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Review Article

Cobalt nanomaterials as a delivery system in combating infectious diseases and cancer

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Abstract

Infectious diseases and cancer possessing the most serious public health hazards throughout the world require the developments of more effective strategies to control them. The conventional therapies such as chemotherapy and radiotherapy have been restricted with their side effects and low efficiency such as insolubility, toxicity, non-specificity, drug resistance and other biological barriers urging for new technologies with more suitable therapeutic efficacies. Cobalt, the essential ultra-trace component, is involved in the metabolism of various organisms owing to its pivotal role in cobalamin (vitamin B12). Cobalt nanomaterials (CoNMs) such as cobalt nanoparticles (CoNPs) and cobalt oxide nanoparticles (CoO, Co_2O_3, Co_3O_4 NPs) have attracted attention not only for their nano-sizes, high surface area to volume ratios, intrinsic spinel crystal structures, photochemical, catalytic and bio-imaging features, ferromagnetic, antimicrobial and anticancer activities but also for their low synthesized costs, hypo-toxicity, photothermal conversion and high drug loading capabilities against anticancer and anti-infection treatments. Their surface-modifications with ligands/coatings and cargos may enhance their therapeutic efficiencies as nano-medicinal delivery system against diseases. This review demonstrates mainly the synthesis of CoNMs and their surface functionalization, characterizations, mechanisms of action, biomedical applications, toxicity, and elimination to consider them as future suitable nano-medicinal delivery system in combating infectious diseases and cancer.

Keywords: Infectious diseases and cancer; Cobalt nanomaterials; Delivery system; Therapeutic efficacies

Introduction

Infectious diseases and cancer, developed mainly owing to the evasion of subject's body defense system against toxicants, contribute to human morbidity and mortality globally [1,2]. The chief symptoms of infectious diseases such as enhanced pulse rate and breathing, high fever, insanity and anxiety, as well as enhancement of malignant cells may lead to rapid demise in a few uncontrolled infections or cancer conditions. The conventional chemotherapy, radiotherapy and immunotherapy have developed drug resistance, destruction of immune system, appearance of cytotoxicity, and other side effects owing to the abuse applications of antibiotics and poor selectivity affecting healthy normal cell-killing, and also progressive life-threatening for uncontrolled anti-cancer immune responses [3-9]. Based on the current status of obstacles for the therapeutic strategies against infections and cancers, there is urgent requirements for developing new technologies and drugs to combat the diseases.

Cobalt (distributed in nature), the essential trace element (cofactor of vitamin B12), cobalt proteins (methionine aminopeptidase-2 in mammals, and nitrile hydratase in bacteria), linked to the metabolism of organisms, may regulate fatty acid metabolism, the synthesis of amino acids and proteins, and bacterial nitrile metabolism [10,11]. Cobalt-based compounds/alloys may be utilized for medical applications such as for making frictional and supportive parts of artificial joints (acetabular liners, femoral heads and constituents and stems) owing to their excellent machinability, disintegration and wear -resistance and strength characteristics [12].

Based on the emerging biological implications of cobalt, Co NPs, CoO NPs, Co_2O_3 NPs and Co_3O_4 NPs have been utilized in various fields for their suitable physico-chemical features [13-15]. The most stable Co_3O_4 NPs have the spinel structures (Fd3m) possessing oxygen ions (32e Wyckoff sites) marginally dispossessed from the optimal position (1/4,1/4,1/4) with cations Co^{2+} (8a Wyckoff sites) and Co^{3+} (16d Wyckoff sites) allocated among tetrahedral and octahedral places, respectively. It also shows p-type semiconducting features owing to its high Young's modules varying between 116 and 160 GPa as well as cationic (cobalt) vacancies leading to an oxygen rich spinel [16].

Based on the favorable physico-chemical properties such as anisotropy constant, coercivity and Curie temperature, ease of fabrication, saturation magnetization and suitable biocompatibility to normal cells, as well as capabilities of producing reactive oxygen species (ROS), and also inducing apoptosis, DNA and cellular damages against pathogens and diseased cells, or stimulating selective anti-cancer immune responses, Co_3O_4 NPs with/without drug/s or antigens have been utilized in various biomedical applications such as pathogenic infections, magnetic resonance imaging, targeted drug delivery and cancer therapy [17-30]. Moreover, CoNMs may be anchored/coated with surfactants, ligands, polymers, cargos and other materials to provide higher therapeutic efficiencies for reducing cytotoxicity and agglomeration, enhancing biocompatibility, and getting targeted and controlled delivery of the bioactive substances in the diseased site/s [31-33]. This review denotes mainly the synthesis, functionalization and progress of CoNMs as well as the future strategies for biomedical applications against infections and cancers to consider them as suitable nano-medicinal delivery systems.

Synthesis and surface-functionalization of cobalt nanomaterials

Different physico-chemical synthesizing methods of CoNMs following hydrothermal synthesis, thermal decomposition, thermal reduction, micro-emulsion, chemical wet processing, precipitation, sol-gel, evaporation-condensation, reverse micelles, microwave-assisted, and laser ablation have gradually been emerged [34,35]. Following top-down method, bulk cobalt materials are transformed into their nanoparticular forms via grinding, milling and sputtering techniques characterized by physical laser ablation, while the self-assembly of miniature compounds is performed into NPs through bottom-up methods characterized by chemical methods [36-38]. As the physical methods need high pressure or temperature, and the most of the chemical methods require chemicals related to toxicity and hazardous to the biological environments/systems, it is necessary to develop greener, safer, eco-friendly and cost-effective synthetic techniques to exclude such complications for the synthesis of CoNMs [39,40]. The synthesis of CoNPs utilizing different green sources such as plants, algae, fungi and bacteria may be performed to get large-scale production with less contamination [41]. The plant extract method compared to bacteria and fungi-based methods for the synthesis of CoNMs may be utilized for higher scaling up and applications against infectious diseases and cancer owing to their favorable biocompatible, reducing and stabilizing, and inexpensive properties/facilities [42,43].

The precursors for the synthesis of CoNMs have been utilized with different cobalt salts such as cobalt chloride, nitrate, sulfate, and other cobalt compounds such as cobalt (salophen), N,N'-bis(salicylaldehyde)-1,2-phenylenediamino cobalt (II), cobalt (II, III) oxide nano-powder, and cobalt acetate tetrahydrate, while the surfactants/stabilizing agents/reducing agents as oleic acid, cetyl trimethyl ammonium bromide (CTAB), isooctane, alcohol, alkali, sodium borohydride, hydrazine hydrate, etc. [44-46].

The CoNMs have also been surface-functionalized with capping agents such as polyvinylpyrrolidone (PVP), starch, polyvinyl alcohol, phosphonomethyl imino diacetic acid (PMIDA), while the plant extracts containing flavonoids, starch, polypeptides, tannins, saponins, terpenoids and phenolics as the primary and secondary metabolites have been utilized to act as reducing and capping agents for the synthesis of CoNMs [44,45,22].

Characterization of synthesized surface-modified cobalt nanomaterials

The particle sizes and morphology (microstructure) of the CoNMs are studied by the high-resolution transmission electron microscopy. The crystalline structures (crystallographic states) and the phase formations of the cobalt oxide NPs are determined by X-ray diffraction study. The zeta potential and hydrodynamic values of CoNMs are determined by utilizing dynamic light scattering (DLS). The conjugations of coating materials with cobalt oxide NPs are investigated by the Fourier transform infrared spectroscopy.

Mechanisms of action of cobalt nanomaterials

The distinguishable mechanisms of action of CoNMs against infectious pathogens/cells involve mainly the interactions with the surface proteins and the disruptions of cell membranes, the productions of ROS, the damages of DNAs, the inhibitions of the synthesis of enzymes associated with the delivery of therapeutic components and the synergistic sterilizations (Figure 1).

The CoNPs may interact directly to the microbial outer membranes to cause membrane damages leading to destruction of microbial activities and growths [47]. The CoNPs owing to their higher surface-to-volume ratios may interact to the microbial outer membranes to cause the changes in the permeability, and the higher permeability produced may allow the NPs and their encapsulated cargos to enter into the microbes leading to more effective microbial killing [48]. The positively charged metal ions (Co^{2+}) released from CoNPs may directly interact to the negatively charged microbial surface membranes (containing lipopolysaccharides) to inhibit the biosynthesis of enzymes [49]. Moreover, CoNPs owing to their optimal and potent antimicrobial activity and suitable biostability are capable to kill drug-resistant pathogens/microbes [13,50].

CoNMs internalized/penetrated into the cancer cell membranes via endocytosis and the release of cobalt ions may induct the production of ROS in the cellular compartments leading to the cytotoxic activations of autophagic, apoptotic, and / or necrotic cell death signals [51-53]. Co_3O_4 NPs may disrupt the intracellular homeostasis and arrest the flux of autophagy owing to their capability to induct the aggregations of autophagosomes [19]. In addition, CoNMs may also induce significantly the generations of ROS, peroxidations of lipids, losses of mitochondrial outer membrane potentials and the

activations of caspase-3 enzymes in cancer cells for their killing [54].

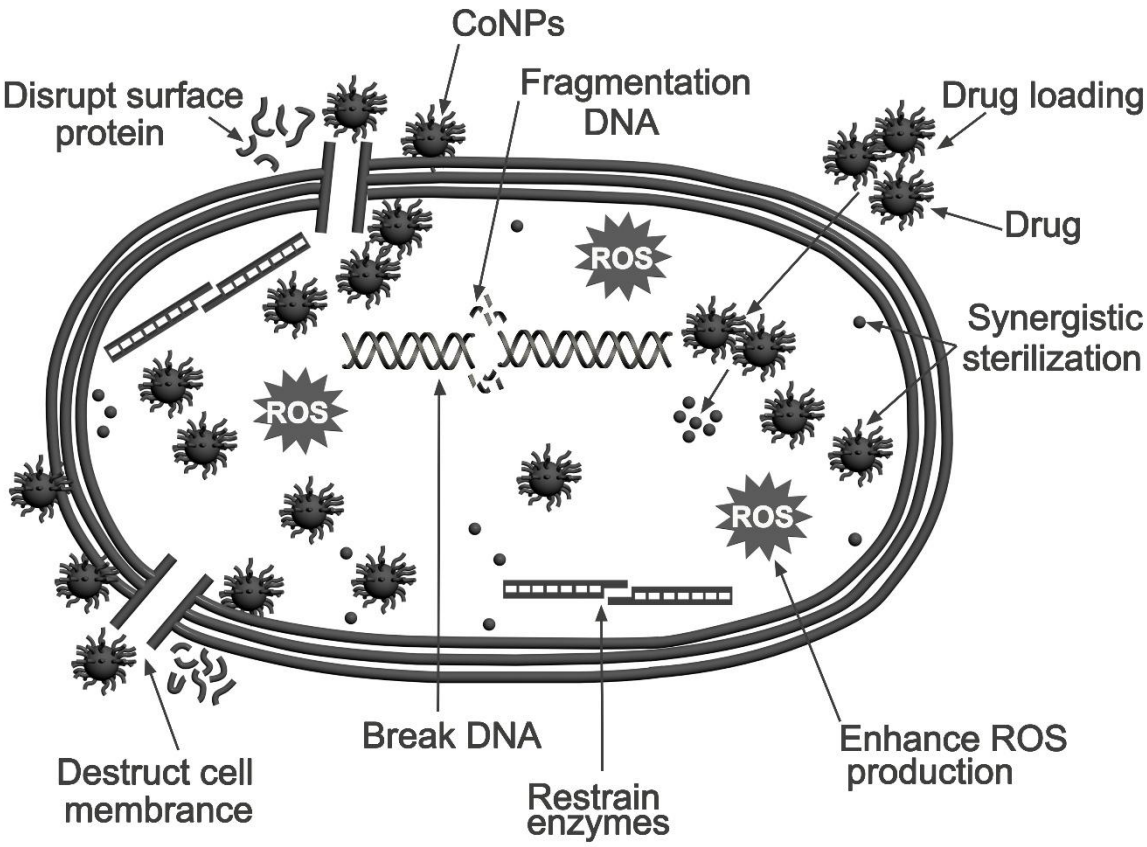

Figure 1: The salient mechanisms of action of cobalt nanoparticles against infections.

Biomedical applications of cobalt nanomaterials

Cobalt nanomaterials as anti-microbial activity

CoNMs with / without antibiotics/other cargos as delivery system have shown their significant anti-bacterial activities / higher therapeutic efficacies *in vitro* / *in vivo* against Gram positive/negative pathogenic bacteria including drug-resistant pathogens such as *Staphylococcus aureus*, *Proteus spp*, *Bacillus substilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebseilla pneumonia* and *Bacillus licheniformia* associated with also the active inhibition zone diameters in a dose-dependent manners utilizing disk diffusion assay [48,47,55-59]. CoNPs have been utilized as delivery system to get higher therapeutic efficacies against virus and retrovirus [60-62]. CoNMs have been utilized as anti-fungal delivery system to avail higher therapeutic efficacies through the generation of ROS [63,64]. The anti-mycotic efficacies of $CoFe_2O_4$ NPs and Co_3O_4 NPs have been monitored against a few fungal strains/pathogens (*in vitro* / *in vivo*) such as *Alternaria solani*, *Aspergillus niger*, *Fusarium oxysporum*, *Candida albicans*, *Dematophora necatrix*, and *Colletotrichum gloeosporiaides* through the colony forming unit [65-69].

Cobalt nanomaterials as anti-cancer activity

CoNMs have been used as anticancer delivery system against MCF-7 breast cancer cells through their bindings with DNAs to cause spiral elongations and cytotoxicity [70]. Methyl iminodiacetic acid phosphate-cobalt oxide (PMIDA-CoO) and Co_3O_4 with chitosan coating NPs have been used to treat human leukemia cells such as Jurkat, KG-1A and K562 to get anticancer effects such as ROS production, DNA damage, cell cycle arrest and secretion of TNF-α followed by apoptosis through the activations of caspase 3, 8 and 9, and enhancement of Bax/Bcl ratio owing to the release of cobalt ions leading to the selective inhibitions of cancer cells along with the cellular membrane damages without any inhibitory effects on normal cells [71-74]. Co_3O_4 NPs have also utilized against U-87 MG cancer cells to get cytotoxic and inhibitory effects on proliferative cancer cells [20]. Co_3O_4@Glu/TSC and $Co(OH)_2$@Glu-TSC NPs have been treated against gastric and breast cancer cells to get their cytotoxic and apoptotic inhibitory effects [20,75]. Co_3O_4 NPs have been utilized as photothermal therapy to inhibit and eliminate tumors [29]. CoNWs-GO-PEG-DOX NMs as targeted antitumor agent have shown their synergistic chemo-photothermal activities to eliminate cancer cells [29]. $Co_{0.5}Ni_{0.5}Nb_xFe_{2-x}O_4$ NMs have been applied to treat cancer cells exhibiting nuclear DNA disintegrations and death of programmed cancer cells [76]. CoNMs such as CoNPs, CoO/Co_3O_4/CoO NPs obtained by the green methods have exhibited their cytotoxic inhibitory effects on cancer cells such as U87, HCT116 and MCF-7 with higher targeted therapeutic efficiencies [17,77-79].

Cobalt nanomaterials as contrast as well as diagnostic/theranostic activity

A hybrid NM based on Co_3O_4 and graphene nanosheets has been utilized to detect glucose [80]. Manganese/cobalt oxide NPs (MnO_2/Co_3O_4) have been used as theranostics as well as contrast agents for MRI against cancer owing to the release of manganese ions in contact with glutathione and the degradation of NPs [81]. Cobalt phosphide NPs have been applied as contrast as well as photosensitizer agents for imaging tumors and in photothermal therapy (PTT) [82]. Cobalt sulfide nanosheets modified with polyethylene glycol (PEG-CoS NPs) have been used as photoacoustic/magnetic resonance as well as photosensitizer agents for imaging and PTT [83]. CoNPs have also been used in several investigations as the potential theranostics as well as photothermal agents [84,85,19,86].

Toxicity and elimination of cobalt nanomaterials

The exposures (1-40 µg/mL) of Co_3O_4 NPs in human alveolar (A549) and bronchial (BEAS-2B) cells have indicated no cytotoxicity for A549 cells, but the reduction of viability at 40 µg/mL and membrane damages at 1,5, and 40 µg/mL for BEAS-2B cells [87]. The exposures of Co_3O_4 NPs in HepG2 cells have exhibited the cytotoxicity and genotoxicity via the production of ROS and the generation of oxidative stress [21]. CoNMs have shown systemic toxicity (such as ROS production, DNA damage and mutation, chromosomal aberration, enhancement in cytosolic calcium, depletion of glutathione, and lipid peroxidation) including cardiovascular, neurological and endocrinal disorders through the attribution of free ionic Co(II) with the higher blood concentrations (>300 µg/L) and the replacement of irons in metalloenzymes to cause anxiety, hypoxia, lung inflammation and injury, mitochondrial dysfunction, and skin sensitization [10,88-96]. Cobalt oxide NPs have shown no significant toxicity at a dose of 10 mg/mL on zebra fatal survival and incapacity [97,98]. Cobalt oxide NPs (100 nm) have exhibited risk level toxicity for 90 days' period of toxic exposure in Sprague Dawley mice, while the concentrations of the NPs above 125 mg/kg have shown the significant toxicity on both the sexes [99].

In general, endocytosed NMs are fabricated to break within the phago-lysosomal compartments and eliminated through hepato-pancreatic biliary system and the small intestine as fecal clearances, while non-decomposed larger NMs (>6 nm) are secluded chiefly in the liver and spleen for fewer months or eliminated out through the renal glomerular bed (<5 nm) [32].

Conclusions and future perspectives

Though CoNMs are biocompatible trace elements having selective affinity to diseased cells (containing more phospholipids), their chemical synthesis, non-targeting activity and exposure of excess amounts may produce cytotoxicity affecting normal health. Therefore, optimizations of cargos in CoNMs delivery systems including eco-friendly green synthesized NMs with their selective physico-chemical features including morphology are highly required to treat infections and cancers to overcome the obstacles such as toxicity, non-selectivity, drug-resistance and other biological barriers. In addition, their proper surface-functionalization with cargos, ligands, sugars, proteins, peptides, polymers, and other biomaterials might be performed to reduce toxicity maximally and to get higher therapeutic efficiencies. Moreover, the interactions of different CoNMs with the biological systems might be investigated in detail to apply them as suitable delivery systems. Furthermore, the thorough investigations regarding the cytotoxicity, immune responses, bio-distribution, pharmacokinetics, elimination, and scaled up productions with batch-to-batch uniformities, and routes of administration specifically intravenous and oral are needed to avail maximum therapeutic efficacies of CoNMs to consider them as favorable nano-delivery system before going to clinical translations.

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