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Outer Membrane Protein-Coated Nanoparticles as Antibacterial Vaccine Candidates

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Abstract
Nanoformulations are novel therapeutic strategies as compared to traditional treatments. The development of biomimetic nanoparticles by combining the natural cellular material with synthetic nanoparticles has inspired innovative vaccine strategies for modifying the antibacterial immunity. A lot of work has been done in which synthetic nanoparticles are coated with biomimetic cellular membranes for enhancement of biological functions and treatments. Outer membrane protein of bacteria not only act as adjuvant but also contain a large number of immunogenic antigens that play an important role in motivating the native immunity and stimulating the immune responses of the body. Outer membrane protein coating onto the surfaces of synthetic nanoparticles has synergistic effects to produce antibacterial responses. This article reviews the recent improvements related to the bacterial membrane-coated nanoparticles for antibacterial immunization.

Keywords Nanoformulation · Membrane coating · Biomimetic nanoparticles · Outer membrane

Introduction

Outer membrane vesicles (OMVs) are secreted by gram negative bacteria as a result of stress condition. Their size may be 20–25 nm in diameter that helps in communication and delivery of intracellular products to stimulate the cellular functions of host cells. Lipopolysaccharides (LPS) are the main element of OMVs. These purified vesicles act as immune stimulators those activate the nuclear factor-kappa B (NF-κB) and nucleotide-binding oligomerization domain (NOD) signaling pathway. According to previous research it was shown that these vesicles act as a vehicle to modify the cytosolic LPS to enter in cytosol that activate the inflammatory response (caspase-II activation) in response to gram negative bacterial diseases. Moreover, these OMVs also have a starring role in mucosal immunomodulation that are produced by bacteria in the gut. These results show that OMVs act as a biological tool that enables the LPS entering in cytosol to activate the immune defense (Vanaja et al. 2016).

Bacterial outer membrane proteins (OMPs) act as an antigen to induce protective immunity against bacterial infection. OMPs have an important role in adaptation and pathogenesis of gram negative bacteria as these are present on the surface of a bacterial cell that linked to environment. Proteins are preferred antigens as compared to carbohydrates. OMPs of *Salmonella gallinarum* were used in vaccine preparation to observe their ability in protective immunity. The research was conducted to study the immunogenic properties of *Salmonella* OMPs. The results showed that OMPs of *Salmonella* having major immunogenic properties and may also be used in Western blot or enzyme-linked immunosorbent assay (ELISA) for diagnosis of salmonellosis in chicken (El-Fakar and Rabie 2009).

The membranes of gram negative bacteria contain two layers, inner membrane (IM) and outer membrane (OM). OM is bilayer and asymmetrical that contains internally glycerophospholipid and externally LPS leaflet. Cell wall of peptidoglycan is present around the cytoplasm in between the IM and OM where aqueous periplasm is present. Integral membrane proteins of IM contain transmembrane helical

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domains but in OM these proteins contain transmembrane ß-barrel domains. LPS of OM contain more than hundred sugar deposits and O-antigen that is important for the representative immunological serotyping (Ranava et al. 2018).

Bacterial Cell Envelope

The envelope of gram negative bacteria is consisted of three layers that include fluid phospholipid bilayer plasma membrane, peptidoglycan cell wall and phospholipid containing OM (Fig. 1). This envelop not only provides shape and mechanical support but also acts as selective barriers. The studies revealed that OM of gram negative bacteria provide larger mechanical support to envelop as compared to universally believed cell wall. There is a great deformation in cell envelop and increase cell lysis upon compromising of OM by genetical or chemical factors. On the bases of review of literature, it can be concluded that cell wall is not a dominant structure and OM of bacteria may provide greater strength and mechanical support as compared to cell wall. OM can bear greater turgor pressure than cell wall because OM contains larger relaxed size as compared to cell wall (Rojas et al. 2018).

Composition of OMVs

OMVs contain protein, lipid, cellular components and periplasm as compositions. The study revealed that OMVs have many types of OMPs like (OmpA, OmpC, OmpF), and periplasmic proteins like AcrA and alkaline phosphatase that are involved in adhesion. OMVs of gram negative bacteria also contain lipid as important structural elements. Mostly Phosphatidylglycerol and phosphatidylethanolamine lipid are present in OMVs along with LPS that help in the formation of biofilms. Nucleic acids also present in vesicles produced by bacteria. OMVs in addition to DNA also carry RNA, chromosomal DNA and plasmid but the mechanism of nucleic acids incorporation is still unclear. OMVs have ability to transport the autolysins, cytotoxins, DNA fragments, biomolecules and many virulence factors. Roles of OMVs in adhesion, stress responses, acquirement of nutrients, toxin delivery and various physio-pathological functions have been revealed (Jan 2017).

Infectious diseases are mostly protective through vaccine strategies to induce immune responses because present pathogens have attained resistance against

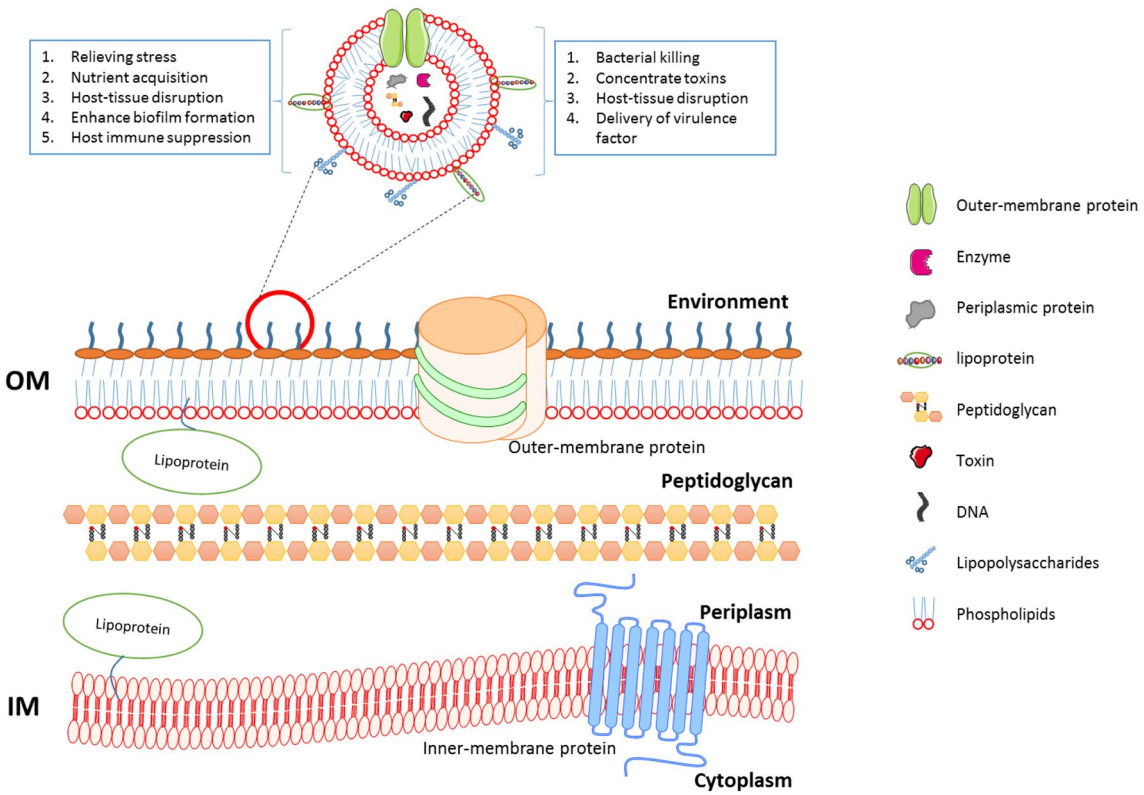

Fig. 1 Bacterial cell envelope possesses two membranes around the cytoplasm. A typical symmetric glycerophospholipid bilayer of inner membrane (IM) and asymmetric bilayer of outer membrane (OM) containing an inner leaflet of glycerophospholipid and an outer leaflet containing lipopolysaccharide (LPS)

conventional therapeutics. Due to safety limitations of attenuated or killed vaccines, new vaccines have been developed by using protein sub-unit of the bacterial outer membrane to induce protective immune responses. These protein sub-unit antigens are combined with adjuvants or protein carriers to enhance the immunogenicity because they do not induce strong immune responses when used alone. These protein sub-unit antigens may also be formulated by using controlled release technologies to deliver the antigens. The research was conducted to observe the immunogenicity by using outer membrane vesicles of *E. coli* by coating with Cytolysin A (ClyA). The results indicated that OMVs of *E. coli* have ability to induce the robust and sustained immunogenicity in vaccinated mice. This result signals that OMVs are robust and easy drug delivery system for development of novel protective and therapeutic vaccines (Chen et al. 2010).

Antibiotic resistance and unavailability of effective vaccines have motivated to develop new therapeutic strategies against serious bacterial diseases. Due to advancement in nanotechnology various synthetic nanoparticles coated with cellular substances has shown remarkable promises to induce the immune responses and antibacterial immunity. Various biomimetic nanoparticle based-vaccines have been developed. The coating of cell membranes on synthetic nanoparticles has synergistic effects to each other as enhanced stability in biological buffer solutions and stimulated innate and adaptive immune responses have been observed.

A lot of work has been done by using this new therapeutic strategy and numerous natural cellular functions have been observed with synthetic nanoparticles as platform for coating of cellular membranes. For example, It was observed that red blood cells (RBCs) membrane coated nanoparticles resulted in increased RBCs circulating ability (Hu et al. 2011). A study revealed that when white blood cells (WBCs) membrane coated on silica nanoparticles there was increase in traversing ability of WBCs through endothelium (Parodi et al. 2013). Similarly, immune activation against tumor cell can be enhanced by coating the membrane of the cancer cell with nanoparticles (Fang et al. 2014).

The research was conducted to observe the antibacterial immunity by coating the outer membrane of *E. coli* on gold nanoparticles (AuNPs). The results revealed that when outer membrane proteins coated with AuNPs not only activate the dendritic cells in lymph node but also induce B and T cell immune responses in vaccinated mice against *E. coli* bacteria. AuNPs were used because they are more stable and provide core and shape for coating outer membrane proteins as natural antigen presentation. It was observed that bacterial membrane AuNPs (BM-AuNPs) coated product showed greater stability in biological buffer solution. Furthermore, BM-AuNPs vaccine induced antibody responses, interferon gamma (IFN-γ) and interlukin-17 (IL-17) but not interlukin-4 (IL-4). This shows the ability to induce strong immune responses by activating T lymphocytes (Th-1 and Th-17) based cell responses (Gao et al. 2015).

The research was conducted to investigate the immunomodulation produced by OMVs of *E. coli.* The results revealed that OMVs induced inflammatory response and prevent the lethality of bacteria by the stimulation of T cell response instead of B cells. Macrophage phagocytosis testing was also done and the results demonstrated that lethality of bacteria is mostly due to the production of IF- γ and IL-17. The results revealed that *E. coli*-derived OMVs persuaded the systemic inflammatory responses by the activation of T helper 1 (Th-1) and T helper 17 (Th-17) cell responses. These results support the development of protein sub-unit vaccines as a novel strategy to control the infectious bacterial diseases (Kim et al. 2013).

Function of OMVs

Spherical shaped OMVs are produced by gram negative bacteria that are filled by periplasmic contents. These OMVs help the bacteria to communicate with their environment. OMVs performed many functions such as promote bacterial pathogenesis, help in interaction within bacteria or environment and survive the bacteria during stress conditions. On the basis of these properties OMVs may be used in bioengineering applications. These OMVs are used by bacteria to improve their survival and bring modifications during bacterial pathogenesis. For example, OMVs not only provide nutrients, structural support as biofilms, environmental protection but also help in providing the factors that modify the immune system of the host (Schwechheimer and Kuehn 2015).

Many types of bacteria particularly gram negative bacteria have adopted resistant strategies like eukaryotes for their survival. One of examples is formation of OMVs by gram negative bacteria. These proteins enriched OMVs enhance the invasive ability of bacteria by promoting the binding of bacteria on the surface of the host cell. Outer surface lipoprotein A (OspA) and outer surface lipoprotein B (OspB) are the OMP that provide adhesive properties to bacteria for binding with host receptor sites. After adhesion of bacteria the host immune responses are modulated by production of different types of toxins like heat labile toxin (LT), cholera toxin (CT), vacuolating toxin (VacA), shiga toxin (Stx1 and Stx2) and other factors like glycoproteins and proteases. Furthermore, these OMVs enhance the survival of bacteria by decreasing the effects of antibiotic agents and bacteriophages. They also have a role in the communication act as cargo for cellular components loading. On the basis of these functional properties with respect to disease pathogenesis, make the OMVs as effective diagnostic tools that can be

used in many biotechnology applications. OMVs have been known for their role in delivery of toxins, adhesion, stress responses, nutrient acquisition and virulence factors to evade host defense system (Alaniz et al. 2007; Biller et al. 2014; Fulsundar et al. 2014; Furuta et al. 2009).

Potential Nanoparticulate Systems for Membrane Coatings and Biomedical Applications

Now a day nanoparticles are being used in all the biomedical and environmental applications due to their unique physicochemical properties especially due to the smaller size. They are used in electronics, cosmetics, medicines, food industry, as an efficient catalyst, in environmental remediation and construction materials. Some nanoparticles are used in UV protective sunscreens like titanium dioxide and in cosmetic iron oxide used as pigment in lipsticks. Some nanoparticles like cadmium sulphide, zinc selenide and lead tellulide are used in light emitting diodes (LED) for high brightness displays. Some nanoparticles like platinum are used in the chemical industry as an efficient catalyst due to larger surface area to volume ratio. In food industries nanoparticles have been used to enhance the production processes and in packaging to avoid xmicrobial contamination. According to recent research, it has proved that durability and mechanical properties of concrete can be enhanced by mixing it with nanosilica (SiO_2). Some nanoparticles are being used to treat the soil, air, water and surface of water by decontamination and purification. The use of nanoparticles in drug delivery system not only reduces the total dose but also decrease the side effects and cost of the drugs by delivery of drug at a specific target site. Nanoparticles are also being used in tissue and bone repairing like the use of carbon nanotube scaffold structures for the growth of bones likewise, the use of AuNPs in medicine to improve the memory. It has proved that some nanoparticle also have antimicrobial activity.

Among the various types of nanoparticles, AuNPs have great importance due to their unique physical and chemical properties that make them ideal choice for use in many biomedical applications like in optical imaging, computed tomography, photothermal and radiotherapy for cancer treatment. AuNPs are non-toxic and have a larger surface area that makes them compatible for coating of different chemicals like target ligand, imaging probe, antibodies, polymers and drug molecules on their surface. AuNPs have variety of shape, size, and surface structure with notable properties like anticorrosive, antioxidative and bacteriostatic. Gold (Au) is a multifunctional material that not only acts as a catalyst in the form of nanoparticles but also has importance like use as carrier and adjuvant in the vaccine formulation, provide stability and stimulate immune responses. Mostly AuNPs are used for targeted delivery of antibiotics and anti-cancer drugs (Zhao and Jiang 2013) (Fig. 2).

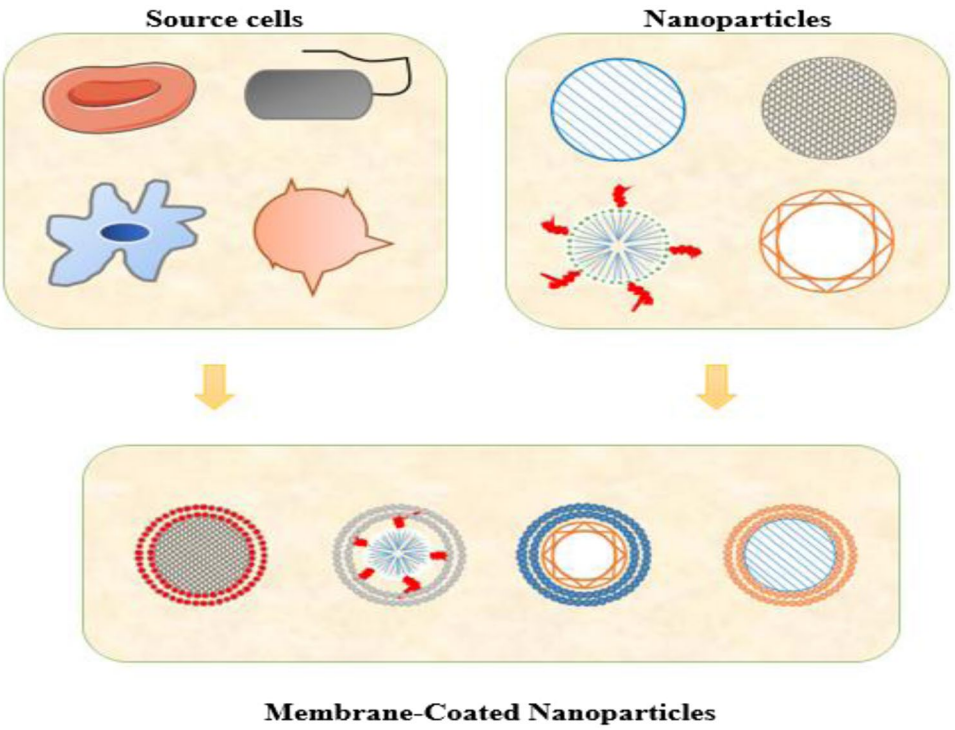

Fig. 2 Demonstration of coating of different types of bacterial outer membrane on the surface of various shapes nanoparticles

Targeting the Drug Delivery

The research was conducted to observe the ability of AuNPs to deliver the small drug molecules to the target site for induced immunity. In this research the small 2–4 nm AuNPs coated with amphiphilic ligands were used. The results revealed that AuNPs not only have ability to adsorbing the drug molecules in their ligand shells but also can transport the drug molecules through the lipid membrane to their target site to activate the signaling cascades. It was observed that encapsulated Transforming growth factor-βi (TGF-βi) inhibitor molecules in the shell of amphiphilic AuNPs (amph-AuNPs) reached in higher concentration in CD8 + T cells in vitro as compared to free form. The amph-AuNPs enhanced 40 times more uptake of targeted TGF-βi inhibitor entry to T cells that increased the cytokines production when conjugated with vaccine against cancer in vivo. These results proved that amph-AuNPs are a good vehicle to deliver the drug molecules with antibody to the targeted T cells (Yu et al. 2018).

The recent studies have proved that many vaccines that are formulated with nanoparticles particularly with Au have shown good results due to their better immune responses, biocompatibility and specific targeted drug delivery potential. It was noticed that cellular immunity can by induced by vaccines prepared by AuNPs. The AuNPs are used in vaccine development for storage stability, boost up immunogenic activity, decreased toxicity and as adjuvant. Furthermore, AuNPs act as vehicle that helps in penetration of drug molecules to target specific site. The study was conducted to observe the potential of Au-based nanovaccines which were synthesized by self-assembling conjugation method. It was observed that Au-based nanovaccines after activating the dendritic cells stimulate greater cytotoxic T-lymphocytes as compared to free peptides without coating AuNPs and also have greater carrier ability. Many Au-based vaccines have been developed for several diseases with potent responses (Carabineiro 2017).

Diffusion of macromolecules can be targeted to the cell without damaging the cell membrane by AuNPs because on heating they are more stable as compared to laser transfection in which there is more chance of cell damage due to extreme laser pulses. The research has shown that the use of monolayer of Au particles on the bottom of microplates in laser transfection reported better and efficient results as compared to laser transfection with random AuNPs attachment in cell cultures (Pylaev et al. 2018).

Role of Coated Nanoparticles in Overcoming the Antibacterial Resistance

Antibiotics resistance of pathogenic strains of bacteria has become a challenge now a day's. The use of peptides with AuNPs is promising strategy to avoid the resistance. The study has shown that antimicrobial peptide coated with AuNPs inhibited the growth of *S. aureus* and also have more antimicrobial potential against *Salmonellla typhi.* The activity of peptide of frog like esculentin can be increased more than 15 times by conjugated on the surface of AuNPs. According to different research it was reported that complex of natural peptides (Listeria adhesion protein and pediocin AcH) with AuNPs not only have antimicrobial activity but also prevent the biofilms formation that are produced by different microbes and fungus. It was also reported that some substances that have no antimicrobial activity but when used with AuNPs may act as antimicrobial agents for example pyrimidines. The conjugated pyrimidines with AuNPs exert their antimicrobial activity by different mechanisms either by inhibiting the bacterial cell membrane by binding with calcium and magnesium ions or cause the removal of cytoplasm contents like nucleic acid by bacterial cell membranes damage or inhibit the protein synthesis. It was also observed that these conjugated complexes are not harmful to human cells and do not show bacterial resistance that makes them valuable clinically. Furthermore similar strategy was used for bisbiquanides and amino sugars (de Alteriis et al. 2018).

Antioxidant activity of AuNPs with tocoferol has been demonstrated that show the potential of nanoformulation in the field of gene therapy for desirable gene expression or suppression. Furthermore, AuNPs are also used for the conjugation of many other drugs including diabetics and HIV infections. It was observed that coated AuNPs preparations have activity against HIV infections as compared to uncoated Au preparations. Similarly the significant results were obtained after administration of insulin coated with AuNPs as compared to uncoated insulin for decreasing the sugar level in blood in diabetic rats. AuNPs can be used as vehicle (alone or drug combination) for delivery of genetic material into the cytoplasm and nucleus for the strategy of gene therapy in the treatment of acquired and genetic diseases. For example AuNPs facilitated the delivery of small interfering RNA (siRNA) to cell and cytosol for the treatment of various diseases like macular degeneration, cancer and hereditary diseases (Artiga et al. 2019).

The role of nanoparticles as immunomodulation has been proved by recent studies. Different types of cells of immune system can uptake the nanoparticle to activate the defense system. There are mostly two main types of immunity named as innate and acquired immunity. The

body initially defensed from foreign microbes and other particulates by innate immunity. Mostly the nanoparticles first interact with innate immune defenses because they are present in high amount in tissues like in skin, respiratory and gastrointestinal tract (GIT) mucosa lining so interface with the external environment. Nanoparticles can easily penetrate through the membrane barriers and reach the blood plasma due to their small size. These nanoparticles after interaction with immune cells like macrophages and neutrophils induce inflammatory responses in the body. Nanoparticles are also up taken by dendritic cell. Foreign antigens are recognized by these dendritic cells of the immune system. The uptake of nanoparticles by immune cells depends on the size, shape, surface charge and deformability properties of the nanoparticles. Furthermore, nanoparticles also provide core for binding of bacterial membranes and preserve the biological properties of the lipopolysaccharides bacterial membrane for natural antigen presentation to immune cells for induction of immune responses. Immune induced potential of nanoparticles has been proved in vaccine efficiency against infectious diseases (Boraschi et al. 2017).

Now a day, antibiotic therapy is not remaining effective due to many reasons. Like in case of oral administration of antibiotic there may be chance of gastrointestinal problems, less solubility in lipid membrane and partial adsorption. To resolve these issues the complexes of antibiotics with AuNPs has been studied. The result shown that AuNPs not only protect the oral antibiotic from degradation in stomach but also increase half-life and help the drug to reach the target site to inhibit or kill the microbes. For example vancomycin was used with AuNPs and observed its antibacterial activity against vancomycin-resistant strains of *E. coli* and *Enterococus faecalis* (Dykman and Khlebtsov 2019). Another study was also conducted by preparing a complex of ciprofloxacin with AuNPs. The result was observed that complex of ciprofloxacin-AuNPs shown better antibacterial activity against *E. coli* as compared to ciprofloxacin alone (Rosemary et al. 2006). Many complexes of antibiotics have been developed with AuNPs like aminoglycosides, lincosamides, fluoroquinolones, polymyxins and cephalosporins (Tom et al. 2004).

AuNPs have proved as adaptable platform in many application of medical science. The study was conducted in-vitro to observe the potential of water soluble antibiotic vancomycin as antibacterial activity against multi-drug resistant bacteria by coating onto the AuNPs. Vancomycin-conjugate AuNPs may act as polyvalent inhibitors for multi-drug resistant bacteria. AuNPs were chosen for this study because of their chemical stability, geometry, surface conformation and smaller size (4–5 nm) in diameter than bacterium. Gold-vancomycin particles were synthesized by mixing the 4–5 nm size AuNPs (in toluene) with vancomycin in water by 12 h stirring. Vancomycin conjugated with AuNPs by Au-S bonds. Characteristic of Au-van conjugates were observed by transmission electron microscopy (TEM). After research it was noted that Au-vancomycin antibiotics have enhanced antibacterial activity and minimum inhibitory concentration (MIC) against the gram negative bacteria including vancomycin resistant bacteria (You et al. 2019).

The various types of antibiotics are commercially available to treat the infections caused by gram positive and gram negative bacteria among drug molecules. The resistance has been developed in bacteria due to broad use of these antibiotics. Antimicrobial effects of antibiotic after conjugated with nanoparticles have been reported in literature. Nanoparticles can deliver large amount of drugs without altering the activity of antibiotics. The use of antibiotic with nanoparticles together induced higher antimicrobial effectiveness. The nanoparticles are ideal substances to use in drug delivery due to their biocompatibility and larger surface area to volume ratio. It has been proved that antibiotic coated on nanoparticles have greater antibacterial activity and also against resistant bacteria. For example, It was reported that vancomycin coated AuNPs have greater antibacterial activity as compared to free vancomycin including against vancomycin resistant bacteria. Similarly, the antimicrobial potential of aminoglycoside, amoxicillin and ciprofloxacillin antibiotics coated nanoparticle has been reported in literature. The study was conducted to check the antibacterial activity of second generation cephalosporin like cefaclor coated with AuNPs as both are capping and reducing agents. The cefaclor was one-step synthesized with spherical AuNPs by reduction at different temperature (20–70 °C). It was revealed that cefaclor reduced spherical AuNPs have potent antibacterial potential against gram positive bacteria like *Staphylococus aureus* and *E. coli* gram negative bacteria with minimum inhibition concentration (MICs) as compared to free cefaclor or AuNPs (Rai et al. 2010a).

There is need of development of new antibiotic groups to counter the multidrug-resistant bacteria in all over the world. The researches have revealed that by conjugating the antibiotics with active substances drug delivery system can be increased. By this novel strategy many antibiotics have been directly synthesized with conjugation of AuNPs. It was revealed that cefaclor in conjugate form not only more stable at different pH 3 and 10 but also has greater antimicrobial action against Gram positive and Gram negative bacteria as compared to alone cefaclor antibiotic (Rai et al. 2010b). The antimicrobial activity of kanamycin, streptomycin and ampicillin were also studied after conjugated with direct reduction of Tetrachloroauric acid ($HAuCl_4$). It was observed that conjugated substances have greater antimicrobial potential as compared to unconjugated antibiotics. In another research ampicillin was used after conjugated with AuNPs by direct reduction of HAuCl4 showed better antibacterial activity against *Streptococcus pyrogenes* with minimum inhibitory

concentration as compared to ampicillin alone (Hur et al. 2014).

In another study aminoglycoside antibiotic (kanamycin) was administered after conjugation with AuNPs. Kanamycin was conjugated with 20 nm AuNPs after one-step preparation. It was observed that kanamycin-AuNPs conjugate have greater antibacterial activity as compared to free kanamycin including those bacteria that are resistant to kanamycin. It was also shown that after conjugate with AuNPs kanamycin has dose dependent activity with broad spectrum activity against both Gram + ve and –ve bacteria and minimum inhibitory concentration. Kanamycin-AuNPs changed the intracellular homeostasis after 6 h penetration to cell wall of bacteria and caused removal of cellular components of the bacteria after 12 h lysis of the cells (Payne et al. 2016).

Tricyclic glycopeptide antibiotic like vancomycin was used with one-step preparation AuNPs and observed its antibacterial activity. It was shown that vancomycin-AuNPs conjugate have broad spectrum antimicrobial activity and lower minimum inhibitory concentration as compared to free vancomycin. On the base of these result vancomycin-AuNPs conjugates was proposed to use in test strip and colorimetric assays for *Bacillus subtilis* and *Staph aureus* (You et al. 2019). Semisynthetic penicillin like amoxicillin was conjugated with AuNPs after one-step synthesis and observed its potential as antibacterial activity. It was revealed after in vivo studies that amoxicillin-AuNPs conjugate were more stable and has selective activity against cell wall of bacteria. After in vitro studies it was shown that amoxicillin-AuNPs conjugated has greater and strong antimicrobial activity against both sensitive and resistant bacteria like *Staph aureus* as compared to free amoxicillin (Silvero et al. 2018).

In another study semisynthetic tetracycline like doxycycline was coated with AuNPs. The result showed that after conjugation susceptibility of the doxycycline was enhanced and has better antibacterial potential against many pathogens (Haddada et al. 2018). The AuNPs were also used with antiprotozoal and antifungal drugs like fluconazoal, Amphotericin B and nystatin and it was observed that these drugs after conjugation with AuNPs were more bioactive against *Acanthamoeba castellanii* (Anwar et al. 2019).

The present restrictions of conventional chemotherapy can be countered by improving the drug delivery system and increasing the efficiency of the therapeutic agents at small doses with respect to side and toxic effects of chemical substances. The use of AuNPs in nanomedicine is promising in view of their cytocompatability and stability to treat the antibiotic resistant infections to resolve the multi-drug resistance problems. The emergence of multidrug resistant bacteria is a major problem for spreading of diseases in animal and human that caused great economical losses. The nanoparticles can be used as antimicrobial agents to treat the infections that are caused by multidrug resistant bacteria. The nanoparticles have ability to stop the growth of bacteria by damaging the capsule of the bacterial cell or by accumulation in the cell. Mostly Au, chitosan and silver nanoparticles are used as antimicrobial agents. As compared to silver nanoparticles, AuNPs are less toxic, more contrasting and may be used in medical imaging, as diagnostic and drug delivery system. The many types of antibiotics and ligands can be coated or conjugated on the AuNPs due to their larger surface area to volume ratio. There are several physical methods like γ radiation and reducing agents can be used for development and stabilization of AuNPs. There may be covalent or non-covalent binding between antibiotics and AuNPs. It has been proved that antibiotic-conjugate AuNPs have greater potential as antibacterial effects as compared to un-conjugated drug form. To observe the antibacterial potential AuNPs were developed from exopolysaccharides (EPS) of *Lactobacillus plantarum.* These AuNPs were coated with different antibiotics including ceftriaxone, ciprofloxacin, cefotaxim and levofloxacin. Antibacterial activity of functionalized AuNPs were observed by using different assays like well diffusion assay, time killing assay, minimum inhibitory and bactericidal concentrations (MIC, MBC). It was revealed from results that nanostructure-conjugated antibiotics have more antibacterial activity against multidrug resistant bacteria as compared to alone antibiotics (Pradeepa et al. 2016).

Generally antibiotics are conjugated with metallic nanoparticles like Au or silver (Ag) by two ways including covalent binding or ionic interaction between molecules for example vancomycin conjugate with AuNPs by Au–S bonds. It was assumed that AuNPs coated antibiotics show enhance antimicrobial activities due to antibiotics degradation and structural changes. AuNPs increase the affinity of antibiotic on the surface of bacteria so due to high concentration of antibiotics produced higher antibacterial activity. In case of one-step synthesis of AuNPs with second generation cephalosporins (cefaclor) it was investigated that cefaclor inhibit the synthesis of peptidoglycan of bacteria together AuNPs causing the holes in cell wall of bacteria leads to leakage of internal cell contents due to bacterial cell wall permeability change finally death of bacteria. It was also noted that AuNPs enhanced the antibacterial activity of cefaclor with MIC. Similar results were reported by using gentamycin, vancomycin, and streptomycin coated AuNPs.

AuNPs have numerous intrinsic physico-chemical properties that make them ideal vehicle in drug delivery system for antimicrobial substances. Two or more antibiotics can be loaded on the nanoparticle due to lager surface area to volume ratio. This combination therapy not only targets the specific pathogen but also decrease the antibiotic resistance, side effects and stability problems of existing antibiotics. The antibiotics loaded nanoparticles have advantages over free antibiotic agents that opens up a wide range of prospects. A

Table 1 Summary of the previous studies on cell membrane-coated AuNPs

Sr. No.	Type of cell membrane	Type of nanoparticles	Functions	References
1	Red blood cells (RBC)	Poly lactic-co- glycolic acid (PLGA)	Long circulating properties and higher stability	Hu et al. (2011)
2	*Shigella flexneri* bacteria	Poly methyl vinyl ether and maleic anhydride	Immunity against shigellosis	Camacho et al. (2013)
3	White blood cells (WBC)	Silica	Endothelium traversing properties	Parodi et al. (2013)
4	Cancer cells	PLGA	Immune activation against tumor and homotypic binding	Fang et al. (2014)
5	*Escherchia coli* bacteria	Mesoporous silica	Targeting drug delivery	Shao et al. (2017)
6	Mesenchymal stem cells	Super magnetic iron oxide	Tumor homing ability and inhibition of inflammation	Lai et al. (2015)
7	*Escherchia coli* bacteria	AuNPs	Modulating antibacterial immunity	Gao et al. (2015)
8	Platlets	PLGA	Immuno-compatibility, high permeability and affinity	Wei et al. (2016)

thoughtful fact about the potential toxicity of these innovative nano-antibiotics is critically needed to promise effective clinical translation (Jijie et al. 2017). Table 1 provides a summary of previous studies on cell membrane-coated AuNPs.

Conclusions

Regardless of the significant success in controlling previously reported epidemics worldwide, vaccines against infections including those caused by pathogenic *E. coli*, *Salmonella typhi*, *Salmonella gallisepticum*, *Salmonella pullorum* and *Staphylococcus aureus* remain unavailable. Another problem is that antibiotic therapy is not effective against bacteria due to bacterial drug resistance. That is why, to solve these problems there is need to find out novel antibacterial vaccine strategies to control these infections. Membrane coated nanoparticles provide a novel platform for developing antibacterial vaccines against infections.

Declarations

Conflict of interest All authors declared that they have no conflict of interest.

Ethical Approval This manuscript does not contain any research involving human participants and/or animals.

Informed Consent This manuscript does not contain any research need informed consent.

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