



Potential of nanoparticles encapsulated drugs for possible inhibition of the antimicrobial resistance development

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ABSTRACT

The immune system is a dynamic network of cells and cytokines are the major mediators of immune responses which combat pathogens. Based on the cytokine production, effector T cells differentiate into subsets known as Th1, Th2, Th17, or Treg. This system serves as a barrier to intracellular pathogens, bacterial infections and stimulates the production of reactive oxygen species (ROS), reactive nitrogen intermediates, and nitric oxide, which diffuses across membranes and engulfs intracellular pathogens. Oxidative stress occurs when ROS, reactive nitrogen species (RNS) production, and antioxidant defences become imbalanced. Oxidative stress generated by infected cells produces a substantial amount of free radicals which enables the killing of intracellular pathogens. Intracellular pathogens are exposed to endogenous ROS as part of normal aerobic respiration, also exogenous ROS and RNS are generated by the host immune system in response to infection. Nanoparticles which are designed for drug delivery are capable of trapping the desired drug in the particles which protect the drug from enzymatic degradation in a biological system. The subcellular size of nanoparticles enables higher intracellular uptake of the drug which results in the reduction of the concentration of free drugs reducing their toxic effect. Research on the modulation of immune response and oxidative stress using nanoparticles used to encapsulate drugs has yet to be explored fully. In this review, we illustrate the immune activation and generation of oxidative stress properties which are mediated by nanoparticle encapsulated drug delivery systems which can make the therapy more effective in case of diseases caused by intracellular pathogens.

1. Introduction

The immune system is constantly in flux, and it encompasses a dynamic network of cells, tissues, and organs within a host that work in a coordinated manner to defend the body against attacks by "foreign" invaders while also protecting against disease by recognizing both "self"

and "non-self". Antigens, usually a toxin or foreign substance identified by the host, are recognized by specialized cells that facilitate their initial destruction, followed by the host's elimination. Any microorganism able to cause disease in a host organism can be termed a pathogen when a pathogen (for example, a bacterium, virus, or protozoan parasite) infects the human body, after which an internal battle ensues between the

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host's innate and adaptive immune system and the pathogen's assorted virulence mechanisms, together with factors which can overcome the immune attack and establish disease. Detection of antigens by the host is complicated as pathogens evolve rapidly; they can adapt quickly and escape the immune surveillance, which allows the pathogens to infect their hosts and cause disease [1]. Pathogens can be extra-cellular and intracellular, and the mechanism to counter their attack by the immune system is varied. As intracellular pathogens reside within the host cell, their elimination and clearing are more complex. The cell-mediated immune response plays a vital role in the host defense against intracellular pathogens such as those causing tuberculosis leishmaniasis [2].

The immune response can be both innate and adaptive; the innate immune response is the first line or primary defense immediately stimulated upon infection. This first line of defense initiated by the host upon the entry of microorganisms into the body involves phagocytic cells' responses that fight pathogens nonspecifically. Antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs), which are spread extensively throughout the body, swallow and process potential microbial antigens via phagocytosis, antigen presentation, and activation of T and B lymphocytes to generate an adaptive immune response [3]. These activated cells cooperate with activated macrophages within the host to abolish intra- and extra-cellular pathogens [4]. Antigens are collected by APCs, after which they migrate to the draining lymph nodes with maturation signified by an enhanced presentation of antigenic material to major histocompatibility complex (MHC) class I and/or class II receptor molecules that are subsequently presented to the immune system for development of the acquired immune response. The antigen presentation alone is not adequate to cause naive T cells to mature into effector T cells. Upon receiving the signal, APCs can initiate critical T cell responses to the antigen, such as cell survival, differentiation of naive T cells to develop into effector T cells, and cytokine secretion [5–7]. CD4⁺ T cells identify antigens that have been processed by APCs, DCs, macrophages, and B cells that express MHC class II molecules.

NPs exert their antimicrobial effects through membrane protein damage, superoxide radical production, reactive oxygen species formation, protein disruption of microbes, damage to proton efflux pump & disruption of electron transport chains, and the generation of ions that interfere with the cell granules leading to the formation of condensed particles (Fig. 1).

2. Immune evasion

Many pathogens which can cause acute infections are often cleared effectively by the host's immune system. However, some pathogens that invade the hosts cells become intracellular pathogens and can establish persistent and sometimes lifelong infections. Several of these intracellular pathogens manage to evade the host immune system causing disease by replicating inside the host cells.

Some bacteria, such as *M. tuberculosis*, can disrupt the phagosome-lysosome fusion using the PtpA tyrosine phosphatase, which prevents the phagosome's acidification [8]. Other mechanisms use the phagosome to create a suitable microenvironment for proliferation: *Legionella pneumophila* safeguards itself from the hosts innate immunity by creating a vacuolar environment which is lacking MHC class II molecules [9], whereas *C. burnetii* needs an acidic environment for growth and virulence which eliminates the other pathogens [10]. Some bacteria can enter a hardy, non-replicating state, termed dormancy for self-protection. *M. tuberculosis* undergoes a period of reduced cellular growth which maintains a basal metabolism called cellular quiescence [11] and true dormancy, a metabolically-arrested spore state promoting survival under adverse conditions exhibited by the *Clostridium* spp.

Endoparasites are parasites that live in their hosts' tissues and organs, and they encompass both parasites and helminths. Protozoa avoid contact with human immune cells by living in immune-privileged sites, *Plasmodium falciparum*, which causes malaria in humans, matures in the liver [12]. The parasite can then travel in the peripheral blood to infect

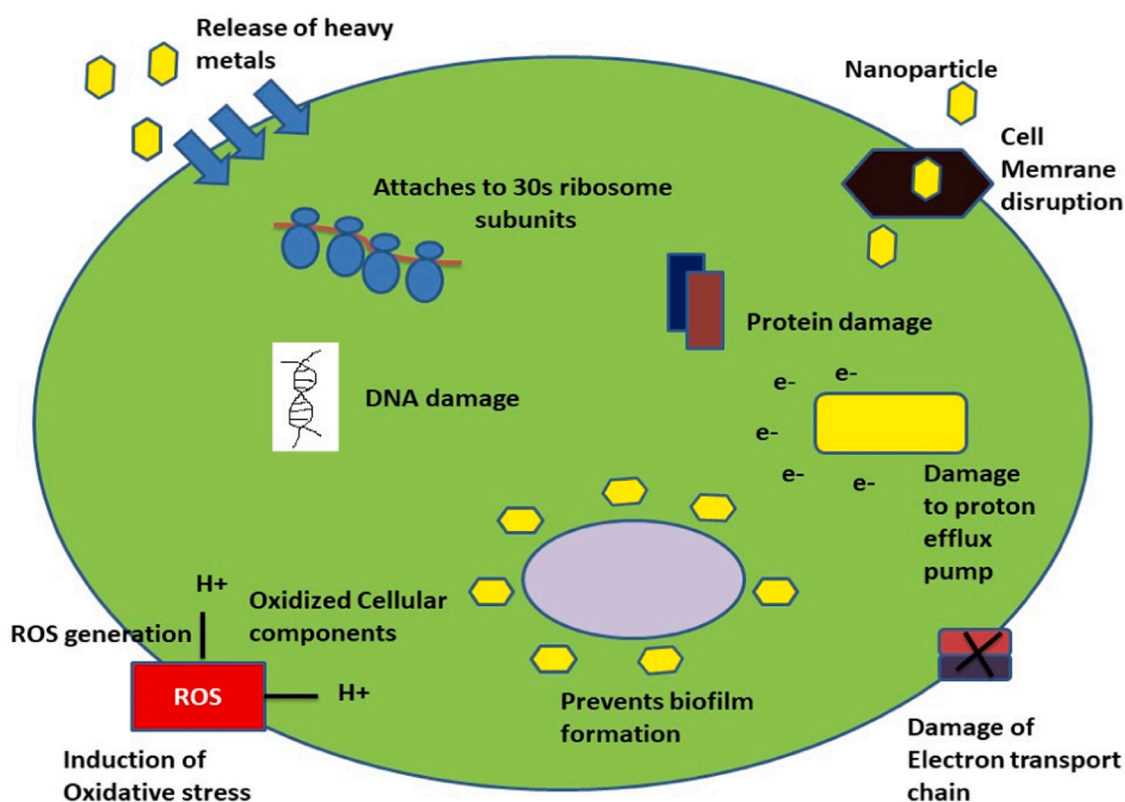


Fig. 1. Antimicrobial activities exhibited by nanoparticles include damage of the proton pump, prevention of biofilm formation, oxidation of cellular components, disruption of the electron transport chain & cell membrane of microbes.

erythrocytes. They target these cells as they lack MHC I receptors and are not recognized by cytotoxic immune cells [13]. *Trypanosoma brucei* can invade the central nervous system causing African sleeping disease. The parasite proliferates in blood and lymph and is not recognized by the immune system [14]. In addition to evading the immune systems, genetic polymorphisms within the parasites also play a role in immune evasion by several protozoans. Two examples are i) *P. falciparum* which has multiple stages during its lifetime, its surface antigens are altered after every stage, and ii) *T. brucei* survives through remodeling its sub-surface protein. This protein is involved in signaling transitions during developmental stages of dormancy and disease progression [15]. These polymorphic modifications reduce B cells' ability to make particular antibodies against the parasitic antigens [16].

T. brucei uses its "vector host" to its advantage, the saliva of the Tsetse fly is transmitted along with the parasite, the saliva contains a Gloss2 peptide which suppresses human host release of cytokines TNF- α , IFN- γ , IL-6, and IL-10 [17]. Helminths can survive in humans for many years due to their ability to secrete immunomodulatory products, including proteases, protease inhibitors, venom allergen homologs, glycolytic enzymes and lectins [18]. As central components of the "respiratory burst" in activated macrophages and neutrophils, the reactive oxygen species (ROS) and reactive nitrogen species (RNS) cause an oxidative burst which plays an essential role in the host immune defenses against pathogens [19] which can be harnessed to tackle drug-resistant infections. Apart from intracellular pathogens, various extra-cellular ones use different modes to evade host immune defense. The Gram-positive organism, *Staphylococcus aureus* (*S. aureus*), is one of the most important human bacterial pathogens, with worldwide distribution, is a commensal organism that also causes infection in almost any human tissue. Effective treatment of staphylococcal infections has been hampered by the emergence of antibiotic resistance [20].

3. Oxidative stress

The excess production of reactive oxygen species (ROS) within the tissue and an imbalance between the production and accumulation of ROS in the cells are termed oxidative stress. The ROS formed in this phenomenon are the metabolic by-products of the biological systems. They are very harmful to the system as it causes damage to the nucleic acids, carbohydrates, membranes, proteins and induces several other diseases which are detrimental to the body. Superoxide radicals ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($\cdot OH$), and singlet oxygen (O_2) are molecules that predominantly form ROS. The increased amount of ROS has caused the impairment of mitochondria and cellular damage. ROS production depends on the enzymatic as well as non-enzymatic reactions. During the activity of enzymes such as NADPH oxidase, the superoxide radical is synthesized [21]. But the ROS can be controlled and to overcome this excess ROS response, the cells actively activate various antioxidant systems either enzymatically or non-enzymatically [22].

There are various nanoparticles whose chemical composition completely differs and they have the potential to induce this oxidative stress within the biological systems. Nanoparticles made up of CNT, metal oxides, and fullerenes are likely to cause oxidative stress [23]. Due to these critical issues involved with nanoparticles, using them as the antioxidant was ignored entirely. Also, very few nanoparticle compositions were suitable for this. But these issues needed solutions so, new functionalized antioxidants from nanoparticles were formed from natural resources. This was believed to be a better alternative for excellent features such as well-targeted delivery, high stability, and biocompatibility. Generally, to scavenge these ROS, antioxidants are required. An antioxidant is a molecule that donates an electron to a free radical species and neutralizes it, thereby controlling the damage. An antioxidant is a stable and low molecular weight molecule that binds with ROS very easily and terminates its reaction before causing any damage. Some of the antioxidants are formed in our body, regulating this function and

those are uric acid, glutathione, ubiquinol, etc. There are some other antioxidants as well, which are consumed with the dietary supplements that are present in the form of phytochemicals such as β -carotene, vitamin C, vitamin E [24]. Various methods have come forward for preparing the nano-oxidants, supercritical fluid technology, solvent displacement method, nanoprecipitation techniques, emulsion/solvent evaporation, and templating method are some of them. Scavenging of ROS was possible with cerium oxide nanoparticles (CONPs), and along with that different other metal oxides, carbon nanotubes have profoundly shown antioxidant features [25]. Chitosan exhibits mucoadhesive characteristics that help to enhance the well-targeted delivery in the mucosal surfaces as well. Also, surprisingly curcumin plays a vital role in this. When curcumin is encapsulated in nanocarrier and stabilized with chitosan, it has shown the power of scavenging free radicals that depict antioxidant behavior [26].

Several forms of antioxidant functionalized nanoparticles are derived from biological extracts. Silver nanoparticles (AgNPs) have great potential in exhibiting antioxidant properties with the help of biological enzymes. Several studies have successfully identified actinobacteria that are natural producers of AgNPs that show antioxidant features [27,28]. The integrated dynamics between oxidative stress and an intracellular pathogen's immune cell function can sense and acclimatize to the continuously changing host environment during infection. Both oxidative and reductive stresses induce redox cascades that can alter pathogens signal transduction, DNA and RNA synthesis, protein synthesis, and drug resistance [23]. Maintaining a suitable redox balance is necessary for an excellent clinical outcome. Many prodrugs are only effective upon bio-reductive activation. Proper homeostasis of oxidoreductase systems is essential for pathogen's survival, persistence, and subsequent reactivation. As in humans, the exposure of bacteria to ROS causes damage to various macromolecules, resulting in mutations and often in cell death thus contributing to the generation of host defences. ROS function as signaling molecules that lead to a coordinated response in bacteria under redox-stress conditions. Metallic nanoparticles (NPs) offer a novel potential means of fighting bacteria because they exert their effects through membrane protein damage, superoxide radicals, and the generation of ions which may cause oxidative stress. Although the presence of the versatile nature of ROS has helped in numerous ways but excess of ROS and lack of ROS can induce several diseases to the host thus proving it to be the cytotoxic component for the host cells. So, the development of ROS drug delivery systems with nanoparticles encapsulated drugs has become an essential part of biomedical applications. In spite of the advantages, several challenges also come up with the proposed method of inducing ROS for treating antimicrobial resistance. The materials used as the carrier has to have high biocompatibility for avoiding inflammation in the host cells. The drugs should circulate in the normal cells with higher stability and lower ROS levels and have the potential to deliver it accurately at the desired pathological site for effective results. Also, the in vivo results of the ROS drug delivery mechanisms are not yet explored and so, evaluation of in vitro results for the drugs always does not show the in vivo efficacy for the respective drugs. Moreover, too many variations in the expression levels of ROS in different individuals, the selection of nanomaterials needs to be considered as well in different individuals for better therapeutic activity.

3.1. Role of nanoparticles in the specific immune response against intracellular pathogens

The propensity of pathogens for acute infection is widespread, but generally, the immune system effectively evades them from the body. There is a category of pathogens named intracellular pathogens, which are more persistent inside the body thereby inducing a lifelong infection [29]. There is a shred of evidence that all the intracellular pathogens accumulate in compartments and can be found residing in the cytosol, endoplasmic reticulum, nucleus, and Golgi apparatus of the host cells.

And this leads to a critical challenge for the drugs to penetrate the lipidic membrane and reach out to the invading pathogens. Therefore, antimicrobial agents do not help in resolving this concern. Eradication of intracellular pathogens is essential, and the conventional methods do not do them because of the possible side effects and emerging resistance against the combination of drugs [30]. Several research pieces came upon loading the antibiotics on different carriers to deliver the desired medications to the specific location for treating the infection and not damaging other cells.

Different types of drug delivery carriers are formed to improve the delivery system for treating intracellular pathogen. Numerous carrier types are in use, which helps control the release of the specific drug into the body. Popular drug carriers involve Liposomes, Polymeric Micelles, Nanoparticles, and Nanospheres. The recovery of damage that occurred by intracellular pathogens can be made using the above methods. As the carrier is used inside the host-specific parameters need to be taken care of. Biocompatibility and Biodegradability are the two critical parameters that are required for the drug delivery carriers to achieve. Among all the popular drug carriers, nanoparticles or nanostructures are the better versions of the drug delivery system. Innumerable synthetic polymers are used along with natural polymers such as chitosan for manufacturing nanoparticles [31]. The nanoparticles enter the cell through different mechanisms of endocytosis depending on the different types of cells. The above schematic diagram (Fig. 2) depicts various mechanisms followed by the nanoparticles for entry into the cell to provide an immune response against intracellular pathogens [32]. Treatment procedures to remove intracellular pathogens actively from within the body require long-term therapy. A massive amount of combinations of the drugs are applied. This has turned out to be a complicated process because of the drugs' delivery to intracellular pathogens. So, there has to be an ideal approach for eradicating these pathogens, and there should be the presence of these following features as well.

- The drug treatment method should have low toxicity.
- It should able to have high efficacy power.
- The penetration ability into the host cells should be high and efficient.
- It should have a site-specific drug release.

All the above features are part of nanomedicine, and therefore this can be a highly effective method for the inhibition of AMR development [22]. Chitosan nanoparticle encapsulated drugs have shown biocompatibility, bioadhesive, biodegradability, and high penetration properties. They are generally actively taken up by the phagocytic cells, which induce an immune response against intracellular pathogens. Research studies have highlighted that chitosan has some immune-stimulating activity that involves activation of macrophages and increases accumulation along with polymorphonuclear cells. Chitosan nanoparticles have shown immense potentiality in the increase of humoral and cellular

immune responses and prompted an equilibrium between TH1/TH2 responses [33,34]. Cellular internalization of NP activates immune cells, including macrophages and neutrophils, contributing to reactive oxygen species and reactive nitrogen species (ROS/RNS).

3.2. Nanoparticles against pathogen

Nanomedicine is an application of nanomaterials that provides solutions to current unmet medical needs. Recent advances include developing innovative nanoparticles to target reactive oxygen species (ROS) (Fig. 3). Oxidative stress has been known to contribute a great deal in altering the bacterial membrane permeability resulting in damage to cell membranes. Various examples of metallic NPs regarding this aspect, such as nano-silver ion activate oxygen and produce reactive oxygen ions and hydroxyl radicals, which can hinder bacterial proliferation or destroy bacterial cells.

Metallic nanoparticles (NPs) offer a novel potential means of fighting bacterial infections and combating drug-resistant infections. Nanoparticle activities can also target multiple biomolecules and potentially reduce or eliminate the evolution of numerous drug-resistant organisms (MDROs) [35]. Different NPs employ different mechanisms to destroy bacteria. Metallic NPs use several modes of action to kill bacteria: they penetrate the bacterial cell wall and form pores on the surface of the membrane, which, in turn, cause the free radical formation to destroy the cell membrane [36]. Due to nanomedicines' favored features, multiple options for nanoparticles have come forward, such as organic and inorganic nanosystems. Under Organic nanosystem (liposomes, polymeric micelles, polymeric nanoparticles) are in great use, and inorganic nanosystem consists of (silver, silica, zinc oxide(ZnO), cobalt, selenium, cadmium) which plays a vital role in antibacterial delivery intracellularly. Below, the advantages of different forms of nanoparticles have been described in their aspect of reducing the antimicrobial activity against pathogens.

3.2.1. Liposomes

Liposomes are believed to be the successful approach in antimicrobial drug delivery nanosystems because of their features as drug carriers for hydrophilic and hydrophobic drug therapeutics. Antibiotics-loaded liposomes for drug delivery have shown several advantages, which had a good response. They can enhance the biodistribution of antibiotics. They have a selective biofilm targeting affinity nature. For specific interactions with the target, the liposomes are complexed with either protein or antibodies to target the particular microbial biofilm. On the other hand, for nonspecific interactions, the presence of charge on the liposome membrane triggers biofilm interaction. One of the promising aspects of liposomes is the tremendous effect in eradicating intracellular pathogens by intensifying the retention of antibiotics in all the infected areas, thereby providing controlled release of the drug with very low toxic effects and increasing the concentration required in the infected

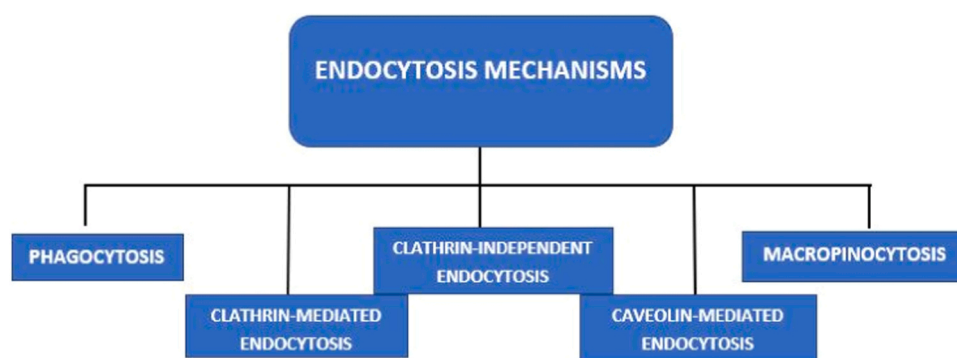


Fig. 2. The schematic diagram depicts various mechanisms followed by the nanoparticles for entry into the cell to provide an immune response against the intracellular pathogens.

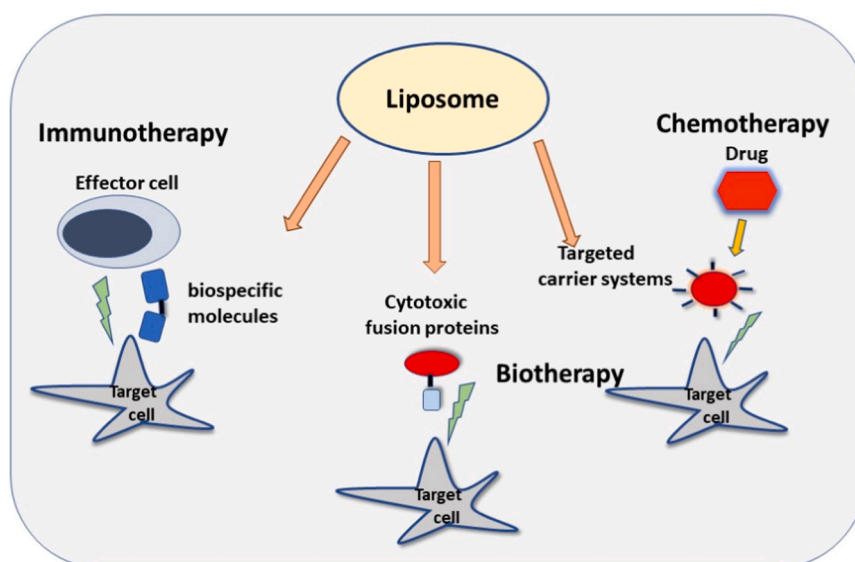


Fig. 3. Schematic representation of nanoparticles as a carrier system and its applications.

regions. The thioether phosphatidylcholins liposomes are developed for ROS responsive drug delivery.

3.2.2. Polymeric Micelles

Polymeric Micelles are 10–100 nm in size, and chitosan plays a vital role in constructing the micellar systems for drug delivery nanosystems. The nanocarriers made of micellar generally feature protecting the poorly water-soluble drug molecules inside their core. They do not allow them to interact with the blood proteins as well. Recent studies have explored that the target efficiency can be enhanced by introducing stimuli dual responsive polymeric micelles. Apart from chitosan, polymeric micelles highlight the development of ROS responsiveness from diselenide bonds. The micelles containing tellurium has got a sharp ROS responsiveness.

3.3. Polymeric nanoparticles

There are several polymeric nanoparticles, but chitosan has been one of the most valuable and efficient materials for antimicrobial drug carriers. Moreover, as the polymeric material is natural and organic, it has a high biodegradability and biocompatibility rate. Although natural polymeric materials have tons of advantages, synthetic polymeric materials do not lead down the research. One of the promising synthetic polymeric materials is PGLA (poly (lactic-co-glycolic acid) or PCL). Similarly, several inorganic polymeric materials are widely used for successful drug delivery carriers to inhibit antimicrobial resistance [37]. Thioketal containing polymers exhibit ROS responsive mechanisms for optimal therapeutic results.

3.3.1. Lipid polymer nanoparticles

Under the lipid polymer nanoparticles, a biosurfactant abundantly emanated by the organism *P.aeruginosa* named rhamnolipid is conjugated with the polymeric nanoparticles to control *Helicobacter pylori* biofilm resistance. The chitosan polymer generally forms them in the core, encapsulated by the antibiotic prescribed clarithromycin, which has shown a considerable reduction of biofilm resistance [38,39]. Metallic nanoparticles such as iron and silver oxide have also been used by coating it with rhamnolipid, and this exhibited significant efficacy against *S.aureus* and *P. aeruginosa* (Table 1).

Table 1

Different types of nanoparticles with their respective purpose in medical science.

ROS Responsive NP Polymers	Purpose
Thioether	Nanocarriers for efficient Cancer therapy
Selenium	Shows efficient antioxidant activities
Thioketal	Drug carrier that shows high anticancer effects
Tellurium	Tellurium-containing molecules exhibits ultrasensitive ROS-responsive properties and biocompatibility.
Nano-silver ion	Nano drug delivery system
Silica	Silica based ROS responsive helps to predict cellular toxicity.
Zinc Oxide	Delivers antibacterial therapy intracellularly
Cadmium	Delivers antibacterial therapy intracellularly
Cobalt	Delivers antibacterial therapy intracellularly

3.4. Bio-polymeric nanoparticulate drug delivery system

There are several bio-polymeric nanoparticles that have proved to be biocompatible and biodegradable materials in the therapeutic world. Generally, bio-polymeric nanoparticles were first designed by using albumin, and later on, several synthetic biodegradable nanoparticles play a vital role in drug delivery systems [40]. The biodegradable and bio-absorbable polymers are the best choice for the drug delivery systems for drug carriers. There are numerous aliphatic polyesters such as poly (lactic acid), poly(glycolic acid), polydioxanone, etc. extensively used in the drug delivery systems. polyanhydrides, poly(amides), poly(phosphodiester), poly(alkyl cyanoacrylates) are some of the biodegradable polymers and natural polymers such as chitosan are commonly used as drug carriers. Studies revealed that synthetic biodegradable polymers are considered favorable because of their immunogenicity as compared to natural polymers [41,42]. The abundant use of bio-polymeric nanoparticles has come forth due to the multiple features but antimicrobial activity is the prime one among them. The use of the biopolymer for various applications might vary but some of the major biopolymer which is under extensive use such as chitosan, cellulose, gelatin, Poly-lactic acid(PLA), etc. [43,44].

4. Conclusion

Infectious diseases caused by pathogenic bacteria are among the most common causes of death worldwide and are a constant health risk in all countries [45]. Today, the burden of infectious disease on health,

the economy, and other social aspects is so complex that the worldwide cost cannot be estimated [46]. Multi-drug resistant (MDR) pathogens constitute one of the most severe worldwide public health problems. Apart from those, the biodegradable polymers can be utilized as a drug delivery system because of several advantages such as biodegradability, biocompatibility, enhanced circulation, and reduced toxicity. The main objective in using the nanoparticles as a delivery system is the controlled release of encapsulated controlled drugs to accomplish the site-specific action at the therapeutically optimal level. Innovative nanoparticles are being developed to elicit the necessary immune responses for successful antimicrobial defence [47]. Besides, they can also influence the entrapment efficiency, the release of the drugs from nanoparticles, and nanoparticles' stability. The area of modulation of immune response and oxidative stress using nanoparticles encapsulating drugs is yet unexplored. In this review, we are trying to discuss the possible hypothesis of whether the immune-activating and generation of oxidative stress properties of nanoparticles encapsulated drug delivery system can be co-related for progressing toward more effective therapy and immune response in case of infections caused by intracellular pathogens. Using antibacterial encapsulated nanoparticulate techniques may lead to a delay or inhibition of the resistance development. The shining ray of hope amidst the plethora of antimicrobial resistance is that the microbes would require multiple gene mutations in the same bacterial cell to become resistant to NPs. It will be interesting to explore further; an interplay of the immune response, ROS, and RNS created by intracellular pathogens, warrant detailed evaluation of the signaling pathways to ascertain the extent of interdependence.

Key points

Question: Demonstrate how nanoparticle encapsulated drug delivery systems can increase the effectiveness of therapy in diseases caused by intracellular pathogens by activating the immune system, and oxidative stress.

Findings: In this review we are trying to discuss the possible hypothesis whether the immune activating and generation of oxidative stress properties of nanoparticles encapsulated drugs delivery system can be co-related for progressing toward more effective therapy. Among all the popular drug carriers, nanoparticles or nanostructures are the better versions of the drug delivery system.

Meaning: It will be interesting to explore further; an interplay of immune response, ROS and RNS created by intracellular pathogens, which warrant detailed evaluation on the signaling pathways to ascertain the extent of interdependence.

CRediT authorship contribution statement

Ramendra Pati Pandey: Conceptualization, Methodology, Formal analysis, Validation, Writing – original draft, Writing – review & editing, Supervision. **Riya Mukherjee:** Methodology, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Anjali Priyadarshini:** Methodology, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Archana Gupta:** Methodology, Formal analysis, Validation. **Arpana Vibhuti:** Methodology, Formal analysis, Validation. **Elcio Leal:** Methodology, Formal analysis, Validation. **Utpal Sengupta:** Methodology, Formal analysis, Validation. **Vishwa Mohan Katoh:** Methodology, Formal analysis, Validation. **Pawan Sharma:** Methodology, Formal analysis, Validation. **Catrin E. Moore:** Methodology, Formal analysis, Validation. **V. Samuel Raj:** Conceptualization, Supervision. **Xiaoming Lyu:** Conceptualization, Supervision, Funding acquisition.

Conflict of interest statement

The authors declare no conflict of interest.

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