Silver Nanoparticles: A novel approach in wound healing

Nitin Padole[1], Nilakshi Mahakalkar[1], Pankaj Dhapke[1], Jagdish Baheti[1], Nandkishor Padole[2]

[1]Assistant Professor, Department of Pharmaceutics, Kamla Nehru College of Pharmacy Buttibori, Nagpur (MS)-India 441108
[2]Assistant Professor, Department of Physics, S. Chandra Mahila Mahavidyalaya, Ashti. Gondwana University, Gadchiroli-442707, India

E mail: nitinpadole27@gmail.com, nandupadole12@gmail.com, mahakalkarng18@gmail.com, pankajdhpk4@gmail.com,

Abstract:

In Recent year's medication obstruction is a quickly developing issue over the whole world in the treatment of infectious diseases. The widespread use of broad-spectrum antibiotics produced antibiotic resistance for many human bacterial pathogens. Anyway right now, nanotechnology research has been engaging more in restorative businesses with various advantages because of the way that surface area to volume proportion of nanoparticles is quite large.

Silver nanoparticles are effective in various diseases as antibiotics with different types of metallic nanoparticles to therapeutics that shows synergistic activity. Different types of antibiotics were used to release the pressure of infections which obliviously affect the wound healing process. Development of novel and potent bactericidal agents is of great clinical importance due to novel strains of the bacteria and other infectious microorganisms. Metallic Nanoparticles were investigated intensively due to their superior properties in physical, chemical, and biological aspects. It is essential to maximizing the proper knowledge of these properties and potential applications of Metallic Nanoparticles in several areas while minimizing their risks to humans and the environment. The aim of this paper to Silver Nanoparticles from the perspectives of research trends in bacterial infection in wound healing.

Keywords: Silver nanoparticles, Wound, Antibacterial activity. Silver nanoparticles, Synergism

1. Introduction

Topical preparations are applied to the skin for surface, local, or systemic effects. In some cases, the base may be used alone for its beneficial properties, such as emollient, soothing, or protective action. Many topical preparations, however, contain a therapeutically active ingredient which is dispersed or dissolved in the base. The combination of active ingredient and base provides the opportunity for a wide range of topical preparations, appropriate for many types of drug delivery and therapy. Terms used to classify the bases of topical preparations in which therapeutically active ingredients may be incorporated, may be based on their physical properties or on their intended use or on their composition. Dermal products applied topically are categorized based on those applied to produce local effects and systemic effects. These systems are generally used for local skin infections [1].

1.1 The Role of Silver in topical infections

The utilization of silver in injury the board is exceptionally old. In Egypt, in 1850 BC, silver was applied to wounds; also, the course books by Hippocrates portrayed the positive effects of silver in injury recuperation. Today, because of their expansive range of antibacterial capacity, silver-based creams, and balms, just as AgNPs-based biomedical items, like injury dressings, are industrially accessible for different clinical applications. Because of the assault of irresistible illnesses and the advancement of anti-microbial opposition, drug organizations and researchers are searching for novel antibacterial. Surely, the logical interest in silver nanoparticles and biopolymers for wound recuperating applications essentially expanded in last a long time, as exhibited by the Scopus distribution history [2].

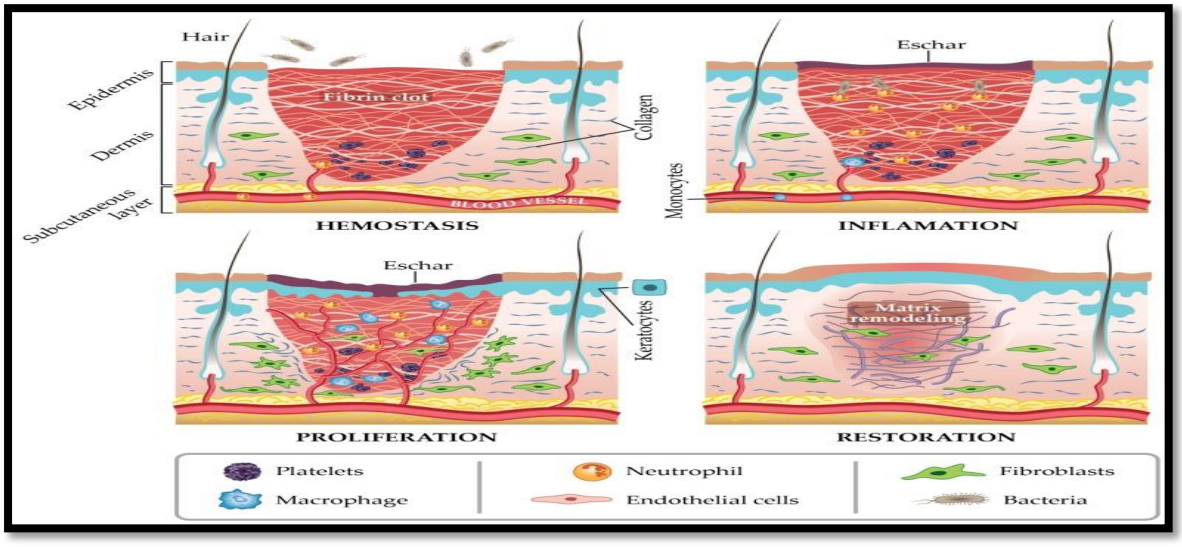
1.2 Wound Infection

Definition of wound contamination “the dangerous chemical system of a foreign-made organization. In a contamination, an inflamed frame desires to use the catching assets to reproduce. The presence of biofilm at the floor of continual wounds (now no longer acute wounds) increases the query of what position biofilm can play in wound healing. The National Institutes of Health (NIH) estimates that 80% of human infections are due to biofilm phenotype microorganism that produces continual illnesses inclusive of endocarditis, continual rhinosinusitis, Crohn's disease, and infections with clinical devices, and incurable wounds. These lesions are characterised through their incomplete reaction to antibiotics as continual infections are predicted to be dealt with organ transplants. The ultimate 20% of infections, inclusive of sepsis and cellulitis, are due to planktonic phenotype microorganism following a totally extraordinary strategy [3].

1.3 Classification of Wounds:

1. According to level of contamination.
2. According objects that caused wound
3. According to burn
4. According to wound ulcer

1.4 Normal Wound-healing Process



Wound healing is a complex four-stage process involving Hemostasis, inflammation, proliferation and remodelling. It is important to consider the needs of the damaged tissue and meet the recovery requirements. The perception of each item depends largely on the stage but also on the duration of the treatment effect, dose, depth and method of operation [4].

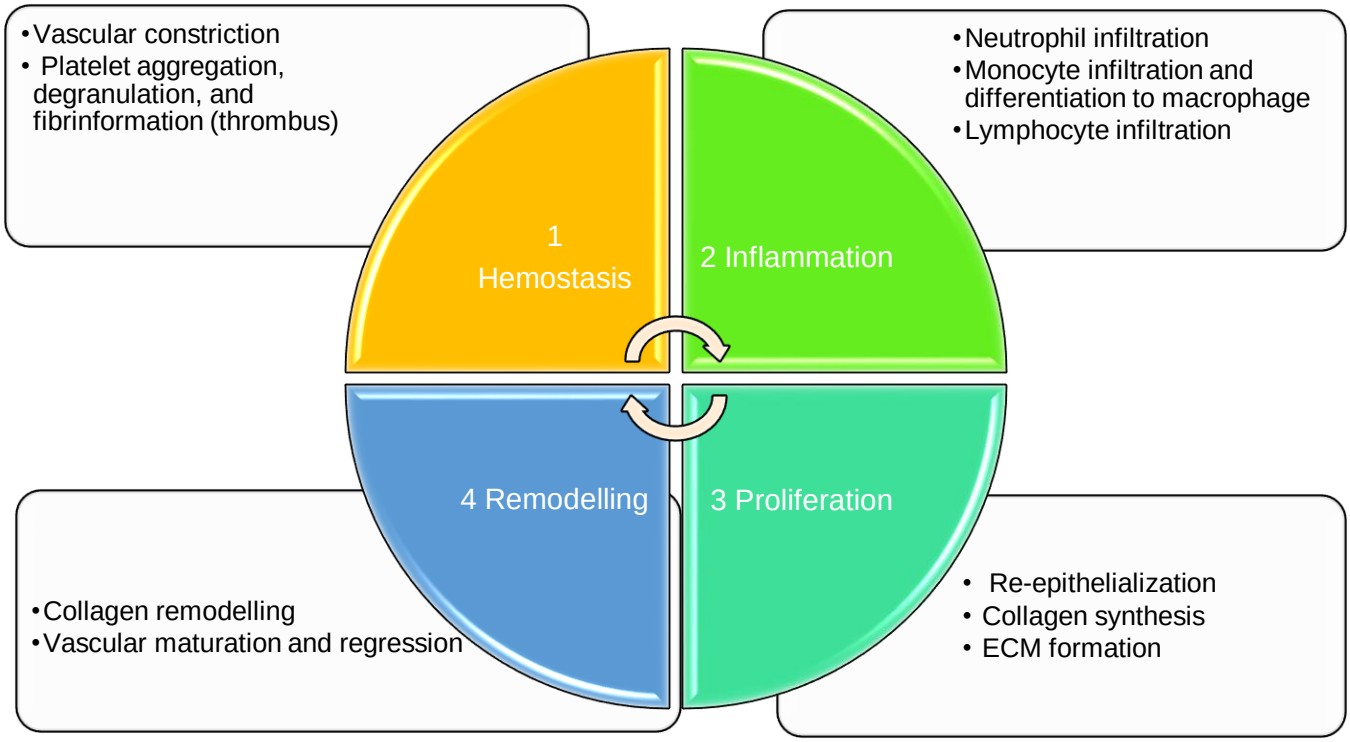


Figure 1: Normal Wound-healing Process with Phase Cellular and Bio-physiologic Events

1.5 Factors frightening the wound healing:

Infection when the pores and skin is damaged, microorganisms are regularly remoted from the floor of the pores and skins to advantage get entry to the underlying tissue. Infection and the recurrence of microscopic situations decide whether or not the wound is assessed as infected, colon, complicated contamination complicated colony, and or the unfold of an infectious disease. Contamination is the presence of non-regenerative wounds within side the wound, whilst the colony is described because the presence of repetitive pathogens at the wound without tissue damage [5].

Local contamination / complicated colony are an intermediate phase, which entails the replication of viruses and the onset of nearby tissue reactions. Infectious infections are described because the presence of recurrent materials within side the wound with next host injury. Wound Characteristics Many traits and phenomena associated with continual wounds are without problems defined through viewing continual cutaneous wounds as continual infections. By intently staring at diffused modifications within side the wound and correlating those modifications with diagnostic equipment and responses to therapy, a faint photo starts off evolved to emerge of some of the strategies taking area at the wound bed. Understanding some of those sports can assist direct our wound control decisions [5,6].

1.6 Importance of Recognizing Signs of Wound Infection

Whether the pathogen causes wound infection depends largely on the immune system. The risks increase when the wound is at a high viral load in the body, the patient has an incurable disease such as diabetes or vascular disease, or poor or incompatible wound care. As the surgical injury is one of the most common cases diagnosed in the hospital and has become a major cause of illness and death; detecting and treating wound infection should be the primary management goal of health workers Injury or surgery breaks the skin and allows bacteria to enter the body and multiply. Here are some of the most common symptoms associated with a wound infection [6].

1.7 Control of Microbial Populations in Wounds

No matter how important a microbiology report is to a physician caring for a wound, there is widespread debate about when and how to treat infected, even if not found, no healing wounds to be treated with antimicrobial agents, what to use, and topical or systemic antimicrobial agents should be included. Although antibiotic treatment is important for the development of acute and chronic diseases tissue, wounds only show local signs of infection or they fail treatment but have no clinical signs of infection (e.g., difficult colony) can initially be addressed by topic ambassadors. Topical antimicrobial agents include both anti-bacterial mechanisms and viruses and the wide range of options available creates more problems for the doctor caring for the wound. Alternative therapies such as HBO therapy, which assists the body with the immune system Response can also have a direct antibacterial effect against other anaerobic bacteria (e.g., perfringens), antimicrobial peptides, as well as plant extracts, can also play a role-play in wound management and they are worth considering [7].

1.8 Acute wounds

Although the main purpose of antibiotics to treat infection, the associated prophylaxis with surgical practice accounts for up to half of all antibiotics set. Most complicated or painful surgery wounds heal normally without the need for prophylactic antimicrobial treatment, despite the involvement of external factors such as sutures, dirt, grafts, or implantable devices may be possibly increasing the risk of infection in clean wounds. Treatment of combination with an aminoglycoside (e.g., gentamicin) or a

cephalosporin (e.g., cefuroxime or cefotaxime) and clindamycin or metronidazole has been shown to be very effective. The cephamycin agent cefoxitin is widely used as one prophylaxis agent in the United States and treatment of an existing disease. Subsequent development of new classes of antimicrobials such as ureido penicillin, carbapenems, and a combination of a b-lactam / b-lactamase inhibitor increase selection in both prophylactic and medical treatment. Antibiotics that target the cell wall of the virus release higher doses of endotoxin than other classes of antibiotics, such as those that inhibit protein synthesis. As S. aureus is considered a major problem a pathogen associated with painful wounds infected, cephalosporins, macrolides, clindamycin, and semisynthetic penicillin as flucloxacillin and oxacillin are usually a treatment option of choice. When methicillin-resistant strains are involved, glycopeptide antibiotics vancomycin and teicoplanin are alternatives [8].

1.9 Chronic wounds

It may be very extraordinary from acute planktonic contamination due to the fact it is able to without problems remaining for decades. But despite the fact that the 2 kinds of infections are very extraordinary on the cell level, they're typically labelled within side the equal class of "viral infections." Biofilm phenotype microorganism produces continual infections in some of ways. However, the enormous view amongst wound care experts is that aerobics or facultative pathogens like Staphylococcus aureus, Pseudomonas aeruginosa, and beta-haemolytic Streptococci are the maximum reasons of behind schedule onset and contamination in each continual and continual wound. Continued use of those broad-spectrum antibiotics additionally allows growing resistance to positive viruses in the one’s drugs.

Nosocomial infections in veterinary medication due to antimicrobials reason a growth in disease, reduced wound, continual wound modifications, and excessive costs, remedy duration, and expanded zoonotic threat because of remedy complications. Burn wound infections Infection is a prime difficulty in new wounds, and it's far expected that as much as 75% of deaths following contamination-associated new injuries. Although uncovered tissue burned is vulnerable to being infected through microbes from the intestines and higher respiration tract, many research has stated a growth in aerobes inclusive of P. aeruginosa, S. aureus, E. coli, Klebsiella spp, Enterococcus sobp, and Candida spp. Treatment of burn wounds consists of the usage of topical and systemic antimicrobials, robust extraction of lifeless tissue, more advantageous immune reaction, and provision of ok nutrition.

Like contaminated surgical wounds, most chronic ulcers (e.g., leg ulcers, foot ulcers, and pressure ulcers) are characterized by polymicrobial aerobic microflora aerobic. As a result, the careful use of broad-spectrum antimicrobial agents may be the most effective treatment for chronic clinical infections. The widespread use of antimicrobials to treat wounds that fail to heal or wounds that are at risk of infection is appropriate on the basis that they provide high concentration on the local site; they avoid allergies and systematic themes are often limited to those toxic when treated systematically. Bacitracin, polymyxin B, and neomycin are used as a combination of two or three times the antibiotics to provide effective functions [9].

2. Nanotechnology in wound healing

2.1 Nanoparticles

Nanoparticles can be defined as objects ranging in size from 1- 100 nm that due to their size may differ from the bulk material. Presently, different metallic nanomaterials are being produced using copper, zinc, titanium, magnesium, gold, alginate and silver Nanoparticles (NPs) research is an emerging branch of science. Tuning size and shape of NPs alter their properties and offer huge opportunities for surprising discoveries [10].

Nanoparticles can be classified into different types according to the size, morphology, physical and chemical properties. They are as follows

- Carbon-based nanoparticles,
- Ceramic nanoparticles,
- Metal nanoparticles,
- Semiconductor nanoparticles,
- Polymeric nanoparticles
- Lipid-based nanoparticles.

Types of Nanoparticles

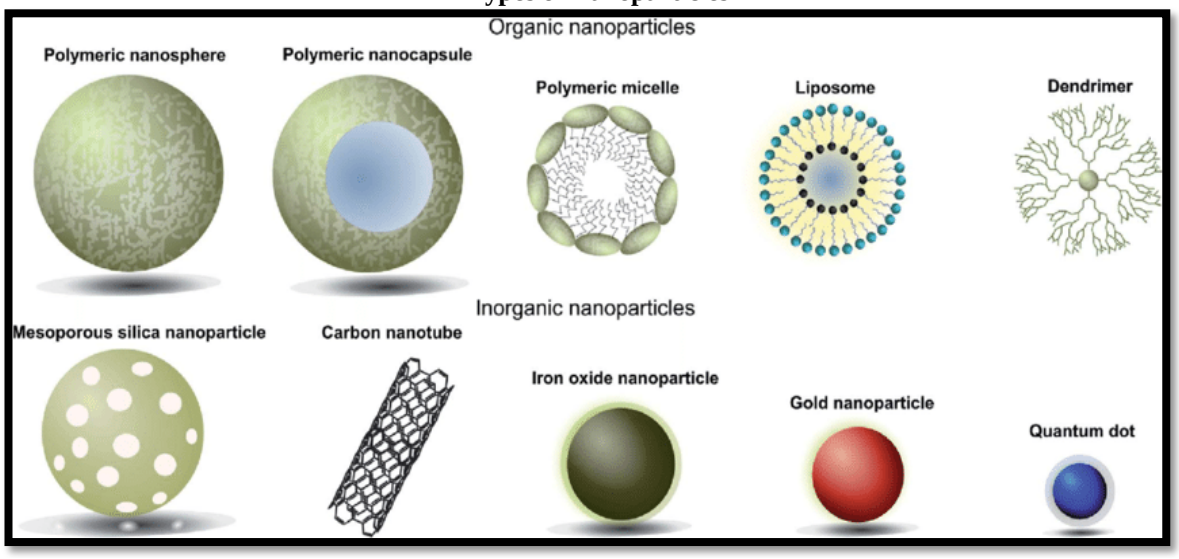


Figure 2: Types of Nanoparticles

2.1.2 Advantages of Nanoparticles

- Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both active and passive targeting.
- Release of the drug can be controlled or sustained so as to achieve increase in therapeutic efficacy of drug and reduction in side-effects.
- Nanoparticles can better deliver drugs to tiny areas within the body.
- Nanoparticles aid in efficient drug delivery to improve aqueous solubility of poorly soluble drugs that enhance Bioavailability for timed release of drug molecules, and precise drug targeting [11].
- Nanoparticles overcome the resistance offered by the physiological barriers in the body.
- Targeted nano drug carriers reduce drug toxicity and provide more efficient drug distribution.
- The surface properties of nanoparticles can be modified for targeted drug delivery for e.g. small molecules, proteins, peptides, and nucleic acids loaded nanoparticles are not recognized by immune system and efficiently targeted to particular tissue types [12].

2.1.3 Disadvantages of Nanoparticles

- These have low encapsulation efficiency.
- Water-soluble drugs can be rapidly leaked out in the presence of blood components.
- Their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in dry and liquid forms.
- They may trigger immune response and allergic reaction [13].

2.1.4 Ideal Properties of nanoparticles:

- Nanoparticles are stable in blood
- Nanoparticles are having nontoxic nature.
- Nanoparticles are non-thrombogenic
- Non inflammatory in nature is one of the properties of nanoparticles.
- It provides the facility of no activation of neutrophils
- The nanoparticles are Biodegradable
- It is having ideal property of avoidance of the reticule-endothelial system
- Applicable to various molecules, such as small molecules, proteins, peptides or nucleic acids (platform technology)

2.1.5 Metallic Nanoparticles in wound Healing

Metallic nanoparticles have antimicrobial properties of silver, gold, iron oxide, copper oxide, Zinc oxide, aluminium oxide, titanium oxide, and gallium nanoparticles. In metal-based nanoparticles that have antibacterial activities that are basically characterized by such things as (1) small size (2) high surface area (3) shape, all of these factors contribute to their cell-taking effect. The activity of nanoparticles in antimicrobial activity is due to their ability to produce active forms of oxygen that can kill bacteria and their ability to attach to DNA or RNA that further disrupts the copying or reproduction of substances [14].

3. Silver Nanoparticles

Silver nanoparticles (AgNPs) are a class of materials with sizes in the range 1–100 nmand atomic mass-107.87. The interest in the study of AgNPs with respect to their various different behaviors has recently increased because of their unique and attractive physical, chemical, and biological properties [15, 24]. AgNPs are also known to have unique properties in terms of toxicity, surface plasmon resonance, and electrical resistance. Based on these, intensive works have been conducted to investigate the properties and

potential applications for several purposes such as antimicrobial agents in wound dressings, anticancer agents, electronic devices, and water treatment [16,17] .

With the rise and increment of microbial living beings impervious to various anti-infection agents and the proceeding with accentuation on medical services costs, numerous scientists have attempted to foster new, successful antimicrobial reagents liberated from obstruction what's more, cost. Such issues and needs have prompted the resurgence in the utilization of Ag-based disinfectants that might be connected to expansive range action and a far lower inclination to actuate microbial opposition than anti-infection. It is explained in the literature that silver nanoparticles can modulate anti-inflammatory cytokine release and promote closure of the wound immediately without the growing scar. See and can promote epidermal regeneration through keratinocyte proliferation [18].

3.1 Synthesis of silver nanoparticles:

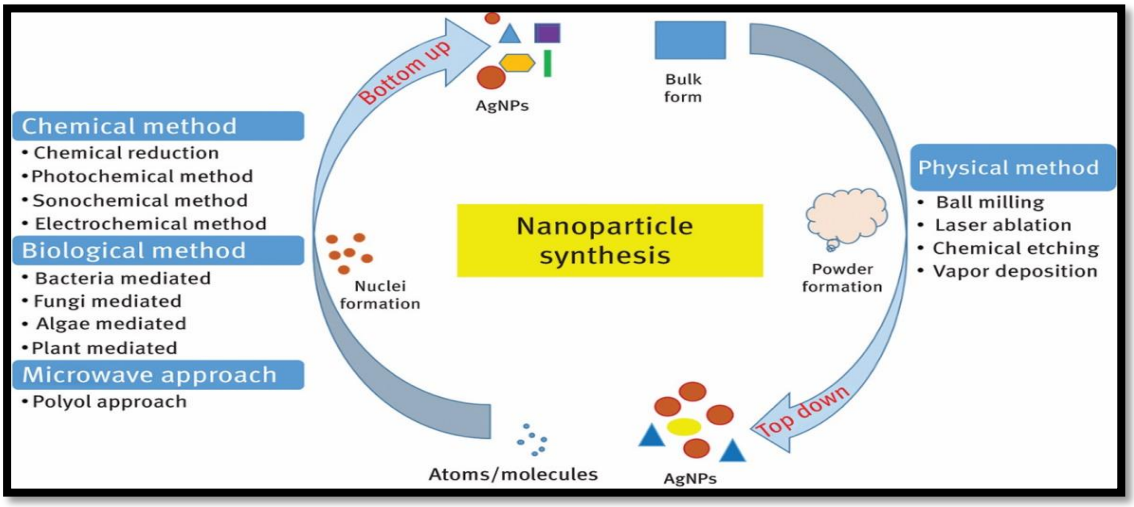


Figure 3: Methods of preparation of silver nanoparticles

3.1.1 Mechanism of action

Due to their large surface area, AgNPs exhibit effective antimicrobial activity functions. Initially, AgNPs attach to the bacterial cell membrane and enter bacteria where they interact with sulfur-containing proteins and the phosphorus group remains, as well as DNA [19]. AgNPs that enter the bacterial cells that will convert the low molecular weight (MW) is central to viruses, and protects the cellular DNA from silver ions, thus protecting the DNA from damage. Nanoparticles first remove the silver ions from the center, inside the virus cells, which reflect and enhance their antibacterial activity. Nanoparticles identify and damage the respiratory tract and obstruction cellular fragmentation, which leads to cell death. In normal wounds, AgNPs shrink inflammation by altering cytokines; thereby reducing their levels, reduces lymphocyte infiltration, and promotes regeneration of promoting wound healing [20].

3.2 Antimicrobial Silver Nanoparticles

There are several uses of silver in our daily life and we had to get lots of good and bad productive outcomes from the same for example, in identification and finding, drug conveyance, for covering of biomaterials and gadgets, for novel antimicrobial specialists, and in recovery materials. Lately, the antimicrobial highlight of AgNPs has prompted expanded interest for its clinical applications, including wound dressings, counterfeit implantation, and antitumor medication transporters. Different models incorporate the utilization of NPs as a covering for implantable clinical gadgets, for forestalling disease and advancing injury recuperating, in anti-toxin conveyance, microbial diagnostics, and in antibacterial antibodies to control bacterial diseases. The wide range of antimicrobial action of AgNPs has energized the turn of events of numerous AgNPs-based items for the material, food, and clinical applications. In everyday life, AgNPs have been proposed in silver-based frameworks for air/water filtration, material materials, creature cultivation, biomedical, food bundling, and so on [21, 22].

3.2.1 Impacts:

The antibacterial impacts of Ag salts have been taken note of since vestige, and Ag is right now used to control bacterial development in an assortment of utilizations, including dental work, catheters, and consume wounds. Truth be told, it is well realized that Ag particles and Ag-based mixtures are exceptionally harmful to microorganisms, showing solid biocidal impacts on upwards of 12 types of microorganisms including E. coli. As of late, Mecking and colleagues showed that crossbreeds of Ag nanoparticles with amphiphilic hyper branched macromolecules shown powerful antimicrobial surface covering specialists. Lessening the molecule size of materials is a proficient and dependable apparatus for working on their biocompatibility [23].

3.2.2 Advantages of silver nanoparticles

- Beneficial in delayed diabetic wound healing as diabetic wounds is affected by many secondary infections
- silver nanoparticlesrecognized in wound healing, antibacterial effect and low systemic cytotoxicity
- Non-toxic to humans and most effective against bacteria, viruses and other eukaryotic microorganisms at low concentrations and without any side effects.
- Silver NPs can be incorporated by physical means into a variety of dressing mats, e.g., cotton fabrics [24,25].

- The chemical stability and catalytic effect of silver nanoparticles have an advantage over the other metallic nanoparticles for antibacterial, antiviral, anticancer, antifungal and to anti-inflammatory activities.
- The concentration of AgNPs has a tremendous effect on the rupture of the cell wall of the bacteria, as the concentration of the AgNPs increases the permeability of the membrane also high [26].

3.2.3 Applications of silver nanoparticles (AgNPs)

- In the field of nanotechnology AgNPs gained unlimited focus because of its unique property.
- Antibacterial
- Antiviral
- Anticancer
- Antifungal
- Anti-inflammatory
- Inhibitory effect on microbes presents in a medical and industrial process

3.2.4 Different methods of Nanoparticle Formulation

Formulation methods of different kinds of metallic nanoparticles are changes as per the material that is used during the process. Metal nanoparticles like silver, gold, and zinc have prominent properties such as stimulants of wound healing and antibacterial activity; of action they are ready to be included in the dressing.

A) Physical method(27)
- Ball milling
- Laser ablation
- Chemical itching
- Vapour deposition

B) Chemical method(28,29)
- Chemical reduction
- Photochemical method
- Electrochemical method

C) Biological method(22,28)
- Bacteria mediated
- Fungi mediated
- Algae mediated
- Plant mediated

D) Microwave approach
- Polyol method

3.2.4.1 Physical approach

By and large, the actual methodology used to blend AgNPs utilizes the dissipation build-up strategy. It is regularly performed utilizing a cylinder heater at climatic pressing factor, which is solid to combine different sizes [30]. Several endeavours have been made an expansion to the previously mentioned examines. Another technique was proposed by Tsuji et al.58 for incorporating AgNPs by a laser removal procedure with engaged and unfocused laser bar light completed at 12 and 900 mJ/cm2 powers, separately. The radiation frequencies utilized in their examination were 355, 532, and 1064 nm. Their examination inferred that the surface plasmon frequency of AgNPs lighted utilizing 355, 532, furthermore, 1064 nm is ~400 nm for both engaged and unfocused plans. In an alternate report, AgNPs were incorporated by utilizing a laser removal strategy in solution. In the arrangement, silver particles were washed utilizing refined water and put in a quartz cell containing 5 mL of high-pressure fluid chromatography (HPLC)- grade water. To investigate the variety of the procedure, AgNPs were integrated utilizing laser removal with various laser wavelengths. The breadths of AgNPs were discovered to be based on 12, 26, and 29 nm while utilizing 355, 532, and 1064 nm frequencies, separately. It was subsequently inferred that the silver molecule size incorporated utilizing laser removal can be constrained by changing the laser frequency. This strategy was found to be dependable for setting up the ideal colloid size in arrangements [31].

3.2.4.2 Chemical approach

The Chemical approach is generally utilized for blending AgNPs utilizing water or natural solvents. It is a simple approach to blend AgNPs in solution. However, a specific measure of harmful material might be delivered as residue. Some decreasing specialists, for example, borohydride, citrate, ascorbate, and glucose have been utilized to address this issue. A substance decrease technique was embraced for combining AgNPs of different sizes (7, 29, and 89 nm) silver salt and gallic corrosive was utilized as the decreasing and balancing out a specialist. For 7 and 29 nm AgNPs, the decrease response was led at pH 11 and 10, separately. Moreover, UV light was applied to ionize the phenol gatherings. In the arrangement, for 89 nm AgNPs, it was not important to build the pH esteem as opposed to the next two sizes. For the 7 and 29 nm nanoparticles, the methodology had the utilizing gallic acid. In this work, $AgNO_3$ was utilized as the option to incorporate round AgNPs [32].

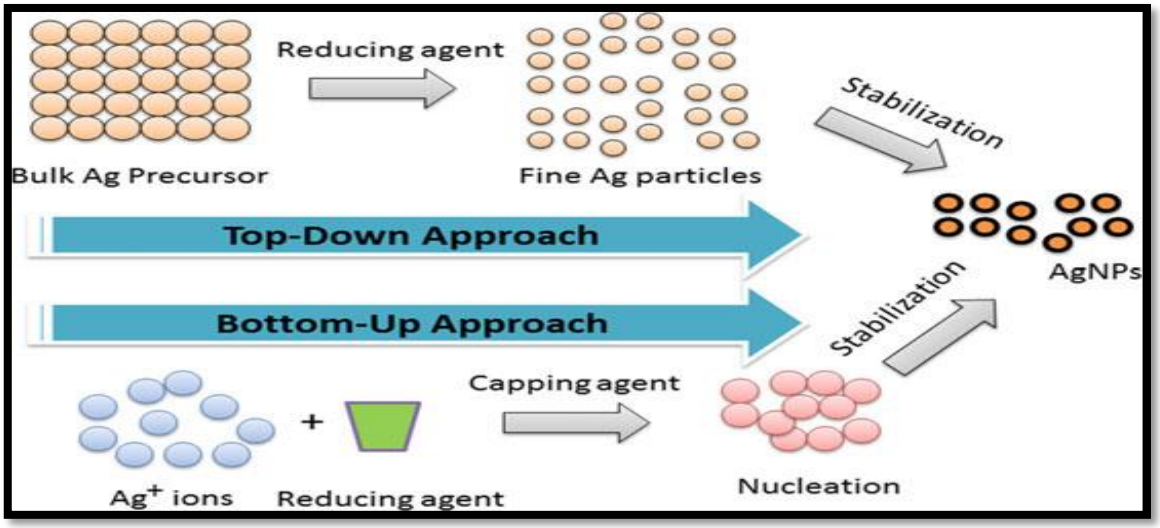


Figure 4: AgNPs synthesis through bottom-up and top-down processes with chemical reduction method.

The chemical approach is widely used for synthesizing AgNPs using water or organic solvents. It is an easy way to synthesize AgNPs in solution. However, a certain amount of toxic material may be produced as residue. Some reducing agents such as borohydride, citrate, ascorbate, and glucose have been used to address this problem.
This is by continuing through a single process to generate a coloured silver solution, this is due to the surface of a metal having free of charge electrons in the conduction band and positively charged nuclei [32].
(i) Metal precursors,
(ii) Reducing agents
(iii) Stabilizing/Capping agents.
The initial nucleation and the subsequent growth of nuclei can be controlled by adjusting the reaction parameters such as temperature, pH, precursor types, solvents, reduction agents, and stabilizing/capping agents [33].

3.3 Natural methodology

As of late, the natural methodology for blending AgNPs is by and large progressively considered. This strategy is a green innovation pointed toward limiting the negative natural effect. It had been realized that the union of AgNPs utilizing the substance approach requires three fundamental fixings: a silver salt, a diminishing specialist, also, a stabilizer or covering specialist. AgNPs can likewise be combined utilizing plant organic product bodies. For example, Tribulus Terrestre's L. natural product bodies were utilized as the decreasing agent. The proposed strategy could be utilized to combine round AgNPs with sizes going from 16 to 28 nm. The investigation asserted that the normal lessening specialist offers a speedy answer for converting the silver particles (Ag+) to metallic AgNPs (Ag0). The utilization of AgNO3 as the silver salt and ethanol as stabilizers to combine AgNPs utilizing the plant R. Hymenosepalus, which went about as the decreasing specialist, was additionally examined. It was tracked down that the widths of the AgNPs got were in the reach of 2–40 nm [34].

3.4 Plant extracts

Plant concentrates can fill in as lessening specialists to combine AgNPs and give an elective arrangement that is harmless to the ecosystem. As a normally happening asset, it is moreover less expensive and richly accessible in the climate. Few plant separates are used to integrate AgNPs from their leaves, seeds, roots, and fruits. In the accompanying, a few plants remove utilized in different examinations to create AgNPs and are of interest are portrayed. A natural methodology was proposed utilizing the leaf concentrates of five plants pine, persimmon, ginkgo, magnolia, what's more, Platanus) as diminishing agents. It was taken note that the response temperature, leaf stock fixation, what's more, $AgNO_3$ could be utilized to control the AgNPs size. The examination presumed that the magnolia leaf stock was the best lessening specialist in integrating AgNPs in the wording of blend rate and change. The methodology was ready to incorporate AgNPs of 15–500 nm estimates on normal. Notwithstanding plant extricates, parasites likewise can be used to blend AgNPs. A methodology was proposed to integrate AgNPs from silver nitrate utilizing the growth Verticillium.147 From the investigation, it was discovered that the normal AgNPs size was 25 -12 nm. Fusarium auxospore was likewise attempted as a natural decreasing specialist to blend AgNPs. Silver nitrate of 10−3 M was blended in with 10 g of Fusarium auxospore biomass in a conelike carafe containing 100 mL of refined water. Utilizing the proposed technique, circular and incidentally, three-sided AgNPs in the size range 5–15 nm was created [35].

4. Antibiotic resistance

Antibiotic resistance is a drug resistance by which many bacteria are able to survive exposure to one or more antibiotics. Accordingly, pathogenic bacteria which have become resistant to several antibiotics cause infections which cannot be treated with the usual, formerly efficacious antibiotic drugs and their usual, formerly efficacious, dosages and concentrations. Resistance can be acquired or intrinsic. Many clinically relevant pathogens have developed resistance to large group of antibiotics and are called as multidrug resistant (MDR) pathogens.

In recent years, the term superbug has become popular. A global challenge antibiotic resistance is a major public health issue worldwide. Although the natural selection of bacteria makes some resistance inevitable, the problem is largely driven by misuse and overuse of antibiotics.
Factors contributing to the resistance are:

- The rising number of healthcare associated infections.
- Over-prescription of broad spectrum antibiotics.
- Increasing cross-continental travel and global trade.

As the gap widens between the rising number of MDRO infections and the development of new antibiotics to treat the resistant bacteria have become one of healthcare's biggest threats. There are few antibiotics in the development pipeline to meet the challenge of multi-drug resistance, and the most prudent use of existing antibiotics is crucial to preserve their efficacy [36].

Healthcare-associated infections (HAI) remain a major cause of mortality, morbidity and excess healthcare cost. In United States, antibiotics resistant Staphylococcus aureus (MRSA) infections alone kill nearly 19,000 people a year and account for over 60% of the total number of hospital onset S. aureus infections.

The global problem of increasing trend in antibacterial resistance is particularly pressing in the developing countries, where the methicillin-resistant Staphylococcus aureus (MRSA) is often the severe casual agent in hospital-acquired infections. There is now an increase in difficulties to treat such patients because of emergence of resistance to all current antibiotic classes. Antibiotic resistance particularly in pathogenic organisms has become a serious and growing phenomenon in medicine and has emerged as one of the public health concerns of the 21st century. Clinically relevant organisms have acquired resistance to first-line antibiotics, thereby necessitating the use of second-line agents.

Typically, the first line antibiotics are selected on the basis of several advantages including availability, cost and safety. Comparatively, the second-line antibiotics are broad spectrum, are more expensive or may be unavailable. In the case of some MDR pathogens, resistance to second and even third-line antibiotics is sequentially acquired; a case illustrated by Staphylococcus aureus in some nosocomial settings [37].

AgNPs have been employed alone or in combination with antibiotics. Antibacterial potency of AgNPs was reported against drug-resistant pathogenic bacteria E. coli, P. aeruginosa, E. Faecalis, and S. Aureus.

Table 1: Multidrug-resistance in gram positive and Gram negative bacterial strains

Gram positive Bacterial strains	**Resistant to**
Corynebacterium diphtheriae	lactam antibiotics, Chloramphenicol Tetracycline, Trimethoprim, Sulfamethoxazole
Enterococcus faecium	Gentomicin, Vancomycin
Listeria monocytogenes	Erythromycin, Gentomicin, Kanamycin, Rifampin, Streptomycin, Sulfamethoxazole,
Staphylococcus aureus	Vancomycin , Methicillin
Streptococcus pneumonia	Erythromycin, Penicillin
Gram negative Bacterial strains	Resistant to
Acinetobacter baumanii	Imipenem, Carbapenems
Escherichia coli	Cephalosporins, Ampicillin, Sulfamethoxazole, Streptomycin, Tetracycline
Klebsiella pneumonia	Imipenem, Carbapenems
Carbapenems	Carbapenems, Chloramphenicol, Fluoroquinolones, Macrolides Novobiocin, Sulfonamides
Salmonella typhi	Ampicillin, Amoxycilin

4.1 Antibiotics synergism

Medical and pharmacological communities have long searched for antimicrobial drugs that increase their effect when used in combination, an interaction known as synergism. These drug combinations, however, impose selective pressures in favour of multi-drug resistance and as a result, the benefit of synergy may be lost after only a few bacterial generations. Furthermore, there is experimental evidence that antibiotic treatment can disrupt colonization resistance by shifting the balance betwee0 and commensal bacteria in favour of the pathogens, with the potential to increase the risk of infections.

The evolution and spread of antibiotic resistance in pathogenic bacteria represent a potentially grave public health problem. A common approach to dealing with the evolution of antibiotic resistance and to increase the efficacy of antimicrobial treatments is to use multidrug combination therapy. It has even been suggested, for example, that synergistic drug combinations, those usually preferred in clinical settings, may serve to promote the evolution of drug resistance. The standard pharmacological approach to therapy design focuses on antibiotic combinations that increase drug efficacy without accounting for the effects drugs might have either on the evolution of drug resistance or on the innate resistance provided by the host's microbiota [38].

The field of synergistic combinations of antibiotics is extremely broad and mostly has been explored in-vitro. Some fixed combinations were successfully developed commercially. A few combinations were tested in animal models, and a smaller number was studied in human patients

Synergy between antibiotics is a strictly defined microbiological phenomenon, requiring two bioactive agents to exhibit enhanced bacterial killing when the two are combined. Because of increasing antibiotic resistance, and few new drugs to treat multidrug-resistant bacteria, combination therapy is often used in the clinical setting. Frequently, these combinations have demonstrated synergistic activity both in vitro and in animal models before being used therapeutically

In the past few decades, the rising risk of antibiotic-resistant bacterial infections has become a global major concern as it makes the conventional antibiotics less efficient and significantly increases the clinical cases of serious infections. There is an urgent need for developing new generations of antibacterial agents, especially considering the decreasing number of new antibiotic drugs that are in the pipeline. Silver (Ag)-based materials, and notably silver nanoparticles (AgNPs), have attracted burgeoning attention in recent years due to their owned broad antibacterial spectrum and long term antibacterial activity. A viewpoint has been gradually accepted that it is the silver ions (Ag+) released from AgNPs rather than the particle itself that plays a key role.

Table 2 : Antibiotics combinations with silver nanoparticles

Antibiotics	Antibacterial agent	Effective against organism
ß-lactams	Silver nanoparticles	E. coli
Quinolones		E. coli
Aminoglycosides		C. difficile
Vancomycin		E. coli
Chloramphenicol		E. coli
Polymixin B		A. baumannii
Tetracycline		E. coli

It has been demonstrated that Ag+ could increase membrane permeability and produce reactive oxygen species (ROS) to damage cell walls and subsequently cause the death of bacteria. Recently found that Ag+ and antibiotic combinations could engender an obvious synergistic effect on killing the drug-resistant bacterial strains, thereby expanding the antibacterial spectrum of the existing antibiotic drugs. It seems that a drug delivery system that integrates silver and antibiotics would be a more promising therapy tool in this field [39] .

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