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The Potential Applications of Nanotechnology in Medicine

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Abstract

Background: Non-communicable diseases management such as cancers often represent a difficult situation. Discoveries of nanotechnology in physics and chemistry were extensively introduced for application in the biomedical field. Nanoparticles imply multimodal uses in bio-detection, drug delivery and diagnostic imaging due to their surfaces ability to interact and interfere effectively with biological environment and targeting cell-surface receptors.

Objectives: To identify the nanotechnology applications in medical fields and illustrate their efficacy and efficiency in diagnosis and management of diseases.

Review of Literature: Nanoparticle applications in management and control of serious diseases such as cancers are promising. Nanoparticles target the drugs delivery system specifically to malignant cells. They are able to penetrate the stratum corneum barrier of the skin and thus have been used widely as a treatment tool in skin cancer imaging, vaccine delivery via the skin, antimicrobials and wound healing. Recently, nanoparticles were used in lung diseases through their ability to accumulation the drugs in the diseased lung areas by providing a local inhalation delivery of active components. Nanotechnology possess as well useful anti-inflammatory effects and can improve wound healing process through acting as antimicrobial agents. Silver nanoparticles have potential effect against gram negative and gram positive pathogens.

Conclusion: Nanoparticles have the ability to potent the diagnosis and treatment in various diseases such as: cancers, lung disease, dermatology and coronary artery diseases via targeting the diseased cells specifically and thus reducing the adverse effects and general toxicity associated with conventional treatments.

Keywords: Cancer and nanotechnology, Dermatology nanoapplications, Nanoethics, Nanomedicine, Nanotechnology in KSA, Nanotechnology inmedicine, Respiratorydiseases and nanotechnology.

1 Introduction

Nanotechnology is defined as the application of nanomaterials in the development of structures, devices, or systems with a length scale of 1 to 100 nm. As most of animal cells are between 10,000 to 20,000 nm in diameter, nanomaterials can interact with biomolecules on both the cell surface and within the cell[1].

This novel field of technology is currently progressing and its applications in medicine are promising specific and sensitive tools for the diagnosis and treatment of chronic diseases and neuro degenerative disorders such as Parkinson's disease and Alzheimer's disease. Furthermore, the nanotechnology is used in lung diseases that can help against certain diseases such as lung cancer, tuberculosis, and pulmonary fibrosis[2],[3].

Nano-structures consist of nano particles. These are dendrimers; i.e. a synthetic polymer with a repetitively branching, micelles, drug conjugates and metallic nano particles. There are several metallic nano particles, however those silver and gold nano particles are of the highest importance in the clinical applications in the medical field[2]. Mihail Roco has defined nanotechnologies with four overlapping generations of nanotechnologies (figure1), which are progressive introduce over time[4].

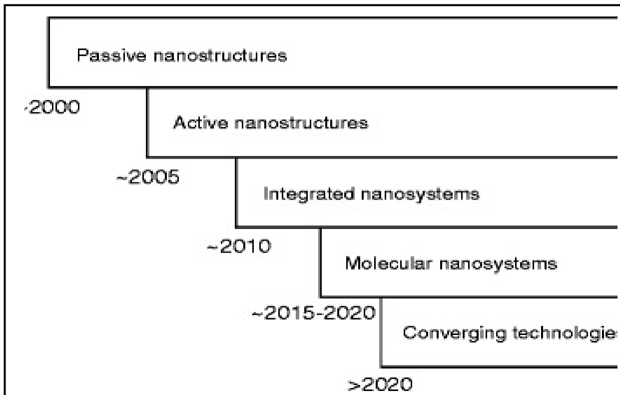

Fig 1 : Generations of Nanotechnologies

- *First-generation nanotechnologies* correspond to passive nanostructures indicate that the behavior of

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the material is supposed to be steady over time. Most frequently, it consists in adding a nanomaterial to another material in order to improve its performances, concentrated on enabling products involving drug reformulation to deliver many otherwise toxic drugs such as antifungal and anticancer agents, more safely and effectively to treat diseases in humans. Most of the current applications of nanotechnologies belong to this first generation.

- *Second-generation nanotechnologies* are active nanostructures, their behavior follow their environment. These active structures ability to perform functions, such as targeting, imaging, and deliver a therapeutic agent and monitor therapeutic efficacy in real-time. The First-Generation Nanotechnologies were less sophisticated than the second generation (1).
- *Third-generation nanotechnologies* correspond to integrated nanosystems, in other words 'systems of nanosystems' such as artificial organs built from the nanoscale. These are supposed to be developed from now on.
- *Fourth-generation nanotechnologies* are anticipated to be heterogeneous molecular nanosystems where each molecule in the nanosystem has a specific structure and plays a different role. It would include macromolecules 'by design' nanoscale machines and interfaces between humans and machines at the tissue and nervous system levels. They are supposed to emerge from 2015/2020.
- *Converging technologies* will be technologies resulting from the convergence of NBICs technologies (Nanotechnologies, Biotechnologies, Information technologies and Cognitive science) such as nano-bio-info from nanoscale, cognitive technologies or large complex systems from nanoscales.

Nanomedicine is the application of nanoscience and technology in management and control of human diseases[5]. It refers to a medical intervention at the molecular scale. It started to be used in medicine based on the discoveries in physics and chemistry[1].

For therapeutic applications of nanotechnology; nanoparticles are designed with chemically modifiable surfaces capable of interacting and interfering efficiently with biological environment and targeting cell-surface receptors, thus can be used as effective transport and delivery systems[6],[1]. Recently, this technology is being used to overcome the barriers in cancer and is currently applied in diagnosis of the earliest stages of cancer, as well as to target the drugs delivery specifically to malignant cells, and then determine if these drugs are killing malignant cells[1].

Societal considerations concerning the use of nanotechnology has been raised lately. Recent research studies explore the impact of nanotechnology on the society namely, the environment, health and safety, medicine and cytotoxicity, environment and Eco toxicity[6].

Factors influencing societal response to nanotechnology applications assume an imperative part in how nanotechnology is improved and popularized. Based on expert stakeholder analysis; the fundamental factors influencing societal response to various utilizations of nanotechnology will be based upon the extent to which these applications are seen to be beneficial, helpful, and essential, and how "genuine" and physically near the person who actually uses these applications are seen to be by the general society[7].

2 OBJECTIVES

1. To demonstrate the applications of nanotechnology in diagnosis and management of human diseases.
2. To illustrate the efficacy and the efficiency of the devices and drugs designed using nanotechnology in treatment of human diseases.
3. To clarify the safety of uses of nanoparticles in medicine.
4. To demonstrate the ethical and societal issues of nanotechnology utilization.

3 REVIEW OF LITERATURE

3.1Applications of Nanotechnology

3.1.1 Dermatology Applications

The nanotechnology field has been used widely in dermatology as it has a role as a diagnostic and a treatment tool in skin cancer imaging, vaccine delivery via the skin, antimicrobials and wound healing. The interaction of nanoparticles with skin may influence skin response to disease and to potential toxicity concerns[9] .

Nanoparticles are able to penetrate the stratum corneum barrier in skin and clear from the body with minimum adverse reactions for effective therapeutic use. However the anatomical locations differences and characteristics of hair follicle sizes and potential follicular reservoir will affect

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nanoparticle penetration through skin[10],[12]. The stratum corneum is lipoidic compartment while the underlying tissues are aqueous environment for this the hydrophilicity of the absorbent play crucial role in absorption which considered the stratum corneum is the main barrier in absorption. Absorption shows two pathways; one of them between corneocytes (bricks) and in the intercellular space (mortar). The other pathway is more suitable for penetration offering channel-like structures providing higher diffusivity although the pathway is much longer[11].

Many types of nanoparticles have been investigated for possible skin penetration such as Titanium Oxide (TiO_2) and Zinc Oxide (ZnO) coated nanoparticles which show unlikely significant penetration toward stratum corneum[12]. Co-administration of protein drug with gold nanoparticles (Au-NPs) exhibited very high skin penetration[10].

The dermal applications of nanoparticles in chemotherapeutics are selective to drug delivery to melanoma cells. In a model of human melanoma the results show that the multimodal silica nanoparticles are effective cancer-targeted probes. Through using rigorous quantitative imaging approaches and analysis tools for evaluation, they exhibited high-affinity binding, better tumor-to-blood residence time ratios, and enhanced tumor-selective accumulation in $\alpha v\beta 3$ integrin–expressing melanoma cells[13].

Also, using anisamide-targeted liposome-polycation-DNA (LPD) nanoparticles to specifically deliver small interfering RNA shows significant inhibition on the growth of melanoma tumor ($p<0.001$ at day 10). The enhanced anti-melanoma activity of LPD nanoparticles is probably due to contain of N,N-distearyl-N-methyl-N-2-(N'-arginyl) aminoethyl ammonium chloride (DSAA) that induced Reactive Oxygen Species, stimulate apoptosis, and inhibit antiapoptotic protein in melanoma cells[14].

3.1.2 Antimicrobial applications:

Nanoparticles can facilitate wound healing and have antimicrobial activity. There are several recent studies that describe different nanoparticles that are used in this field. Silver nanoparticlesin particular have gained increased attention in antimicrobials applications against bacteria, yeast and fungi as they possess useful anti-inflammatory effects and improve wound healing[15]. This excellent antibacterial activity that silver nanoparicles do exhibit is due to its properties that related to the total surface area which is the larger surface of the particle in relation its volume[16].

The antimicrobial activity of silver nanoparticles synthesized by CB2 (*Ochrobactrum anthropi*) was investigated to explore its potential effect against medically important gram negative pathogens (*Salmonella Typhi, Salmonella Paratyphi, Vibrio cholerae*) and gram positive *(Staphylococcus aureus)* compared to AgNPs synthesized by another *Bacillus* strain and the results showed good antimicrobial activity against pathogens, (Table 1)[17].

Table 1 : Diameter of zone of inhibition by biosynthesized AgNPs against pathogenic bacteria.

Bacteria	Zone of inhibition (mm)		
	AgNPs synthesized by *Ochrobactrum anthropi*	AgNPs synthesized by *Bacillus* sp.	Control ($AgNO_3$)
S. aureus	15	15	No zone
S. Typhi	14	13	No zone
S. Paratyphi	15	17	Nozone
V. cholerae	16	17	No zone

Although Silver nanoparticles had a significant antifungal effect against *Trichosporon asahii* growth in a concentration-dependent manner, yet minimum inhibitory concentration of silver nanoparticles are lower than other drugs against *T. asahii* such as AMB, 5-flucytosine, caspofungin, terbinafine, FLC, and itraconazole. The surface morphology of *T. asahii* showed serious damage of mycelium at higher concentrations of silver nanoparticles through using SEM[18].

3.1.3 Applications in malignant tumors:

Cancer is characterized by abnormality in cell growth and proliferation caused by mutations or inherited factors. Chemotherapy is the current choice of treatment, its aim is to induce cancer cell death and stimulate the mitochondrial apoptosis pathway[19].

Unfortunately, chemotherapy affects also the normal cells and can develop drug resistance such as alterations in membrane lipids that reduce cellular uptake,efflux pumps reducing the cellular concentration of the drug and altered drug targets that caused by abnormal gene expression after many administrations[20].

Cancer nanocarriers deliver safe and efficient therapeutic manner. They provide the possibility to encapsulate poorly soluble drugs, enhance their blood circulation and modify their tissue distribution to contribute in improving the clinical outcome and patient adherence[21]. To achieve this combination it's require to enclose the small-molecule anticancer drugs within the nanocarriers via hydrophobic force while the gene agents are compressed by the carriers through electrostatic force[22].

Several co-delivery nanocarriers are recently reported to provide great opportunity achieve synergistic effects to promote the efficacy of therapies. The best carrier should be multifunctional, and has the ability to transport both chemotherapeutic drugs and gene agents to the target cells and releasing therapeutic loads in specific time and accurate dose to maximize the efficacy and reduce the drug resistant tumors[23].

A study was done in 2008 compared three different widely used nanocarrier: linear polymer, dendrimer and liposome carrying a similar payload. It was documented that the parameters of nanocarriers, including size, composition, architecture don't play critical role in anticancer effect of tumor-targeted chemotherapy, despite they can be play role in other considerations, such as type of imaging or therapeutic agents, their aqueous solubility, electric charge, chemical structure[24].

The surface properties of actively-targeted nanoparticles will affect the interactions with their target molecules that could be proteins, sugars or lipids present on the surface of cells. The charge nanoparticles which is determined by the combinations of their ligand densities, materials, and nanoparticle formulation strategies can interfere with the interaction of actively targeted nanoparticles with cells and affect the cellular uptake. For instance, the interaction between positively cationic NPs and negatively charged cell membranes increased cellular binding and uptake[25].

3.1.3.1: Applications in colorectal cancer:

Colorectal cancer in Saudi Arabia most common cancer among men and the third commonest among women since 2002. The incidence is high in the capital city, Riyadh, where it reached 14.5/100000 in 2010[26]. Lymph node evaluation after surgical resection is important for prognosis and measurment of quality in colon cancer care that positively associated with survival of patients with stage II and stage III colon cancer[27].

Activated carbon nanoparticles suspension (ACNS) and methylene blue (MB) were used to show their staining effectto trace and detected number of colorectal cancer lymph nodes. The comparison was done between three groups involve 60 colorectal cancer patients. There was no significant difference between group A(ACNS group) and group B (MB group). However, the mean number of detected lymph nodes per patient was significantly higher in group A than in group C (non-stained conventional surgical group)(26.8 ± 8.4 *vs* 12.2 ± 3.2, $P < 0.001$). However, there were significant difference in lymph nodes detected in group B than in group C (23.8 ± 6.9 *vs* 12.2 ± 3.2, $P < 0.001$)[28].

3.1.3.2: Applications in oral Cancer

Oral cancers of tongue and floor of mouth are the most common head and neck cancers. The common treatments include surgery, radiotherapy, or chemotherapy[29]. Recently, application of anticancer nanoparticles targeting metastasis foci of cervical lymph nodes was established. Target delivery of Cucurbitacin BE (CuBE) by Cucurbitacin BE poly-lactic acid nanoparticles (CuBE-PLA-NP) with peri-oral-cancer submucosal injection to cervical lymph nodes was performed to evaluate its treatment efficacy and general toxicity. After CuBE-PLA-NP injection, the CuBE concentrations in cervical lymph nodes were higher by106.46 times than those after CuBE injection. The concentrations-time curve of the cervical lymph nodes in CuBE-PLA-NP group was 43.67 times as many as that in CuBE group. The CuBE concentrations in the blood in CuBE-PLA-NP group was lower to decrease the general toxicity. Also, necrosis and degeneration in the metastasis foci of cervical lymph nodes were found in CuBE-PLA-NP group[30].

3.1.3.3: Applications in breast Cancer

Breast cancer is the most common cancer among Saudi females. In 2010, 27.4% of all newly diagnosed female cancers were breast cancer[31]. There is no curable treatment for breast cancer, thus the main goals are prolongation of survival and quality of life improvement, and this is mediated by using the least toxic methods, as long as they provide sufficient disease control. Nanosomal docetaxel lipid suspension formulation (NDLS) was applied to show its therapeutic efficacy in metastatic breast cancer patients compared with taxotere. 72 patients were randomized in two groups. It was found that the general therapeutic response rate in patients treated with NDLS and Taxotere were 35.5% and 26.3%, respectively that indicate better response[32].

3.1.4 : Applications in Lung diseases

The application of nanotechnology to design drug delivery systems enhance treatment outcomes in organ tissues and cells including lungs due to their ability to pass the blood air barrier of the lung. Recently, achievements in nanotechnology contribute in improving the efficacy of inhalation treatment of different lung diseases through providing a local inhalation delivery of active components and accumulation of drugs in the specific diseased lung areas or cells to limit the exposure of healthy organs to potential toxicity via penetration in blood circulation[33]. Consequently, targeting nanoparticles containing drugs by a local inhalation delivery directly to the lung cells will improve the distribution, pharmacokinetics and reduce the adverse side effects compared with systemic delivery via intravenous injection nanoparticles[34].

Not all drug delivery systems are suitable for the administration by inhalation, Optimal drug formulation requires important criteria to play effective role in inhalable treatment. Thus, it is necessary to formulate carriers capable to remain in the lungs for the needed length of time. However, lipid-based particles (liposomes and micelles) are most considerable higher accumulation and longer retention time drug delivery systems inhalation treatment of lung cancer when compared with other studied particles[35]. Although, for effective deposition, the particle size must be in the range of 0.5-5 μm, it's possess unique aerosol and deposition effects that increase bioavailabilitycompared to large particles of same active pharmaceuticals as well as increase adhesivenessto mucosal surface to enhance solubility and speed up the rate of drug absorption[36].

Various therapeutic agents of respiratory disease such as β agonists, anticholinergics, corticosteroids and anti-inflammatory drugs have been approved for effective outcome in combination with delivery system by inhalation.Uncooperative children minimize the effectiveness of drugs while crying and screaming then drug delivery will be adversely affected because they have highly variable breathing patterns. Consequently this help clinicians and researchers in treatment of paediatric patients to dedicate more efforts in drug delivery[37].

3.1.5 Applications in Coronary Artery Disease

Coronary artery disease (CAD) is narrowing of the lumen of the artery by atherosclerotic plaque accumulation causing decreasing of blood supply to the myocardium[38]. The World Health Organization (WHO) estimates there will be about 20 million cardiovascular disease (CVD) deaths in 2015. Coronary artery disease (CHD) is a major cause of morbidity and mortality worldwide, it's was one-third of death causes in people more than 35 years old[39].

Current coronary artery disease treatment is by removal of the plaque by invasive techniques such as percutaneous transluminal coronary angioplasty (PTCA), atherectomy and stenting. All these methods lead to close the vessels upon themselves that called restenosis. The placement of stents has lowered the percentage of restenosis to occur[40]. In 25–50% of the patients with stent implantation there is stimulation in platelet adhesion producing in-stent restenosis[41]. Small vessel size and stent design are risk factors for restenosis[40].

Nanoparticles can provide a variety of delivery systems for payloads that used to inhibit restenosis such as drugs and genes, using of localized NP delivery via stents is new strategy to prevent restenosis through providing a continuous drug release in the target region of the artery. (Figure 2) shows the schematic structure of important NPs could use them in coronary artery disease treatment[41].

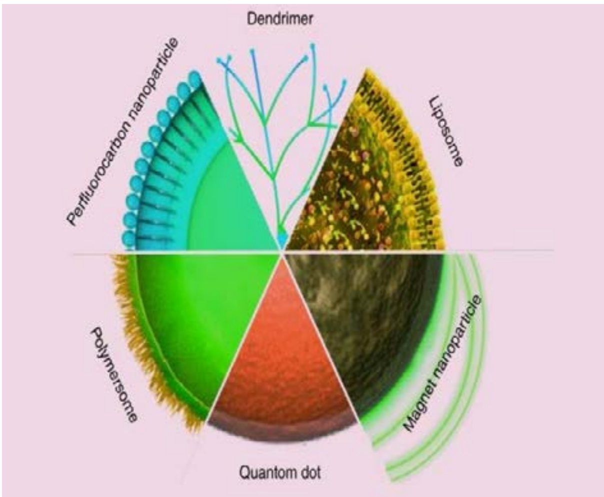

Fig 2: Schematic structure of important nanoparticles

Nanotechnology can improve the performance of stents as well. Stent-coating materials have been formulated from polymers and ceramics, despite that the polymeric one is more common than ceramic coating. The improvement enhance re-endotheliazation and lead to reduction of inflammation and angiogenesis[42]. A study was done on 2011 aimed to show the effects of Imatinib mesylate-incorporated nanoparticle-eluting stent on decreasing the neo-intima formation and endothelial healing in a pig coronary artery stent model. Imatinib-NP markedly prevent in-stent restenosis and attenuated neo-intima formation and stenosis by approximately 50% as assessed by angiographic, histopathological, and intravascular ultrasound imaging analyses[43].

3.2 Ethical Issues

Nanotechnology has made many achievements in the past decades. Nevertheless still raises many ethical concerns and potential risks when used. Among these risks: the impact of nanotechnology on the environment as well as associated health risks raised when using nanoparticles in the treatment of human diseases. In addition there are issues related to justice and principles of autonomy and the distribution of benefits and risks[30]. These ethical issues are usually associated with the social desirability, uncertainties surrounding nanotechnologies and difficulties to understand the meaning of nanotechnology properly because it seems that it is unrealistic for a single technology can do all these applications in the same time[8].

Nanotechnology has impact on the economy as well. Economic impact result in increased economic gap between developed and developing countries. However, these ethical problems arise during development of first generation nanotechnology with difficulties to define nanotechnologies but the emphasized ethical issues are associated with generations 2, 3, and 4 because these involve direct intervention on the human being[8].

The barriers between the nanoscientists and nanoethicists are likely to be one of the main challenges in nanoethics are facing. Multidisciplinary approaches and engagement between nanoscientists and nanoethicists are better way of doing nanoethics. Educational reform as well as increasing the capacity of scientists to consider the ethical and social issues in their work through bring these issues directly from ethicists creating more attention to the broader issues and increased encouraging and rewarding[45].

3.3 Nanotechnology in Saudi Arabia

Saudi Arabia started to set several new centers and nanotechnology-related institutions such as the *Center of Excellence of Nano-manufacuturing Applications (CENA)* that aim to promote and facilitate the researches in nanotechnology and provide financial scholarship packages for students and it works to prevent the emigration of highly trained or intelligent people from the region. Although the universities in Saudi Arabia provide research and educational opportunities in many nanotechnology fields involved the biomedical fields. *King Abdulaziz University Center of Nanotechnology (CNT)* established in Jeddah in 2006 develops innovative researches work in nanotechnology , as well as *King Abdullah Institute for NANO Technology (KAIN)*and King *Fahd University of Petroleum and Minerals Center of Research Excellence in Nanotechnology (CENT)*, for example: between November 11 and 13\ 2012, the 2nd Saudi International Nanotechnology Conference (2SINC) was held in Riyadh its theme was about "Nanotechnology innovation opportunities for the future " there was researchers group from King Abdulaziz University have extracted nanoparticles from camel urine to attack cancer cells[46].

4 Conclusion

Nanotechnology provides bright future for medicine improvement, involving therapy techniques, diagnostic techniques, anti-microbial techniques and applications in cancers, lung disease, dermatology and coronary artery diseases. In the following decade, nanomedicine may progressively turn into a mainstay of safer and more efficacious technique in diagnosis and treatment by using nanoparticles to deliver drugs to the specific site in various important human conditions. The current researches about nanotechnology involves the use of manufactured nano-robots to detect and treat damages at the cellular level.

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