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Health concerns of various nanoparticles: A review of their in vitro and in vivo toxicity

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Abstract

Nanoparticles (NPs) are widely used in diverse disciplines, including biology, medicine science. The central question that need to be answered is whether NPs have toxic effects on biological cells and molecules or are they safe. The safety of NPs including targeted drug delivery is critical and so is their toxicity in the environment. In recent years, *in vitro* and *in vivo* research on animals has generated abundant information about the toxicity of NPs. However, due to varying laboratory conditions, the comparison of the results from ensuing studies is somewhat unreliable. It should be noted that, depending on the type of production, NPs can enter the body through inhalation, skin and via digestive routes. Due to the diversity of NPs and their properties, there is paucity of accurate information on their toxicological effects; particle size, shape, surface area and the chemical levels are considered as key factors in creating health and toxicological effects. Consequently, there is a need for reliable information about their effects on various organs so as to deal with NPs effectively and their impact on health and the environment. This review covers the existing knowledge base on the subject that hopefully prepares us better to address these challenges.

Keywords: Nanoparticles; Toxicological effects; Organ-specific effects

1. Introduction

The rapid advancements in nanotechnology has revolutionized all aspects of science, including industry, agriculture, material science and medicine (Figure 1) as it uses nanomaterials and nanoparticles in diverse fields ranging from nanodevices, nanosensors and nanorobots to medicine. Nanoparticles (NPs) are approximately between 1-100 nm in size and possess unique physicochemical characteristics, including small size, high surface to volume ratio and finely-tuned properties [1-3]. They have potential benefits in assorted areas of nanomedicine as drugs,

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drug-delivery systems and theragnosis (simultaneous diagnosis and therapy) agents [4]. Currently, there are many NP-based products in the form of powder and spray that are used in several car parts, scratch resistant sunglasses, anti-stain fabrics, and solar panels to name a few; particle concentration, prewetting, dispersion media, sonication, and dispersants is effective on Toxicity severity NPs [5]. Another worrisome factor in dealing with NPs is that they can attach to other hazardous pollutants in the air or water or react with them and consequently facilitate their transmission to the body. Due to the diversity of NPs and their unique properties, there is an urgent need for attaining more information about their toxicological and biological effects, especially regarding their exposure and transfer routes into the body and body's response to them [6]. NPs can enter into the body through inhalation, skin, and digestion, depending on their physicochemical characteristics and mode of their production [7]. The interactive contact with the body, depending on the type of compounds in NPs, can be respiratory, digestive, or through skin or blood [8]. There is an extensive use of NPs such as ZnO and TiO_2 with the ability to block UV rays in various health products on the market; concerns being the risks of NPs to health, safety and the environment as they are dispersed in the environment. According to primary studies, NPs can enter human body in different ways and they can access vital organs in the body through the blood flow and induce damage to tissues and cells [1, 9]. The extensive use and exposure to NPs has resulted in sustained damages in tissues and organs of humans and animals [10, 11]. Thus, despite their advantages, NPs may cause severe side effects, making them risk factors for human health. Consequently, the issues related to their toxicological profiles should be taken into account [12-14]. Although the mechanism of NPs in this regard is not truly established, researchers have associated the toxicity of NPs to parameters such as particle shape, size, dispersity, and surface charge and protein corona effects. A number of studies have indicated that NPs activate oxidative stress and expression of genes involved in inflammation [15-17]. Other parameters that ensue toxic effect in the body

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include the dose and its distribution in the body so that there is a direct correlation between dose and toxicity. NPs can enter the human body through respiration, ingestion, and injection and consequently accumulate into different tissues and organs [17-20]. NPs can even reach the brain by breaking the strong connection between cells and passing through the blood–brain barrier (BBB); they attach to the cells containing CXCR6 chemokine receptor and overcome tight injunction in the BBB [21]. NPs' passage through the membrane, their performance, and their cell metabolism are still being studied and discussed. Thus, herein, we attempt to explain as part of NPs performance that hopefully can answer whether NPs have destructive and toxic effects on organs or are they safe enough [8] (Figure1). In this review, *in vivo* and *in vitro* exploration of the toxicity and the underlying mechanism of metal, magnetic, carbon, and quantum dot NPs that have become common in clinical and medical levels (drug delivery), consumer products and various other industries are discussed.

2. Sources of toxic NPs

The sources of NP production applicable to various industries are different. In terms of production sources, NPs can be divided into three categories [22]:

1. Natural NPs, such as emanating from forest fires or volcanic eruptions that are created and dispersed naturally by different means.
2. Human generated engineered NPs that are often byproducts of human activities in industry and are produced by daily activities such as cigarette smoking, candle burning, etc.
3. Synthetic NPs that are made by engineering and chemical modifications of NPs.

Recent studies on the biological effects of NPs indicate that some of these particles have a high level of toxicity and pose major threat to human health [23, 24] in view of the fact that they can be randomly dispersed through air, soil, and water in living systems, initially harming plants and animals and ultimately becoming a threat to humans. In 2004, a report suggested

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that the carbon nanotubes, that are among the most widely used engineered NPs, create uncommon problems in mice lungs that interfere with oxygen absorption [22].

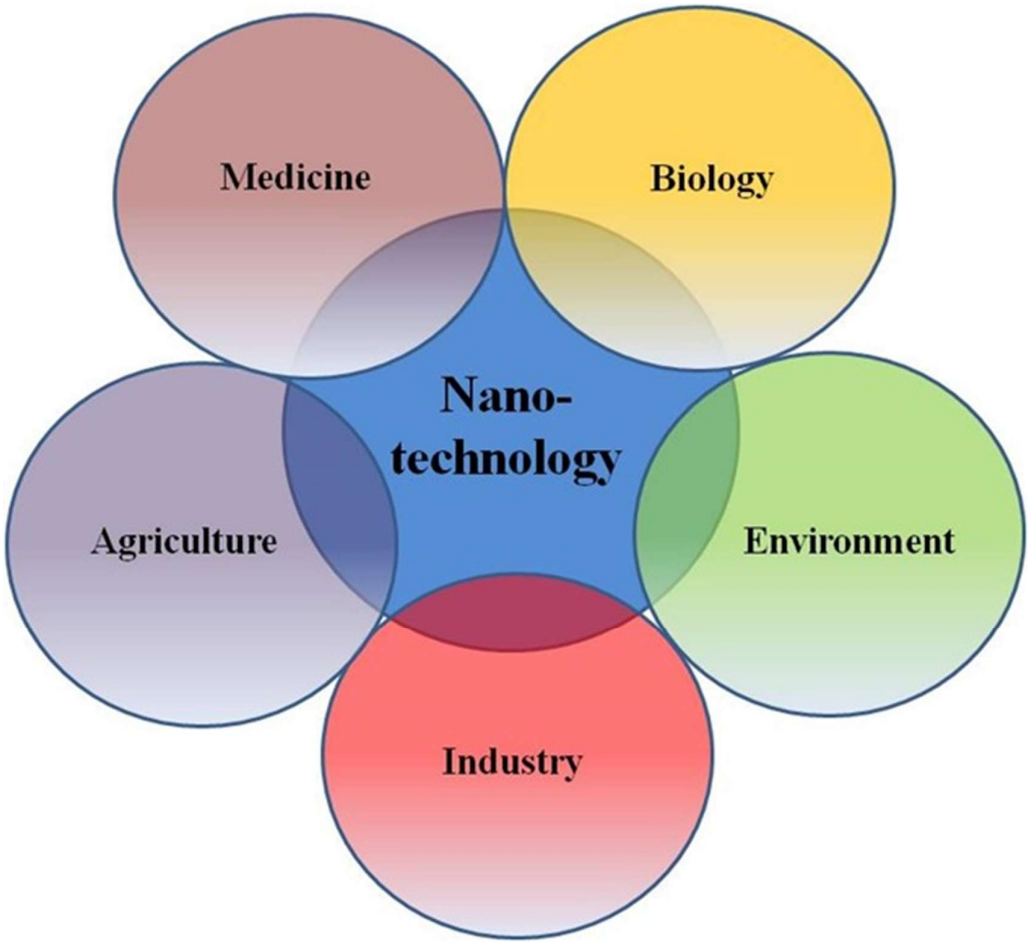

Figure 1: Nanotechnology transformative innovations in medicine, agriculture, industry, environment, and basic biological sciences

3. How do NPs affect human body?

Due to the highly diverse nature and characteristics of NPs , their associated toxicological and biological effects are related to exposure pathways, the way they are transmitted to the body and the body's response to them [5, 23] (Figure 2).

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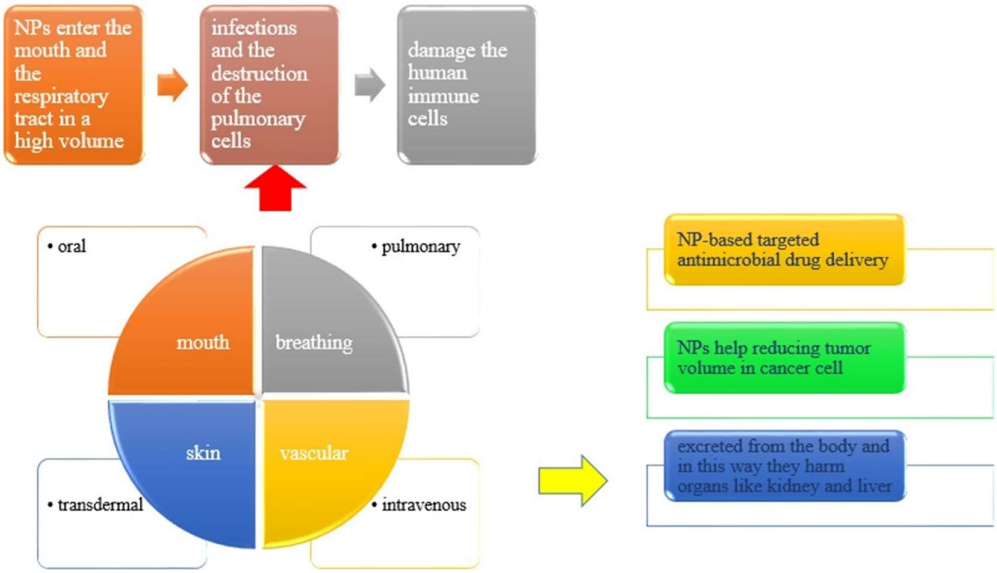

Figure 2: Nanoparticles, depending on their synthesis, can enter the body through different pathways, including inhalation, skin, and digestion.

3.1 Nose, mouth, and skin

Small particles that enter the respiratory tract through inhalation may exit through exhalation or enter the cells that cover the respiratory tract and exit from nose and mouth via sneezing. Nanoparticles with varying shapes, doses and concentrations have sundry toxic effects in the respiratory tract. Fibrous nanoparticles enter the lung pathway through inhalation and, due to the prolonged inability of the macrophages in phagocytosis, induce inflammatory response. If the nanoparticles are soluble, their toxic effect will be eliminated after a time period, but if they cannot be solubilized in the respiratory tract, they can cause long-term toxicity [25].

The outermost layer of the skin is epidermis which has a layer of dead cells (*stratum corneum*) that serves like a barrier and prevents external particles from entering the body. There is a hydrophobic layer of antimicrobial lipids on the surface of these dead cells. Above the

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epidermis, there is a layer called dermis that has blood vessels [26]. The immune cells enter the tissue through these vessels and eliminate the external particles whenever they enter the body through skin. Although epidermis is impenetrable, skin scratches and cuts result in damage to the epidermis which makes it possible for external particles to enter the body. Also, the injection of NPs into the skin results in NPs passing through epidermis. One of the important applications of NPs, in the domain of public health and cosmetics, is the use of TiO_2 in sunscreens; toxicity studies of NPs is highly important in such scenarios due to their direct contact with the skin. Some reports suggest that the penetration of TiO_2 into the skin can result in skin cancer [27].

3.2 NPs uptake via injection

A significant application of NPs is in targeted drug delivery systems for antimicrobial treatments[28]. NP-based targeted antimicrobial drug delivery can be effective in overcoming some significant challenges in the treatment of infections such as the systemic toxic effect of antibiotics, reduced absorption and increase of the drug flow, biofilm formation, and intracellular bacterial infection [29]. Nano-systems are currently proposed for drugs that have poor bioavailability [30, 31].

In this context, different NP systems such as liposomes, solid lipid NPs, polymer NPs, and silica NPs have been developed [32]. The classification of pharmaceutical nano-carriers is presented in Figure 3.

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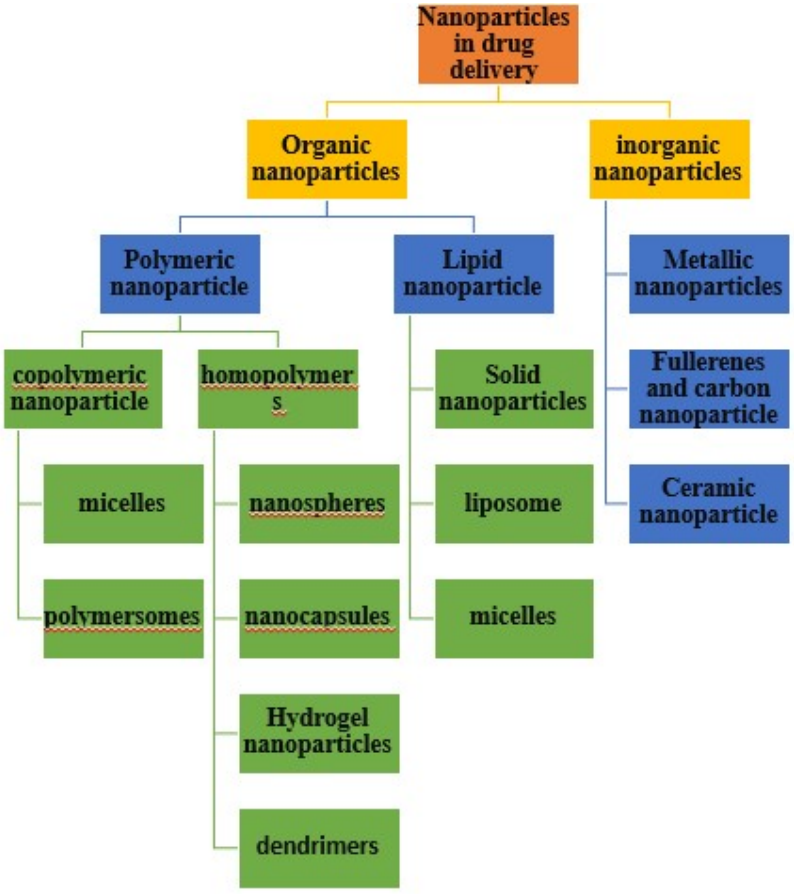

Figure 3: The classification of pharmaceutical nanocarriers.

3.2.1. Inorganic Nano carriers

Ceramic nanoparticles are often made of inorganic materials such as silica, alumina and other metal oxides such as iron and silver oxides as well as metal sulfides in various sizes and shapes. These particles can also be porous and create spaces in which medications are loaded and preserved from destruction. By designing these particles in different sizes and shapes, structures can be made to escape the reticuloendothelial system and thus contribute to enhanced drug delivery [33]. Metallic nanoparticles have been used extensively in drug delivery, diagnosis of diseases and the provision of biologic sensors; several nanometals have been produced and evaluated, but gold and silver are the most widely used. These particles can be prepared in different sizes and shapes, with a small particle size distribution. One of the unique

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features of these particles is their optical behavior change by changing the particle size, meaning that nanoparticles of different sizes exhibit different colors at visible wavelengths. This feature can be used for diagnosis of the disease and eventual drug delivery to facilitate both these processes. The surface variation of these particles is easy to manipulate as various ligands such as sugars, peptides, proteins, and DNA can bind to these particles [33]. Iron oxide superparamagnetic nanoparticles are an important and widely used category of inorganic materials used in drug delivery that can be prepared by chemical procedures such as co-precipitation method or via biological means with the help of bacteria. Easy modification of the particles' surface, as well as direct bonding of the ligand to them, are salient features of these compounds. In addition, having superparamagnetic property enables the use of these compounds in targeted drug delivery via the magnetic field. Magnetic NPs loaded with a drug can be guided to a specific place in the body by the application of an external magnetic field, thereby bringing the drug to a specific place. For example, Fe_3O_4 (magnetite), γ-Fe_2O_3 (maghemite, ferrimagnetic) and superparamagnetic iron oxide nanoparticles (SPIONs) are the major NPs used in drug delivery. These particles are typically coated with polymers such as dextran or chitosan to enhance their biocompatibility [34]. Two classes of compounds that have recently been highly emphasized in the drug delivery are carbon nanotubes and fullerenes (also known as Buckyballs); their size, shape and surface properties have empowered their use in drug delivery. Single-wall carbon nanotubes and C60 fullerenes have a diameter of about 1 nanometer, which is half the diameter of a DNA helix. Because of their small size, these particles can easily pass through the membranes and biological barriers and penetrate into the cell. These structures allow for surface engineering with their high surface to volume ratio. The surface of these particles can be coated with various compounds to enhance solubility and biocompatibility, as well as the delivery of different materials including biological molecules such as proteins, DNA and drugs. Pharmaceutical compounds are often loaded onto or inside

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these structures. Targeting and simultaneous transfer of two or more compounds are additional interesting features of importance in drug delivery by these particles [33].

3.2.2. Organic Nano carriers

The term, liposome was coined in 1961 by Alec D. Bangham. These double-layer vesicles consist of a liquid part enclosed in a double layer lipid membrane, which is often a natural or synthetic phospholipid. Amphiphilic nature, biocompatibility and the ease of surface changes are among the factors that initiated the use of these structures as an option for drug delivery [33, 35]. Another example of lipid nanoparticles is solid lipid nanoparticles (SLNs) that form a solid lipid matrix consisting of triglycerides, lipids, fatty acids, steroids and waxes, and have a size less than 1 μm. In order to increase the stability of these particles, surfactant compounds are often deployed in their formulation. These nanoparticles can be used to load and carry drugs with very low solubility in an aqueous medium, release them in a specific time frame, and transfer them to the desired site via, for instance, oral methods or injection [36]. Another very commonly used materials, in the form of nanoparticles for drug delivery, are polymers, natural or synthetic, which need to be biocompatible, non-toxic and free from leachable impurities besides comprising an appropriate physical structure and a desired half-life. Polymer nanoparticles are often selected from biodegradable types, the main advantage being their high stability and their scale-up production in large quantities. Polymer nanoparticles involve a large number of compounds and form vesicular systems (nanocapsules) and matrix systems (nanospheres); the drug is kept inside a polymeric cavity in nanocapsules, while it is dispersed in a polymer matrix in nanospheres [33, 36]. Polymer micelles are self-assemblies of macromolecules that consist of block copolymers with non-covalent bonds; block copolymer micelles have a core-shell structure. Specific properties of the micelles, such as critical micellization concentration (CMC), aggregation number, size and shape of their final structure

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depend on the structure and length of the polymer chains in the copolymer block. Polymer micelles usually have a low CMC, which affects their ability to increase the solubility of loaded drugs and the resistance of micelles [36, 37].

Micelles have been widely used in drug delivery due to their high capacity for drug loading, stability in physiological conditions, reduced dissolution rate, increased accumulation of the drug at the site and the surface change ability. The polymer micelles termed NK911 containing doxorubicin and NK105 containing paclitaxel are in the final phases of clinical studies to enter the global pharmaceutical market [38]. Dendrimers are synthetic and branching macromolecules that are structurally similar to a tree with specific sizes and shapes. These structures are monodispersed and their surface can be easily altered by chemical reactions or physical interactions. Therefore, the molecules of the drug can be combined with dendrimers either through complexing with the structure or encapsulation within the structure. Polymerzomes are made up of amphiphilic copolymers that form double-layer structures in water; three block copolymers containing material would form triple-layer structures. These entities have lower penetrations into the cell than liposomes, which also have vesicle-like phospholipid structure. The greater the copolymer hydrophobic part, the more obvious this property is which can be effective in reducing the speed of drug release. These structures also have more mechanical and biological stability compared to liposomes because the interaction of vesicles and macrophages is less common in these structures, resulting in more protection for the drug. Despite all these advantages, there is still no formulation for this structure class in the pharmaceutical market. Hydrogel nanoparticles are three-dimensional polymer structures used to encapsulate and transfer drugs. These structures swell in water or in the bioenvironment and carry a large amount of fluids inside. There are also stimulus-responsive hydrogels which release the drug under specific environmental changes, such as temperature and pH changes. These systems have been used to transfer DNA and proteins, heal wounds, make biosensors,

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and engineer tissues [33]. Nanoparticles generally deliver drugs through active targeting and passive targeting. In the passive mode, the systems reach the target site using the physico-anatomical conditions. Nanoparticles less than 100 nm easily pass through the capillaries of the reticuloendothelial system and reach the hepatic and spleen-related macrophages and are swallowed by them. This feature can be used to treat liver and spleen diseases, which means that the drug first enters the macrophage and exerts its effect through accumulation, and then the macrophage acts as a defense system to treat liver and spleen diseases. Another example of this condition is vascular permeability associated with defective lymphatic and vascular system in cancerous tumors. This means that after exiting the circulatory system and entering the areas infected with the tumor, the drugs are less likely to leave the site due to a defect in the lymph system and, as a result, accumulate there and can induce more therapeutic effect. Liposomes and polymer and micellar particles use this approach well for tissular drug delivery. In addition, the environmental conditions of cancerous tissues will also change. In cancerous tissues, the temperature is often slightly higher than the surrounding tissues (usually more than 40 degrees) and the pH is slightly lower (about 5.4). This feature can be exploited to increase the efficiency of passive drug delivery sensitive to pH and temperature [33, 35, 36, 39]. In contrast, active drug delivery, entails the possibility of more specific drug transfer to tissues and cells which can be achieved by conjugating the carrier with targeting compounds (targeting ligands) such as antibodies. These changes can be made on most nanocarriers, which has been extensively studied in recent years [40].

For example, nano-doxorubicin which is used for treatment of cancer has serious side effects on other organs due to its high metabolism [41]. Carbon polymers were mostly used and, despite the reduction in the drug side effects, they had negative effects on organs when the drug is released from the NPs. The reasons for some of these complications were not the drug but the type of the NPs used. This resulted in the exploration of NPs in the form of emulsion,

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polymer, etc. to determine which one had more biocompatibility with the body. Another type of injectable NP that is used for treatment of cancer is Au NPs. Due to their warm property, these NPs assist in reducing tumor volume in the breast but, during the separation of the NPs from the drug, they need to be excreted from the body and consequently may have detrimental effect on organs like kidney and liver [42].

3.3 NP generation by implant

The use of NPs for enhancing the improvement of materials is something new. For example, due to its close similarity to the mineral part of the teeth and having tissue characteristics similar to those of the bone, hydroxyapatite has caught researchers' attention for replacing bone. The use of nano-hydroxy particles results in the increase of molecular purity and mechanical characteristics; nano-hydroxyapatite particles have more contact area and higher solubility, compared to common hydroxyapatite. Thus, they have been proposed as a new effective bone graft [43] and used for increasing osseointegration of dental perforation repair implant, reduction of dental sensitivity, and increase of regeneration bone defects in orthopedics. Due to their very small size, NPs can easily enter human tissues which may ensue disorders in the natural biochemical environment of the cell; nano-hydroxyapatites can result in inflammatory reactions and cell death [44]. Nano-hydroxyapatite particles have toxic effects on cells in some concentrations; 2 and 5 mg/ml concentrations of nano-hydroxyapatite have toxic effects on gingival fibroblast cells [45]. Shahoon et al. explored the vital activity of human peripheral blood mononuclear cells and mouse fibroblast cells L929 in the proximity of nano-hydroxyapatite particles and observed that the vital acidities of the cells reduced in a time and dose dependent manner, but the reduction was not significant [46]. The cytotoxic effects of different concentrations of hydroxyapatite on mouse macrophage cell line RAW 264t7 have been explored; the highest inflammatory effect being reported at 100µg/ml concentration [47].

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4. NP-cell interactions

Surface properties of nanoparticles, namely hydrophobicity and hydrophilicity, affect many of the biological environmental responses of these structures, such as interaction with plasma proteins, cellular uptake and phagocytosis, stimulation of the immune system and particle removal. The surface properties of nanoparticles result in different cellular responses such as adhesion, growth and differentiation. Nanoparticles induce oxidative stress through physicochemical interaction in the cell membrane as they generate ions which cause toxicity in the cell membrane surface and that can be exploited to eliminate cancer cells. The higher the diameter of the nanoparticles, the more their interaction with the surface of the cell membrane and the higher the level of cellular toxicity. The cell membrane is complex and dynamic comprising lipopolysaccharides, proteins and extracellular polymeric materials. The penetration of nanoparticles occurs through intrusion at the phospholipid layer, but the mechanism is still unknown. The toxicity of Au NPs with a diameter under 100 nm have been explored. In the range of 3, 5, 50 and 100 nm, the toxicity was observed for the biggest and smallest sizes which included apoptosis, oxidative stress, organelles and DNA destruction, and mutagenesis [48]. NPs enter cell through endocytosis and their toxicity is in the form of ROS reduction in cell. Another study showed that this type of NPs increase inflammatory factors such as TNF-α, ll-8, ll-6, ll-1, and ultimately cause mitochondrial damage [48-50].The interaction of NPs with the cell surface ligand and membrane receptors is the main connection route for drug delivery and this is implemented through endocytosis. For example, Au NPs are amphipathic compounds as they pass through membrane without damage, a behavior reminiscent of the cyclic citrullinated peptides (CCP). α-helix protein has a hydrophilic part and a hydrophobic part and CCP bonds with cationic group, enters the cell and connects with the negative charge remained from the membrane [51]. The factors that are important in the

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connection of NPs to the cell surface protein are surface charge and hydrophobicity of the particles and the particles reaction with the protein tail or phospholipid head; the cationic level being stronger than the anionic level in this process. The interaction of NPs with water molecules, their hydrophobic property, is in fact a factor for drug delivery properties for medications whose transfer is otherwise difficult.

Coating NPs with ligands impacts the size, ligand density, receptor emission, and free energy changes. The rod and cylindrical shapes of NPs, compared with the spherical shape, need more time for wrapping and this is due to the thermodynamic force for engulfment [52]. The interaction of NPs with macromolecules such as protein has been explored and such interface can result in structural changes of proteins [53]; proteins have multiple 3D structures and some structures change after attachment of NPs due to diversity of amino acids and the protein performance. NPs such as C60 fullerenes and SWCNTs, with attachment or destruction of the activity of enzymes such as HIV-1 protease (HIV-1P) and S-DNA-glutathione, are used for therapeutic purposes [54]. The key mechanism responsible for the cytotoxic effects of NPs is oxidative stress that results in an intracellular disharmony and consequently the increase of ROS and reduction of antioxidants. DNA strand damage is hydroxy deoxyguanosine formation base changes and, when DNA is not repaired, the cell cross-links result in the occurrence and progress of cancer. Oxidative stress activates special signaling pathways (Figure 4) [55].

The entry of NPs into living cells causes the following changes:

1- Potassium ions exit the cell causing a change in the electrical balance of the cell membrane and its malfunction.

2. Building components of proteins in the cell are deactivated and proteins are denatured (most enzymes are proteins and NPs can cause their denaturation). Engineered nanomaterial (ENMs) have been directly connected to lysosomal membrane permeabilization (LMP) and cathepsin

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release to cytosol and induced autoimmunity, cancer, rheumatoid arthritis, psoriasis, neuropathic pain. It is possible, therefore, that anti-cathepsin agents can used for the treatment of diseases associated with ENM exposure, mechanism of lysosomal membrane permeabilization is similar to other endogenous inflammatory agents for example cathepsin B active cysteine amino acid and induced Cancer Lung Disease [56]

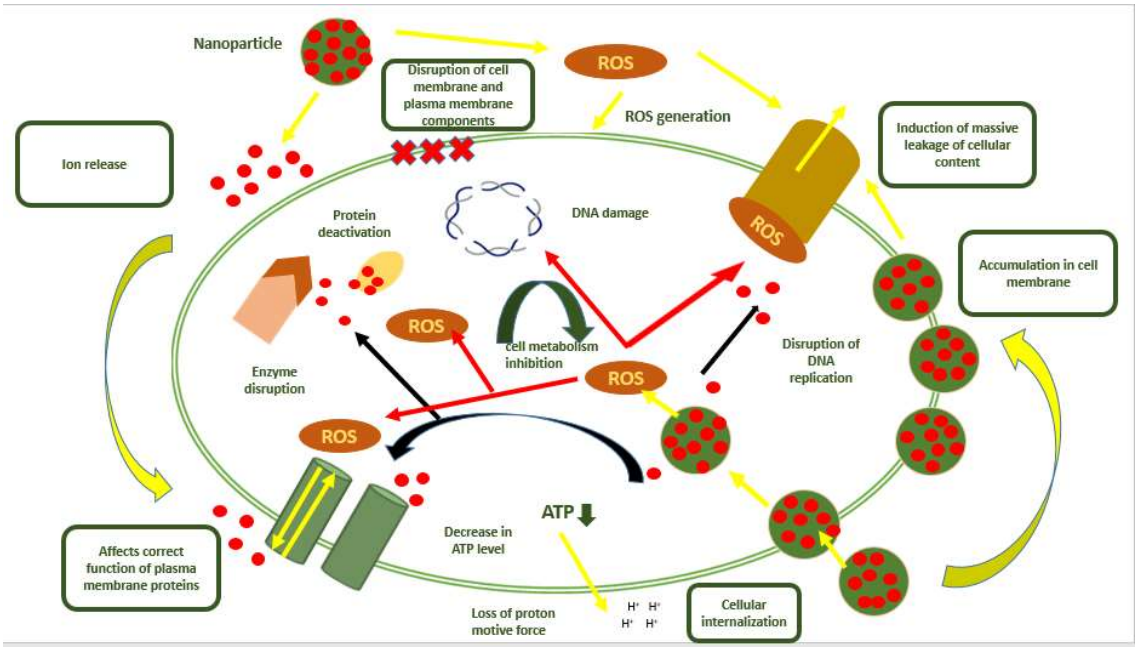

Figure 4: Nanoparticle-cell interactions: molecular structure of the protein and cellular outcomes [57]

3. The genetic material of the cell (nucleic acid) is damaged, which damages the cell's function and growth [55].

The main mechanistic function of nanoparticles under these conditions is not yet known, but various *in vivo* and *in vitro* studies suggest that they can produce reactive oxygen species (ROS), and therefore can play a role in intracellular calcium concentration, activation of

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transcription factors, and inducing changes in cytokines. ROS can damage cells in several ways, including damage to the DNA, interference with cellular signaling pathways, changes in the process of gene transcription, etc. [22] (Figure 5).

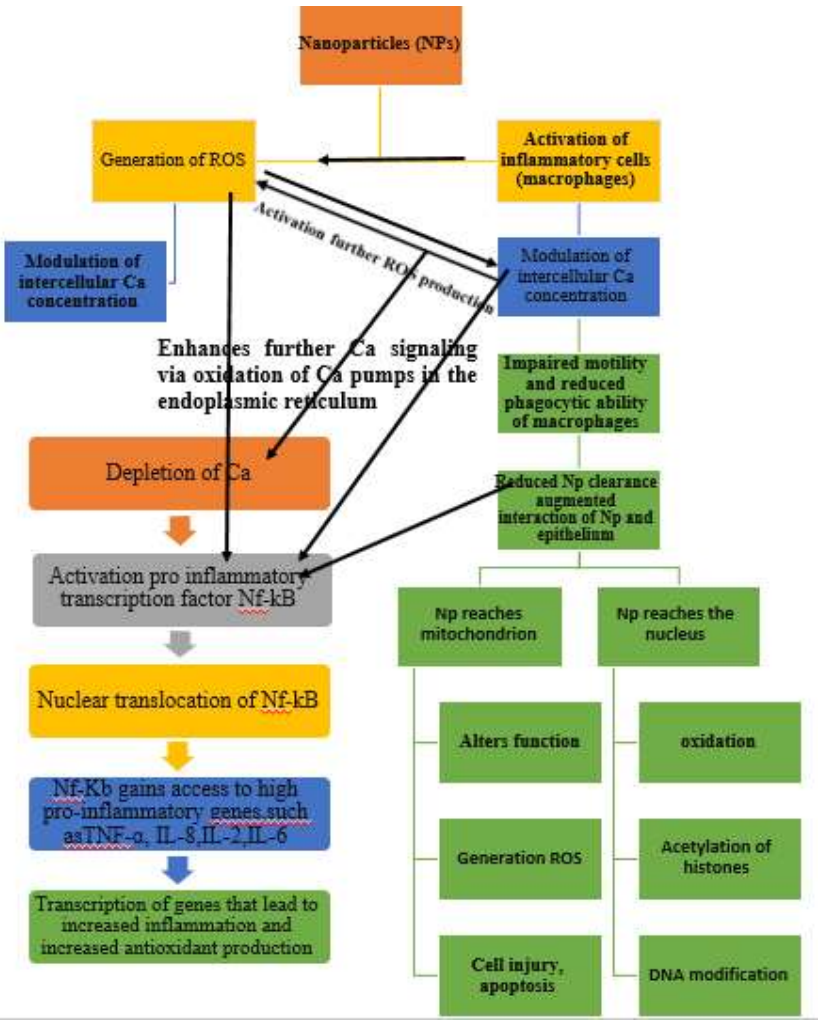

Figure 5: Entry of nanoparticles into the living cells.

The oxidative stress caused by nanoparticles can have several causes:

1- ROS can be produced directly from the surface of nanoparticles when both oxidants and free radicals are present on the surface of particles [58].

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2. Entering the mitochondria. Several studies have shown that very small nanoparticles can enter mitochondria and cause physical damage that results in oxidative stress [59].

3. Activation of inflammatory cells, such as macrophages and alveolar neutrophils that are involved in nanoparticles phagocytosis process. This can lead to the production of reactive oxygen and nitrogen species [10].

4- Metal nanoparticles (iron, copper, chromium, vanadium, etc.) can produce ROS.

Although some NPs, such as Ag NPs, are used as an antimicrobial agent because of this mechanism, incorrect use of these NPs can damage other cells instead of microbes. For example, Ag NPs can be used to disinfect wounds and prevent the growth of bacteria in that area. They can prevent bacterial growth and replication through the above mechanisms and heal the wound. But, it should be noted that the same NPs can also affect the cells of human body around the injury site and cause cell death (Figure 4).

5. The effects of physicochemical properties of NPs on cytotoxicity

In fact, a unique property of nanomaterials is their high surface-to-volume ratio which endow them with useful characteristics, but is ironically that trait is also associated with unique mechanisms of toxicity. Toxicity has generally been thought to originate from nanomaterials' size and surface area, composition, shape, and so forth as reviewed in the following sections.

5.1. The effect of NPs size on cytotoxicity

NP cytotoxicity is affected by changes in NP size [60] and is dependent on the surface-to-volume ratio [61]. Sedimentation velocity, mass diffusivity, attachment efficiency, and deposition velocity depend on the size of the nanoparticles [62]. The size of nanoparticles plays an important role in interacting with the biological system, and it has been revealed that various

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biological mechanisms such as endocytosis, cellular uptake, and particle processing efficiency in the endocytic path depend on the size of materials [63]. NP size affects the ion release rate, the smaller the size, the faster the release rate and the more the interaction with cell membrane; therefore, it will penetrate into the cell and induces higher toxic effect [64]. In general, size-dependent toxicity of NPs can be related to their ability to enter biological systems.

NP sizes of less than 50 nm administered through intravenous injection reach the tissues faster than 100-200 nm NPs and exert stronger toxic effects. If the size of NPs is reduced, their contact surface will increase and the level of oxidation and DNA damage will also rise. The size of NPs indicates their pharmaceutical behavior, that is, sizes of less than 50nm quickly connect to all tissues and exert toxic effects. NPs larger than 50 nm are used by the RES, which stops its path to other tissues. But again, organs like the liver and spleen are the main targets of oxidative stress.

The size of NPs has a direct effect on their physiological activity. NPs of size less than 1 μm enter the cell and their effects are unknown; those larger than 1 μm do not easily enter the cell, but they replace a series of proteins that are absorbed at their surface and react with the cell. Accordingly, the NPs size is effective in cell endocytosis [65]. For example, Kim et al. showed that the toxicity of Ag NPs in *in vitro* model on MC3T3-E1 and PC12 cells is size-dependent. NPs size and dosage affected cell viability as it produced intracellular ROS, released LDH, and changed the cellular morphology that induced smaller apoptosis [66].

5.2. The effect of NPs structure and shape on cytotoxicity

NPs come in a variety of shapes, such as spherical, rod-like, filament, and plate-shaped which influences their toxicity [67].

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The shape of NPs is effective in the membrane packaging process in endocytosis and phagocytosis [68]; endocytosis of spherical NPs is faster than tubular NPs [69]. Non-spherical NPs are more exposed to blood flow and have more toxic effects.

CNTs can be of single-walled CNTs (SWCNTs) or multi-walled (MWCNTs) class that affect their mechanisms on cell viability; SWCNTs produce more ROSs that MWCNTs [70]. The toxicity of nano-carbons was found to be dependent on shape and concentration [71]. TiO_2 NPs cause oxidative damage to DNA, induce lipid peroxidation and micronuclei formation in the presence of light, and these NP-induced effects change with shape [72].

5.3. The effect of NPs surface on cytotoxicity

Surface charge of NPs affects biological aspects such as absorption, colloidal behavior, plasma protein binding, and passage through the blood-brain barrier [73]. Negatively charged NPs have more cellular absorption than the positive and neutral NPs due to resistance by plasma proteins, which causes hemolysis and platelet aggregation and eventually toxicity.

NPs surface affects absorption level of ions and biomolecules that may alter cellular response. In addition, surface charge determines the colloid behavior which is the response of the organism to changes in NPs shape and size in the form of cellular accumulation. The effect of surface chemistry of NPs on human immune cells and RBCs in *in vivo* and *in vitro* models has been investigated [74]. For instance, the effect of silicon surface charge on cell lines reduced the ATP and genotoxicity for negative hydrophilic and hydrophobic charge relative to hydrophilic, positively charged amine-modified surfaces. The interaction between NPs and cells initially depends on the nature of NPs surface. The incubation of NPs with cells may interfere with cell adhesion, affecting cellular properties such as morphology, cytoskeleton, proliferation, and even survival. Of course, it is worth noting that the surface of NPs and the groups on their surface have a significant effect on adhesion. For example,

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bare iron oxide NPs with an approximate diameter of 50 nm have 64% less cell adhesion compared to polyethylene glycol (PEG) coated ones. This can be due to the difference in the interaction of NPs/cells with different charges in the presence or absence of surface-coating agents, while the metabolism of the nanotube function is different [75].

5.4. The effect of NPs concentration on cytotoxicity

The 2 mg/ml concentration of silicon had a toxic effect on the cell, but no toxic effect was observed in 4 mg/ml [76]. Varied concentrations of Ag NPs altered mitochondrial function and induced LDH leakage; the toxicity changed with changing concentrations, however [15] (Figure 6).

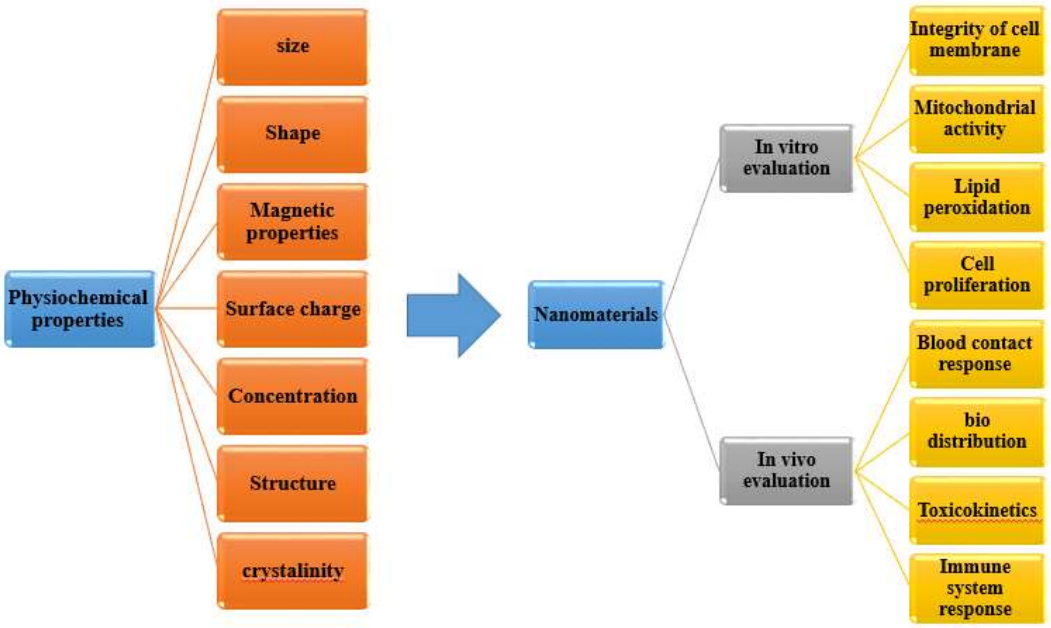

Figure 6. Physicochemical properties of NPs and evaluation of their effect on in vitro and in vivo. [77]

5.5. The effect of NP on the protein conformational changes

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A number of techniques such as nuclear magnetic resonance (NMR) spectroscopy [78], X-ray crystallography [79], circular dichroism spectroscopy [80], isothermal calorimetry [81], differential scanning calorimetry [82], fluorescence spectroscopy [83], and UV-visible spectroscopy [84] have been widely used for analyzing the protein-NP interactions. The NP-induced conformational changes and subsequent corona formation depends on several factors such as, protein type, NP type, size of NP, shape of NP, pH and the temperature.

Subtle changes in the structure of NPs affect their surface properties and subsequent interaction with proteins. The interaction of the single wall carbon nanotube (SWCNT) and multiwall carbon nanotube (MWCNT) of varying diameter with tau protein was investigated by different methods [85]. The circular dichroism bands of the tau protein after concentration variation of SWCNT showed a remarkable increase of β-sheet content indicating that the binding of tau with SWCNT causes the protein folding and more compact structure of natively unfolded structure of tau protein (Figure 7). Also, as shown in Figure 7, the binding of MWCNT has not altered the secondary structure of tau protein and has resulted in the protein aggregation. This study showed that SWCNT induced stronger interactions with tau protein, causing more pronounced structural changes [85]. Also, TEM observation showed that tau protein can bind to the surface of SWCNT thus dispersing it, whereas tau protein cannot attach on the MWCNT surface and eventually ends up in MWCNT agglomeration [85]. Surface functionalization of NPs can also influence the protein adsorption and subsequent NP-induced conformational changes. Protein surface residues form an interaction with energetically favorite counterparts on the NP surface based on their charge, hydrophobicity, and hydrophilicity [86]. Thermodynamic parameters can stipulate the kind of interaction between protein and NPs namely standard enthalpy change (ΔH°), standard entropy change (ΔS°), and standard Gibbs free energy change (ΔG°). For example, if ΔH° and ΔS° are negative, then the main interacting forces between NP and protein is hydrogen bonds and van der Waals interactions. However, if

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ΔH° is almost zero and ΔS° is positive, then the common involving bonds between NP and protein is electrostatic interactions (Figure 8) [87].

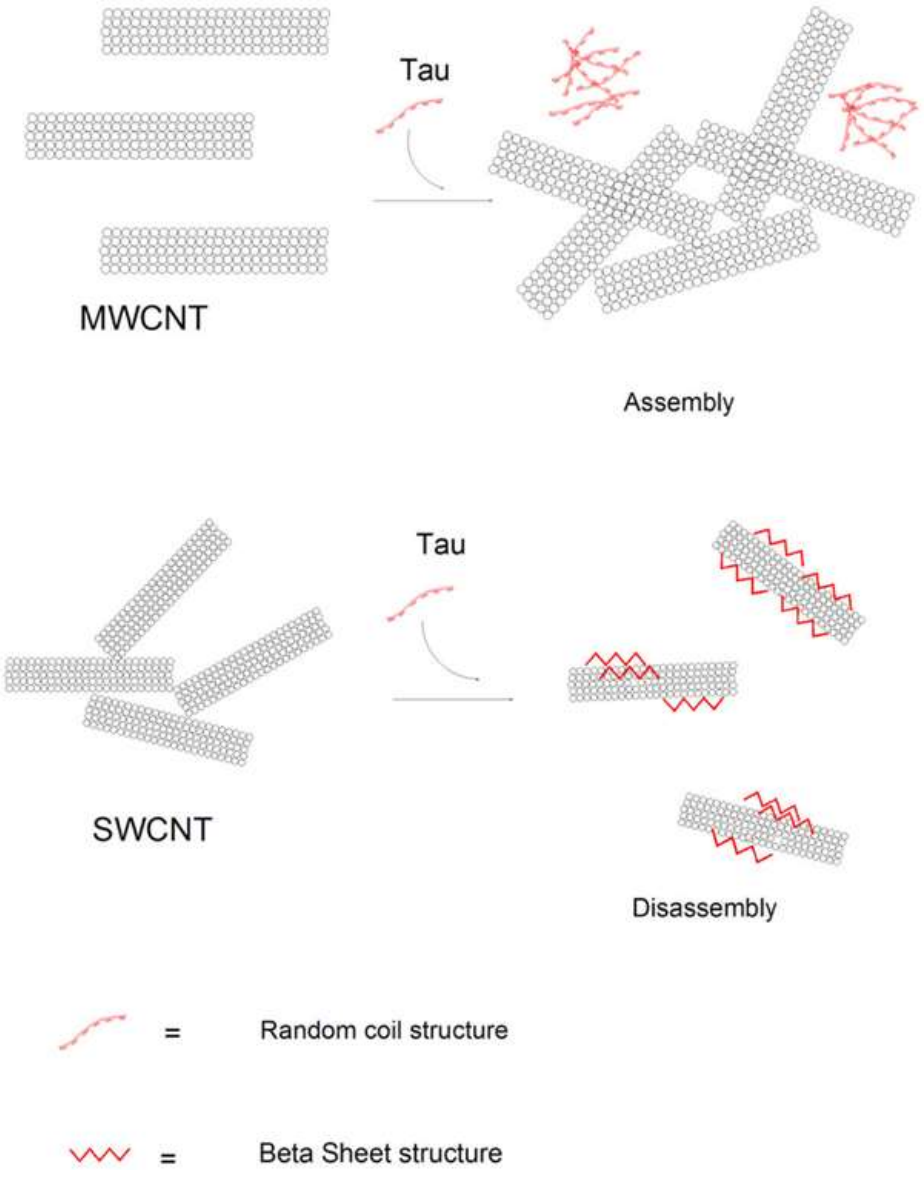

Figure 7: Schematic illustrating SWCNT-induced interactions with tau protein structure, resulting in pronounced conformational changes and corresponding denaturation compared to MWCNT [85].

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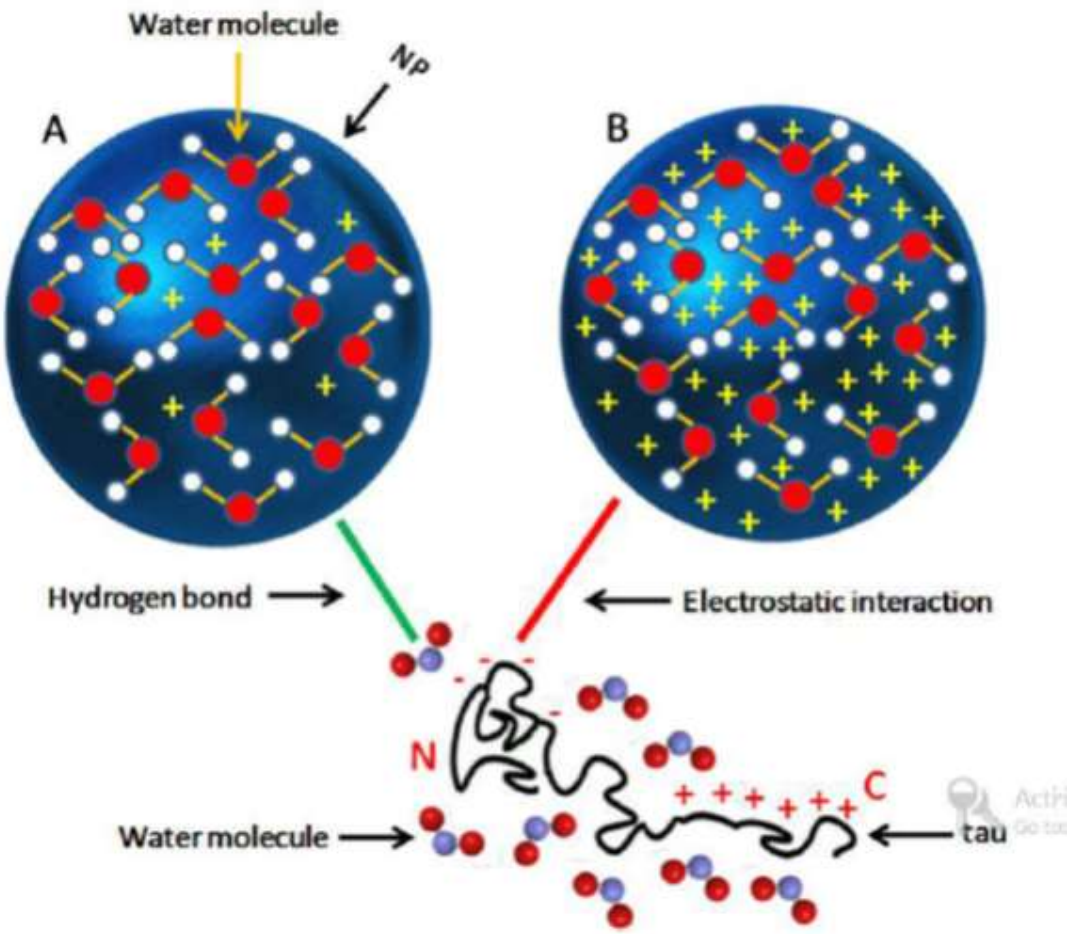

Figure 8. Schematic representation of interaction between Fe-NP and Tau protein; interaction based on the hydrogen bonding or electrostatic type. [87].

5.5.1. The effect of protein corona on the toxicity of NPs

After injection of NPs into the bloodstream, there is a competition between different biological molecules to interact with the surface of NPs (Vermann effect). In the first step, the smallest abundant proteins are adsorbed onto the surface of the NPs, however, over time, they are replaced by proteins with higher affinity [88]. The structure and composition of the protein corona depends on the physicochemical properties of the NPs, the physiological environment and the duration of exposure in that environment. Protein corona changes the size and surface

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composition of nanomaterials and provides them a new biological identity which determines the physiological responses including aggregation, cellular absorption, and the half-life of NPs in the blood, signaling synthesis, transfer, accumulation and toxicity. The corona on NPs is complex with no general protein corona specific to NPs. [89]. Albumin, immunoglobulin G (IgG), fibrinogen, and Apo lipoproteins are found in the corona of all studied NPs; these proteins are prevalent in the blood plasma and hence, over time, may be replaced by proteins with lower concentration but higher affinity on the surface of NPs. Molecules that are weakly attached to the NP and interact with it are soft coronas. NPs with a pre-formed agent group, such as PEGylated NPs, contain only one weak covering corona and no hard corona [90]. Protein corona reduces the toxicity of NPs by reducing their cellular absorption. In other words, NPs with less protein corona have more cellular absorption and are thus more cytotoxic. This phenomenon has been reported for CNTs [91], graphene oxide nanosheets [92] and biopolymer NPs in various cell environments [93]. In the case of common toxic nanomaterials, such as positively charge polystyrene NPs, protein corona has a protective role against membrane damage [94, 95].

5.5.2. The effect of protein corona on non-specific cellular uptake

The specific entry of NPs into the cell is accomplished by a receptor-specific ligand. Non-specific cellular uptake is a random process of the cell performed without biomolecular control. The amount of NP entry into the cell depends on protein corona. The non-specific cellular uptake of oligonucleotide-mediated AuNPs has been investigated which showed that their absorption significantly increased in an environment free of serum proteins [96]. Similarly, the cellular absorption of Fept NPs with QDs (QDs) is reduced dramatically in HeLa cells through the formation of protein corona [96].

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5.5.3. The effect of protein corona on bio-distribution of NPs

The nature of the NP's core, whether non-polymeric or polymeric, shows that pre-coating increases NP's persistence in the blood and reduces the clearance rate. A study disclosed that the life of BSA-coated nano drugs was 6 times more than that of non-coated ones [93].

5.6. The effect of surface charge of NPs on their toxicity

NP hydrophobicity and surface charge changes the biological distribution of NPs due to their effect on the level of interactions between NPs and the immune system, plasma proteins, extracellular matrix, and non-target cells. Hydrophobic/charged NPs are less persistent in the circulation due to the opsonization of particles by plasma proteins and ultimately by the RES system. Positively charged NPs are attached to negatively charged non-target cells in a non-specific manner; hydrophobic groups on the NP surface induce NP aggregation, which accelerates the identification and relocation by the RES system. In order to reduce this interaction, the surface of the particle is covered with hydrophilic PEG, which reduces the level of opsonization and hence increases particles' persistence in the circulation [97] (Figure 9).

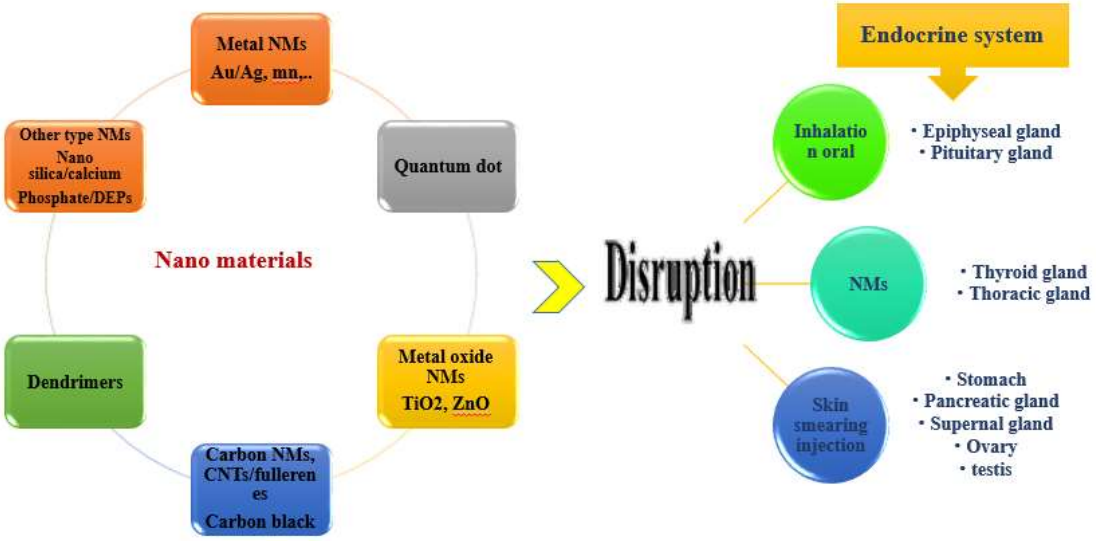

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Figure 9: Toxic effects of diverse types of nanoparticles on various organs

6. Toxic effects of diverse types of NPs on various organs

Table 1. *Toxic effects of nanoparticles on different organs/tissues.*

Target	NP	Concentration (time/size)/ route of administration	Major outcomes	cell	*In vitro* effect
Brain	AuNP	0.8-50 µg/mL (3, 5, 7, 10, 30 and 60 nm) (24 h)	No morphological changes could be detected after 24 h suggesting cytocompatibility of the NP tested. Only the smallest NP tested (3 nm) induced mild signs of cellular toxicity [98]	rBMEC (primary rat brain microvessel endothelial cells)	No morphological changes could be detected after 24 h [98]
		6–120 h post fertilization, 50 µg/ml		Zebrafish embryos.	Impact on nervous system development and/or visual and/or neuromuscular system[99]
	AgNP	6.25-50 µg/mL (25, 40 or 80 nm in size) (24 h)	Time- and dose-dependent rise in pro-inflammatory cytokine release and related rises in permeability and cytotoxicity of cells [98]	rBMEC (primary rat brain microvessel endothelial cells)	Time- and dose-dependent increase in pro-inflammatory cytokine release and correlating increases in permeability and cytotoxicity of cells.[100]
	Cu	30-50 mg/kg	BBB penetration [100]		
	AL	30-50 mg/kg	BBB penetration [100]		

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	CdSe	1,10,20 nm/24h		Primary rat hippocampal neuron cells in culture	Decrease in cell viability [101]
	(U) SPION	208 or 1042 µg/mL of: • Ferumoxtran-10 (20-50 nm) • Ferumoxytol (20-50 nm) • Ferumoxide (60-185 nm) (3 months) Intracerebral inoculation or Intra-arterial injection after BBB disruption	Direct inoculation of all 3 SPION agents led to the uptake into the CNS parenchyma. No pathological alterations were observed [102]	Murine neural stem cells (NSCs)	Depleted intracellular glutathione levels, altered activities of SOD and GPx, hyperpolarization of the mitochondrial membrane, dissipated cell-membrane potential, and increased DNA damage [103]
	TiO_2 ZnO Fe_2O_3 Al_2O_3 CrO_3	30-45nm/ 2-72h	leakage of lactate dehydrogenase (LDH) [104]	Neuro-2A	permeability of plasma membrane, apoptosis, cellular morphology, mitochondrial function [104].
	CNT	PEG-SWCNTs at	Accumulation in the hippocampus	PC12 cells	Decreased mitochondrial

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		concentrations of 0.5, 2.1 and 1 mg/mL	which induces oxidative stress [105]		membrane potential (MMP), induced the formation of reactive oxygen species (ROS) and increased the level of lipid peroxide and decreased the activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT) and glutathione (GSH)[106]
	QD	0.68 mg containing 50 nmol Cd (13.5 nm in size) (6 h) Intraperitoneal	Moderately high quantities of Cd ions was observed in brain tissue but no signs of inflammation or parenchymal damage were detected [107].	Neuron like PC12 cells	Cell death, toxic effect on axons, axonal degeneration [108]
Lung	AgNP	515 _g/m3 (6 h/day, 5 days/week for 13 weeks) Inhalation	Dose- and time-dependent increase in blood Ag NP concentration was observed along with correlating increases in alveolar inflammation and small granulomatous lesions [109]		
	Cu Zn CO	0.1-3300 µg/ml, 3 and 24 h		Human pulmonary cell line(lung	Increased ROS. [110]

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	Sb			adenocarcinoma epithelial cell line (A549))	
	Ag				
	Ni				
	Fe				
	CuO	0–40 µg/cm2		human lung epithelial cells (A549)	DNA damage [111]
	SPION	200–1000 µg/mL 24h	Increased cytokines and inflammation, TNF-α [112] .	Human lung epithelial cells (A549)	Activation of JNK, stimulation of tumor necrosis factor-alpha (TNFα), reduction of NF-kB, increased ROS [113]
	SWCNT	10-100 µg/mL (24 h, 48 h and 72 h)	Dose- and time-dependent decline in cell viability: up to 50% decrease at maximum dosage after 72 h. Oxidative stress was exhibited as a mechanism of cytotoxicity [114].	A549 human lung cancer cells	Low acute cytotoxicity was further reduced by dispersion of SWCNTs in serum. [115]
	QD	12.5µg, 7 days	Increased levels of LDH and albumin [116]	Human lung adenocarcinoma cells	Apoptotic and necrotic cell death [117].
Heart	AgNPAgNPs	100, 1000 and 10000 ppm a (period of 13 weeks)	Caused cardiocyte deformity, congestion and inflammation [118].	Catla heart cell line (SICH)	Increased lipid peroxidation (LPO) level and decreased level of GSH, SOD and CAT [119].
	Iron oxide NPs	100, 200, 300 and 500µg/ml a (period of 2 weeks)	Showed that baseline maximal oxidative capacities were proteins in the heart [120].	*cardiac* microvascular endothelial cells	Induced a concentration- and time-dependent cytotoxicity

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	CNT	1-0.3 mg/kg body weight	Blocks potassium channels. The suppressed and inhibited IK and potassium channels lead to increased heart rate [121].	Microvascular Endothelial Cells	DNA Damage, NP distribution was independent of concentration and time [122].
	QD			human hepatocellular carcinoma, HepG2 cells	Changes in mitochondrial morphology and structure, as well as impairing their function and stimulating their biogenesis [123].
Dermal	AgNP	50 and 100 µg/mL (24 h)	Mitochondria-dependent cellular apoptosis related to ROS at a concentration of ≥50 µg/mL [124].	A431 (human skin carcinoma)	No evidence for cellular damage up to a concentration of 6.25 _g/mL. Morphological changes at concentrations between 6.25 and 50 _g/mL with concomitant rise in GSH, SOD and lipid peroxidation. DNA fragmentation suggests cell death by apoptosis[125].
	TiO2	15 µg/cm^2 (24 h)	Cytotoxicity was detected to be affecting cellular functions like cell proliferation, differentiation and mobility leading to apoptosis [126].	HaCaT (keratinocyte cell line), human dermal fibroblasts, human immortalized	Cytotoxicity was observed to be affecting cellular functions such as cell proliferation, differentiation and mobility resulting in apoptosis [127].

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				sebaceous gland cell line (SZ95)	
	Fe_3O_4	65nm		Skin tumor cells	Increases ROS, removes cancer cells [128]
	CNT	10 μg/mL 72 h	Induction of oxidative stress and cellular toxicity by accumulation of peroxidative products. Increased interleukin, (IL)-8 release, and a decline in cell viability [129].	Human Dermal Fibroblast Cells	DNA damage and programmed cell-death [130].
	QD	4.6 nm core/shell diameter QD for 8 h and 24 h	Increased cell release of IL-1b, IL-6, and IL-8.These results indicate that surface coating of QDs does not affect the uptake by keratinocytes but is a main determinant of cytotoxicity and immunotoxicity [131].	Human epidermal keratinocytes (HEKs)	Increased IL-1β, IL-6, IL-8, and TNF-α concentrations [132]
Liver	AgNPs	10, 50, 100, 150, 200, 400 ppm for 24 h	Decline of cell viability [133].	Primary mouse fibroblasts, primary hepatocytes	NPs enter cells which results in the production of mediators of oxidative-stress. However, protective mechanisms could be observed which

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					increase GSH production to avoid oxidative damage [134].
	Cdse	62.5-1000 µg/ml/1-8h		Primary rat hepatocytes	62.5 µg/ml, cytotoxicular oxidative, photolytic conditions. No toxicity was observed when adding ZnS cap [135]
	ZnO NPs	100, 300, and 600 mg/kg. Allowed for 7 days	The cytotoxic potential of ZnO NPs in mammalian cells [136].	Human hepatocyte (L02)	Cellular morphological modifications, mitochondrial dysfunction. Inducing reduction of SOD, depletion of GSH, and oxidative DNA damage [114].
	Al_2O_3	235,245ppm	Blood cell and melanomaxicophage accumulation, hepatocyte necrosis, vaculation and portal vein alteration [137]		
	TiO_2	5, 10, 50, 100, or 150 mg/ kg daily for 14 days.	SOD, CAT, and GSH-Px keep ROS at low levels and successfully protect cells from the toxic effects [136].	Rat liver derived cell line (BRL 3A)	Depletion of GSH level, reduced mitochondrial membrane potential increase in ROS levels [15].
	CNT	Concentrations ~25 µg/cm^2	Production of apoptotic signals [138].	Human hepatoblastoma C3A cell line	DNA damage, increased intracellular ROS and IL8 [139]

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	QDs	62.5, 250 and 1000 _g/mL (24 h)	Reactive oxygen species (ROS) and other free radicals are important intermediates in the typical physiology and pathophysiology of the liver [140]	Primary rat hepatocytes	Cytotoxicity was thought to be due to the release of free cadmium ions which could not be fully eliminated by ZnS coating of the OD core [135]
Kidney	Au nano-particle	5, 10,100 ppm Au via IP injection for 7 successive days	Increase levels of CREA, UREA, total bilirubin ALP in rats' blood serum were examined to show a degree of kidney functionality [141]	Embryonic kidney cells (HEK293).	Toxicity was dose dependent. In a dose of 44 mg ml_{-1} for 4 h, toxicity was observed on DNA/transferrin [142]
	ZnO NPs	100, 300 and 1000 mg/kg in 2 weeks	Significant increase in serum creatinine and blood urea nitrogen, decrease in hemoglobin, haematocrit and mean corpuscular hemoglobin concentration, and overt tubular epithelial cell necrosis [143].	Human embryonic kidney (HEK293) cells	Lead to cellular morphological modifications, mitochondrial dysfunction, and cause reduction of SOD, depletion of GSH, and oxidative DNA damage [114]
	CuO NPs	A dose of 10 mg/kg three times a week up to 19 injections	DNA (RAPD) test for DNA fragmentation. [144]	Embryonic kidney cells (HEK293)	Increased ROS, decreased cell viability [145]
	TiO_2	1, 10, 100 µg/ml	Embryonic kidney cells		DNA damage and genomic toxicity [146]
	CNT	4mg/kg seven days	IL-8 production, LDH release, and lipid peroxidation increased more considerably and glutathione levels declined in cells	Embryonic kidney cells (HEK293)	Decreased cell viability, cell membrane damage (lactate dehydrogenase activity (LDH) assay), reduced

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			exposed to MWCNT2 as compared to those exposed to MWCNT1 [147]		glutathione (GSH), interleukin-8 (IL-8), lipid peroxidation [148]
	QD	1.5 µmol/kg at 1, 7, 14, and 28 days	Changes appeared in MDCK cells, toxicity by ABC transporters. [149]	Embryonic kidney cells (HEK293)	Time-dependent decrease of mitochondrial transmembrane potential, Bcl-2 expression, alleviated apoptosis [150]
Splee n	AgNPs	For 28 days of oral administration of 30, 300 and 1,000 mg/kg doses of AgNPs (60 nm)	AgAg induces the permeability of cell membrane to potassium and sodium and interrupts the activity of Na-K-ATPase and mitochondria. Inhibition of NF-kB activity, a decrease in bcl-2, and an increase in caspase-3 and survivin expression [151, 152]		
	Fe_2O_3	0.1, 0.5 and 1.0mg/L (9.2×10(-4), 4.6×10(-3) and 9.2×10(-3) mM) aqueous suspensions for 60days	Majority of them were accumulated in the spleen [153]		
	CNT	1.5 ml; 2 mg multi-walled (MW) CNT	Promotes allergic responses,		

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		per body weight (bw)] 1, 6, 24, 48 and 144 h	aggregation in spleen.		
	QD	6000 g for 10 min,	Distribution in different body organs [154-156]		
Stomach	AgNPs	28-day repeated oral dose of AgNPs of 60 nm, 2.6 mg Ag/kg b.w./day	Aggregation in stomach tissues [157]		
	Au NPs			Gastrointestinal cancer cells	Removing tumor cells from healthy cells [158]
	Cdse	0.84×10^5 µm		Human colon carcinoma cell line	Removing tumor cells from healthy cells [159]
	TiO_2 NPs	1012 particles/person per day in 2 weeks	Aggregation in stomach tissues [160].		
	ZnO NPs	5, 50, 300, 1000 and 2000 mg/kg b.w	Aggregation in stomach tissues [161].		
	CNT	<5 µm, 10–20µm in 7 days	Inflammation [162];[163-165]		
	QD	2 to 200 nmol/ml within 24 hour	Induces much higher amount of ROS and cell death [166]		

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Pancreas	Ag NPs	24 h exposure to AgNPAgNPs (100 µg/ml)	Increased the level of reactive oxygen species [167].	Pancreas cancer BxPC-3 Cells	Inhibition of NF-kB activity, a decrease in bcl-2, and an increase in caspase-3 and survivin expression [168].
	AuNPs	50 nm, 2.5 mg/kg, Male Wistar diabetic with autism spectrum disorder pups, ip. 7 day	Reverse of oxidative stress, damage in pancreatic B cells[169]		
	cobalt ferrite NPs			human pancreatic cancer cells	Accumulation in cells, apoptosis [170].
	ZnO NPs	0, 500, 1,000, and 2,000 mg/kg/day for 14 days.	Decreased body weight, feed consumption, HB, HCT, MCV, MCH, MCHC, and LYM and increased WBCs, NEUs, ALP, and histopathological alterations in the pancreas[171].		
	TiO_2	42 days		Pancreatic cancer	Tumor growth inhibition, cell toxicity [172].
	CNT	Application of 5, 10 and 50 µg/mL doses on pancreatic cancer cells (PANC-1)	Hyperthermia; necrosis of malignant cells [173]		
	QD	0.2mL after 7h.	Enhanced the generation of		

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			reactive oxygen species [174]		
Ear	AgNPs	4000 µg/ml AgNPs induced hearing loss with partial recovery within 7 d	Impairment of the mitochondrial function [175]	BALB/c 3T3 cell line	Impairment of the mitochondrial function [175]
	SPION	150 µL of 15 mg/mL 1,2,4 h, 4 and 7 days	Uptake into the CNS parenchyma [176]		
	CNT	150 µL of 15 mg/mL 1,2,4 h, 4 and 7 days	Lead to the uptake into the CNS parenchyma. No pathological alterations were observed[177].		
	QD	1 mg/mL or 4.5 mg/mL) after 24 h	Limb abnormalities, body wall defects, neural tube defects[177]		
Eye	AuNPs	2,20 and 200 nm, 72h	Cell death or developmental growth [178]	Human corneal cells	Apoptosis, aberrant expression factor pigmentation, development (pax6a, pax6b, otx2, and rx1) and pigmentation (sox10). [178]
	Iron oxide	2, 20 and 200 nm, 72h	Cell death or developmental growth [178]		

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	Silica NPs	50, 100 and 150nm sizes / 48 h		Human corneal epithelial cells (HCECs)	Cellular reactive oxygen species generation [179].
	CNT	Up to 750 nm every week for 9 weeks	Eye-irritation, retinal degeneration [180]		
	QD	17 weeks of age, in the range of 2.7–3.6 kg in body weight	Eye-irritation, retinal degeneration [181]		

6.1. Brain targets

The structure of the brain is maintained by the BBB, which protects the Cerebrospinal fluid (CSF) to prevent the entry of pathogens. This organ, in contrast to the liver which is protected by various barriers, has only this protection barrier. The capillaries surrounding the brain are protected by tight intercellular joints, but materials that can overcome this barrier have the ability to damage the brain through their toxicity. Today, for the treatment of diseases such as Parkinson's it is necessary to pass the drug through this barrier. Drug for such diseases is thus delivered using NPs which can cause damage to the central nervous system (CNS), affecting epithelial cells of the cerebellum by inducing oxidative stress. The use of oxide NPs has a special place in restorative dentistry besides other NPs metal oxides such as zirconium oxide NPs. These particles have high strength and transparency relative to light but prevent the passage of X-rays, so they are ideally suited in cases where the filled teeth are treated with UV radiation. Using NPs with plasma laser in dentistry has interesting results because of the variation in TiO_2 size [182]. This NP is reduced to nano level (20 to 50 nm) and is applied to

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the skin in the form of emulsion gels [1]. NPs was found in lung, blood, bone marrow, kidneys, liver, intestine, femur, thymus, gut, heart, spleen, and brain which TiO2 penetrate BBB [183].

When these particles are exposed to laser pulses, particles are disintegrated and show a collective effect [1]; ensuing particles turn into smaller particles again inducing immediate kinetic movements. Therefore, this process can be used in the micro exfoliation of hard tissues; in addition to increasing speed and accuracy, the protocol is cleaner, smoother, and without the need for anesthesia. Metal NPs such as Ag NPs have healing and anti-inflammatory effects and they are invariably present on the wound healing list. Ag NPs disturb the balance of plasma membrane potential, resulting in decreased intracellular levels of adenosine triphosphate (ATP) [98, 184]. This is achieved by targeting the cell membrane of the bacteria which causes its death. Au NPs increase the radiotherapy efficiency in cancer patients as they penetrate cancer cells and increase energy absorption. Most cancer patients undergo radiotherapy during their treatment [185, 186]. Cancer cells need high amounts of folic acid due to their rapid growth. Hence, Au NPs with folic acid molecules attached onto their surface are absorbed by cancer cells on exposure because they have a small size and have an active agent on their surface. During radiation, when cancerous cells are exposed to photons, a certain phenomenon, called photoelectric effect, occurs which absorbs a significant amount of the colliding radiation [187]. One of the main points of focus in diagnostic medicine is molecular imaging. NPs allow us to effectively depict and capture various components of a molecule with high contrast [184]; study discusses various factors that should be considered when synthesizing contrast NPs and highlights some of the most important examples. The production of new contrast agents

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especially for molecular imaging and cellular process detection benefits from the use of NPs. Advantages of using these NPs include the ability to produce high contrast, ease of integration of multiple properties, persistence in the circulation, and the ability to carry materials with high volumes (such as medication). The principles and methods of producing NPs have extensively developed over the past years, hence more complex examples of nano-sized contrast agents have been reported, such as paramagnetic particles, macrophages with QDs, QDs, and machines that can deliver materials to the atomic and molecular levels.

MRI of micro emulsions is used for examining the vessels and drug delivery [181]. CNTs are among the nano-carbon structures that, due to their hollow and small structure (smaller than red blood cells), play a special role in the field of medicine, such as drug delivery to target cells, bio-sensoring blood glucose, detecting and destroying cancerous cells, tissue engineering, and so on. Recent studies have shown that CNTs can be used for biological purposes, such as crystallization of proteins, and the production of bioreactors and biosensors. The intrinsic fluorescence properties of nanotubes make them suitable biosensors for identifying specific targets in human body tissues, such as cancer tumors. Numerous methods have now been devised to connect DNA molecules and proteins to the internal and external surfaces of nanotubes; this enhances the ability to target and destroy single cancer cells or viral infectious cells [180]. The assembly of special enzymes to nanotubes has resulted in their widespread use as enzymatic biosensors, which allows the identification and measurement of a variety of biological molecules most widely used in the rapid measurement of blood glucose. Recently, the use of CNTs in tissue engineering has attracted the attention of researchers; the key role of CNTs in the culture of tissue cells such as fibroblasts is such an example [180].

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6.1.1. Metal NPs

AuNPs

AuNPs have the potential to connect to the CNS cells and induce toxicity. Brain micro vascular endothelial cells (BMECs) are among those important cells that can attach to NPs [188]. This increases cytokines expression such as TNF-α, IL-β, and IL-2, which cause inflammation in the brain. The toxicity of AuNPs depends on the dose, concentration, shape, and exposure time. For example, with regard to the particle diameter used for neuroimaging, 3 nm particles are found to be more toxic than 5 nm, indicating that the toxicity for brain cells is size-dependent [189].

The reason is that smaller NPs have a higher permeability to the brain and are easier to pass through the BBB. No morphological changes have been reported for the dose range of 0.8-50 μg/ml, diameters of 3, 5, 7, 10, 30 and 60 nm, and exposure time of 24 h; 3 nm diameter only induced cell cytotoxicity [184]. The toxicity of Au NPs on primary rat brain microvessel endothelial cells (rBMEC) showed that these NPs had different effects in different sizes, so that smaller NP sizes had higher toxicity NPs with a diameter of 3nm caused morphological changes in the cell [98].

*Ag NP*s

This class of NPs is widely used today in drug delivery and antibacterials systems as they have neurodegenerative potential by damaging mitochondria and DNA conjugates of Au NPs with drug molecules could improve drug efficacy; drug molecules can directly conjugate with Au NPs via ionic or covalent bonding, or by physical absorption. As an example, 13 nm colloidal Au has been combined with methotrexate, an anticancer drug. The carboxylic groups appended

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to the surface of 30 nm Au NPs after overnight incubation or doxorubicin (DOX) through a pH-sensitive linker enables the increase in intracellular DOX concentration, thereby enhancing therapeutic effects. The surface of Au NPs can be modified by using polyethylene glycol (PEG) as a spacer. The amphiphilic characteristics of polymers ensure excellent stability of Au NPs under physiological conditions and provide numerous possibilities for Au NPs [190, 191]. Like AuNPs, AgNPs induce tight junction disruption and astrocyte neurotoxicity in a rat blood-brain barrier and induce cerebral edema [192]. AgNP toxicity is size-dependent so that a size of 25, 40 or 80 nm and a concentration of 6.25-50 µg/mL, and exposure time of 24 h increases inflammatory cytokine, cell permeability and cell toxicity. These types of NPs are distributed systemically and precipitate in different tissues based on their size. By producing Ag^{+}, AgNPs increase serotonin and dopamine neurotransmitters and increase anxiety [98].

The toxicity of Ag NPs on primary rBMEC is dose- and time-dependent; increased NP and cell co-culture time induced increased the expression of inflammatory factors and increased cell penetration [98]. Intravenous and intraperitoneal injection of Ag, Cu, and Al NPs of 30-50 µg/ml in mice caused BBB penetration [98]. The toxic effects of CdSe on hippocampus neuronal cells of the rat at 1, 10, and 20 nm for 24 h reduced cell viability; the toxicity was dose- and time-dependent [101].

6.1.2. Metal oxide NPs

SPION is approved by the FDA and is used in MRI for neuroimaging. One of the toxic side effect reported is that it causes cancer [193], and increases LDH, ROS, and ROS-mediated neuronal damage [194]. It is important to know when and where the coating material, which is effective in causing toxicity, breaks as a result of chemical reaction; coating materials include

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ferumoxytol and ferumoxidem dextran. The strength of these materials is very important; concentration of 208 or 1042 μg/mL of ferumoxtran-10 in sizes of 20 to 185 nm and exposure duration of 3 months caused permeability through the BBB and penetration into parenchymal tissue [102]. The FDA approved SPION has been used in sizes of 20-50 nm to kill tumors in *in vitro* studies on brain cell-line which could destroy the cancer within 5 days [102]. The oxidizing NPs like (U)SPION caused toxicity on murine neural stem cells (NSCs) in the form of increased levels of glutathione, changes in the activity of SOD and GPX, mitochondrial membrane hyperplasia, destruction of cell membrane, and increased DNA damage [103]. One study examined the toxicity of oxide NPs (TiO_2, ZnO, Fe_2O_3, Al_2O_3, CrO_3) at 45-30 nm exposed to neuro-2A cells for 2-72 h; toxicity was observed was found to be related to the morphological changes in the cell, changes in mitochondrial function, increased membrane LDH, plasma membrane penetration, and apoptosis [104].

6.1.3. Carbon-based nanostructures

In vivo studies generally show good compatibility of CNTs with neuronal tissues; intravenous injection of ^{13}C-enriched CNTs in mice showed that NPs of 10-30 nm can pass through the BBB. Intraperitoneal injection of a concentration of 68 mg containing 50 nmol of Cd with a diameter of 13.5 nm within 6 h resulted in Cd accumulation but no damage to the brain. These NPs can accumulate in the brain tissue and exert a toxic effect [195]. Research has shown that PEG-SWCNTs at concentrations of 0.5, 2.1 and 1 mg/mL, present in cellular scaffolds in tissue engineering, can accumulate in the hippocampus and cause oxidative

stress [105]. Therefore, the toxicity of these NPs is concentration-dependent and they are precipitated in the CNS. The toxic effects of carbon NPs on PC12 cells were decreased

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mitochondrial membrane potential (MMP), induced formation of reactive oxygen species (ROS), increased levels of lipid peroxides, and decreased activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), and glutathione (GSH) [106].

6.1.4. QDs

The primary application of QDs is now in the field of photography and disintegrating biological compounds. Their additional applications include marking single molecules and optical tracking of their behavior. In these methods, QDs act as chemical marks. Biological molecules, such as antibodies, bind to QDs which makes QDs attach, in a purposeful and specific manner, to target molecules or target cells whose surface is covered by supplemented antigens. The binding of antibodies on the surface of QDs to antigens attached to the surface of these specific cells or proteins results in the emission of light from QDs. If there is no target cell or protein in the sample, no emission will be observed (Figure10). Therefore, optical tracking of cells or biomolecules is possible over an extended period of time. It should be noted that QDs are extensively used in the detection of cancerous tumors. It passes through the BBB pathway and through trigeminal nerve or olfactory epithelium. CdSe/Zn NPs with a diameter of 13 nm have the ability to reach tumor tissue in laboratory mice. Six days after the injection, brain nuclei were isolated and Cd was observed in the brain tissue, but there was no indication of astrocyte damage and nerve inflammation. However, the toxicity of this particle for the nerve tissue needs further investigation. QD toxicity is size-dependent; sizes below 20 nm accumulate in the brain parenchyma. *In vitro* studies used these NPs to target brain tumors in the cell-line, which in the long term were able to reduce the volume of cancer cells [107]. The toxicity of QD NPs on neuron-like PC12 cells has been examined which showed that these NPs cause cell death and axon damage [108].

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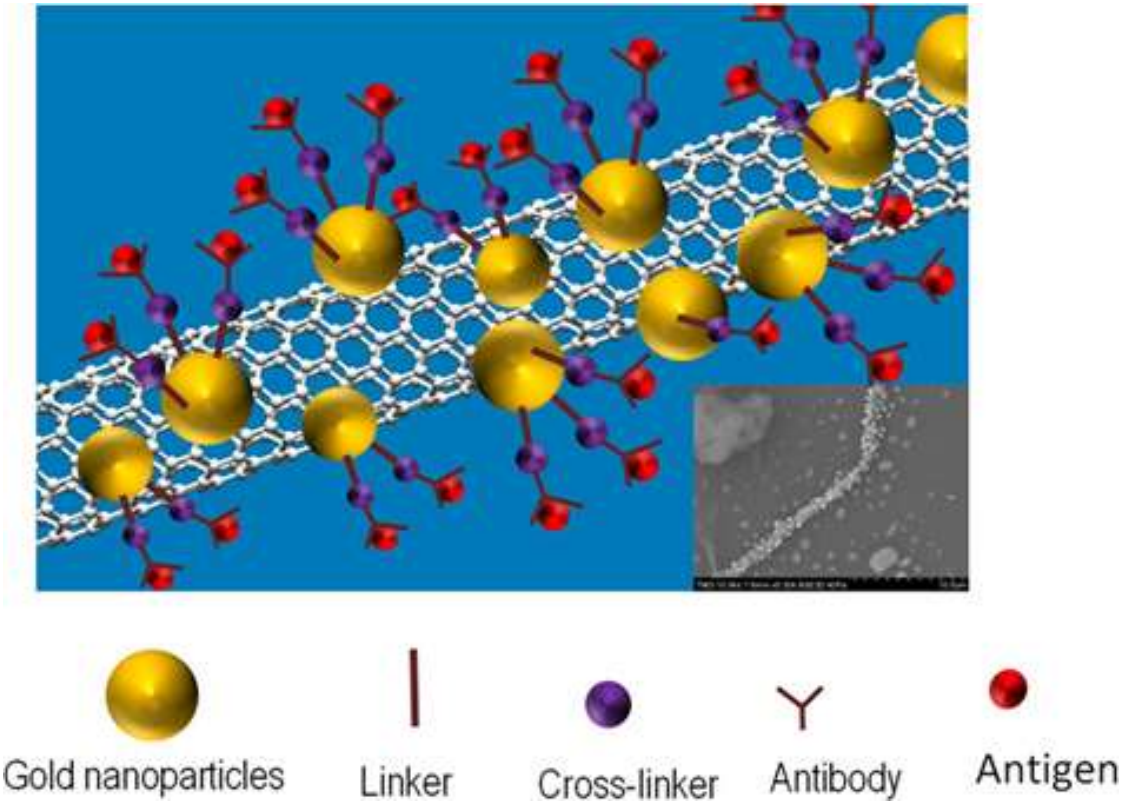

Figure 10: CNT decorated with gold nanoparticle for plasmonic detection. [196].

6.2. Lung target

One of the properties of NPs entry (into tissues) is their ability to transfer a drug. There are various ways to transfer a drug into body such as injection, skin contact, inhalation, and oral entry. For inhalation drugs, the most important tissue to pass through is the lungs. Due to their large size, the lungs are a good target to accumulate NPs and cause toxicity [197].

6.2.1. Metal NPs

Various studies have reported Ag NP-induced inflammation as the most important damage to the lungs. The toxic effect of Ag NP on laboratory animals has been investigated; the toxicity being dependent on diameter. NPs with 20 and 110 nm were compared; after 7 days they increased BALKC, CCL11, and IL-13 in the lung tissue of rats and rabbits. As oxidative stress

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occurs following inflammation, the level of malondialdehyde in the lung tissue reduces and ROS level increases [198].

The toxicity of metal NPs such as Cu, Zn, Co, Sb, Ni, Ag, and Fe on lung cells (lung adenocarcinoma epithelial cell line (A549) was investigated at the concentration of 0.1-3300 µg/ml and exposure time of 3 and 24 h; these NPs increased ROS [109, 110] .

6.2.2. Metal oxide NPs

Like metal NPs, the most important damage of TCL-SPION is inflammation [199]. Examples of these NPs are ZnO and CuO which have a damaging effect on the immune system in the lung tissue by increasing IL-1β; they also increase cytokines expression because they change pH in the tissue [200, 201]. Other studies have reported the toxic effect of CeO_2 and NiO NPs on lung tissue to be the expression of TNF-α in the lung cell-line[202].

The study of SPION cytotoxicity on human lung epithelial cells (A549) showed that these NPs trigger activation of c-Jun N-terminal kinases (JNK), stimulation of tumor necrosis factor-alpha (TNFα), reduction of NF-kB, and an increase of ROS [113].

6.2.3. Carbon-based nanostructures

The most important damages to the lung tissue by carbon NPs are oxidative stress, neutrophilic inflammation and genotoxicity inducing asbestosis, fibrosis, and lung tumor [203]. In rats, the toxicity of these NPs includes neutrophilic inflammation, granulomatous inflammation, cytokine production, thickening of the tissue, and fibrosis [204]. In the cell-line, it produces ROS, H_2O_2, $HO^{\bullet}$, O^{2-}, and RNS and directly causes cell inflammation. At a concentration of 10-100 µg/ml and exposure time of 24 to 72 h, it showed that the toxicity was dependent on dose and time and caused oxidative stress [205]. The study of the effect of carbon NPs on A549 human lung cancer cells indicates that these NPs cause acute toxicity in lung cells [115].

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6.2.4. QDs

Cadmium selenide nano crystals are highly toxic under ultraviolet light. In fact, the energy of ultraviolet light is as much as the energy of the bond between cadmium and selenium which leads to the release of cadmium ion into the cellular environment in the cell-line. In the absence of ultraviolet light, they will be non-toxic if the QDs are covered with polymer coatings. This toxicity affects lung tissue. In animal studies, a dose of 12.5 µg for 7 days resulted in elevated LDH and albumin levels [206]. QDs, inorganic semiconductor nanocrystals, have become one of the most attractive tools for bioimaging and cancer therapy. Studies have shown that QDs with a cadmium selenide (CdSe) core induce cell death by increasing reactive oxygen species (ROS) and inhibiting survival related signaling events. QDs also induce apoptosis via mitochondrial-dependent pathways involving Fas upregulation and lipid peroxidation in human neuroblastoma cells. Previous studies focused on the toxicity of quantum NPs at the level of human lung adenocarcinoma cells and found that these NPs induce cytotoxicity in the form of apoptosis and necrosis [117].

6.3. Heart targets

As one of the entry routes of NPs is through air into the respiratory tract which can affect the heart and circulatory system, today it has been reported that workers and those working in industries that use NPs are more susceptible to arterial cramps. Therefore, researchers have focused their attention on identification of damage and the type of toxicity of NPs on the heart [118]. Nano materials (NM) long-term exposure caused cardiovascular, cancer diseases and increase ROS, inflammation, and genotoxicity [207].

6.3.1. Metal NPs

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AgNPs have been extensively used in diameters of size less than 100 nm. A study examined the toxicity of AgNPs in various concentrations of 100, 1000 and 10000 ppm in the circulatory system of pigs; acute toxicity was discerned within 13 weeks and the pathological examination of heart tissue revealed inflammation. The administration of various Ag NPs (100, 1000 and 10000 ppm) adversely impacts the heart, especially in medium- and high-dose Ag NPs treated groups when compared with micron sized Ag as determined via histopathological analysis. Some reports have proved that medical devices loaded with silver could release silver ions (Ag^{+}) which could translocate in blood circulation and accumulate in some organs. It has been suggested that the administration of AgNPs, in doses of 0.1 mg/kg (100 mcg) were not safe dose for dermal application[118]. The study of cytotoxicity of AgNPs on catla heart cell line (SICH) showed that they increase lipid peroxidase (LPO) and reduce the level of GPx, CAT, and SOD [119].

6.3.2. Metal oxide NPs

Iron oxide NPs (IONs) affect the mitochondrial respiratory chain of the heart and increase the ROS, which changes the oxidative capacity of the cell. Studies have investigated the effect of 100, 200, 300 and 500 µg/ml concentrations of Fe_3O_4 and it was revealed that its toxicity was concentration-dependent; higher NP concentrations reduced oxidative capacity and increased ROS in the heart [120].

The examination of the cytotoxicity of iron oxide NPs on cardiac micro vascular endothelial cells showed that these NPs induced higher levels of LDH, but the cytotoxicity of this NP increased with increasing dose and time. In fact, cytotoxicity was both, dose- and time-dependent [208].

6.3.3. CNT

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CNTs which are used today in the manufacture of cellular scaffolds and tissue engineering as well as in the circulatory system can cause significant toxicity in this organ. Studies showed that CNT increases the heart rate of rats and blocks the potassium channel leading to impaired blood pressure and uncoordinated heartbeat [121].

The study of cytotoxicity of carbon NPs on micro vascular endothelial cells showed that they induce DNA damage; cytotoxicity in these NPs was dependent on dose and time [122].

6.3.4. QD

CdTe-QD is another type of NPs used in the industry whose toxic effects have been evaluated [209] which include mitochondrial respiratory chain disturbance, ATP reduction, and decreased cellular calcium levels. Due to the accumulation of cadmium ion in mitochondria, its morphology changes causing disruption of mitochondrial pathway genes and cell biogenesis [123]. These in turn can alter the rhythm of heart rate and cause artery occlusion.

6.4. Dermal targets

The skin is the largest organ in the body that protects all tissues from damage and entry of pathogens. The entry of toxins and NPs through the skin into circulatory pathway creates side effects. When NPs are smaller than cells and cellular organelles, they can easily penetrate these components. The skin is composed of three layers of epidermis, dermis and fat. Absorption of NPs through the skin is controversial but several studies have shown the penetration of NPs through the external protein of the epidermis, hair follicles, or epidermal holes, and the damaged skin which increase skin sensitivity [210].

6.4.1. Metal NPs

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Skin is the largest target organ for AgNPs due to exposure to cosmetic products containing AgNPs and expectedly several studies have examined their toxicity on the skin and hepatocytes. One study showed that AgNPs have a toxic effect on skin cells [118]; most important toxicity being the increase in ROS, skin inflammation, apoptosis, and DNA damage. Even a study of special wound dressing, impregnated with AgNPs, showed that AgNP can cause skin discoloration and oxidative stress [211].

The effect of AgNP cytotoxicity on A431 (human skin carcinoma) showed no evidence of cellular damage up to a concentration of 6.25 µg/ml. However, morphological changes were observed at concentrations between 6.25 and 50 µg/ml with concomitant increase in GSH, SOD, and lipid peroxidation. DNA fragmentation also suggests cell death by apoptosis [125].

6.4.2. Metal oxide NPs

One of the most widely used metal oxide NPs that has UV-blocking properties is TiO_2 which is essential component of sunscreens. Studies have reported its toxic effect on the skin to be apoptosis of hepatocyte cells. Other studies concluded that TiO_2 NPs penetrates through hair follicles and dermal layer of the skin to the lower surface where it reaches skin cells thus causing apoptosis and over a period of time can develop into cancer [126]. A study on the toxicity of TiO_2 NPs on HaCaT (keratinocyte cell line), human dermal fibroblasts, and human immortalized sebaceous gland cell lines (SZ95) showed that it triggered cytotoxicity which affected cellular functions such as cell proliferation, differentiation and mobility, resulting in apoptosis [127].

The toxicity of Fe_2O_3NPs on skin tumor cells increases ROS and eliminates cancer cells, but no significant toxicity on healthy cells has been reported for these NPs [128].

6.4.3. Carbon-based nanostructures

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The effects of SWCNTs on keratinocyte cells has been examined; they cause oxidative stress, increase ROSs and cytotoxicity by increasing the accumulation of peroxidation products, free radical production, and loss of macrophages [208, 212]. Also, CNTs induce morphological changes in the skin and increase NF-kB [121]; [213], toxicity of these NPs being dose-dependent. In a study of the toxicity of SWCNTs, increased (IL)-8 and cytokine expression and decreased cell viability has been reported; toxicity effects on skin cells in *in vitro* models were reported to be the toxicity of skin fibroblasts [129].

The study of the cytotoxicity of carbon NPs on human dermal fibroblast cells indicated that this type of NP induces apoptosis and cell cycle impairment [130].

6.4.4. QDs

The toxicity of QDs on the skin and their penetration into skin cells has been investigated wherein different shapes, doses, and sizes of this class of NPs were used which accumulated based on their size and duration of exposure [131]. Also, QD621 penetrates the stratum corneum and is deposited near the hair follicle [129]. In fact, it has been stated that different types of QDs accumulate at different sites in the skin [132]. For example, QD NPs on glycated polyethylene keratinocyte cells increased IL-1b, IL-6, and IL-8 while other studies on QD toxicity have shown that the type of QD, size, coating, and the doses used are influential in skin toxicity [131].

Investigation of the effect of quantum NPs on human epidermal keratinocytes (HEKs) showed that they increase concentrations of IL-1β, IL-6, IL-8, and TNF-α[214].

6.5. Liver targets

NPs can enter the human body in various ways, they can access vital organs through the bloodstream, causing damage to the tissues and cells. The liver is the most important organ for

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metabolism of drugs and toxins. Serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can help physicians to diagnose liver and heart disorders. Serum levels of these enzymes are directly connected with most liver disorders, in a way that liver damage can increase the levels of the enzymes in the blood by 10 to 20 times.

6.5.1. Metal NPs

In a study, 3-100 nm AuNP was injected into rats at a dose of 8 mg/kg for 4 weeks. Sizes of 3, 5, 50, and 100 nm did not show harmful effects, but 8-37 nm sizes induced severe sickness in mice had toxic effects such as fatigue, loss of appetite, weight loss, and skin discoloration. A pathological study showed the deformation of Kupffer cells, increase of tissue apoptosis, and induction of inflammation. Studies have shown that the form of injection (intravenous or intraperitoneal) dictates the type of toxicity and its level [215]. Another metal NPs widely used in medicine today is AgNPs wherein toxicity to the liver is Kupffer cells mortality and increased ROS level in this organ. In rats, its toxicity modified mitochondrial function in the liver tissue and increased LDH level [216, 217]. Several studies have investigated the toxicity of AgNPs in hepatocytes which were mostly focused on HePG2 cells. The toxicity of AgNPs with a size less than 10 nm at different doses were examined on these cells; their effect was reduction of cell viability. These NPs can be used to treat cancer. Studies have shown that NPs above 100 nm are deposited in the spleen tissue and less than 100 nm are deposited in the liver. The capillary diameter is also effective in the transfer of NPs [102, 184]. Another metal NPs used in drug delivery is silica whose toxicity was reported to be liver inflammation and increased cytokines expression for NPs above 100 nm [133].

In *in vitro* models, the toxicity of AgNPs on primary mouse fibroblasts, primary hepatocytes, appeared to be oxidative damage and increased GPX levels [125]. The toxic effect of CdSe

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NPs on primary rat hepatocytes cells at a concentration of 62.5-100 µg/ml for 1-8h was shown to be increased ROS level [218].

6.5.2. Metal oxide NPs

Zinc oxide NPs have anti-tumor properties on liver cells in the *in vitro* model and hence they can be used in chemotherapy studies. Studies indicated that human cancer cells in myeloblastic leukemia (HL60) reduced in response to these NPs in the cell-line model. The number of liver cancer cells (HepG2) also reduced in the presence of zinc oxide NPs. In rats, TiO_2 NPs can increase ROS and induce inflammation. In *in vitro* model, these NPs inhibited the tumor, induced lipid peroxidation damage, increased the transformation of H_2O_2 to H_2O and O_2, disturbed the balance of liver oxidation system, and led to fatty liver and increased apoptosis [136].

The toxicity of ZnO NPs on human hepatocyte (L02) is in the form of cellular morphological alteration, mitochondrial function change, reduced SOD level, reduced GSH level, and DNA damage [114].

Al_2O_3 NPs up on injection into mice at 235, 245 ppm level induced the accumulation of blood cells and melanomacrophages , hepatocyte necrosis, vaculation, and structural alteration of portal vein [137].

The toxicity of TiO_2 NPs on rat liver derived cell line (BRL 3A) was in the form of depletion of GSH levels, reduced mitochondrial membrane potential, and increase in ROS levels [15].

6.5.3. Carbon-based nanostructures

Like other NPs discussed here, carbon NPs are distributed in the body and reach the target organ through the circulation; some the target organs include the spleen, the lymph node and the immune system whose function is disrupted leading to increased levels of allergy and

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platelet activation. These NPs attach to the protein on the surface of membrane and exert their toxic effect. The binding of these NPs to the COOH results in immunotoxicity and inflammation of the spleen [138]. Nano-carbon structures at the level of the human hepatoblastoma C3A cell line increased inflammatory factors such as IL-8, increased ROS level, and induced DNA damage [139].

6.5.4. QDs

QDs cause heavy damage to the body due to the release of metal ions from heavy nuclei. The liver tissue is more exposed to this damage as it is responsible for removing these toxins. Some of the damages include oxidative stress, increased ROS, the accumulation of ions in the liver, and increased LDH levels. The toxicity of this type of NPs is also size-dependent, sizes more than 100 nm cause hepatocyte damage [41]. Accordingly, for medical use, QDs should be coated with biocompatible materials.

The toxic effect of quantum NPs on primary rat hepatocytes was reported to be due to the release of free cadmium ions, which could not be fully eliminated by ZnS coating of the OD core [218].

6.6. Kidney targets

NPs used today in various industries enter the human body and create special toxicity dependent on their dose, size, shape and entry pathways. They induce changes in metabolic pathways in the body. Examples of these damages are increased ROS, inflammation, deformation of body organs, and cellular damage in detoxification pathways. The most important examples of these cells are liver and kidney cells because NPs are essentially removed from the body through the liver or kidneys. These NPs can damage nephron cells in the kidneys.

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6.6.1. Metal NPs

In animal models, different shapes, sizes, and doses of AuNPs were injected to address the adverse effects of NPs. One of the reported side effects was damage to the kidneys because these NPs are excreted through the kidneys [219]. There is a direct relationship between dose and kidney damage, because the higher the volume, the more they need to be excreted from the kidneys and the higher renal tissue damage [220]. The levels of creatinine, urea, total bilirubin, and ALP in rat serum showed the level of renal function which changed significantly [141]. Investigation of the toxicity of AuNPs on embryonic kidney cells (HEK293) showed that their toxicity was dose-dependent; at concentration of $44mg^{-1}$ for 4 h, they caused toxicity in the form of DNA damage and transferrin level alteration [142].

6.6.2. Metal oxide NPs

In a study to evaluate the toxicity of ZnO NPs on kidneys, 100, 300 and 1000 mg/kg doses were injected into laboratory rats. After 14 days, acetate, lactate, creatine, phosphoculin, α-glucose, tri-methylamine-N-oxide, and 3-dihydroxybutyrate increased and fat, citrate, succinate, alpha ketoglutarate, and 4-hydroxyphenyl lactic acid in urine decreased. Different doses of these NPs alter fat and glucose in the metabolic pathways and induce liver and kidney damage which is more intensive at a dose of 100 nm, because it includes kidney epithelial necrosis [143]. At a dose of 10 mg/kg, CuO NPs caused DNA damage in kidney cells and apoptosis of renal epithelial cells in *in vitro* model [144].

In previous studies, the toxicity of ZnO on HEK293 cells was in the form of cellular morphological modifications, mitochondrial dysfunction, reduction of SOD, depletion of GSH, and oxidative DNA damage [114]. The toxicity of Cu NPs on HEK293 cells was reported as a decrease in cell viability and increased ROS level [145]. A study of the toxicity of TiO_2, ZrO_2, and Al_2O_3 oxide NPs at doses of 1, 10, and 100 µg/ml on HEK293 showed that these NPs caused DNA damage and genomic toxicity and their toxicity was dose-dependent [146].

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6.6.3. Carbon-based nanostructures

Shang et al. (2015) used MWCNTs as scaffolds in human embryonic stem cells, causing cellular toxicity to HEK293 cells, resulting in penetration of NPs into cells and cell membrane damage by increasing necrosis. MWCNTs increase cytokines expression and IL-8, which is an inflammatory factor, rise lipid peroxidation and decrease glutathione levels. The toxicity varies depending on the type of MWCNT, for example, the toxicity of MWCNT2 is greater than SWCNT1, and the smaller the size of the NP, the more toxic it will be as it raises the ROS level [147].

The toxicity of carbon NPs on HEK293 was in the form of decreased cell viability, reduced glutathione (GSH), interleukin-8 (IL-8), and lipid peroxidation[148].

6.6.4 QDs

As mentioned before, QDs causes substantial body damage due to the release of metal ions from heavy nuclei, especially the kidneys are more exposed to damage as they remove these toxins. Some of the damages include oxidative stress, increased ROS, changing the metabolic pathways of proteins which itself represents DNA damage, and increases apoptosis in *in vitro* models [149].

The toxicity of quantum NP on HEK293 was reported as a reduction in mitochondrial membrane potential, increased Bcl-2 expression, and increased apoptosis [150].

6.7. Spleen targets

The spleen is an organ of the immune system that can purify blood, store lymphocytes for immunity and defend the body against infection. NPs, as described above, increase

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inflammation and damage to the immune system, and one of their target tissues is certainly the spleen.

6.7.1. Metal NPs

NPs can enter the body orally and intravenously and thus they can be a source of serious damage to the gastrointestinal tract. In a study, the toxic effects of orally consumed Ag NPs of 323 nm size were measured on the spleen. While Ag NPs in sizes less than 22 and 71 nm were absorbed in the intestines and stomach, 300, 30 and 1000 mg/kg of Ag NPs in a diameter of 60 nm induced the accumulation of Ag salts in the spleen, inhibited the permeability of cell membrane and Na-K-ATPase activity and eliminated mitochondria [151].

The toxicity of Ag NPs was reported to be inhibition of NF-κB activity, down regulation of Bcl-2, and an increase in caspase-3 activity and surviving gene expression [221].

6.7.2. Metal oxide NPs

Iron NPs also cause iron ion accumulation in the spleen and damage the organ. These NPs are often used to treat cancer tumors. The reticuloendothelial system (RES) is generally effective on the biological distribution of NPs and their accumulation in the spleen. NPs stay for a long time, up to 100 days, in the spleen [153].

6.7.3. Carbon-based nanostructures

Most NPs damage the immune system and induce toxicity. One of the target organs is the spleen. SWCNTs accumulate in the spleen and, by binding to proteins, damage the membrane and cause cellular toxicity. The most significant toxic effect is the increase in inflammatory factors caused by these NPs [222].

6.7.4. QDs

Tissue imaging through infrared stimulation is a problem due to the phenomena of tissue fluorescence. Using the light properties of QDs, one can reach deeper levels of the tissue than organic pigments. The imaging and sentinel lymph node surgery in pigs showed that these

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images could be obtained through intracutaneous injection of 400 pmol fluorescent QDs in the red area. The marked points have better color and quality with QDs, but there is a discussion about the toxicity of mineral QDs containing Pb, Hg, Te, Zn, Se, and Cd. These materials can damage the nervous system, the digestive system, and the liver depending on the doses used and the way they are complexed and accumulated into tissues [154]. For this reason, the QD toxicity has been studied only in animals.

One study examined the negative effects of Se and Cd-containing QDs used in medical lasers for treatment of mice and concluded that quantum particles accumulate in body organs, one of which was the spleen. In fact, the toxicity of these lasers is due to their metal particles [155]. Previous studies on the toxic effect of QDs injected these NPs intravenously into rats' tail. The NPs were eventually accumulated in the spleen and were collected by single-nucleus phagocytes; long-term observation revealed pathologic damage of the spleen [156].

6.8. Stomach targets

The intestinal epithelial cells are different from other parts of the body, because their main activity is transferring digested substances through themselves into the bloodstream; therefore, they simply let many particles, especially small particles (such as NPs), pass through and enter the bloodstream. Oral targeted drug delivery, thus, can be very critical due to the absorption of NPs in the intestines and their entry into the circulation. The acidity of the stomach also causes the death of germs and destruction of some particles and drugs. Therefore, it should be noted that gastric acid does not destroy the drug, but drugs can sometimes be toxic and destructive to the stomach.

6.8.1. Metal NPs

AgNPs, when used for drug delivery, should pass through the intestines and stomach, causing damage to the stomach. One study examined the effect of coated Ag NPs with a diameter of

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60 nm given to rats for 28 days. The toxic effect of these NPs on the stomach of the rats was dose-dependent; 12mg/kg had the lowest toxic effect which increased with higher doses and led to increased ROS level and inflammation [157].

One study examined the toxic effects of Au NPs on gastrointestinal cancer cells as Au NPs have thermal properties which can kill tumor cells [158].

The exposure of CdSe to colon cancer cells at $10^5 \times 0.84$ for 24 h reduced cell viability, which was in a dose- and time-dependent manner [159].

6.8.2. Metal oxide NPs

Metal oxide NPs enter human body from food sources through the pathway of the stomach. TiO_2 NP used in agricultural toxins enters food products and can increase gastric inflammation and the breakdown of macrophages [160]. ZnO NPs of 20 nm in concentrations of 5, 50, 300, 1000, and 2000 mg/kg when administered orally to rats increased the serum alanine aminotransferase. Higher doses increased toxicity in tissues such as stomach; the most important damage was inflammation and increased ROS level [161].

6.8.3. CNT

CNTs have multiple effects on mammalian cellular systems as they are biologically resistant and cause inflammation and increased ROS in mice. The toxicity of this type of NP depends on the physical state of the tubes, whether they are soluble or aggregated, the presence of unformed impurities in CNTs, and the refining type for the preparation of CNTs. For example, soluble CNTs are less toxic than aggregated CNTs [162].

Although CNTs are widely used in water processing plants, tissue engineering, and rehabilitation medicine, they have harmful effects on health and the environment. For example, abandoning CNTs in the environment can have harmful effects on natural ecosystems. In addition, CNTs may have adverse effects on the organs of the body due to interference or DNA damage [165]. Existing research has shown that CNTs are able to enter the body through the

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skin, the respiratory tract, or the digestive system, and accumulate in the organs. Different entry routes to the body have been reported for CNTs with a greater focus on the respiratory tract. Few studies point to the digestive tract through which CNTs in the contaminated drinking water enter the body. In addition to being the entry route of macromolecules needed for the body, the entire gastrointestinal surface is a complicated obstacle [164]. Because of the impairment of the immune system (such as macrophages, neutrophils, and dendritic cells), these substances go elsewhere through the gastrointestinal tract. CNTs used in cellular scaffolds to differentiate the mesothelioma cells of the digestive system were investigated. In the long term, they induced apoptosis and increased expression of inflammatory factors due to the release of carbon in the environment and its penetration into cells [163].

6.8.4. QD

In vitro studies confirm the toxicity of QDs; the growth process of living cells and their viability are affected in the presence of QDs. The toxicity of these compounds depends on a variety of factors, including the size of the NP, surface coating material, the amount of QDs, and the surface chemistry. Different mechanisms have been reported as to how QDs affect living cells; one of them entails the release of Cd in Cd Telluride (CdTe) or Cd Selenide (CdSe). Another mechanism is the process of producing oxygen free radicals. In addition, the interaction of QDs with intracellular components is yet another possible mechanism for QD toxicity [223]. The core and the shell are typically composed of type II–VI, IV–VI, and III–V semiconductors, with configurations such as CdS/ZnS, CdSe/ZnS, CdSe/CdS, and InAs/CdSe, the typical notation being: core/shell. The III-V QDs have higher stability and less toxicity than II-VI QDs, because the bond between the components in the III-V group is of the covalent type, while it is ionic in the II-VI group. Despite the lower toxicity of the III-V group, the synthesis of QDs in this category is more difficult and time-consuming and their quantum efficiency is also low [224]. Coated QDs enter the body, open-up in the stomach and cause iodine cadmium

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congestion, leading to increased ROS, apoptosis, loss of gastric juice, and stomach structure damage [166].

6.9. Pancreas targets

The enzymes necessary for food digestion are inactive and stored in microscopic bags inside the pancreas. They are injected into the duodenum by means of neuromuscular and chemical stimuli after ingestion of foodstuff. Different toxins are agents that cause acute inflammation of the pancreas due to their high toxicity. In this case, enzymes act inside the pancreas instead of duodenum. NPs are examples of these toxins.

6.9.1. Metal NPs

Stensberg et al. (2011) investigated the toxic effect of AgNPs on the pancreas. These NPs entered the organ in the form of endocytosis and increased the level of ROS. In this study, the dosage, the form, and duration of administration were important factors which had an effect on the destruction of this organ. The effect of AgNPs on the pancreas cell-line was investigated;. it included increased apoptosis factors, indicating that this NPs could be used to treat cancer [167].

The toxicity of cobalt NPs on human pancreatic cancer cells was observed to be accumulation of NPs in the cell and apoptosis, which was dose-dependent [170].

6.9.2. Metal oxide NPs

The toxic effects of Ag oxide NPs were evaluated using different doses (500, 1000, 2000 mg/kg) for 14 days. The effects included increased clinical symptoms involving weight loss, appetite loss, HB, HCT, MCV, MCH, MCHC, and LYM reduction; and increased WBCs, NEUs, and ALP which increased with higher doses. Sedimentation in the spleen was observed at all doses, but higher doses increased sedimentation in both males and females [225]. Another

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study examined the toxicity of (ZnO (SM 20(+)) NPs of 20 nm in rats for 90 days at doses of 125, 250, and 500 mg/kg. These NPs caused anemia and changes in blood parameters; lower doses had lower toxicity[171].

The toxicity of TiO_2 NPs that were co-cultured for 42 days was investigated on pancreatic cancer cells [172].

6. 9.3. CNT

In one study, PEGylated CNTs were used for pancreatic cancer cell scaffolds. They were effective at 5, 10, and 50 µg/ml doses for induction of apoptosis and death of cancer cells. This was induced by the effect on mitochondrial membrane and increased ROS which reduced the viability of cancer cells. These NPs, thus, can be used to reduce the size of tumors [173].

6.9.4. QD

CdTe-coated QDs are used to induce toxicity in pancreatic carcinoma cells that are stimulated by ultraviolet light and, by releasing quantum particles, produce ROS and reduce cancer cells viability. Therefore, QDs can be used for radiation therapy [174].

6.10. Ear targets

Recently, NPs, especially AgNPs, are used to increase the antibacterial properties of antiseptics and antibiotics. Today, NPs are used in antibiotics to treat middle ear infection. Any damage to the middle ear is very dangerous as it is a good pathway to brain nerves; the toxicity of NPs in the ear is thus being studied.

6.10.1. Metal NPs

In *in vitro* studies, Ag NPs were used for MRI imaging. Their toxic effect on the structure of the ear was investigated in rats; they reduced hearing frequency in rats, were effective on the mitochondrial membrane and increased ROS level [175].

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The toxicity of Ag NPs was evaluated on BALB/c 3T3 cell line using 20 and 40 µg/ml doses. After 5 h, NP penetration into cells was observed which caused mitochondrial dysfunction; the toxicity was dose- and time-dependent [175].

6.10.2. Oxide NPs

One of the commonly used NPs for drug delivery into the middle ear is SPION whose toxic effects on the ear and nerve were examined. Three months after its passage from the BBB, it penetrated the CNS parenchyma, but no pathological changes were observed in the brain. However, a small amount sedimented in the middle ear which was detected by TEM microscope and showed increased mitochondrial membrane degradation [176].

6.10.3. CNT

Toxic effects of CNT on ear cells (BALB/c 3T3 cell line) were investigated and the only reported toxicity was mitochondrial membrane degradation and ROS production [177]. Most studies considered it to be safe although there is still controversy over the toxicity of CNTs.

6.10.4. QD

QD is extensively used in MRI and one of its pathways is through the middle ear. Studies have reported its toxicity on the face, including eyes and ear defects, body wall defects, neural tube defects, organ disorders, and heart, lung, and kidney abnormalities. Cd penetrates into the ear canal and can lead to the middle ear defects and damage to the auditory nerve [177].

6.11. Eye targets

Today, one of the methods for transmitting nano drugs is through the eyes. Such drugs are used for treatment of cornea disorders often in the form of eye drops. Due to their unique

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properties, NPs can enter the veins and nerves of the eye, causing toxicity in the eye and disorders in the cornea.

6.11.1. Metal NPs

AuNPs have been used for drug delivery to the eyes and hence the toxicity of these NPs to the eyes was necessary to be investigated. As these NPs are coated with dimethylammonium ethanethiol, the toxicity of TMAT (*N,N,N*-trimethylammoniumethanethiol)-Au NPs was studied. Doses of 0.08 to 50 mg/l were injected to rats and the effects on neonates were investigated, which included negative effects on the pigmentation of the eye. In the long term, it caused cell apoptosis and abnormal expression of the factors that are effective in the evolution of eye pigments (pax6a, pax6b, otx2, rx1) and pigmentation (sox10). Hypo activity and axonal growth inhibition were observed in infants whose mothers were exposed to TMAT-Au NPs during pregnancy leading to the conclusion that this type of NPs causes damage to mammals [178].

One study reported the toxicity of silica NPs on human corneal cells to be size-dependent; NPs of 50, 100, and 150 nm induced ROS generation 4 h after co-culture [178].

6.11.2. Oxide NPs

One of the organs that is severely exposed to damage during nano-MRI is the eye; it damages blood vessels of the eye and causes apoptosis. This type of NPs can also be used to eliminate eye tumors [178].

6.11.3. CNT

One study examined the toxicity of SWCNTs and MWCNTs in rabbit eyes; MWCNTs induced more eye irritation than SWCNTs. The only reported damage was burning eyes and corneal tissue damage [180].

6.11.4. QD

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The toxicity of QD to the eye has been examined recently in rats. After 6 weeks, it led to degeneration of eye tissue, reduced cell viability and apoptosis [181].

7. Conclusion

Nanoparticles have many biomedical applications due to their unique characteristics such as size, shape, chemistry and charge. However, the signaling pathways through which NPs can produce toxic effects need to be understood better. Recent studies have shown that inflammation, necrosis, ROS and apoptosis are key factors that mediate the mechanism of toxicity of NPs. These results may create a barrier to the use of NPs in diagnosis and in the treatment of diseases for which they are ideally suited. It is important to identify the dose, shape, and the properties of NPs that are responsible for their toxicity in order to reduce their harmful impact by appropriately modifying the formulation or to use a nanoparticle with lower toxicity. The dose of NPs is an important factor in their toxicological profile, along with their accumulation, distribution, metabolism and disposal. In line with this, intravenously injected NPs have a higher toxicity than those administered to the skin. According to the results of various studies, there should be protocols that show which doses and what structures of NPs are more toxic. In general, the problems in the evaluation of NP toxicity are due to the disparity between different toxicological studies performed on the NPs of diverse origins and make-up. Accordingly, the study of NP toxicity in various applications, especially biological applications such as drug delivery, bio-security and NP toxicity, is very crucial. Consequently, there is a need for the development of accepted and specific protocols to identify the actual particle with its surface surroundings and the composition of NPs that renders them toxic. It is hoped that

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our increased knowledge of NPs lead to their safer design with reduced toxicity so that they can be used for treatment of assorted diseases and drug delivery.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Ajdary M, Moosavi MA, Marveh Rahmati, Falahati M and Mahboubi M wrote the manuscript and contributed in conceptualization of the work. Mandegary A, Jangjoo S Mohammadinejad R and Varma RS provided ideas and critically edited the entire composition of the manuscript.

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List of abbreviations

Albumin Derivatized (AD)…… …….. AD

Blood–Brain-Barrier (BBB)……... BBB

Brain Microvascular Endothelial Cells (BMECs)……..…….... BMECs

Central Nervous System (CNS)……..……... CNS

Cerebrospinal Fluid (CSF)……..……... CSF

Dextran Derivatized (DD)…….……...……... DD

Silver Nanoparticle …….……. Ag NP

Dopamine (DA)……... DA

Gold Nanoparticles……...……... Au NP

Magnetic Resonance Imaging…….....……... MRI

Carbon nano tubes …….……. CNTs

Multi-Walled Carbon Nanotubes……...……... MWCNTs

Nanoparticles……...……... NPs

Quantum Dots……...……... QDs

Single-Walled Carbon Nanotubes…….……... SWCNTs

Superparamagnetic Iron Oxide Nanoparticles……. SPIONs

Ultra-Small Superparamagnetic Iron Oxide Nanoparticles…….... USPIONs

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