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Silver Nanotechnology for wound healing

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ABSTRACT:
Wound healing disorders affect millions of people worldwide, leading to increased mortality and associated costs The ideal technique is used to achieve expeditious recovery of wound healing, reduces minimum scarring,andensures function preservation. Topical treatment is the classical method to treat wound management which is antibacterial and colloidal treatments. Nanotechnology studies are having a submicroscopic particle (diameter of 100nm). Some metals which are used in nanotechnology like silver, gold, and zinc are extremely used in dermatology, due to their beneficial effects on wound healing and preventing bacterial infections. Nanomaterials can excite the cellular and molecular processes that help in the wound microenvironment through antimicrobial, anti-inflammatory, and angiogenic effects. In this paper, we study how silver nanotechnology help in the treatment of wound healing, the pathophysiology of the wound, and types of nanoparticles used to treat the wound.

INTRODUCTION:

The human body is covered by the skin, skin is a defensive barrier between the hominoid body and external environment. With extended exposure, the skin accepts the effect of numerous external stimuli.

Wound healing disorders affect millions of people worldwide, leading to increased mortality and associated costs.There are this three main complications related to wounds: Lack of a suitable environment to allow cell migration, proliferation, and angiogenesis, Microbial Infections, and Unbalanced and Persistent Inflammation.

Wound healing is the "ideal" to achieve rapid recovery and minimize scarring thereby ensuring the preservation of function. To develop the technology, it has been extensively researched.Classical approaches to wound management consist of topical treatments such as antimicrobials and colloids to prevent infection and promote proper wound-healing processes. Nanotechnology studies ultrafine particles (up to 100 nm in diameter) and related phenomena. Metallic nanoparticles (silver, gold, zinc, etc.) are increasingly being used in dermatology due to their positive effects in treating and preventing bacterial infections as well as promoting wound healing. Other advantages include easy handling, infrequent dressing changes, and a constantly moist wound environment. This review high Nanoparticles can stimulate a range of cellular and molecular processes that can help the wound microenvironment through antibacterial, anti-inflammatory, and angiogenic effects that can aid in healing to non-healing points. Artificial silver Nanoparticles (AgNPs) are used in a variety of applications, including textiles, household products, and antimicrobial additives for medical applications.The recent trend of increasing production (estimated at 500 tons per year worldwide and applications) has led to increased release of AgNPs and ionic silver to the environment, which is associated with higher levels of Ag in aquatic environments. AgNPs and ionic silver aquatic species have been studied primarily in laboratory experiments using single test species and sometimes clonal cultures (e.g., Chlamydomonas spp.) As a general trend, the toxicity of silver seems to be due to ionic silver as a molecular toxin. The toxicity of AgNPs remains relevant. This is because the particles can continuously produce Ag^+ with subsequent toxic effects. Silver nitrate nanoparticles have attracted much attention as an antibacterial agent slights recent knowledge about the use of nanoparticles in wound management. Use effective antibacterial agents. Because it contains silver, silver has antibacterial and antibacterial properties. Silver nanoparticles have attracted the attention of researchers due to their special properties. There are mainly three main sources for the synthesis of silver nanoparticles: bacteria, fungi and plant extracts. The biosynthesis of silver nanoparticles mainly involves oxidation and reduction reactions.

1. Methods for synthesis of silver nanoparticle

i. **Physical approaches:** Evaporation and condensation play an important role in physical approaches to the synthesis of AgNPs. The temperature gradient plays an important role in cooling the steam at the desired rate. The physical approach eliminated the possibility of solvent contamination, as the physical method did not use solvents and accurately yielded uniform particle size distributions. Minimal inhibitory concentrations in toxicity studies can be easily achieved by preparing high concentrations of nanoscale nanoparticles. AgNPs are also synthesized by laser ablation of metal particles. An important advantage of the laser ablation technique over other methods of producing metal colloids is the absence of chemical reagents in solution. Therefore, using this technique, pure and uncontaminated metal colloids can be produced for further applications. Synthesis of AgNPs by tube furnace has many drawbacks, including: B. Enlarged footprint, high power, rapid rise in ambient temperature, etc.

ii. **Chemical Approaches:** Chemical reduction is the most commonly used method to prepare AgNPs as stable colloidal dispersions in water or organic solvents. The most commonly used reducing agent is citric acid. In aqueous solutions, the reduction of silver occurs to produce nano-sized colloidal silver ions. The stability of the colloidal dispersion is of the most importance and can be achieved by a stabilizer (dodecanethiol) adsorbed to the surface creating a protective shell. System agglomeration and crystal growth can be avoided. During the synthesis of AgNPs, small changes in parameters (polymers) lead to large changes in size, shape, morphology, polydispersity index, selfassembly, and zeta potential (stability). Commonly used components in the synthesis of AgNPs are the glycol derivatives polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG). Polyacrylamide plays a dual role as a reducing agent and stabilizer in the synthesis of AgNPs. Surfactants containing functional groups such as amines, thiols and acids play an important role in the stability of colloidal dispersions and protect the system from crystal growth, coalescence, and aggregation.

iii. **Biological Approaches:** Biotechnology is a new tool to develop the biological synthesis of AgNPs. Apart from that, due to the improved surface, magnetic nanoparticles have excellent antibacterial power to treat the increased resistance of microorganisms to many antibiotics and drugs. Currently, green chemistry is rapidly growing and used to synthesize AgNPs using naturally occurring stabilizers, reducing agents, and capping agents to synthesize AgNPs without toxic side effects. technology Successful reduction of metal ions by working herbs with specific enzymes, proteins, microorganisms, bacteria, and fungi in biological synthesis has been successfully reported.

iv. **Synthesis of Silver Nanoparticles by Fungi:** AgNPs with high production yields synthesized by fungi have higher amounts of proteins that are directly involved in increased production by fungi compared to fungi. The higher production rate is mainly due to silver ions penetrating the fungal cell wall, resulting in the reduction of silver ions by fungal enzymes such as naphthoquinones and anthraquinones. The slow rate and process is just one drawback associated with fungal synthesis of AgNPs, so the green synthesis approach is preferred over other techniques.

v. **Bacterial Synthesis of Silver Nanoparticles:** Many bacterial strains and microorganisms develop tolerance to metals at low concentrations. Resistance primarily arises from efflux, solubility changes, oxidation/reduction toxicity, and precipitation of metals. There is evidence of low concentrations. Microorganisms are alive, but once exposed to high concentrations. Metal ions lead to the death of microorganisms. Nitrate reductase converts nitrate to nitrite in the biosynthesis of silver enzymes.

vi. **Synthesis of silver nanoparticles by plants:** Green synthesis is an excellent tool that can be used to synthesize AgNPs. This is due to the use of naturally derived medicinal herbs and their extracts. It contains various metabolites, especially water-soluble flavones, etc., and is fast compared to fungi. Rapid reduction of microbes and silver. The green chemistry approach is safe, cost-effective, and easily scalable for mass production, and raw materials are readily available on cheap coasts. Phytochemicals are directly involved in the silver ion reduction process during the

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synthesis of AgNPs. In Figure 1. Formation of silver nanoparticles by Biological methods.

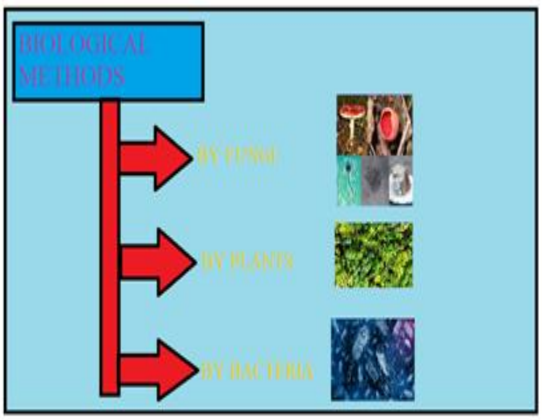

Figure 1. Biological methods of silver nanoparticles

2. Mechanism of action of silver nanoparticles

i. **AgNP's antimicrobial MOA:** When AgNP reaches the cell, it releases Ag+ ions. These released ions interact with sulfur- and phosphorus-containing compounds present in the cell walls. This disrupts cell wall formation and causes small depressions in the cell wall. The pits formed allow ions and other foreign matter to enter the cell. This increases intracellular osmotic pressure. When pressure is applied inside the cell, it begins to swell. Ultimately, all of these events lead to cell wall rupture and cell lysis. This type of antibacterial activity is more present in Gram -ve cells than in Gram + ve cells. This is because gram + ve cells have more crosslinked layers of peptidoglycan and teichoic acid in their cell walls. Gram ve cells have little or no peptidoglycan layer and their cell walls are rich in lipopolysaccharide. Therefore, AgNPs have a low barrier and readily interact with Gram-ve cells. In Figure 2. Mechanism of action of antimicrobial activity of silver nanoparticles in cells.

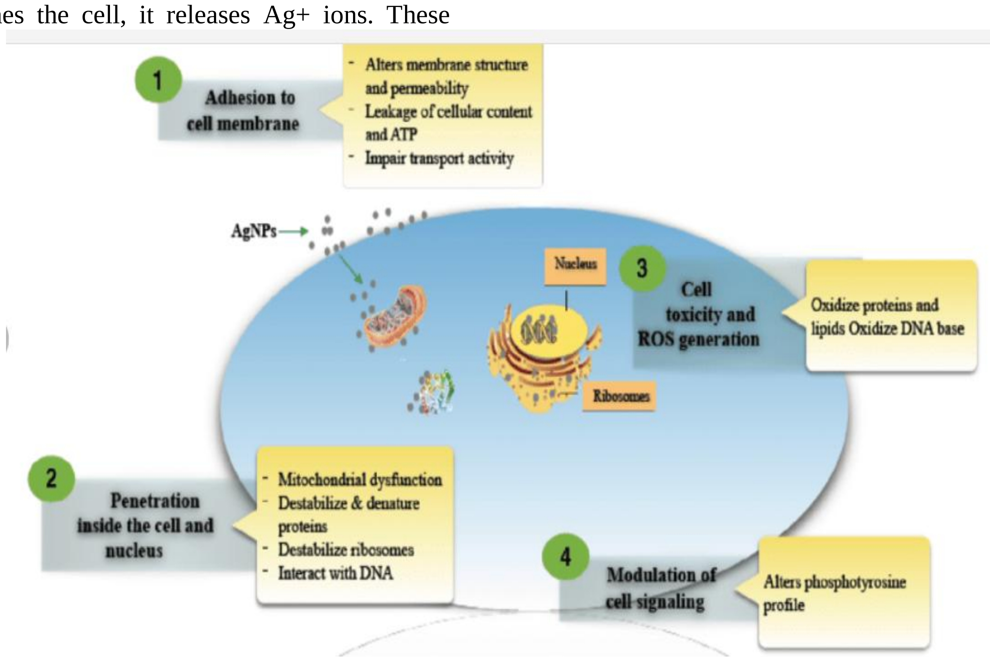

Figure 2. Mechanism of Antimicrobial activity of silver nanoparticles

ii. **Anticancer activity of AgNP:** As mentioned above, when pits are formed in the cell wall, Ag+ ions released from AgNP are taken into the cell. It then reaches the mitochondria where it interacts with thiol groups to bind to the NADPH dehydrogenase enzyme and release ROS. and damage the respiratory cycle. Formed ROS also interact with cellular components including proteins, sulfur and phosphorus. These formed ROS also bind to the phosphorus elements of DNA and RNA, inhibiting cell replication and protein

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synthesis. Binding to DNA causes toxic protein aggregation leading to cell death. Another possible action is autophagy. AgNPs have the ability to induce autophagy by accumulating autophagolysosomes in human ovarian cancer cells. This autophagy mainly he works in two ways. At low levels, it prolongs cell life. H. viability decreases, but elevated levels lead to cell death. In Figure 3. Mechanism of action of anticancer activity of silver nanoparticles in a cancerous cell.

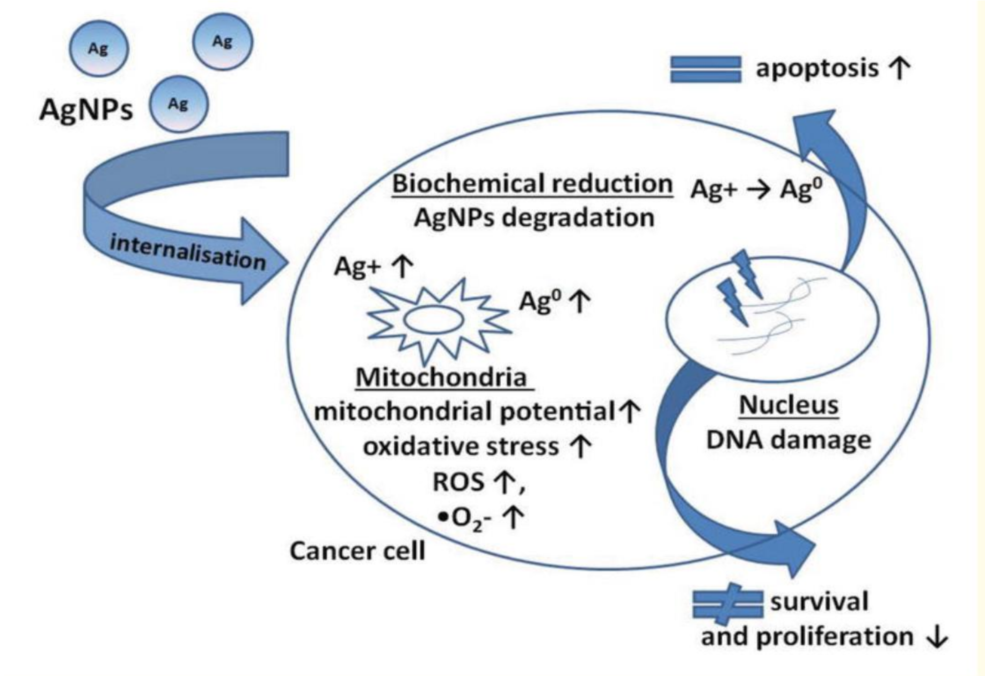

Figure 3. Mechanism of action of Anticancer activity of Silver nanoparticles

Role of Silver nanopartilcles in wound healing: The use of silver to heal wounds has a long history. 1850 BC In Egypt, silver was applied to wounds; Also, the positive effects of silver on wound healing are described in Hippocrates' textbooks Today, AgNP-based biomedical products such as silver-based creams and ointments as well as wound dressings are commercially available for a variety of medical applications due to their broad antibacterial properties.

Due to the attack of infectious diseases and the development of antibiotic resistance, pharmaceutical companies and scientists are looking for novel antibacterial. Indeed, the scientific interest in silver nanoparticles and biopolymers for wound healing applications significantly increased in last years, as demonstrated by the Scopus publication history during the period 2013–2017 based on the keywords “silver nanoparticles”, “silver nanoparticles biomaterial” and “silver nanoparticles-wound healing”, which generated 25, 593, 316, and 273 documents, respectively [91]. Sim et al. reviewed the patented silver-based products in the decade 2007 to 2017, including the use of antimicrobial silver for clinical and medical use, for personal care, for domestic, agricultural, and industrial applications. In 10 years, about 5000 new applications have been registered, mainly from Asian countries and in the Chinese language with 20% of patents in English. Therefore, interest in antibacterial silver has increased significantly in recent years, as evidenced by the increase in the number of publications and patents. In 2000, the number of patent applications based on antimicrobial silver was less than 200, and in 2017 it reached almost 1500In wound dressing applications, silver-based products have been patented and commercialized with more complex designs and improved efficacy compared to standard dressings.Biopolymers combined with bioactive antimicrobial, antibacterial, and anti-inflammatory nanoparticles have great potential in wound care to promote wound healing, particularly in the management of diabetic foot ulcers (DFUs), which still represent an enormous issue and are related to high amputation rates and clinical costs Dai et al. developed an antimicrobial peptide-AgNPs composite and have tested its wound healing properties in vivo on a diabetic rat model, demonstrating improved wound healing without side effects on dermal tissues and enhanced interactions between peptide and lipopolysaccharide moieties on bacteria, thus also indicating a wide-spectrum activity without inducing bacterial resistance. The multilevel antibacterial effect of silver considerably reduces the chances for microorganisms to develop resistance and increases the effectiveness against multi-drug-resistant organisms. The ability of AgNPs to heal wounds was demonstrated by Kumar et al. in an albino rat wound model. Animals treated with cream formulations containing varying ratios of AgNPs showed reduced wound area, increasedcollagen deposition, fewer macrophages, tissue edema, and more fibroblasts at the highest silver ratio. In heat-injured BALB/C mice, silver NP coating (14 nm) on dressings reduced inflammation and scarring, eliminated bacterial growth, and accelerated healing. gong etc. We also developed an ointment based on AgNP biosynthesis and demonstrated the efficacy of AgNPs in increasing wound healing activity and improving wound contraction in albino rats Results obtained by Adibhesami et al. demonstrated the positive effect of AgNPs on wounds in mice infected with Staphylococcus aureus, the most common causative agent of wound infections in vivo. In this study, rapid healing of infected wounds and increased area of reshaped wounds were observed without side effects. A nanocomposite impregnated with silver nanoparticles in a mouse model of streptozotocin-induced diabetes was reported by Singla et al.demonstrated accelerated wound healing through significantly increased expression of collagen and growth factors, improved re-epithelialization, vasculogenesis, and collagen deposition compared to control groups.Indeed, an active role in wound healing was attributed to silver, and, along with its distinctive role in preventing infection, silver nanoparticles can also drive the differentiation of fibroblasts into myofibroblasts, which in turn promotes the wound contraction, quickens the healing rate, and stimulates the proliferation and relocation of keratinocytes. Liu et al. studied the effect of AgNPs on keratinocytes and fibroblasts in an excisional wound model in rodents. Their histological studies and ex vivo wound model experiments demonstrated that AgNPs improve the proliferation and migration of keratinocytes from the edge to the center of the wound center and trigger the differentiation and maturation of keratinocytes, thereby promoting wound contraction. Wound closure was faster in the group treated with AgNPs . Frankova et al studied the response of primary human keratinocytes and fibroblasts after incubation with AgNPs, and they compared the effects of AgNPs on cell lines most affected during wound healing. The authors suggested that AgNPs could support the wound-healing process by inhibiting bacterial growth and pro-inflammatory cytokine production. you and others

The effects of nanosilver on wound healing were investigated in vitro and in vivo. They found that silver nanoparticles at a concentration of 10 ppm promoted fibroblast migration, and fibroblasts expressed more of the α-SMA (α-SMA) marker, which indicates silver's ability to convert and accelerate fibroblasts into myofibroblasts. do. healing process. The authors concluded that appropriately sized and concentrated silver nanoparticles could be a useful tool to maintain reasonable macrophage activation by modulating the local inflammatory response. The inflammatory response associated with the topical delivery of silver nanoparticles was described by Tian et al. in the mouse model.In particular, because of the important role of cytokines in wound healing, the authors analyzed the expression patterns of IL-6, TGF-β1, IL-10, VEGF, and IFN-γ using real-time quantitative RT-PCR. When they checked the cytokine profile modulated by the silver nanoparticles, they found differences in the mRNA levels of various cytokines. The authors also demonstrated scar reduction in the presence of nanosilver and supported the beneficial use of AgNPs for wound healing

Velázquez-Velázqueza et al.'s study. About AgNP-containing dressings. demonstrated antibiofilm activity against P.aeruginosa and human fibroblasts. The authors attribute the antibiofilm ability of AgNPs (metals and ions) to potential interference, inhibition, and/or regulation of exopolysaccharides (EPS) produced by bacteria.Prevention of microbial accumulation plays an important role in the rapid healing of wounds and avoids the high cost of antibiotics Controlling the bacterial load in the wound is critical for successful wound healing, and reducing the bacterial load in vivo with silver-containing

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dressings has been shown to accelerate the wound healing process

Rath et al.described the use of collagen nano matrices incorporating AgNP reservoirs for accelerated wound healing. In vivo, studies demonstrated excellent wound healing properties due to its unique antibacterial, anti-inflammatory, and hemostatic properties. Metcalfe et al studied the use of a silver-based antibacterial dressing on 112 difficult-to-heal wounds, and exudates, biofilms, and progression of wound healing were observed in 83% of cases. Various products can be functionalized with silver nanoparticles such as bandages, gauze, threads, bandages, and many other creams and ointments that may contain AgNPs for wound healing. In Table 1.there are some clinical trials of silver nanoparticles seen with year and outcome.

Nanoparticles	**Type of Wounds**	**Procedure**	**Outcome**	**Year**
AgNPs and AgSD	Particle thickness burns	RCT of AgNPs compared to AgSD in 54 pts	AgNPs were superior to topical AgSD for wound healing	2014
Aquacel Ag dressing	Venous leg ulcers	Multi-centre RCT comparing Aquacel Ag to Urgotul in281 pts	Better wound healing progression with Aquacel Ag	2012
Ag nylon (Silerlon)	Colorectal surgical wound	Prospective RCT comparing Ag with gauze dressings in pts undergoing colorectal op	Silverlon was safe and three times more effective	2011
AgNPs (nanocrystalline silver)	Leg ulcers	RCT OF AgNPs compared with cadexomer iodine in 281 pts	Similar antibacterial properties, Healing within 2 weeks AgNPs	2010
ANPs hydrofibre	Pilonidal sinus	RCT of Ag hydrofibres compared to sponge dressings in 43 pts	Ag hydrofibre is more cost-effective & wound healing	2010
AgNPs(Acticoat)	Freshly grafted burn	RCT of Acticoat compared to the standard management in 20 pts	Acticoat was cheaper & the effect on wound healing	2007
AgNPs	Partial thickness burn	RCT of AgNPs compared to 1% AgSD in 191 pts	Similar bacterial colonization.AgPs significantlyreduced healing time	2006
AgNPs	Superficial burn wounds	120 patients were randomized to receive:AgNPs/carbo n fibre/hydrogel/Vaseli ne gauze dressings	Water retention capacity was significantly higher in carbon fibre dressings	2007

Table 1. Clinical trials of silver nanoparticles on wound healing

Along with antimicrobial properties, silver treated textile materials and surgical sutures demonstrated in vitro improved wound healing properties, thus also indicating a positive effect of silver in terms of cell migration and proliferation For further improved wound healing, a synergistic effect of silver and sericin was demonstrated for wound healing, suggesting a successful combination between silver and silk proteins for improved antibacterial properties and tissue

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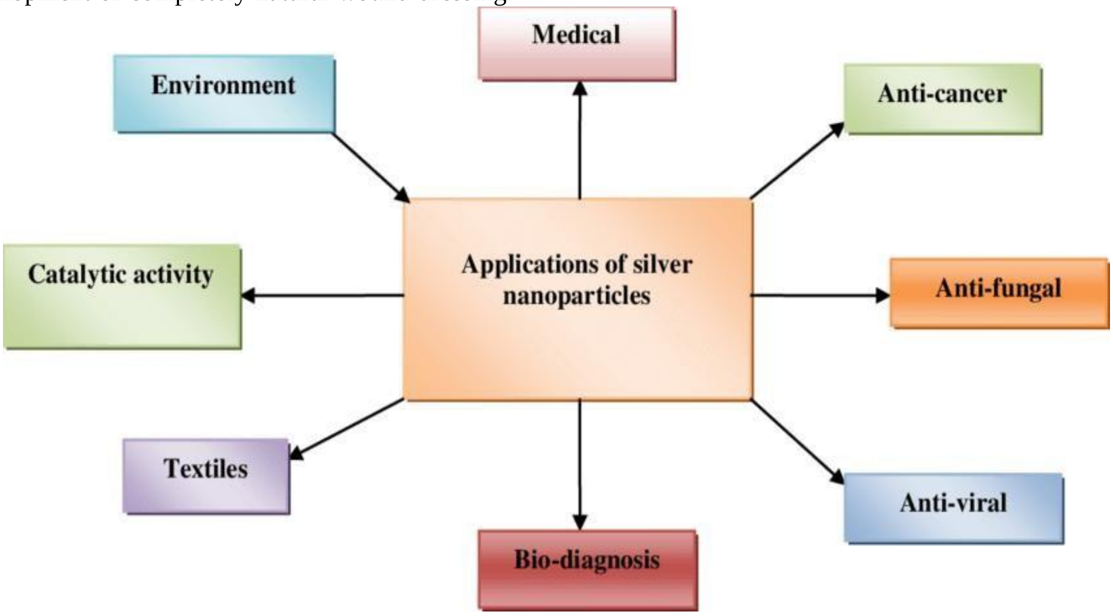
regeneration and opening new options for the development of completely natural wound dressing biomaterials.



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