Anticancer Properties of Silver nanoparticles

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***Abstract*: In recent years, there has been escalating interest in the biomedical applications of nanoparticles (NPs). In particular, silver nanoparticles (AgNPs) are increasingly being investigated as tools for novel cancer therapeutics, capitalizing on their unique properties to enhance potential therapeutic efficacy. However, questions as to are we able to contain or control the toxicity effects of AgNPs, and how much do we know about the toxicological profile of AgNPs which are commonly used in emerging nanotechnology-based applications, still remain. Hence, serious considerations have to be given to the hazards and risks of toxicity associated with the use of AgNPs. This review focuses on the current applications of AgNPs, their known effects and toxicity, as well as the potential of harnessing them for use in cancer therapy.In the present review silver nanoparticles (AgNPs) due to their superior physicochemical, and biological properties are intensively dealt with. The proper knowledge of these characteristics is essential to maximize their potential applications in many areas while minimizing their hazards to humans and the environment. Nanotechnology is a most promising field for generating new applications in medicine. However, only few nanoproducts are currently in use for medical purposes. A most prominent nanoproduct is nanosilver. Nanosilver particles are generally smaller than 100nm and contain 20-15,000 silver atoms. At nanoscale, silver exhibits remarkably unusual physical, chemical and biological properties. Due to its strong antibacterial activity, nanosilver coatings are used on various textiles but as well as coatings on certain implants. Further, nanosilver is used for treatment of wounds and burns or as a contraceptive and marketed as a water disinfectant and room spray. Thus, use of nanosilver is becoming more and more widespread in medicine and related applications and due to increasing exposure toxicological and environmental issues need to be raised. In sharp contrast to the attention paid to new applications of nanosilver, few studies provide only scant insights into the interaction of nanosilver particle with the human body after entering via different portals. Biodistribution, organ accumulation, degradation, possible adverse effects and toxicity are only slowly recognized and this review is focusing on major questions associated with the increased medical use of nanosilver and related nanomaterials.. This manuscript aims to critically review AgNPs synthesized via different approaches, its utilization in cancer treatment and future challenges.**

***Keywords*: Silver nanoparticles, antibacterial, anticancer, Medical application, treatment of cancer.**

Introduction

Nanotechnology is a most promising field for generating new applications in medicine. However, only few nanoproducts are currently in use for medical purposes. A most prominent nanoproduct is nanosilver. Nanosilver particles are generally smaller than 100nm and contain 20-15,000 silver atoms. At nanoscale, silver exhibits remarkably unusual physical, chemical and biological properties. Thus, use of nanosilver is becoming more and more widespread in medicine and related applications and due to increasing exposure toxicological and environmental issues need to be raised. Silver nanoparticles are one of the most commonly utilized nanomaterials due to their anti-microbial properties, high electrical conductivity, and optical properties. Incorporation of silver particles into plastics, composites, and adhesives increases the electrical conductivity of the material. Silver pastes and epoxies are widely utilized in the electronics industries. Silver nanoparticle based inks are used to print flexible electronics and have the advantage that the melting point of the small silver nanoparticles in the ink is reduced by hundreds of degrees compared to bulk silver. When sintered, these silver nanoparticle based inks have excellent conductivity. The medical properties of silver have been known for over 2,000 years. Since the nineteenth century, silver-based compounds have been used in many antimicrobial applications. Nanoparticles have been known to be used for numerous physical, biological, and pharmaceutical applications. Silver nanoparticles are being used as antimicrobial agents in many public places such as railway stations and elevators in China, and they are said to show good antimicrobial action. The optical, thermal, and catalytic properties of silver nanoparticles are strongly influenced by their size and shape. Additionally, owning to their broad-spectrum antimicrobial ability, silver nanoparticles have also become the most widely used sterilizing nanomaterials in consuming and medical products, for instance, textiles, food storage bags, refrigerator surfaces, and personal care products.

In recent years, there has been escalating interest in the biomedical applications of nanoparticles (NPs). In particular, silver nanoparticles (AgNPs) are increasingly being investigated as tools for novel cancer therapeutics, capitalizing on their unique properties to enhance potential therapeutic efficacy. However, questions as to are we able to contain or control the toxicity effects of AgNPs, and how much do we know about the toxicological profile of AgNPs which are commonly used in emerging nanotechnology-based applications, still remain. Hence, serious considerations have to be given to the hazards and risks of toxicity associated with the use of AgNPs.

The biological synthesis of nanoparticles has provided a means for improved techniques compared to the traditional methods that call for the use of harmful reducing agents like sodium borohydride. Many of these methods could improve their environmental footprint by replacing these relatively strong reducing agents. The problems with the chemical production of silver nanoparticles is usually involves high cost and the longevity of the particles is short lived due to aggregation. The harshness of standard chemical methods has sparked the use of using biological organisms to reduce silver ions in solution into colloidal nanoparticles.In addition, precise control over shape and size is vital during nanoparticle synthesis since the NPs therapeutic properties are intimately dependent on such factors.Hence, the primary focus of research in biogenic synthesis is in developing methods that consistently reproduce NPs with precise properties.

Medical applications

Silver nanopaticles are widely incorporated into wound dressings, and are used as an antiseptic and disinfectant in medical applications and in consumer goods. Silver nanoparticles have a high surface area per unit mass and release a continuous level of silver ions into their environment. The silver ions are bioactive and have broad spectrum antimicrobial properties against a wide range of bacteria. By controlling the size, shape, surface and agglomeration state of the nanoparticles, specific silver ion release profiles can be developed for a given application. It is a well-known fact that silver ions and silver-based compounds are highly toxic to microorganisms which include 16 major species of bacteria[1,2]. This aspect of silver makes it an excellent choice for multiple roles in the medical field. Silver is generally used in the nitrate form to induce antimicrobial effect, but when silver nanoparticles are used, there is a huge increase in the surface area available for the microbe to be exposed to. Though silver nanoparticles find use in many antibacterial applications, the action of this metal on microbes is not fully known. It has been hypothesized that silver nanoparticles can cause cell lysis or inhibit cell transduction. There are various mechanisms involved in cell lysis and growth inhibition. The high efficient antibacterial activity of AgNPs is due to the large surface area that comes in contact with the microbial cells and they have a higher percentage of interaction than larger particles of the same parent material. Recently AgNPs are combined with medical supplements, catheters, wound dressings and implants routinely for inhibition pathogen growth and also incorporate to cosmetics as an antiseptic and used in medical textiles to eliminate microbes from the clinical environment. AgNPs have a cytotoxic effect on cancer cells that AgNPs toxicity depends on their size, surface functionalization and concentration.

Dental caries represent one of the most extensive oral-cavity-related affections worldwide, being also an economic burden .By enhancing the remineralization process and controlling biofilm development, nanotechnology-derived dental-related strategies aim to limit or even eliminate the clinical impact of caries .In addition to their intrinsic highly biocompatible behavior, the materials for dental barrier membranes (DBM), which are often used for efficient alveolar bone reconstruction, must accomplish some specific and additional features and functions .Different metal-coated implants were evaluated against various pathogens responsible for dental-related biofilm formation and subsequent implant failure .

In order to prevent the pathogenic contamination of dental implants, proper tooth-brushing techniques, prophylactic antibiotics, and antimicrobial mouthwashes are specifically recommended . A major goal in dentistry is to provide the proper protection of the oral cavity, which represents a pathogenic-susceptible gateway for the entire body . Biofilms developed on dental implant surfaces may additionally cause inflammatory lesions on the peri-implant mucosa, thus increasing the risk of implant failure.
Silver was used for centuries in oral care and gained worldwide attention in the 19th century, being a major component in dental amalgams used for tooth restoration . AgNPs were also used in various fields of dentistry, such as dental prostheses, restorative and endodontic dentistry, and implantology . Thanks to their unique properties feasible for different domains of real interest in modern society, silver nanoparticles hold a prominent place in nanomaterial-related restorative, regenerative, and multifunctional biomedicine.

At the moment, the combination of therapy and diagnosis, known as theranostics, represents the most important, attractive, and challenging approach embraced by healthcare practitioners and researchers with respect to the effective and personalized therapy of cancer desideratum . AgNPs are also plasmonic structures, capable of particularly scattering and absorbing the light impinging certain areas. After their selective uptake into cancerous cells, AgNP-derived scattered light can be used for imaging purposes, whereas absorbed light can be used for selective hyperthermia.

Anticancer properties:

Cancer is multifaceted disease, extremely variable in its presentation, development as well as outcome. It is well established that cancer is a multifactorial disease caused by a complex mixture of genetic and environmental factors. However the knowledge of the genetic, molecular, and cellular basis of cancer can provide new targets and strategies for the therapy. Many anticancer drugs are unable to reach their target site in sufficient concentrations and efficiently exert the pharmacological effect without causing irreversible unwanted injury to healthy tissues and cells [3-5]. Nanotechnology offers a wealth of tools to treat cancer by passing biological barriers to deliver therapeutic agents directly [6]. The unique physicochemical characteristics of metal NPs, such as high surface-to-volume ratio, broad optical properties, ease of synthesis and surface functionalization offer new opportunities for cancer therapeutics. The production of silver nanoparticles (AgNPs) has become the object of intense research and several methods have been developed to synthesize noble metal NPs, including physical and chemical ones [7-9]. Their better penetration, and the possibility to track Ag NPs in the body make them a more efficient tool in cancer treatment with less risk compared to standard therapeutic procedures [10]. In addition, Ag NPs are used as an ablation tool for cancer cells due their ability to convert radiofrequencies into heat [11]. The Ag NPs induce autophagy in cancer cells by activating the PtdIns3K signaling pathway. The autophagy induced by Ag NPs was characterized by enhanced autophagosome formation, normal cargo degradation, and no disruption of lysosomal function. Consistent with these properties, the autophagy induced by Ag NPs promoted cell survival, as inhibition of autophagy by either chemical inhibitors or ATG5 siRNA enhanced Ag NPs-elicited cancer cell killing. Biological activity of Ag NPs in inducing cytoprotective autophagy, and inhibition of autophagy may be a useful strategy for improving the efficacy of Ag NPs in anticancer therapy.

The Metallo-pharmaceuticals were included within the research field that was previously dominated by organic compounds and natural products. Many platinum and platinum-based compounds including carboplatin and oxaliplatin were approved as antitumor agents [12]. However, numerous drawbacks of platinum-based pharmaceuticals were reported proving, therefore, their curative effects.Many cancer types are not susceptible to platinum drugs, and there are many toxic side effects, including gastrointestinal and haematological toxicity[13]. Moreover, several cancer cells have either intrinsic or acquired resistance to other platinating agents and cisplatin[14]. Consequently, current anticancer research has been devoted to the discovery of novel transition metal compounds. While silver was initially investigated because of its advantageous antimicrobial activity, there has been a recent interest in its anticancer functions. The biosynthesized silver nanoparticles are found to be effective in cytotoxic activity against tumor cells. Despite the widespread use of synthetic AgNPs, very few studies are conducted to determine the cytotoxic effects of biosynthesized AgNPs. Green synthesized silver nanoparticles inhibit the proliferation of cancer cells by activating the apoptosis process or changing the cellular chemistry. Biosynthesized AgNPs may also block the tumor growth by damaging the function of mitochondria or generaration of ROS. Plants are the natural treasures of secondary metabolites. In the green synthesis these phytochemicals acts as reducing and stabilizing agents of silver nanoparticles. The plant mediated AgNPs have shown dose and time dependant antitumor activity on cancer cells. The present study deals with the nature of different plants used in the synthesis of silver nanoparticles.

Combined cancer therapy allows limitation of the side effects of chemotherapy, decreasing effective doses or inducing cellular self-protection against damaging agents [15]. For many aspects of conventional therapies, combinations of novel drugs and NPs together with already well known compounds, is still tested. Searching for more effective protocols for drug administration leads to the modification of already existing procedures and combining pharmacological agents with natural, unconventional molecules. Metal-based AgNPs, known as pro-oxidative in different cancer cell lines [16] including breast MCF-7 and lung A549 cells [17] and squamous carcinoma SCC-25 cells [18], have shown novel applications in photodynamic therapy [19]. The alkaloid berberine was tested on squamous carcinoma cells as an antiproliferative and pro-apoptotic agent alone [20,21,22,23] or in combination with AgNPs that improved its anticancer properties [24]. The antimicrobial activity of AgNPs as aseptic or preservative agents has been known since decades, and they also serve for synthesis of novel nanomaterials with potential applications in regenerative medicine [25]. For many applications, compounds such as metal NPs should be carefully examined, especially when they are easily applied by living organisms. However the knowledge of the genetic, molecular, and cellular basis of cancer can provide new targets and strategies for therapy. Many anticancer drugs are unable to reach their target site in sufficient concentrations and efficiently exert the pharmacological effect without causing irreversible unwanted injury to healthy tissues.

There is increasing demands for anticancer therapy.In vitro cytotoxicity testing procedures reduces the use of laboratory animals and hence use of cultured tissues and cells have increased .The discovery and identification of new antitumor drug with low side effects on immune system has become an essential goal in many studies of immuno-therapies . Despite many efforts, multi drug resistance is still considered as a major drawback in chemotherapy of cancer which has been the subject of exhaustive experiments recently. Consequently, many attentions have been paid to natural compounds in marine organism and microorganisms. Many medically relevant nanoparticles such as AgNPs were investigated for their cytotoxicity aspect. AgNPs showed different degrees of in vitro cytotoxicity . Many attempts have been made to use silver nanoparticles as an anti-cancer agent and they have all turned up positive .The role of silver nanoparticles as an anti-cancer agent should open new doors in the field of medicine. Recently, AgNPs were also found to play an effective role in tumour control via their cytotoxic effects .

Several silver N-heterocyclic carbene complexes (SCCs) have been synthesized and tested for their anticancer activities that are active against ovarian, breast, melanoma, colon, renal, bladder, and prostate human cancer lines. The results of silver complexes SCCs provide effective inhibition of cancer cell growth against various cell lines, in which to eliminate the challenge of silver precipitating out in chlorinated solutions, SCCs have been successfully encapsulated into nanoparticles. AgNPs that biologically synthesized, have an efficacy of an anti-tumor agent using Dalton's lymphoma ascites (DLA) cell lines in vitro and in vivo.23 The antitumor properties of AgNPs may be a cost-effective alternative in the treatment of cancer and angiogenesis-related disorders. AgNPs synthesized by a microbiological method, were tested for their antitumor activity against MCF-7 and T47D cancer cells and MCF10-A normal breast cell line. These test results indicated in cell viability, apoptosis induction, and endo-cytosis activity of those cell lines that the effects of the biosynthesized AgNPs were directly related with endocytosisactivity.Moreover,AgNPshadhigherinhibitionefficacy in tumor lines than in normal lines of breast cells, which is due to the higher endocytic activity of tumor cells compared to normal cells. Green synthesis of silver nanoparticles (SNP) opens a new path to kill and prevent various infectious diseases and tumor.The activities of SNP were checked with human pathogens, plant pathogen and marine pathogen and studied the scavenging effect and anticancer properties against MCF-7 cell lines, in which the

SNP appears extremely fast, cost efficient, eco-friendly and alternative for conventional methods of SNP synthesis to promote the usage of these nanoparticles in medicinal application.

Conclusion: The silver nanoparticles proved unique anticancer activity against different types of cancer cells. The several syntheses approaches significantly affect the cytotoxic activity of the achieved Ag nanoparticles. Future challenges on AgNPs synthesis and their release into the environment other than scaling up production, assess several potential avenues for future works are to promote a safer and more efficient utilization of these nanoparticles. Taking all these data together, it is concluded that green synthesized Ag-NP's might be a potential candidate for the prevention and treatment of cancer. Furthermore, in order to use easy and safe green methods in scale-up and industrial production of well-dispersed silver nanoparticles, plant extracts are certainly better than plant biomass or living plants. However, better experimental procedures are needed for synthesis of well-characterized nanoparticles.

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