Nanoparticle’s Significance as Antibacterial Agents & Other Pharmaceutical Applications and Their Limitations: A Critical Review

Ranajit Nath¹, Ratna Roy², Banani Mondal², Barshana Bhattacharya² and Lokesh Ravi³*

¹Department of Pharmaceutics, NSHM Knowledge Campus, Kolkata- Group of Institutions, Kolkata-700053, West Bengal, India.
²Department of Pharmacology, NSHM Knowledge Campus, Kolkata- Group of Institutions, Kolkata-700053, West Bengal, India.
³Department of Botany, St. Joseph’s College (Autonomous), Bengaluru, Karnataka-560027, India.

Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i38A32093
Editors:
(1) Dr. Syed A. A. Rizvi, Nova Southeastern University, USA.
(2) Joseph Kiambi Mworia, Kenyatta University, Kenya.
Reviewers:
(1) Rajesh Kumar, Lovely Professional University, India.
(2) Joseph Kiambi Mworia, Kenyatta University, Kenya.
Complete Peer review History: https://www.sdiarticle4.com/review-history/71299

Received 15 May 2021
Accepted 20 July 2021
Published 26 July 2021

ABSTRACT

Nanoparticles (NPs) a potential next generation candidate for human well-being in the world of healthcare, have been observed to be effective anti-bacterial agents. The significance of nanoparticles as anti-bacterial agents has taken spotlight, due to the inability of pathogenic bacteria to develop resistance against NPs. In this review, mode of action of some scientifically important anti-bacterial NPs were discussed, along with summary of recent pre-clinical and clinical studies reported on anti-bacterial NPs are discussed. Some of the current hurdles and barriers that should be addressed to complete marketability and human applications, in regards to NPs as nanomedicines are also critically discussed along with focus on reported toxicity in NPs. Some additional pharmaceutical effects of NPs, reported in the recent years, such as antidiabetic and anticancer are also included for discussion. This review provides significant information on recent...
discoveries in the field of nanomedicines as antibiotics, that show promising future for drug development and drug delivery. As in every human domain, evidence begins to point to the actual undeniable fact that in conjunction with the existing medicine, nanomedicines could be the future of the healthcare that replace or enhance the potential current pharmaceutical drugs.

Keywords: Nanoparticles; pre-clinical study; clinical study; mechanism of action; challenges; antibacterial NPs.

1. INTRODUCTION

Nanotechnology is the study and manipulation of matter with measures ranging from 1 to 100 nanometers. Nanomedicine, or the application of nanotechnology to medicine, is the use of precisely designed materials at this length scale to establish novel therapeutic and diagnostic modalities[1]. A variety of nanoparticle-based pharmacological agents have been developed in the last twenty years. [2] Nanoparticles are found to have various applications in the field of medicine and biology including delivery of genes, pathogen detection, protein detection, DNA testing, tissue engineering and heat destruction of the tumor (hyperthermia).[3,4]

Among various types of nanoparticles, Metals (copper, zinc, silver, gold) are being used as antibacterial agents widely. The Egyptians used copper salt as a constringent around 1500 BC. Silver and copper were used by the Greeks, Egyptians, Persians, Romans, and Indians to disinfect water and preserve food. Metal nanoparticles were incorporated in traditional many civilizations, such as Egypt, Greek, Rome and India. It is known fact that these nanoparticles have smaller uniform size and a higher surface area, with strong anti-microbial properties.[4-6]

Copper has been one of the important elements in household utensils in ancient times, devoting to its anti-microbial property. CuNPs are effective against both gram-positive and gram-negative bacteria. According to some previous researches the Kirby–Bauer diffusion method was used to investigate the anti-bacterial property of CuNPs against three bacteria: Staphylococcus aureus, Bacillus subtilis, and Escherichia coli and it was found that CuNPs were effective growth inhibitors against all these microorganisms.[7-9] Silver is one of the most well known metallic element that is popular for its anti-microbial and for its ornamental properties. It is also an element that is incorporated in dinning utensils, such as spoon, cup, plate, etc., in royal/rich families also aiding to its well known antibacterial and medicinal benefits. For these reasons, AgNPs (AgNPs) are one of the most popular anti-bacterial NPs in this field. AgNPs are reported to accumulate in the bacterial cell membrane, increasing permeability and causing the proton gradient to be disrupted. AgNPs also attach to a wide range of functional groups, including thiols, phosphates, hydroxyls, imidazoles, indoles and amines. They also inhibit ADP phosphorylation to ATP and meddle with NADH dehydrogenase and cytochrome oxidase. AgNPs also have a negative impact on DNA. AgNPs also induce production and aggregation of reactive oxygen species, as well as the modification of free DNA to a compact form.[10,11] One among the common metal nanoparticles includes zinc nanoparticles (ZnNPs). According to reports Zinc Oxide (ZnO) nanoparticles has a variety of morphologies and exhibits significant anti-bacterial activity against a diverse range of bacterial species. According to some researches when the surface morphology of ZnO is lowered to the nanometer range, it can engage with the bacterial cell surface and/or the core, where it enters the cell and exhibits distinct bactericidal mechanisms, there by exhibiting anti-bacterial property.[12,13]

For any given drug like molecules, pre-clinical studies with animal models helps to establish the safety, side effect, dosage, toxicity and all other vital information before entering human trials. NPs are also extensively studied for their pre-clinical efficacy in several pharmaceutical applications such as anti-bacterial, anticancer, etc.. In this review summary of pre-clinical studies reported in the recent years on the Composite nanoparticles (Graphene + acid treated CNTs), PLGA nanoparticles, polymeric nanoparticles, gadolium based nanoparticles, chitosan solid lipid nanoparticles, lipid-polymers hybrid nanoparticles, silver, gold nanoparticles [14-16]. There are many particulate related preparations/technologies now in use in pre-clinical research on nanoparticle delivery systems. Pre-clinical research practises for 1. Oral distribution; 2. Local delivery; 3. Systemic delivery; 4. Topical application approaches are mostly focused on developing new technologies and optimising execution and performance.[17]
One such report by Tadas Juknius et al. 2020 on pre-clinical study of anti-microbial patch mounted with AgNPs observed that, the patch is suitable for usage on the methicillin-resistant S. aureus (MRSA)-infected skin surface.[14]

While the interactive nature of engineered nanomaterials in biological systems can be strengthen able via in-vivo animal experiments and ex-vivo laboratory studies, the entire uncertainties of a human being's exposure to the nanoparticles cannot be eliminated. Even after a product has successfully tested in Phase I pre-clinical studies, and is clinically tested for Phase II or III, substantial risks are still possible. In addition, because of the use of engineered nanoparticles increases in nanomedicine field, issues of social justice, and healthcare access are becoming increasingly essential for physical enhancement.[18] In this review, clinical studies on the different nanoparticles such as ZnONPs, AgNPs, gold nanoparticles, magnetic nanoparticles etc., which are conducted based on their pre-clinical data, have been summarised along with the outcome to deliver a in depth understanding of the current scenario.[19-22]

Perfection is a myth, nanoparticles are no exceptions. NPs have both their advantages and disadvantages. Along with the applications of nanoparticles, some of the disadvantage of the nanoparticles applications which may affect humans and the society are also discussed in this review. Since manufactured nanoparticles are not a natural element, nanoparticles can hardly handle live organisms. Nanoparticles with humic agents, which include speciation of nano flocculants in the treatment of water or wastewater, may be deposited in aquatic sediments; they can also easily enter the cells of plants and animals and cause undesired consequences [23,24,25]. To eliminate and prevent the side effects of this potent participant, it is mandatory to continue research in this field to understand the nanoparticles from every scientific aspects.

2. MECHANISM OF ACTION ON ANTI-BACTERIAL ACTIVITY OF NPS

Some of the recent publications that depicts the mechanism of anti-bacterial activity of NPs are discussed, focusing on metal nanoparticles.

2.1 Silver Nanoparticles (AgNPs)

A study by Sukumaran and Eldho stated that AgNPs were found to be an anchoring agent to the bacterial cell membrane and are penetrative, thereby causing permeability of the cell wall and death of the bacterial cell. Accumulated nanoparticles were also found on the cell surface, attributing to the formation of pits. Some reports also state that, AgNPs damage the cell wall and make it porous, ultimately resulting in necrobiosis. According to some proposed data, the nanoparticles releases silver ions that interact and inactivate many vital enzymes, via their thiol groups. This interaction with vital enzymes, results in inhibition of several functions within the cell and thereby damage the cells. According to some reports AgNPs induces free radical production that kills the bacterial cell. Reactive oxygen species, which are produced probably through the inhibition of a respiratory enzyme by silver ions also contributes to destroy the cell. Being a soft acid, silver tends to react with base sulphur and phosphorus (known as soft bases) that also contributes to necrobiosis. The interaction of the AgNPs with sulphur and phosphorus of the DNA creates errors within the DNA replication of the bacteria and thus terminates the microbial cell. The phosphotyrosine profile of bacterial peptides are altered by the nanoparticles. The peptide substrates get dephosphorylated with the cooperation of nanoparticles on tyrosine residues, induce signal transduction inhibition, and therefore the stop page of growth. [26-28]

A study by Atiqah et.al., stated that being a heavy metal AgNPs have oligodynamic effect because of their large surface areas with the binding affinity towards the bacterial biomolecules, which induces the penetration of cells and produces reactive oxygen species (ROS) and behaves like modulators in signaling pathways (transduction) of microorganism. Reports show that, half encapsulation of antibacterial AgNPs with loose polyimide enhances the anti-bacterial activity of AgNPs.[29-32]

Report by Akhil et.al. demonstrated that, green synthesized AgNPs using Tectona grandis seed possess significant anti-bacterial activity against E. coli and S. aureus, where silver ions were found to be released by nanoparticles and are collected along the cell wall or within the cell, affecting DNA replication. Parallel interactions with protein thiol groups, causing protein inhibitory effect were also observed. An alternative study shows that, the mode of action of anti-microbial activity of some synthesized AgNPs are due to leakage of reducing sugars and proteins from the cell, detected using DNS
and Bradford's system, indicating that microorganisms were killed by destroying membranous structure and permeability. [33] A graphical representation of the possible mechanism of actions discussed in this section, in regards to the anti-bacterial activity of AgNPs are shown in Fig. 1.

2.2 Zinc Nanoparticles (ZnNPs)

Zinc Oxide Nanoparticles (ZnONPs) are widely accepted anti-bacterial metal NPs that executes the function by entering the bacterial cell and disrupting the cellular metabolism. Khwaja et al. (2018) demonstrated that, ZnONPs induces oxidative stress within the bacterial cell, that plays an important role by damaging biochemical polymers such as RNA, DNA, proteins and carbohydrates. Lipid peroxidation due to the oxidative stress, causes realignment of cell membrane, leading to disruption of important cellular functions and cell death. Being an amphoteric molecule in nature, zinc oxide tends to have reacting power with both acid and alkalies and give Zn$^{2+}$ ions. These Zn$^{2+}$ ions interact with biomolecules and inhibit multiple cellular functions of bacteria. According to the comparative study of ZnNPs, zinc based molecules such as zinc oxide, ZnSo$_4$.7H$_2$O, ZnSo$_4$.7H2So$_4$ were found to be six times more toxic than ZnNPs and proved to be effective anti-bacterial agent against Vibrio fischeri. Reports also suggest that ZnONPs are a potent cell wall synthesis inhibitor in bacteria. [34-38]

Satarupa et al. investigated the anti-bacterial and anti-biofilm mechanism of pancreatin doped ZnONPs against S.aureus and reported that, some of the probable mechanism of action of ZnONPs would include 1. ROS generation; 2. Membrane damage; 3. Membrane potential alteration. [39] Osama et al. reported that the anti-bacterial action of ZnONPs could be attributed to the electrostatic interactions between the bacterial cell surface and ZnONPs. This interaction of ZnONPs causes damage to the bacteria's cell wall leading to cell death. Furthermore, particles in the shape of massive agglomerates are far less likely to enter the cell wall and damage the bacteria from within. [40] Hence, agglomerates of NPs could possibly effect from the external contact rather from the internal biomolecules regulation. A graphical representation of probable mechanism of actions of ZnONPs antibacterial activity are shown in Fig. 2.

![Graphical representation of probable mechanism of actions of ZnONPs antibacterial activity](image)

**Fig. 1.** Possible reported anti-bacterial mechanism of actions of AgNPs [26-31]
2.3 Copper Nanoparticles (CuNPs)

Copper is a known element that exhibits anti-bacterial potential, even when used as element in house hold utensils. Reports strongly support that CuNPs are a potential anti-bacterial agents, aiding the natural property of copper to kill microbes.

A study by Ramyadevi et al., (2012) reported that CuNPs showed significant anti-bacterial activity against Micrococcus luteus, S. aureus, E. coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa. Among these pathogens, E. coli was the most susceptible bacterium followed by S. aureus, M. luteus, and K. pneumoniae, while P. aeruginosa was found to be resistant to the tested CuNPs. [41] A study by Maqusood et al. (2014) performed multiple assay for anti-bacterial activity, such as well diffusion assay, disc diffusion assay and minimum inhibitory concentration (MIC Value). Based on these assays, it was determined that the synthesized CuNPs have anti-bacterial activity against the tested pathogens. MIC was determined for Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Enterococcus faecalis, Shigella flexneri, Salmonella typhimurium, Proteus vulgaris, and Staphylococcus aureus and streptomycin was used as positive control. Among the panel of pathogens, E.coli and E. faecalis were found to be most sensitive against synthesized Copper Oxide Nanoparticles (CuONPs). [42]

Harikumar and Anisha (2016) investigated the anti-bacterial property of CuNPs against E. coli culture. It was observed that the tested CuNPs demonstrates bactericidal effect on E. coli.

Evidences suggest that, on tested E. coli strains, CuNPs have comparable bactericidal effects to that of AgNPs. Such anti-microbial NPs, typically inhibit the synthesis of functional biomolecules or obstruct normal cellular functions. Alternatively NPs interacting with microbial cell surfaces can reduce cell mobility and nutrient flow between the exterior and internal compartments of the cell.
A graphical representation of probable mechanism of action of CuNPs antibacterial activity are shown in Fig. 3.

2.4 Titanium Peroxide Nanoparticles (TiO$_2$NPs)

Author, Joanna et. al., organized an investigation on titanium dioxide in a plethora of studies that associate cytotoxicity and genotoxicity with their photocatalytic activity. TiO$_2$ NPs can both scatter and absorb the UV light. Absorption is possible due to the conduction band which photogenerates holes in the valence band. These holes and electrons can recombine or migrate to the NPs surface where different redox processes take place, which causes reactive oxygen species (ROS) production. The valence band holes react mainly with the moisture on the surface of particles, which results in the production of hydroxyl radicals. Although the conduction band electrons can interact with oxygen molecules. Therefore, it leads to the formation of hydrogen peroxide and superoxide anion radicals. The cell function with may impair by the products such as hydroxyl radical, hydrogen peroxide, and superoxide anion radical, constitute a group of reactive oxygen species. The study also investigates the toxicity of TiO$_2$ NPs additives in food and cosmetic products. The authors also found that TiO$_2$ toxicity in sunscreens has turned to the surface and the entourage of TiO$_2$ nanoparticles. For example, Y$_2$O$_3$-decorated TiO$_2$ nanoparticles were found to display enhanced UV attenuation and reduced photoactivity and consequently, cytotoxicity, compared with a commercial TiO$_2$ sample.

3. PRE-CLINICAL STUDY OF NANOPARTICLES

Pre-clinical studies using animal models has always been a primary screening stage for elimination or acceptance of drugable compounds, molecules and composites. In this section, some of the recent pre-clinical studies reported in the field of nanomedicine and NPs are summarised. The literature summary of pre-clinical studies on NPs are tabulated in Table 1. The pre-clinical studies summarised in this reviews, includes Conjugated NPs (with suitable drug molecules), Metal NPs, Magnetic NPs and Organic NPs.

![Graphical representation of probable mechanism of action of CuNPs antibacterial activity](image)

**Fig. 3. Possible reported anti-bacterial mechanism of actions of CuNPs [41-43]**
An investigation by Chein-Ju et al. (2016) constructed “CRLX101” a camptothecin containing NPs, that demonstrates anti-tumor activity, by inducing apoptosis in glioma cells. It also induced G2/M cell cycle arrest and supresing Topo-I enzyme. [44] Related studies by Vitalii et al., proposed that an increasing size of modified PEG-neridronate magnetic nanoparticles to be effective for clearance of Fe3O4 from blood stream to prolonged blood circulation. [45] Study by Shady et al., reported gadolinium based nanoparticles as radiosensitizer to conflict against brain melanoma metastases. In this study, B16F10 tumor bearing animals were observed to have diminished tumor cells & positive prognosis, when treated with the NPs. This study has been noted as a successful pre-clinical study in anti-tumor application of the NPs. [46] These mentioned studies can work on the vulnerability of diseases & gives a new sun shine reflection towards the modern treatment strategies.

Scientist Juliana de Oliveira Silve and her colleagues designed doxorubicin loaded liposomes that are observed to prevent breast cancer by reducing pulmonary metastasis foci and also was observed to inhibit topoisomerase II enzyme that prevent further proliferation of the cancer cells. [47] Report by Varun et.al. demonstrated that the level of ALT, AST, ALP, bilirubin, urea, uric acid and creatinine and also the level of TBARS, GSH and MDA in serum and in liver tissue respectively, of the animals were significantly altered due to NPs treatment in relation to MCF-7 cancer cell study. Authors estimated the highest apoptosis index by inducing lipid polymer hybrid nanoparticles containing methotrexate and beta-carotene. [48] This study established a combination therapy that reveals new possibilities to develop controlled & targeted delivery with respect to the lipid-polymer used as nano-carrier system.

A study by Tadas et al., observed that, an anti-microbial patch consisting of AgNPs enhanced the wound healing capability as well as dismantled the bacteria cell wall resulting in cytoplasm leakage. It had also observed that this patch possessed ant-stick property, determined by SIAL embedding into holey silicone carrier membrane. [14]

These pre-clinical studies (additional reports summarised in Table 1) provides evidence that nanomedicines and NPs show positive attribute to become future of pharmaceutical research. Nevertheless, further clinical research and human compatibility are mandatory for these nanoparticles to become commercial.

4. CLINICAL STUDY OF NANO-PARTICLES

Literature evidences show that, FDA has approved few NPs-based technologies for diagnostic and therapeutic applications. These approvals are strongly based on the pre-clinical and clinical studies reported on those NPs. Here in this review, some clinical studies of nanoparticles reported in the recent years are summarised in Table 2. Modern advances in nanotechnology and nanomaterials have emerged from different elements such as gold, silver, iron, cobalt, zinc, silica, selenium etc.,

Priyanka Singh et al., reported that the cytotoxicity of synthesized gold nanoparticles are highly dependent on the size and morphology of the particles, environmental scenario and the method of production. The authors also found that the dose of recombinant human tumor necrosis factor alpha (rhTNF) administered after immobilization with gold nanoparticles could be three times higher than its usual dose without any toxic effect. The polyethylene glycol (PEG) layer also decreased the uptake of nanoparticles by the mononuclear phagocytic system (MPS) and aided in their accumulation in the tumor masses via the enhanced permeation and retention (EPR) effect. Due to the favourable ability of gold nanoparticles to absorb NIR-light, interest towards (photothermal therapy) PTT has increased lately. Researchers are mainly focusing on the photothermal conversion efficiencies, selective targeting of cancer cells, enhanced cancer cell destruction using nanoparticles [62].

Zakieh Boroumand et al., performed clinical trials on AgNPs for wound healing effect. AgNPs use unique anti-bacterial mechanisms which prevents the possibility of resistance development. Silver dissolve in water and forms Ag+ ions which acts as anti-microbial agents. One of the anti-bacterial mechanisms of Ag+ ions is their interaction with sulphur and phosphorus groups of proteins of the cell wall and plasma membrane of bacteria that lead to dysfunction of this protein that threatens organisms life. Other hand, Ag+ ions binds to negatively charged parts of the membrane which creates holes in the membrane, causing cytoplasmic contents to flow out of the cell, therefore the H+ gradient dissipate across the membrane and finally cause cell death [63].
Table 1. Summary of Recent Pre-clinical study of NPs

| Nanoparticles                      | Activity                                         | Animal model    | Outcome                                                                                     | Reference |
|-----------------------------------|--------------------------------------------------|-----------------|---------------------------------------------------------------------------------------------|-----------|
| AgNPs & Chitosan oligosaccharide  | A pre-clinical study of in vitro anti-bacterial activity & in-vivo wound healing | Sprague Dawley Rats | PVA/ COS- Ag NP nanofibre mats were biocompatible, nontoxic and giving admirable antimicrobial activity against gm+ve S. aureus and gm-ve E. coli. Also, it is having effective capacity for wound healing compared to PVA/COS/ AgNO3 nanofibre mats. | Chenwen Li, 2013 [49]. |
| AgNPs                             | Pre-clinical study of anti-microbial patch        | Guinea Pigs     | From this study it is demonstrated that the patch is workable on the methicillin-resistant S. aureus (MRSA)-infected wound on skin surface healed faster as well as kill all MRSA bacteria strains in the wounds. | Tadas Juknius. 2020 [14]. |
| Cadmium sulphide nanoparticles.   | Pre-clinical evaluation of disposition & elimination of dextrin coated cadmium sulphide nanoparticles | Wistar Rats     | It is demonstrated that this nanoparticles distributed widely in tissues & produced degenerative alterations in testis and chronic inflammation in lungs after continuous administration during the 90 days without toxicity. | Gerardo Gonzalez De La Cruz. 2019 [50]. |
| Chitosan nanoparticles.           | Exploration of allantoin-loaded chitosan nanoparticles to eliminate ethanol-induced gastric ulcer: A pre-clinical study. | Sprague-dawley rats | ALL-loaded CS/STPP NPs (F-9) possessed remarkable antiulcerogenic activity against gastric ulceration in rats, which was emphasized by histopathological, immunohistochemical (IHC) and biochemical studies. | Reham Mokhtar Aman. 2021 [51]. |
| Chitosan nanoparticles.           | In-vivo study of Lovanstatin loaded chitosan nanoparticles on fracture healing | Wistar Rats     | From this experiment Lovanstatin loaded nanoparticles exhibits bone healing capacity by increasing bone density. From histopathology the normal, thick, continuous and connected trabecullae were observed in animals. | Peng Zhu. 2019 [52]. |
| Chitosan solid- lipid nanoparticles. | Pre-clinical systemic toxicity study.             | BALB /c mice    | The combination of Cslp and aspirin, curcumin with sulforaphane (ACS c-SLNs) doesn’t reflects on the body weight, blood count and blood biochemistry data and establish a safe toxicological profile of the nanoparticle in evaluation of in-vivo efficacy models. | Arvind Thakkar. 2016 [53]. |
| Nanoparticles Type | Pre-clinical Evaluation | Test Animals | Study Findings | Authors and Year |
|--------------------|-------------------------|--------------|----------------|------------------|
| Chitosan-whey protein nanoparticles. | Pre-clinical evaluation of Tamarind Trypsin Inhibitor in chitosan- whey protein nanoparticles decreases fasting blood glucose levels. | Wistar Rats | It had been noted that it decreased glycemia & HOMA IR. This nanoformulation provided TTI protection as well as improved the biochemical parameters without affecting insulinemia. | Lidia L. R. Matias. 2019 [54]. |
| Composite nanoparticles (Graphene + acid-treated CNTs). | Evaluation of safety & antileishmanial efficacy of amine functionalized carbon-based composite NP appended with amphotericin B: an in vitro & pre-clinical study | Swiss albino mice Golden Syrian hamsters | f-Comp-AmB showed better variation in vitro & in-vivo antileishmanial efficacy compare to AmB & f-CNT-AmB or f-Grap-AmB in J774A.1 | Mallikarjuna Rao Gedda. 2020 [15]. |
| CRLX101. | Pre-clinical study of CRLX101 a camptothecin containing nanoparticle drug conjugate on glioblastoma multiforme. | Female nude mice | It inhibits carbonic anhydrase IX vascular endothelial growth factor & provides antitumor ability by inducing cell cycle arrest as well as apoptosis in glioma cells. | Chein- Ju Lin. 2016 [44]. |
| Gadolinium- based nanoparticles. | Pre-clinical evaluation of Gadolinium- based nanoparticles for multiple brain melanoma metastases. | Multiple mouse brain metastases model | Study supports that this Gd- based nanoparticles as radiosensitizer improved the survival rate of mice bearing aggressive brain tumors. | Shady Kotb. 2016 [46]. |
| Genexol-PM nanoparticles formulation. | Pre-clinical study on Non-small cell lung cancer of Genexol-PM nanoparticles chemo therapeutics | nu/nu mice | Study suggested that Genexol-PM produced extraordinary tumor targeting capability & slow drug release improved the synergistic effects between paclitaxel and radiation therapy to reach to a great therapeutic efficacy. | Michael E. Werner. 2013 [55]. |
| Gold nanoparticles. | Pre-clinical study on prostate cancer radiotherapy by gold-DTDTPA nanoparticles | Male Fox Chase SCID mice | After conjugated with DTDTPA helps to maintain a stable protection against nanoparticles agglomeration & protein absorption to get a potent radiosensitization in both in vitro & in-vivo models. | Karl T Butterworth 2016 [56]. |
| Gold nanoparticles. | Treatment of heart failure by gold nanoparticles conjugated with Simdax: a pre-clinical study. | Wistar Rats | Intrapleural administration gives effectiveness compare to intravenous delivery. Also, it has the capability of cardioprotective effect & safe in cytotoxicity as well as genotoxicity. | Mykola Ya Spivak. 2013 [57]. |
| Nanoparticles Type                        | Description                                                                 | Subject Specimen                        | Results and Findings                                                                                           | Author & Year       |
|-------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------|
| Gold nanoparticles                        | In-vivo study on tumor targeting by GNSs & GNRs for single & multiple dosing. | Swiss albino nu/nu mice                 | The results suggest that both increase in GNRs & GNSs aggregation in liver for higher doses & causing of promising tumor targeting activity. | Priyaveena Puvana Krishnan 2012 [58]. |
| Lipid-polymeric hybrid nanoparticles      | A pre-clinical study for breast cancer                                        | Wistar Rats                             | BC and MTX loaded with LPNHPs with fructose conjugated revealed low cell viability against tumor cells, promising cellular localization & antitumor activity. | Varun Kushwah. 2017 [48]. |
| Liposomes                                 | Pre-clinical study of liposomes enhanced doxorubicin antitumor effect in breast cancer | BALB/c mice                             | This study demonstrated that pH-sensitive folate-coated DOX-loaded liposomes (SpHL-DOX-Fol) gradually decreased pulmonary metastasis foci by didn’t alter the QT & QTc level. | Juliana de Oliveira Silva. 2019 [47]. |
| Magnetic nanoparticles                    | Synthesis of PEG-neridronate-modified magnetic nanoparticles to evaluate prolonged blood circulation | C57BL/6NCrl mice                        | From this study it had been noticed that increased in particle size exhibited Fe3O4 clearance from the blood stream in linear time.PEG-Ner-20 particles circulated in the blood for the longest period of time. | Vitalii Patsula. 2019 [45]. |
| PLGA nanoparticles                        | Construction and optimization of crocetin filled PLGA nanoparticles against diabetic nephropathy via suppression of inflammatory biomarkers: a pre-clinical study. | Swiss albino wistar rats                | From this study it has been found that the nano-formulation of crocetin (CT-PLGA-NPs) down-regulated the production & expression of fibrotic factors like TGF-β1and fibronectin, MCP-1, TNF-α in renal. It diminished NF-kB expression & PKC activation. | Xiaodong Yang. 2019 [59]. |
| Polymeric nanoparticle                    | Exploration of injectable sirolimus formulated with polymeric nanoparticle for cancer therapy-pre-clinical study. | Athymic nude mice                       | Intravenously administration of PNP-sirolimus enhanced in-vivo anticancer efficacy in xenograft tumor mice. | Ha Na Woo. 2012 [60]. |
| Solid lipid nanoparticles                 | Pre-clinical evaluation of the oral bioavailability of Insulin-Loaded Solid Lipid Nanoparticles. | Wistar rats                             | The inclusion of L- and D-penetratin into INS-SLNs improved hypoglycemic response in rats following oral administration & LP-INS-SLNs also enhanced INS absorption. | Bader B Alsulays. 2019 [61]. |
| Nanoparticles                        | Activity                                                                 | Outcome                                                                                                                                   | References                                                               |
|-------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Calcium phosphate nanoparticles     | Calcium phosphate nanoparticles as potent adjuvant and drug delivery agent  | Calcium phosphate nanoparticle show great potential as a safe and effective vaccine adjuvant for humans, and its relative absence of side effects and lack of IgE antibody induction. | Artem Bisht et. al., 21 March 2017 [65].                                  |
| AgNPs                               | Anti-cancer activity of AgNPs                                             | The genotoxicity of AgNPs is supported by the generation of double-stranded DNA breaks along with chromosomal instability that drives the initiation of apoptotic execution. | Wafa I Abdel-Fattah et. al., 09 February 2018 [66].                      |
| Silica nanoparticles                | Clinical study for cancer therapy                                        | NP core was loaded with miR-34a, a microRNA that targets genes associated with cell proliferation and apoptosis, and the particle surface was sensitised with an antibody that specifically binds to disialoganglioside, a glycolipid that is expressed in high levels on the surfaces of neuroblastoma cells. | Vladimir Gubala et. al., 2020 [67].                                      |
| Magnetic nanoparticles              | Clinical applications of magnetic nanoparticles for hyperthermia         | Boundary effects between tissues of different dielectric constants and conductivity and skin reactions due to current density increases caused by the narrowing of the current path in skin folds. | Burghard Thiesen et. al., 09 July 2009[68].                                |
| Albumin coated Cadmium nanoparticles | Albumin coated Cadmium nanoparticles as chemotherapeutic agent against MDA-MB 231 human breast cancer cell line | CdNPs@BSA exhibited 57 times higher toxicity towards MDA-MB-231 cancer cells than normal cells, indicating more specificity of this nanocomposite to cancer cells. | Marzieh Azizi et. al., 09 February 2018 [69].                            |
| Selenium nanoparticles              | Selenium nanoparticles have potent antitumor activity against prostate cancer cells through the upregulation of miR-16 | Cyclin D1 and BCL-2, key proteins in the proliferation and apoptosis of cancer cells, might bind with miR-16 at a GCUGCU sequence site. | Guolong Liao et. al., 01 May 2020 [70].                                   |
| Cobalt oxide nanoparticles          | Surface-modified cobalt oxide nanoparticles for anti-cancer drug development | DNA fragmentation in two cell lines can be seen on the results of staining with PI, which indicates the occurrence of apoptosis. | Sourav Chattopadhyay et. al., 26 June 2013 [71].                           |
| Nanoparticles                  | Effects                                                                 | Observations                                                                 | References                  |
|-------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------|
| ZnONPs                        | ZnONPs with antiproliferative effects through apoptosis induction and MicroRNA modulation in breast cancer cells | Morphological changes were observed, including the destruction of membrane integrity, cell growth inhibition, cytoplasmic density, and cell retraction | Amir Hossein Aalami et al., 20 November 2020 [72]. |
| Titanium dioxide nanoparticles| Titanium dioxide (TiO2) nanoparticles in food and personal care products | No penetration through viable skin, however, TiO2 particles penetrated relatively deeply into the skin, possibly via empty hair follicle. | Joanna Musial et al., 04 June 2020 [64]. |
| Gold nanoparticles            | Gold nanoparticles in diagnostics and therapeutics for human cancer     | PDT is a photosensitizing agent such as porphyrin is intravenously injected into the tissues and excited by specific wavelengths, leading to the energy transfer that generates reactive (ROS) and causes cell death by apoptosis | Priyanka Singh et al., 06 July 2018 [62]. |
| Gold nanoparticles            | Gold nanoparticles in tumor diagnosis and treatment                     | AuNPs have been demonstrated to selectively accumulate in the mitochondria of tumor cells, decrease mitochondrial electrical potential, increase reactive oxygen species and eventually lead to apoptosis of tumor cells, while normal cells and stem cells have not shown the same effect. | Xue Bai et al., 03 April 2020 [20]. |
| AgNPs                         | AgNPs potentiate cytotoxicity and apoptotic potential of camptothecin in human cervical cancer cells | The combination of CPT and AgNPs significantly inhibits cell proliferation and increases cytotoxicity and apoptosis by increasing FOS generation and leakage potential and activation of caspase 9, 6, and 3. | Yu-Guo Yuan et al., 12 Dec 2018 [73]. |
| Iron oxide nanoparticles      | Cancer therapy with iron oxide nanoparticles                            | Iron oxide nanoparticles clearly indicate that nanoparticle-immune interactions are complex, depend on host disposition as well as nanoparticles, and that they are likely unavoidable. | Frederik Soetaert et al., 27 June 2020 [74]. |
| AgNPs                         | Clinical trials on AgNPs for wound healing                             | Existence of Ag+ ions inside the cell can disturb the function of the bacteria. Ag+ ions also bind to DNA and RNA of the bacteria and inhibit cell division. | Zakieh Boroumand et al., 2018 [63]. |
Study by Joanna et. al., suggested the inclusion of TiO₂NPs into sunscreen products. In another study, coating of TiO₂NPs with dihydroxyphenyl benzimidazole carboxylic acid (Oxisol) not only led to photolytic activity reduction, but also boosted its antioxidant effects and stabilization of the formulation. By modifying the surface of TiO₂ NPs, it is also possible to improve the appearance of a sunscreen formulation, as formulations containing TiO₂ NPs modified with a complexing compound, para-toluene sulfonic acid, were found to be more transparent [64]. The study also investigated the toxicity of TiO₂NPs additives in food and cosmetic products.

These clinical studies on humans based on the pre-clinical analysis, adds credit to the field of nanomedicine research and their application in human healthcare in the immediate future.

5. LIMITATIONS OF NANOPARTICLES

Despite its varied application and benefits, nanomedicine can’t be termed as flawless. A cogent reason for this assessment is that because, when the transition from micro particle to nano particles begins, the dimensions range decreases to an outsized extent and thus the quantity of surface atoms increases [75–77] because the planet of particle surface become larger , the parameters such as interparticular friction and sticking becomes significant. NPs have several advantages such as, being small in size they have high clearance rate to preclude their use in diagnosis or drug delivery. In hepatic targeting with NPs, their entrapment by the mononuclear phagocytic system is employed to advantages. Although some drawbacks are concerns, such as, an equivalent property can become a drag for nano-structures meant for drug action elsewhere within the body. The phagocytic system of mononuclear cells recognizes and results in subsequent phagocytosis of that particles, leading to removal of that particles from the body [23,78–81].

5.1 PEGylation of NPs

Possible solutions to some of these drawbacks of NPs include PEGylation. PEGylation of NPs, elongates the NPs existence within the body. Assuming that polyethylene glycol (PEG) - conjugated or PEGylated nanocarriers, always offer outstanding physicochemical and pharmacokinetics profiles as compared to non-PEGylated. Drug-loaded PEGylated nanocarriers for cancer treatment have several benefits such as, detouring RES sequestration and clearance, gain from the tumour leaky vasculature’s enhanced permeability and retention (EPR), and preferentially accumulate within the target tissue or cells. Several disadvantages of PEGylation are being addressed during this study, like how PEGylation may end in unfavourable physicochemical characteristics (e.g. particle size and release patterns) and post-in-vivo administration limitations of the formulated nanocarriers (e.g. restricted RES absorption evasion, production of hypersensitivity reactions, reduced intracellular aggregation and interfencing) [82–86].

These studies provide understanding on the benefits and drawbacks of PEGylation; encourages cautious use of PEGylation; suggests to avoid misunderstanding that PEGylation will provide all of the benefits required to deliver nanocarriers to the target tissue; appearance for alternatives to maximise nanocarrier use within the delivery of chemotherapeutic agents for the treatment of cancer. [87–91]

5.2 Non Specific Drug Targets

Unlike the traditional drug molecules that are currently in clinical use, NPs do not have a specific individual target. Although the NPs are proven to work selectively for different type of cells (i.e., different bioactivity for prokaryotes & eukaryotes, etc.,) NPs do not have a specific drug target, that provides a great advantage and disadvantage to the clinical applications.

Each type of NPs must be evaluated individually and their bioactivity changes greatly even by slightest changes in the NPs. Changes in shape and size causes difference in physical and chemical interactions, for example, a material that is non-toxic at 100nm can become toxic at 1nm, and vice versa. Another disadvantage is that the NPs reliance on the encircling environment. These particles can disintegrate or accumulate, causing size changes and toxicity, based on the environmental parameters. Parameters specific to the NPs, such as chemical composition, surface area, surface structure, surface charge, solubility, and functional groups on the NPs are all factors that greatly regulate the bioactivity and toxicity of NPs. [77,92–97].
The increased surface area of the NPs leads to an augmented chemical reactivity of those particles resulting in a pressing uncertainty on how these particles will react under different conditions. The increased chemical reactivity of NPs brings about the assembly of reactive oxygen species (ROS), which can cause oxidative stress, inflammation, and damage to DNA, proteins and membranes, ultimately resulting in toxicity. A major drawback of nanomedicine is that NPs does not have any similarity with each other, except the nanoscale size and elemental composition. Quite contrasting to the traditional organic drugs, that usually encase a chemical structural skeleton that lays the base of the bioactivity. Hence, each different NPs should be assessed individually for their bioreactivity.

5.3 Toxicity of NPs

Some of the non-specific and undesirable interactions observed from NPs application in an in-vivo system could include; entering capillaries and translocation from site of injection to other body parts; crossing the blood brain barrier; entering vital cell organelles such as nucleus or mitochondria and trigger damage; initiating blood clotting pathway. These are some of the unforeseen effects observed by administration of NPs in an in-vivo system. Though NPs were designed to decrease the systemic adverse effects of the drug, the carrier NPs systems themselves may cause some of these unfavourable side effects. [82,98–101].

According to studies, NPs can accumulate within the organs of varied animals. While biodegradable NPs are usually excreted from animal body, the non-biodegradable ones may accumulate in organs and potentially cause harm. The particles that don't degrade or degrade slowly may build up/accumulate in vital organs and cause chronic inflammation. NPs produce ROS and oxidative stress, which can cause neurodegenerative diseases like Alzheimer's and Parkinson's diseases.

Nanomedicine features a promising future especially for diseases like cancer. Scientists hope that nanomedicine will improve the efficacy of drug delivery to the target tissue also as regulate the discharge of drug at the precise site, thereby leading to a rise within the therapeutic index. However, one major hurdle is that the tendency of NPs to cause damage to the lungs. NPs are also suspected to cause pulmonary inflammation. [6,102–105] Although it is unclear as to how the NPs cause lung injury, but a recent study published within the Journal of Molecular Cell Biology showed that Polyamine dendrimers (PAMAM’s) trigger a programmed necrobiosis called as autophagic necrobiosis thereby causing lung damage. Autophagy could even be a typical cell scavenging process. It disintegrates damaged cells and regulates normal cell growth. Over-activity of this process results in death of lung cells, resulting in organ damage. It is not confirmed whether other group of NPs (apart from PAMAM’s) work by an equivalent mechanism but some NPs may do so and blocking autophagic cell death and prevent lung damage in most cases.

Pulmonary inflammation also can cause changes in membrane permeability which may cause the NPs to distribute beyond the lungs. The pulmonary inflammation and thus the particle distribution (beyond the lungs) - both have the potential of enhancing the danger of disorder. NPs are stronger than larger particles. The charge of the NPs is critical in determining their cardiovascular toxicity. The anionic NPs are quite non-toxic, whereas the cationic NPs are found to initiate hemolysis and blood coagulation. Some studies have revealed that fullerenes may cause brain damage by causing lipid peroxidation. In-vitro study on the recently developed nanotubes has showed that they're capable of inducing ROS production, oxidative stress, lipid peroxidation, mitochondrial dysfunction and induce platelet aggregation. Their intratracheal instillation at high doses may end in Chronic lung inflammation and lung toxicity. Also, these carbon nanotubes may block the oxygen receiving capacity of the lungs by clumping the airways.

5.4 Expensive

Apart from the normal health effects, poverty and injustice are the thought problems of nanomedicine implementation. As a result, if modern innovative innovations aren't affordable, they're useless to the poor.

Another limitation of using nanotechnology in medicine is its high cost. Utilization of nanomedicine would increase the price of health care, which could make its access difficult to the poor. [106–109]

5.5 Ethical & Misuse

Since nanomedicine is out there at the nanoscale, it is often used maliciously. Often, medicine's
original intent could even be misappropriated for other reasons, posing a harmful threat to humans. [88,110–115] The moral, social and legal facets of nanomedicine got to be handled tactfully to know civic backing. Though are being made to extend the understanding of using nanomedicine in living beings, there’s still ambiguity surrounding the risks that humans would be exposed to with its use. As a result, the clinical trials involving nanomedicine pose distinctive challenges. The leading ethical issues encompass assessing, managing and communicating the danger during clinical trials. To evade the likelihood of public criticism, it becomes imperative to means the people about the benefits and perils of nanomedicine [106–109].

Other than these evident risks to the patient, NPs could be toxic to the environment also, and thus require prior processing before disposal. The non-biodegradable NPs are likely to cause land and/or water pollution. It is difficult to predict their effects on the environment and, it's unknown whether or not they're harmful to the biome. If they enter the bionetwork through the plants, their eradication would be highly demanding.

6. CONCLUSION

In this review, mechanism of actions, preclinical study, clinical study and disadvantages of some significant nanoparticles (copper, silver, gold, zinc oxide, iron, cobalt, silica, selenium etc.,) which are synthesized either biologically or physiochemically that reported in the recent years have been discussed and summarised. Mechanism of action of NPs for their antibacterial activity is mainly focused. Preclinical studies on NPs strongly suggest its positive impact in the pharmaceutical industries. However, clinical trials on the possible toxicity via dermal exposure are not sufficient enough, and thus more clinical studies are recommended on the potential toxicity via dermal exposure of NPs. Moreover, NPs fate in environment and human body are equally important and substantial aspect to acknowledge before exploiting it in the clinical trials applications. Hence, in this respect, a great deal of research will be required to focus on internalization of the NPs. Some of the aspects needs to be focused include their subsequent localization, relevant immunological response, and most importantly, their excretion from the human body. Based on the literature review in this article, it could be concluded that, NPs are promising agents that could change the pharmaceutical approach in treating diseases, however further investigations and understandings are in demand to overcome the barriers and hurdles that are discussed in this review.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

The authors thank NSHM Knowledge Campus, Kolkata- Group of Institutions and St. Joseph’s College (Autonomous) Bengaluru, for supporting this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Yin L, Zhong Z. Nanoparticles. Biomater Sci 2020:453–83.
2. Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles in medicine: Therapeutic applications and developments. Clin Pharmacol Ther 2008;83:761–9.
3. Salata O V. Journal of Nanobiotechnology. J Nanobiotechnology 2004;6:1–6.
4. Ijaz I, Gilani E, Nazir A, Bukhari A. Detail review on chemical, physical and green synthesis, classification, characterizations and applications of nanoparticles. Green Chem Lett Rev 2020;13:59–81.
5. Nisar P, Ali N, Rahman L, Ali M, Shinwari ZK. Antimicrobial activities of biologically synthesized metal nanoparticles: an insight into the mechanism of action. J Biol Inorg Chem 2019;24:929–41.
6. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The history of nanoscience and nanotechnology: From chemical-physical applications to nanomedicine. Molecules 2020;25:1–15.
7. Ingle AP, Duran N, Rai M. Bioactivity, mechanism of action, and cytotoxicity of copper-based nanoparticles: A review. Appl Microbiol Biotechnol 2014;98:1001–9.
8. Amer MW, Awad AM. Green synthesis of copper nanoparticles by Citrus limon fruits extract, characterization and antibacterial activity. Chem Int 2021;7:1–8.

9. Noor S, Shah Z, Javed A, Ali A, Hussain SB, Zafar S, et al. A fungal based synthesis method for copper nanoparticles with the determination of anticancer, antidiabetic and antibacterial activities. J Microbiol Methods 2020;174:105966.

10. Mikhailova EO. Silver Nanoparticles: Mechanism of Action and Probable Bio-Application. J Funct Biomater 2020;11:84.

11. Pietrzak K, Glińska S, Gapińska M, Ruman AK, Vermulst A, Mahmoudi E, et al. The potential of silver nanoparticles as permeation enhancers and targeted delivery options for skin: Advantages and disadvantages. Int J Nanomedicine 2020;15:9125–57.

12. Sirelkhatim A, Mahmud S, Seeni A, Kaus SB, Zafar S, et al. A fungal based nanomedicine for advanced cancer theranostics: Perspectives on clinical trials to clinical use. Int J Nanomedicine 2020;15:9125–57.

13. Resnik DB, Tinkle SS. Ethics in nanomedicine. Nanomedicine 2007;2:345–50.

14. Mirza Z, Karim S. Nanoparticles-based drug delivery and gene therapy for breast cancer: Recent advancements and future challenges. vol. 69. Elsevier Ltd; 2021.

15. Gedda MR, Madhukar P, Vishwakarma AK, Verma V, Kushwaha AK, Yadagiri G, et al. Evaluation of Safety and Antileishmanial Efficacy of Amine Functionalized Carbon-Based Composite Nanoparticle Appended With Amphotericin B: An in vitro and Preclinical Study. Front Chem 2020;8.

16. Bastami TR, Ghaedi A, Mitchell SG, Javadian-Saraf A, Karimi M. Sonochemo synthesis of polyoxometalate-stabilized gold nanoparticles for point-of-care determination of acetaminophen levels: preclinical study in an animal model. RSC Adv 2020;10:16805–16.

17. Anselmo AC, Mitragotri S. Nanoparticles in the clinic. Bioeng Transl Med 2016;1:10–29.

18. Resnik DB, Tinkle SS. Ethics in nanomedicine. Nanomedicine 2007;2:345–50.

19. Mukherjee S, Liang L, Veiseh O. Recent advancements of magnetic nanomaterials in cancer therapy. Pharmaceuticals 2020;12.

20. Bai X, Wang Y, Song Z, Feng Y, Chen Y, Zhang D, et al. The basic properties of gold nanoparticles and their applications in tumor diagnosis and treatment. Int J Mol Sci 2020;21.

21. Ziental D, Czarzynska-Gosliniska B, Mlynarczyk DT, Glowacka-Sobotta A, Stanisz B, Gosliniski T, et al. Titanium dioxide nanoparticles: Prospects and applications in medicine. Nanomaterials 2020;10.

22. Dhupal M, Chowdhury D. Phytochemical-based nanomedicine for advanced cancer theranostics: Perspectives on clinical trials to clinical use. Int J Nanomedicine 2020;15:9125–57.

23. A Mini Review of Antibacterial Properties of ZnO Nanoparticles. Front Phys 2021;9.

24. Prabhu S, Poulose EK. Silver nanoparticles: mechanism of antimicrobial action, synthesis, medical applications, and toxicity effects. Int Nano Lett 2012;8:526–37.

25. Danilczuk M, Lund A, Sadlo J, Yamada H, Michalik J. Conduction electron spin resonance of small silver particles. Spectrochim Acta - Part A Mol Biomol Spectrosc 2006;63:189–91.

26. Kim JS, Kuk E, Yu KN, Kim JH, Park SJ, Lee HJ, et al. Antimicrobial effects of silver nanoparticles. Nanomedicine Nanotechnology, Biol Med 2007;3:95–101.

27. Salleh A, Naemi R, Utami ND, Mohammad AW, Mahmoudi E, Mustafa N, et al. The potential of silver nanoparticles for antiviral and antibacterial applications: A mechanism of action. Nanomaterials 2020;10:1–20.

28. Peng S, Chen Y, Jin X, Lu W, Gou M, Wei X, et al. Polyimide with half encapsulated silver nanoparticles grafted ceramic composite membrane: Enhanced silver stability and lasting anti-biofouling performance. J Membr Sci 2020;611:118340.
31. Dakal TC, Kumar A, Majumdar RS, Yadav V. Mechanistic basis of antimicrobial actions of silver nanoparticles. Front Microbiol 2016;7:1–17.

32. Vázquez-Muñoz R, Meza-Villéczas A, Fournier PJG, Soria-Castro E, Juarez-Moreno K, Gallego-Hernández AL, et al. Enhancement of antibiotics antimicrobial activity due to the silver nanoparticles impact on the cell membrane. PLoS One 2019;14:1–18.

33. Rautela A, Rani J, Debnath (Das) M. Green synthesis of silver nanoparticles from Tectona grandis seed extract: characterization and mechanism of antimicrobial action on different microorganisms. J Anal Sci Technol 2019;10.

34. Siddiqi KS, ur Rahman A, Tajuddin, Husen A. Properties of Zinc Oxide Nanoparticles and Their Activity Against Microbes. Nanoscale Res Lett 2018;13.

35. Kahru A, Ivask A, Kasemets K, Pöllumaa L, Kurvet I, François M, et al. Biotests and biosensors in ecotoxicological risk assessment of field soils polluted with zinc, lead, and cadmium. Environ Toxicol Chem 2005;24:2973–82.

36. Heinlaan M, Ivask A, Binova I, Dubourguier HC, Kahru A. Toxicity of nanosized and bulk ZnO, CuO and TiO2 to bacteria Vibrio fischeri and crustaceans Daphnia magna and Thamnocephalus platyurus. Chemosphere 2008;71:1308–16.

37. Brayner R, Ferrari-liiou R, Brivois N, Djediat S, Benedetti MF, Fiéret F. Toxicological impact studies based on Escherichia coli bacteria in ultrafine ZnO nanoparticles colloidal medium. Nano Lett 2006;6:866–70.

38. Stojmenov PK, Klinger RL, Marchin GL, Klabunde KJ. Metal oxide nanoparticles as bactericidal agents. Langmuir 2002;18:6679–86.

39. Banerjee S, Vishakha K, Das S, Dutta M, Mukherjee D, Mondal J, et al. Anti-bacterial activity and mechanism of action of pancreatin doped zinc oxide nanoparticles against methicillin resistant Staphylococcus aureus. Colloids Surfaces B Biointerfaces 2020;190:110921.

40. Yamamoto O, Komatsu M, Sawai J, Nakagawa ZE. Effect of lattice constant of zinc oxide on antibacterial characteristics. J Mater Sci Mater Med 2004;15:847–51.

41. Ramyadevi J, Jeyasubramanian K, Marikani A, Rajakumar G, Rahuman AA. Synthesis and antimicrobial activity of copper nanoparticles. Mater Lett 2012;71:114–6.

42. Ahamed M, Alhadiqa HA, Khan MAM, Karupppiah P, Al-Dhabi NA. Synthesis, characterization, and antimicrobial activity of copper oxide nanoparticles. J Nanomater 2014;2014.

43. S. Harikumar P. Antibacterial Activity of Copper Nanoparticles and Copper Nanocomposites against Escherichia Coli Bacteria. Int J Sci 2016;2:83–90.

44. Lin C-J, Lin Y-L, Luh F, Yen Y, Chen R-M. Preclinical effects of CRLX101, an investigational camptothecin-containing nanoparticle drug conjugate, on treating glioblastoma multiforme via apoptosis and antiangiogenesis. vol. 7. n.d.

45. Patsula V, Horák D, Kučka J, Macková H, Lobaz V, Francová P, et al. Synthesis and modification of uniform PEG-neridronate-modified magnetic nanoparticles determines prolonged blood circulation and biodistribution in a mouse preclinical model. Sci Rep 2019;9.

46. Kotb S, Detappe A, Lux F, Appaix F, Barbier EL, Tran VL, et al. Gadolinium-based nanoparticles and radiation therapy for multiple brain melanoma metastases: Proof of concept before phase I trial. Theranostics 2016;6:418–27.

47. de Oliveira Silva J, Fernandes RS, Ramos Oda CM, Ferreira TH, Machado Botelho AF, Martins Melo M, et al. Folate-coated, long-circulating and pH-sensitive liposomes enhance doxorubicin antitumor effect in a breast cancer animal model. Biomed Pharmacother 2019;118.

48. Jain A, Sharma G, Kushwah V, Garg NK, Kesharwani P, Ghoshal G, et al. Methotrexate and beta-carotene loaded-lipid polymer hybrid nanoparticles: A preclinical study for breast cancer. Nanomedicine 2017;12:1851–72.

49. Li CW, Fu RQ, Yu CP, Li ZH, Guan HY, Hu DQ, et al. Silver nanoparticle/chitosan oligosaccharide/poly(vinyl alcohol) nanofibers as wound dressings: A preclinical study. Int J Nanomedicine 2013;8:4131–45.

50. Rodríguez-fragoso L. Disposition and Biocompatibility of Dextrin-coated Cadmium Sulphide Nanoparticles after a Single Dose and Multiple Doses in Rats. n.d.
51. Aman RM, Zaghoul RA, El-Dahhan MS. Formulation, optimization and characterization of allantoin-loaded chitosan nanoparticles to alleviate ethanol-induced gastric ulcer: in-vitro and in-vivo studies. Sci Rep 2021;11.

52. Zhu P, Huang G, Zhang B, Zhang W, Dang M, Huang Z. Assessment of fracture healing properties of lovastatin loaded nanoparticles: Preclinical study in rat model. Acta Biochim Pol 2019;66:71–6.

53. Thakkar A, Chenreddy S, Thio A, Khamas W, Wang J, Prabhu S. Preclinical systemic toxicity evaluation of chitosan-solid lipid nanoparticle-encapsulated aspirin and curcumin in combination with free sulforaphane in BALB/c mice. Int J Nanomedicine 2016;11:3265–76.

54. Matias LLR, Costa ROA, Passos TS, Queiroz JLC, Serquiz AC, Maciel BLL, et al. Tamarind trypsin inhibitor in chitosan-whey protein nanoparticles reduces fasting blood glucose levels without compromising insulinemia: A preclinical study. Nutrients 2019;11.

55. Werner ME, Cummings ND, Sethi M, Wang EC, Sukumar R, Moore DT, et al. Preclinical evaluation of genexol-pm, a nanoparticle formulation of paclitaxel, as a novel radiosensitizer for the treatment of non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2013;86:463–8.

56. Butterworth KT, Nicol JR, Ghita M, Rosa S, Chaudhary P, McGarry CK, et al. Preclinical evaluation of gold-DTDTPA nanoparticles as theranostic agents in prostate cancer radiotherapy. Nanomedicine 2016;11:2035–47.

57. Spivak MY, Bubnov R V., Yemets IM, Lazarenko LM, Tymoshok NO, Ulberg ZR. Development and testing of gold nanoparticles for drug delivery and treatment of heart failure: A theranostic potential for PPP cardiology. EPMA J 2013;4.

58. Puvanakrishnan P, Park J, Chatterjee D, Krishnan S, Tunnell JW. In vivo tumor targeting of gold nanoparticles: Effect of particle type and dosing strategy. Int J Nanomedicine 2012;7:1251–8.

59. Yang X. Design and optimization of crocetin loaded PLGA nanoparticles against diabetic nephropathy via suppression of inflammatory biomarkers: a formulation approach to preclinical study. Drug Deliv 2019;26:849–59.

60. Woo HN, Chung HK, Ju EJ, Jung J, Kang HW, Lee SW, et al. Preclinical evaluation of injectable sirolimus formulated with polymeric nanoparticle for cancer therapy. Int J Nanomedicine 2012;7:2197–208.

61. Alsulays BB, Anwer MK, Soliman GA, Alshehri SM, Khafagy ES. Impact of penetratin stereochemistry on the oral bioavailability of insulin-loaded solid lipid nanoparticles. Int J Nanomedicine 2019;14:9127–38.

62. Singh P, Pandit S, Mokkapati VRSS, Garg A, Ravikumar V, Mijakovic I. Gold nanoparticles in diagnostics and therapeutics for human cancer. Int J Mol Sci 2018;19.

63. Boroumand Z, Golmakani N, Boroumand S. Clinical Trials on Silver nanoparticles for wound healing (review). Nanomed J 2018;5:186–91.

64. Musial J, Krakowiak R, Mlynarczyk DT, Goslinski T, Stanisz BJ. Titanium dioxide nanoparticles in food and personal care products—what do we know about their safety? Nanomaterials 2020;10:1–23.

65. Ramnarain R. A Retrospective Analysis of Ibrutinib-Associated Pneumonia. Curr Trends Biomed Eng Biosci 2016;1:2016–8.

66. Abdel-Fattah WI, W Ali G. On the anticancer activities of silver nanoparticles. J Appl Biotechnol Bioeng 2018;5:43–6.

67. Kubala V, Giovannini G, Kunc F, Monopoli MP, Moore CJ. Dye-doped silica nanoparticles: Synthesis, surface chemistry and bioapplications. vol. 11. Springer Vienna; 2020.

68. Thiesen B, Jordan A. Clinical applications of magnetic nanoparticles for hyperthermia. Int J Hyperth 2008;24:467–74.

69. Azizi M, Ghourchian H, Yazdian F, Alizadehzeinabad H. Albumin coated cadmium nanoparticles as chemotherapeutic agent against MDA-MB 231 human breast cancer cell line. Artif Cells, Nanomedicine Biotechnol 2018;46:787–97.

70. Liao G, Tang J, Wang D, Zuo H, Zhang Q, Liu Y, et al. Selenium nanoparticles (SeNPs) have potent antitumor activity against prostate cancer cells through the upregulation of miR-16. World J Surg Oncol 2020;18:1–11.

71. Chattopadhyay S, Dash SK, Ghosh T, Das D, Pramanik P, Roy S. Surface modification of cobalt oxide nanoparticles using phosphonomethyl iminodiacetic acid
followed by folic acid: A biocompatible vehicle for targeted anticancer drug delivery. Cancer Nanotechnol 2013;4:103–16.

72. Aalami AH, Mesgari M, Sahebkar A. Synthesis and Characterization of Green Zinc Oxide Nanoparticles with Antiproliferative Effects through Apoptosis Induction and MicroRNA Modulation in Breast Cancer Cells. Bioinorg Chem Appl 2020;2020.

73. Yuan YG, Zhang S, Hwang JY, Kong IK. Silver nanoparticles potentiates cytotoxicity and apoptotic potential of camptothecin in human cervical cancer cells. Oxid Med Cell Longev 2018;2018.

74. Soetaert F, Korangath P, Serantes D, Fiering S, Ivkov R. Cancer therapy with iron oxide nanoparticles: Agents of thermal and immune therapies. Adv Drug Deliv Rev 2020;163–164:65–83.

75. Hua S, Wu SY. Editorial: Advances and challenges in nanomedicine. Front Pharmacol 2018;9:1–3.

76. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: Progress, challenges and opportunities. Nat Rev Cancer 2017;17:20–37.

77. Flynn T, Wei C. The pathway to commercialization for nanomedicine. Nanomedicine Nanotechnology, Biol Med 2005;1:47–51.

78. Wicki A, Witzigmann D, Balasubramanian V, Huwyler J. Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications. J Control Release 2015;200:138–57.

79. Roco MC, Mirkin CA, Hersam MC. Nanotechnology research directions for societal needs in 2020: Summary of international study. J Nanoparticle Res 2011;13:897–919.

80. Sandhiya S, Dkhar SA, Surendiran A. Emerging trends of nanomedicine - an overview. Fundam Clin Pharmacol 2009;23:263–9.

81. Su S, Kang PM. Systemic review of biodegradable nanomaterials in nanomedicine. Nanomaterials 2020;10.

82. Kargozar S, Mozafari M. Nanotechnology and Nanomedicine: Start small, think big. Mater Today Proc 2018;5:15492–500.

83. Juliana FR, Kesse S, Boakye-Yiadom KO, Veroniaina H, Wang H, Sun M. Promising approach in the treatment of glaucoma using nanotechnology and nanomedicine-based systems. Molecules 2019;24.

84. Graur F, Pitu F, Neagoe I, Katona G, Diudea M. Applications of nanotechnology in medicine. Acad J Manuf Eng 2010;8:36–42.

85. Ahmad Wani K, Kothari R. Nano Technology in Medicine and Future Implications: A Mini Review. J Nanomed Nanotechnol 2018;09:9–11.

86. Augustine R, Mathew AP, Sosnik A. Metal Oxide Nanoparticles as Versatile Therapeutic Agents Modulating Cell Signaling Pathways: Linking Nanotechnology with Molecular Medicine. Appl Mater Today 2017;7:91–103. 2

87. Metselaar JM, Lammers T. Challenges in nanomedicine clinical translation. Drug Deliv Transl Res 2020;10:721–5.

88. Wright PF. Potential risks and benefits of nanotechnology: perceptions of risk in sunscreens. Med J Aust 2016;204:369–70.

89. Mignani S, Shi X, Rodrigues J, Roy R, Muñoz-Fernández Á, Ceña V, et al. Dendrimers toward Translational Nanotherapeutics: Concise Key Step Analysis. Bioconjug Chem 2020;31:2060–71.

90. Contera S, Bernardino de la Serna J, Tetley TD. Biotechnology, nanotechnology and medicine. Emerg Top Life Sci 2020;4:551–4.

91. Agrahari V, Hiremath P. Challenges associated and approaches for successful translation of nanomedicines into commercial products. Nanomedicine 2017;12:819–23.

92. Hare JI, Lammers T, Ashford MB, Puri S, Storm G, Barry ST. Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. Adv Drug Deliv Rev 2017;108:25–38.

93. Barry NPE, Sadler PJ. Challenges for metals in medicine: How nanotechnology may help to shape the future. ACS Nano 2013;7:5654–9.

94. Liu Y, Yang G, Zou D, Hui Y, Nigam K, Middelberg APJ, et al. Formulation of Nanoparticles: Using Mixing-Induced Nanoprecipitation for Drug Delivery. Ind Eng Chem Res 2020;59:4134–49.

95. Martins JP, das Neves J, de la Fuente M, Celia C, Florindo H, Günday-Türel N, et al. The solid progress of nanomedicine. Drug Deliv Transl Res 2020;10:726–9.

96. Bawa R. Patents and nanomedicine. Nanomedicine 2007;2:351–74.

97. Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J.
big picture on nanomedicine: the state of investigational and approved nanomedicine products. Nanomedicine Nanotechnology, Biol Med 2013;9:1–14.

98. Limaye V, Fortwengel G, Limaye D. Regulatory roadmap for nanotechnology based medicines 2014;2014:33–41.

99. Gwinn MR, Vallyathan V. Nanoparticles: Health effects - Pros and cons. Environ Health Perspect 2006;114:1818–25.

100. DS A, MJ S. Nanotechnology: The Risks and Benefits for Medical Diagnosis and Treatment. J Nanomed Nanotechnol 2016;7:1–2.

101. Bohr A, Colombo S, Jensen H. Chapter 15 - Future of microfluidics in research and in the market. In: Santos HA, Liu D, Zhang H, editors. Microfluid. Pharm. Appl., William Andrew Publishing; 2019, p. 425–65.

102. Wu L-P, Wang D, Li Z. Grand challenges in nanomedicine. Mater Sci Eng C Mater Biol Appl 2020;106:110302.

103. Patil M, Mehta DS, Guvva S. Future impact of nanotechnology on medicine and dentistry. J Indian Soc Periodontol 2008;12:34–40.

104. Maynard RL. Nano-technology and nanotoxicology. Emerg Health Threats J 2012;5.

105. Parvanian S, Mostafavi SM, Aghashiri M. Multifunctional nanoparticle developments in cancer diagnosis and treatment. Sens Bio-Sensing Res 2017;13:81–7.

106. Welpe I, Fiedler M. Antecedents of cooperative commercialisation strategies of nanotechnology firms. Res Policy 2010;39:400–10.

107. Morrow KJ, Bawa R, Wei C. Recent Advances in Basic and Clinical Nanomedicine. Med Clin North Am 2007;91:805–43.

108. Venkatraman S. Has nanomedicine lived up to its promise? Nanotechnology 2014;25:3–7.

109. Gioria S, Caputo F, Urbán P, Maguire CM, Bremer-Hoffmann S, Prina-Mello A, et al. Are existing standard methods suitable for the evaluation of nanomedicines: some case studies. Nanomedicine (Lond) 2018;13:539–54.

110. Shreen N, Malik U, Sunil MK, Johar N, Mehfooz A. Unbridge Treasure of Nanotechnology in Dentistry-A Review. Int J Drug Res Dent Sci 2020;2:48–54.

111. Loscalzo DEHRCJ. NIH Public Access. Bone 2011;23:1–7.

112. Sharma D. a Review on Current Advances in Nanotechnology Approaches for the Effective Delivery of Anti-Cancer Drugs. J Drug Deliv Ther 2014;0:1–4.

113. Kumar R, Griffin M, Butler PE. A Review of Current Regenerative Medicine Strategies that Utilize Nanotechnology to Treat Cartilage Damage. Open Orthop J 2017;10:862–76.

114. Mostafavi E, Soltantabar P, Webster TJ. Nanotechnology and picotechnology: A new arena for translational medicine. Biomater Transl Med A Biomater Approach 2018;191–212.

115. Omlor JA, Nguyen J, Bals R, Dinh QT. Nanotechnology in respiratory medicine. Respir Res 2015;16:1–9.

© 2021 Nath et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here: https://www.sdiarticle4.com/review-history/71299