WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 15, Issue 2, 379-394. Review Article ISSN 2277–7105

SELF-SERUM CAPPED SILVER NANOPARTICLES: ULTIMATE SAFE VERSION FOR THERRAPEUTIC USE IN SEPSIS AND CANCER WITHOUT ENVIRONMENTAL RISK

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Article Received on 15 Dec. 2025,
Article Revised on 05 Jan. 2026,
Article Published on 16 Jan. 2026,
https://doi.org/10.5281/zenodo.18264446

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How to cite this Article: Maiti Prasanta Kumar* (2026). Self-Serum Capped Silver Nanoparticles: Ultimate Safe Version For Therrapeutic Use In Sepsis And Cancer Without Environmental Risk. World Journal of Pharmaceutical Research, 15(2), 379–394.

ABSTRACT

At present two major problems of modern-medicine are management of drug refractory sepsis and cancers. As an alternative, colloidal nanomedicines have proved highly promising for cytotoxicity on any microbes or cancers by all theory-testing, but are kept in abeyance for clinical applications due to unacceptable toxicity risk on some host cells and most of environmental microbes. Filling many research-gaps, high-precision self-serum capped silver nanoparticles have brought new ray of hope, being small but wide cluster range colloidal particles with compatible range of surface charge for suspending cellular particles in blood and identical molecular signs on surface-cap. These can more precisely encounter high anionic invader microbes and cancer cells by high attractive charge affinity, particularly on narrow contact-points of ion-diffusible tuneable caps, according to rule of physics. High anionic nanoparticles in blood, take time to transform into low anionic serum compatibility after corona-like protein deposition on surface. So, they repel target cells but can encounter many host cells on the way, including RBC and endothelial cells, while larger nanoparticles are restricted to enter into bacteria, though clathrin-mediated endocytosis is possible in eukaryotic cells. For molecular-sign differences, non-serum capped nanoparticles may endocytose into many host-cells and microbes. As personalised nanomedicine has no chance of massive spillage, are safe for environment. In this review, scopes and limitations of such novel class nanoparticles have been discussed from therapeutic point of view.

KEYWORDS: Colloidal silver-nanoparticles, Serum capped-nano, Nonspecific Anti-microbial, Mechanism of internalisation, Safe systemic drug, Personalised medicine.

1. INTRODUCTION

1.1. Viewpoint on topic

In view of alarming forecast about high tide of super-bug insurgence.[1-3] due to irrational use of antimicrobial drugs in medical, veterinary, agriculture and fisheries, search for resistance-proof non-conventional potent antimicrobials is gaining importance.[4-7] High promising colloidal nanomedicine as ultra-small, physical-force guided target delivery agent for a payload of several thousand pan-cytotoxic heavy metal ions, are researched to increase precision with top priority for host and environmental safety.[8,9] As "holy-water" silver-nitrate is known to use as long as 2000 years back. Of known heavy-metal antimicrobials, this being only mono-valent agent, is easy to reduce by many harmless organic components, thus has become popular for nano synthesis. Engineered nanoparticles (NPs) are increasingly used recently in various fields including health sectors, exploiting advantages of unique materialistic state.[10,11] Estimated annual global production of AgNPs in 2020 has reached more than 500 tonnes for various purpose of applications that led to accumulation in soil and water bodies to alarming level.[12] Colloidal AgNPs, being most promising resistance-proof omnipotent antimicrobial and anti-cancer agents, have been tested for prospective therapeutic uses. In spite of high efficacy by in-vitro studies, for unacceptable risks to host and environment, none are qualified as intra-venous usable approved drug to combat two major causes of drug-failure deaths in modern medicine e.g. septicaemia and cancers. Yet, scientists are optimistic to develop high precision NPs by filling known research gaps.

1.2. Prospective nano-antimicrobials

Common therapeutic usable NPs are classified as; 1) Inorganic heavy metal or metallic oxide NPs in colloid or crystalloid form e.g. silver, gold, copper, iron, silicon, cobalt, zinc NPs. Some aqueous solution of metal salts are known cytotoxic antimicrobial agents and their nano materialistic state as suspending nano sized colloidal particles, exhibit very potent cytocidal action by transporting huge bulk of toxic atoms into encountered cells.[13] Such NPs may come-out as systemic usable omnipotent drugs, if are made reasonably safe for host cells and leave no scope for targeting environmental microbes; 2) Nanofibers / Carbon-based NPs e.g. carbon nanotubes (f-CNT conjugated with Amphotericin B). Here, NPs in conditionalized state act as carriers for selected conventional drug molecules, thereby a

narrow spectrum of antimicrobial action is expressed with marginal benefit of reduced toxicity. Thus, antifungal activity of Amphotericin B (AMB), AMB-Deoxycholate and f-CNT conjugated AMB have been demonstrated comparable or slight better result with nano-conjugate[14]; 3) Organic NPs e.g. liposome[15] / dendrimers / micelles carried NPs. For larger size, these may not be suitable for internalisation into bacteria. They may carry some contra-indicated toxic NPs including cationic NPs e.g. poly-ethylene-imine stabilized AgNPs bearing positive surface charge (~ +55 mV zeta potential), to cancer cells or few larger microbes, so long ensures host safety.

1.3. *Next-generation Nano-antimicrobials*

Understanding scientific basis, suitably engineered high precision target-acting colloidal silver nanoparticles (AgNPs) can be prepared as a prospective novel drug.[16] For that purpose, some ready solutions have been applied for filling the following research gaps: 1) Optimization of hemocompatibility by using same serum as primary capping agent, so that alterations of size and surface charge after further corona-protein capping.[17] cannot happen in blood; 2) Surface-charge optimization to a closer anionic level, as that of normal colloidal cellular particles of blood, has been possible after synthesizing NPs in same serum medium; 3) Using cocktail of compatible capping components present in serum at different concentrations, wide cluster-range, surface-charge tuneable smaller NPs can be obtained those may allow target-cell internalization, both in prokaryotes and eukaryotes; 4) Applying physical forces (both mechanical and electrostatic forces) for instant affinity attachment to maximal target cells in a strategic manner; 5) Designing surface molecular signatures, identical for host cells but recognisable foreign markers in invader microbes or neoplastic target cells; 6) Restricting excess availability of personalised medicine, for spillage into environment; 7) Developing minimal dosage schedule of NPs with synergistic use of conventional medicines; 8) Eliminating chance of adverse reaction to host from surplus capping or reducing components, being self-serum components. No other plant or animal source as capping and / or reducing agent can be better “green synthetic agent” than self-serum.

1.4. Total range antimicrobial action of colloidal AgNPs

Any agent capable of delivering a bulk of cytotoxic agent to contracted cells can be suitably designed for killing any Gram positive, Gram negative or acid-fast bacteria, fungi or parasites in blood. Colloidal AgNPs have been successfully tested in-vitro against all such microbes,

irrespective of their resistance status to conventional drugs by different multi-targeted actions.[18-23] Time has come to repeat same test with haemo-compatible safe AgNPs to remove ban for earlier nano-preparations, justifying those will not disturb normal functions of host by diffusion of toxic end-products into circulation. Particular attentions are to be given for assessing effect on RBC for haemolysis[24] with release of toxic-products, those may effect adversely on rapidly regenerating cells like haemopoietic cells, reproductive cells and mucosal cells.

The antiviral role of NPs may be restricted, because cytotoxic mechanisms of action can't be attributed for nano size acellular particles. Smaller NPs can target viral envelop or attach to viral receptors and internalised indirectly into viral infected cells, thereby inhibit viral replication. In-vitro tests indicate such possibility against many infective viruses, including HIV, Covid-19, Ebola etc.[25-27]

1.5. Additional Anti-cancer role of nanoparticles

Because drug part of AgNP is pan-cytotoxic Ag atoms, apart from anti-microbial role same can be used as non-specific anticancer agent.[28] Surface charge of cancer cells is high anionic (-55mV) than that of originator cells due to higher rate of glycolysis with shifting of intra-tumour pH to high acidic level up-to 5.5.[29-30] This may be one reason for greater affinity for low anionic intra-venous usable safe nanoproducts. Apart from this, cancer cells are studded with different signature molecules on surface which may be responsible for higher chance of clathrin mediated receptor-ligand based particle endocytosis. Though other mechanisms of action, including immune-modulation are considered, personalised nanomedicine has scope of synergistic use in future against solid tumours as well as blood cancers. In each blood-circulation cycle, fixed solid tumour has lesser chance of target attachment of NPs compared with blood-cancers. Due to renal and biliary clearances from circulation, bio-availability for solid tumours will decrease with time and may require more NPs in proportion with target cell number. Intra-tumour injections may enhance their bio-availability.

2. Current development

2.1. Matched serum how useful for developing ideal systemic usable nanoproduct

Chemical reduction method is preferred for preparing heavy-metal based colloidal nanoparticles, those can be best adopted in destine blood-stream, another perfect colloidal mixture. Human blood is well buffered alkaline (primarily bicarbonate in carbonic acid buffer system maintain blood pH 7.35 to 7.45) fluid containing optimized ~ -14 mV surface charge

bearing cellular components with acellular component containing water, electrolytes, nutrients, vitamins, minerals, metabolites, enzymes and plasma proteins. Thus, it has become rich source of reducing substances like Dextrose (~ 100 mg/ dL or 5.6 mM), Uric Acid 200-400 µM, Ascorbic Acid 50-60 µM, traces of Lipoic Acid, Amino Acids, Vitamin E, Glutathione etc. It has been observed that reducing contents of plasma / serum are sufficient for reduction of 1 mM effective concentration of $AgNO_3$ solution in blood alkaline pH. Such reduction process can be performed at permissible lower temperature, that will not denature capping protein components. Almost all protein components of plasma can participate as capping agents of AgNPs.[31] When those are used as primary capping agents, initially high abundant components like albumin, fibrinogen form outer coat on naked clusters of reduced metal ions with incorporated electrolytes from suspending fluid, to impart colloidal state with mutual repelling surface charge. Gradually minor components with higher affinity like immunoglobulins are incorporated into outer flexi-layer of stable nanoparticles. Former being nonspecific marker for individual host, makes safer for same host but when armed with different blood-group antibodies or organ-specific hetero-antibodies may be hostile for mis-matched signature immunoglobulin in serum of random doners. So, for therapeutic purpose, only matched serum capped NPs are recommended.

When stable colloidal NPs are formed using polymeric surfactant molecules or green biomolecules as capping agents, usually products become higher anionic (> -30 mV) with non-identical signature molecules and unpredicted amount of adverse organic substances. So, various plant extracts containing flavonoid group of reducing substances along with protein contents have been tried to develop nanoproducts for surface applications at lower cost, ignoring environmental risk by heavy-metal end-products. Those are if used by intravenous route to mitigate septicaemia by multi-drug-resistant microbes (MDR), may target both host cells and invader eukaryotes by receptor-ligand based endocytosis until secondary “corona-protein caps” are formed in circulation. Initially soft-corona like deposit is formed within 10 to 30 minutes, then stable hard corona is formed within 3 hours.[31] Due to charge dependent instant attachment of NPs to target cells, many host cells are vulnerable during the “window-period”, including early encountered cells like erythrocytes and vascular endothelial cells. Nano transformation by acquiring secondary plasma protein capping in circulation not only increases their size but also reduces bio-efficacy. So, those are restrictedly used for surface wound management, device capping or sanitization purposes.

2.2. *Factors modulating efficacy of nano-products*

At the formative stage, concentrations of capping agent regulate core size of colloidal NPs (represents volume of pay-load toxic metal ions by electron microscopy imaging) by prompt adherence of charge stabilizing surfactant molecules and ions as outer flexi-layer to maintain charge-stable colloidal state at the suspension fluid.[32] So, single capping agent if added in bulk to metal reduction mixture, generates wide cluster range of similarly capped nanoproduct due to gradual declining concentrations during formative stage. If same is used in small fractions with continual stirring, yield will be mostly of uniform size. When a cocktail of capping agents at different concentrations of different serum proteins is used rapidly in stirring condition, can generate different cluster size range nanoproducts, but capping component-wise little different according to sequence of declining concentrations of individual components. Their size and shape may differ, not the surface charge. So, it is expected that AgNP-serum-18 prepared[16] by mixing human serum with 2mM silver nitrate solution and 4 mM dextrose solution at ratio 1:1:2 (v:v); if modified by dropping dextrose part, available serum concentration in mixture will increase to double, hence average size of nano-product will attain half with greater bio-efficacy for same total metal ions. Rationale of omitting dextrose is that, human serum normally contains average 5.6 mM dextrose along with many other reducing components, which are enough for reduction of 1 mM effective concentration $AgNO_3$ in buffered alkaline serum.

As charge-sign dependant affinity-based target attachment is instant phenomenon according to rule of physics[33-35], while ROS mediated cell toxicity manifest through cascade of chemical reactions, appear as late outcome. Scientists have demonstrated bacterial killing of NPs[36] by two phases; a rapid killing phase within $5\pm$ 30 minutes during rapid membrane disintegration of charge neutralisation process, followed by late-killing phase at 1 ± 4 hours due to reactive oxygen species (ROS) mediated programme cell death (PCD). So, intravenous used high anionic AgNPs have chance to encounter different healthy cells during “window period” of secondary corona protein capping. May be for such reason, relatively safe bovine serum albumin treated 80 nm citrate capped AgNPs[37] have also failed to be safe approved drug.

During in-vitro cytotoxicity studies for different nanoproducts, many workers in earlier time have failed to consider importance of nano-product alterations in test medium by presence of potential high affinity capping components, electrolytes, oxidants, pH and light exposure.

Many microbial culture media and all tissue-culture media contain such potential capping agents, so efficacy and safety assessment results have not been reflected correctly. In case of studies in liquid medium, importance of charge sign and molecular sign-based target affinity along with changing van dar Waals attractive force in turbulent fluid as expressed by DVLO (Derjaguin-Landau-Verwey-Overbeek) theory, has not been considered for knowledge-gap at that time. So, sometimes internalisation of much larger anionic NPs for ion-channel limits of bacteria[38] has been wrongly considered as membrane disintegration phenomenon like cationic NPs or a receptor-ligand based endocytosis mechanism,[39] which is restricted to eukaryotic cells, only for larger (optimum 25 nM) particle sizes. However, in the light of present knowledge, right observations of bacterial membrane disruption in electron microscopic imaging can be explained. (Fig. I)

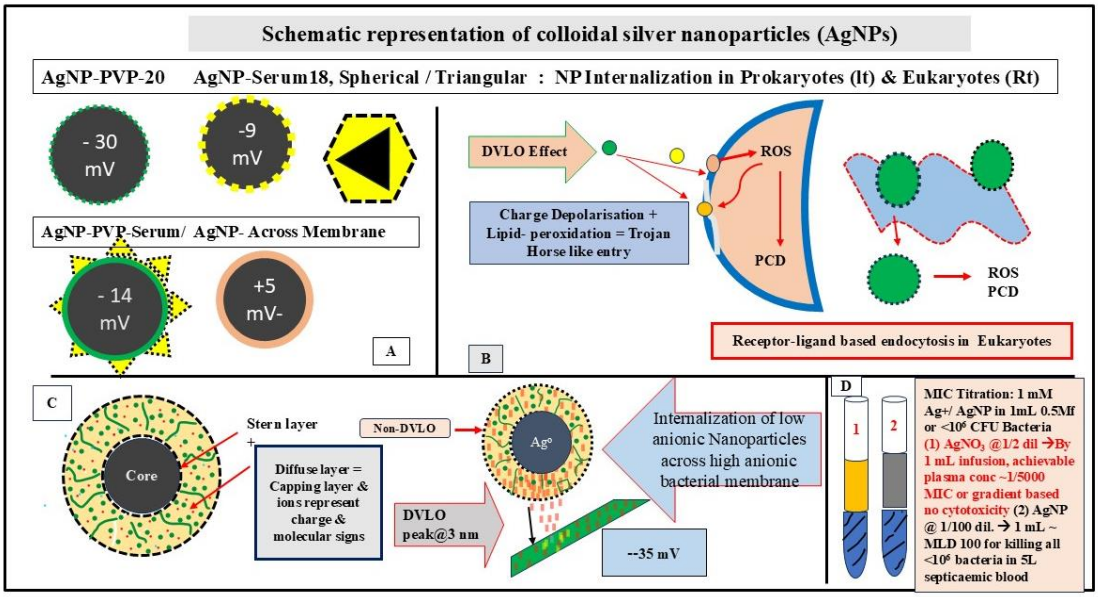

Figure: I. Structural characteristics of colloidal silver nanoparticles & Mechanism of internalisation into Target cells: [A] Schematic structures of various colloidal silver nanoparticles (AgNPs) with primary capping or secondary corona-protein cap and charge sign alteration during membrane depolarisation; [B] AgNPs internalization by bacterial membrane disintegration, initially by charge diffusion from outside followed by ROS mediated lipid membrane peroxidation from inside. Internalization into eukaryotic cell by receptor-ligand based endocytosis shown in right; [C] Structural details of AgNPs with alteration by physical forces; [D] Mathematical example of in-vitro and in-vivo dose requirements of AgNPs for killing target number bacterial cells.

Attachment of two charge-repelling colloidal particles is only possible by influence of three dimensionally acting electro-magnetic forces of adjacent particles facilized by non-DVLO mechanical forces, like fluid turbulence from different directions or motility of microbe itself. So, probability of collision between such particles is condition dependent and DVLO effect is initiated when particles having charge tuneable outer layer reach to as close as 10 nm to attain peak attraction by accelerated van dar Waals force, reaching maximum nearly at 3nm distance.[40-42] This is comparable with charge neutralisation phenomenon of thundering cloud by nearby sharp points of lightning conductors.

That is why, results of bacterial susceptibility tests for NPs by broth dilution methods are more reliable and reproducible method than that of agar diffusion method. Even results of broth dilution method with all identical test conditions without thorough mixing nano and bacterial emulsion, may vary due to non-homogenous attachments by instant charge affinity. Similarly, during nanomedicine infusion into blood, optimum result is expected following slow injection for about 10 minutes or one cycle-time of blood flow in man. Same is not applicable for control study with equivalent silver ions, where competitive consumption principle is not active. From pharmaco-kinetic point of view, Ag+ will be uniformly diluted in about 5L of blood in adult person, then according to gradient can reach to cell through ion-channel influx, while same payload carrying AgNPs, each carrying about one to ten thousand Ag+ will attach to a few target cells by charge-affinity, creating high local surface gradient for internalization.

Though, predictive bio-efficacy depends on achievable plasma concentration in respect of MIC level of diffusible organic or inorganic drugs, paradoxically, MIC of prepared nano-product only indicates maximal killing number of microbes challenged with test particles in titrated suspension. In standard broth dilution method about 10^5 to 10^6 viable bacteria per mL is challenged, those are present in 0.5 McFurland (Mf) turbid bacterial emulsion. An adult usually contains 10 to 100 such bacteria per mL in bacteraemia or total number < 10^5 in 5L blood, so undiluted 1 mL nanoproduct will be theoretically enough for treatment, which often represents > 100 MIC nanoproduct. For chance of non-uniform attachment on target cell by competitive consumption, we recommend total dose 5-10 mL infusion of safe AgNPs as single or several mop-up dosages. That can be prepared using 2.5 – 5 mL homologous serum obtainable without creating appreciable risk for doner.

Another paradox of nano efficacy on target cell is dependent on surface: volume ratio. According to concentrations or chain length of polymeric surfactant capping molecules, core size of colloidal NPs varies, not respective surface charge. Core represents payload of carrier drug which follows rule of chemistry while target affinity forces are predominantly driven by rule of physics from surface. Thus, one 50 nM AgNP-PVP carries active cytotoxic Ag molecules present in 125 smaller 10 nM AgNP-PVP, but available surface area for attachment is five times more in those smaller 125 particles carrying same payload. Due to 5 times more probability of three-dimensional target attachment, here smaller NPs are more potent. So, size and zeta potentials (ZP) are always to be mentioned for understanding efficacy. Similarly, during preparation of AgNP, used solution of Ag salts in terms of mM concentrations of Ag is to be adjusted. Thus, to obtain 1 mM silver (106.8µg/mL), 1 mM $AgNO_3$ (168µg/mL) is to be used. This will help to indicate active drug contents in differently prepared nanoproducts. Core shape of colloidal nanoproducts also can alter efficacy according to sharp contact points or ridges where surface charge distributions are greater. So, for a similar payload carrying NP, a triangular nanoproduct is more effective than spherical one.

2.3. *Microbial resistance to nanoparticles*

Though, precise mechanisms of cytotoxic action by AgNPs and probability of their resistance development are not clearly understood, scientific suggestions[43] indicate towards affinity-based attachment, internalization, release of bulk Ag+ in cytosol, generation of reactive oxygen species (ROS), damage to various biomolecules and cell-signalling process leading to further lipid membrane damage, cell osmotic disbalance like phenomena. As a result, increased influx of antimicrobial drugs including larger AgNPs, induction of programmed cell death (PCD), blockage of efflux-pump mechanism ensures cell death. The Trojan horse type membrane disruption of NPs by two different mechanisms and their consequences are absolute resistance-proof. Also, possibility of building bacterial resistance for suggested therapeutic use by synchronous transformation of so many genes at a time to other target molecules, is remote. This is more applicable for controlled use of personalised nanomedicine.

However, due to huge amount spillage of AgNPs to the environment apart from health sector, plasmid mediated co-resistance of heavy metals and some antibiotics can happen by alteration of common regulator genes[44], applicable only for chemical pathway interactions

of heavy metals excluding physical force mediated entry of massive dose cytotoxic agents by NPs. Exploiting resistance-proof mechanism of NPs at membrane level disruption, non-specific synergism for dose-dependent conventional antibiotics, can be advantageously used for therapeutic purpose.[45] This may reduce chance of resistance development for both nanomedicine and conventional drugs.

2.4. *Time-honoured approach towards nanomedicine*

As NPs at a time can target all different types of invaded microbes in blood-stream, irrespective of replication cycle and can freely permeate into biofilm matrix, their frequent dose may not require. Thus, all major reasons of banning such high promising novel class of "all-in-one" drug should be over-ruled.[46] Novel Nanomedicine is "of the patient, for the patient, by the service doctors", has no chance for environmental spillage and bad impact on environmental microbes. Thus, one colloidal nanomedicine can be better substitute of more than hundred different anti-microbials and dozens of anti-cancer agents. Used containers or little unused personalised AgNPs can be safely discarded into hypochlorite solution.[47] Early empirical use will not only help better disease management, but also curtail cost of many investigations to clinch precise diagnosis. Such game-changer policies in medical practice may invite bad impact on commerce at the expense of good impact for the community.

2.5. *Scopes and limitations*

The specificity of such nanoproducts can be improved by adding high affinity antibodies against signature molecules of target cells with capping serum. Though, serum contains very low quantity of immune-globulins compared to high abundance serum albumin, former plays crucial role of identifying incompatible blood groups, transplanted organs, neoplastic cells and invader microbes. So, serum from convalescence patient of similar infection with matched blood-group may be used for preparation of such novel class AgNPs, as substitute. Even surface cap attached suitable anti-microbial peptide[48] or bacteriophages can be advantageously used for better management.[49] As we are in the door-step of "post-antibiotic era", case wise rational use of conventional antibiotics along with nanomedicines can be wise policy to overcome impending crisis and ready answer for combating superbugs or newer microbial insurgence.

Though novel AgNPs can cross blood-brain barrier, and no neural or behavioural changes are observed in mice-model studies, further confirmation is required on higher animal studies, which is at present restricted for earlier generation low-precision nanoproducts on ethical and

biosafety ground. Other toxic NPs may have affinity for non-replicating neural cells or may intervene neural functions by released Ag+ following degradation of AgNPs in circulation. Colloidal nanomedicines may not be equally effective against spore-bearing bacterial infections or intra-cellular parasitism. Further tests are required to conclude.

Deaths by some bacterial infections are predominantly caused by liberated toxins e.g. diphtheria, tetanus, shigellosis etc. Their management should be done by convention methods; otherwise, sudden massive killing of bacteria may exaggerate toxin mediated complications. Other probable contraindications for use of novel AgNPs are pregnancy, auto-immune diseases and risk of precipitating "Tumour-lysis Syndrome". For surface infections like infected burn wound, surgical-site infections, skin ulcers, ophthalmic infections, are better to be managed by conventional antibiotics and /or topical usable safe nanoproducts.[45,50], preferably avoiding light and oxygen exposure as much as possible. Also, most of non-invasive gastro-intestinal, urinary tract and upper respiratory tract infections including ear-nose-throat cases are to be managed by existing standard medical practice.

3. CONCLUSIONS

For identical molecular sign and charge sign, endocytosis of novel AgNPs into host cells can be guarded, while still capable of encountering foreign molecular sign bearing high negatively charged invader microbes. This may drastically curtail cost of treatment and investigations of intractable microbial infections by early empirical use of this novel-class AgNPs as primers for synergistic actions of conventional drugs. A few pulses therapy of such "super drug" may be required to mop-up all "super-bugs" by instant physical force mediated attachment followed by oxidative stress induced multi-level disruption of cell biology. It may be called as high-precision "Nano-Bio-ballistic Missile".[42,46] It may serve community interest by lowering trends in resistance development of microbes, both against NPs and synergistic drugs. Same class of drug may be synergistically used for cancer therapy with or without coexisting infections. The knowledge may create scope for further improvement of similar products and to develop automatic nano vending machine as usable tool for every point of care. Necessary infrastructure development can be buildup on need base, to preserve matched group nanoproducts in nanomedicine-bank. Such novel class nano-products, being "all in one" personalized medicine (Nano-PM) may not carry risk for environmental microbes for least possible spillage.

Abbreviations: Nanoparticle = NP, Silver nanoparticle = AgNP, nanometre = nM, Zeta-potential = ZP, milli-volt = mV, functionalised carbon nanotube = f-CNT, Minimum inhibitory concentration =MIC, Colony forming unit = CFU, McFarland's standard = mF, Reactive oxygen species = ROS, Programme cell death = PCD, Derjaguin-Landau-Verwey-Overbeek theory = DVLO, Multi-drug resistant = MDR, Silver nitrate = $AgNO_3$, Silver ion = Ag+

Declarations

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ACKNOWLEDGEMENT: I thankfully acknowledge my fellow researchers who contributed my concept testing, in particular Prof. Nupur Pal, Dr. Rehana Parveen, Dr. Archi Ghosh.

Funding: No funding support.

Conflict of interest: Nil.

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