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Review Article

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Role of multifunctional nanomaterials in disease diagnosis and therapy

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ABSTRACT

Theranostic is a specialized clinical disease management that renders highly specific, non-invasive diagnosis and therapeutic approach within the ambits of patient physiology, drug compliance and safety. Nanomedicine helped to transform this concept into clinical reality enabling rapid assessment and adjustment of treatments to be target specific, enabling controlled drug release, circulation and bioavailability, and interestingly provide platforms for the online-realtime imaging of disease site. This review paper is intended to briefly emphasize the mediating role and importance of multifunctional nanoparticles in the development of rapid, sensitive and effective diagnostic and therapeutic tools for the deadliest diseases. In this, we discussed the role of nanotechnology and nanomaterials for the diseases like cancer, HIV-AIDS, tuberculosis, diabetes, brain and cardiovascular related diseasesetc, as the therapeutic administration becomes easier in early stages and has been the most important component of advance prognosis.

Keywords: Theranostics, nanoparticles, drug delivery, cancer, HIV-AIDS, tuberculosis etc.

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INTRODUCTION

In the current medical research, there has been an increasing demand for the development of rapid, sensitive and effective diagnostic tools for the deadliest diseases like cancer, HIV-AIDS, tuberculosis, diabetes etc as the therapeutic administration becomes easier in early stages and has been the most important component of advance prognosis [1-3]. The disease diagnosis and treatment processes over the years is based upon the old traditional concept of tedious preclinical examination, usually characterized by faulty prognosis and in must cases lacks the inherent properties of specialization and differentiation [3-4]. For a favorable clinical outcome to be achieved, a new concept came into play called "Theranostic" that recognized the basic clinical disease management to render a highly specific diagnosis and therapeutic efficacy within the ambits of patient physiology, drug compliance and safety [5-6]. Research has provided significant progress in this regard by opening up advanced opportunities to rapidly access and adjust treatments to be target specific, favouring the development of diagnostic and therapeutics tools into one single construct [4-5,7]. Theranostic is a well thought-out technique that deployed simultaneous dual-purpose approach to diagnosis and therapy. Therefore, the objective of this review is to summarize our understanding of the concept of theranostic medicine, its applications and role played in diagnosis and treatment of various diseases including cancer, HIV-AIDS, tuberculosis, cardiovascular and brain-related diseases (neurological).

2. Theragnosis

Diagnosis and therapy are linked approaches in theragnostic and are pursued simultaneously in the clinical treatments of diseases and management using the unique techniques provided by the advanced improvements in recent nanotechnology [2,8]. One of the success stories in the twenty first century is the break through recorded in theranostic medicine; simplifying disease management, reducing the tedious clinical processes and clumsy prognosis that characterized diagnosis and therapy centuries before the advent of nanotechnology [5-6]. Futhermore, its provided scientist with an essential tools to fabricat devices with the sensibility and ability to detect even the minutest biological and chemical entities that can be used for noninversive screening and therapy simultaneously [9-10]. Theragnosis is an integrated nanotherapeutic system which can diagnose the disease, deliver targeted therapy and monitor the response to therapy, i.e. a very ideal process that employ recognized nanomaterials for both diagnostic and therapeutic functions simultaneously (figure-1) [2,6]. The use of materials on nanoscale level provides the flexibility to modify the fundamental properties of particles specifically to suet therapeutic applications [11-12]. Thus, provided a great opportunity for reseachers to modify nanomaterials to assume multiple functionalities especially in the area of personalized theranostics [7,13-14].

In addition to these interesting characteristics, NPs can be made to assume multiple platforms for more than one kind of imaging or therapeutic agents due to the following unique signatures: 1) large surface area that provides binding platforms for further bioconjugation with imaging agents or cargo of interest [7], 2) surface modification that allows the flexibility to redirect functions to suit specific targeting abilities towards receptor expressing diseases [7], 3) multifunctional NPs (MNPs) are characterized to posses enhanced target-binding and specificity compared to single molecules due to their multivalent effects [15], and 4) ability to tune or adjust the surface size that was

observed to promote controlled drug delivery, enhance dbiodistribution and reduced opsonization (ingestion and destruction by phagocytes) [16].

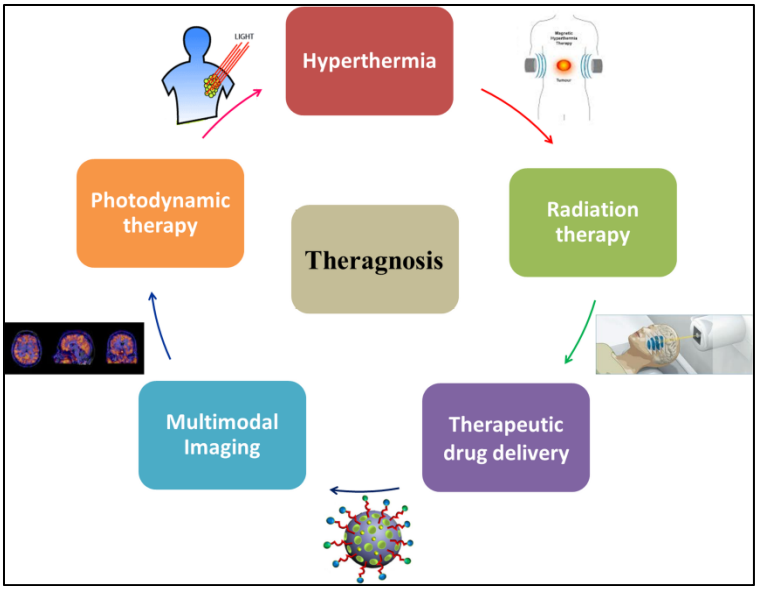

Figure-1: Schematic representation of theragnosis for a combination of diagnosis as well as therapy for the deadliest diseases.

3. Types of NPs and their importance in medicine:

NPs are the materials with three external dimensions of equal nanoscale and exhibits unique electronic, optical, mechanical, and magnetic properties. In addition, their size specific properties attracted global interest for further study, provided the blue print on how to customize nanomaterials for specific biological purposes such as cell isolation, labeling and imaging [2,17, 18]. The nanoscale size of materials provided the flexibility to manipulate their structure to assume multiple functionalities similar to the scale of biological entities with an intrinsic characteristic that allows interactions on a cellular (10–100 nm), subcellular (20–250 nm), protein (3–50 nm), or genetic scale (10–100 nm) [19-21]. This ability to assume multiple changes in surface area interestingly changed the entire physicochemical properties of NPs that exemplified the quantum confinement (discrete energy) effect in semiconductor particles, surface plasmon resonance (oscillation of electron in solid or liquid simulated by incident light) in some metal particles and superparamagnetism in metal particles [22-25]. All these concomitment changes are expected to significantly enhance the field of medicine to improve disease diagnosis and quality of treatment (see Table 1).

Table 1: Functions and applications of NPs in theranostic along with the modaling of MNPs [11].

Functions	Contrast agents	Applications
Biocompatible, stable NPs	PNPs	Encapsulation of drugs for delivery. Ensuring efficient drug circulation, retention and controlled release.
Targeting moieties	Folic acid, Peptides, Aptamer etc	Enabling specific targeting of receptors expressed at disease sites, reducing possible side effects of drugs on healthy cells. Can be used as signal antaener in biosensing.
Imaging NPs	QDs, Iron oxide, Ag, CNTs, Au etc	Enabling online-real time visualization of disease site for specific non-invasive therapy. Can also be applied as signal transducer in biosensing.

3.1 Polymeric NPs

Polymeric NPs (PNPs) as the name implies derived from biocompatible and biodegradable polymers with size rages between 10-1000 nm, largely employed to enhance and improve unique NP constructs suitable for numerous applications such as in electronic, photonics and as conducting materials. Of greater interest, is in the field of biosensors application, formulation of drug capsules, stabilizers and as targeting moieties [26-27]. The PNPs can be found both in natural forms as chitosan, albumin, gelatin, sodium algenate etc and in synthetic forms as poly(lactic

co-glycolic acid) (PLGA), poly(vinyl alcol) (PVA), poly(ethylene glycol) (PEG), poly(acrylic acid) etc [7,28]. In biomedicine, the PNPs displayed countless advantages in a number of ways such as by changing the properties of the NPs to assume stability, enhance the controlled drug release behavior and bioavailability. Among all, the greatest interest of PNPs is due to its intrinsic ability to encapsulate/or conjugate easily with biomolecules such as antibiotics, vaccines and contraceptives for specific targeting and delivery [29]. The mentioned advantages were found to be possible because PNPs following the hydration processes absorbs the drug easily and releases the same through diffusion, allowing the degradation of encapsulated payloads by enzymatic reactions at the target sites possible; which were observed to occur both inhydrophilic as well as hydrophobic moieties [5,29].

Some literature studies on PNPs documented that, PLGA vesicles demonstrated efficient behaviour as excellent nanocarries for bioimaging and drug delivery purposes [96]. Similarly, the biocompatibility and optical stability of chitosan encapsulated CdSe/ZnS quantum dot (QD) hybrid nanospheres were observed to enhance the bioimaging capability under optical microscopy [25]. In another study, the cross linked chitosan NPs were observed to have significantly enhanced the imaging properties of living cells nucleoli [30]. Huang et al in clinical trials designed dopamine biosensor from carbon dots and chitosan composite film modified with glassy carbon electrode [31]. In a related study, the graphene oxide-chitosan nanocomposites based electrochemical DNA biosensor was used for the detection of salmonella typi single stranded in serum samples which was observed to enhance the movement of electrons between DNA and electron surface sending out sensitivity [32]. Further to this succesess, chitosan-based polyaniline-gold biosensor was successfully designed by some reseachers for the detection of cholesterol [33]. Similarly, a biosensor designed from chitosan-platinum NPs and graphene-gold nanocomposites were reported to enable efficient detection of erythromycin, an antibiotic effective against gram-positive bacteria and some gram-negative bacteria [9].

3.2 Gold NPs

Gold (Au) is a global name that signifies beauty and class profile. It is a very old rare metallic element with high melting and boiling points, having medievial medicinal applications such as in the treatment of dysentery, epilepsy, syphilis and heart disease among others. Michael Faraday in 1857 called the infinitely minute size gold entity “activated gold” [34-35]. The ruby-red (colloidal) color finds applications in cosmetics and in pottery; of typical examples is the legendary Lycurgus cup and Purple of Cassious, elegant materials with implicit characteristics to color changes, appearing red on transmitted light and green on reflected light [36]. The Au NPs (colloidal gold) are stable particles of 1-100 nm diameter obtained in either spherical or rod-like shapes [37]. The solid cylinderical shapes of gold nanorods (10 nm) can be made to change its wave length by the use of nanorods with different size, length and diameter; similarly, the variations in the thickness of Au coating and the diameter of nanospheres also found to change the wave length. The nanosphere absorbs gives the Au NPs two plasmon bands (visible and near infrared, NIR) that are tunable and size dependent suitable for the use as biosensing agents [34]. For Au, the oscillation of free electrons in the conduction band provides easy binding sites for the attachment of ligands especially through the availability of thiol or amine functional groups [36].

The Au NPs can be modified or manipulated for theranostic applications through the bioconjugation of either its thiol or amine binding platforms with polymers such as PEG, poly(vinyl pyroliidone) (PVP), serum bovin albumin, several proteins, peptide molecules and oligonucleotides [38]. The dielectric shells such as silica, graphene oxide, aluminiumoxide, titanium dioxide found to encapsulate Au NPs, change and enhance its fluorescence and optical properties, making it suitable for numerous imaging and phototherapeutic applications [33,39-40]. The graphene-Au NPs are reported to have the desired sensitivity suitable for the fabrication of sensors for detecting erythromycin, an antibiotic effective against gram-positive and some gram-negative bacterias [9]. Guahari et al designed an electrochemical immunosensor by assembling Au NPs on nitrogen-doped graphene for ultrasensitive electrochemical detection of matrix metallo protainse-2 [39]. The system also reported equally the effective reduction of the formation of reactive oxygen species (ROS) in diabetic mice by the control of a number of antioxidant enzymes such as super oxidase dismutase (SOD), glutathione S-transferase (GSH) and catalase [41].

3.3 QDs

QDs is one of the success story of nanotechnology, owing to its unique physical and chemical properties contributed immensely in shaping the world, breaking somewhat impossible barriers and modeling materials for specific needs and future applications. QD is a semiconductor material of nanoscale diameter ranging between 2-10 nm, consisting of elements in group II-V (CdS, CdSe, CdTe, ZnO, ZnS, ZnSe), some in group III-V (Inp, InAs, GaN, GaP, GaAs),

IV-VI (PbS, PbSe, PbTe) and I-VII (CuCl) [42-44]. QDs have a peculiar physiocochemical and photophysical behavior which is directly proportional to their size, demostrating intense ability to emit discreet light that can be tunable [45]. This phenomenon can be observed in fluorescence dye where the frequency of the emitted light were observed to increase in relation to a decrease in the size of QDs, allowing the excitation and emission of the quantized light to be tunable [45-47]. The electrons in the conduction band of QDs on absorption of light gets excited and jump to its valence band and thus emit photonenergy of larger wavelength than the absorbed light, a development that makes QDs as excellent materials for bioimaging and labeling [48].

QDs can be synthesized by colloidal method following precipitation processes involving controlled nucleation and growth of particles in solution. For biomedical applications, however, the synthesis of QDs using surfactants in organic solution renders them hydrophobic behavior and is found to be unsuitable for use in aqueous solution [43,46]. Thus modification and rendering its hydrophilic, compatible and non-toxic behavior is very crucial for any biomedical application [44]. The surface modification of QDs with hydrophilic ligands such as polymer molecule renders them soluble/dispersible in aqueous solution, protects the QDs from aggregation and offers the possibilities for the surface bioconjugation especially by reaction with various functional groups such as thiols, amine, carboxylic, etc [47,49-51]. These functionalization processes were used by some researches to formulate QDs with excellent imaging capabilities and as biomarkers for the imaging of specific proteins in malignant tissues [52-53]. They reported that QD can be useful during the profiling of biomarkers especially when conjugated with antibody. And similarly observed to play a significant role in the effective monitoring of erythrocyte membrane destructions in malarial infection and in the imaging of neural cells by detecting and monitoring axon growth of the neurons [48,54].

3.4 Silver NPs

Silver (Ag) which is also referred to as augentum in Latin is a white lustrous and soft transition metal that exists in its pure natural form, either in the form of an alloy or in combination with other metals. The intrinsic size dependent characteristics of Ag NPs were deployed by artisans to fabricate ceramics and status with iridescent or metallic glazes dated back to the medieval age and also finds applications as an antibacterial agent [55]. They were reported to accelerate wound healing by suppressing the generation of local matrix metallo proteinase activity and cytokines and increases neutrophil apoptosis activities [55-56]. The saponin, quinine compounds found in Naringicrenulata were reported to be effective in reducing Ag^{+} to Ag^{0} and the ointment extracted from Naringicrenulata were found to play an active role in wound healing process *in vivo* in winter albino rats [57]. In another study, the Ag NPs generated from marine brown alga (*colpomeniasinuosa*) were observed to inhibit both α-amylase and α-glucosidase enzymes *in vitro* in a dose depended manner and observed to induce antidiabetic activities [58-59]. In an effort to find a cure for HIV, some scientists observed that the Ag NPs bind gp120 units was able to prevent possible infection of the CD4 by virus, exerting a protective shield that inhibits post-entry of the HIV-1 life cycle [60]. Despite the wide range of biomedical applications, it was observed that the Ag NPs synthesis without surface modification lacks uniform dispersion and in most cases forms agglomeration. Therefore, it became necessary to modify the surface in order to avoid the agglomeration of particles and to make it more hydrophobic so as to allow good platform for attaching functional groups and enhancing its properties for biosensing, imaging, targeted delivery etc [58-60]. This is achievable through the functionalization of its thiol or amine groups which are observed to form strong and stable metal-sulfur or metal-amine bonds with Ag surface [61].

3.5 Silica NPs

Silica (Si) NPs have attracted considerable interest especially as drug delivery vehicle owing to their excellent chemical stability and biocompatibility, large surface area and pore volumes. In addition to these characteristics, the mesoporous form of Si (pore size of 2-50 nm) due to its great adsorption capabilities are widely used for carrying payloads, while the non-porous form (solid) type is used typically for the conjugation and encapsulation of biomolecules [62-63]**.** The Si NPs has very low cytotoxicity and can undergo surface modification without much stress and this enabled strong versatility such as enhancing cellular interactions and biodistribution in biological system [64]. The modification of Si NPs surface with bio-recognition moieties can allow for a specific controlled drug delivery, bioavailibity and/or biodistribution, targeting and imaging to be achieved [65-66]. The modifications were observed to be successful because the large surface area can be easily tuned by covalently conjugating with functional groups of polymer materials [21,67]. In addition to the large surface area, the optical properties and high luminescence of Si NPs were successfully deployed by some researchers for the real time detection and monitoring of biological activities *in vivo* [68-69].

3.6 Iron/Iron oxide NPs

Recent event in the utilization of NPs in research and development shifted its emphasis towards exploring iron oxide NPs because of their unique size and magnetic properties [8,70]. For biological applications, the surface coating of iron oxide NPs with entities such as gluconic acid, lactobionic acid and polyacrylic acid makes its water soluble, highly dispersed and biocompatible with remarkable hydrodynamic size [71]. Their superparamagnetic properties allow its use as a contrast enhancement agent, drug delivery agent, magnetically controlled targeting, imaging etc [72]. The high biocompatibility, biodegradable and non-toxic property making them excellent materials for *in vivo* applications because the SPIONs can be guided under the influence of magnetic field to a localized target site for efficient drug delivery and imaging [11,70]. The oxidative stress induced by the catalysis of ROS by iron oxide NPs was reported to activate radiosensitivity of human cervical in mice model [73-75].

3.7 Carbon nanotubes

Nanotechnology expanded research in carbon and produced carbon nanotubes (CNTs) with suitable characteristics that exist in different forms either as a single walled CNT (SWCNT) or multiwalled CNT (MWCNT); these characteristics were exploited and channeled to specific applications especially as supercapacitors, conductive films, solar cells, fuel cells, transistors, sensors etc [20,76-77]. CNTs have unique electrical, mechanical, optical and thermal properties and were reported to be directly dependent on the factors such as number of walls, diameter, length and chiral angle of the CNTs [78-80]. The CNTs before using for any bio-related applications are functionalized to render it more biocompatible, make it non-toxic and biodegradable either by covalent oxidation with strong HNO_3 and/or conjugated with amino acid [81-83]. Coating with amphiphilic surfactant molecules or polymers enhances non-covalent interactions with macromolecules such as DNA, proteins, nucleic acid, genes, enzymes and making it essentially suitable for diagnostic and therapeutic purposes [77,81,83]. These were reported to easily conjugate with antibiotics, drugs for efficient targeted delivery [84-85].

3.8 Zinc NPs

Zinc (Zn) NPs either in its sulphide or oxide forms are widely used by scientist for numerous applications that included and not limited to theranostics applications [86-87]. The zinc sulphide (ZnS) form is one of the active sources of natural zinc found in black color in its impure or in pure white form and exhibiting wide optical transparency across both visible and far infrared region. This makes it an excellent choice as luminescent material because of its wide bad gap of 3.5-3.8 ev and high exciton binding energy that can be tunable in the UV region [88-89]**.** This characteristic makes ZnS as prominent semiconductor material among the group II-IV [89]. Also, the ZnO NPs because of its wide bad gap are found to be very useful for short wavelength magneto-optical applications which were observed to increase the optical properties of ZnO NPs on doping with manganese [86]. For example, the manganese ions doped ZnS (ZnS:Mn) NPs were reported to exhibit visible luminescent properties combined with multiphoton absorption demonstrating its possible applications as biolabels [89]. The oxide form of Zn NPs is a white powder found in its mineral form as zincite, but exist largely in synthetic form with longer half-life optical phonon, relatively large bad gap and widely used in the fabrication of emission devices, solar cells and luminescent probes [90-91]. Another essential property of ZnO was discovered during a separate clinical experiment; the researchers observed that the ZnO NPs with positive surface charges and smaller size demonstrated higher cellular uptake compared to ZnO NPs with negative surface charge and larger particle sizes [87].

4. Nanoparticle-mediated disease diagnosis, therapy, and management

4.1 Cancer

Globally today, millions in resources and unquantifiable amount in human energy has being expended to halt and find lasting therapy for all classes of malignant diseases like cancer. It is on record that cancer remain one of the major causes of mortality and always tag “terminal disease” due to the progressions of cell degeneration across healthy one [92]. The statistics of cancer reported cases globally were estimated at 14.1 million new cancer cases and 8.2 million cancer-related deaths in 2012 and the most commonly diagnosed cancers worldwide were those of the lung (1.8 million, 13.0% of the total), breast (1.7 million, 11.9%), and colorectum (1.4 million, 9.7%). The most common causes of cancer death were cancers of the lung (1.6 million, 19.4% of the total), liver (0.8 million, 9.1%), and stomach (0.7 million, 8.8%) [93-94].

The development of cancer cells is localized and highly deceiving, progressing slowly through cell signaling and apoptosis processes and then jumping across neighboring cells without creating visible alert until maturity. The current medical response to cancer chemotherapy usually follows invasive techniques that required carrying out detail morphological and histopatholigical study, radiological analysis and consequently surgery. These invasive techniques lacks the ability to deliver specific anti-tumor agents and more or less induces intolerable cytotoxicity and drug resistance levels [80,92]. For that, nanotechnology-based theranostics can be a practical understanding and veritable tool that allows manipulation, modification and control of matters within nanoscale dimension to suite specific diagnostic and therapeutic needs [80,95]. The combination of findings from several clinical trials highlighted that the nanomaterials: (i) can be modified to carry a large therapeutic 'payload', (ii) can be made to conjugate with multivalent targeting ligands with strong binding affinity and specificity to target the cells, (iii) can be made to accommodate multiple drug molecules that allows simultaneous cancer cell diagnosis and therapy, and finally, (iv) can be made to bypass traditional drug resistance mechanism [92,96-97]. The cancer treatment using nanomaterials can be applied either based on size mediated targeting (passive) or receptor mediated targeting (active) [95,98]. Further in this section, we shall discuss different treatment options by the use of various NPs in cancer diagnosis and therapy.

Engineered platforms created using nanotechnology-based appliances allowed for non-invasive strategies for effective cancer therapy. The treatment options such as photo dynamic therapy, radio therapy, hyperthermia etc are mediated by NPs such as liposones, micelles, dendrimers, CNTs, QDs and host of others as contrast agents and backbone for carrying therapeutics. For example, liposomal NPs due to its membrane permeability were observed to support and trigger control release of encapsulated drug under photo thermal therapy of cancer following an experiment using Au nanoshell in miceller form exposed to light irradiation [99-100]. Similarly, virus-based liposomes (Sendai virus) were reported to facilitate targeted binding of QDs to cytosolic epidermal factor receptor cells for early detection of malignant brain tumors by suppressing the quantity of non-specific endocytosed NPs (by 50%) in human glioblastoma *in vivo* [101]. The practical applicability of liposomes for cancer therapy can also be demonstrated when the curcurmin-loaded liposomal particles were observed to initiate a cascade of caspase process (protein degradation and organelles clearance), resulting in apoptotic cell death *in vitro* [102]. Nucleic acid NPs such as DNA and RNA macromolecules are efficiently used as substrate agents [13] and can be modified as core system for sustain drug release [103]. Chlorotoxin (CTX), a peptide covalently capped to liposome encapsulating antisense oligonucleotides or RNAs (siRNAs) were observed to show specific binding selectivity towards glioma cells without causing any damage to non-neoplastic cells. This enables specific targeted delivery of nucleic acids to glioblastoma (GBM) and allowing CTX-conjugated liposomes to penetrate easily into the glioma cells *in vivo* due to its size and neutral surface charge, thereby causing an increased level of tumor cell suppression by silencing U87 human GBM and GL261 mouse glioma cells [104]. In a related development, the ribonucleic acid interference (RNAi)-based gold-nucleic acid NPs were observed to neutralize oncogen expression in GBM and are reported to target and reduce oncoprotein (Bcl2L12) expression in intracerbral GBM, accelerate apoptosis with no adverse side effects reported [105]. Other PNPs is micellar NPs, an amphiphilic surfactant molecules, highly accepted as materials for drug delivery due to their relatively uniform size, ease of formation and ability to encapsulate hydrophobic molecules [106-107]. For example in a study, the Curcumin (Cur) loaded methoxy PEG/poly-e-caprolactone were observed to diblock co-polymeric micelles and enhanced the efficacy of the micellar system over the native drug using pancreatic cell lines [108].

Similarly, a non-ionised polymeric micelle acted as a vehicle to deliver siRNA to tumor sites from poly(ethylene glycol)-block-poly(L-lysine) (PEG-b-PLL) consisting of lysine amines modified with 2-iminothiolane and cyclo-Arg-Gly-Asp (cRGD) peptide. The siRNA containing cRGB peptide were observed to increase gene silencing ability following the intravenous injection, accelerating subcellular distribution *in vitro* and also improved accumulation in both the tumor mass and tumor-associated blood vessels [109]. In a different study, tumor specific targeting and drug delivery were successfully achieved using dual-decorated polymeric micelles modified with folic acid and nuclear localization signal (NLS) to form a composite of Doxorubicin (Dox) loaded micelles [110]. Another milestone achievement in inhibiting colon carcinoma with the use of polymeric micelles was reported when Cur-loaded biodegradable polymeric micelles prepared by single-step nano-precipitation method were observed to strongly inhibit angiogenesis on transgenic zebra fish model by maintaining the cytotoxicity of Cur on C-26 colon carcinoma cells [111]. Also, the Cur-Dox loaded micelles decorated with GLU1 were administered to female nude mice model to determine its tumor therapeutic efficacy. Results of the study show a significant improvement in the specimen administered GLUT1-Cur and GLUT1-Cur+Dox [112].

Epigallocatechin gallate-loaded polysaccharide NPs, a type of dendrimer NPs were reported to play an essensial role in reducing cell viability and apoptosis of Du145 in prostate cancer cells and also enhances inhibitory effects on cell proliferation by 10-20% [113]. In a separate clinical trials a composites made of gold-dendrimers were observed to enable the detection of cancer cells under X-ray microtomography (micro-CT) with good attenuation and excellent circulation time of 5 minute in vascular tissue imaging and about 20 to 60 minutes recorded for imaging the urinary system [114]. The RNAi was observed to suppress the proliferation of cancerious cells by 75% under the influence of homeobox A1 protein coding gene (HoxA1). This gene was employed to track and monitor early mammary cancer progression in transgenic C3(1)-SV40T Ag mice model [115]. Similarly, polyamido-amine (PAMAM) dendrimer-conjugated fluorescein isothiocyanate composite were reported to show excellent imaging and tumor targeting capability [116].

QDs with NIR emission can be applied to sentinel lymph-node mapping including peptides and antibodies for targeting tumors *in vivo* [117] and folate receptor were reported to facilitate cellular uptake of folic acid-functionalized nanocomposites of QDs for cancer imaging by emitting fluorescence [118-119]. The oscillation of free electrons in the conduction band (surface plasmon) of Ag NPs were observed to surface enhanced raman spectroscopy (SERS) signals which are promising for cancer cell imaging and also found to selectively destroy cancer cells using folated Ag-dendrimers [120-121]. Some researchers reported that proteins attached to SiNPs are used to label cell membrane proteins for imaging of cancers [62]. The folic acid encapsulated with dye-doped Si NPs shows target efficiency towards SCC-9 cancer cells over-expressing folate receptors cells on the cancer tissue [122]. Simiilarly, Ciobanu et al reported that liver hepatocellular carcinoma cells (Hep G2 cells) strongly adhered on thin films of dextran coated iron oxide NPs and observed to exhibit a normal actin cytoskeleton, showed normal cell growth and demonstrating its strong efficacy as biosensing materials [123]. The iron oxide NPs loaded microspheres were reported to be excellent transverse relaxation contrast agents on MRI and for magnetically guided drug delivery [124] and citrate conjugated superparamagnetic iron oxide nanoparticles (SPIONs) displays high heating capacity and excellent properties for cancer hyperthermia treatment [125].

CNTs NPs were reported to exhibit efficient role in drug delivery and disease targeting with the cancer cells that overexpress folate receptors [126]. In *in vitro* clinical trials, the drug moieties capped on CNTs were shown to be more effectively internalized into cells than free drug alone [127]. Similarly, the PEG-linked 17B-estradio (E2) impregnated with cell-penetrable MWCNTs was observed to have successfully delivered Dox to the nucleus of a cancerous breast *in vivo* and *in vitro* [80]. In a related development, the SWCNT, because of its high surface to mass ratio are interestingly taken up easily by monocytes at the tumor cells [78]. CNTs impregnated with SPIONs were observed to improve cellular uptake of fluorosphore fluorescein isothiocyanate for bioimaging both *in vitro* and *in vivo* [128]. In a different study, the poly(ethyleneimine), PEI-based carbon dots were reported to show bright photoluminescence with greater potentials for bioimaging [22]. Further, the ZnO NPs found to induce cytotoxic effect in tumor cells, triggers ROS generation that causes apoptosis and its smaller size allows easy cellular uptake and localization [87,129-130]. Also, the ZnS NPs were used as a novel fluorescence signal transducer for the detection of C-reactive protein in human serum for monitoring coronary heart disease [131].

4.1.1 Gene therapy

The large surface area, high reactivity, charged density and colloidal stability of NPs served as a driving force behind the application of non-viral gene in supporting delivery of DNA or siRNA molecules into cells for therapeutic purposes [132-133]. The simple principle behind gene therapy is based on the concept that specific exogenous genes such as DNA can be incorporated into the tumor cell genome to produce a tumoricidal effect [17]. For example in a study, the poly(ethyltenimine)-DNA (PEI/DNA) NPs were administered intravenously to mouse model with acute lung injury induced with lipopolysaccharide (LPS). The result of the study shows accelerated expression in the lung targeting alveolar cells and the addition of B2-adenergic receptor (PEI/B2AR) were observed to further accelerate the healing process from 28-64% and the study demonstrating the clinical efficacy of PEI/DNA NPs in treating acute lung injury [132]. Similarly, mutant methlyguanine methyl trasferas (P140) gene-modified hematopoietic stem was used in a clinical trial to extend median survival time of patients with glioblastoma [133].

4.1.2 Photo dynamic therapy

Photo dynamic evolves when a photo sensitizer is exposed to activated light at a certain appropriate wave light and in the process, the agent transfers or induces the release of cytotoxic ROS, free radicals and peroxides that consequently causes infractions or cellular damage to the adjacent tissues [17]. In this, the NPs are endowed with the

characteristics to absorb optical irradiation across the NIR region, channeling the light deep across the skin without any damage to healthy tissues [38]. The frequently used NPs are the gold nanoshell and SWCNTs. For example, the fabrication of a novel photo sensitizer-conjugated hybrid Au NPs was observed to produce fluorescence signal at the GSH intracellularly and generated the ROS in the process that has the potentials to destroy the cancer cells [107]. Similarly, in an effort to determine the efficacy of photosentisizer on tumoregic cells, the free phthalocynine and gold-bound phthalocynine were intravenously injected to animal models. The recovery of phthalocynine from the amelonotic melanoma and the skin after 24 h of injection shows a significant response rate on the tumor cells of the mice that received the NPs-bound photo sentisizer [134]. The generation of ROS was utilized for the fabrication of a nano-photo sensitizer for efficient photo dynamic therapy. For that, the model utilizes NIR light upconversion nanoparticle (UCNP) and Zn(II)-phthalocyanine photo sensitizer to enhance the energy efficiency of ROS ($^1O_2$) under minimum radiation in order to facilitate for a better photo dynamic therapy [135].

4.1.3 Hyperthermia therapy

Humans often made concluding remarks over cancer related diseases due to its dead profiles, tagging it as an incurable disease depending upon the stage of diagnosis. This has also generated response into research at the same proportion in finding cure. Applying heat to cancer cells (hyperthermia) is one option being practiced widely, hyperthermia [136-137]. In this, the administration of therapy usually follows two heating protocols [137]. The first protocol runs at a temperature between 41-46°C to stimulate immune response in cancer cells and also act on magnetic fluid containing magnetic NPs, generating heat in response to the magnetic field [138]. The second process called thermoablation, running at a temperature between 46-56°C that consequently causes denaturation of proteins, melting of lipid bilayers, inducing apoptosis, generates necrosis sometimes and finally leads to coagulation or carbonization of cancerous cells [137-139]. In a study, Kikumori et al carried out a research to demonstrate the effect of hyperthermia on cancer cells using magneto-nanocomposites on cancer cell nodules of BT474. They observed that the NPs accumulated in the BT474 tumor cells absorbs the irradiation and causes the regression of tumor cells [136]. In another clinical study, the magnetite cationic liposomes injected rat model when subjected to alternating magnetic field generated heat, the re-growth and regression of rat mammary cancer were observed in rats following the hyperthermia treatment [138].

4.1.4 Radio therapy

Halting cancer profelaration is not easy as it requires highly specialized approach due to the dogged nature of micrometastases cells, their small size makes them easily dispersed and hidden deep across the body tissues and thus making localized treatment nearly impossible [140]. Recently, Peiris et al's work around this limitation using multicomponent flexible chain-like NPs that were observed to easily break down deep into the micrometastic site under the influence of radio frequency and delivering the therapy [141]. The energy emitted by an ionizing radiation gets easily absorbed by biological molecules and in the process, triggers the excitation of cellular components especially on water molecule, producing ROS and other free radicals such as hydrogen radical ($H^{\bullet}$), hydroxyl radical ($OH^{\bullet}$), Superoxides ($O_2^{-\bullet}$ and H_2O^+) that may end up causing apoptosis, proten denaturation and DNA damage [142]. The workings is quiet different in metal NPs such as Au NPs, here the lattice structure composed of packed particles absorb radiation and in the process, scatter the photons in a quantized localized form that allows sufficient ability to redirect the photons energy to the site of action [143-144]. To substantiate the efficacy of Au NPs in radio therapy, Joh et al reported that Au NPs enhance radiation effect *in vitro* on glioblastoma cells causing endothelial cell damage [145]. Similar result was reported by Bobyk et al's work on a semiconductor material such as QDs for radio therapy, as QDs usually work within the visible region and generates radicals upon absorption of light [146].

Gadolinium (Gd) NPs are of another interest in radio therapy, as it has the ability to generate radical cation on exposure to hydrated electrons, notably used in neutron-capture therapy [147]. Ultrasmall Gd-based NPs were designed to perform dual function by producing both positive contrast agents for MRI and radio sentizing effect in tumor cells. The Gd NPs accumulated at the tumor site and are activated by X-ray microbeams, produced an image-guided radio therapy and thus significantly improved the life-span of rat models [148]. In a separate study, the CNTs-coated with silver was applied as a radio sensitizer and the material seems to produce cytotoxic effect in cancer cells on exposure to X-ray radiation *in vitro* [149]. Similarly, the SPIONs were also reported to cause damage to DNA by activating generation of ROS that allows radio sensitivity detection on exposure to radiation, resulting in oxidative stress and other cytotoxic effects [73-74]. In a different study, the oxidative stress induced by the catalysis of ROS with SPIONs carrying the E1A gene was reported to activate radio sensitivity of human cervical in mice model [75].

4.2 Tuberculosis and other pulmonary diseases

Lung diseases are quite common in some part of the world, mostly associated with life style like smoking, work place toxic exposure, societal use of toxic chemicals from domestic and industrial sources, while others like Tuberculosis (TB) are infectious, some could be referred under genetic conditions [150-151]. Of greater interest is the lung related diseases like Tuberculosis (TB), tagged as one of the world's most pandemic infectious disease reaching a frightening proposition on a global scale [151]. Currently, the developing countries are indeed considered to be at a high risk of the wide spread of TB and it has a significant role in suppressing the immunity in the same way as HIV [151-152]**.** Other possible routes in which TB takes advantage were observed to be connected to drop in immunity as fallout of malnutrition, ageing, excessive stress and type-2 diabetes [153-154]. It is on record that the HIV-infected patients are in danger of activating dormant TB reservoir within the body system due to the severity of immune deficiency; this was observed to be responsible for the killing of at least one fifth of all the HIV related death cases [151,154]. In 2012, about 8.6 million people reported to be infected and 1.3 million people lost their lives and with that about 95% of these deaths related cases are found among the poor driven societies and men/women aged 15 to 44. Sadly in 2012, about 530,000 children ended up as the victims of TB related cases and 74,000 HIV-negative children reported to be dead due to TB during the same year [151].

Mycobacterium tuberculosis (MTB), the source agent of TB is considered to be the most dreadful pathogen that is still infecting the humans on a dangerous scale mostly in quiescent state, sleeping. Any stimulus such as a drop in the immune system can wake up the pathogen from slumber to a more active state acquired in most cases through exposure. The inhalation of particles containing these pathogens which are quite easily taken up by alveolar macrophages builds the disease slowly and proliferates until it overwhelms the entire body's immune system [150,153,155]. The only visible preclinical examination of TB infection usually follows a prolong cough, chest pain, fever, continuous fatigue, perspiration, loss of weight and appetite [151]. Bacillus Calmette-Guerin (BCG) is one of the success story for preventing TB infection at infant level only but higly ineffective as a preventive cure for related pulmonary TB beyond this level which according to statistic is hitting a frightening proportion globally [150].

Some researchers proffered ways to enhance the immunogenicity of DNA vaccines for TB by improving the transfection of host cells and antigen expression, heightening co-stimulation and T-lymphocyte enlargement by taking advantage of the biocompatibility, biodegradability and other physiological aspects of NPs [150,155]. For that, the delivering platform is the key as it needs to ensure effective drug biodistribution in addition to overcoming the side effects associated with the present TB vaccines. In that way, the vehicle forms a stable aqueous suspension and increases the drug dosage circulation time by preventing the drug leakages [50,156]. The factors such as the size of NPs make it an excellent TB-delivery platform because of its ability to allow increase in transcytos is in the gut lumen M cells, enhancing intracellular uptake and in the lining epithelium and the peyer's patch [157]. In an effort to find a biocompatible, non-toxic and water soluble platform for TB delivery, the chitosan and PEG-600 NPs were used to encapsulate anti-TB drug Rifampicin and was observed to have significantly prolonged the *in vitro* drug release retention and circulation time [158]. In TB therapy, it has became a clinical fact that the NPs-loaded with drugs demonstrated target specificity and prolongs drug release profile compared to administering free drugs only [152]. To further highlight on this, two different coating materials (PEI and cyclodextrin-based pH-operated valves) on mesoporous silica NPs (MSNPs) were employed to demonstrate the efficacy of coated and uncoated Rifampicin (RIF) drug as delivery platforms. The result shows that PEI-coated MSNPs-RIF and pH-operated nanovalve-SNPs-RIF shows greater efficacy against MTB infected macrophages than uncoated free drugs because the MSNP facilitated the intracellular uptake of the drug RIF [66]. The same efficacies were observed on using Fe_3O_4-Glu-PEI NPs encapsulated with DNA vaccine as a prophylactic vaccine in the MTB-infected mouse model [159]. Similarly, Lee et al designed a probe using the ultrasensitive imaging of biomarkers to monitor extrapulmonary MTB infection. For that, they conjugated SPIONs with MTB surface antibody (MTB-SPIONs) and the results showed contrast enhancement reduction on MIR for MTB that is proportional to the concentration of MTB-SPIONs [160].

In a clinical experiment, the anti-TB econazole (ECZ) and moxifloxacin (MOX) were used to evaluate the drug potency, biocompatibility, biodistribution and drug retention period on MTB infected tissues. For the study, poly-(dl-lactide-co-glycolide) (PLG) NP-encapsulated ECZ and MOX were evaluated against murine TB. From the analysis, the ECZ drug retention was observed upto 5 days and 8 days on MOX and the drug concentrations were observed to be retained in the mice organs for up to 8 days, making it possible to remodel anti-MTB drug potency [161]. In another study, anti-mycobacterial activity of RIF was significantly improved when solid lipid nanoparticles

(SLNPs) prepared by microemulsion–based method were employed as drug delivery vehicles. The formulation used was consisting of cetylpalmitate (1.5 g) as the lipid core, Tween 80 (2 g), and Poloxamer 188 (0.2 g) as the surfactant and thus formed composite, RIF-loaded SLNPs were observed to be highly effective against MTB than free RIF, demonstrating about eight times potency against TB than simple RIF solution [162]. Similarly, the RIF-loaded poly-e-caprolactone NPs (PCLNPs) shows a controlled drug release for up to 8 days with increased bioavailability; the outcome demonstrate the possibility that may help to reduce possible drug overdose, prevent side effects and increases the potency for the application of nanodrug delivery systems in MTB therapy [163].

4.2.1 Pulmonary lung diseases

The large alveolar surface area, thin epithelial cells of the lung system allows easy particle uptake and plays a significant role in the retention and prolong drug release processes in a situation where the particle is carrying the drug payloads [164]. The large alveolar epithelium surface area of the lung provides great advantage and access to central circulation, enough transportation channels suitable for therapeutic administration [165-167]. By taking advantage of this, the NPs can be designed with appropriate size range that allows for the preservation and deter exhalation in order to enhance the bioavailability, retention and prolonged drug efficacy rates [168-170].

In a study for the treatment of pulmonary diseases, the PLGA-PVA to form DEAPA (3-(deethylamino) propyl amine)-PVA-g-PLGA) NPs were observed to have successfully delivered siRNA into lung cancer cells and further the use of fluorescent metal nanoshell was able to detect even the single miRNA in lung cancer [171]. Similarly, chitosan owing to its biodegradable and biocompatible nature were also used as vehicles to deliver pCMV-MuB-encoding murine interferon-B in mice carrying loaded CT26 cells [172]. A remakarble success rate of about 60-80% was recorded in gene silencing activity in human lung cancer cells using siRNA/thiolated chitosan polyplex system [173]. In a different study, the chitosan-dextran were used to deliver gemcitabine to human lung cancer cells [174] and gold NPs were reported to conjugate with antibody emitted photo thermal heat under NIR causing destruction of lung cancer cells *in vivo* [175].

4.3 Diabetes

Most of the wellknown deadly diseases such as HIV and TB are infectious, however, diabetes mellitus nicknamed “ever ending diseases acquired for eternity” emanated from a chronic metabolic disorder or as a result of multiple genetic anomalies and other associated individual eating behavior [41,176]. The disorder pops up in response to a relative deficiency of insulin secretion in the body [177-179]. The activities of insulin resistance to the cells are characterized by high circulating glucose, a process that leads to hyperglycemia [180]. Also, hypoglycemia (low blood) is a situation not easily controlled or regulated in diabetic patients and can transform into further complications that leads to organ damage, ulcer, allergies, asthma and arthritis [181]. The preventive and therapeutic approaches mostly came from the same mechanism that generates the disease. In diabetic activity, a number of processes are involved which includes the generation of ROS due to a rise in glucose level, creating metabolic abnormalities and chronic complications overwhelming natural ROS suppressor that finally leads to a marked increase of oxidative stress [181-183].

Unquantifiable efforts are being deployed over the years in diabetes therapy including the use of herbal drugs and insulin-related drugs; however, research has confirmed some observed deficiencies using this available therapy such as lacking drug target specificity, poor solubility and bioavailability and finally easy degradation by the enzymes [184]. Gold NPs were observed to effectively reduce the formation of ROS in diabetic mice by controlling antioxidant enzymes such as SOD, GSH and catalase and exerting strong oxidative control over the blood glucose level, lipids and serum biochemical activities in streptozotocin induced diabetic mice; thus increasing the organ function for better utilization of blood glucose [41]. Recent research demonstrated that the gas-injection of anti-oxidant epigallocatechin (EGCG) and Au NP liquid mixture using Au-mediated-liquid delivery system were observed to have rapidly enhanced the wound healing of diabetic species [182]. In a different study, Gu et al designed a platform for self regulatory delivery of glucose-mediated insulin using an injectable and acid-degradable polymeric network with porous structure that dissociates easily.This helps in releasing insulin through the catalytic conversion of glucose into gluconic acid, demonstrating an efficient process that allows systemic and well regulated steady insulin-mediated drug delivery into a diabetic patient [183]. In other trails, Kim et al and Kong et al developed a method for sustained delivery of Exenatide,aglucagen-like peptide-1(GLP-1) used for treating Type 2 diabetes using NPs of core/shell structure [177-178].

Other metallic NPs such as silver, zinc, vanadium, chromium, magnesium also contributed in their novel state towards glucose metabolism as related to diabetes mellitus disorder [58,185-187]. For example, the Ag NPs synthesized from marine brown alga (*colpomeniasinuosa*) were observed to inhibit both α-amylase and α-glucosidase enzymes *in vitro* in dose dependent manner [59]. ZnO and Ag NPs were observed to show great anti-diabetic activity, enhanced glucose bioavailability by influencing hepatic glycogenesis in albino rat model, demonstrating the efficacy of ZnO and Ag NPs as anti-diabetic agents [58]. In general, the patients of Type 1 or advanced Type 2 diabetes usually have to go through a series of painful proces of injecting insulin daily and a system was developed to help this category of patients to avoid the rigor of painful injections daily. The technique involves the implanting of a biocompatible and biodegradable coated PLGA having both positively charged coated-chitosan and a negatively charged alginate in the mix. On inducing the ultrasound wave direct signal wave at the nano-network implant causes the composite to relax and gradually release insulin from the pool into the body stream [179].

4.4 HIV-AIDS

Finding a cure for HIV-AIDS has become a mirage for researchers for almost three decades. Despite been an elusive effort in some cases over the years, the unrelenting strive by most scientist helps in increasing life expectancy and quality of living among the patients infected with the virus [188-190]. Globally, the number of HIV infecting patients continues to decline; thanks to the wide spread awareness campaign and access to retroviral drugs. About 2.3 million new infections recorded in 2012, a sharp drop as compare to the figure recorded in mid-late 1990s having an average figure of 3.5 million each year [190]. The HIV-AIDS been an acquired deficiency syndrome carries along with it an associated burden of opportunistic diseases, compounding and putting pressure on natural immunities and thereby causing patient on existing therapy to develop resistance. However, the therapy using Zidovodine, Didanosine, protease inhibitors and the highly active antiretroviral (HAART) are one of the many success stories among several that helped to increase the life expectancy of patients suffering with this virus [188-189,191]. The challenges experienced by researchers in finding cure or prevention amidst the success so far did not deter their efforts in ending the deadly disease. A novel approach that requires target specific and safe delivery platforms thus became a strategy to develop. In fulfilling the ideas, NPs might be an alternative, owing to their unique characteristics and ease of modification/manipulation remains as a classical discovery that fit into this struggle of finding the cure for HIV/AIDS [191]. Before we discuss the various efforts in using nanotechnology for HIV-AIDS therapy, understanding the nature of the viruses in relation to NPs is accorded priority in this review.

HIV-1 virus outer structure consists of a lipid membrane interspersed with glycoprotein units with trimers consisting of two subunits; gp120 surface glycoprotein and gp41 transmembrane glycoprotein [192]. The HIV matrix proteins made up of p17 protein sandwiched between the envelope and the core. The viral core contains the viral capsule protein p24 which surrounds two single strands of HIV RNA and the enzymes needed for HIV replication such as reverse transcriptase, protease, ribonuclease, and integrase [192-194]. The gp120 glycoprotein units readily bind to the CD4 receptor on the macrophages of the host cells. The protruding gp120 glycoprotein units has 9 disulfide bonds, 3 are located very close to the CD4 binding sites and being on the exterior of the HIV-1 virus are much easily accessible to potential NP's interactions [192]. HIV first line of action is to attack the vital cells in human such as the $CD4^+$T cells, macrophages and dendritic cells [195-196]. When the human body lost $CD4^+$T cell activity, the result is increase in apoptosis and protein denaturation and finally gets exposed to diverse other possible pathogens on the loss to devour the dying cells [195].

Designing the strategies for a systemic, controlled-release platforms with reasonable half-life efficacy and retention across the infected cells is one reason where nanotechnology harnessed in this noble effort in finding the cure for HIV/AIDS [193,197,198]. The NPs found were to have the ability for bioconjugation and modulate biodistribution of both hydrophobic and hydrophilic anti-retroviral drugs to the $CDC4^+$T cells [199]. The human cells contain army of receptors on macrophage cells called D4T cells and the daily job of HIV virus is to destroy the D4 T cells by curdling it to interact with its HIV-1 gp120 glyocoprotein located at the exterior part of the virus [193,198]. Following this pattern of behavior, scientist discovered that, the CD4-functionalized mesoporous silica-based systems were able to selectively isolate, recognize and capture HIV-gp120 glycoprotein [193]. Similarly, the nanoformulated anti-retroviral drugs were reportedly conveyed by macrophages into the brain of maurine model [200]. Also, the NPs containing siRNA were reported to have silenced the CD4 and CCR5 transcriptors by reducing the expression of these receptors and inhibited the HIV-1 infection in human female reproductive tract tissue

explants [198]. In search of a suitable formulation for anti-retroviral drug Rilpivirin, some researchers successfully stabilized the drugs by impregnating with polyethylene-polypropylene glycol and PEGylated to copheryl succinate ester. A single dose of this suspension were observed to have sustained longer retention and circulation availability for 3 months, contrary to the 38 h repeated dosage following each dose when applied in its bare uncoated forms [201]. In different approach, targeting the receptor's surface for receptor-mediated internalization of therapeutics were considered to be another strategy for effective delivery of HIV drugs [202]. For that, Garg et al used stavudine-loaded 99 mtc-galactosylated liposome to deliver drugs by binding the liposome to the receptor on the macrophage surface and thus increased the stability and half-life of the Stavudine drug [202]. Similar modalities were adopted to deliver Zidovudine [203-204]. In another study, the surface modified chitosan NPs were employed for the delivery of Stavudineby taking advantage of its sphroidal size as a suitable platform for anti-HIV delivery, thus demonstrated the efficacy of using chitosan-based NP formulations for sustained and systemic release of Stavudine [205].

Immunogenicity studies in mice following intradermal vaccination with HIV-gp140 antigen-adsorbed Carnauba wax NPs induced high levels of specific immunoglobulin (IgG) and also enhanced serum, vaginal IgG, IgA cellular and humoralimmune responses [206]. In a study, the Au NPs-based biocarcode amplification (BCA) assay shows about 100-150 times enhancement in the detection limit over traditional colorimetric ELISA [194]. The Au NPs conjugated to raltegravir derivative observed to have penetrated deep into the lymphocytes, macrophages, astrocytes and brain microendothelial cells (HBMECs), by penetrating through the BBB both *in vitro* and *in vivo* when viewed under confocal microscopy using CD4, CD14, anti-GFAP, β-catenin and DAPI, respectively [197]. Similarly, the spherical Au NPs and PEG coated Au NPs (Au-PEG) when tested for their cytotoxicity and anti-viral activity, the result shows that Au NPs at 4 ppm concentration were observed to effectively neutralize the virus, while the Au-PEG NPs at 2 and 4 ppm concentrations were proved to be more effective in inhibiting viral entry [207]. Interestingly in a Bee venom study containingthe potent toxin called melittin, which when bound to NPs found to break and penetrate through the shield surrounding HIV and inhibit CXCR4 and CCR5 tropic HIV-1 infectivity and viability of TZM-bl reporter cells [208]. The studies related to viruses confirming the potentials of applying different NPs for the treatment of HIV/AIDS and other infectious diseases.

4.5 Cardiovascular diseases

Cardiovascular disease (CVD) is the heart related problem that is often takes place as a result of the disruption or blockage of blood circulatory system, in most cases as a result of occlusion or clot of the blood vessels or artery. If this happens, without immediate remedy may end up producing insuffient blood flow, suppressed oxygen supplies and end up indusing atheroclerisis (plaque), myocardial infarction and other related diseases such as stroke, seizure etc [209-210].The global reports on CVDs are estimated to about 17.3 million deaths in 2008 constituting 30% global dead toll. The report break further that 7.3 million are due to coronary heart, while 6.2 million are stroke related deaths [211-212]. We shall discuss other CVDs such as atherosclerosis in detail separately due to its global rate in CVD related issues.

4.5.1 Atherosclerosis

Arteriosclerosis is a general term for the thickening and hardening of arteries usually associated with fatty substances, cholesterol, cellular waste products, calcium and fibrin building up in the inner lining of the artery (called plaque). The continuous thickening causes the diameter of the artery to shrink up, causing insufficient blood flow and circulation which decreases the oxygen supply [209].

Caruther et al reported that the molecularly-targeted diagnostic imaging agents when applied for CVD allows for the detailed visualization of pathophysiological conditions without going through the rigor of invasive anatomy [213]. The success for atherosclerosis therapy was recorded following a two week administration of discoidal high-density lipoprotein (HDL)-like NPs prepared from trimeric peptide to an animal model. The result demonstrated an exceptional 50% reduction in the plasma total cholesterol levels confirming the potentials of treating atherosclerosis [214]. In another clinical study, HDL was also used to deliver drugs to atherosclerotic cells by using statin as the delivering moiety. It was observed that the statin without any counter effects towards lipid level, significantly reduced plaque growth in atherosclerotic mouse model by suppressing the activity of mRNA on the monocytes recruited cells and pro-inflamatory genes in the macrophages [215]. Similarly, Pitavastatin-incorporated NPs inhibited MCP-1-induced monocyte chemotaxis and the secretion of MCP-1 and MMP-9 from cultured macrophages. The NP-mediated anti-MCP-1 gene therapy reduced the incidence of plaque destabilization and rupture [216-217]. In general, atherosclerosis triggers inflammations on the macrophages and the NP

composites are designed to block the pathogens responsible for mimicking the inflammations. This was contained in a research where collagen IV- targeted Ac2-26 NPs were observed to significantly block tissue damage in hind-limb ischemia-reperfusion injury, limiting the secretion of polymononulcear neutrophils and thus helped in halting inflammations related to atherosclerosis [218]. Metals are not left in this regard; the Gd-containing lipd-based NPs targeting macrophages were used to detect murine atherosclerosis.The result shows that macrophages-specific CD36 NPs bind to human macrophages and help to enhance the detection of human plaque and this model expected to arrest the onset of atherothrobism [219].

4.6 Brain related diseases

Human brain is designed in such a way that without continuous suppy of blood and oxygen, it cannot function and remain active. Any short coming or disruption can be catastrophic and can result to complications such as cerebral ischemia, Alzheimer's, Parkinson's, mycodial infarction and Amyotrophic lateral sclerosis (ALS) [220-225]. Brain reacts readily to oxidative stress generally in response to cut in oxygen supply, non-availability of endogenous antioxidant within the systems and high concentrations of unwanted polyunsaturated fatty acids (PUFAs) [226-227]. Giving therapy to the brain is a big hurdle to cross and the researchers in this regard have to find ways to cross this barrier so as to introduce safer and efficient methods. It was observed that the BBB, formed by the endothelial cells of the brain capillaries are engulfed by the tight junctions called zonulae occludentes. This blockage inhibits the transport of 98% of all micro-molecule drugs and 100% of macro-molecule therapeutics to the brain, making it near impossible to administer target specific drugs [228-229]. The capillaries of the brain are designed like a filter that regulates the movement of molecules and cells between the blood and the brain cells, detecting and blocking toxic encroachments entering into the brain [230].

Several strategies have been proposed for the delivery of therapeutics across the BBB. Gabathuler reported that since small hydrophilic molecules such as amino acids and glucose exists naturally within the body's system (brain and endothelial cells), modifying them into nanoform to help to transport payload across the BBB. The report reveals that hormones, transferrin in erythromycin, insulin and lipoproteins are widely overexpressed onthe brain endothelial cells can also serve as the receptors for specific targeting and delivery of cargo across BBB [230]. Brun et al reported that TiO_2 NPs systemically break the tight junctions of endothelial cells and the BBB [231], while SiO_2 and TiO_2 NPs in another work were reported have found ways to penetrate the BBB and accumulate in the brain parenchyma of mouse model [232]. Similarly, the PEGylated poly(lactic acid) (PLA) NPs with two different targeting peptides, TGN and QSH were reported to have successfully targeted amyloid plaques in the brain of a mice [233]. All the above clinical trials further ignite the hope that the NPs can be designed to break the BBB and deliver therapeutics to the brain.

4.6.1 Parkinson's disease

Parkinson's disease is a neuro-degenerative disorder that arises when the dopaminergic neurons (that regulate movement) in the substantia nigra pars compacta of the midbrain stops functioning due to excessive oxidative stress and neurodegeneration [226,234]. Researchers during a clinical trial on an animal model with Parkinson's disease investigated that the cerium oxide NPs remain intact in striatal dopamine and dopaminergic neurons in the substantia nigra, demonstrating a viable route to treat Parkinson's disease [235]. In a related clinical trial, Odorranalectin-conjugated PEG-PLGA NPs were successfully tested to have like neurotransmitter behavior and the tyrosine droxylase test was performed to enhance the therapeutic effects of urocortin peptide (UCN)-loaded NPs on Parkinson's disease [236].

4.6.2 Cerebral ischemia or stroke

Insufficient flow of blood to the brain either due to clot, hemorrhage or plaque can lead to a stroke (cerebral ischemia) [224]. Any disruptive activity that tempers with glucose and oxygen supply to the brain canjeopardise the ability of the brain to make necessary energy and may end up forcing biochemical reactions, termed as the ischemic cascade. This can lead to oxidative stress, inflammation, cellular degradation, BBB dysfunction and ultimately cell death occurs [226-227]. Micelles and liposomal NPs containing superparamagnetic and fluorescence QDs can enable the easy detection of cerebral ischemia under MIR and conforcal laser scanning microscope (CLSM). Their small size gives it the initia to easily accumulate at the myocardium, providing the platforms for efficient imaging and drug delivery for myocardioum infaction [221]. Also, the hydrogen peroxide ($H_2O_2^-$) responsive antioxidant NPs formulated from copolyoxalate containing vanillyl alcohol were observed to degrade and released vanillyl

alcohol in the process, which reduced the formation of ROS and consequently fought against the inflammatory and apoptotic activity [237]. In a different study, the single intramuscular injection of pioglitazone-incorporated NPs to non-diabetic murine model significantly improved the blood flow inducing endothelia, NO synthase phasphorylation, and the expression of multiple angiogenic growth factors *in vivo* [217].

4.6.3 Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neuro-degenerative disorder that affects the cognitive faculty and is the cause of memory loss (dementia) in the old and aging people, following slow and gradual degeneration of neurons at the initial stage and progresses further to affect the hippocampus and finally impact heavily on the neocortex at later stages [226]. This situation in most cases end up producing a state of total relapse of memory and complete distortion of cognitive ability such as speaking and working [238].

In an effort to establish the safer therapeutics for AD, Fibroblast growth factors (bFGF) were encapsulated in NPs which are conjugated with Solanum tuberosum lectin (STL) and bound to N-acetyl glucosamine on the nasal epithelial membrane for its brain delivery. The results obtained following the administration of STL modified NPs (STL-bFGF-NP) shows that the disease state in AD rats were significantly improved compared to AD model group and further the safety of this delivery method was also confirmed histopathologically [225]. In another study for the treatment of AD, a platform for high sensitivity trasferrin receptor was developed using peptide sequence conjugated with Au NPs. The NP conjugate with strong sensitivity of the peptide sequence easily interacts with transferrin receptor present in the microvascular endothelial cells of the BBB, causes an increase in the permeability of the conjugate in brain *in vivo* [223]. In a related development, the dual-functionalized PEGylated PLA polymer NPs was fabricated to deliver drug targeting amyloid plaques to the brain of a mice model carrying AD. The delivering vehicle was designed to target 2 peptides, TGN and QSH; TGN was made to target ligands at the BBB while QSH is to bind AB (1-42) component of amyloid plaque. Both peptides were conjugated to the surface of NPs and the result shows optimal activity for both TGN and QSH on the surface of the NPs enhancing precise targeted delivery to amyloid plaque in the brain of AD model mice [233].

4.6.4 Multiple sclerosis

Destruction of myelin and oligodendrocytes by autoreactive lymphocyte cell-mediated immunity (T and B cells) leads to focal damage of the myelin sheath of the neurons and nerve loss throughout the brain and the spinal cord causes an autoimmune disease called sclerosis. If unchecked, it will impede signal discharge to the muscle fibers, affecting movement and may result to paralysis [220,222]. New Northwestern medicine researchers reported that the biodegradable NPs can be successfully used to deliver antigen to arrest immune system's autoreactive activities on myelin following multiple sclerosis in mice [239].

4.7 Liver diseases

Liver is one of the most essential organs that is always alert and vigilant doing virtually all the clean up exercise and conversion of substances into usable forms. Like an organic machine that monitors materials intake into the body, converting nutrients to needed forms and eliminating unwanted substances [240]. Because of this essential and demanding task, liver is exposed to a danger of diverse compounds ranging from gene abnormalities or mutations to man made induced factors such as drugs, chemicals, alcohol etc [241]. Infections from viral sources or toxins causes inflammation of the liver such as viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, cirrhosis etc [242-243]. All the aforementioned compounds triggers the activation of cells imbedded on the macrophages generating ROS, free radicals, lipid peroxides, cytokines etc that end up causing further damage to the hepatic cells [237,241,244]. Liver diseases are characterized to be dangerous, of particular concern is hepatitis B viral (HBV) infections, liver fibrosis and hepatocellur carcinoma (HCC) that were reported to impact to global dead toll figures [242,244-245]**.**

4.7.1 HBV Infection

HBV infection is dangerous and easily contagious with multiple channel of transmitting infections ranging from infected sputum, mucus, infected blood, seminal and vaginal fluids, parental transmission and other unsafe social activities [246]. HBV according to HB foundation updated report 2014 is 100 times more infectious than the AIDS virus with about 2 billion people likely infected (1 out of 3 people), 400 million people chronically infected and an estimated 1 million people die each year from hepatitis B and its related complications [247]. Utilizing the RNAi to suppress HBV gene expression has became one of the veritable tools for effective therapeutic delivery [242]. In

view of that, researchers fabricated a siRNA designated platform called A- component and with a cationic liposome as B- component to form a core AB particle impregnated by aminoxycholesteryl lipid and this was encapsulated with PEG forming the third C-component. Thus fabricated nanoparticulate component (PEGylated siRNA-ABC) inhibit and influence the suppression of markers of HBV replication, demonstrating that the PEGylated siRNA NPs may have valuable application in RNAi-based HBV therapy [242]. Similarly, NPs containing HBV- cytosine-phospahateguanosine (CpG) referred as HBV-CpG were observed to reverse the HBV-oligodeoxy nucleoride (ODN)-mediated suppression of interferon (IFN-α) secretion and influence serious immune-stimulating effects on lymphocytes, enhancing HBV clearance and exerting an anti-HBs Ag response in HBV infected mice model [243]. In a related effort to deliver HBV therapy, the HB surface antigen (sAg) surface-adsorbed cationic PLGA NPs were used to deliver INF- α for specific targeting of hepatocytes. The result of the study shows that the recovery of HBs Ag-coated-PLGA in the liver after 4 hour injection reaches 75%, nearly 3 time greater in magnitude recorded on injection of plain PLGA NPs for targeting hepatic cells [248].In another attempt, gamma amino butyric acid (GABA) and serotonin (5-HT) chitosan NPs administered hepatectomised rats shows that GABA and 5-HT chitosan NPs shield the neurons from ROS-mediated damage [249].

4.7.2 Liver fibrosis

Several factors are reported to cause liver fibrosis such as chronic hepatitis, hepatic carcinoma and in some cases continuous alcohol abuse can induce alcoholic fatty liver that may leads to irreversible situation of liver cirrhosis [250-251]. A biodegradable NP of Silybin (a natural antioxidant) prepared by emulsion solvent techniques was used as a targeting agent against kupffer cells to treat liver fibrosis by reducing elevated enzymes and reversing liver toxicity level. The Silybin NPs shows good encapsulation efficiency and sustained drug release both *in vitro* and *in vivo* by the accumulation in the liver and released the drug at the cellular level [251]. Other researchers reported that low density lipoprotein incorporated NPs can be used to transport fat molecules such as cholesterol across the body. The attempt was made using cationic solid lipid NPs (CSLNs) generated from apolipoprotein-low density lipoprotein (LDLs) to specifically target growth factor siRNA (siCTGF) as therapy for liver fibrosis. The result shows that CSLN/siCTGF complex significantly reduced collagen and alpha (TNF-α) growth factors activity and expressions in the rat model [250].

4.7.3 HCC

HCC is rated to one of the most common cancer diseases that impacted heavely to the global cancer related mortality figure manifesting in response to unattended, prolonged HB infections and other hepatic related diseases as a fallout of genetic activation and epigenetic alterations [245,252]. In a study, galactose-conjugated liposome NPs (Gal-LipoNP TLR4 siRNA) administered during the therapy of liver disease observed to cause a decrease in liver enzymes (ALT and AST) along with attenuation of neutrophils accumulation and lipid peroxidase, blocking the secretion of ROS, increasing the Gal-LipoNP accumulation and gene silencing in the liver [244]. Furthermore, lipopolymeric vector was observed to enhance the level of luciferase gene expression and higher transfection activity in the liver following the administration of a formulation containing PLGA-cationic lipid 1,2-dioleoyl-3-(trimethylammonium) propane (DOTAP) and the ligand asialofetuin (AF) (PLGA/DOTAP/AF) NPs [253]. The excess of galactose residues on the polymer structure was observed to enhance specific targeting ability towards hepatocellular carcinoma [254]. In a differentstudy, Pictin-loaded 5-fluorocil (5-FU) NPs were reported to induce prolong circulation effect and killing of cancer cells which overexpressed asialogylcoprotein receptor (ASGPR) on the cell surface [254]. Similarly, biodegradable polymer NPs (Galactosylated chitosan-5-flurocile, GC/5-FU) used to administer specific target therapy and biodistribution to HCC shows sustained release and high accumulation in the cancer cells and inhibition of tumor progression [255]. In detail, the GC/5-FU upregulates p53 expression at both protein and mRNA levels, reduce Bcl-2/Bax expression, influencing the release of cytochrome C by mitochondrial and caspase-3 activation. The caspase-3 expressions were observed to decrease with poly ADP-ribose polymerase-1 (PARP-1) at mRNA and protein levels and accelerate apoptosis [255]. Also, to increase the bioavailability of Dox with simultaneous reduction in the cardiotoxicity, a Dox-loaded lactoferrin NPswere formulated and the results of the study shows that the administed Dox-loaded lactoferrin NPs to HCC rat model results tolocalization of the particles in the liver and plasma and with consequent reduction in tumor progression [256].

4.8 Malarial infection

One of the world's oldest diseases is malaria infection, a mosquito-borne disease that affects millions of people especially in most tropical countries. It is largely infecting children and pregnant women and presently

circumventing global resolves in attacking the insidious infection as a result of the continues drug resistance exhibited by the parasites [257-259]. According to WHO malaria report for 2013, about 3.4 million resides in area at risk of malaria transmission in 106 countries and territories andabout207 million clinical cases of malaria infections were reported in 2012 and 627,000 deaths are recorded [259].

Several therapeutics are presently in the market notably chloroquine, amodiaquine, mefloquine, lumefantrine, piperaquine, pyronaridine, artesunate etc and these drugs fall short in delivering efficient treatment due to the level of drug resistance exerted by the parasites [260]. Some of these drugs have low retention and bioavailability rate and some are poorly soluble in aqueous solution, others suffers degradation in stomach acids such as artemether [257]. Because of these short comings in present drugs in circulation, Raina et al recently introduced an approach for the use of lipid nanocarriers to prepare antimalarial drug, Artemeter (ARM)-loaded solid lipid NPs (SLN) by hot homogenization method as effeicent delivery platforms. The result shows that SLN interaction with erythrocytes didn't cause much haemolysis and ARM uses the iron in the hepatic blood circulation and converts the prodrug to active dihydro artemisnin that attacks and exert antimalaria activities [257]. Nayak et al on the other hand uses Curcuminoids lipid NPs prepared by nanoemulsion techniques to study the antimalarial activity. They reported that the curcuminiods encapsulated lipid NPs revealed 2-fold increase in antimalarial activity compared to free curcuminoids [261]. Similarly, hydrogel NPs containing hydroxyl propyl methyl cellulose and PVP were also used to enhance the absorption and prolong circulation time of Cur. The result shows that Cur NPs posses superior antimalarial activities and prolong bioavailability with drug content of over 99% [262]. Also, the Saponin, quinine compounds found in Naringicrenulata were reported to be effective in reducing Ag^{+} to Ag^{0} and the ointment extracted enhances wound repair *in vivo* in winter albino rats [57].

The SPIONs were also observed to efficiently deliver gene through magnetofection and efficiently target vectors and thus can be used to deliver malarial DNA vaccine. The SPIONs-PEI polymer were observed to condense DNA and the gene expression *in vivo* and shows greater binding capability with PyMSP119 gene-containing pDNA at pH 4.0 that improve the transfection efficiency and even much greater transfection under external magnetic field [263]. To aid in efficient diagnosis of malaria, magneto immunoassay-based approach for the detection of plasmodium falsciparum histidine-rich protein 2 (HRP2) were developed. The magnetic particles were observed to be easily detected under graphite-epoxy composite (m-GEC) magneto sensor, presenting excellent limit of detection, excellent coupling efficiency and higher sensitivity. These developments were reported to have greater potential in simplifying diagnosis of malaria infection [264].

Table 2: Summary of NPs mediated biomedical application for disease diagnosis and therapy.

Disease	NPs functions & applications	Ref
Cancer	1. Au nanoshell in miceller form improves photo thermal activity,	[101-102,109,135]
	2. PNPs increase the targeting efficiency to cytosolic epidermal factor for detection of tumor cells and initiate cascade of caspase process using curcurmin loaded liposome NPs,	[13,103,105-117]
	3. QDs used for targeting tumor and fluorescence imaging and promote efficiency in radio therapy.	[118-120,147]
	4. Ag NPs enhances raman signals for cancer cell imaging,	[121-122]
	5. Silica used to label cell membrane protein for cancer imaging and targeting efficiency towards overexpressed receptors,	[64,123]
	6. Iron NPs exhibit strong efficiency as biosensing material for HCC cells and shows excellent transverse relaxation contrast for MIR and support magnetically guided drug delivery,	[124-125]
	7. CNT aided efficient drug delivery and selective targeting towards overexpressed folate receptors and facilitate internalization into cells,	[22,82,127-129]
	8. ZnO induces cytotoxic effects in tumor cells, allows easy cellular uptake and localization and serves as an efficient fluorescence signal transducer.	[89,130-131]
TB	1. Chitosan and PEG aided controlled and efficient rifampicin drug delivery,	[159]
	2. Mesoporous silica NPs also increase rifampicin drug delivery and cellular uptake,	[68]
	3. Effective delivery of DNA vaccine for TB using Iron composite and its SPIO exerts ultra sensing imaging capability as biomarker for monitoring TB.	[160-161]
Diabetes	1. Au NPs effectively reduce formation of ROS by controlling antioxidant inflammatory control over glucose level and enhances wound healing,	[41,183]
	2. PNPs supported the design self regulated glucose-mediated insulin and enable sustain delivery of exernide. Chitosan coated PLGA induces ultrasound wave for gradual release of insulin from nano-network implants in the body stream,	[178-179,180,184]
	3. Ag and ZnO NPs enhances glucose bioavailability by influencing hepatic glycogenesis.	[60]

HBV	Liposome fabricated siRNA encapsulated PEG used as a marker for the suppression of HBV replication	[246]
Malaria	1. Cur loaded NPs induces antimalaria activity and prolong drug efficiency, 2. SPIONs improve transfection efficiency under magnetic field to detect malaria DNA vaccine activity and graphite-epoxy composites demonstrated excellent detection capability for malaria diagnosis.	[266] [267,268]
HIV	1. CD4-functionalized MSNPs selectively isolate HIV-gp 120, 2. PEG use for the stabilization and control release of antiretroviral drug rilpivirin and galactosylated liposome exert a binding efficiency to receptors on macrophages and equally increase half-life of stavudine anti-HIV, 3. Au conjugated with Raltegravir allows easy penetration into macrophages and inhibit viral entry.	[203] [198,208]
Atherosclerosis	High density lipoprotein help in the reduction of plasma total cholesterol level and suppressed the activity of mRNA on monocytes pro-inflammatory genes.	[125,216]
Brain	1. SiO_2 and TiO_2 NPs were able to penetrate across the BBB toward the brain parenchyma and odorranalectin conjugated to PEG NPs serves as neurotransmitter and enhances therapeutic effects on Parkinson's disease, 2. Au NPs decorated with peptide sequence demonstrated high sensitivity toward transferrin receptor for AD and PEGlyated PLA successfully deliver drug to amyloid plaque model.	[234,224]

5. Factors affecting the efficacy of disease diagnosis and treatment

The efficacy of theranostic using MNPs over decade of research proved to be a promising exercise that require continues support and global interest because it provided an interesting machinery for rapid diagnosis and therapeutic delivery working hand in hand [156]. Based on the observations made by some researchers, the following are some of the factors militating against the efficacy of MNPs for theranostic uses. The lack of detailed knowledge of the chemistry surrounding NPs bioaccumulation, degradation and clearance processes within the biological systems, the physicochemical behavior of NPs *in vivo*, possible routes and cellular uptake processes and more importantly lack of available cytotoxicity data on NPs [11,13,98].

We are made to understand from the outcomes of several clinical trials that MNPs physical nature such as size avertedly affects their efficacy *in vivo* [265-266]. Therefore balance must be established on the choice of size specificity to allow for efficient cellular uptake and the same time hindering possible premature escape of the NPs from circulation under the preying hands of phargocytic activities [267]. Other factors such as surface charges were observed to critically and significantly affect the efficacy of theranostics especially its impact on therapeutic retention, circulation and intracellular uptake [49,268]. NPs circumventing protocols reportedly maneuvers its way out from the endosomes into the cellular cytoplasm under the influence of changes in surface charges from negative to positive state [269]. The positively charged particles are reported to randomly clue on cells [98]; this is further substantiated because phagocytosis were reportedly observed to be more pronouns on mNPs attached with functional groups such as primary amine as compared to nanomaterials having surface functional groups such as carboxyl groups, hydroxyl and sulfate groups; an evident that positive NPs tend to have a higher cellular uptake than NPs with negatively or neutral surface charges [265,268].

Carrying out a thorough and detailed nano-toxicological study to determine the potential negative impacts exerted by nanomaterial's interaction with biological entities is indeed noble task to pursue and one of the biggest drawback in achieving efficiency in nanomedicine [98]. Several clinical trials fully establish that NPs induces the generation of ROS and other free radicals causing oxidative stress, apoptosis, protein denaturation and cellular damage [87,129-130]. From the fallout and various contributions drawn by the above researchers, we can therefore highlight the key points that are very necessary in nanomedice in these reduced forms:

- Indepth analysis and understanding of biodistribution of NPs and its sensitivity across various biomolecular compartments of the body systems is essential towards ensuring the safe and efficient diagnosis and therapy.
- Systemic and accurate evaluation of all NPs toxic level effects in biological interactions in but free and associated forms is a very important factor to consider for efficient theranostic.
- Method of functionalization, duration of exposure, particle response to environmental changes and biological ambience are also sacrosanct.
- Ensuring that the complete payload or drugs dosage as prescribed are delivered and release adequately.
- Selective functionalization of the nanocomposites to be target specific with high sensitivity for accuracy.

SUMMARY AND CONCLUSION

In this review, we explore the beauty of MNPs flexible nature and unique dispositions especially its intrinsic capability to assume multiple and diverse functionalities especially as a veritable tool in diagnostic and therapeutic applications. NPs multifuctional nature has given us an advantage to apply ideal processes that recognized careful functionalization of nanomaterials for both diagnostic and therapeutic applications following a well defined concept called "Theranostic" [5,7]. We defined the concept as an integrated clinical management that can diagnose, deliver targeted therapy and monitor the response to therapy simultaneously [2-3]. Interestingly, we touch briefly on NPs and their unique characteristics and freedom to assume several personality owing to its physicochemical properties such as size and surface area that were recognized to play a critical role in enhancing its solubility, biodistribution, biocompatibility, diffusivity, and biodegradability [11,266,268]. We went further to discuss few applications of NPs in medicine from its minute biological entities to its meadiating role in drug delivery and imaging for example, modified gold NPs plays a mediating role for the detection of cholesterol [33] and also monitor the sensitivity of transferrin receptor for treatment of AD [223]. We have seen that QDs help in specific targeting and fluorescence imaging of protein cells in malignant tissues [52] and profiling biomakers and monitoring of erythromycyte membrane destructions in malarial infection [270-271]. Similarly, silver selectively isolate gp120 and prevent CD4 virus in HIV test model [60] and in the same development mesoporous silica recognized HIV-gp120 and was used to selectively deliver drugs and destroys it [193]. We went further in detail on cancer based therapy such as gene based [133], photo dynamic, hyperthermia [134,138] and radiology [141] using various NPs as contrasting agent. In the course of the review, we also work down briefly on the role played by NPs in relation to other diseases such as CVDs (atherosclerosis), brain related diseases (Parkinson disease, ischemia, Alzheimer and multiple sclerosis), liver diseases (Hepatitis B, liver fibrosis and HCC) [242,251,253], malarial infection [261], TB and diabetes [161,186, 239]. We finally close our discussion by looking at factors militating against the efficacy of disease diagnosis and therapy to include lack of cumulative knowledge surrounding NPs accumulation, degradation and clearance *in vivo*, physicochemical properties of NPs in biological environment, cellular uptake processes and toxicity information on NPs [11,13,98,269].

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