



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

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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

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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 anti-bacterial agents widely. The Egyptians used copper salt as a constrictant 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 dining utensils, such as spoon, cup, plate, etc., in royal/rich families also aiding to its well known anti-bacterial 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, gadolinium 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 strengthened able via *in-vivo* animal experiments and *ex-vivo* laboratory studies, the entire uncertainties of a human being's exposure to the nanomaterials 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 anti-bacterial 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, $ZnSo_4.7H_2O$, $ZnSo_4.7H_2So_4$ 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.

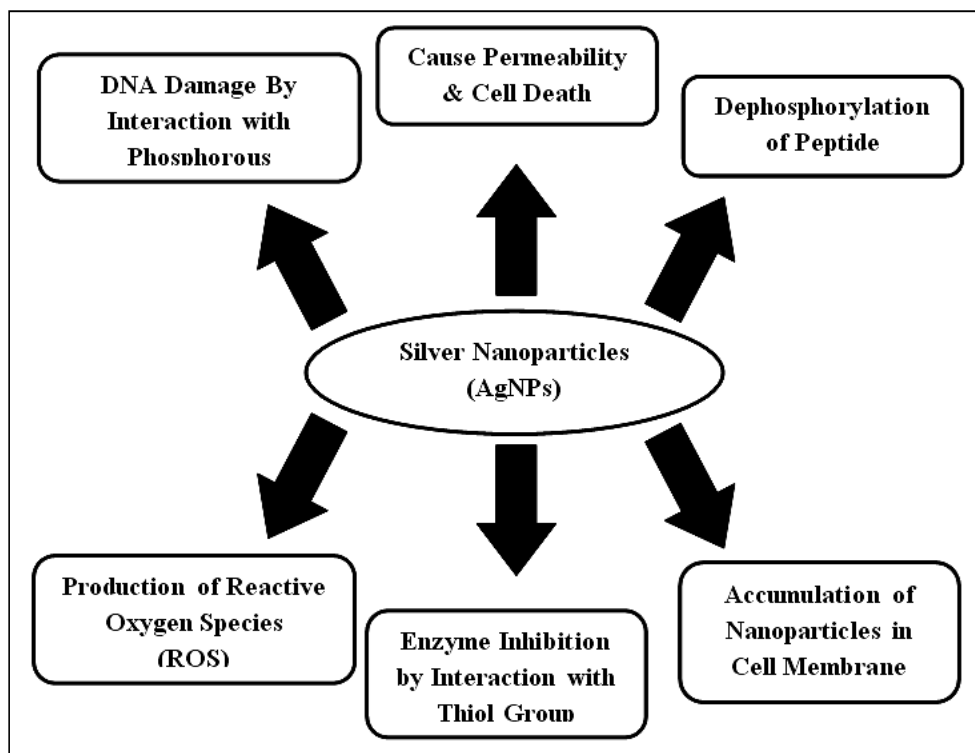


Fig. 1. Possible reported anti-bacterial mechanism of actions of AgNPs [26-31]

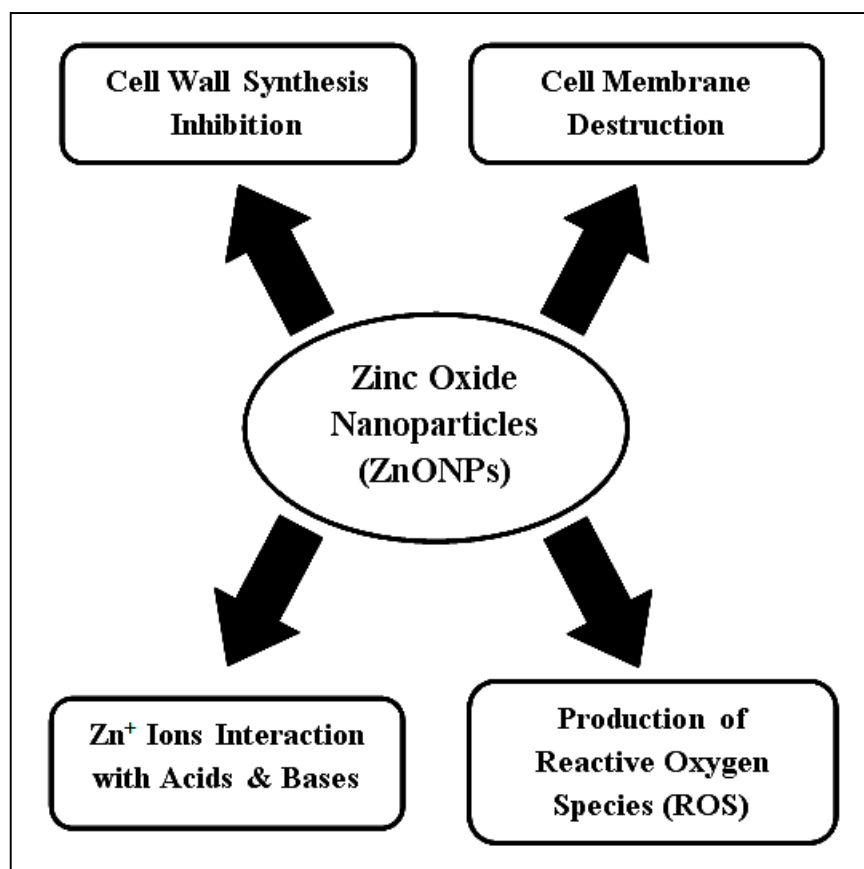


Fig. 2. Possible reported anti-bacterial mechanism of actions of ZnONPs [34-38]

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 pneumoniae*, *Enterococcus faecalis*, *Shigella flexneri*, *Salmonella typhimurium*, *Proteus vulgaris*, and *Staphylococcus aureus* and streptomycin was used as positive control. Among the panel of pathgoens, *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.

[43] A graphical representation of probable mechanism of action of CuNPs antibacterial activity are shown in Fig. 3.

2.4 Titanium Peroxide Nanoparticles (TiO₂NPs)

Author, Joanna *et. al.*, organized an investigation on titanium dioxide in a plethora of studies that associate cytotoxicity and genotoxicity with their photocatalytic activity. TiO₂ 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 TiO₂ NPs additives in food and cosmetic products. The authors also found that TiO₂ toxicity in sunscreens has turned to the surface and the entourage of TiO₂ nanoparticles. For example, Y₂O₃-decorated TiO₂ nanoparticles were found to display enhanced UV attenuation and reduced photoactivity and consequently, cytotoxicity, compared with a commercial TiO₂ 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.

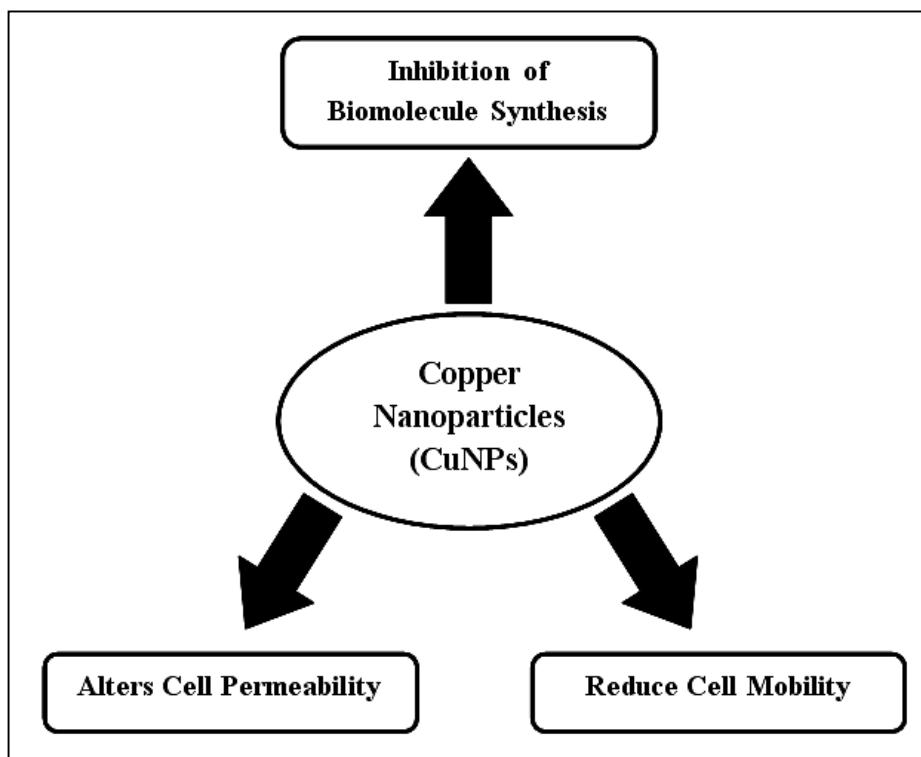


Fig. 3. Possible reported anti-bacterial mechanism of actions of CuNPs [41-43]

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 NANOPARTICLES

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 polyethyleneglycol (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 threats 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 & <i>in-vivo</i> wound healing	Sprague Dawley Rats	PVA/ COS- Ag NP nanofibre mats were biocompatible, nontoxic and giving admirable anti-microbial activity against gm+ve S. aureus and gm-ve E. coli. Also, it is having effective capacity for wound healing compared to PVA/COS/ AgNO ₃ 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.	<i>In-vivo</i> 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 hisopathology 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 sulfuraphane (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 <i>in-vivo</i> efficacy models.	Arvind Thakkar. 2016 [53].

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 & anti-leishmanial 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 & <i>in-vivo</i> 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	<i>nu/nu</i> 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 & <i>in-vivo</i> models.	Karl T Butterworth 2016 [56].
Gold nanoparticles.	Treatment of heart failure by gold nanoparticles conjugated with Simdax: a pre-clinical study.	Wistar Rats	Intraleural 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].

Gold nanoparticles.	<i>In-vivo</i> study on tumor targeting by GNSs & GNRs for single & multiple dosing.	Swiss albino <i>nu/nu</i> 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 Fe ₃ O ₄ 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- β 1 and fibronectin, MCP-1, TNF- α in renal. It diminished NF- κ B 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 <i>in-vivo</i> 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].

Table 2. Summary of Clinical study of Nanoparticles

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.	Arteam Bisht <i>et. al.</i> , 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 <i>et. al.</i> , 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 <i>et. al.</i> , 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 <i>et. al.</i> , 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 <i>et. al.</i> , 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 <i>et. al.</i> , 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 <i>et. al.</i> , 26 June 2013 [71].

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 <i>et. al.</i> , 20 November 2020 [72].
Titanium dioxide nanoparticles	Titanium dioxide (TiO ₂) nanoparticles in food and personal care products	No penetration through viable skin, however, TiO ₂ particles penetrated relatively deeply into the skin, possibly via empty hair follicle.	Joanna Musial <i>et. al.</i> , 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 <i>et. al.</i> , 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 <i>et. al.</i> , 03 April 2020 [20].
AgNPs	AgNPs potentiates 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 <i>et. al.</i> , 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 <i>et. al.</i> , 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 <i>et. al.</i> , 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 interfering) [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 anti-bacterial 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.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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