind with drugs, antibodies and ligands which are the substances of high interest in biomedical field.

The study of metallic nanoparticles and synthetic biology is related to each other. Metallic nanoparticles possess many, very useful, and unique properties. Their small size allows for increased surface area and more points of contact when compared with the same materials in bulk form. This reduction in size, makes the nanoparticles as excellent candidates for catalysts or for when increased levels of binding are required. Metallic nanoparticles cannot simply be treated as minute blocks of a metal, as implied by the term "divided" metals.

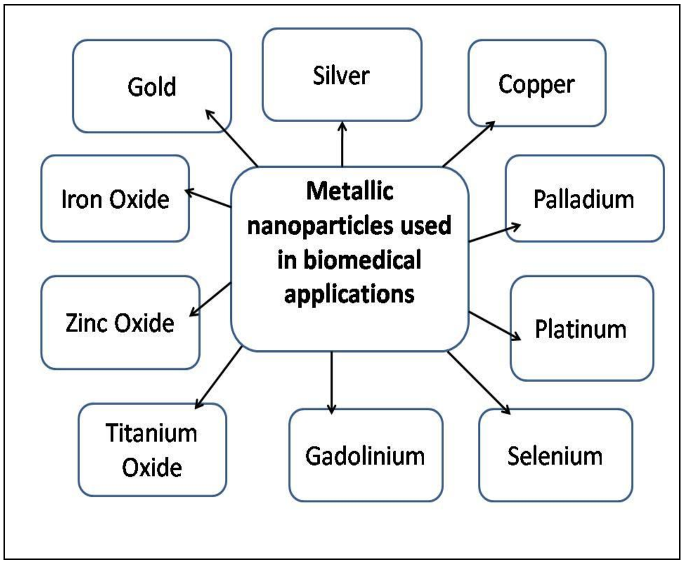

FIG. 2: MAJOR METALLIC NANOPARTICLES USED IN BIOMEDICAL APPLICATIONS

4.0 Biomedical Applications of metallic NPs: Metallic nanoparticles have shown the most extensive applications in the field of synthetic biology [67]. It is because of the fact that the nanoparticles of metals possess very unique properties. Metallic nanomaterials exhibit diverse optoelectronic properties, due to their reduced sizes and shapes. Another major advantage of metallic NPs, is their tunability. They also have some levels of good biocompatibility. Metallic NPs are chemically stable and suitable for cellular uptake. These materials can be synthesized and modified with various chemical functional groups, which allow them to be conjugated with antibodies, ligands, and drugs of interest. Because of these unique characteristics, the metallic NPs have a wide range of potential applications in biology and medicine [69-70]. The prominent applications of metallic nanobiomaterials are enlisted, in the following sections.

4.1 Gold Nano Particles (AuNPs): Gold Nanoparticles are around 10-20 nm diameter. They are synthesized as nanodots or nanopowder. These are brown spherical high surface area metal particles possessing distictive optical and physical properties. When AuNPs get really small, with a diameter of 5 nm or less, they can be used as a catalyst to help reactions. AuNPs are most frequently synthesized and kept in colloidal suspension. The gold colloidal suspension, with spherical particles in water, shows an intense red color. This color is due to the localized surface plasmonic resonance. The most dominant property of AuNP is the intense absorbance capability and scattering of incident light, at its surface plasmon resonance wavelength. The optical properties of gold nanoparticles are governed by their morphology, i.e. size, shape and aggregation status. The gold nanoparticles are found to have strong absorption of light, which peaks around 520 nm, in aqueous solutions. By precisely engineering these nanoparticles, with different morphologies and surface chemistries, these particles can be tuned to suit a variety of applications, in several fields. NPs are also used as versatile research and diagnostic tools.

The surface of gold nanoparticles can be tuned by ligand functionalization in order to bind some biomarkers. AuNPs have prominent application in cancer treatment using radio waves to heat and destroy a tumor, lymphoma, or metastasized cancer. AuNPs are found to be employed in a stream of biomedical applications [71]. Today, the AuNPs play a very significant role in the field of nanomedicine [72]. The biomedical applications of Au NPs have been reviewed by several scholars [72-77].

Biomedical Applications of Au NPs: After the perusal of about 12500 articles, the major biomedical applications of GNPs are confined to the areas like, targeted drug delivery [78-80], anti-cancer therapy [81-88], contrast agent in medical imaging [89-90], molecular imaging in living cells [91], anti-microbial activities [91-96], antibacterial activities [97], antiviral treatments [98-99], biosensors & intracellular analysis [100], photothermal therapy [101-102], hyperthermic effects to treat tumors [103-105], biocatalysts [106] and biomarkers.

Apart from the biomedical field, gold nanostructures are heavily exploited in areas such as sensors, electronic goods, microscopic analysis, solar cell and fuel cell research.

4.2 Silver nanoparticles (AgNPs): Silver is a historically significant metal used in medical treatments. AgNPs are one of the most heavily used nanomaterials in the world. Numerous shapes of AgNPs are synthesizd depending on the applications. The commonly used NPs are spherical silver nanoparticles. Their extremely large surface area permits them to coordinate with a vast number of ligands. The properties of silver nanoparticles applicable to human treatments are still under investigation for assessing their potential efficacy, toxicity, and costs [107]. AgNPs are also widely prepared and stored as a metal particle dispersion. The colloidal suspensions of spherical AgNPs are bright yellow in color, typically showing maximum absorption around 420 nm. They are most commonly prepared by reduction of silver salt into zerovelent state using reducing agents.

AgNPs possess unique optical, electrical, and thermal properties. Currently, these nanomaterials are being incorporated into products that range from photovoltaics to biological and chemical sensors. By taking the advantage of the novel optical properties of AgNPs [108], they are employed in molecular diagnostics and photonic devices. They are also used as conductive inks, pastes and fillers which utilize their high electrical conductivity, stability, and low sintering temperatures. Due to these, AgNPs are found to have a lot of industrial applications [109].

Biomedical Applications of Ag NPs: Among the noble metal nanoparticles, AgNPs present a series of features like simple synthesis routes, adequate and tunable morphology, and high surface to volume ratio, intracellular delivery system, a large plasmon field area recommending them to be considered as ideal biosensors, catalysts or photo-controlled delivery systems. In bioengineering, AgNPs are considered as potentially ideal gene delivery systems for tissue regeneration. Extensive amount of research works have been oriented towards the AgNPs due to their simplicity in handling and holding varieties of biomedical applications [110-111]. Silver nanoparticles have been found in many therapeutic applications. The application potential of Ag NPs have been analysed in addition to their toxicological effects [112].

The prominent biomedical applications of AgNps are found to be such as, Anti-cancer Therapy [113-115], catalysis [116], anti-microbial activities [117-124], antibacterial activities [125-130], antifungal treatments [131-132], antiviral activities [133-134], wound healing [135], wound dressing [136], implanted material [137], tissue engineering, medical devices (catheters, prostheses, vascular grafts). Diagnostic applications in bio-sensing [138-139], antipermeability agent (in management of diabetic retinopathy) and dental preparations [140].

4.3 Gadolinium Nanoparticles (GdNPs): Gadolinium is a soft, shiny, malleable, ductile, silvery metal belonging to the lanthanide group in the periodic table of elements. Gadolinium is a Block F, Period 6 element. The metal does not tarnish in dry air but an oxide film forms in moist air. Gadolinium reacts slowly with water and dissolves in acids. Gadolinium becomes superconductive below 1083 K. It is strongly magnetic at room temperature. Gadolinium is one of the more abundant rare-earth elements available on the earth's crust. It is never found as free element in nature, but it is contained in many rare minerals, like monazite and bastnasite. Morphologically it is spherical, and appear as a black powder.

Biomedical Applications of GdNPs: A rapid development of gadolinium-based nanoparticles is observed due to their attractive properties as MRI-positive contrast agents. In addition to these imaging properties, it has been recently shown that they can act as effective radio sensitizers under different types of irradiation (radiotherapy, neutron therapy, etc). Liposomal-based gadolinium (Gd) nanoparticles have elicited significant interest for use as blood pool and molecular magnetic resonance imaging (MRI) contrast agents. GdNps are used in Neutron capture Therapy to treat tumours. Theranostic magnetic resonance imaging (MRI) is now receiving a growing interest in imaging-guided drug delivery, monitoring the treatment and personalized administration [141], and anti-cancer treatments [142].

4.4 Iron oxide nanoparticles(IONPs): Iron is the largest occurring metal found in the earth's crust. Iron ore is the starting material to produce iron oxides which are used in various applications ranging from the production of steel to the present day data storage devices. If iron is left in the rain, it will rust, and rust is composed of iron oxide. Like iron, iron oxide also has magnetic properties. Iron has four unpaired electrons, whereas iron oxide has only two unpaired electrons. Because the unpaired electrons make a material magnetic, iron oxide is less magnetic than iron. Iron oxide is therefore called a paramagnetic material. The paramagnetic properties of iron oxide nanoparticles are not changed from the bulk material except that these tiny particles can go where larger particles never could. Iron oxide nanoparticles (IONPs) occupy a privileged position among magnetic nanomaterials with potential applications in medicine and biology. They are also classified as Super Paramagnetic Iron Oxides Nanoparticles(SPIONs). The magnetic iron oxide nanoparticles, their synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications were analysed by several workers.

Biomedical applications of Iron Oxide NPs: Among all types of nanoparticles, the SPIONs are biocompatible. With proper surface architecture and conjugated targeting ligands/proteins, they have attracted a great deal of attention for drug delivery applications [143-145]. Magnetic nanoparticles (MNPs) are characterized by biocompatibility, biodegradation, and safety for human ingestion. For biomedicine applications, MNPs require surface modification to become water-soluble and be stable enough to resist the effects of proteins and salts in the physiological environment [146].

The major areas of applications of SPIONs are found to include, targeted drug delivery [147-148], anti-cancer therapy [149-150], diagnosis and treatment of cancer[151], contrast agent in medical imaging [153], tissue engineering, target liver tumours and metastasis, ultra-sensitive molecular imaging, cancer treatment by hyperthermia [154], anti-microbial activities [155-156], biosensors & intracellular analysis [157] and photothermal cancer therapy [158-159]. The unique properties of iron oxide magnetic nanoparticles are suitable for using in biocatalysis and bioseparation areas [160].

4.5 Copper Nanoparticles(CuNPs): Copper nanoparticles are copper based particles of 1 to 100 nm in size. These nanoparticles are of particular interest due to their historical application as coloring agents. Copper nanoparticles received much attention due to its high electrical conductivity, high melting point, low electrochemical migration behavior and their low cost. Copper (Cu) Nanoparticles, nanodots or nanopowder are black brown spherical high surface area metal particles. Commercially available CuNPs are typically 10-100 nanometers (nm) with specific surface area (SSA) in the 5 - 70 m2/g range. CuNPs are also available in passivated and in Ultra high purity and high purity, carbon-coated and dispersed forms. The nanostructures include nanorods, nanowhiskers, nanohorns, nanopyramids and other nanocomposites. There are biogenic nanoparticles which include copper, copper oxides, copper sulphides and complex copper nanostructures [161-162].

Biomedical applications of CuNPs: The Biomedical applications of CuNPs are found to be mainly in, medical diagnosis [163], antibacterial and anti-fungal activities [164-165], molecular imaging [166], cancer imaging & cancer therapy [167], photothermal ablation of tumor cells [168], theranostic applications [169], and as catalysts [170-171].

4.6 Zinc Oxide Nanoparticles (ZnO NPs): Zinc oxide is an inorganic white powder. It is insoluble in water. It is present in the Earth's crust as the mineral zincite. Zinc oxide is commonly found in medical ointments where it used to treat skin irritiations. Zinc oxide is being used in semiconductors, concretes, ceramic and glass compositions and even cigarette filters. Zinc oxide has become one of the most important ingredients in ointments, creams, and lotions to protect against sunburn and other damage to the skin caused by ultraviolet light (sunscreen).

Zinc (Zn) Nanoparticles**,** nanodots or nanopowder are spherical or faceted high surface area metal particles. They are typically of 20-40 nanometers (nm) with a surface area (SSA) in the range of 30 - 50 m2/g. Zinc Nanorods are elongated particles ranging from 10 to 120 nanometers (nm) with specific surface area (SSA) of 30 - 70 m 2 /g.

ZnO NPs are used as anti-microbial, anti-biotic and anti-fungal (fungicide) agents by incorporating them in coatings, bandages, nanofiber, nanowire, plastics, alloy and textiles. They possess suitbale electrical, dielectric, magnetic, optical, imaging, catalytic, biomedical and bioscience properties.

ZnO nanostructures have many advantages including the high surface to volume ratio, nontoxicity, chemical stability, electrochemical activity, and high electron communication features. Applications for Zinc nanorods generally involve their magnetic properties. Because of this they are used as catalysts, medical sensors, and as a contrast enhancement agents for magnetic resonance imaging (MRI). Zinc particles are being tested for site specific drug delivery agents for cancer therapies. Zinc oxide (ZnO) is a unique material that exhibits semiconducting, piezoelectric, and pyroelectric multiple properties. The nanostructures have also shiown some novel applications in optoelectronics, sensors, transducers, and biomedical science [172]. There are several biomedical applications of ZnO nanoparticles [173] and ZnO Quantum Dots [174].

Biomedical applications of ZnO NPs: The prominent biomedical applications of ZnO NPs are found to include, targeted drug delivery-destruction of tumor cells [175-176], bioimaging and drug delivery [177], tumor detection [178-179], anti-cancer therapy [180-181], contrast agent in medical imaging [182], anti-microbial activities [183], biomarkers [184] and biosensors [185-187].

4.7 Platinum nanopartcles (PtNPs): Platinum is one of the rarest metals on the earth's crust. It has unquie physical and thermal properties. It has high corrosion resistance and numerous catalytic applications including automotive catalytic converters and petrochemical cracking catalysts. Platinum nanoparticles come in wide variety of shapes including spheres, rods, cubes, and tetrahedra. Platinum Nanorods are elongated particles ranging from 10 to 120 nanometers (nm) with specific surface area (SSA) in the 30 - 70 m 2 /g range. Applications for Platinum nanorods generally involve their magnetic properties and include in catalysts and magnetic recording and in medical sensors and bio medicine as a contrast enhancement agent for magnetic resonance imaging (MRI). Platinum particles are being tested for site specific drug delivery agents for cancer therapies and in coatings, plastics, nanowire, nanofiber and textiles and in certain alloy and catalyst applications. Platinum-group metals (PGMs) are superb catalysts for a variety of industrial reactions. Platinum is one of the rarest and most expensive metals.

It has high corrosion resistance and numerous catalytic applications including automotive catalytic converters and petrochemical cracking catalysts. Platinum nanoparticles are usually used in the form of colloid or suspension in a fluid. The particles exhibit ferromagnetism up to room temperature. They are the objects of extensive research due to their antioxidant properties. Platinum NPs exhibit fascinating optical properties. Being a free electron metal NP like Ag and Au, its linear optical response is mainly controlled by the surface plasmon resonance.

Platinum containing films are used for enzyme immobilization, optical applications, and catalytic activity. Platinum nanoparticles are the subject of substantial research, with their potential applications in a wide variety of areas in biomedicine [188]. PtNPs are also used in electrochemical applications [189].

Biomedical applications of Pt NPs: The prominent biomedical applications of PtNPs are found to include, therapeutic effects [190], anti-cancer therapy [191], anti-tumor applications [192], contrast agent in medical imaging[193], antimicrobial activity [194], anti-bacterial activities [195], anti-oxidant effects [196], cancer chemotherapy [197], biosensors and intracellular analysis [198], photothermal therapy[199], as biocatalysts [200] and as biomarkers [201-202].

4.8 Selenium nanoparticles (SeNPs): Elemental selenium naturally possesses antibacterial properties. Selenium nanoparticles, nanodots or nanopowder are typically 10 - 45 nanometers (nm) with specific surface area (SSA) in the 30 - 50 m^2/g range and also available in with an average particle size of 75 - 100 nm range with a specific surface area of approximately 2 -10 m 2 /g. Nano Selenium Particles are also available in passivated and Ultra high purity and high purity and coated and dispersed forms.

They are also available as a nanofluid through the AE Nanofluid production group. Research on Se nanoparticles have shown a strong absorption around 565 nm. Their bright red color, made them to be used as biological sample staining reagents. In addition, Se nanoparticles have shown strong anti-cancer effect both in vitro and in vivo. Compared with Se element, Nanostructured Se showed less toxicity both *in vitro* and *in vivo*.

Nanofluids are generally defined as suspended nanoparticles in solution either using surfactant or surface charge technology. Nanofluid dispersion and coating selection technical guidance is also available. Other nanostructures include nanorods, nanowhiskers, nanohorns, nanopyramids and other nanocomposites. Selenium has been known to be analogous to sulphur in its structure and has shown many pharmaceutical and industrial applications including the formulation of pesticides and algaecides.

Biomedical Applications of SeNPs: The major biomedical applications of SeNPs include, targeted drug delivery [203-205], drug delivery vehicles and artificial enzymes [206-207], anti-cancer therapy [208-210], anti-bacterial activities [211], biosensors and intracellular analysis [212].

4.9 Palladium Nanoparticles: Palladium (Pd) is a lustrous silver-white metal. It has a face-centered cubic crystalline structure; at ordinary temperatures it is strongly resistant to corrosion in air and to the action of acids. It is attacked by hot acids, and it dissolves in aqua regia. It forms many compounds and several complex salts. Palladium nanostructures are characterized by remarkable catalytic and optical properties.

Palladium Nanorods are elongated particles ranging from 10 to 120 nanometers (nm) with specific surface area (SSA) in the 30-70m2/g range. Palladium, together with rhodium, ruthenium, osmium, iridium, and platinum form a group of elements referred to as the platinum group metals (PGM). Palladium nanoparticles are of great importance as catalytic materials, as well as for a number of other applications such as hydrogen storage and sensing. Palladium is regarded for its low toxicity, poor adsorption when ingested.

Biomedical applications of Pd NPs: The major biomedical applications of Palladium NPs include, targeted drug delivery [213-214], anti-cancer therapy [215-216], anti-microbial activities [217], biosensors & intracellular analysis- hydrogen sensors [218-219], biocatalysts [220], and calalysis [221].

4.10 Titanium dioxide (TiO2) NPs: Titania (titanium dioxide) has three natural forms: rutile, anatase, and brookite. Titania nanoparticle (TNP) is a widely used nanomaterial; cosmetics and sunscreen products alone account for 50% of TNP usage. TNPs have been added to selfcleaning sanitary ceramics, antimicrobial plastic packaging, and cement. Because light-mediated TiO_2 surface hydroxylation makes it fouling-resistant, it is used in window glass, pavement, and walls. TNPs have also been used as additives in sugar, film, toothpaste, and many other consumer products. Titanium dioxide (TiO_2) and zinc oxide (ZnO) have unique physicochemical properties including a bright white color, ability to block UV light, and antimicrobial activity. It is used in Bone tissue Response applications.

Titanium dioxide or titania (TiO_2) is a material used for many different applications, due to its photocatalytic properties. Under suitable light irradiation, TiO_2 can react with water vapor and/or oxygen present in the atmosphere, to generate reactive oxygen species (ROS). Such active species can subsequently interact with other molecules present on the surface of the material, leading to further chemical reactions. Such photocatalytic behaviour [222] is due to the semiconductor nature of TiO_2; in fact light irradiation generates charges (negative electrons and positive holes) across the bandgap. The major application areas of all these metallic nanobiomaterials are shown in **Fig. 3**.

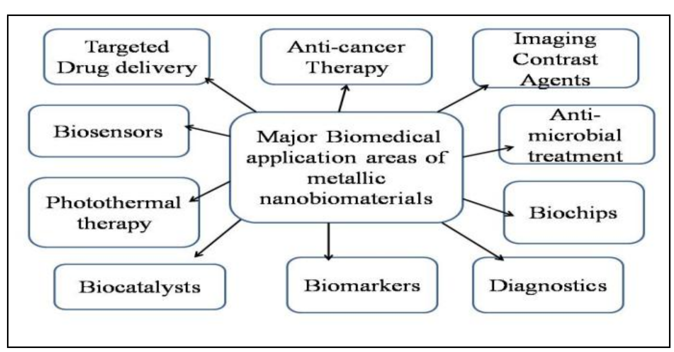

FIG. 3: MAJOR APPLICATION AREAS OF METALLIC NANOBIOMATERIALS

Table 1 summarizes the major application areas of these metallic nanobimatreials.

TABLE 1: PROMINENT BIOMEDICAL APPLICATIONS OF METALLIC NANOMATERIALS

Application areas (X marked)	**Metallic NBMs (references)**									
	Au	**Ag**	**Cu**	**Fe2O3**	**ZnO**	**Pt**	**Se**	**Gd**	**Pd**	**TiO2**
Targeted Drug delivery	X				X	X	X	X	X	
Anti-cancer Therapy	X	X	X	X	X	X	X	X	X	X
Contrast agent in Medical imaging-MRI, CT, etc	X	X	X	X	X	X	X	X		
Anti-microbial activities	X	X	X	X	X	X	X	X	X	
Antibacterial activities	X	X				X				
Anti-fungal activities	X	X	X							
Hyperthermic treatments	X							X		
Wound healing		X								
Wound dressing		X								
Tissue engineering		X						X		
Molecular Imaging	X	X						X		
Biosensors & intracellular analysis	X	X		X	X	X		X	X	
Photothermal therapy	X		X	X		X		X	X	
Biocatalysts	X		X		X	X	X	X	X	X
Biomarkers	X	X	X	X	X	X				

It could be seen that almost all these metallic nanobiomaterials have some significant role in the field of biomedical applications, except TiO_2 which has its own limitations and also some carcinogenic effects. There is a growing stream of contributions in almost all these areas, of which some of them have been highlighted.

CONCLUSION: One of the major applied areas of nanotechnology is biomedicine. Nanobiomaterials have a lot of potential in biomedical and therapeutic applications. The unique properties of metallic nanomaterials have been identified and utilised for specific studies that are relevant to nanomedicine. Among the metallic nanomaterials, gold, silver, copper, iron oxide, zinc oxide, platinum, gadolinium and palladium NPs have shown the maximum areas of proven biomedical applications. There are some applications that are made by combining the metallic NPs in the form of alloys and bimetallic modes. Such applications would have provided some more insights into the role of metallic NPs. It is certain that nanomedicine has got a good scope for the future of nanobiotechnology.

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