EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 6
226-229
Year: 2018

BIOFABRICATED TOPICAL SILVER NANO MISSILES AGAINST INFLAMMATION

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Article Received on 29/03/2018 **Article Revised on 19/04/2018** **Article Accepted on 10/05/2018**

ABSTRACT
Nanobiotechnology is a new emerging dynamic domain of scientific research, being exploited extensively to overcome the size limitations to face many challenges in the divergent fields and almost revolutionarised the medical and pharmaceutical fields. Among various nano particles synthesized, silver nanoparticles biofabricated through green route are preferred due their unique catalytic, antimicrobial, anti inflammatory effects and wound healing efficacies, which could be exploited in developing better wound healing dressings and topical ointments. In our present review we have concisely reported on potentiality of silver nanoparticles in the process of wound healing, one of the major breakthrough in the medical field.

INTRODUCTION
Nanotechnology is a fast growing area in the field of science which is interdisciplinary field of both science and technology that increases the scope of investigating and regulating at cellular level between synthetic material and biological system (Du *et al.*, 2007; Sinha *et al.*, 2009). The term nano indicates one billionth of or 10^9 of a unit. Nanoparticles are defined as particles with size in range of 1 to 100nm at least in any one of the three dimensions. Due to very small size scale, they possess an immense surface area per unit volume, a high proportion of atoms in the surface area and near surface layers. So these nanoparticles serve as fundamental building blocks for many nanotechnology applications. Now this nanotechnology is gaining importance in various fields such as health care, food and feed, cosmetics, environmental health, biomedical science, chemical industries, drug and gene delivery, energy science, electronics, mechanics and space industries (Hassan *et al.*, 2012).

The various nanoparticles like gold, silver, copper, palladium, zinc and quantum dots (CdS, ZnS) are synthesized. Among these, silver nanoparticles are preferred due to their important properties such as optical, chemical, electronic, catalytic, magnetic, antimicrobial and biological labeling. Historically silver has found many applications in various fields, right from preparing culinary items to traditional medicinal extracts (Chiramane *et al.*, 2010). Nanosilver in the form of colloidal silver has been used for more than 100 years and 53% of the EPA (Environment Protecting Agency) registered biocidal silver products likely contain nanosilver (Nowack *et al.*, 2010). It has been reported that at lower concentrations silver nanoparticles are nontoxic to human beings and very effective against bacteria, virus and other eukaryotic microorganisms (Sharma *et al.*, 2009). So this antimicrobial capability of silver nanoparticles has been exploited in food storage containers, textiles, home appliances and in medical devices (Marambio-Jones *et al.*, 2011). They have been extensively utilized to make ointments to prevent infection against burn and open wounds (Ip *et al.*, 2006) and also used for binding with HIV gp 120 protein (Elchiguuerra *et al.*, 2005). It was recently found that they show cytotoxicity to human breast cancer cell line (MCF-7) (Devraj *et al.*, 2013).

A number of physical, chemical and microbial approaches are available for the synthesis of silver nanoparticles. In most cases, the surface passivator reagents (stabilizing agents) are needed to prevent nanoparticles from undergoing aggregation. Unfortunately many organic passivators such as thiophenol, thiourea, mercapto acetate, etc. are toxic enough to pollute the environment if large scale nanoparticles are produced. On the contrary green method of synthesis of nanoparticles is easy, efficient and eco-friendly in comparison to chemical-mediated or microbe-mediated synthesis. The chemical and physical synthesis involves toxic solvents, high pressure, energy and high temperature conversion and microbe involved synthesis is not feasible industrially due to its lab maintenance. Secondary metabolites from plant origin not only reduces silver ions but also act as capping agents to stabilize the synthesized silver nanoparticles through green route.Hence, green synthesis is the best option for the synthesis of nanoparticles.

Wound healing process

Wound is defined as damage or disruption to the normal anatomical structure and function. This can range from a simple epithelial integrity break to deep cuts into subcutaneous tissue by damaging other structures such as tendons, muscles, vessels, nurves, parenchymal organs and even bones. They can rise from an accident or internal injury or can be result of disease processes, whatever is the origin of wound it damages tissues and disrupts the local environments near wound. Wounds can be clinically categorized into acute, chronic and complicated wounds based on the time taken for healing.

Wound healing is a complicated and dynamic process, which involves a cascade of precise, continuous, co-ordinated, independent and sometimes overlapping of events including haemostasis, inflammation, proliferation (granulation of tissue formation), epithelization, maturation and remodelling of scar tissue (Lazurus, 1994). Despite the fact that the process of repair begin immediately after an injury in all tissues that all wounds go through similar phases of healing, specialized tissue such as liver, skeletal tissue and eye have distinctive forms of regeneration and repair and follow separate pathway (Skover, 1991).

Topical wound healing medication

Topical wound healing medications fall into 6 main categories,

- **Antiseptics:** Antiseptics are disinfectants that have a broad antimicrobial spectrum. The major advantage that they hardly ever select for resistant microbial strains, making them preferable to antibiotics with regard to the development of bacterial resistance.
- **Topical antibiotics:** Antibiotics are chemicals, produced synthetically or naturally, that act on specific targets to kill microorganisms, resulting in a narrower spectrum of activity than antiseptics. they are more likely to lose their efficacy to bacterial resistance.17 An additional known disadvantage of topical antibiotics is the occurrence of contact allergy
- **Granulation tissue suppressing agents:** Corticosteroids may be applied to suppress the early formation of healthy exuberant granulation tissue, thus facilitating epithelialization and wound contraction, but they should not be applied to an infected wound.
- **Topical herbal therapeutics:** A large number of herbal therapies and combinations of therapies currently exist for wound care. In general, these preparations consist of small amounts of the plant combined with a delivery substance (eg, ointment).
- **Enzymes:** Enzymes for wound debridement, trypsin, elase, and granulase are commonly used in the wound healing process.
- **Other topical agents:** Honey, lanolin, scarlet oil, vitamin E etc.

Silver as wound healing agents

Silver therapy, in principle, has many benefits, such as (1) a multilevel antibacterial effect on cells, which considerably reduces the organism's chances of developing resistance; (2) effectiveness against multi-drug-resistant organisms; and (3) low systemic toxicity. However, silver compounds such as silver nitrate and silver sulfadiazine are used for topical applications because they may be neutralized by anions (chloride, bicarbonate, and protein) in body fluids or cause cosmetic abnormality (Argyria, or blue-gray coloration) on prolonged use, and they can arrest the healing process via fibroblast and epithelial cell toxicity. Despite these shortcomings, silver sulfadiazine is the most popular topical antimicrobial silver delivery system in use because safer alternatives are unavailable**.**

Silver nanoparticles as Anti-inflammatory agents

Silver nanoparticles exhibit significantly novel and distinct physical, chemical, and biological properties and functionality due to their nano scale size. The major advantages of silver nanoparticles are,

- It is easy to synthesize silver nanoparticles in large scale by several simple, inexpensive, safe, and reliable ways, including wet chemical, physical and biological methods.
- They can be synthesized in sizes from 2 to 500 nm by changing the reaction parameters.
- They can be easily synthesized in different shapes (spheres, rods, tubes, wires, ribbons, plates, cubes, hexagons, triangles) by the selection of templates and reaction conditions (Patra, 2008).
- Because of the presence of a negative charge on their surface, they are highly reactive, which makes their surfaces modifiable by means of several biomolecules, a factor that aids in drug delivery. Because of the strong interaction between the silver surface and molecules containing thiol or amine (organic molecules, DNA, proteins, enzymes, etc), the surface of silver nanoparticles can be easily modified.
- Silver nanoparticles exhibit antibacterial effects against a large number of bacterial species (Silver, 2003).
- Bacterial resistance to elemental silver is extremely rare, emphasizing the presence of multiple bactericidal mechanisms acting in synergy (Srivastava, 2007).
- Anti-inflammatory properties of silver nanoparticles also promote wound healing by reducing cytokine release, decreasing lymphocyte and mast cell infiltration. Silver Nanoparticles as Antimicrobial Agents (Kim, 2007).

Mechanism of action of silver nanoparticles

Nanoparticles show strong antimicrobial activity and have no negative effect on the human body (Panyala, 2008). Application of nanoparticles on wound provides moist environment to wound for reducing infections and also act as a barrier to microorganisms to prevent secondary infection.

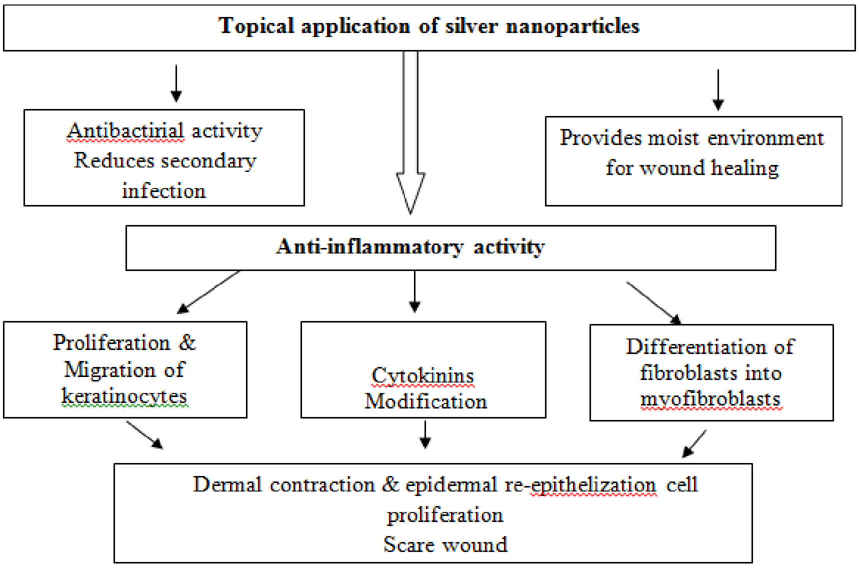

Fig1: Mechanism of action of silver nanoparticles.

Silver nanoparticles promote all of anti-inflammatory activities. A vital mediator in this anti-inflammatory cascade appears to be interleukin 10 (IL-10), which can be produced by keratinocytes as well as inflammatory cells involved in the healing process, including T lymphocytes, macrophages, and B lymphocyte. Decreases the production of cytokinins such as TGF-β, TGF-α, IL-6 and also decrease lymphocytes, mast cell proliferation and inducing apoptosis in inflammatory cells. By increasing the production of VEGF, vascular endothelial growth factor keratinocytes are motivated which helps in epithelization and wound healing.

CONCLUSION AND FUTURE PERSPECTIVES

Biocompatibility of any material can be improved through its size reduction. So the nanosized particles synthesis and their intrusion in medical field, after discovering the cellular and subcellular mechanisms underlaying the wound healing process had led to tremendous progress. Moreover, applying the knowledge of nanotechnology in preparing dressing material and topical wound healing ointments, could obviously lead to better future therapeutic invensions and also further conductin of *in vivo* molecular work to identify the exact mechanisms of nanosilver particles, might help to explore them more in medical field for the betterment of human race

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