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ROLE OF NANOPARTICLES IN THE EFFICACY OF ANTIBIOTICS

[1]Muhammad Ukashah, [2]Bareera Ijaz, [3]Muhammad A. Riaz and [4]Muhammad K. Javed
[1]Department of Biotechnology University of Sargodha, Sargodha
[2]Center for Agriculture Biochemistry & Biotechnology University of Agriculture Faisalabad
[3]Center for Agriculture Biochemistry & Biotechnology University of Agriculture Faisalabad [4]Institute of Molecular Biology & Biotechnology Bahauddin Zakariya University Multan

Abstract: Now a day, the reason of greater mortality rate is due to bacterial diseases. The cure of bacterial diseases is the use of antibiotics but there is a problem that bacteria have become multidrug resistant and so antibiotics can't be used for treating bacterial diseases. A great revolution in this aspect is the use of nanoparticles. Nanoparticles can be made from different metals like gold, copper, zinc etc. The mode of action of nanoparticles is that they enter into the cell membrane of pathogen and affect their molecular pathways. Nanoparticles are used in combination with different drugs. The nanoparticles which have been extensively studied are silver nanoparticles. Experiments were performed of check the efficiency of silver nanoparticles in gram positive and gram negative bacteria. Silver nanoparticles were not used with the combination of any drug. Nanoparticles are stable for long time as they are surrounded by capping layers because of which they are stable for long time. Another important function of these capping layers is that they are also providing active surface area for the interaction with other biological components. Shortly, we can say that nanoparticles can be used as an alternative to antibiotics and they can serve us in better way.

Introduction: The term antibiotic is derived from the word "antibiosis" which means (against life). When we look on the definition of antibiotics these are defined as chemical compounds that can either kill or inhibit the growth of bacteria or other pathogens. These antibiotics can be antifungal, antibacterial or antiviral. However, in general terms the term antibiotic is used for antibacterial compounds. These antibiotics are used to treat bacterial disease. Their mode of action is to either interfere with DNA, RNA or protein of the host. The bacterial diseases are lethal as they can cause death. Recently, the greater mortality rate is due to bacterial diseases as due to the rapid use of these antibiotics the bacteria has developed resistance against these antibiotics. The main reason of resistance to antibiotics is horizontal gene transfer which is by means of biofilm creation, transformation, transduction or bacterial conjugation.

The complete removal of resistance is necessary in order to compete with bacterial diseases. Both gram positive and gram negative bacteria can create biofilms on medical apparatus. The bacteria related to human diseases are Enterococcus faecalis, Staphylococcus epidermidis, E.coli and many more other bacteria. The greater revolution in this aspect is the use of nanoparticles. These nanoparticles can be effectively used in the treatment of different bacterial and infectious diseases. The nanoparticles are metallic in nature and the metals used are gold, silver or zinc etc.

In order to inhibit the growth of pathogenic microbes the ions used are copper and cobalt. The complexes of metals are also used to inhibit growth of pathogens that can cause diseases. The nanoparticles are used in

combination with the different drugs in order to cure bacterial and other infectious diseases. The nanoparticles that are extensively studied are silver nanoparticles. In this review article we will study how nanoparticles are used in the treatment of different diseases as an alternative to antibiotics.

Antibiotic Resistance:

Antibiotics were first discovered by Sir Alexander Fleming in 1928. At that time the antibiotics were the only possible solution to treat different diseases. The first antibiotic discovered was "Penicillin". Later on, these drugs were extensively used and because of their extensive use the bacteria developed resistance to these drugs leading to higher mortality rate. Resistance genes were transferred to progeny in order to transfer resistance to next progeny. This type of resistance is known as "**acquired resistance**".

Another type of resistance is "**intrinsic resistance**". In this type of resistance the genetic traits don't depend on the exposure to antibiotic that was previously done. Resistance is the development of different molecules that are utilized when pathogen is exposed to any drug.

As the bacteria have developed multidrug resistance the pharmaceutical companies are not focusing greatly on the development of new antibiotics. Those bacteria that are multidrug resistant meaning when they are exposed to different antibiotics they show resistance and be killed, the bacteria of this type are known as "**Super bugs**".

More than 35000 people are subjected to death every year because of the multi drug resistant bacteria. This is an alarming situation as we have never won war against microorganisms. If we want to eliminate this situation we have to do something as soon as possible.

The alternative to this alarming situation is the use of Nanoparticles which can effectively eliminate this situation.

Mechanisms of Antibiotic Resistance:

Here we will discuss some of the mechanisms of antibiotic resistance. These mechanisms are divided into following categories.

- **Enzymatic Inhibition**:

This type of inhibition happens when the antibiotics that are used are being neutralized by bacteria before these drugs can perform their action. The antibiotics beta lactam is targeted at transpeptidase enzymes which are playing their role in the synthesis of cell walls by the breakage of amide bonds of the four members[1-3]. In case of gram negative bacteria the genes of beta lactamase are present inside the periplasmic space but in case of gram positive bacteria in them beta lactamase is excreted [4].

The genes of beta lactamase are present in transposons or plasmids that result in swift movement and the genetic material is conveyance to alternative bacteria. The additional changes to these genes of beta lactamase result in the systems that are for multidrug resistance that consist of sulphonamides, macrolides, aminoglycosides and chloramphenicol.

- **Target Site Alteration**:

The alteration of target site occurs when the product of target gene of antibiotics is changed and the interaction between the bacteria and drug is avoided. There are both 30S and 50S ribosomes which are the target for antibiotic [7-8].

Both of these ribosomes permit the changes and because of these changes permit the cells of bacteria of the maintain their homeostasis even during the presence of any antibiotic [10].

- **Alteration of a Metabolic Pathway**:

Sulphonamides are the example of inhibition which occurs in dihydropteroate synthase present in folic acid. Folic acid and nucleic acid can be synthesized by using PABA which confirms resistance in sulphonamide bacteria [12].

The antibacterial activity of antibiotic can be inhibited by activating PABA [14-15] ▪

Membrane Permeability Shifts:

The membrane of bacteria is made up of transport proteins, phospholipids and lipopolysaccharides. The hydrophobic antibiotics penetrate the membrane and then enters into the cell [15, 16]. When we change the penetrability of the membrane the arrangement of lipopolysaccharides is changed. If there is the expression of entire length of polysaccharides than the strains of bacteria show resistance to antibiotic [17, 15].

These strains which are resistant to antibiotic limit the penetration of the hydrophobic antibiotics.

Experimental:

The alternative to antibiotics is the use of metallic nanoparticles. Here we will discuss the preparation of nanoparticles through some examples.

- **Preparation of citrate capped gold nanoparticles**:

Take boiling solution of the $HAuCl_4.6H_2O$, distilled water and trisodium citrate because of this addition the color of solution gold chloride that was yellow than turned into wine red and show absorbance at 518nm at UV spectrum. The diameter of these nanoparticles is 12-15 nm.

- **Preparation of antibiotic coated gold nanoparticles**:

In the preparation of drug coated nanoparticles following steps are performed. The stabilized 0.1 mM citrate gold nanoparticles were mixed with $5cm^3$ of 3mM drugs in water and then stir them for 2h. Two different concentrations of gold particles 0.3mM and 0.5mM were prepared.

- **Preparation of Co nanoparticles**:

In order to prepare cobalt nanoparticles reduce a cobalt (2) salt by using a reducing agent hydrazine hydrate. Take 10 gram of cobalt chloride and dissolve it into 150ml of ethylene glycol and water and then stir the solution until it is dissolved completely. Adjust the Ph of the solution to 12 by adding NaOH solution. Than treat the solution of cobalt chloride with 50% of hydrazine hydrate.

After that centrifugation of reaction mixture is carried out. Than collect the black particles and wash it with water in order to remove chloride, sodium and hydrazine. Than dry the final product in oven at 60C.

- **Preparation of Silver nanoparticles**:

Take 1.2% of metallic silver and than stabilize it with 18.8% of PVP (polyvinyl chloride) in water. When observed on UV spectrum they show absorbance at 400nm. The shape of silver nanoparticles is sphere and diameter is 35 -15nm.

- **Preparation of ZnO nanoparticles**:

Take 0.2 gram of the CTAB and than add it into the bi-distilled water in a flask. Take 10mL of the $Zn(CH_3COO)_2.2H_2O$ was added into the solution. Than stir the solution at different conditions. Add NaOH drop wise and after that the solution turns milky. Than retain the solution for half hour and cool it, than centrifuge and dry it at room temperature and thanwash with methanol and water.

- **Bismuth based nanoparticles**:

Bismuth is a brittle and crystalline metal, and when we freeze this metal it expands. Its thermal conductivity is low than any other metal. This method of preparation of nanoparticles is cost effective and can be employed on industrial scale. These bismuth based nanoparticles are used in the treatment against different pathogens.

- **Gold based nanoparticles**:

The gold combinations can be used in the treatment of different diseases like juvenile arthritis, palindromic rheumatism, and rheumatic diseases [84]. Apparently gold nanoparticles have no antibacterial activity, Vidya et al. [85] synthesized and then functionalized in a process in which antibiotics of third generation are used and also of second generation.

Nanoparticles as Antimicrobial Agents:

The number of first line antibiotics is decreasing and the number of last line antibiotics is increasing in order to treat infectious diseases thus, decreasing the options of treatment for patients. Nanoparticles can be used in combination with the different antibiotic drugs. For example, silver nanoparticles used in combination with drugs can be used to overcome bacterial resistance.

When we observed the effect of silver nanoparticles used in combination with antibiotics like vancomycin, amoxicillin and erythromycin showed that this combination is effective only against gram positive bacteria [34]. Deng showed that when silver nanoparticles alone were used they resulted in antibacterial activity against Salmonella typhinium.

When the complex of tetracycline-silver nanoparticles were used it showed elevated drug action because of the accumulation of silver outside the cell and this inhibited the action of bacteria. Banoee and his colleagues when used zinc oxide it showed increased antibacterial activity against S.aureus and E.coli [36]. It was observed that if we use zinc oxide nanoparticles combined with nitrofurantoin and amoxicillin than antibacterial activity was decreased against S.aureus and E.coli. This combination with drugs not all the times the antibacterial activity is increased it can also be decreased depending on the drug and nanoparticles [36]. ▪

Mechanisms of drug resistance to antimicrobials:

These mechanisms are as follows:

- **Decreased Uptake**:

When drugs uptake is decreased than it does not allow the storage of drugs in cells to such level that is not effective for the killing of cells. Bacteria contain the resistance genes against specific antibiotics. For example, gram negative and gram positive bacteria possesses genes for tetracycline TetK, TetB, TetA. Under native conditions the TetA gene is repressed by its repressor gene TetR.

When tetracycline binds to TetR and then inactivates it and TetA is expressed. The TetA gene than flushes out tetracycline making the bacteria resistant to tetracycline. Other such examples of resistance are resistance against fluoroquinolones in gram negative bacteria and also the resistance against macrolide in gram positive bacteria [5]. Examples of less uptake of drugs include resistance against aminoglycoside in gram negative bacteria.

- **Alteration of Antimicrobial Target**:

In bacteria, resistance is also developed by expressing genes that codes for alternative version for antibiotic target. The wild type versions have more binding affinity than altered substrates so altered substrates can decrease the activity of antibiotics. For example, Staphylococcus aureus is resistant to methicillin. In case of PBP2A and PBP the beta lactam has low binding affinity and mccA confers resistance against beta lactams [5, 38, and 39].

The resistance against glycopeptides is conferred by gene vanA which is involved in the expression of enzyme known as D-alanine D-lactate ligase. The peptidoglycan precursor D-ala-D-ala is converted into D-ala-Dlactate by this enzyme. The wild type version of this precursor is 1000 times greater than this modified precursor and thus showing resistance towards vancomycin [5 , 40]. Other examples are sulfonamide resistance in E.coli, resistance in gram positive and gram negative bacteria against quinolones [5, 41].

- **Modification of Antimicrobial Drugs**:

Bacteria also has resistance genes that code for enzymes that modify antibiotic. For example, the acetylation of NH_2 group of aminoglycoside is catalyzed by ACT N-acetyltransferase, the phosphorylation of OH group of aminoglycoside catalyzed by APH O-phosphotransferase, the adenylation of OH group of aminoglycoside catalyzed by ANT O-adenyltransferase. In all these cases it is observed that due to modification the affinity of antibiotics is reduced, the antimicrobial activity is also reduced by 30S ribosomal subunit. The development of chloramphenicol resistance is done by inactivation of chloramphenicol by acetyltransferases.

- **Production of Competitive Inhibitor:**

A competitive inhibitor is also produced to develop antibiotic resistance. For example, species like S.aureus and N.meningitides both produce enhanced concentration of PABA that is involved in competition with sulfonamide for its target that is dihydropteroate synthetase and thus developing resistance against sulfonamide drugs.

- **Persister Cells:**

When small number of bacteria slow down their metabolic activity when they express toxin-antitoxin and then they become more tolerant towards antimicrobial drug. Such type of cells is known as persister cells. When bacterial population is exposed to antibiotics than most of the bacteria are killed leaving behind the persisters. When the metabolic activity of persisters is resumed than the chances of reoccurrence of infection are there [5, 36].

- **Biofilm Formation**:

When the bacterial cells attach to medical implants and human tissues than they immobilize themselves. Due to the presence of extracellular polymeric substance around the bacterial cells the treatment of infections that are associated with biofilm are difficult to treat. This EPS matrix is resistant towards many antibiotics thus causing chronic infections in humans [5, 43]. The barrier between bacterial cells and antibiotics is caused by this EPS matrix.

The molecules that have greater size than a certain size, also including antibiotics, are unable to pass through this EPS matrix. In case of antibiotics because of their negative charge they are also trapped into EPS matrix. In EPS matrix certain enzymes are present that reduces the affinity of antibiotics. If the concentration of antibiotics below their MIC value than EPS matrix also develops resistance in bacteria [5, 44].

- **Swarming**:

In case of bacteria the multicellularity observed is known as swarming. This situation occurs when on semisolid surfaces the swarm cells come together as a single unit. In case of planktonic cells they are elongated and then develop multiple flagella. The swarm cells migrate with each other like raft. These swarm cells are resistant towards several antibiotics. When we culture the swarm cells in a liquid media they restore their susceptibility towards antibiotics [5, 38].

- **Intracellular Microbes**:

As the drugs have limited affinity to enter into the bacterial cells so, when the intracellular microbes are inside the host cells they are protected [5].

- **Factors which affect antimicrobial activity:**

Size:

The size of nanoparticles is important in this aspect that this determine the degree of penetration of nanoparticles in the bacterial cell wall. This has direct correlation with the degree to which the nanoparticles penetrate into the cell wall. The mechanism of action through which the nanoparticles adhere to the surface of cell wall also depends on the type of nanoparticles being used.

The nanoparticles of size 50nm can penetrate beyond the cell wall and can also target the DNA that is present inside the cell. Morones and his colleagues observed that the silver nanoparticles having the size 10nm have the ability to penetrate bacteria and showed antimicrobial action [66]. Hsueh and his colleagues reported the activity of silver nanoparticles against Bacillus subtilis [51].

Besides the size, the morphology of nanoparticles is also important in their affectivity. Sadeghi and his reporters showed the activity of silver nanoparticles against S.aureus and E.coli [67]. They also observed that regardless of shape the activity of nanoparticles can be achieved. So, this one showing that morphology is not playing an important role in the activity of nanoparticles [67].

Zeta potential:

Zeta potential is also important in the antimicrobial activity of nanoparticles. Zeta potential determines the interaction of nanoparticles with the surface of bacterial cell wall [68]. Zeta potential also determines that how nanoparticles can be used as drug carriers. This zeta potential also determines the pharmacokinetic behavior of the nanoparticles, it is important because of the ph changes that occur inside the body that can affect the charge of nanoparticles.

In case of bacteria, this zeta potential determines that how much associations and repulsions occur between the bacterial cell and the nanoparticles [69]. In case of gram positive bacteria teichoic acid is present on the cell surface and inn case of gram negative bacteria, lipopolysaccharides are present on the cell surface [9]. These components present on the surface of cell affect the stability of nanoparticles. As in case gram negative bacteria most of the cell surface is covered with LPS which gives negative charge to the surface. This negative charge explains that why nanoparticles rather than penetrating the prokaryotic cell they accumulate on their surface [71]. In case of bacteria that are susceptible to antibiotic the antibiotics like aminoglycosides which are lipid soluble they can easily penetrate.

In case of MDR bacteria the composition of cell wall is changed in order to prevent the entry of antibiotics inside the cell wall [73]. Due to opposite charges the nanoparticles remain on the surface of cell wall [75].

Pharmacokinetic And pharmacodynamic Characteristics Of Nanoparticles:

The pharmacokinetics of nanoparticles depend on different factors like surface charge, size, surface coating, exposure route, animal species and dose. Their comprehensive study of these factors is important for biosafety and risk assessment in clinical practice [Lin et al, 20150]. Most of the nanoparticles are distributed into spleen and liver but silver nanoparticles can be modified to enhance the distribution of these nanoparticles towards the specific organ [Lin et al, 2015].

- **Dose Optimization**:

The optimum dose is very important for treating any disease and minimizing the toxic effects of the drugs [Khan et al., 2016; Hua et al., 2018]. The dose of nanoparticles to kill the cell is very high and we can't apply this higher dose to humans. The data that we collect from animal studies cannot be applied directly to humans [Khan et al., 2016; Hua et al., 2018]. Experiments are being applied on adult volunteers to observe which dose is effective in treatment and these studies are continue.

- **Clearance and Elimination**;

Nanoparticles can be long term accumulated in the spleen and liver [Lin et al, 2015]. Nanoparticles are not biodegradable and they can accumulate into tissues for long time [Zaidi et al., 2017]. A greater accumulation of nanoparticles has been observed in the kidneys but the reason for this accumulation was that less number of large nanoparticles were present as their greater concentration was accumulated in liver and spleen [Hoshyar et al., 2016].

- **Toxicity:**

In terms of toxicity the nanoparticles themselves and their degradation products cause toxicity as they cause hemolysis and also interfere with coagulation pathways of blood [Kandi and Kandi., 2015]. The toxic complications that are caused by nanoparticles, their exact mechanism is unknown but it is observed that large size of nanoparticles is the cause of toxicity [Dos Santos et al., 2014].

When the toxicity of nanoparticles is studied, the extensive study is performed on silver nanoparticles and these nanoparticles have proven to be more toxic against cells [Bondarenko et al., 2013; lvask et al., 2014]. The accumulation of silver nanoparticles in lungs, liver and spleen and in other organs result in the damage of organs and their loss of function [Hemeg, 2017].

These nanoparticles can also be accumulated in bone marrow, lymphatic system, liver and spleen [Hagens et al., 2007] and also their inhalation may cause cytotoxicity in the organs like lungs [Leucuta, 2013]. No life threatening toxicity is caused by nanoparticles [Pfurtscheller et al, 2014; Sengupta et al, 2014; Wei et al, 2015;

Zazo et al, 2016].The evaluation of toxicity is important for clinical practices and in order to check any therapeutic effect [Khan et al, 2016].

- **Targeted antibiotic therapies**:

The infection site of bacteria is rich in molecular and physiological cues that are useful in the release of drug and also support the attachment of nanoparticles to bacteria. There are three ways for targeted drug delivery which are physical-chemical gradients, Passive targeting and active targeting. [71,72]In case of passive targeting there is dysfunctional lymphatic drainage and also enhanced permeability and these changes occur at infection site.

At the surface of gram negative bacteria, the negative charge is present and that negative charge can be used to affect target site but some bacteria can resist this by secreting acetic acid and lactic acid.[82] In order to overcome this problem, many groups have developed micelles in order to switch charge and also the nanoparticles that affect the cell wall that has negative charge.[83,84]

A ph sensitive polymer that is zwitterion is used that can slow down the growth of S.aureus and E.coli at low ph.[85] In order to synthesize nanoparticles and the micelles that can switch the charge this includes beta-amino ester,[86] poly-L-histidine,[84] and many other chemical functionalities.[87]

Nanoparticles can be used to treat bacterial infections in stomach but the challenge in this aspect is that to develop nanoparticles that can work at various ph values in gastrointestinal tract. In addition to problems of ph gradients and negative charge, the bacteria can also secrete several virulence factors like collagen adhesions, toxins, fibronectin and many enzymes.[97] The simplest way to target the infection site is to dope the surface of delivery vehicle with antibody.

If the bacteria either facultative or obligate escapes the site of infection than the chances of reoccurrence of this infection increases. It is now observed that bacteria can escape by hiding in the phagocytic cells, osteoblasts and erythrocytes.[9] The role of these pathogens is that they disrupt the microbicidal mechanism of phagocytic cells by interfering with the fusion of phagosomes with lysosomes thus increasing the duration of their survival.[102]

Many of the pathogenic bacteria have been discovered who can perform this function and their examples are B.pseuomallei. S.aureus, M.tubercolosis.[10] The cytoplasm of mammalian cells is used by the pathogens to exchange resistance and virulent genes.[103] When a macrophage is infected, than in next step the intracellular pathogen is targeted. Xiong et al,[20] the optimum activity of any antibiotic against any cell which is infected by bacteria is dependent on the quantity of active drug inside the subcellular compartments, which in turn depends on the activity, subcellular distribution and cellular retention.

One method to achieve this is to distribute this antibiotic to infection site or to cell should be through biodegradable vehicle. Many biodegradable delivery systems consist of synthetic or natural polymers like CS[78] and albumin can be used for this purpose. The major infection site is found in liver and spleen. Outside the liver and spleen the macrophages that are infected by bacteria are also present in pulmonary cavities.[112] The intake of antibiotic by infected macrophages depends on concentration and size of delivery vehicles and the amount of macrophages present at the site of infection.

- **Vaccination Vehicles**:

The large surface area of nanoparticles can be used for the killing of bacteria and also capturing bacterial toxins. A simple solution for the removal of active toxins is to use nanosponges and erythrocyte membrane coated polymer nanoparticles. Gold nanoparticles have adjuvant activities and can be used for the development of antibacterial vaccines. Gold nanoparticles also have the ability to distribute bacterial antigens.

However, now a days such investigations can be conducted by using cheaper biodegradable polymer nanoparticles. Adjuvants can be used incorporation with polymer nanoparticle. Such ways have proven successful in the treatment TB. BCG vaccination is also used for TB and anti-TB protectin is inferior to

BCG.[166] A single dose of antigen vaccine is not sufficient for the treatment of TB. For example, there are three mycobacterial antigens which are Ag85B, MPT-64 and MPT-83 were placed onto PLGA nanoparticles and then introduced into mice through injection. After this injection the increased humoral and cellular responses were produced.

Conclusion:

This review article is aimed to provide detailed study on the role of nanoparticles in the efficacy of antibiotics. As bacteria are widely available on earth and they are available in different life forms. Bacterial population is important for our survival as they are involved in many processes and at the same time they are lethal for us as they can cause harm to us by causing many diseases. For centuries, thousands of humans have been died due to epidemics.

Than studies lead to the discovery of antibiotics and first antibiotic was discovered by Alexender Fleming known as Penicillin. The antibiotics saved human life for many years but due to increased and repeated use of antibiotics the bacteria developed resistance towards these antibiotics. In the treatment of bacterial diseases the antibiotics are of no more use as bacteria are tolerant towards several antibiotics.

In this situation when bacterial diseases are common and their sole treatment antibiotics are not effective than we require an alternative and the revolution in this aspect is nanoparticles. The nanoparticles are small metal particles that are tested to be effective in the treatment of many microbial infections. We have provided detailed study on the use of nanoparticles in the efficacy of nanoparticles and in future these nanoparticles will serve more functions and their efficiency will be enhanced soon.

- **Data Availability**:

The data that is used in this review article is provided by the relevant authors on request.

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Mohammadd Farhan Khan1,2, Akhter H. Ansari1, M. Hameedullah1, Ejaz Ahmad3,Fohad Mabood Husain4,5, Qamar Zia6,7, Umair Baig8, Mohd Rehan Zaheer2, Mohammad Mezbaul Alam9, Abu Mustafa Khan10, Zeid A. AlOthman9, Iqbal Ahmad4, Ghulam Md Ashraf11 & Gjumrakch Aliev12,13,14

Vo Van Giau Seong Soo A An John Hulme Department of Bionano Technology, Gachon Bionano Research Institute, Gachon University, Seongnam-si, Gyeonggi-do, South Korea.

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Alka Hasani1 · Masoumeh Madhi2 · Pourya Gholizadeh1 · Javid Shahbazi Mojarrad3 · Mohammad Ahangarzadeh Rezaee4 · Gholamreza Zarrini5 · Hossein Samadi Kafil6.

R. Vazquez-Muñoz 1,2☯, A. Meza-Villezcas1,2☯, P. G. J. Fournier2, E. Soria-Castro3, K. Juarez-Moreno 1, A. L. Gallego-Herna´ndez4, N. Bogdanchikova1, R. Vazquez-Duhalt1, A. HuertaSaquero

Madhuree Kumari, Shipra Pandey, Ved Prakash Giri, Arpita Bhattacharya, Richa Shukla, Aradhana Mishra, C.S. Nautiyal.

Bizhan Malaekeh-Nikouei a, Bibi Sedigheh Fazly Bazzaz b,c, Elaheh Mirhadi a, Amineh Sadat Tajani d, Bahman Khameneh .

Mayur Kumar, Anthony Curtis and Clare Hoskins * School of Pharmacy, Institute of Science and Technology for Medicine, Keele University,

Keele, Staffordshire ST5 6DB, UK; w2v11@students.keele.ac.uk (M.K.); a.d.m.curtis@keele.ac.uk (A.C.)

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