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Review article

Prospects of nanodentistry for the diagnosis and treatment of maxillofacial pathologies and cancers

Henry A. Adeola [a,b,*], Saheed Sabiu [c], Tayo A. Adekiya [d], Raphael T. Aruleba [e], Christiana E. Aruwa [c], Babatunji E. Oyinloye [f]

[a] Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, University of the Western Cape and Tygerberg Hospital, Cape Town South Africa
[b] Division of Dermatology, Department of Medicine, Faculty of Health Sciences and Groote Schuur Hospital, University of Cape Town, Cape Town South Africa
[c] Department of Biotechnology and Food Technology, Durban University of Technology, Steve Biko Campus, Steve Biko Road, Berea, Durban 4001, South Africa
[d] Wits Advanced Drug Delivery Platform Research Unit, Department of Pharmacy and Pharmacology, School of Therapeutic Science, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, 7 York Road, Parktown, 2193, South Africa
[e] Department of Molecular and Cell Biology, Faculty of Science, University of Cape Town, Cape Town 7701, South Africa
[f] Phytomedicine, Biochemical Toxicology and Biotechnology Research Laboratories, Department of Biochemistry, Faculty of Sciences, Afe Babalola University, P.M.B 5454 Ado Ekiti 360001, Nigeria

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ABSTRACT

Despite the commendable milestones achieved in molecular maxillofacial pathology in the last decade, there remains a paucity of utilization of ancillary nanomolecular tools that complement the omics-based approaches. As the advent of omics science transforms our understanding of tumour biology from a phenomenological to a complex network (systems-oriented) paradigm, several ancillary tools have emerged to improve the scope of individualized medicine. Targeted nano drug delivery systems have significantly reduced toxicity of chemotherapeutic agents in a precise manner. Many conventional cancer therapies are limited in efficacy and this has led to the emergence of nanomedical innovations. Despite the success of nanomedicine, a major challenge that persists is tumour heterogeneity and biological complexity. A good understanding of the interaction between inorganic nanoparticles and the biological systems has led to the development of better tools for individualized medicine. Tools such as the composite organic-inorganic nanoparticles (COINs) and the quantum dots (QD) have significantly improved the identification and quantification of disease biomarkers, histopathological detection methods, as well as improving the clinical translation and utility of these nanomaterials. Nanomedicine has lent credence to several multipronged theranostic applications in medicine, and this has improved the medical practice tremendously. Despite the palpable influence of nanomedicine on the delivery of individualized medical therapies, the term "nanodentistry" remains in the background without much hype, albeit some progress has been made in this area. Hence, this review discusses the potential and challenges of nanodentistry in the diagnosis and treatment of maxillofacial pathologies, particularly cancer in resource-limited settings.

1. Introduction

Globally, cancer is reportedly a major cause of death, and a commonly diagnosed disease [1]. A 2018 estimate revealed the global incidence and mortality rates of cancer to be 18.1 and 9.6 million, respectively [1]. It is caused by the uncontrollable proliferations of abnormal cell growth or cell division which has ability to invade other parts of the body through metastasis [2]. Over the years, the use of radiation, surgery, hormonal therapy and chemotherapy have gained popularity in cancer treatment. Unfortunately, these approaches come with several limitations and side effects some of which includes; destruction of healthy cells, hair loss, vomiting, loss in some parts of the body, nausea and vulnerability to different kinds of infections. These therapies can also result in cardiovascular diseases such as, myocardial ischemia, hypertension, hypotension, edema, conduction disorders, thromboembolic complications and pericarditis, among others [3,4]. Repopulation of tumour cells has also been reported during fractionated radiotherapy which can lead to the delocalization of tumour cells. Also, the occurrence of multidrug resistance is another significant challenge [5,6]. These shortcomings put together, birthed the evolution of nanotechnology in cancer treatment.

* Corresponding author.
E-mail address: henry.adeola@uct.ac.za (H.A. Adeola).

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Nanotechnology is a burgeoning field, involving the application of nanostructured materials (typically in the 1–100nm size range) to provide solutions based on knowledge in various fields of science [7]. Nanomaterials have been described by the International Organization for Standardization (ISO) as a "material with any external nanoscale dimension or having internal nanoscale surface structure" [8]. Based on this definition, materials like nanotubes, nanofibers, nanowires, nanoplates, quantum dots (QDs) etc., are referred to as nanomaterials. Nanomaterials can be organized into four classes, viz: inorganic-based, carbon-based, composite-based and organic-based nanomaterials [7, 8, 9, 10]. Albeit, several other classification systems have been advanced based on crystalline form/chemical composition [11], particle shape/-dimensionality (0D,1D, 2D, or 3D) [12,13], and origin (natural or synthetic) [14, 15, 16].

Human activities and other biological species can influence the generation of natural nanomaterials. Artificial surfaces with nano/microscaled characteristics can be produced by natural nanomaterials which are present in the atmosphere, lithosphere and biosphere [7]. Synthetic nanomaterials can be generated from engine exhaust smoke or by mechanical grinding. They can also be engineered by biological, chemical, physical or hybrid methods [7]. Considering that the fate and behavior of synthetic nanomaterials is difficult to predict in various environments (as compared to natural nanomaterials); the fabrication and release of synthetic nanomaterials for industrial application and consumer products, has called for caution and careful risk assessment in recent times [7].

2. Nanotechnology in cancer diagnosis

Despite the various available diagnosis techniques, till date, cancer is still responsible for millions of deaths globally and several recurrence cases after treatment are still reported. From a chronologic point of view, this could be as a result of late (after metastasis) diagnosis in over half of cancer patients. Other reasons have to do with sensitivity and specificity of available diagnostic combination chemotherapies [17,18]. Still in the same context, available diagnostics are insufficient to detect and forecast successful treatment and survival of cancer patients who rely immensely on early detection [17,18].

In recent years, the application of nanotechnology for cancer has received considerable attention, cutting across various interdisciplinary research areas and is believed to enhance researches focused on cancer detection, diagnosis and treatment. The growing nanotechnology field presents matchless promises in cancer diagnosis over the existing clinical diagnostic devices because nanotechnology substantiates a multilevel diagnosis cutting across tissue imaging, cell imaging to molecular imaging [19].

In molecular cancer diagnosis, the interface between biomarker discovery and nanotechnology holds significant prospect, particularly because panels of biomarker on complete cancer cells and tissue specimens can be quantified using nanoparticle (NP) probes [20]. Cancer biomarkers are inevitably one of the most valuable tools for early detection, precise cancer pre-treatment staging, evaluating response to chemotherapy and monitoring disease progression [21]. Although, found in blood, serum or urine, biomarkers can also be detected in or on tumour cells. With the development of proteomic technologies, many promising protein biomarkers have been uncovered for various types of cancer. A typical example was carried out among a South African cohort [22], where they identified several urinary proteins as potential biomarkers for prostate cancer.

2.1. Application of nanotechnology in bioimaging and detection

Nanoparticles with sizes between 10 to 100 nm have prolonged circulation time, a familiar drawback to the delivery of small molecular imaging agents [23]. Overlooking their shortcomings and focusing on various properties, a smart NP containing target-specific contrast agents, multimodality imaging probes or multifunctional reagents for concurrent imaging and therapy can be designed [24]. Remarkably, several studies have highlighted that molecular imaging of living cells and whole organisms is a crucial tool for investigating cancer and evaluating efficacy of cancer therapies [18,25].

2.1.1. Nanomaterials in biomedical imaging applications

Imaging plays a key role in cancer diagnosis, staging, and assessment of treatment efficacy. There is a wide range of nanomaterials used in biomedical imaging which includes NIR-absorbing carbon (such as graphene and carbon nanotubes), metal (Au, Ag, Pt, Pd), quantum dots (such as CdTe, CdSe) based nanostructures, magnetic (iron oxides) and upconversion composite NPs (e.g NaGdF4:Yb:Er) [26]. However, this review would focus on commonly used NPs such as quantum dots, gold NPs and magnetics in biomedical imaging applications.

2.1.2. Quantum dots (QDs)

QDs are fluorescent semiconductor nanocrystals with unique optical and electrical properties and about ~ 3–8 nm in size [27]. QDs possesses a narrow linewidth in the emission spectra, wide array of optical properties when compare to other organic fluorophores, continuous emission maxima as a result of quantum size effects, a comparatively long fluorescence lifespan and insignificant photobleaching over minutes to hours. These properties make QDs good for medical imaging applications after conjugation with specific bioactive moieties [28,29]. In recent trends, there is an increasing application of QDs in the biomedical field particularly as fluorophores for *in-vivo* fluorescence imaging. Several studies have provided compelling evidences of the efficacy of QDs in biomedical imaging. For example, a work done by Kim and co-workers developed a type-II band engineered QDs (CdTe/CdSe(core/shell) and CdSe/ZnTe(core/shell)). Using mouse and pig, they showed that these QDs allows sentinel lymph node mapping and major cancer surgery to be executed in large animals under complete image guidance [30]. Gao et al., have also developed a new class of polymer-encapsulated and bioconjugated QD probe for in-vivo cancer imaging and targeting. These NP probes have triblock polymer structure, targets tumour sites using both passive and active mechanisms and allow sensitive and multicolour imaging of cancer cells in living animals when coupled with wavelength resolved imaging [31]. Recently, a hybrid QD was developed by combination of Gd3+ and QDs as dual modal agent for in vivo imaging and magnetic resonance imaging (MRI) [32]. Dubertret et al., showed that encapsulated QDs in phospholipid block-copolymer micelles acted excellently as a fluorescent probe by providing significant reduction in photobleaching and low non-specific adsorption [33]. Another interesting long-term study using BALB/c mice documented that QDs remain fluorescent in the bone marrow and lymph nodes in vivo for over four months, signifying remarkable stability of these probes [34].

2.1.3. Gold nanoparticles (AuNPs)

Over the years, AuNPs have gained attention of researchers in the field of bioimaging because of their distinctive optical properties due to their localized surface plasmon resonance (SPR), facile conjugation to biomolecules and biocompatibility [35]. The synthesis of this nanomaterial could be in benign environment, an important factor in view of nanomaterial toxicity and safety in biomedical settings. As highlighted by Chen et al., AuNPs are tolerable, and colorimetric contrast in AuNPs treated cells could be regulated by size, shape, and interestingly, the SPR of AuNPs could scatter or absorb light in the near-infrared spectrum when excited, making them excellent *in vivo* optical imaging agents [36]. For the first time, Hainfield and co-workers, investigated the use of Au as an X-ray contrast agent in detecting tumour in BALB/c mice and showed that AuNPs were cleared via the kidney and bladder and do not concentrate in the liver and spleen, probably due to their small size. They concluded that AuNPs are valuable X-ray contrast agents when compared with existing agent because they present novel pharmacokinetic and physical benefits. Au nanorods have also been conjugated with UM-A9 antibodies in squamous cell carcinomas of the head and neck (SCHNN)

and it was reported that the existence of SCCHN may be identified. The increased assembly of AuNPs on targeted SCHNN cells generated efficient X-ray attenuation when compared with normal cells or untargeted cells [37]. Other interesting works have evaluated and documented the role and promise of AuNPs [35,38, 39, 40, 41].

2.1.4. Magnetic nanoparticles

Like other nanomaterials, magnetic nanoparticles (MPs) are gaining popularity as tools in biomedical field based on their biocompatibility and functional surfaces. Metallic nanoparticles such as gold and iron oxide can be employed as X-ray contrast imaging agents due to their short-term low toxicity and X-ray absorption capabilities [29], hence demonstrating a relatively better biocompatibility at lower concentrations, as well as acceptable functional surfaces and magnetic saturation [29]. Recently emerging magnetic particle imaging (MPI) techniques have employed a non-ionizing imaging technique for specific non-invasive diagnostic imaging, with better temporal and spatial resolution [29,42,43]. This takes advantage of the dynamic quantifiable superparamagnetic nature of magnetic nanoparticles during cellular binding to achieve tissue specificity and lower toxicity levels [43].

Based on this, iron oxide NPs have been functionalized with enzymes, proteins, antibodies and nucleosides for infected tissues such as tumour [29]. A review by Frey et al., highlighted the techniques involved in obtaining MPs and how to functionalize these nanomaterials for biomedical usages, specifically in bioimaging [42]. Iron oxide NPs are well known for their strong magnetization with transient toxicity *in vivo*, more so, they have been employed as vehicles for genes, drug and radionuclides in human medicine [43,44]. When conjugated with paclitaxel, iron oxide and Au released paclitaxel when exposed to phosphodiesterase, additionally, paclitaxel-conjugated NPs had magnetic tracking ability and good hydrophilicity [45]. Extensive work investigating MPs as MRI contrast have shown that they are excellent tools in detection, diagnosis and management of cancer. Xie et al., synthesized ultrasmall c(RGDyK)-coated Fe_3O_4 NPs by thermal decomposition of $Fe(CO)_5$ with 4-MC followed by air oxidation. The study documented a novel method of synthesizing and functionalizing Fe_3O_4 NPs as contrast tool for probable *in vivo* tumour-specific targeting abilities using MRI [46]. Montet et al., (2006) [47] designed a magneto/fluorescent nanoparticle conjugates that enhanced visualization of normal and tumour cells by MRI. The magneto/fluorescent NPs labelled with bombesin targeted bombesin binding receptors of rodent pancreas, hence resulting in reduction of T2 signal of normal pancreas tissue.

3. Nanotechnology in cancer treatment

Nanotechnology approach for cancer treatment came to limelight over two decades ago following its first approval by FDA [48], and it is fast growing due to its effectiveness in the treatment of cancer and fewer side effects posed to the patient.

Nanotechnology has been considered as a vital field that encompasses knowledge from other areas of science such as; chemistry, physics, biology, medicine and engineering. Cancer nanotechnology is an aspect of nanotechnology which make use of nanomaterials applications (NP for tumour-targeted drug delivery, tumour imaging and hyperthermia, and other nanotechnology approaches (NP-based theranostics)) to treat and diagnose cancer [49, 50, 51, 52]. This approach presents the means of targeting or delivering anticancer drugs directly and more precisely to neoplasms and cancerous cells without harming the healthy or normal cells. Nanotechnology has been shown to increase the survival rate and have lesser risk to cancer patients. This technique has been used in monitoring surgical resection of tumourous/cancerous cells, improvement in the therapeutic effectiveness of radiation-based and other existing treatment methods.

3.1. The concepts and mechanisms of nanotechnology-based therapy in cancer

Nanoparticulate materials are very unique in properties such as; size, morphology and distribution [53]. Drug-loaded nanoparticulate system can promote natural key components of immune system (antibodies and cytokines) which simultaneously fight and overcome diseases at the molecular level [54,55]. There are several types of nanoparticulate systems which have been employed in cancer treatment some of which include carbon nanotubes [9], liposomes [11], dendrimer [17], metallic NP, polymeric micelles [10,11], polymeric NP [11] and nanocrystals [7]. This approach provides suitable opportunities for multimodal, site-specific drug delivery to the tumour sites and increase the survival rate of cancer patients.

The use of prodrug micelle nanomaterials in cancer treatment is not only restricted to the delivery of drugs into a specific tumour sites (Figure 1), they can also be used in the encapsulation of several smaller molecular compounds due to their properties [49,52]. In tumour cells or tissues, the nanoparticulate delivery systems enhances the permeability and retention of anticancer drugs than normal tissues [53]. Plasmonic materials (such as gold and magnetic NPs) can photothermally activate photosensitive drug conjugate release [35]. This photo-ablative mechanism can improve cancer drug delivery in a controllable manner, via a targeted cancer cell pore widening and improved drug absorption [41]. The localized SPR and intra-band activation and decay of AuNPs electrons, plays a key role in this photothermal drug conjugate induction by light in the visible to infrared wavelength range [40].

More so, due to the large surface area of nanomaterials, they can be employed as site directed targeted therapy in cancer when functionalized or conjugated with peptides, antibodies, DNA or RNA strands, aptamers and other small molecules (Figure 2). The site directed targeted therapy concept has been an effective approach in cancer treatment due to the presence of several molecular receptors located on the surface of the endothelial layer of the tumour cells which aids the endothelial cell adhesion molecule-mediated targeted drug delivery process [56,57]. Nanotechnology has also offered an alternative approach in circumventing multidrug resistance due to the capacity of nanoparticulate systems to by-pass the drug efflux mechanism [50,51].

Recently, Carton and co-workers [49] used nanotechnology approach in delivering a cationic hydrophilic drug, pentamidine isethionate, in an *in vitro* study using breast (MDA-MB-231) and human lung (A549) cancer cell lines; based on the drug sensitivity to these two types of cancers. In this study, it was discovered that there was formation of polyelectrolyte complexes following the interaction between the cationic pentamidine and anionic hyaluronic acid, and these interactions result in the production of polyarginine and hyaluronic acid loaded pentamidine NP. Succeeding the *in vitro* cell studies, it was shown that the pentamidine-loaded NP are more cytotoxic to the cancerous cells when compare to the free drug. This study corroborated an *in vivo* experiment carried out by Zhong et al [52], where hyaluronic acid-activated acid-shelled paclitaxel prodrug micelles was used to target CD44-overexpresion in xenografts model of human breast tumour. It was discovered in this study that hyaluronic acid moieties of the nanoparticulate system (micelles) loaded with paclitaxel had significant effectiveness in treating mice with MCF-7 human breast tumour xenografts by completely inhibiting the breast tumour growth, and the mice showed 100% survival rate throughout the experimental period of 55 days with little or no side effects. It was concluded in the experiment that, hyaluronic acid-based micelles loaded paclitaxel has a great ability to localize and target the CD44 receptor overexpression in human breast tumour.

Li and co-workers [51] investigated the activity of mesoporous silica nanoparticulate nucleus targeted system, loaded with thermotherapy and hypoxia-activated chemotherapy, as well as surface engineered with anti-CD133 and thermal-triggered exposure of TAT peptide on cancer stem cells. It was shown that, the release of the drugs from the NP system

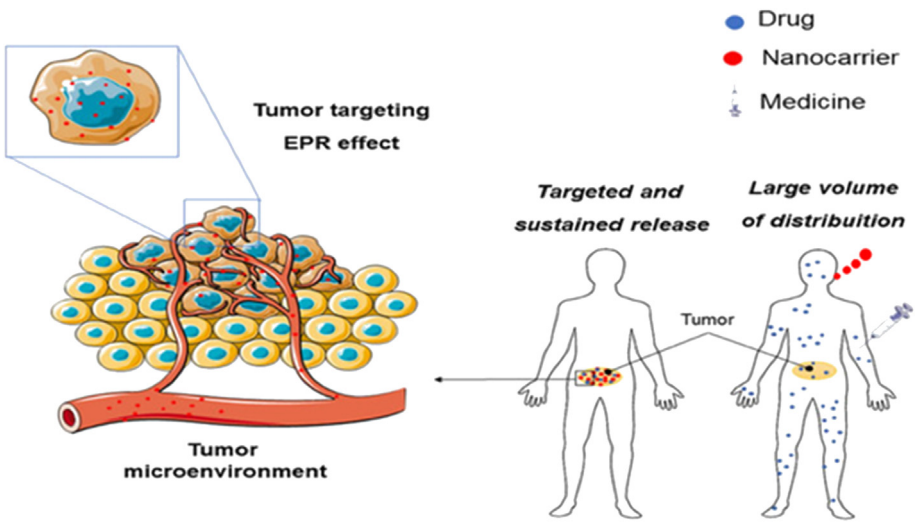

Figure 1. Schematic diagram of nanotechnology application in cancer treatment: the nanocarriers passively target the tumour and enhanced the permeability and retention effect of long-circulating polymeric therapy. There is a preferential extravasation of nanocarriers circulation in tumour vasculature. The nanocarriers act either extracellularly or after endocytic internalization once it enters the tumour interstitium [53].

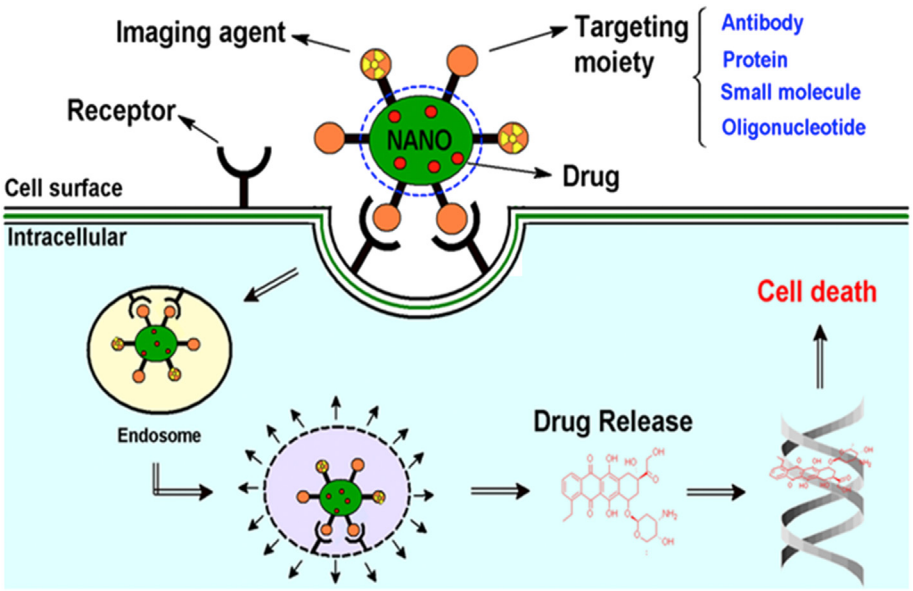

Figure 2. Schematic diagram showing the mechanisms of action of targeted functionalized nanoparticulate system. The anticancer drug is loaded into the nanoparticles, and the surface of nanoparticles is engineered with cell-specific ligand that can recognize and target cancerous cell. The engineered nanoparticles then localize and binds to the receptors found on the surface of cancer cell, thereby resulting in internalization of the nanoparticles by endocytosis. Inside the cancerous cell, the nanoparticles undergo endosomal escape, which lead to the release of the drug for its cytolytic activity that causes cell death [58].

into the nucleus significantly induced the apoptosis of hypoxic cancer stem cells. More so, the nano-system inhibits the tumour growth efficiently by blocking the signalling pathways of hypoxia cancer stem cells without causing any significant adverse effect during the period of the treatment. In another related study by Wang et al [59], the activity of mesenchymal stem cells (MSC) targeted drug delivery and NP loaded docetaxel as lung cancer treatment was investigated. Since it has been reported that MSC can be isolate from the bone marrow of patients and culture with ease, and transplant back into the patients for treatment so as to avoid immune rejection. MSC also possess high natural affinity for tumour which enable them to house tumour cells, although, the mechanisms have not been well elucidated. More so, lung-predominant circulation is the most significant characteristics of MSC employed as lung-targeted drug delivery system. This was buttressed by Wang and his colleagues [59] where the distribution of MSC was observed in lung of mice, rabbits and monkey following intravenous injection, whereas, all MSC transplanted are xenogenic. It was further reported that the MSC targeted drug delivery nanoparticulate system have a greater ability to inhibits primary tumours similar to that of NP loaded docetaxel drug system.

Ye et al. [60], investigated the efficacy and influence of folate-functionalized and chitosan-coated doxorubicin nanoparticulate system (FA–CS–DOX) on cell cycle arrest and cell apoptosis of hepatoma cell. It was reported that FA–CS–DOX nanoparticulate systems has stronger cytotoxicity activity than chitosan-coated doxorubicin (CS-DOX) against the cells growth of liver cancer by increasing and arresting cell cycle at G2/M phase via p53/PRC1 pathway. The effect of folate receptor targeted nano-system (liposomes) for the delivery of 5-fluorouracil in tumour cells was examined in another related study by Handali and co-workers [61], and it was shown that the targeted liposomes stimulated the mitochondrial apoptotic pathway by reducing the mitochondrial membrane ability, stimulating the significant activity of caspase 3/7 and releasing of cytochrome c in HT-29 cells. While in HeLa cells, the nanosystem particularly triggered necrosis pathway via the overproduction of reactive oxygen species (ROS). In all, folate-liposomal 5-fluorouracil showed greater anticancer activity when compared to

free drug. Some other studies which have used nanotechnology-based approach in cancer treatment include the use of cell-penetrating peptide PepFect 14 in preparing CPP-mRNA nanoparticulate systems in treating ovarian cancer [62], surface functionalized polymeric iron oxide nano-delivery systems as a vehicle for targeted delivery of docetaxel in breast cancer [63]. The technique has also been employed for co-delivery of pyrrolidinedithiocarbamate and doxorubicin in overcoming the cases of multidrug resistance in breast cancer [50], as well as, the development of a nuclear targeted doxorubicin-aptamer loaded liposome to thwart drug resistance in breast cancer [57].

3.2. Green synthesis of nanoparticles: a new approach in cancer treatment

The use of plant materials in the synthesis of NP (biogenic synthesis) is gaining more recognition due to its biocompatibility which is an important parameter for biomedical applications. Additionally, the synthesis of biocompatible NPs from plant has some great advantage over lipid-based vectors such as non-toxic, safe, cost-effective and easily produced accessible materials, prolonged circulating half-life, solubility, high binding affinity, easy functionality, good permeability, controlled pharmacokinetics and ability to protect and preserve the drug. Green biosynthesis of NPs offers an attractive alternative over chemical and physical methods. Some of its advantages include cost minimization, steps involved, it does not require high energy, temperature, pressure, and it is eco-friendly since it uses enzymes and not highly toxic chemicals as reducing [64,65].

The green synthesis of NP is evolving as potential anticancer agent, and they have been discovered as drug carriers and diagnostic agents in diseases treatment due to their predominantly distinctive set of biological, chemical, physical and photonic properties [64]. Their anticancer activity was evaluated by Al-Sheddi and co-worker [66] where the anticancer property of green synthesized silver NPs extracted from *Nepeta deflersiana* was tested against human cervical cancer cells. The biosynthesized *Nepeta deflersiana* silver NP-induced cell death in HeLA cells (human cervical cancer cells) via the SubG1 cell cycle arrest and apoptotic/necrotic process. In another related study by Sarkar and Kotteeswaran [67] where the anticancer activity of green synthesized silver NP from aqueous leaf extract of *Punica granatum* on human cervical cancer cells was evaluated. In that study, the cell viability assay showed the inhibitory activity of the silver NPs against human cervical cancer cell growth. Also, the silver NPs increased the percentage toxicity of the HeLA cells in the lactate dehydrogenase cell cytotoxicity assay. More so, the DNA fragmentation analysis indicated that the silver NPs synthesized from the leaf of *Punica granatum* had ability to induce apoptosis.

In 2014, Chung and co-workers [68] developed a self-assembled micellar nanocomplexes using epigallocatechin gallate (EGCG); a major antioxidant ingredient in green tea, and herceptin (protein drug), a breast cancer drug. In their study, it was shown that the successful engineering of the herceptin-loaded micellar nanocarriers can deliver more drugs selectively into the cancer cells, and killed them more efficiently, as well as displayed longer blood half-life than the native drug. Other studies which have employed green synthesis of NPs in cancer treatment include the anticancer activity of green synthesised gold NPs from *Scutellaria barbata* on pancreatic cancer cell (PANC-1) [56]. The anticancer potential and photodynamic therapy of green synthesized silver NPs from *Cynara scolymus* leaf extracts on breast cancer cells [69], and the green synthesis of anisotropic gold NPs from cocoa aqueous extracts for cancer photothermal therapy [70].

4. Nanodentistry and maxillofacial pathology

4.1. Benefits and applications

As a multidisciplinary field, nanotechnology embodies a range of technological developments linked with the use of NPs/nanostructures. Both the natural and synthetic NPs find applications in nanodentistry (ND) and maxillofacial pathology (MP). MP is a specialty area of dentistry and pathology involved with "cause-and-effect" disease studies and diagnosis/treatment as they affect the oral and maxillofacial regions of the mouth, jaw and face [71]. As a branch of medicine, dentistry entails the diagnosis, prevention and treatment of oral cavity and maxillofacial diseases. Common oral pathologies include enamel hypoplasia, caries, tooth resorption, fractured teeth, oral neoplasia, stained teeth, lymphoplasmacytic gingivostomatitis and "missing" teeth. Some of these conditions may be systemic or localized and show little or no clinical signs while others nay cause considerable discomfort and pain [72,73]. It is therefore interesting that both MP and dentistry have embraced the application of nanotechnological tools and materials with the aim of improving diseases management and reducing some of their associated adverse effects [74].

Nanodentistry involves the use of NPs in the development of novel, innovative platforms for dental applications related to diagnosis (for early disease detection), tissue engineering/rejuvenation, drug delivery (local anaesthesia etc.), treatment and maintenance of general oral health care [71,75]. It provides dentists an alternative approach to tackling oral health challenges with negligible complications and high degree of specificity and therapeutic efficiency. It also promises to save on doctor-patient time and reduce patient mental trauma, while reducing cost. The NP may also be implanted in dental products and interventions to enhance material properties [76]. The world has gone the way of NP, given their immense benefits for health and other fields of science. The application of nanotechnological principles and materials has redefined the face of oral diagnosis, therapy, surgery, dentistry and maxillofacial pathologies, globally. Nanodentistry has evolved due to the attendant adverse effects and complication attributed to dentistry and its offshoots such as painful and invasive dental surgeries, as well as disfigurement [77]. In addition, there is also an increased awareness amongst individuals on the need to maintain above average dental hygiene/care for aesthetics and/or enhancement of beauty, to boost physical/facial appearance and confidence [76,78].

Practical examples of the benefit of nanodentistry, includes the use of empty nano-sized liposome vesicles, for non-invasive drug delivery in dental therapies [77]. Also, despite current challenges there is hope for NP-delivered enzymes (collagenase) which have a high probability for remodelling periodontal fibres in targeted oral surgery, without the need for scalpel invasion. This promises faster and painless surgery time [77, 79]. Other benefits include novel substances for preventative dental care such as dentifrices for dentine and enamel that impart antimicrobial and/or other rejuvenating potentials. Again, improving the physiological and mechanical functions of the tooth using engineered nanomaterials (ENMs) such as nanocomposites and nanofillers in restorative ND is being explored [74]. ENMs may significantly decrease dental implants failure rates. It may further serve for infection control, direction and control of pulp stem cells for tooth regeneration and osseointegration enhancement [80]. On the other hand, despite current data showing low oral toxicity of ENMs, some ENMs could cross the gut and cause systemic disruptions, possibly with organ pathology. Nevertheless, toxicity studies on ENMs still need to be intensified to assure on long term use and safety. Other devices explored in ND include nanoassemblers, nanocrystalline hydroxyapatite, and nanorobots (mainly composed of diamond, 0.5–3 μm in diameter, and programmable) [74, 75, 76].

Furthermore, novel therapeutic potentials of ND in dentistry and MP include: dentition renaturalization and major tooth repair, local anaesthesia (nanoanaesthesia), tooth-sensitivity cure, covalently bonded diamondized enamel, orthodontic realignment in a single visit, and dental care/maintenance using nanorobotic dentifrices, which repairs carious blemishes and kill caries-causing germs [81,82].

Oral fluid and optical nanobiosensors and nanoelectromechanical system (exosome vesicles with genomic markers which can be upregulated for use in malignant cancer detection) function for oral cancer diagnosis and treatment [71]. In cancer treatment nanobeads/shells have been used to selectively target and kill cancerous cells while

healthy/normal cells remain unharmed [83]. Other nanotherapeutic options for oral cancer include nanomaterials for brachytherapy e.g. BrachySilTM (which delivers ^{32}P radioisotope treatment); and utilization of nanovectors for gene therapy [81]. Also, in MP advancements in stem cell research, tissue engineering has made periodontal tissue/ligament regeneration, bone augmentation/graft, orofacial fractures, pulp repair, cartilage regeneration of the temporomandibular joint and implant osseointegration therapies possible, easier and faster [84,85]. While navigating the periodontal tissues, orthodontic nanorobots facilitate painless and swift tissue repair, tooth rotating, straightening and vertical repositioning. This is a significant improvement from the usual excessive force which result in root resorption and anchorage loss [86]. Nanocomposite artificial teeth have also demonstrated significant durability and corrosion resistance compared to conventional microfill composite teeth [87].

The early onset of tooth enamel lesions can be treated via inclusion of nanosized calcium carbonate in toothpaste which facilitates tooth remineralization [88]. Another nanoproduct that may emerge in dental practice are wear-resistant, biocompatible, easy-to-clean nanocomposite tooth coatings to manage biofilm formation [83,89]. Graphene/zinc oxide nanocomposite (GZNC) has therapeutic potential against *Streptococcus mutans* biofilms [90]. In addition, nanocrystals with nanopores modified to allow protein adsorption due to their added silica molecules, as well as hydroxyapatite NPs have found application in bone replacement and bone defect therapies. In anaesthetic applications, mobile nanorobots carry active analgesics to the tooth pulp through the lamina propria, gingiva sulcus and dentine tubules. At the pulp site, all sensation and nerve-impulse traffic is shut down around the tooth being treated, but is thereafter restored when therapy ends. Nanorobots for treatment of gingivitis, halitosis and periodontal infections also exist and this is documented as complication-free [91,92].

There are also NP solutions and composites (adper, dentiflow etc.) used as bonding agents with orthodontic brackets that help maintain acceptable bond strength and decrease procedure time for bonding. Nano-sized sterilant solutions/emulsified oil droplets have also been developed to attack pathogens [93]. More applications include use of near-infrared luminescent QD nanodevices capable of targeting specific cancer proteins [75] for sensitive cancer cells detection and SPIONS (superparamagnetic iron oxide NPs) which carry contrasting components with varied aqueous solubilities that enable their retention in different tissues and makes for enhanced MRI. Claw-shaped nano-punch biopsy devices also function for specimen collection from target sites. Carbon-based 'buckyballs', as well as gold/magnetic NPs have also been used as drug delivery nanodevices. Highly sensitive and specific nanochips/biosensors for detection of oral cancer using salivary biomarkers [interleukin-8 (IL-8), IL-1β, thioredoxin etc.] are also being explored [81,94]. An overview of current applications of NP in MP and dentistry is presented in Table 1.

4.2. Potential hazards and risks

In relation to potential hazards, a study by Libonati *et al.* [95] demonstrated that leaked components from nanocomposite materials caused embryotoxicity in mouse blastocyst *in vitro*, but the reverse was the case with no toxicity when subcutaneously implanted *in vivo*. Similarly, a lower toxicity was recorded for orthodontic adhesive nanocomposite composed of titanium dioxide (TiO_2) NPs (at 1% by weight of TiO_2 NPs) compared to the NP free material [96,97]. In our opinion, while the benefits of ND seem to outweigh the harms, the exercise of some caution remains relevant. The carcinogenicity of nanobiomaterials may need to be further verified and improved upon. Their biocompatibility with tissue also depends on the constituting materials/particles. It is also worth noting that the large surface area to volume ratio of NP enhances their probability of being transported through body fluids and being absorbed into other body tissues/organs (brain, lung, liver, kidney, digestive tract, skin, spleen) besides the target tissues where they were originally meant to execute their therapeutic or preventative effects. In this state, their bioaccumulation as non-degradable toxic substances may result in adverse health responses in distant organs [98,99]. Other legislative challenges and ethical issues include privacy, metaphysical, security and equity [78], as well as regulatory and public acceptance issues [100] related to nanotechnological products and their applications.

4.3. Recent application of nanomaterials for maxillofacial diseases and oral cancer management

The use of nanomaterials has revolutionized the field of nanomedicine and emerging trends in its application for dentistry has tremendously improved the investigation, diagnosis, treatment and monitoring of maxillofacial diseases and oral cancer. For instance, nanodiagnostics have been used to for in-vivo visualization (up to single cell resolution) and selective chemotherapeutic drug delivery to cancer cells, with the aid of QDs, supraparamagnetic carbon nanotubes, dendrimers, nanowires, nanodiamonds and nanosponges [101]. Also, an emerging complement of lipid-coated targeted QDs, are currently being used for multiplexed quantification of cancer-specific biomarkers on single cells [102]. Near-infrared (NIR) excitable upconversion nanoparticle (UCN) based PDT agents have been developed to improve the

Table 1. Current applications of nanotechnology in the field of dentistry and maxillofacial pathology.

Nanotechnology	Application	Field of Application	Reference
nano-sized liposome vesicles	non-invasive drug delivery for dental therapies	Dentistry	[77]
Nanoparticle-delivered enzymes	remodelling periodontal fibres	Periodontal Surgery	[74]
Engineered nanomaterials	Nanoomposites and nanofillers	Restorative dentistry	[74,87]
Nanoassemblers	Computer-aided Microbial control and repair of carious lesions	Restorative Dentistry	[74]
Nanocrystalline hydroxyapatite	Improved osteointegration for maxillofacial implants	Oral and Maxillofacial surgery	[75]
Nanorobotic dentifrices	Repairs carious blemishes	Restorative dentistry	[81,82]
Nanobiosensors and nanoelectromechanical system	Oral cancer Diagnosis	Maxillofacial Pathology and Cancer Diagnosis	[71]
Nanobeads/shells	Selectively target and kill cancerous cells	Cancer Treatment	[83]
nanomaterials for brachy therapy	Radiotherapy	Cancer Treatment	[81]
Nanovectors	Gene therapy	Maxillofacial Pathology	[81]
Nano stem cell systems	tissue engineering	Endodontics and Maxillofacial pathology	[84,85]
Nanosized calcium carbonate in toothpaste	Tooth remineralization	Pedodontics	[88]
Graphene/zinc oxide nanocomposite	Antimicrobial caries control	Restorative dentistry	[90]
Quantum dot nanodevices	Cancer cells detection	Maxillofacial pathology and cancer Diagnosis	[75]
Nano-sized sterilant solutions	Antimicrobial/antiseptic	Dentistry	[93]
Salivary Nanochips/biosensors	Cancer detection	Maxillofacial pathology and cancer diagnosis	[81,94]

conventional PDT by targeting epithelial growth factor receptor (EGFR) in advanced, solid oral head and neck cancers [103]. Using an in-vivo rat model, Abbasi *et al.*, showed that orally and intravenously administered doxorubicin-methotrexate-loaded nanoparticles (DOX-MTX NPs) down-regulated MMP-2 mRNA levels in 4-nitroquinoline-1-oxide induced oral squamous cell carcinoma [104]. In addition, biodegradable nanoparticles have been employed *in-vivo*, as vehicle for targeted drug and vaccine delivery [105]. CALAA-01 nanoparticles have been used to suppress oral cancer tumour growth using a RRM2-siRNA [106]. Furthermore, using a novel multifunctional self-assembling nanoparticle construct, a non-receptor tyrosine kinase (Src), has been successfully targeted as an effective therapy for metastatic head and neck squamous carcinoma [107]. Not least, AuNPs in combination with irradiation (X-ray) has been demonstrated to enhance cytotoxicity on human head and neck cancer [108].

5. Concluding remarks and future perspectives

Although the application of nanotechnology in medicine, dentistry and MP holds interesting possibilities for the future, they remain as developing fields. For now, medical and dental practitioners still require guidance on the use of nano-incorporated products with respect to patient safety and occupational health. Risk assessments which encompass the effects of NP from and in medical/dental materials, for patients, personnel and environment cannot be overemphasized. Nano-labelling protocols for medical materials also need to be improved for informed and clear identification of nano-ingredients [76,80]. Despite the several ongoing global developments in nanomedicine, ND and MP, several countries in the Asian and African continents remain far off in terms of nanotechnological developments in these fields, despite a high burden of cancer [109]. This has been primarily fuelled by factors such as poor funding, inability to retain trained nanotechnology manpower/experts, poor technological transfer principles, slow strategic decisions at relevant levels of governance and research, absence of private enterprises participation and collaborations. Overcoming these challenges would facilitate further advancements in ND and MP in these regions, and indeed worldwide.

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