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Research Article

ZINC OXIDE NANOPARTICLES AS DELIVERY SYSTEM TO COMBAT DISEASES

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A B S T R A C T

The potential delivery of nanoparticles to targeted cells has attracted attention in the therapeutic applications for cancer and infectious diseases as the nanoparticles having the capability to attach the therapeutic components effectively. Interestingly, so far studies indicate that zinc oxide nanoparticles (ZnO NPs) may hold considerable promise not only as delivery carrier but also as antimicrobial and anticarcinogenic agent for in vivo biomedical applications. These nanomaterials are also equally suitable to overcome biological barriers, multidrug resistance and biofilm development. This review demonstrates the synthesis, functionalization, characterization, mechanism of action, biodistribution, toxicity, immune response and elimination of ZnO NPs *in vitro* or *in vivo* as current approaches for improving their targeting to specific site of interest in combating diseases. The surface modifications of these nanoparticles with specific biomolecules based components delivery may drive new direction for modulating the biodistribution, pharmacokinetics, toxicity and increasing efficiency of the targeted agents. These new strategies are considered for minimizing degradation and loss, and enhancing bioavailability of components to open up newer horizons for delivery system.

INTRODUCTION

Cancer and infectious diseases are caused by the pathogenic agents such as toxicants and microbes and responsible for the demise of millions of people annually. Although the living body has the capability to defend infections by its own antioxidant defence system, and innate and acquired immune system (Sana *et al*., 2017; Mandal, 2017a), some contagious and virulent micro-organisms after transmission to the host body grow and replicate well intra and extra -cellularly resulting in tissue damage characterized by the presence of clinical symptoms (National Institutes of Health (US), 2007). The treatment of these diseases is hampered by biological barriers such as blood brain barrier (BBB), multidrug resistance (MDR) expressed by several drug efflux proteins and biofilm formation especially in alimentary gut. Cell membranes and walls are important defensive barriers for microbial protection to the external environments. MDR develops due to over-expressions of drug efflux pump proteins such as P-gp and other MDR proteins and genes induced by the massive application of antibiotics or other drugs for remedial and prophylactic treatment without proper medical instructions, the inappropriate alternate antimicrobials selection and the frequent switching between microbicidal treatments.

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In addition, hindrance of biofilm formation in the treatment of drug shows another important mechanism of drug resistance as biofilms play a crucial role in the cell-resistance development (Peulen and Wilkinson, 2011). The unique structure and composition of bacterial biofilms provide protection or shelter to the embedded pathogens to help them from escaping most antibiotics supported by a microbial breeding ground for frequent resistance mutations and their alterations and exchanges among various microbial cells (Khameneh *et al*., 2016). Furthermore, BBB is a physiological and physical bar that defends the brain from toxic materials within the blood stream to retain brain homeostasis. This barrier is made up with firmly interconnected endothelial cells for forming the circumferential interior lining of the cerebral blood vessels - walls characterized morphologically by the lack of fenestrations, decreased pinocytic activity and more large tight junctions (Silva, 2008). To overcome these obstacles, it is necessary to develop new antibiotics and designing of a drug delivery system which not only can act as anticarcinogenic and antimicrobial agent but also can carry a small amount of drug for avoiding toxicity to target its maximum amount to specific site of interest efficiently. Nanotechnology has become the forefront of research representing its tremendous potentiality for revolutionizing the livestock sector as nanomedicine product showing improved use of technologies for biomedical and biological applications (Zhao and Castranova, 2011). The metal oxide NPs due to their ultra-small sizes (<100 nm) are akin to naturally occurring biomolecules and proteins in the cell (McNeil, 2005) which are smaller than many human cells (~7 μm). Their reduction to the nanoscale can alter their

magnetic, structural, electrical, chemical and morphological features to enable them for interacting with biomolecules and enabling their transportation into the interior cells-structure in unique ways, while these particles posses a larger % of atoms at the surface leading to enhanced surface reactivity (Nel *et al*., 2006) for maximizing their capability to be loaded with therapeutic components for targeted delivery to cells or tissues. In this regard, most of the drug resistance mechanisms are irrelevant for these metal NPs as their mode of action are to contact directly with the microbial cell wall to disrupt the cells. The anchoring of new drug and coating with ligands to the nano-size particles enhances their synergistic efficiency not only to overcome the drug efflux protein pump barrier but also the BBB through transcytosis. ZnO NPs, as a novel type of low cost and low toxicity material, are comparatively insoluble in physiological environments, but are dissolved as zinc ions in acidic environments such as, in the late endosomal or lysosomal compartment of the tumor cells to induce cytotoxicity, excessive reactive oxygen species (ROS) generation and cell death (Xiong, 2013; Cho *et al*., 2011; Muhammad *et al*., 2011; Abdelmonem *et al*., 2015). Many investigators suggest that microbicidal mechanism of ZnO NPs may involve the disruption of the cell membrane proteins and lipids through their attachment to the cell membrane resulting in the intracellular contents leakage supported by cell death (Xie *et al*., 2011). Another group of researchers demonstrates the generation of Zn^{+2} ions and hydrogen peroxide (H_2O_2) involved to kill the pathogenic or infected cells as the key microbicidal mechanism (Lipovsky *et al*., 2009). Owing to their excellent characteristics, ZnO NPs have been explored as multifunctional nanocarrires for facilitating the drug delivery and release process (Zhang *et al*., 2013). By appropriate engineering the NPs-surface functionalization with drugs, ligands, sugars, proteins, antibodies, genes or vesicles, these high surface to volume ratio NPs can acquire the capability for selectively targeting the specific types of cells or passing through the physiological obstacles and invading deep into the tumor sites with a sustained manner of components release. This review illustrates the biological efficacies of ZnO NPs as potent therapeutical delivery system for the consideration to treat cancer and infectious diseases.

Synthesis and functionalization of zinc oxide nanoparticles

NPs can be synthesized by a variety of techniques of which colloidal chemical synthesis by precipitation method and eco-friendly green synthesis method are very important for biological applications. In a precipitation method, a reducing agent is allowed for the reaction to zinc salt and the resultant precipitate is produced by controlling temperature, time, concentration of reactants and pH followed by washing and calcinations to obtain NPs of desired characteristics and morphology (Mantzaris, 2005).

ZnO NPs may be synthesized (Wu *et al*., 2006) with a modification from aqueous solutions of hexamethyltetramine (HMT) ($C_6H_{12}N_4$) and zinc nitrate ($Zn(NO_3)_2.6H_2O$). The two reagents are mingled separately with milli-Q water to the concentrations of 1.5M for the HMT solution and 0.05M for the ($Zn(NO_3)_2$) solution following stirring for 30 min each, and then are mixed with 130 rpm stirring. The solutions are adjusted to the pH at 5, 6 and 7.2, heated to 80^{o}C for 45 min and the yield is gathered by spinning. The ammonium hydroxide solution (1N) is adjoined to pH 5 synthesized solutions for enhancing the ZnO NPs-formation at 80^{o}C.

In another way, ZnO NPs may be synthesized utilizing zinc nitrate and urea as precursors. For this synthesis, 0.5M (4.735 g) zinc nitrate is liquefied in 50 mL distilled water by keeping under stirring for 30 min for entire dissolution. 1M (3.002 g) urea is also dissolved in 50 mL distilled water under stirring for 30 min which generally acts as precipitating agent. The urea solution is mixed drop-wise into zinc nitrate solution and stirred vigorously at 70^{o}C for 2h for allowing complete formation of NPs while precipitating solution turns cloudy white. The white product is spun at 8000 rpm for 10 min and cleansed with distilled water for removing absorbed ions or any impurities present. The product is calcinated at 500^{o}C in air atmosphere for 3 h with the use of muffle furnace (Chen *et al*., 2008).

In other method of ZnO NPs synthesis, 0.02M aqueous zinc acetate dihydrate ($Zn(CH_3COO)_2.2H_2O$) is liquefied in 50 mL distilled water under stirring. Aqueous 2M sodium hydroxide (NaOH) is then added drop by drop to get pH 12 at room temperature following the placement of this solution on a magnetic stirrer for 2 h. After the ending of the reaction, the white obtained precipitate is cleaned with distilled water and followed by ethanol for removing impurities present. After that, the precipitate is dried in a hot air oven at 60^{o}C for overnight to convert completely $Zn(OH)_2$ into ZnO NPs (Gnanasangeetha and Thambavani, 2013). For stabilizing the NPs, cetyl trimethylammonium bromide (CTAB) may also be used as precursor to get antimicrobial NPs (<50 nm) (Khan *et al*., 2016).

The other procedure (Yadav *et al*., 2006) for the synthesis of ZnO NPs, demonstrates the reagents sodium hydroxide and zinc nitrate as precursors, and soluble starch as stabilizing agent. In this preparation, 0.1% starch solution is prepared by using a microwave oven and 0.1M zinc nitrate is adjoined to the above solution and kept under constant stirring on a magnetic stirrer for dissolving zinc nitrate completely. After that 0.2M NaOH solution is added drop-wise along the side walls of the solution vessel under continuous stirring, and allowed to maintain reaction for 2 h and followed to settle overnight. The supernatant solution is then decanted and the residual solution is spun at 10000xg for 10 min. The precipitated NPs are then washed 3 times using distilled water for removing any by-products or starch bound to the NPs and followed by drying overnight at 80^{o}C to convert $Zn(OH)_2$ to ZnO completely.

ZnO NPs are also synthesized following the method (Moussodia, 2008). In this procedure, 220 mg zinc acetate is liquefied in hot 20 mL ethanol under robust stirring. 70µL oleic acid is then adjoined and the mixture is refluxed. In another flask, 360 mg tetramethylammonium hydroxide is liquefied in 5 mL refluxing ethanol. The solution is then quickly injected in the mixed solution of oleic acid and zinc acetate, refluxed for 2 min and diluted with 50 mL ethanol following cooling to 0^{o}C until a white precipitate of ZnO NPs appears. The particles are then centrifuged at 4000 rpm for 15 min to detach supernatant. The product oleate capped ZnO NPs are washed 3 times with ethanol and dispersed in 10 mL toluene, and stored in dark at 4^{o}C.

ZnO NPs may be synthesized with the use of leaves extract such as *Coriandrum sativum*. In this method, 50 mL distilled water is taken where 0.02 M aqueous zinc acetate dehydrate is adjoined under constant stirring. After 10 min stirring, the

aqueous leaf extract is introduced at various sets (0.25, 0.5 and 1 mL) into the above solution. Then 2 M NaOH is added to make pH 12 for getting a pale white aqueous solution followed by placing on a magnetic stirrer for 2 h. After that pale white precipitate is taken out and cleansed 2-3 times with distilled water and followed by ethanol for making it free from any impurities. Then it is dried at 60°C in vacuum oven overnight to obtain a pale white powder of ZnO NPs (Anastas and Warner, 1998; Clark and Macquarrie, 2002).

Another way of ZnO NPs synthesis by utilizing leaves extract such as plant *Calotropis gigantean* is described here (Clark and Macquarrie, 2002). 50 mL leaves extract is taken and boiled to 60-80 °C with the use of stirrer-heater or hot plate. 5g zinc nitrate is then added to the solution until the temperature reaches to 60°C. The whole mixture is boiled until it reduces to a deep yellow paste color following its collection in a ceramic crucible and heated in furnace at 400°C for 2 h for obtaining a light yellow color ZnO NPs powder.

In order to encapsulate drug into ZnO NPs, drugs such as amoxicillin trihydrate is dissolved in 100 mL distilled water at various concentrations (1,3,5 and 10 %). 1g of various sizes ZnO NPs is adjoined to all the 3 drug solutions, and stirred with the use of magnetic stirrer at 600 rpm for different time durations (30, 60 and 120 min) at room temperature. The solution is then kept undisturbed overnight. After that, the suspension is spun at 5000 rpm for 5 min to collect the precipitate and the supernatant for further experimentations.

Before conjugation of ZnO NPs with BSA, 5 mL ZnO suspension is admixed with 5 mL of 5 mg/mL BSA prepared in 100 µL PBS. After the reaction for 10 min, the pH of the solution is adjusted to 7.4 by adding borate buffer. The conjugation of ZnO NPs-BSA is acquired by incubating the above solution with 1 mL BSA (1 mg/mL) for 90 min at 37°C and stored at 4°C for further use.

For proper biological applications, surface attachments of ZnO NPs with biomolecules such as antibodies, genes, proteins, peptides, lipids and carbohydrates may be carried out to increase their potential efficiency (Veerpandian and Yun, 2011; Tallury *et al*., 2010). Biomolecules may be anchored to NPs through either chemical covalent coupling reactions or physical adsorption (Tallury *et al*., 2010). Covalent chemical modifications take place by NPs-functinalization with carboxyl, amine or sulphide groups while physical adsorptions by electrostatic and hydrophobic interactions between NPs and biomolecules.

Characterization of zinc oxide nanoparticle composites

The morphology and size of nanocomposites are determined using atomic force microscope, scanning electron microscope and transmission electron microscope. The particle zeta potential and size are measured by the use of dynamic light scattering. The particle size and nature i.e. the composition and purity of the NPs are ascertained by using X-ray diffraction analysis. Information about vibration modes regarding the shift energy in the NPs system is obtained by FT-Raman spectroscopy analysis. To identify NPs, UV-visible spectrophotometer is utilized. The quality of the NPs is analyzed by Fourier transform infrared spectroscopy.

Mechanism of action of zinc oxide nanoparticles

ZnO NPs are considered as a strategic, functional and versatile promising metallic material with a broad range of applications including biomedical for their electrostatic features (Neumark and Kuskovsky, 2007). ZnO NPs contain neutral hydroxyl groups anchored to their surface for taking part in their surface charge activity (Qu and Morais, 1999; Qu and Morais, 2001). In aqueous medium with high pH, the chemisorbed protons (H^+) move out from the NPs-surface leaving a negative charged surface having partially bonded oxygen atoms (ZnO^-), while at lower pH, environmental protons are transferred to the NPs-surface resulting a positive charge from surface $ZnOH_2^+$ groups. The isoelectric point (9-10) demonstrates the NPs' strong positive surface charge useful for the interactions with the cells in addition to electrical, catalytic, optoelectronic and photochemical activities owing to their large surface to volume ratio and low dimensionality (Degen and Kosec, 2000; Brida *et al*., 2002; Wang, 2004; Suchea *et al*., 2006; Ashour *et al*., 2006; Huang *et al*., 2006; Baruah and Dutta, 2009). As microbes and cancer cells contain anionic phospholipids on their outer membrane with high membrane potentials, it is assumed that positively charged ZnO NPs should be attracted to the cell membrane by electrostatic interactions advancing cellular uptake, endocytosis and ultimately cytotoxicity (Abercrombie and Ambrose, 1962; Bockris and Habib, 1982; Papo *et al*., 2003). As the concentration of different chemical groups (ZnO^-, ZnOH and $ZnOH_2^+$) on the NPs-surface is pH dependent, the accessibility of these reactive groups provides ZnO NPs to protein / antibody / other functionalization through 1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide / N-hydroxy succinimide (EDC / NHS) coupling chemistry or other approaches for the improvement of diseased cell targeting (Nagao, 1971; Grabarek and Gergely, 1990). ZnO NPs also demonstrate strong protein adsorption characteristics that may be utilized to modulate metabolism, cytotoxicity or other cellular response (Horie *et al*., 2009). As the cytotoxic property of the NPs depends on their size, shape and ligand coating, the spherical, nanosized, coated NPs exhibit their potential efficiency in targeting effected cells on regulating enhanced permeation and retention effect, clearance, zeta potential, surface coating, chemical precursors and reaction medium (Guo *et al*., 2008; Nair *et al*., 2009; Hanley *et al*., 2009; Brannon-Peppas and Blanchette, 2004; Gorelikov and Matsuura, 2008; Brayner *et al*., 2006).

The semiconductor ZnO NPs have the capability to produce ROS that can lead to cell death (Xia *et al*., 2006; Ryter *et al*., 2007; Long *et al*., 2006; Lovric *et al*., 2005; Lewinski *et al*., 2008). The electrons in semiconductor may have energies within their bands while light exposure may forward electrons (e^-) to the conducted band for leaving behind electron holes (h^+) or unoccupied condition in the valence band (Lany *et al*., 2007). The holes and electrons may recombine and migrate to the NPs-surface to react with adsorbed species for empowering electrons to react with oxygen, and holes to react with OH^- or H_2O for forming O_2^{-} and $^{\cdot}OH$ utilized for the photo-oxidized destruction of cancer cells and bacteria (Cai *et al*., 1992; Nair *et al*., 2009).

For nanosized ZnO particles, large numbers of conduction band electrons and / or valence band holes are assumed to be a variable for serving in redox reactions (Yang *et al*., 2009) leading to enhanced oxygen vacancies, interstitial zinc ions and acceptor / donor impurities resulting a huge number of electron-hole pairs ($e^- - h^+$) in cellular environments (Sharma *et al*., 2009). The holes may act as powerful oxidants that may split water molecules obtained from ZnO NPs-aqueous

environment into OH^- and H^+. The conduction band electrons may act as good reducers and proceed to the NPs-surface for reacting with suspended oxygen molecules to produce $O_2^{\cdot-}$, which in turn, may react with H^+ to produce $HO_2^{\cdot}$. $HO_2^{\cdot}$ molecules may then generate HO_2^- ensuing a subsequent confront with electron while HO_2^- may react with H^+ to produce H_2O_2 (Salem, 2000; Padmavathy and Vijayaraghavan, 2008). These ROS molecules may activate redox-cycling cascades in the cells or on surrounding cell membranes resulting in depletion of endogenous cellular antioxidants followed by irreparable cellular oxidative damage.

Zinc oxide nanoparticles as vehicle for drug delivery

The development of nicrobicidal or tumor-specific NPs as vehicle for self-sustained drug delivery and release is presently an intense research area to maintain potentiality for revolutionizing the disease treatments as the nanotechnology has made an improvement on the delivery of hydrophobic drugs with other co-drugs and their targeting to specific cell or tissue sites supported with imaging modalities (Farokhzad and Langer, 2009). The significant advantages of these NPs for drug delivery include their abilities to target specific sites in the body system and to diminish the overall used drug amount, and their potentiality for reducing drug concentrations at non target sites leading to fewer side effects. ZnO NPs, loaded with doxorubicin and encapsulated with chitosan, showed their effective drug carrier characteristics with an initial rapid drug liberation following sustained release owing to the NPs-stability on chitosan's hydrophilicity and cationic charge potential establishment (Yuan *et al*., 2010). ZnO NPs also exhibit their wide range antimicrobial activities (Reddy *et al*., 2014; Raghupathi *et al*., 2011; Hsueh *et al*., 2015; Narasimha *et al*., 2014; Xie *et al*., 2011; Gunalan *et al*., 2012; Venkataraju *et al*., 2014) by altering the membrane permeability and inducing oxidative stress through the release of zinc (II) ions and ROS generation resulting in microbial cell damage. The antimicrobial activity of the NPs is further increased when combined with ultrasound stimulation accompanied by a significant H_2O_2 production (Seil and Webster, 2012). Thus, the antimicrobial activity of ZnO NPs, used alone, in combination with different drugs, antibiotics or ultrasound stimulation is affected by their particle shapes, sizes, concentration, methods of preparation, while the particles are accumulated in the cytoplasm or on the microbial outer membrane to induce oxidative stress resulting cell death.

Zinc oxide nanoparticles as vehicle for gene delivery

Nanoparticles as carriers for targeted gene delivery to diseased sites are attracting attention. The advantage of this perspective is that the expression plasmid enclosure or absorption / conjugation of the nucleic acid or other genes to the NPs-surface ensure efficient and safe gene delivery to the desired cells or tissues. Another advantage of their delivery system is their capabilities where NPs are taken up by particular cells accompanied by internalization to the nucleus of cell in accordance with their surface chemistry. In this concern, silica-coated amino attached tetrapod-like ZnO nanostructures are capable to bind effectively plasmid DNA via electrostatic interaction and can increase transfection efficiency of A375 cells (Nie *et al*., 2006; Nie *et al*., 2007). In another aspect, polycation-capped ZnO quantum dots have exhibited to impart DNA transfer effectively into COS-7 cells accompanied by real-time gene transfer imaging (Zhang and Liu, 2010). Thus, ZnO nanomaterials can provide the effective targeted deliveries for gene materials in the biomedical applications of diseases.

Toxicity of zinc oxide nanoparticles

There are controversial reports regarding the studies of ZnO-toxicity in the mammalian cells. Some reports have exhibited ZnO as biocompatible and nontoxic (Zvyagin *et al*., 2008; Kachynski *et al*., 2008; Vanheusden *et al*., 1996) while others have shown their *in vivo* and *in vitro* toxicities depending upon the particles concentration used in mammalian cells (Tian *et al*., 2015; Frohlich and Frohlich, 2016; Chen *et al*., 2015; Vandebriel and De Jong, 2012). Further, such toxicity is very important for the treatment of pathogenic, cancerous and leukemic T cells (Wang *et al*., 2009; Yuan *et al*., 2010; Rasmussen *et al*., 2010; Premanathan *et al*., 2011; Muhammad *et al*., 2011; Guo *et al*., 2008; Lin *et al*., 2015).

From the micron to larger size, ZnO is judged to be normally known as safe material by the FDA, while nanosized, toxic ZnO particles should be surface functionalized with ligand-coating to reduce toxicity, aggregation and to increase biocompatibility for suitable taken up by cells through endocytic or phagocytic mechanisms in vitro and in vivo for drug delivery applications (Hafeli *et al*., 2009; Lanone and Boczbowski, 2006). The mechanism of ZnO NPs-cytotoxicity is mainly related to the generation of ROS. When NPs interact with cells, cellular defence mechanisms become activated to reduce damage but when ROS generation exceeds the anti-oxidative cellular defensive capability, it causes damages of biomolecules such as proteins, lipids and DNA, accompanied by an enhancement in potent pro-inflammatory cytokines resulting in inflammation, mitochondrial perturbation, and enhanced liberation of lactate dehydrogenase, leading to cellular death either by apoptosis / necrosis or by both (Carmody and Cotter, 2001; Ryter *et al*., 2007; Sayes *et al*., 2007; Lin *et al*., 2009; Jeng and Swanson, 2006; Nel *et al*., 2006; Xia *et al*., 2006). Some degree of ZnO NPs-cytotoxicity depends on the potential dissolvability of ZnO NPs into free Zn^{2+} ions in medium (Nel *et al*., 2006 ; Mortimer *et al*., 2010; Franklin *et al*., 2007; Kasemets *et al*., 2009; Zhu *et al*., 2008; Deng *et al*., 2009; Brunner *et al*., 2006). In some instances, NPs become dissoluted in acidic intracellular lysosomal compartment where hydrated zinc ions in concomitance with intact ZnO NPs cause mitochondrial damage accompanied by osmotic disruption with cellular zinc homeostasis misbalance resulting in cell death while their toxic severity depends on the shapes, sizes, the route of administration, concentration, dosage, synthesis conditions and procedures (Shankar and Prasad, 1998; Lim *et al*., 2004; Choi and Koh, 1998; Hanley *et al*., 2008; Sayes *et al*., 2007; Wang *et al*., 2009).

Immune responses of zinc oxide nanoparticles

An appropriate concentration of ZnO NPs has shown to produce a diversity of pro-inflammatory cytokines such as TNF-α, IL-12 and IFN-γ in *in vitro* and *in vivo* rat pulmonary inhalation studies (Sayes *et al*., 2007; Hanley *et al*., 2009; Gojova *et al*., 2007; Beyerle *et al*., 2009). Their capability in application for enhancing tumor cell killing especially through TNF-α production is crucial for directing the Th1-mediated immunity development (Croft, 2009; Lappin and Campbell, 2000). In this concern, Th1 lymphocyte subset takes part in increasing the natural cytotoxic potential of T cytotoxic and natural killer -cells against cancerous cells suggesting an

appropriate NPs-concentration which has a pivotal role in achieving desired therapeutic efficacy without potential systemic damages.

Biodistribution

Before therapeutic application of ZnO NPs as delivery system against diseases, it is needed to determine their fate exactly in living organism. So far spectroscopic studies indicate different biodistribution patterns of the particles due to variations of animal model, route of application, shape, size, surface charge, ligand coating, methodological approaches, dose and frequency of the NPs-applications. In one study, 20 nm negatively charged ZnO NPs were administered to rats intragastrically at the doses from 125 mg/kg to 500 mg /kg b wt daily for 90 days. The results showed higher level of total zinc concentration in the liver, kidneys, small intestine and blood serum in each experimental group (Park *et al*., 2014). Similar studies with 20 and 70 nm negatively charged ZnO NPs with different doses upto 300 mg/kg b wt were performed for 30 min to 96 h showing their bioaccumulation mainly in liver, kidney and lungs (Baek *et al*., 2012). In another experiment, researchers indicated enhanced level of zinc in liver and kidneys, initiated by oral ZnO NPs administration for 14 consecutive days in mice (dose of 50 / 300 mg/kg b wt) (Sharma *et al*., 2012). The other group studied the biodistribution of ZnO NPs in the liver, lungs, kidney, spleen, brain, testis and ovary at the dose of 50 / 300 mg/kg b wt and measured the total zinc level (Baek *et al*., 2012). Another group of researchers evaluated tissue distribution of capped ZnO NPs in whole animals where 20 and 70 nm ZnO NPs coated with L-serine / hepes or citrate / hepes were gavaged once to rats for determining of zinc bioaccumulation in liver, lungs and kidneys (Choim and Choy, 2014).

Elimination

Zn^{2+} is an essential element and required to maintain cell homeostasis. Free Zn^{2+} is very reactive, and at high concentration, it is cytotoxic (Maret *et al*., 1999). Under normal state, the cell has comparatively high concentration of zincs which are bound to different proteins, while free Zn^{2+} ions-level remains very low and strictly regulated by homeostatic mechanisms (Shankar and Prasad, 1998; Lim *et al*., 2004). Thus, some amount of zincs is utilized in recycling after the therapeutic application of ZnO NPs against diseases. ZnO NPs with or without ligand coating when administered into the body either orally or through other routes such as intravenous, intraperitoneal, subcutaneous and intra muscular, get exposed to acidic or alkaline biological fluids (Li *et al*., 2013; Mudunkotuwa *et al*., 2012; Henderson *et al*., 1995) in stomach, pancreas or phagolysosome where enzymatic degradation takes place resulting ionic zinc accumulation in free and bound forms from the particulate form in the systemic circulation or RES. NPs are eliminated mainly through hepato-pancreatic biliary, hepato-mononuclear phagocytic and renal system (Yu and Zhang, 2015; Moghimi *et al*., 2001). In hepato-pancreatic biliary clearance, hepatocytes can endocytosed NPs following their lysozyme breakdown and excretion into the bile through biliary system (Longmire *et al*., 2008) and finally secreted to duodenum and a portion of which undergoes re-absorption cycling into the blood or remaining portion goes to fecal clearance through small intestine. Hepatocytes and kupffer cells bind and sequester efficiently comparatively larger NPs through their surface-scavenger receptors (Wang *et al*., 2015; Poelstra *et al*., 2012; Bartsch *et al*., 2002) and processed for lysosomal degradation to liberate Zn^{2+} ions (Xia *et al*., 2008) for their subsequent removal from the body through biliary and fecal mechanisms (Watson *et al*., 2015; Paek *et al*., 2013; Krebs and Hambidge, 2001). In systemic circulation, adsorption of serum proteins i.e. the opsonisation by complement factors, immunoglobulins and fibrinogen, activates the processing and elimination of the NPs from the blood by the mononuclear phagocyte system (MPS) (Moghimi *et al*., 2001). The phagocytosed NPs generally undergo intracellular enzymatic degradation inside the MPS cells but non-decomposed NPs (>6 nm) with the intracellular processes remain within the cells and are sequestered in the liver and spleen for few months or eliminated through the kidney (<6 nm) after their administration into the body (Longmire *et al*., 2008; Sadauskas *et al*., 2009; Karmali and Simberg, 2011; Desai, 2012; Sun *et al*., 2014; Yu and Zhang, 2015). As entities of <6 nm in hydrodynamic diameter (HD) are capable of renal glomerular filtration while the renal protein filtration threshold is <5 nm in HD, NPs (<5 nm) coated with biodegradable and biocompatible -ligand may be ideal for undergoing urinary excretion without any systemic toxicity efficiently for therapeutic use (Mandal, 2017b).

CONCLUSIONS AND FUTURE ASPECTS

The treatments of cancer and infectious diseases have emerged so many barriers such as drug toxicity and insolubility, BBB, MDR and non-selectivity. To overcome these barriers, nanotechnology-based delivery is gaining importance faster owing to its continuous elucidations based on enhancement in scale and novelty to combat diseases. Specific characteristics and properties of ZnO NPs owing to their ultra-small size and higher surface area, inherent toxicity against infectious agents and cancerous cells have make them capable to induce intracellular ROS production leading to cell death through the damage of microbial cell wall, the capability of binding to RNA or DNA and the hindering microbial replication, the disruption of microbial enzyme and mitochondrial activity and the hindrance of electron trans-membrane transport or the apoptosis of cancerous cells. The physicochemical properties of ZnO NPs lead to their cellular uptakes and ease of surface functionalization for making them a promising candidate for biomedical use.

As metal-based NPs show good cellular interactions with biomolecules on the cell surfaces or within the cells and can be engineered by anchoring the selected biological moieties for specific binding to the selected target cells, their applications may be very useful to get potential therapeutic effectiveness at the pathological sites of different diseases though their therapeutic efficacies depend upon several factors such as shape, size, concentration, dosage, pH in medium and methods of preparation. However, with so far studies, it is needed to do more research in the proper design of ZnO NPs with surface modifications accompanied with toxicological pharmacokinetics to get maximum efficacies against diseases. In this concern, it is also necessary to have synergies from biologists, material scientists and clinicians to strengthen the future research on ZnO NPs for developing them as an effective tool of delivery system against diseases.

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