IJPSR (2023), Volume 14, Issue 4 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 July 2022; received in revised form, 30 August 2022; accepted, 17 October 2022; published 01 April 2023

AN APPROACH TOWARDS THERAPEUTIC INTERVENTION USING CARBON-BASED NANOMATERIALS AND METAL-BASED NANOPARTICLES: A MECHANISTIC REVIEW

Sreelekha Das, Romita Guchhait and Tamalika Chakraborty *

Department of Biotechnology, Gurunanak Institute of Pharmaceutical Sciences and Technology, Kolkata - 700114, Bengal, India.

Keywords:

Nanotechnology, Carbon-based nanomaterials, Metal-based nanoparticles, Therapeutics

Correspondence to Author:
Ms. Tamalika Chakraborty

Assistant Professor,
Department of Biotechnology,
Gurunanak Institute of Pharmaceutical Sciences and Technology, Kolkata - 700114, Bengal, India.

E-mail:tamalika.chakraborty@gnipst.ac.in

ABSTRACT: Nanotechnology is an interdisciplinary field of science that refers to the research and technology development at atomic, molecular, and macromolecular scales, which leads to the controlled manipulation and study of structures and devices with length scales that range from 1nm to 100 nm. During the past few decades, a surfeit of nanomaterials (NMs) and nanoparticles (NPs) has evolved and been evaluated for their potential to improve the clinical treatment and diagnosis of a patient as diagnostic and therapeutic agents. Real exposure has been generated around the probable effects of the NMs and NPs for novel therapeutic approaches against several diseases, including cancer, to cope with the threats of the malignant tumour. Few nanoparticles also exhibit strong antimicrobial activity against Gram-positive and Gram-negative bacteria and act as antibacterial agents for treating different bacterial infections. A wide variety of nanomaterials, both carbon nanomaterials (CNMs) such as graphene, fullerenes, carbon nanotubes, and metal nanoparticles (MNPs), including gold, silver, and zinc oxide with distinctive physicochemical properties, provides opportunities to be explored in the emerging field of nanomedicine. These NMs and NPs have attracted great interest in biomolecular imaging for diagnosis and theranostic approach to cancer. This review article addresses a great deal of potential application of novel NMs and NPs with their approach toward improved therapeutic interventions such as antibacterial, anti-inflammatory, and anticancer.

INTRODUCTION: NMs and NPs are promising tools that have been examined for the advancement over characteristics of drugs or agents such as solubility, blood pool retention times, controlled release over short or long durations, environmentally triggered controlled release, and highly specific site-targeted delivery [1, 2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(4).1649-59

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(4).1649-59

NM and NP-based anticancer methodologies can surpass conventional cancer treatments with their evolving applications in cancer theranostics [3, 4]. NMs and NPs exhibit specific properties, including smaller size, large surface area, higher reactivity, and optical properties, which can be tailored to increase their efficacy as a therapeutic tool [5, 6, 7].

In addition, their large surface area makes them a significant candidate for nano-drug delivery systems (DDS) for loading and delivering chemotherapeutic agents to the specific site [8]. To properly understand the diversity of NMs and NPs, some form of classification is required based on their physical and chemical properties.

Among these, carbon NMs and metal NPs are of particular interest to the scientific community due to their unique morphology, dimensionality, uniformity, surface structure and charge, chemical composition, aggregation and/or agglomeration, solubility, and great ability to influence their interactions with biomolecules and cells [8, 9, 10]. Carbon-based nanomaterials (CBNs) are becoming a highly attractive class of nanomaterials due to the inimitable features exhibited by the carbon allotropes such as graphene, fullerene and carbon nanotubes, carbon quantum dots, nanodiamonds [11]. Their unique chemical properties and their diversity in nanostructures make them highly relatable to commercial and medical uses owing to the variations in sp, sp2, and sp3 hybridizations [10, 11]. Among the recent gains, CBNs have been differently applied to biological and biomedical applications ranging from biosensing and tissue engineering to anticancer drug delivery, cancer therapy and diagnostic, stem cell transplantation, and their translation to the clinic [12, 13, 14]. CBNs also showed potential therapeutic roles in delivering pharmacologic and diagnostic imaging agents for detecting and treating cancer [15, 16].

Metal NPs are made of metal precursors commonly regarded as nano-gold, silver, and zinc-oxide [7]. Among the different nanoparticles employed in biomedical research, metallic NPs are the most convenient and suitable for possessing unique optoelectrical properties due to their well-known localized surface plasmon resonance (LSPR) characteristics [7, 11]. This is why it is commonly focused on the biomedical and pharmaceutical industries. Metal NPs find applications in many research areas for their facet, size, and shape, a controlled synthesis important in present-day cutting-edge materials [2, 3, 7].

Also, it can typically be engineered or modified by changing the relative influence of interfacial and bulk properties through the characteristic dimensions of the components. In recent years, metallic NPs and their alloys have been studied extensively for their significant applications in a wide spectrum of biomedical utilities such as sensor technology, imaging, optical devices, gene targeting, catalysis, biological labelling, drug delivery systems, and treatment of some cancers [2, 3].

Carbon-Based Nanomaterials:

Graphene: Graphene, a single carbon layer of the graphite structure, is extensively studied and explored for its uses. Graphene derivates, commonly called graphene-family nanomaterials (GFNs), have been synthesized and categorized based on their chemical modifications into graphene oxide (GO), reduced graphene oxide (rGO), and graphene quantum dots (GQDs) [17]. Being the world's stiffest, thinnest and strongest materials, graphene-based nanomaterials (GFNs) gained popularity for extraordinary physicochemical properties, including large planar surface area (2630 m2 g−1), unparallel thermal conductivity (5000 W m−1 K−1) high intrinsic mobility, π–π stacking with electrostatic interactions which made it possible to facilitate drug loading of partially soluble drugs with high efficiency and potency [18]. GFNs are carrier molecules for Therapeutics used in biomedical applications to improve drug delivery, gene therapy, and anticancer therapy [19, 20].

Due to the colloidal stability and free surface π electrons, GO functionalized better with other biomolecules such as proteins, small organic molecules, peptides, etc to improve unique physicochemical properties, allowing larger payloads of drugs for its delivery to the tumor site for therapy [18, 21]. It can squeeze itself into the tumour microenvironment (TME) and modify itself based on payloads and functionalization [17]. For example, GO can functionalize as a cancer-targeting molecule along with folic acid (FA) and doxorubicin (DOX), and camptothecin can be loaded onto the large surface area of GO via π–π stacking[17, 21].

The lateral size of graphene has the immune-stimulatory capability that activates macrophages and dendritic cells (CD40, CD83, and CD86) and enhances immunity, attacking cancer cells. Due to the immunological properties of graphene, it is utilized in DC-based immunotherapy by triggering anti-glioma effects in the T98G cell line when treated with GO-antigen peptide [17, 22]. GO can exclusively target cancer stem cells (CSCs) without harming normal cells by the technique known as differentiation-based nano-therapy. The formation of CSCs is inhibited by small GO (0.2–2 μm) and bigger ones (5–20 μm) [17].

Recent studies have shown the implementation of graphene quantum dots (GQDs) in bioimaging applications, including photodynamic therapy (PDT) [21]. The limitation of conventional agents with low singlet O_2 quantum yields was overcome by GQDs, which produced high singlet O_2 quantum yield, attained only in the region of visible light [20, 22]. But then can only treat near-skin tumours, not deeply buried ones. GO can also conjugate with labeled molecular beacon (MB) through π–π stacking interactions for imaging and detecting miRNA by efficiently inducing fluorescence quenching of dyes on MB. GO with noble metals such as gold (Au) promote Raman sensitivity and intensity by serving as a flexible Raman probe for bioimaging applications through Raman mapping [18].

Fullerenes: Fullerenes, soccer-ball-shaped molecules composed of carbon atoms, are a distinct allotrope of carbon family nanomaterials [23]. Its properties, such as its unique cage-like hollow sphere structure and its electron-deficient nature made it a promising nanomaterial in biomedical uses [24]. It is modified both endohedral and exohedral with attractive physiochemical and optoelectronic properties [21, 25]. Metallofullerenes (metal atom incorporated inside fullerene) is highly used in magnetic resonance imaging due to the transfer of intra-fullerene electrons from the encaged metal atom to the fullerene cage. Gadolinium-metallofullerenols can serve as specific CSC inhibitors and can be exploited for the effective arrest of malignancy, thus playing an important role in various modalities of cancer therapy. By suitable functionalization, the photosensitivity of fullerenes can be improved, that are known to increase their relaxivity.

Moreover, the free radical scavenging ability exhibited by fullerenes acts as antioxidants that can be applied to various cancer therapy modalities [17, 18]. Over the years, intrinsic toxicity and poor water solubility of fullerenes remain of a high challenge; for cancer therapy, the development of injectable fullerene formulations was unsuccessful [17, 24]. To make them water-soluble, various concoctions of fullerenes are functionalized with water-soluble biopolymers for tuning their tumour homing capability [17, 23]. According to earlier studies, fullerenes proved to be good as MRI contrast agents, radiotracers with their potential application in cancer theranostics and photothermal tumour therapy that are investigated with promising results [18]. Fullerenes act as a strong antineoplastic agent, making cancer cells more sensitive to chemotherapy. Among these, a high antineoplastic efficiency (≈60%) has been shown by gadofullerene in mice. Therefore, gadofullerene being an effective therapeutic tool, serves as an antiangiogenesis agent with no side effects and less toxicity compared to anticancer drugs [17].

Water-soluble fullerene (C60) shows promising aspects in anti-human immunodeficiency virus (HIV) activity. It inhibits HIV protease activity by binding to its active site because of its hydrophobicity and unique properties molecular structure. Since then, various C60 derivatives have been developed, displaying anti-HIV activity that can target important HIV enzymes, such as reverse transcriptase. This depicts C60 derivatives as a potent group of AIDS therapeutics in the future [24].

Carbon Nanotubes (CNTs): CNTs, nano-sized hollow and cylindrical forms of carbon, have shown excellent results in fields of science and technology [26]. Several studies demonstrated the strong antimicrobial activity of SWCNTs on E. coli, causing membrane damage and cell death and antibacterial activity depending upon its size [23, 27]. The graphene sheets can be rolled in many arrangements that can be structured as single-layered (single-walled carbon nanotubes SWCNTs), two-layered (double-walled carbon nanotubes, DWCNTs), as well as triple-walled carbon nanotubes (TWCNTs) or multiple layers (multi-walled nanotubes MWCNTs) [21, 28].

SWCNTs and MWCNTs, when investigated, promising results have been shown by SWCNTs over MWCNTs. When tested for their antibacterial effect against E. coli, SWCNTs were more toxic to bacteria than MWCNTs [23]. Due to the smaller nanotube diameter of SWCNTs, they could penetrate better than MWCNTs, into the cell wall. SWCNTs initiate better cell surface interaction due to their superior surface area. Also, SWCNTs with surface groups of -OH and -COOH exhibit significant antimicrobial activity to gram-positive and gram-negative bacteria compared to MWCNTs, which show no antimicrobial effect.

Furthermore, SWCNTs indicate improved aggregation with bacterial cells, thus having stronger antimicrobial activity [17, 28]. The natural morphology of CNTs allows non-invasive penetration across the biological membranes (including bacteria, yeast, and mammalian cells), making CNTs a highly competent vehicle for transporting varieties of drug molecules into living cells [18, 29]. Generally, drug molecules are functionalized by attaching them to the sidewalls of CNT via non-covalent or covalent bonds. But both kind of attachment plays different roles. Drug-loaded CNTs are made stable by the covalent bond in both intracellular and extracellular compartments, therefore lacking the sustained release of the drug inside the cellular microenvironment of cancer cells. In contrast, the controlled release of the drug is facilitated by non-covalent interaction in an acidic condition of tumour site but lacks stability in extracellular pH [17, 22]. Hence inner hollow cavity of CNTs, utilized for drug loading, demonstrate ideal drug isolation from the physiological environment. Therefore, CNTs are proven to be a promising nanocarrier for therapeutic agent delivery by entrapping them inside CNT [21].

CNTs have been considered new-generation nanoprobes, exceedingly fitting for biosensing applications due to their exceptional mechanical, structural, electronic, and optical properties. CNTs-based biosensors enhance the recognition and signal transduction process by immobilizing biomolecules on their surface [22]. CNTs act as mediators for photodynamic and photothermal therapies and destroy cancer cells directly. But due to their poor interactions with their surroundings, SWNTs have not yet been regarded as competent theranostic agents, leading to inefficient instability and loading ratio [21]. Therefore, research has been going on for SWNTs functionalization in bioimaging, including imaging-guided chemo-photothermal therapy.

Metal-Based Nanoparticles:

Gold Nanoparticles (Au NPs): Au NPs are among the important NPs among various inorganic and organic NPs, possessing distinctive chemical, physical and optical properties such as stability against oxidation and degradation *in-vivo*, ease of conjugation to biomolecules and low cytotoxicity and biocompatibility [30, 31]. Therefore, it provides significant benefits in the field of nanomedicine. The optical property of Au NPs offers its utilization in imaging-based therapeutic techniques and ultrasensitive detection for treating lethal diseases like cancer. The NP-based drug delivery approach for cancer cells helps overcome the limitations of conventional treatment methodologies. More research is needed to explore gold nanoparticle-based nanocarrier development, including their potential application in cancer biology [32].

Microorganisms can absorb and accumulate Au NPs by secreting enzymes involved in the enzymatic reduction of gold ions. This shows their potential to use as a tool for PDT, PTT, photoimmunotherapy (PIT), photoimaging, biosensors, and targeted drug delivery [32]. Various Au NPs, nanostars, nanorods, nanospheres, nanocubes, and nanocages, act as effective tools against human cancer. Their favourable physical and optical properties allow cancer diagnostics and therapeutic development, providing a potential platform for developing cancer theranostic [32, 33]. Au NPs are a good candidate for light-based therapies (PDT, PTT, and PIT) that irradiates photosensitive materials by utilizing the application of light and are directly responsible for destroying tumour cells and desired therapeutic effect [31, 34].

Au NPs tend to scale biological responses with surface area, and so their surface functionalization evinced considerable interest. Au NPs can conjugate with various biologically active moieties, thiol, and amine groups, providing a significant biological application in target-specific drug delivery, imaging, diagnostic, *etc.* [32]. Their broad range of core sizes (1 to 150 nm) makes their dispersion easier and controllable. Au NPs can be easily modified due to a negative charge on their surface, making their functionalization easy by adding biomolecules such as drugs. Recent studies have shown that when methotrexate (MTX), a drug used for treating cancer, is conjugated with Au NPs, it results in higher cytotoxicity towards many tumour cell lines as opposed to free MTX and accumulating into them at a much faster rate [32, 35]. Au NPs showed anti-microbial activity against human bacterial pathogens *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Bacillus subtilis*. The peptidoglycan layer of Gram-

positive bacteria is 50% higher than Gram-negative bacteria; thus, larger doses of gold nanoparticles are required for Gram-positive bacteria to show antimicrobial action. The Au NPs bind to thiol groups of enzymes such as NADPH dehydrogenase and disrupt their respiratory chains with the release of oxygen species, due to which significant damage occurs in the cell structures and finally leads to cell death [36, 37, 38].

Reactive Oxygen Species (ROS) have a strong oxidizing property and are produced by NADPH oxidases present in phagocytes and as by-products of the Electron Transport Chain(ETC). They oxidize lipids and proteins in the cell and cause DNA damage. They also oxidize cellular signalling proteins, *i.e.*, tyrosine phosphates, which promote endothelial dysfunction and cause membrane damage. Superoxide anion (O_2^-) combines with NO to form Reactive Nitrogen Species (RNS), which promotes ROS production in phagocytes in a dose-dependent manner, thereby acting as an anti-inflammatory agent [39].

Au NPs inhibit the production of some pro-inflammatory cytokines IL-17, IL-1beta, and TNF-alpha, down-regulating the proliferation of epithelial cells induced by IL-1beta. It also reduces the release of IL-17 and TNF-alpha triggered by LPS [40, 41]. Au NPs modulate various signalling pathways like MAPK (Mitogen-Activated Protein Kinase) pathway and PI3K (Phosphatidyl Inositol 3-Kinase)pathway, thereby negatively regulating the production of pro-inflammatory cytokines in Kupffer cells and hepatic stellate cells affecting their oxidative stress and cytokine profile [42].

Silver Nanoparticles (AgNPs): AgNPs have been an area of great interest and have been extensively investigated for their superior biological, physical, and chemical characteristics as well as their unique electrical, optical and magnetic properties depending upon their size, composition, crystallinity, and shapes [43]. Numerous studies have been made to explore its attractive properties for its practical application that can be incorporated biosensor materials, anticancer, anti-inflammatory and anti-bacterial Therapeutics, diagnostics and enabled their use in fields of biomedical engineering, nanomedicine, biosensing, and pharmacy industry [44]. But the instability, such as oxidation in fluid containing oxygen, of AgNPs has made their use limited. AgNPs have proven their potential as antibacterial agents by exhibiting toxicity to many microorganisms. AgNPs, when oxidized, result in Ag+ ion flow, which causes electrostatic attraction between negatively charged microbial cells and positively charged silver nanoparticles that are deadly to bacteria [45].

In addition, AgNPs demonstrate a strong affinity towards sulphur, due to which Ag^+ ions adhere to the cytoplasm, disrupting the bacterial casings. The free Ag^+ ions are uptake by the cells; the respiratory enzymes get deactivated (ROS), leading to cellular disruption and alternation in the DNA. When DNA comprises soft bases like phosphorus and sulphur interacts with Ag+, which is also soft, it leads to DNA replication and cell propagation and ultimately causes cell death. The Ag^+ ions denature cytoplasmic components by hindering protein synthesis.

The Ag^+ ions also interact with disulphide bonds of protein clusters, leading to the alternation of the 3D structure of the protein. It seems a workable alternative to antibiotics due to its overcoming bacterial resistance against antibiotics. It has also been demonstrated that treating *E. coli* cells with AgNPs resulted in an accumulation of AgNPs in the cell wall, forming "pits" bacterial walls, ultimately causing their death [46].

Studies have also revealed that the silver nanoparticles could easily penetrate Gram-negative bacteria compared to Gram-positive bacteria. This is because of the thin single peptidoglycan coat present in Gram-negative bacteria. Gram-positive bacteria contain thick and several peptidoglycan layers, which hinders the permeation of Ag^+ ions [47, 48]. AgNPs have also been revealed for their aspect in anti-viral therapy. AgNPs exhibited efficient inhibitory activities against hepatitis B (HBV) and human immunodeficiency virus (HIV). Much research has been done on creating nanomaterials as an alternative tool for developing formulations targeting tumor cells. Scientists investigated the molecular mechanism of AgNPs and observed that AgNPs sensitize cancer cells by inducing apoptosis. Cancer cells, when analyzed morphologically, it suggested significant cell death that biologically synthesized AgNPs can induce.

It has been observed that AgNPs combined with 1% aqueous extract of carotenoid phytopigment 'Lycopene' extracted in benzene showed anticancer activity against Hella, COLO320DM, H29 cancer cell lines respectively [48, 49]. Another study exhibited that AgNPs induced autophagy of cancer by activating the ptdlns3K pathway. The inhibition of autophagy was also observed by autophagic inhibitors like wortmannin which enhanced cancer cell killing in mouse melanoma cell model (B16 cell lines) [48, 50].

An enhanced anticancer potential was observed when AgNPs were conjugated with Doxorubin and Alendronate compared to Doxorubin or Alendronate used alone. AgNPs synthesized from *Tamarindus indica* fruit shell show effectiveness against the MCF -7 cell lines (human breast cancer) [48, 51]. AgNPs absorb and scatter particular wavelengths of visible light, commonly known as Surface Plasmon Resonance (SPR) which facilitates the diagnosis of tumour location, size, stage of cancer, and angiogenic process. There is various mechanism through which anticancer properties of AgNPs can be justified. Interaction of AgNPs with cancer cells showed enhanced permeation and retention effect (EPR), which results in the entry of more NPs, leading to the death of cancer cells [48, 52]. AgNPs help in early apoptosis or checking the rapid pace of division of tumour cells by activating p53, caspase -3, and p-ErK1/2 [48, 53, 54].

AgNPs as anti-inflammatory agent decreases Vascular Endothelial Growth Factor (VEGF) levels. It enhances antigen sensitization, allows plasma protein leakage into extravascular spaces, which results in the widening of windpipe wall, and enhances T_H2 cell-mediated inflammation [55, 56, 57]. AgNPs block the Y419 phosphorylation and inactivate the Src kinase pathway, which stimulates by VEGF and IL-1beta.AgNPs reduce VEGF-induced cell proliferation by blocking solute flux induced by VEGF and IL -1B.AgNPsinhibit the secretion of pro-inflammatory cytokines (TNF -alpha,IL-6 and IL-1 beta) [57,58].

AgNPs decrease the activity of Hypoxia Response Element (HRE) reporter induced by HIF 1-alpha protein in human breast cancer cell lines, thus inhibiting target genes like GLUT1 and VEGF -A [57, 59]. AgNPs prevent mucin hypersecretion in mouse models' epithelial goblet cells of the lungs. It shows a significant decrease in perivascular and peribronchial inflammation [57, 60].

Zinc Oxide Nanoparticles (ZnO NPs): Zn is a vital element found ubiquitously in all human tissues. It plays an essential role in cell division and maintains epithelial cells and metabolic processes. Over the last few years, ZnONPs have become popular as a multifunctional and inorganic compound, showing varied morphologies in many dimensions. For therapeutic, diagnostic, and biomedical applications, ZnO is a promising candidate for bioimaging, biosensing, antimicrobial effect, and drug delivery [61].

Besides conventional chemotherapy and radiation therapy, surgical removal of tumours also has its drawbacks, as chemotherapeutic agents show cytotoxicity to both normal and cancerous cells, and high-energy waves are not target-specific. In light of these drawbacks, NPs have exceptionally been studied as carriers for drugs for a novel therapeutic tool where ZnOs have contributed to enhancing nanoparticle stability when encapsulated with the drug. ZnOs are hydrophilic and cationic with a high surface area to volume ratio, enabling them to be loaded with a therapeutic agent for enhancing the imaging of cancer cells for diagnostic purposes or therapeutic purposes by inducing cancer cell death [62, 63].

Following the non-invasive way of cancer therapy, in photodynamic therapy, ZnO NPs exhibit their ability to induce pro-inflammatory cytokine expression for enhancing tumour necrosis factor-alpha (TNF-α) production, which could eventually increase the tumour cell killing ability. ZnO NPs are also believed to improve the antitumoral efficacy through surgery by inducing apoptosis by themselves. ZnO has also been widely explored in immunotherapy to enhance T-cell response by bounding with the antigen, labelling the dendritic cells, and using image-guided antigen delivery [62, 64].

There are many numbers of ways in which ZnO NPs act against inflammation. It inhibits the production of thymic stromal lymphotein (TSlP) [65]. TSLP is released by epithelial cells as a response to

pathogenic bacteria and increases the production of Interleukin-13(IL-13), a pro-inflammatory cytokine that causes mast cell proliferation through p53 protein level regulation. Constant p53 activation is known to promote pro-tumourgenic inflammation by causing the release of High Mobility Group Protein 1(HMG-I), which promotes chemotaxis [66, 67].

ZnO NPs can significantly reduce the Inducible Nitric Oxide Synthase (iNOS), which is toxic to cells as it causes the destruction of local tissues and thus becomes one of the direct causes of inflammation. It also reduces the production of NO by IFN-gamma plus LPS-stimulated macrophages in a dose-dependent manner [68].

Recent studies have shown that zinc oxide nanoparticles show antimicrobial activities against both Gram-positive and Gram-negative bacteria, namely *E. coli*, *Salmonella*, *Listeria monocytogenes*, and *Staphylococcus aureus*. However, Zinc oxide nanoparticles also have shown antimicrobial activity against *Camphylobacter jejuni*, a gram-negative bacterium. The antibacterial mechanism is from the disruption of cell membrane activity. It has been reported that ZnO NPs generate high reactive oxygen species such as OH^-, H_2O_2, and O_2^{2-} activated by UV and visible light to generate. The negatively charged hydroxyl radicals and superoxides remain on the cell surface as they cannot penetrate the cell membrane; however, H_2O_2 can penetrate bacterial cells [69]. Zn has potentially been used as an antidiabetic agent by reducing glycogenolysis and gluconeogenesis, thus enhancing the structural integrity of insulin. Zn protects against oxidative stress-mediated complications in diabetes by regulating glucose in beta cells of the islets in the pancreas, thereby controlling insulin secretion. ZnO emerges as a promising agent in medical applications, but no such studies have yet been done on humans. Therefore, Zn is required to be studied more for its safe uses to address the formulations in medical applications [69, 70.]

Zn plays a major role in maintaining the activation of p53 gene, which leads to apoptosis and simultaneously activates of caspase -6 enzyme, responsible for activating caspase -3 and other enzymes for nuclear membrane dissolution and cell death. ZnO NPs play an important role in inducing cytotoxicity towards cancer cells through oxidative stress *via* ROS generation [70, 71]. ZnO NPs exhibit positive charge under physiological conditions such as blood or tissue fluid. Cancerous cells usually have anionic phospholipids on their outer membrane, leading to an electrostatic attraction between ZnO NPs and cancerous cells promoting selective localization, cellular uptake, phagocytosis, and finally, cytotoxicity. However, the exact mechanism of selective cytotoxicity of ZnO NPs towards cancer cells is still unclear [69].

The table below shows the summary of various antimicrobial, anti-inflammatory, and anticancer activities of the carbon-based nanomaterials and metal-based nanoparticles mentioned above:

Types of Nanoparticles	Antimicrobial activity	Anti-inflammatory activity	Anticancer activity
Fullerenes	Inhibit energy metabolism, disable respiratory chain, thus inhibiting bacterial growth [72]	Fullerene C60 is used to control ROS -dependent inflammation, including allergic diseases [73] Fullerene C60 shifts immune responses from Th2 to Th1, restoring the function of the skin barrier, thus helping in the treatment of allergic and other inflammatory diseases [73]	Gadolinium-metallofullerenols can serve as specific CSC inhibitors. Acts as a strong antineoplastic agent, making cancer cells more sensitive to chemotherapy. Gadofullerene being an effective therapeutic tool, serves as an antiangiogenesis agent [25]
CNTs	Physically interacts with cell membrane: form cell-NTs aggregates; induce cell membrane disruption [72]	Act as a carrier of anti-inflamatory drugs: Dapsone, Dexamethasone, Ketoprofen [74]	Anticancer molecules carrier: DOX, CP, CPT, PTX28, PTT; CNTs absorb NIR light; transmit heat to CNTs; kill cancer cells [27].
GO	Disruption of cell membrane takes	Inhibits IL-1beta release and	Functionalised as cancer

	place on interation of GO [72]	interleukin mRNA expression [75]. By inhibiting interleukine expression upon TLR4 stimulation,it shows inhibitory effect on cytokine production in macrophages [75]	targeting molecule when loaded with FA, DOX [76]. Activates macrophages and dendritic cells (CD40, CD83, and CD86) and enhances immunity thus attacking cancer cells [17]. Utilized in DC-based immunotherapy [17]
Gold (Au)	Binds to the thiol groups such as NADPH, disrupt respiratory chains, release oxygen species, damage cell membranes and led to cell death [36,37, 38]	Satiate ROS production in a concentration-dependent manner [39]. It shows inhibitory effect in some pro-inflammatory cytokines IL-17,IL-1beta, and TNF-alpha [40, 41]	Gold nanoparticles conjugated with methotrexate are used to treat many tumour cell lines [35].
Silver(Ag)	Denature cytoplasmic components by hindering the protein synthesis [46]. Interact with disulphide bonds of protein clusters which leads to the alternation of 3D structure ofprotein46. DNA comprises of soft bases like phosphorus and sulphur, interacted with Ag+ which is also soft, leads to the DNA replication, cell propagation and cell death [46, 47]	Decreases VEGF levels [55, 57]. Blocks the Y419 phosphorylation and inactivates the Src kinase pathway56. Inhibitory effect in pro-inflammatory cytokines TNF -alpha, IL-6 and IL-1 beta [57, 58]. The activity of Hypoxia Response Element (HRE) reporter induced by HIF 1 alpha is decreased [57, 59]	Effective against the MCF-7cell lines(human breast cancer) [48, 51]. Helps in early apoptosis or checking the division of tumour cells by activating p [53], caspase 3 and pErK1/2 [48, 53, 54]
Zinc oxide(ZnO)	Disruption of cell membrane activity [69]. Shows antimicrobial activity against Camphylobacter jejuni, a gram-negative bacteria [69]	Reduce the inducible Nitric oxide synthetase (iNOS) [68]. Inhibits the production of Thymic Stromal Lymphotein (TSIP) [65.] Reduces the production of Nitric oxide by IFN gamma [68]	Helps in activating p53 gene which leads to apoptosis [70, 71]. Induces cytotoxicity *via* ROS generation [69]

CONCLUSION: So, far in this review article, it is concluded that various NMs and NPs still have both positive and negative effects on human beings with desired and undesired effects when compared to drugs. Carbon-based nanomaterials and metal-based nanoparticles have been known to be explored for many applications, including catalysis, sensing, photovoltaic, energy, environment, and biomedical. But the increasing hazards of NMs and NPs may also have indirect effects on human beings. Therefore, increased attention is needed to direct these NMs as the knowledge of this NP development is still in its infancy. Extensive research is needed to be made to fully understand their synthesis, characterization, and possible toxicity which is a crucial concern when processing NMs and NPs for life science applications. NMs and NPs have equal importance as diagnostic tools to identify malignant and non-malignant tissues or the interaction of living cells with the surrounding environment. Through the technology nanoceramics, one can assess the fundamental behaviour of living cells and biomolecules, such as the mechanical interaction of cells with their surrounding structures, as well as with other cells; measuring nanoscale forces exerted by proteins on cells can potentially afford new understanding on various diseases, such as osteoarthritis, cancer, and malaria due to cells elasticity and adhesion alterations. Each of these single analyses can contribute to the biological understanding of disease initiation and progression, developing improved diagnostic tools and innovative therapeutic approaches. Numerous applications of inorganic nanostructures as biomarkers open new opportunities and provide powerful tools in the fields such as genomics, proteomics, molecular diagnostics, and high throughput screening. Nanoscale probes can be generated for detailed monitoring and analysis of biological components.

As it stands now, the applications of NMs and NPs are commercially geared toward drug delivery. But despite the potential biological applications of NMs and NPs, one still needs to have a fundamental understanding of the interactions of NMs with intracellular structures and processes. Therefore, it is important to focus on *in-vivo* biomedical

applications of the NMs to develop nanobiotechnology.

ACKNOWLEDGEMENT: We would like to show our sincere gratitude and respect to our mentor Ms. Tamalika Chakraborty, Assistant Professor, Department of Biotechnology, Guru Nanak Institute of Pharmaceutical Science and Technology, for providing us with the necessary guidance and helping us throughout our work. We would also like to express our gratitude to the Guru Nanak Institute of Pharmaceutical Science and Technology for providing us with the necessary resources throughout our work.

CONFLICTS OF INTEREST: The authors have no conflicts of interest.

REFERENCES:

1. Salata OV: Applications of nanoparticles in biology and medicine. Journal of Nanobiotechnology 2004; 2(1): 1-6.
2. Kush P, Kumar P, Singh R and Kaushik A: Aspects of high-performance and bio-acceptable magnetic nanoparticles for biomedical application. Asian Journal of Pharmaceutical Sciences 2021; 4.
3. Bratovcic A: Different Applications of Nanomaterials and Their Impact on the Environment. International Journal of Material Science and Engineering 2019; 5(1): 1-7.
4. Egbuna C, Parmar VK, Jeevanandam J, Ezzat SM, Patrick-Iwuanyanwu KC, Adetunji CO, Khan J, Onyeike EN, Uche CZ, Akram M and Ibrahim MS: Toxicity of nanoparticles in biomedical application: nanotoxicology. Journal of Toxicology 2021; 2021.
5. Espinosa A, Teran F, Ortega D. Introduction to Nanomaterials Applied to Life Sciences. Nanoscale Advances 2021; 3(5): 1165-1166.
6. Dong L, Craig M, Khang D and Chen C: Applications of Nanomaterials in Biology and Medicine. Journal of Nanotechnology 2012; 1-2.
7. Khan I, Saeed K and Khan I: Nanoparticles: Properties, applications and toxicities. Arabian Journal of Chemistry 2019; 12(7): 908-931.
8. Casais-Molina M, Cab C, Canto G, Medina J and Tapia A: Carbon Nanomaterials for Breast Cancer Treatment. Journal of Nanomaterials 2018; 1-9.
9. Elveny M, Khan A, Nakhjiri AT and Albadarin AB: A state-of-the-art review on the application of various pharmaceutical nanoparticles as a promising technology in cancer treatment. Arabian Journal of Chemistry 2021; 14(10): 103352.
10. Cui L, Liang J, Liu H, Zhang K and Li J: Nanomaterials for Angiogenesis in Skin Tissue Engineering. Tissue Engineering Part B: Reviews 2020; 26(3): 203-216.
11. Baig N, Kammakakam I and Falath W. Nanomaterials: A review of synthesis methods, properties, recent progress, and challenges. Materials Advances 2021; 2(6): 1821-71.
12. Contera S, Bernardino de la Serna J and Tetley T: Biotechnology, nanotechnology and medicine. Emerging Topics in Life Sciences 2020; 4(6): 551-554.
13. Wang X, Zhong X, Li J, Liu Z and Cheng L: Inorganic nanomaterials with rapid clearance for biomedical applications. Chemical Society Reviews 2021; 50(15): 8669-742.
14. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA and Langer R: Engineering precision nanoparticles for drug delivery. Nature Reviews Drug Discovery 2021; 20(2): 101-24.
15. Grumezescu AM: Nanomaterials for drug delivery and therapy. William Andrew 2019; 14.
16. Nguyen HL, Nguyen HN, Nguyen HH, Luu MQ and Nguyen MH: Nanoparticles: synthesis and applications in life science and environmental technology. Advances in Natural Sciences: Nanoscience and Nanotechnology 2014; 6(1): 015008.
17. Saleem J, Wang L and Chen C: Carbon-Based Nanomaterials for Cancer Therapy via Targeting Tumor Microenvironment. Advanced Healthcare Materials 2018; 7(20): 1800525.
18. Patel KD, Singh RK and Kim HW: Carbon-based nanomaterials as an emerging platform for theranostics. Materials Horizons 2019; 6(3): 434-69.
19. Du C, Zhang Q, Wang L, Wang M, Li J and Zhao Q: Effect of Montelukast Sodium and Graphene Oxide Nanomaterials on Mouse Asthma Model. Journal of Nanoscience and Nanotechnology 2021; 21(2): 1161-1168.
20. Cheng Z, Li M, Dey R and Chen Y: Nanomaterials for cancer therapy: Current progress and perspectives. Journal of Hematology & Oncology 2021; 14(1): 1-27.
21. Hosnedlova B, Kepinska M, Fernandez C, Peng Q, Ruttkay-Nedecky B and Milnerowicz H: Carbon Nanomaterials for Targeted Cancer Therapy Drugs: A Critical Review. The Chemical Record 2018; 19(2-3): 502-522.
22. Maiti D, Tong X, Mou X and Yang K: Carbon-Based Nanomaterials for Biomedical Applications: A Recent Study. Frontiers in Pharmacology 2019; 9: 1401.
23. Alavi M, Jabari E and Jabbari E: Functionalized carbon-based nanomaterials and quantum dots with antibacterial activity: a review. Expert Review of Anti-infective Therapy 2020; 19(1): 35-44.
24. Cha C, Shin S, Annabi N, Dokmeci M and Khademhosseini A: Carbon-Based Nanomaterials: Multifunctional Materials for Biomedical Engineering. ACS Nano 2013; 7(4): 2891-2897.
25. Li Z, Chen Y, Yang Y, Yu Y, Zhang Y, Zhu D, Yu X, Ouyang X, Xie Z, Zhao Y and Li L: Recent advances in nanomaterials-based chemo-photothermal combination therapy for improving cancer treatment. Frontiers in Bioengineering and Biotechnology 2019; 7: 293.
26. Fernandes N, Rodrigues CF, Moreira AF and Correia IJ: Overview of the application of inorganic nanomaterials in cancer photothermal therapy. Biomaterials Science 2020; 8(11): 2990-3020.
27. Vashist SK, Zheng D, Pastorin G, Al-Rubeaan K, Luong JH, Sheu FS. Delivery of drugs and biomolecules using carbon nanotubes. Carbon 2011; 49(13): 4077-4097.
28. Xin Q, Shah H, Nawaz A, Xie W, Akram MZ, Batool A, Tian L, Jan SU, Boddula R, Guo B and Liu Q: Antibacterial carbon-based nanomaterials. Advanced Materials 2019; 31(45): 1804838.
29. Loh K, Ho D, Chiu G, Leong D, Pastorin G and Chow E: Clinical Applications of Carbon Nanomaterials in Diagnostics and Therapy. Advanced Materials 2018; 30(47): 1802368.
30. Chen W, Zhang F, Ju Y, Hong J and Ding Y: Gold Nanomaterial Engineering for Macrophage-Mediated Inflammation and Tumor Treatment. Advanced Healthcare Materials 2020; 10(5): 2000818.

31. Ding X, Li D and Jiang J: Gold-based inorganic nanohybrids for nanomedicine applications. Theranostics 2020; 10(18): 8061.
32. Singh P, Pandit S, Mokkapati VR, Garg A, Ravikumar V and Mijakovic I: Gold nanoparticles in diagnostics and Therapeutics for human cancer. International Journal of Molecular Sciences 2018; 19(7): 1979.
33. Liu Y, Crawford B and Vo-Dinh T: Gold nanoparticles-mediated photothermal therapy and immunotherapy. Immunotherapy 2018; 10(13): 1175-1188.
34. Kim JE, Choi JH, Colas M and Kim DH, Lee H: Gold-based hybrid nanomaterials for biosensing and molecular diagnostic applications. Biosensors and Bioelectronics 2016; 80: 543-559.
35. Álvarez-González B, Rozalen M, Fernández-Perales M, Álvarez M and Sánchez-Polo M: Methotrexate Gold Nanocarriers: Loading and Release Study: Its Activity in Colon and Lung Cancer Cells. Molecules 2020; 25(24): 6049.
36. Shamaila S, Zafar N, Riaz S, Sharif R, Nazir J and Naseem S: Gold Nanoparticles: An Efficient Antimicrobial Agent against Enteric Bacterial Human Pathogen. Nanomaterials 2016; 6(4): 71.
37. Bruna T, Maldonado-Bravo F, Jara P and Caro N: Silver nanoparticles and their antibacterial applications. International Journal of Molecular Sciences 2021; 22(13): 7202.
38. Umadevi M, Rani T, Balakrishnan T, Ramanibai R. Antimicrobial activity of silver nanoparticles prepared under an ultrasonic field. International Journal of Pharmaceutical Sciences and Nanotechnology 2011; 4(3): 1491-1496.
39. Mittal M, Siddiqui M, Tran K, Reddy S and Malik A: Reactive Oxygen Species in Inflammation and Tissue Injury. Antioxidants & amp; Redox Signaling 2014; 20(7): 1126-1167.
40. Kingston M, Pfau J, Gilmer J, Brey R. Selective inhibitory effects of 50-nm gold nanoparticles on mouse macrophage and spleen cells. Journal of Immunotoxicology 2015; 13(2): 198-208.
41. Sumbayev V, Yasinska I, Garcia C, Gilliland D, Lall G and Gibbs B: Gold Nanoparticles Downregulate Interleukin-1β-Induced Pro-Inflammatory Responses. Small 2012; 9(3): 472-477.
42. de Carvalho T, Garcia V, de Araújo A, da Silva Gasparotto L, Silva H and Guerra G: Spherical neutral gold nanoparticles improve anti-inflammatory response, oxidative stress and fibrosis in alcohol-methamphetamine-induced liver injury in rats. IJP 2018; 548(1): 1-14.
43. Lee S and Jun B: Silver Nanoparticles: Synthesis and Application for Nanomedicine. International Journal of Molecular Sciences 2019; 20(4): 865.
44. Zhang X, Liu Z, Shen W and Gurunathan S: Silver Nanoparticles: Synthesis, Characterization, Properties, Applications, and Therapeutic Approaches. International Journal of Molecular Sciences 2016; 17(9): 1534.
45. Xu L, Wang YY, Huang J, Chen CY, Wang ZX and Xie H: Silver nanoparticles: Synthesis, medical applications and biosafety. Theranostics 2020; 10(20): 8996.
46. Swolana D and Wojtyczka R: Activity of Silver Nanoparticles against Staphylococcus spp. International Journal of Molecular Sciences 2022; 23(8): 4298.
47. Yin IX, Zhang J, Zhao IS, Mei ML, Li Q and Chu CH: The antibacterial mechanism of silver nanoparticles and its application in dentistry. International journal of Nanomedicine 2020; 15: 2555.
48. Abass Sofi M, Sunitha S, Ashaq Sofi M, Khadheer Pasha S and Choi D: An overview of antimicrobial and anticancer potential of silver nanoparticles. Journal of King Saud University - Science 2022; 34(2): 101791.
49. Shejawal K, Randive D, Bhinge S, Bhutkar M, Todkar S and Mulla A: Green synthesis of silver, iron and gold nanoparticles of lycopene extracted from tomato: their characterization and cytotoxicity against COLO320DM, HT29 and Hella cell. Journal of Materials Science Materials in Medicine 2021; 32(2).
50. Lin J, Huang Z, Wu H, Zhou W, Jin P and Wei P: Inhibition of autophagy enhances the anticancer activity of silver nanoparticles. Autophagy 2014; 10(11): 2006-2020.
51. Gomathi A, Xavier Rajarathinam S, Mohammed Sadiq A and Rajeshkumar S: Anticancer activity of silver nanoparticles synthesized using aqueous fruit shell extract of *Tamarindus indica* on MCF-7 human breast cancer cell line. Journal of Drug Delivery Science and Technology 2020; 55: 101376.
52. Torchilin V: Tumor delivery of macromolecular drugs based on the EPR effect. Advanced Drug Delivery Reviews 2011; 63(3): 131-135.
53. Gurunathan S, Park J, Han J and Kim J: Comparative assessment of the apoptotic potential of silver nanoparticles synthesized by Bacillus tequilensis and *Calocybe indica* in & amp; nbsp; MDA-MB-231 human breast cancer cells: targeting p53 for anticancer therapy. International Journal of Nanomedicine 2015; 4203.
54. Buttacavoli M, Albanese N, Di Cara G, Alduina R, Faleri C and Gallo M: Anticancer activity of biogenerated silver nanoparticles: an integrated proteomic investigation. Oncotarget 2017; 9(11): 9685-9705.
55. Lee C, Link H, Baluk P, Homer R, Chapoval S and Bhandari V: Vascular endothelial growth factor (VEGF) induces remodeling and enhances TH2-mediated sensitization and inflammation in the lung. Nature Medicine 2004; 10(10): 1095-1103.
56. Barnes P. Th2 cytokines and asthma: an introduction. Respiratory Research 2001; 2(2): 64.
57. Agarwal H, Nakara A and Shanmugam V: Anti-inflammatory mechanism of various metal and metal oxide nanoparticles synthesized using plant extracts: A review. Biomedicine & amp; Pharmacothe 2019; 109: 2561-2572.
58. Sheikpranbabu S, Kalishwaralal K, Venkataraman D, Eom S, Park J and Gurunathan S: Silver nanoparticles inhibit VEGF-and IL-1β-induced vascular permeability *via* Src dependent pathway in porcine retinal endothelial cells. Journal of Nanobiotechnology 2009; 7(1).
59. Yang T, Yao Q, Cao F, Liu Q, Liu B and Wang XH: Silver nanoparticles inhibit the function of hypoxia-inducible factor-1 and target genes: insight into the cytotoxicity and antiangiogenesis. Inter J of Nanomedicine 2016; 11: 6679.
60. Jang S, Park JW, Cha HR, Jung SY, Lee JE, Jung SS, Kim JO, Kim SY, Lee CS, Park HS. Silver nanoparticles modify VEGF signaling pathway and mucus hypersecretion in allergic airway inflammation. International Journal of Nanomedicine 2012; 7: 1329.
61. Ng C, Baeg G, Yu L, Ong C and Bay B: Biomedical Applications of Nanomaterials as Therapeutics. Current Medicinal Chemistry 2018; 25(12): 1409-1419.
62. Rasmussen J, Martinez E, Louka P and Wingett D: Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications. Expert Opinion on Drug Delivery 2010; 7(9):1063-1077.
63. Makvandi P, Wang C, Zare E, Borzacchiello A, Niu L and Tay F: Metal-Based Nanomaterials in Biomedical

Applications: Antimicrobial Activity and Cytotoxicity Aspects. Advanced Functi Mat 2020; 30(22): 1910021.
64. Baetke S, Lammers T and Kiessling F: Applications of nanoparticles for diagnosis and therapy of cancer. The British Journal of Radiology 2015; 88(1054): 20150207.
65. Agarwal H, Nakara A and Shanmugam V: Anti-inflammatory mechanism of various metal and metal oxide nanoparticles synthesized using plant extracts: A review. Biomedicine & Pharma 2019; 109: 2561-2572.
66. Yan H, Wu H, Zhang H, Ashton C, Tong C and Wu H: p53 promotes inflammation-associated hepatocarcinogenesis by inducing HMGB1 release. Journal of Hepatology 2013; 59(4): 762-768.
67. Magna M and Pisetsky D: The Role of HMGB1 in the Pathogenesis of Inflammatory and Autoimmune Diseases. Molecular Medicine 2014; 20(1): 138-146.
68. Tripathi P, Tripathi P, Kashyap L and Singh V: The role of nitric oxide in inflammatory reactions. FEMS Immunology & Medical Microbiology 2007; 51(3): 443-452.
69. Sirelkhatim A, Mahmud S, Seeni A, Kaus N, Ann L and Bakhori S: Review on Zinc Oxide Nanoparticles: Antibacterial Activity and Toxicity Mechanism. Nano-Micro Letters 2015; 7(3): 219-242.
70. Dhawan DK and Chadha VD: Zinc: a promising agent in dietary chemoprevention of cancer. The Indian Journal of Medical Research 2010; 132(6): 676.
71. Bisht G and Rayamajhi S: ZnO Nanoparticles: A Promising Anticancer Agent. Nanobiomedicine 2016; 3: 9.
72. Dizaj SM, Mennati A, Jafari S, Khezri K and Adibkia K: Antimicrobial activity of carbon-based nanoparticles. Advanced Pharmaceutical Bulletin 2015; 5(1): 19-23.
73. Shershakova N, Baraboshkina E, Andreev S, Purgina D, Struchkova I and Kamyshnikov O: Anti-inflammatory effect of fullerene C60 in a mice model of atopic dermatitis. Journal of Nanobiotechnology 2016; 14(1).
74. Vashist SK, Zheng D, Pastorin G, Al-Rubeaan K, Luong JH and Sheu FS: Delivery of drugs and biomolecules using carbon nanotubes. Carbon 2011; 49(13): 4077-97.
75. Hoyle C, Rivers-Auty J, Lemarchand E, Vranic S, Wang E and Buggio M: Small, Thin Graphene Oxide Is Anti-inflammatory Activating Nuclear Factor Erythroid 2-Related Factor 2 (NRF2) Metabolic Reprogramming. ACS Nano 2018; 12(12): 11949-11962.
76. Shafiee A, Iravani S and Varma RS: Graphene and graphene oxide with anticancer applications: Challenges and future perspectives. Med Comm 2022; 3(1): 118.

How to cite this article:
Das S, Guchhait R and Chakraborty T: An approach towards therapeutic intervention using carbon based nanomaterials and metal based nanoparticles: a mechanistic review. Int J Pharm Sci & Res 2023; 14(4): 1649-59. doi: 10.13040/IJPSR.0975-8232.14(4).1649-59.