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NANOPARTICLES ANTIBIOTIC DELIVERY SYSTEM: AN ALTERNATIVE TREATMENT PROTOCOL FOR CASEOUS LYMPHADENITIS.

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ABSTRACT

Caseous lymphadenitis is an infectious zoonotic disease of goats with severe economic implications. A major reason why management of the disease is a problem in the small ruminant livestock industry is because *Corynebacterium pseudotuberculosis* forms biofilm in the host and is resistant to antibiotic drugs resulting in a chronic granulomatous condition. The use of nanoparticles as a means of direct drug delivery to this organism may provide a solution to tackling it. This review focuses on caseous lymphadenitis and the different nanoparticles for antimicrobial drug delivery

Keywords: caseous lymphadenitis, antibiotic resistance, nanoparticle, drug delivery

INTRODUCTION

Caseous lymphadenitis caused by *Corynebacterium pseudotuberculosis* is a disease of severe zoonotic and economic importance in the small animal livestock industry (Galvao *et al*., 2017). It is difficult to treat with antibiotics because *Corynebacterium pseudotuberculosis* evades the hosts immune system allowing it to multiply within the host tucked away in a pool of abscess surrounded by a thick fibrous capsule therefore making it difficult for the conventional formulations of antibacterial agents to get to the organism (Williamson, 2001). A number of approaches have been used in the management of CLA which includes administration of vaccine of the strain isolated from the herd, lancing and flushing with antibiotics, surgical removal of the abscess with identification and culling of affected animals however persistence of the disease in a herd even after long vaccination programs, recurrence of abscess following lancing and surgical removal and resistance to conventional antibiotics pose significant obstacles to achieving optimized therapeutics (Oreiby, 2015). The use of nanoparticles in the delivery of antibiotics to target sites is advantageous because it enhances pharmacokinetics and improves biodistribution of the loaded antibiotics whilst maximizing their delivery to target tissues, recently, Gold nanoparticles have been shown to demonstrate intracellular antibacterial activity against *C. pseudotuberculosis* (Mohammed *et al*., 2017)

The delivery of antimicrobials using nanoparticles is better compared to the conventional methods of antimicrobial delivery since the bacterial outer (membrane plays a role in permeability of these drugs, hence improving antibacterial activity (Torres *et al*., 2012). This review will dwell on caseous lymphadenitis and nanoparticles for antimicrobial delivery.

METHODS

The databases used to search for articles used in this review includes peer reviewed journals on nanoparticle drug delivery published in PubMed and Medline. References from these articles were also examined for additional articles.

Caseous lymphadenitis

Caseous lymphadenitis (CLA) is a chronic suppurative disease of cattle, sheep and goats, characterized by palpable abscess or granulomatous noodles containing cheesy exudates in lymph nodes, skin and/or internal organs (Oreiby, 2015). CLA manifests with external lesions or visceral lesions. These two forms may occur together or separately in the same animal (Al-Gaabary *et al*., 2009). In the external form of CLA, a distinct clinical manifestation is the swelling of external lymph nodes especially that of the parotid, submandibular, and supra mammary nodes though other lymph nodes may be involved. The internal form, it is characterized by chronic weight loss, coughing and other respiratory signs such as dyspnoea, tachypnea and nasal discharge. The clinical signs seen in either forms of CLA is usually related to which internal organ is affected (Habus *et al*., 2015). Also, the disease may be asymptomatic with internal lesions only that may lead to chronic diseases related to the internal organs affected usually detected at post mortem (Ribeiro *et al*., 2013).

Aetiology

Corynebacterium pseudotuberculosis is a Gram positive pleumorpic, microaerophillic (5% CO_2), intracellular bacterium which is neither encapsulated nor motile (Oreiby *et al*., 2015; Nassar *et al*., 2015).

The presence of two virulence factors facilitates its pathogenicity: phospholipase D (PLD), an exotoxin which enhances its spread by weakening endothelial cells and increasing vascular permeability and a mycolic acid rich toxic cell wall which protects it from host enzymes and prevents entry of antibiotics (Mahmood *et al*., 2015). Two biotypes of the bacteria have been identified namely the nitrate reducing group which affects sheep and goats and the non-nitrate reducing group which affects horses. Cattle is affected by both groups (Washburn, 2018).

Pathogenesis

Corynebacterium pseudotuberculosis gains entry into the body mostly through the intra dermal route either by scratches, wounds, cuts, or via other less common routes like inhalational or intraperitoneal. Upon entry, the bacteria activate the immune system and phagocytes are attracted to that area. The phagocytes transport the bacteria to the lymphnodes through the regional draining lymphatic system (Bastos *et al*., 2012). The bacteria replicates in the lymphnodes leading to the development of a pyogranuloma (as the external lipid coat protects it from the phagocytic action of the phagocytes.) The abscess becomes bigger and it is walled in a thick fibrous capsule which prevents further actions from the host immune system therefore making it inaccessible to antibiotics (Bastos *et al*., 2012; Habus *et al*., 2015; Washburn, 2018). The abscess formed is not limited to the lymph nodes alone, it can also be found on internal organs like liver, kidney, spleen and lungs.

Diagnosis

Diagnosis is based on presenting characteristic lesions of external abscess (Nassar *et al*., 2015) and this may be challenging because some infected animals may be asymptomatic for a long time thereby facilitating the disease spread in the herd. CLA is usually confirmed by isolation, culture and biochemical identification of *C. pseudotuberculosis* to differentiate it from other bacterial organisms that are characterized by formation of pus in goats though this may not be efficient in chronic infection where the external lesions contain little pus and viable organisms (Ribeiro *et al*., 2013). Serological test like ELISA and PCR are more efficient in diagnosis because they can be used to detect asymptomatic infection in a herd Ribeiro *et al*., 2013; Hariharan *et al*., 2015; Nassar *et al*., 2015)

Treatment

Treatment with antibiotics have been ineffective (Hariharan *et al*., 2015) though other methods such as administration of vaccine of the strain isolated from the herd, lancing, flushing and surgical removal of abscess with identification and culling of affected animals have been used (Washburn *et al*., 2013). Though these methods involve heavy economic implications (Washburn *et al*., 2013). Treatment with antibiotics does not completely clear the infection and this may not be unrelated to the mycolic acid rich toxic cell wall and bacterial virulence factors (Mahmood *et al*., 2015; Washburn *et al*., 2013). Experimental intralesional and systemic administration of a new macrolide antibiotic tulathromycin demonstrated positive results in goats when this antibiotic was used in flushing of lesions (Washburn *et al*., 2013).

Resistance of *C. pseudotuberculosis* to antibiotics

Antibiotics are effective in treating most bacterial infections and cost effective unfortunately, unregulated, widespread use and misuse have led to the emergence of multidrug drug resistance strains. *Corynebacterium spp* have been demonstrated to develop resistance genes against most of the common antibiotics used for treatment (Oleander, 2012). *Corynebacterium pseudotuberculosis* forms biofilm which the animal's immune system cannot get rid of with resultant damages to surrounding tissues in trying to curtail its spread (Sa *et al*., 2002). High microbial virulence and resistance to antibiotics are the major differences between planktonic and biofilm (sessile) forms of bacteria (Jamal *et al.*, 2018). Which makes biofilm associated infections difficult to treat as they do not yield to treatment with antibiotics which have been proven successful against the planktonic forms (Kostakioti *et al*., 2014). The bacteria acquire resistance by: developing genes responsible for resistance, modification of the ribosome binding site associated with methylation or mutation, effective pumping active efflux of antibiotic out of the organism and enzymatic inactivation of the antibiotics (Oleander, 2012). Most antibiotics do not get access to the organism due to the development of bacterial biofilms which can evade the immune system, thus results in persistence and development of chronic infections (Wang *et al*., 2017).

Nanoparticle antibacterial mechanism of action

Nanoparticle antibacterial mechanism of actions are not related to and does not depend upon any of those mentioned above as it involves direct contact with the bacterial cell wall, where it penetrate and destroy the bacterial generates free radicals which interact and interfere with cellular macromolecules and the direct reaction with functional groups of proteins, lipids and genetic materials (Wang *et al*., 2017). Nanoparticles increases the rate of reactive oxygen species (ROS) formation in bacterial cells which is one way the nanoparticles exert their antimicrobial effects (Khan, 2017). The high surface area to volume ratio and small size characteristic of nanoparticles qualify them as suitable candidates in the treatment of infections caused by biofilms as this facilitates closer interactions with bacterial membranes. Nanoparticles are highly advantageous in the target drug delivery systems because they bypass bacterial resistance mechanisms to conventional antibiotic treatment thereby decreasing virulence and eradicating resistance as well as reducing cost expended on antibiotics in the treatment of infections (Ranghar *et al*., 2014). Their ultra-small size

makes them have a higher surface to volume ratio with increased number of active atoms at their outer surfaces, makes contact with target site or organism better compared to large scale molecules (Mohamed *et al*., 2017). It is engineered in such a manner that it has a more rapid onset of therapeutic action, non-immunogenic and are cost effective taking into consideration the effect of physicochemical properties such as pH, osmotic pressure and temperature (Aruguete *et l*., 2017).

Types of nanoparticles for drug delivery

Inorganic nanoparticles

Inorganic nanoparticles are those nanoparticles that are free of carbon in their composition and they are usually metal or metal oxides based. Metal oxide based nanoparticles such as iron oxides (magnetite (Fe_2O_4) and maghemite (Fe_2O_3) (Chertok *et al*., 2007), Aluminium oxide (Al_20_3), Silicon dioxide (SiO_2) Zinc oxide (Mishra *et al*., 2017) have been used as drug carriers for due to their biocompatibility and antimicrobial activity (Mukherjee *et al*., 2011).

Metallic Nanoparticles

These are nanoparticles with inherent intrinsic optical, supra magnetic and biological properties. These optical and supramagnetic potentials have been harnessed in micro systems such that they can be used for highly technical tests in medical devices which is very rapid with high volume and minimal cost (Ladj *et al*., 2013). Nanosized metals are within a size range of 1-100 nm. Their physicochemical properties and functionality have been optimised such that ligands such as sugars, peptide, protein and DNA can be linked to their surface (Bhatia, 2016). They have been used in biomedicine for the delivery of drugs and biosensors. Metallic nanoparticles like superparamagnetic iron oxide nanoparticles, zinc oxide nanoparticles, copper oxide nanoparticles, gold nanoparticles, titanium dioxide nanoparticles, gallium based nanoparticles which have been reported to have antibacterial activity, antiviral and antiparasitic activities (Aderibigbe *et al*., 2017; Mohamed *et al*., 2017).Gold and titanium dioxide nanoparticles also have been reported as resonance imaging contrast enhancers and anticancer agents carriers (Khanna *et al*., 2015)

Quantum dots

These are nanocrystals of few nanometres consisting of pure heavy metals or a mixture of metals. It is commonly composed of selenium or cadmium or a mixture of both. They are used both for *in vitro* biomedical labelling in complex media due to their photostability and fluorescent properties (Ladj *et al*., 2013).

Organic nanoparticles

Polymeric nanoparticles

These are solid colloidal nanoparticles made of biodegradable and biocompatible polymers and lipids (Mallakpour and Behranvand, 2016). They are in form of nanospheres or nanocapsules depending on the method of preparation. In nanocapsules, the drug is contained within the cavity surrounded by the polymer whereas in the nanosphere, the drug and the polymer are embedded in a drug polymer matrix (Muhamad and Selvakumaran 2014). Generally two polymers are used in preparation of polymeric nanoparticles, the naturally hydrophilic polymers (Proteins and polysaccharides) and the synthetic hydrophobic polymers which can either be pre-polmerized or polymerized. Natural polymers such as cellulose, starch, chitosan, carrageenan, alginates, xantham gum, gellan gum and pectins have been used as drug carriers due to their biodegradability, so also the synthetic ones which are synthesized from poly(lactide) (PLA) and its copolymers with glycolide, poly(lactic-*co*-glycolic acid) (PLGA) to give rise to poly (lactic acid) (PLA), poly (cyanoacrylates) (PACA), poly (acrylic acid), poly (anhydrides), poly(amides), poly (ortho esters), poly(ethylene glycol), and poly(vinyl alcohol) (PVA) , poly (isobutylcynoacrylate) (PIBCA), poly (ethylene oxide) (PEO), poly(å- caprolac- tone) (PCL) (Muhamad and Selvakumaran 2014; Álvarez-Paino *et al*., 2017). Polymeric nanoparticles have been used as carrier molecules to deliver antimicrobials with promising therapeutic results (Zhang *et al*., 2010).

Solid Lipid Nanoparticles (SLN)

These are nanoparticles which comprises of lipids that are solids at room temperature with a surfactant for emulsification. These lipids include fatty acids like triglycerides, steroids, partial glycerides and waxes. Surfactants that are commonly used as emulsifiers to stabilize lipid dispersion includes soybean lecithin, phosphatidylcholine, poloxamer 188, sodium cholate, and sodium glycocholate (Zhang *et al*., 2010). They are more stable with longer release time when compared to liposomes and are safer than polymeric liposomes (Naseri *et al*., 2015). SLN retains moisture in skin by preventing evaporation, this makes it useful in delivering pharmaceutical preparations meant for the skin due to its occlusive property (Zhang *et al*., 2010). Although large scale production of SLN is cheap, it has a major disadvantage of low loading rates because of the crystalline nature of the SLN (Naseri *et al*., 2015).

Dendrimer

These are "tree-like", highly branched cascade molecules, comprising of a central stem from which branches arise from due to chemical reactions. Recently, this nanomolecule has been used in drug delivery, and the drug is loaded into the dendrimer either by encapsulation, complexation, or conjugation at the end of each branch (Abbasi *et al*., 2014) like other nanoparticles, they have an advantage of increased

solubility and stability with low cytotoxicity. Increased addition of PEG to Poly (amido amine) PAMAM dendrimers decreases their toxicity (Lopez *et al*., 2009)

Liposomes

Liposomes are small size spherically shaped vescicles made up of phospholipids, cholesterol and nontoxic surfactants which are used as carrier systems to deliver both hydrophilic and hydrophobic drug (Alavi *et al*., 2017). Bangham in 1961 described liposomes as spherical vescicles quickly formed as a result of contact of phospholipids with water due to the bilayer nature of the lipids (Bangham *et al*., 1965). "Liposome" is derived from two Greek word "lipo" and "soma" meaning fat and body, respectively (Anwekar *et al*., 2011).

The spherical vesicles can be used as carriers to deliver drugs to target sites and these drug particles can either be encapsulated within the centre of the liposome (aqueous phase) or matrixed into the phospholipid bilayer. Advantages of liposomes includes carriers for both hydrophobic and hydrophilic drugs in one liposome, stability and prevents the decomposition of the drug. It reduces the toxicity of the drug and prevents exposure of sensitive tissue to toxic drugs and can be designed to release the drugs only at specific target site (Anwekar *et al*., 2011 ; Akbarzadeh *et al*., 2013). Despite this advantage, liposomes have short half-life, high production cost, leakage and fusion of encapsulated drug molecules and the covering phospholipid may undergo oxidation. Study of liposomes allows for improvement in drug delivery system and demonstrates its use in infectious diseases (Beaulac *et al*., 1998; Drulis-Kawa *et al*., 2009: Jung *et al*., 2015) and cancer (Malam *et al*., 2009) .

Structural contents of liposome

The two major structural components of liposomes are phospholipids and cholesterol. Glycerol containing phospholipids are the most commonly used phospholipids for liposome formulation. They represent greater than 50% of weight of lipids in biological membranes (Anwekar *et al*., 2011). These phospholipids include Phosphatidyl choline (Lecithin) (PC), Phosphatidyl ethanolamine (cephalin) (PE), Phosphatidyl serine (PS), Phosphatidyl inositol (PI) and Phosphatidyl Glycerol (PG)Phosphatidic acid. Cholesterol is incorporated in the phospholipid in a high ratio of 1:1 or 2:1 of cholesterol to phosphatidine choline with its hydroxyl group placed towards the aqueous phase and aliphatic chain placed parallel to the acyl chains in the centre of the phospholipid (Anwekar *et al*., 2011).

Classification of liposomes

Liposomes can be classified structurally using their size and number of lipid bilayers. (Akbarzadeh *et al*., 2013; Rani, 2013). They are classified as (1) Small unilamellar vesicles (SUV) (20 -100nm), (2)Medium sized unilamellar vesicles, (3) Unilamellar vesicles (UV) (this could be in all size ranges), (4) Large unilamellar vesicles of (>100nm) (LUV), (5) Multilamellar large vesicles (MLV) (> 0.005µm), (6) Giant unilamellar vesicles (GUV) (> 1µm), (7) Oligolamellar lamellar Vesicles (OLV) and (8) Multivescicular vesicles (MVV) (Rani, 2013).

By composition and application, liposomes are classified as

Conventional/Ordinary liposomes which are composed of negatively or neutral charged phospholipids and cholesterol only that can be easily phagocytosed by the reticulo endothelial system (RES) (Paliwal *et al*., 2015). The easy and fast removal of these liposomes from circulation by RES makes it possible to produce liposomes against parasites of the liver and spleen. Though the fast and early removal of the liposomes from circulation is a draw back as it makes them unable to be used to treat diseases for a long time (Storm and Crommelin, 1998).

P^H sensitive liposomes: These are liposomes made up of P^H sensitive lipid contents like cholesterol hemisuccinate (CHEMS), phosphatidyl ethanolamine (PE), oleic acid (OA) or dioleoylphosphatidyl ethanolamine (DOPE) (Karanth and Murthy, 2007). These vesicles fuse with cells and empty their contents into cytoplasm at low P^H, but are quickly recognized and removed by phagocytes of the RES. They addition of a hydrophilic polymer polyethylene glycol (PEG) increases their half-life and are of use in delivery of drugs in disease associated with low P^H conditions (Paliwal *et al*., 2015).

Stealth (Stearically stabilized) liposomes: They are produced to make up for the disadvantage of quick elimination of conventional liposomes from the circulation by attaching polyethylene glycol (PEG) covalently to the outer surface of the liposome. The hydrated components of the PEG provide a barrier between the liposome and cellular environment (Storm and Crommelin, 1998; Karanth and Murthy, 2007).

Immunoliposomes are liposomes with antibodies or antibody fragments which facilitate binding at target site to enable them to bypass the adenosine triphosphate binding cassette transport so as to be internalized by endocytosis where the drug can be deposited near the nucleus (Tomuleasa *et al*., 2014). This is important in overcoming resistance in cancer chemotherapy. PEG is usually added to it to prolong the lifespan of liposomes (Rani, 2013).

Cationic liposomes are made up of a positively charged lipid and a co or helper lipid like dioleoyl phosphatidyl ethanolamine (DOPE) and dioleoyl phosphatidylcholine (DOPC) (Rani, 2013). Interaction of the cationic lipid with DNA results in the formation of a cationic lipid DNA complex which provide protection and promote cellular internalization and expression of the condensed plasmid (Storm and Crommelin, 1998).

Fusogenic liposomes are liposomes made up of ultraviolet-inactivated Sendai virus and conventional liposomes. Fusogenic liposome targets the fusion mechanism of entry of the virus into the cell to deliver its content directly rather than depend on the been taken up by phagocytes of the RES as seen in the other liposomes. This has the advantage that it can cross with drugs into the cytoplasm or nucleus with minimal lysosomal enzyme interference. It is mostly used in the delivery of anticancer agents (Akbarzadeh *et al*., 2013)

Based on the method of preparation, liposomes can be classified as (1) single or oligolamellar vesicles made by reverse phase evaporation method (REV), (2) multilamellar large vesicles made by reverse phase evaporation method (MLV-REV), (3) vesicles produced from the dehydration rehydration method (DRV), (4) stable plurilamellar vesicles (SPLV) (5) frozen and thawed multilamellar vesicles (FAT-MLV) (6) vesicles prepared by extrusion techniques (VET) (7) vesicles prepared by fusion (FUV), (8) vesicles prepared by French pressure cell (extrusion) (FPV) (Akbarzadeh *et al*., 2013; Rani, 2013).

Calcium carbonate nanoparticles

Cockle shell is the waste by product derived from processing cockles or *anadara granosa*, a type of bivalve shellfish enjoyed as a delicacy in South East Asia (Mohamed et al., 2012). The main component of the cockle shell is calcium carbonate (Bharatham *et al*., 2014), an abundant biomaterial produced by a living organism which through biomedical engineering has been used as a source of biominerals for the treatment of bone lesions (Kiranda *et al*., 2018). Synthesis of calcium carbonate nanoparticles (Nurul Islam *et al*., 2013; Pan *et al*., 2018) has shown promising results in the delivery of antibiotics (Kamba *et al*., 2013; Isa *et al*., 2016).There are four different forms, namely armophous calcium carbonate (ACC), vaterite, aragonite and calcite (Bharatham *et al*., 2014), with vaterite been the least thermodynamically stable and most soluble (Ni and Ratner, 2008; Weiss *et al*., 2014). All the polymorphs are found in cockle shell with aragonite been the least abundant (Kamba *et al*., 2013). During synthesis, all the 4 forms are affected by variables of P^H and temperature with P^H been the most significant (Weiss *et al*., 2014). ACC phase is unstable and short-lived and serves as a precursor of crystal growth of the other polymorphs (Weiss *et al*., 2014) Vaterite, also known as μ-CaCO3 is the least common compared to aragonite and calcite because of its low thermodynamic stability. It can be converted to calcite and aragonite in aqueous solution (Ni and Ratner, 2008). Calcite is the most stable form of the four, it has a rhombohedral unit cell, found to form large single crystal cubic-like crystalline particles (Boyjoo *et al*., 2014). Aragonite is thermodynamically unstable and an important biomedical tool, due to its denser nature when compared to calcite. Among the four, aragonite has been deeply researched into because of its s high mechanical strength, biocompatibility and biodegradability. Aragonite can be synthesized and its surface characteristics modified to ensure efficient drug loading and delivery (Kamba *et al*., 2013; Jain *et al*., 2014; Declet *et al*., 2016; Isa *et al*., 2016; Saidykhan *et al*., 2016).

Summary of antimicrobial effect of nanoparticles

Gold nanoparticles have been used for treatment of experimental infections caused by *Corynebacterium pseudotuberculosis, Bacillus calmette Guerin, Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus, Bacillus subtilis, S. typhimurium DT104, and S. aureus* in recent years (Zhou *et al*., 2012; Mohamed *et al*., 2017; Shamaila *et al.*, 2016; Shareena Dasari *et al*., 2015; Payne *et al*., 2016). Results from the research showed excellent antibacterial effect of gold against these microorganisms. Similarly, gold nanoparticles capped with Kanamycin enhanced the antibacterial effect of kanamycin as reported by Payne *et al*., 2016). Loading antibiotics into silver nanoparticles resulted in synergistic effect of silver nanoparticles with antibiotics. None of the None of the silver nanoparticle-antibiotic combinations demonstrated antagonistic effect. (Smekalova *et al*., 2016). Commercially available zinc and titanium dioxide nanoparticles tested against biofilm producing methicillin-resistant staphylococcus aureus showed considerable antibacterial and antibiofilm activity (Jesline *et al*., 2015). Testing Escherichia *coli*, *Staphylococcus aureus* and *Enterococcus faecalis* with copper nanoparticles loaded with amino acid chelates showed a significant enhanced antimicrobial activity of the copper chelates (Dealba-Montero *et al*., 2017). PLGA-PLH-PEG nanoparticles demonstrated an increase in minimum inhibitory concentration against microorganisms when compared with PLGA-PEG nanoparticles loaded vancomycin or vancomycin alone (Aleksandar *et al*., 2012). Simeonova and Ivanova, (2017), reported that the antibacterial activity of ciprofloxacin- poly (butyl cyanoacrylate) nanoparticle combination was similar to that of ciprofloxacin alone. Nanoparticles increase the antimicrobial activity of antibiotics encapsulated in them and also reduces the amount of antibiotics required to inhibit micro organisms (Pavan Kumar Reddy *et al*., 2014; Nicolosi *et al*., 2015; Yegin *et al*., 2016; Shadzly, 2017; Xie *et al*., 2017; Severino *et al*., 2017). The synergistic activity of nanoparticles loaded with antibiotics is enhanced because some nanoparticles possess antibacterial activity (Pignatello *et al*., 2011 Aboutaleb *et al*., 2012 ; Winnicka *et al*., 2013; Vembu *et al*., 2015; Cheung Lam *et al*., 2016; Bartomeu et al., 2017;Gholami *et al*., 2017)

CONCLUSION

The unique characteristics of nanoparticles can be exploited in the treatment of bacterial infections where resistance have been developed against antibiotic drugs. The induction of oxidative stress in antibiotic resistant microorganisms which leads to its death has opened a new pathway in the treatment of bacterial

infections by nanoparticles whose causative agents have defied antibiotic treatment. The major problem with treatment in CLA is because antibiotics do not reach the organisms due to development of islets of infection walled away in pus, biofilm formation and the ability of *Corynebacterium pseudotuberculosis* to acquire resistance genes. Development of nanoparticles loaded with antibiotics may bring an end to the menace of antimicrobial resistance in the treatment of CLA therefore reducing the economic burden placed on livestock owners.

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