Available online on 15.05.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Review Article

Nickel nanomaterials as delivery system in combating diseases

Ardhendu Kumar Mandal *

Central Instrumentation Division, CSIR-Indian Institute of Chemical Biology, Kolkata, India

Article Info:

Article History:

Received 18 Feb 2025
Reviewed 06 April 2025
Accepted 28 April 2025
Published 15 May 2025

Cite this article as:

Mandal AK, Nickel nanomaterials as delivery system in combating diseases, Journal of Drug Delivery and Therapeutics. 2025; 15(5):166-176 *DOI: http://dx.doi.org/10.22270/jddt.v15i5.7124*

*Address for Correspondence:

Ardhendu Kumar Mandal, Central Instrumentation Division, CSIR-Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Jadavpur, Kolkata – 700032, India

Abstract

Many people suffer from the aggravation of infections and inflammations initiated by the exposure of virulent microorganisms or other toxicants globally owing to the development of drug resistance accompanied with drug toxicity, insolubility, non-specificity, and the occurrence of biological barriers. Nanotechnology-based nickel nanomaterials (NiNMs) such as nickel oxide nanoparticles (NiONPs) and nickel hydroxide nanoparticles ($Ni(OH)_2$NPs) have attracted attention as nano-medicinal delivery system to inhibit the disease-development and spreading due to their suitable physicochemical characteristics such as nano sizes, effective shapes, high surface to volume ratio, increased reactivity, easy surface-functionalization, and photo-thermal activity. Metallic NiNMs are capable to penetrate cellular membrane causing cellular leakage, and to generate reactive oxygen species (ROS) for interaction with cellular molecules to damage DNAs, proteins, and lipids leading to microbial or cellular deaths. Moreover, their surface-functionalization with specific ligands, drugs, and other biomolecules may direct their modulations as suitable targeted delivery system on lowering cytotoxicity, minimizing drug degradation and loss, and increasing bioavailability of drug compounds. This review elucidates chiefly on the synthesis, drug loading and functionalization, mechanisms of action, biomedical applications, toxicity, biodistribution and elimination of NiNMs as delivery system in combating diseases.

Keywords: Infections and inflammations; Nickel nanomaterials; Delivery system; Bio-medical applications

Introduction

Infectious diseases caused by the biological pathogens such as bacteria, virus, fungi or protozoa may lead to the development of life-threatening diseases globally owing to the organisms' nano- sizes and shapes compatible for their transportations to the specific biological compartments. After the exposure of pathogenic agents or other toxicants into the biological system, the anti-oxidant and immune body defense mechanisms may interact to suppress the pathogenic loads by killing the pathogens and / or scavenging the free radicals generated[1]. However, when the pathogenic burdens and free radical stresses overpower the body defense mechanisms, diseases are initiated, developed and progressed with the reflections of sometimes progressive inflammations, cancers and other diseases, even with the emergence of drug resistance characterized by the cell-wall thickening of organisms, efflux of drug molecules, enzymatic destructions, and target variations[2-7].

The process of inflammation is regulated by mast cells, containing heparin, serotonin, bradykinin and histamine, through the release of their contents in response to their degranulation, transmitted infection and injury, and also under the influence of other controls such as liberations of serotonin and histamine in reaction to progesterone and estrogen respectively[8]. Another inflammatory pathway is arachidonic acid cascade regulated by eicosanoids, dependent on the genetic or other factors to control the size and extent of tumor metastases[9]. In severe conditions, inflammation may lead to mental disorders through the degradation of tryptophan by cytokines and the enhanced activity of indolamine 2,3-dioxygenase (IDO) (the rate limiting enzyme), and the subsequent depletion of serotonin, allied to mental depression[10].

The interactions of the cellular immune system with endogenous or exogenous antigens may initiate the generations of reactive oxygen species (ROS) and reactive nitrogen species (RNS) promoting to signaling cascades to produce the liberations of proinflammatory chemokines and cytokines related to the hemopoiesis, ion-channel regulators, non-specific and specific immune responses and tissue repairs. Transmission of extracellular information into the cytoplasm and nucleus activated by the anchoring of cytokines to their specific receptors is processed through various signaling pathways such as nuclear factor kB and mitogen-activated protein kinase (MAPK)[11]. Sustained vigorous information may proceed to cellular injury or

hyperplasia followed by the overproductions of free radicals in non-phagocytic cells from inflammatory cells, while interactions of ROS with DNA in mitotic cells may lead to persisted genomic mutation. During chronic inflammations, cellular antioxidant systems may activate genes linked to DNA repair responding to free radical overproductions and causing depletion of cellular antioxidants[12]. Acute or chronic inflammatory processes reflected by trauma or arthritis, and infection or other progressive inflammatory diseases relate the genetics and molecular biology to basic cellular responses as the pivotal role for identifying the genetic predisposition to various inflammatory mediated sequences[13,14].

A few novel therapeutic lead drug compounds including non-steroidal anti-inflammatory drugs (NSAIDS), and drugs derived from natural sources have been utilized against inflammatory diseases to modulate inflammatory mediators (calcium, protein kinases, cAMP and cGMP), the expressions of pro-inflammatory molecules such as cytokines (TNF-α and IL-1β), cyclooxygenase (COX-2), inducible NO synthase (iNOS), neuropeptides, and proteases, and the expressions of lead transcription factors such as AP-1, NF-kB, and proto-oncogenes (c-fos, c-jun, and c-myc)[15-17]. However, a larger number of patients suffer from conventional therapies owing to their side effects of drug-toxicity, drug-resistance, drug-non-specificity, and other biological barriers against chronic inflammatory diseases, and therefore, require effective therapeutic efficacies with least side effects to give relief from the symptoms of systematic inflammations[18-20].

Nanotechnology-based drug delivery has attracted attention owing to its capability to reduce the toxicity and side effects of therapeutics, to cross the blood-brain and other biological barriers, and to overcome the drug-resistance[1,21]. Nickel is an essential element having the roles in the reduction of carbon monoxide to acetate through the activation of carbon monoxide dehydrogenase, the interaction with iron in hemoglobin for the transport of oxygen, the stimulation in the metabolism, the transmission of genetic code (RNA and DNA), and the co-ordinations in nerve impulses, muscle excitations and contractions via substitution of calcium in the process of excitation, and the involvement in the anchoring to membrane ligands (e.g. phosphate groups of phospholipids), and also regulates the formation of cyclic nucleotide cGMP to control various physiological signaling processes. Ni NMs have gained attraction for their higher stability and excellent optical, electronic, magnetic and catalytic characteristics as well as their existence of higher inexpensivity, non-toxicity, stable P-type semi-conductivity with an extensive band-gap of 3.6-4.0 eV in the usages for medical applications, imaging, drug delivery, diagnostics and antibiotics against various diseases[22-26]. This review provides mainly the biomedical applications of Ni NMs against infections, cancer, and inflammatory related other diseases to consider them as suitable nano-medicinal delivery system.

Synthesis of nickel nanomaterials

NiNMs are prepared mainly by self-assembly of small particles through the generation of atoms, nucleation and growth phenomenon utilizing chemical as well as biological synthesis methods via bottom-up approaches[27-31].

The counterions determine the solubility of the precursor nickel salts in the solvents and influence the electrostatic stabilizations, the pH modifiers, and the complexing agents. NiNMs may be synthesized via various nickel salts such as nickel chloride ($NiCl_2$), nickel (II) nitrate ($Ni(NO_3)_2$), nickel (II) acetate ($Ni(CH_3CO_2)_2$), nickel (II) oxalate (NiC_2O_4), nickel (II) bis (acetylacetonate) ($Ni(C_5H_7O_2)_2$), nickel (II) sulfate ($NiSO_4$), nickel (II) dodecyl sulfate ($Ni(DS)_2$), while various concentrations of nickel salts are utilized to control nucleation and growth ratio for forming the different shapes, sizes and morphology of the NPs[32].

Strong reducing agents such as hydrazine and $NaBH_4$ in alkaline medium, medium-strength reductants such as polyols in various alcohols and citric acid, and weak reductants such as sodium hypophosphite (NaH_2PO_2) and ascorbic acid are used for the synthesis of NiNPs with a variety of nucleation and growth processes dependent on precursors' concentrations, and variations of temperature and pH of the reaction mixture, while nickel ions (Ni^{2+}) are reduced to nickel atoms (Ni^0) after gaining two electrons from the reducing agents[32].

Various stabilizing agents, including surfactants, capping agents and other compounds, such as cetyl-trimethylammonium bromide (CTAB), tetra-butylammonium bromide (TEAB), tetraethylammonium bromide (TBAB), tetra dodecyl ammonium bromide ($TC_{12}AB$), sodium dodecyl sulfonate (SDS), citric acid, tween 40 and 80, PEG 6000, D-sorbitol, hydroxyethyl carboxymethyl cellulose (HECMC), sodium carboxyl methylcellulose (Na-CMC), trioctylphosphine (TOP), trioctylphosphine oxide (TOPO), and poly (vinyl pyrrolidone) (PVP) are employed in nickel synthesis to counteract van der Waals' forces and magnetic dipole-dipole interactions by utilizing electrostatic forces, π-π interactions and hydrogen bonding to inhibit the agglomerations and stabilize the surface charges of the NPs[32].

Chemical synthesis

In the presence of alkaline medium and reducing agent-hydrazine (N_2H_4), NiNPs may be synthesized through a complex reaction to a controlled size and morphology when the ratio of N_2H_4/Ni^{2+} becomes <4.5, and in the absence of OH^-, the nickel complex may be reduced to metallic nickel by direct hydrazine reduction, while the presence of OH^- in the reaction solution may produce a color change to gray via ligand exchange of Cl^- by OH^- for forming nickel hydroxide ($Ni(OH)_2$) and subsequent Ni^0 NPs through the consequent color changes from gray to black owing to the subsequent reduction by hydrazine, and the production of adsorbed hydrogen atoms (H*) via the interaction of remaining hydrazine with OH^- for generating electrons and water, while nuclei-formed may function as an active site and center for the adsorptions

of hydrogen atoms to capture Ni^{2+} from the solution[32]. NiONPs have been produced through monitoring nickel-containing gels by utilizing chemical reagents and exposing gel to heat-treatment upto 1000ºC[33,34]. Cubic NiONPs have been formed through utilization of chemical stabilizers such as isopropanol and ethylene glycol, and nickel nitrate hexahydrate as a precursor, and also surfactant triton X-100 as detergent for avoiding aggregation[35]. NiONPs have been synthesized utilizing citric acid and malic acid respectively without addition of any reducing agent and surfactant[36,37]. NiONPs (25 nm) have been fabricated utilizing $Ni(octa)_2$-oleylamine complex through thermal decomposition at 200ºC, where triphenyl phosphine ($C_{18}H_{15}P$) and oleylamine ($C_{18}H_{37}N$) have been utilized as surfactants, and the $C_{18}H_{37}N$ has been used also as the medium as well as the stabilizing agent[38]. Hydrazine and alcohols have been utilized as complexing agents during the synthesis of NiONPs[39]. NiONPs have been synthesized through solvo-thermal protocol utilizing nickel nitrate and citric acid as the precursor and the chelating agent, respectively[40]. NiONPs have been synthesized by chemical precipitation without utilization of surfactant, or stabilizing and capping agents[41]. NiONPs have been also synthesized via combustion by using organic fuels[42].

The synthesized NPs, carrying by-products and un-reacted components, may be purified utilizing different methodologies such as centrifugations, magnetic separations, membrane separations (dialysis, filtrations, and ultra filtrations), chromatography procedures, and thermal treatment methods[43-47].

Biological synthesis

Biological synthesis is a bottom-up approach utilizing natural stabilizing and reducing agents, such as plant extracts, microorganisms and biomolecules, including polysaccharides, amino acids, proteins, enzymes and vitamins to synthesize NPs[48].

Plant-mediated synthesis of nickel oxide nanoparticles

The various plant species and their extracts as phytochemicals for the reduction of nickel ions from the solution of nickel salts have been utilized to fabricate NiONPs, while the polyphenols and the hydroxyl groups of flavonoids as well as the hydroxyl and carbonyl groups of amino acids act as reducing agents to stabilize the synthesized NPs[49,50]. For the preparation of NiONPs, plant extracts and solutions of nickel salts are admixed followed by heating with constant stirring. The mixture is spun after the completion of the reaction. The clear supernatant is discarded, and the deposited pellets are cleansed, oven-dried, and calcined to get NiONPs.

Microbes-mediated biosynthesis of nickel oxide nanoparticles

Microbial fabrications of NPs occur through either extracellular or intracellular approaches. Intracellular synthesis involves the transport of metal ions into the microbial cells and the formations of NPs by coenzymes, proteins and heterocyclic derivatives exist within the cells. Extracellular synthesis involves the entrapment of metal ions on the surface of microbial cells and the proteins and / or enzymes exist on the surface reduce the metal ions, and stabilize the synthesized NPs[51,52]. Different microbes such as bacteria, fungi, algae and yeasts, and various nickel salts as precursors have been utilized for the green synthesis of NiONPs[53-59].

Other green source-mediated synthesis of nickel oxide nanoparticles

Other green environmentally benign and biodegradable natural substances utilizing hydroxyl, carboxyl, or carbonyl groups of gums, tannic acids, chitosan, amino acids, or polysaccharides as reducing, capping, or stabilizing agents, and nickel salts as precursors have been used for the biogenic synthesis of spherical NiONPs and Ag-NiO nanocomposites with their photocatalytic activities[60-65].

Generally, under optimal conditions (such as pH of the reaction medium, quantity of NPs, and reaction time), 10 mg NPs are added to 5 mL of drug (0.1 M at pH 7) followed by stirring for 9 h at 25ºC in the dark. The sample is then spun for 10 min, and the supernatant is separated. The amount of drug may be determined by utilizing HPLC technique[66].

Functionalization of nanoparticles with biomolecules

Surface attachments of NPs with biomolecules such as antibodies, proteins and DNA are generally carried out utilizing conventional bioconjugation techniques[67]. Biomolecules may be attached to nanoparticles via either physical adsorption or chemical covalent coupling reactions[68]. In physical adsorption, electrostatic and hydrophobic interactions take place between NPs and biomolecules, while in covalent chemical modifications, functionalization of NPs takes place with amine, carboxyl, or sulphide groups.

Characterizations of nickel nanomaterials

The morphological features i.e. the sizes of the NMs are determined through the utilizations of atomic force microscope (AFM), transmission electron microscope (TEM), and scanning electron microscope (SEM). The phase purity and crystallite sizes of NiONPs are determined through using X-ray diffractometer (XRD). The reduction of Ni^{2+} ions in solution, and the interactions of drugs with NPs through their binding groups are monitored through using UV-VIS spectrophotometer, Fourier transform infrared (FT-IR) spectrometer, or Gas chromatography mass spectrometer (GC-MS). To detect the elemental compositions or existing elements in the NMs and also in their surface compositions such as stabilizing and / or capping agents, energy dispersive X-ray spectroscope (EDS) or X-ray photoelectron spectroscope (XPS) may be utilized. The hydrodynamic diameters of NiONPs in aqueous suspension as well as their polydispersity index (PDI) and zeta potential are investigated through dynamic light scattering (DLS) analysis. The thermal behaviors of the primary gels, and the magnetic features of the produced NiONPs are investigated utilizing thermo-gravimetric analyzer (TGA), differential thermal

analyzer (DTA), and vibrating sample magnetometer, respectively.

Mechanisms of action of nickel nanomaterials

Antimicrobial as well as anticancer activities of NiNMs are linked to nickel ion contents that interpenetrate the microbial or diseased cells and reach the cellular surface membranes and intracellular milieu. The influx of nickel cations destroys organelles such as ribosomes and affects cellular metabolisms owing to the electrostatic attractions of negatively charged intercellular membranes and positively charged nickel ions[69,70]. Owing to the higher surface activity and larger surface-to-volume ratios of NiNMs, their exposures / direct contacts / adsorptions to cells may disrupt the cell membrane morphology and cellular transport[50,71,72]. Moreover, the higher affinity of NiNMs to phosphor and sulfur -containing ingredients such as proteins and DNAs may disrupt cellular DNA replications leading to protein deformations[73]. The killing of cell is also related to the generations of free radical species produced by the photo-excitations of NiNMs and their interactions with cellular components resulting in damages of cell walls and DNAs, formations of membrane-pores, cell cycle arrests, and ultimately inhibitions of cellular growths[74].

Investigators have unveiled the antimicrobial mechanisms of NiNMs that the reactive oxygen species (ROS) such as super oxides ($O_2^{\cdot-}$), hydroxyl radicals ($\cdot OH$) and hydrogen peroxides (H_2O_2) are generated through the activation of NiONPs by visible and ultraviolet light, while $O_2^{\cdot-}$ and $\cdot OH$ ions are unable to penetrate the cell membranes owing to their excessive negative charges, however, H_2O_2 can enter into the cells to induce cell death via the disruption of cell membrane integrity and damaging of DNA, mitochondria (electron transport), and proteins (tertiary structures) within the cells, associated with the formations of pores, shrinking and fragmentations of cell membranes[72,75-78]. Additionally, the uncoupling of ATP productions, the loss of protein motive forces, and the interference with the phosphate efflux mechanisms exposed by the interactions of NiONPs with thiol groups of cellular proteins may lead to the separation of the cell membranes from the cytoplasm resulting in condensation of genetic materials, loss of replication, or the release of intracellular components[78] (Figure 1).

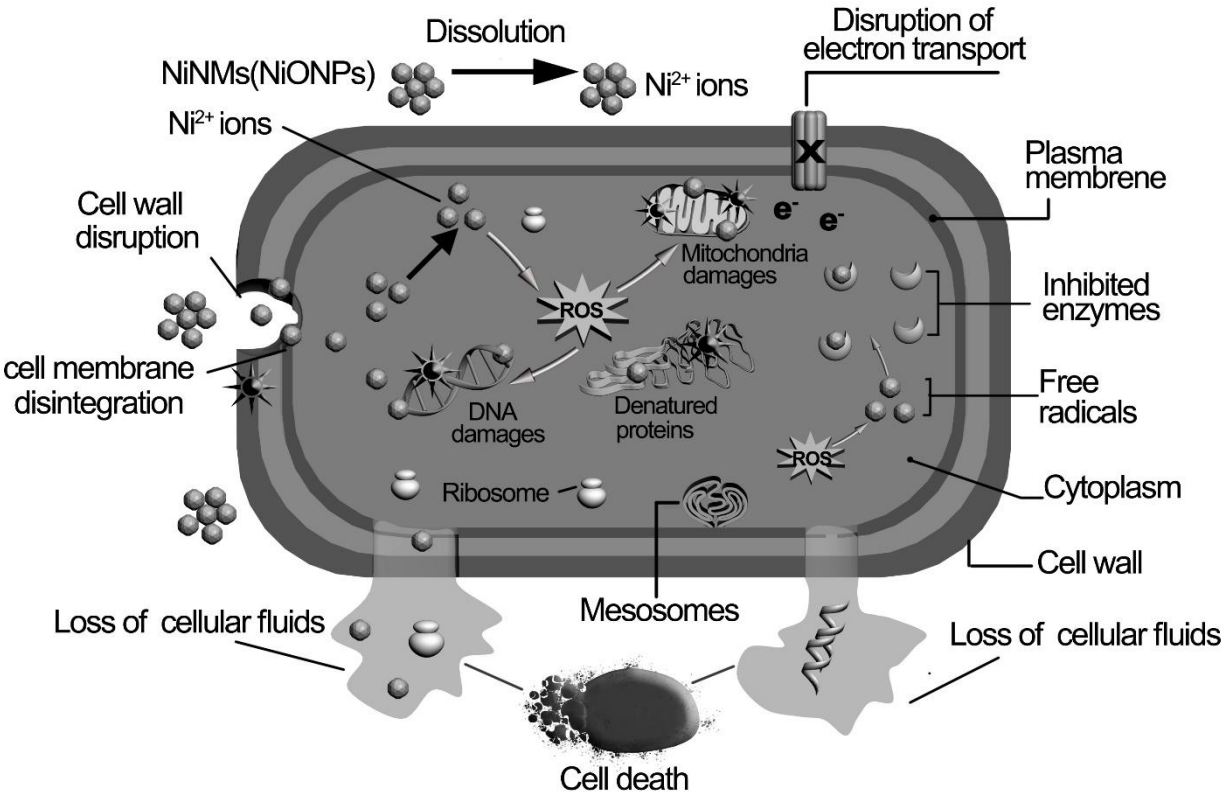

Figure 1. Anti-microbial mechanisms of NiNMs (NiONPs).

Many investigators have proposed the plausible anticancer mechanisms of NiONPs through the ROS-dependent and caspase-mediated apoptosis in cancer cells[49]. The contact of NPs with the surface-membrane of cancer cells may trigger invaginations of NPs through endocytosis for generation of intracellular membrane-bound vesicles followed by their liberations to produce ROS resulting in mitochondrial dysfunctions, nuclear damages, protein oxidations, DNA damages, decrements of major free radical scavengers, and cell cycle arrests, leading to apoptotic cellular deaths via the activations of caspases 3, 8 and 9, and the enhancements of the levels of tumor protein P53 for inhibiting growth of cancer cells[49,79-82]. Moreover, the internalization of nickel (II) ions into the cells may activate the calcium-dependent cascades to disrupt DNA repair mechanisms leading to apoptotic cellular killing[49,83] (Figure 2).

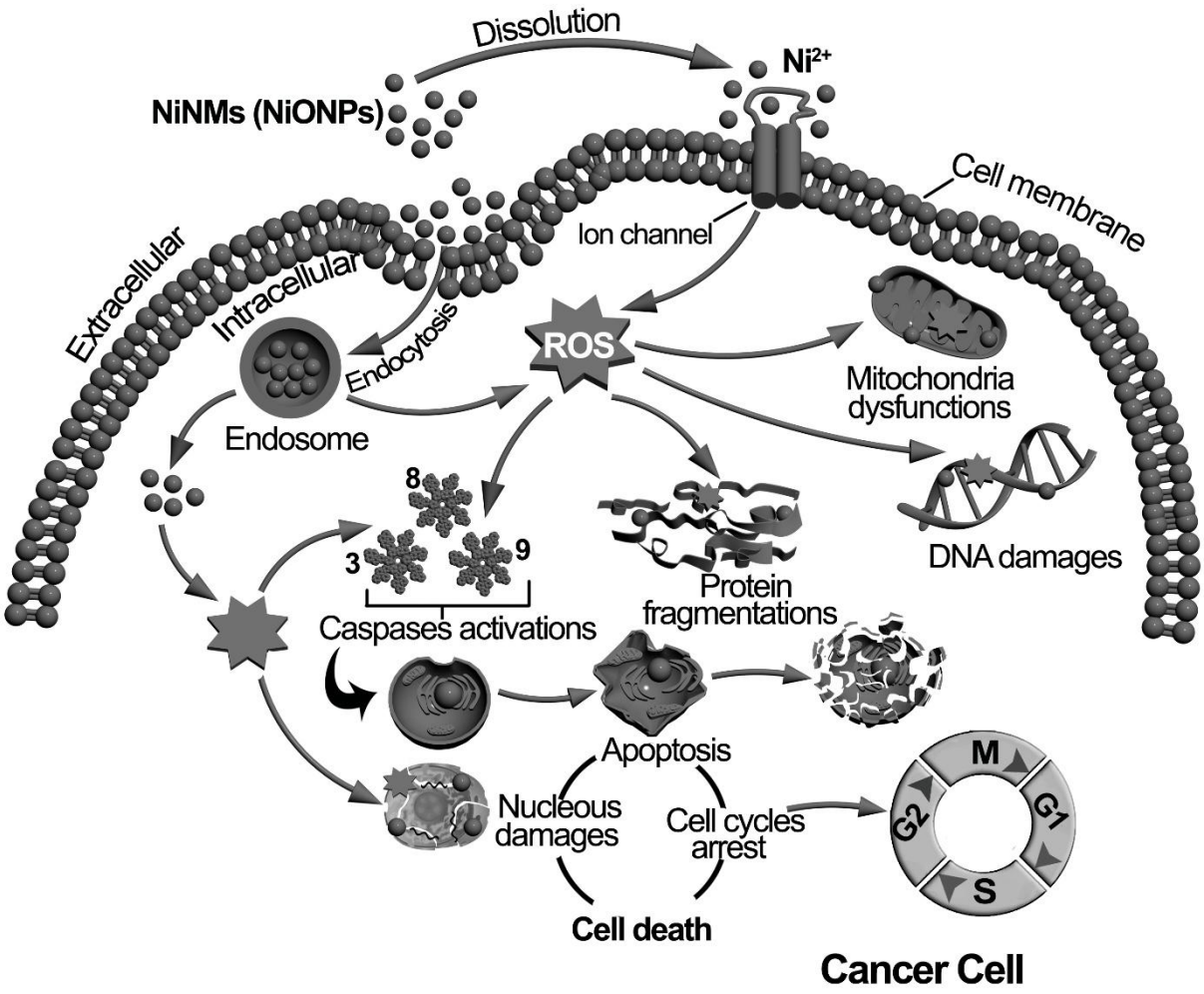

Figure 2. Anti-cancer mechanisms of NiNMs (NiONPs).

Biomedical applications of nickel nanomaterials

NiNMs with or without drug/s as delivery systems have been utilized to treat various diseases/ pathogens/ diseased cells such as against microbes, fungi, drug-resistant biofilms, inflammations, cancer cells, leishmania parasites and diabetes.

Antimicrobial activities

NiONPs have been used to treat various human pathogenic microorganisms with substantial anti-pathogenic outcomes[49,78.] NiONPs synthesized utilizing *Aegle marmelos* and *Moringa oleifera* leaf extracts have shown potential bactericidal effects towards multi-drug-resistant Gram positive and negative bacteria with a variation owing to the polarity differences between their membranes[49,71]. Gram positive bacteria having excess positive charges and multiple layers of thicken peptidoglycans on their surrounding cell walls compared to Gram negative bacteria having a single layer of thinner peptidoglycan and lipopolysaccharide contents on their outer membranes lead to easy penetration of negatively charged free radicals to cause more cells damages and cell deaths in Gram positive than Gram negative bacteria, while the outer membranes of Gram negative bacteria act as permeability barriers to reduce the entry of ROS into the cells[84-86].

The antibacterial and antibiofilm activities of biosynthesized NiONPs with or without drugs such as chloramphenicol and gentamicin, and the exposure of UV illumination towards *S. aureus*, *P. aeruginosa*, *E. coli*, *B. subtilis*, *K. pneumonia*, *E. faecalis*, *A. baumannii* and *S. typhi* have exhibited shrinking, fragmentation, and disorganization of outer surfaces including the formation of gaps and pits, and higher zones of bacterial growth inhibitions evaluated on agar plates[50,74,76-78,87-90].

Antifungal activities

The antifungal activities of biosynthesized NiONPs utilizing *Rhamnus virgata, Rhamnus triquetra* and *Sageretia thea* leaf extracts against various pathogenic fungal strains such as *A. flavus*, *R. solani*, *M. racemosus*, *A. niger*, *C. albicans*, and *F. solani* have exhibited their various levels of growth inhibition rates correlated with ROS-produced mitochondria and DNA damages in the dose-dependent manners[75,77,88]. The antifungal applications of the biosynthesized NiONPs@C-dots against *C. albicans* fungus strain have shown their higher inhibition zones compared to NiONPs[74].

Anti-inflammatory activities

The ROS-induced TNFα and NFkB activations, the secretions of pro-inflammatory cytokines, and the over-expressions of adhesion molecules by the endothelial

cells lead to endothelium dysfunctions and chronic inflammatory atherosclerosis[31,91]. The applications of biosynthesized NiNPs with *Aegle marmelos correa* (AmC) accompanied by β-sitosterol have shown their synergistic anti-inflammatory activities through the elimination of free-radical oxidants in extracellular regions through H-atom donations and the supporting proliferations of lymphocytes to enhance the cytotoxic efficiency of natural killer cells[92].

Anti-cancer activities

The various concentrations of NiONPs (500-3.9 µg/mL) synthesized with *Geranium wallichianum* plant extract have shown their anticancer activities exposed on human hepatocarcinoma (HepG2) cells for 24 h as the dose-dependent inhibitions of cancerous cells[50]. Fabricated NiONPs utilizing *Andrographis paniculata* leaf extract have exhibited the concentration-dependent inhibitions against human breast cancer cells (MCF-7)[93]. NiONPs synthesized with *Moringa oleifera* have shown higher toxicity and gradual decrement in cell viability through ROS-generated mitochondrial dysfunctions towards human colorectal adrenocarcinoma (HT-29) cells in a dose-dependent manner[71]. The NiONPs synthesized with *Euphorbia heterophylla* leaf extracts have exhibited the dose-dependent anticancer activities against human lung cancer cells (A549), and HepG2 cells[94]. NiONPs orchestrated with *Rhamnus virgata* leaf extracts have shown their anticancer potentiality towards HepG2 cells in the dose-dependent manners[75]. Biosynthesized NiONPs utilizing *Abutilon indicum* leaf extracts have shown their anticancer activities against cervical cancer cells (HeLa)[48]. NiONPs fabricated *Salvia macrosiphon* extracts have exhibited the concentration-dependent cytotoxicity towards Neuro 2A cells, while the liberation of nickel (II) ions inside the cells results in cell death[95]. NiONPs fabricated utilizing egg white have exhibited significant toxicity against gliobastoma cancer cells (U87MG)[65]. Biosynthesized NiONPs utilizing *Calendula officinalis* extracts have exhibited their anticancer efficacies towards esophageal carcinoma cells (FLO-1, ESO26, OE33, and KYSE-2700[96].

Anti-leishmanial activities

Bio-synthesized NiONPs utilizing *Geranium wallichianum, Rhamnus virgata*, *Rhamnus triquetra* and *Sageretia thea* extracts against amastigotes and promastigotes cultures of *Leishmania* have exhibited dose-dependent anti-leishmanial activities suppressing the leishmanial growths[50,75,77,88].

Anti-diabetic activities

NiONPs fabricated with *Averrhoa bilimbi* and *Arcea catechu* leaf extracts have shown their potential anti-diabetic activities on α-amylase inhibitory efficacies, and also higher anti-diabetic activities than metformin[97,98].

Toxicity

The accumulations of Ni at intracellular targeted zones lead to free radicals-induced inflammations, damages of different cell structures including proteins, lipids, nucleic acids, and membranes, resulting in apoptosis and cytotoxicity at high exposure levels of NiNMs (mainly NiO and $Ni(OH)_2$ NPs) affecting the various levels of toxicities generated in the biological systems[99-101].

Acute and chronic exposures of NiNMs may induce lung inflammations characterized by delayed type-hypersensitivity (DTH), pulmonary alveolar proteinosis (PAP), lymphocytic foci, epithelial proliferation, granulocytic infiltration, enhanced levels of lactate dehydrogenase (LDH), 8-hydroxy-2'-deoxyguanosine (8-OHdG), total polymorpho nuclear leukocytes (PMNs), γ-gutamyl transferase, amylase, alkaline phosphatase and aspartate amino transferase[102-105].

The cardiovascular toxicity may appear by the exposures of NiNMs at high concentrations characterized by inflammations, contractile and Vaso-relaxation responses, enhanced population of bone marrow and circulating endothelial / progenitor cells, down-regulated MCP-1 levels in the aorta correlated with diminished chemotaxis signaling, down-regulated transferrin, up-regulated Ccl-2, IL-6 and HO-1, mitochondrial DNA damage in aorta, and enhanced plaque lesions, Vcam-1 and Cd68 levels in the aorta[106-109].

The acute / chronic exposures of NiO and $Ni(OH)_2$ NPs in various dose and time -dependent manners have shown the damages of systemic organs (such as liver, spleen, kidney, lung, heart, aorta, stomach and brain) through changes of biochemical, functional and histopathological indices in animals administered via intra-tracheal instillations, inhalations, intra-peritoneal injections or oral gavages. Various authors have reported significant enhancements in liver weight and lactate dehydrogenase, leukocytosis, systemic inhibitions of the oxidation-reduction energy metabolisms, increased lipid peroxidation, stimulation of erythropoiesis (elevated hemoglobin contents, erythrocytes count, reticulocytes and hematocrits), increased numbers of akaryotic and bi-nucleated hepatocytes, and kupffer cells, cellular edema, disappearance of hepatic sinus, spleens growing increased diameters of the follicles, and kidneys growing brush border loss in proximal tubules, up-regulated HO-1, SAP, Ccl-2 and IL-6 mRNA levels, up-regulated TNF-α levels, decreased GSH levels, enhanced glutathione-S-transferase and catalase activities, significant decrements in total antioxidant capacity and increments in MDA levels, including hyperemia, gliosis, necrosis and spongy changes in brain[105,109-118].

The exposures of NiONPs at various dose and time dependent manners have shown their genotoxicity and carcinogenicity related to increased DNA fragmentations in circulating nucleated blood cells, enhancement in % tail DNA in peripheral blood leukocytes, kidney and hepatic cells, increment in polychromatic erythrocytes micronuclei and chromosomal aberrations in bone marrow cells[105,112,119].

The administrations of NiONPs (200 mg/kg/day) daily through oral gavage for 28 days have exhibited no mortality to rats except a few symptoms such as irritation, dullness and distress[114].

Biodistribution and elimination

The accumulations / eliminations of NiNMs in / from different systemic organs and blood depend on the various routes of exposures (such as intratracheal instillation, inhalation, intravenous, intraperitoneal, subcutaneous, and oral) and assay variables such as species, methodology, time, dose, chemical / green / biological synthesized forms, shapes and sizes of NPs. The intratracheal instillations of spherical / irregular shaped NiONPs (0.67- 6.0 mg/kg) to rats have shown the higher NiO accumulations in most of the thoracic lymph nodes and liver[120]. The oral administrations of NiONPs (125-500 mg/kg) to rats have exhibited accumulations of Ni more in liver followed by the brain, kidney and spleen[113]. In general, endocytosed NPs are processed and broken within the phago-lysosomal compartments and eliminated through hepato-pancreatic biliary system and the small intestine as fecal clearances, while non-decomposed larger NPs (>6 nm) are sequestered chiefly in the liver and spleen for a few months or excreted through the glomeruli bed (<5 nm)[1].

Conclusions and future perspectives

As NiNMs having toxic features to eukaryotic cells at high level and their chemical synthesized forms carrying toxic impurities, eco-friendly green synthesized NiNMs encapsulated / functionalized with ligand-binding cargo/s may be suitable approach to overcome these obstacles as well as non-specificity and drug-resistance as targeted delivery system owing to their high surface-to-mass ratio, capability of adsorbing and transporting additional compounds[121]. In this context, the explorations of the proper optimizations of the synthesized delivery formulations, functionalization, characterizations with or without ligands and cargos, repeated batch-to-batch uniformed large scale productions of the NiNMs along with their interactions with biomolecules are needed before applications to avail higher therapeutic efficiencies against diseases. Additionally, a thorough investigation regarding their cytotoxicity, immune responses, biodistributions, pharmacokinetics and eliminations, and routes of administration is required for achieving maximal therapeutic efficacies of NiNMs for considering them as suitable delivery system as well as nanomedicine before clinical translation against diseases.

Acknowledgement: This study was supported by the Council of Scientific and Industrial Research (CSIR), Government of India.

Authors contribution: The author has full contribution in the preparation of manuscript and compilation.

Funding source: The author declares that this study has received no financial support.

Conflicts of interest: The author declares no conflicts of interest.

Ethical approval: Not applicable.

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