Biosynthesized Silver Nanoparticles for Cancer Therapy

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Biosynthesized silver nanoparticles using Olax scandens shows the potential application as drug delivery system along with fluorescence properties and anticancer, as well as antibacterial, activity.

Keywords: silver nanoparticles ; green chemistry approach ; Zinnia elegans ; cancer therapeutic

1. Introduction

Cancer is considered the foremost basis of mortality as well as morbidity worldwide. Millions are being affected by cancer every year as per global statistics, with 19.3 million new cases, followed by deaths of 10 million, in the year 2020 [1][2][3][4]. The conventional treatment therapies available for cancer treatment are surgery, chemotherapy, radiation therapy, hormonal therapy, and immunotherapy, with chemotherapy being the most popular. However, all of these conventional therapies have several limitations, including bioavailability, non-specificity, and toxicity [5][6]. Considering these limitations, researchers in the area of biomedical sciences have revolutionized cancer therapeutics with nanotechnology [7][8][9][10]. Nanotechnology is explored for cancer therapeutics and diagnostics using different nanoparticles as they aid either through active (using targeting agent) or passive (by enhanced permeability and retention effect) mechanisms for increased efficiency and low toxicity [7][8][9][10][11]. Among the different inorganic nanoparticles, silver is the most popular nanoparticle for cancer therapeutics [7][8][9][10][12]. However, the silver nanoparticles produced from the chemical and physical methods have certain disadvantages, which mainly include the use of harsh environmentally degrading chemical reagents and reaction protocols that use a lot of energy producing considerable amount of waste. Henceforth, scientists are focusing on the silver nanoparticle synthesis using biological sources such plant and animal extracts [8]. Biosynthesis is a feasible, easy, ecofriendly, and non-toxic method. Our group has already developed several biosynthesized nanoparticles (silver- and gold-based) using different sources of plant leaf extract, and demonstrated their biological properties in various ways. For example, biosynthesized silver nanoparticles using *Olax scandens* shows the potential application as drug delivery system along with fluorescence properties and anticancer, as well as antibacterial, activity [13]. Gold nanoparticles synthesized using *Eclipta alba* show biocompatibility and would be useful for drug delivery applications [14]. On the other hand, gold nanoparticles synthesized using *Hamelia patens* extract show pro-angiogenic properties [15]. Therefore, different nanoparticles produced with different plant extracts show varying biological properties due to the presence of various active phytochemicals and reducing agents. The biosynthesis of nanoparticles is a bottom-up process with biological agents assisting reduction, capping, and stabilization [13][16][17][18].

Other than the anticancer therapeutics, nanotechnology is also explored for disease diagnosis using their unique physico-chemical features such as radioactivity, fluorescence, magnetic properties, high electron density in nature, etc. [19]. Recently, non-invasive *NIR*-region (700–900 nm) based fluorescence imaging has been produced using nanotechnology. The *NIR* photons dig deeper into the biological tissues as compared to visible light, providing information about their structural and functional features without damage [20][21][22]. Different chemical based-*NIR* fluorophores are available but are associated with several limitations such as low sensitivity, issues with tissue penetration, large photon scattering losses, toxic in nature, etc., resulting in many opting for nanotechnology [6][19][23][24][25][26][27]. Recently, using nanotechnology, the *NIR* based fluorescent nanoparticles, especially those that are biologically synthesized, are preferred for non-invasive bioimaging [28]. To this end, our group already reported biosynthesized gold nanoparticles (AuZE), obtained by the reduction of gold salts using extracts of *Zinnia elegans*, that exhibit fluorescence at both the green (emission: 450 nm; excitation: 350 nm) and red regions (emission: 720 nm; excitation: 450 nm). The AuZE when injected intraperitoneally in C57BL6/J mice exhibited non-invasive *NIR* bioimaging (excitation: 710 nm; emission: 820 nm) [29]. However, these gold nanoparticles do not exhibit anticancer activity unless researchers use any chemotherapeutic drug. Hence, design of *NIR* based fluorescent nanoparticles having its own anticancer activity (without any drug) is always preferable for the study of cancer theranostics. Considering the above fundamental issues and knowing the anticancer

activity of silver from various published literature, researchers designed and developed silver nanoparticles (AgZE) using the leaf extract of *Zinnia elegans* (ZE). The *Zinnia elegans* plant has been selected for biosynthesis as it emits fluorescence in the *NIR* region as per the published literature [29]. Additionally, the ZE plant has several medicinal values such as hepatoprotective, antifungal, antihelmintic, antimalarial, anti-infective, phytoremediation, etc. [29][30][31]. During synthesis, some of the bioactive molecules can attach to the surface of the nanomaterials that show some biological activity. Interestingly, the biocompatible AgZE exhibits efficient anticancer activity as well as in vivo *NIR* based imaging (excitation: 710 nm; emission: 820 nm). The anticancer properties of the AgZE are thoroughly studied in vitro with its underlying mechanisms. The non-invasive in vivo imaging of AgZE is evaluated in the C57BL6/J mice (with and without tumor) illustrating their potential bioimaging activities. These new observations of anticancer as well as *NIR*-based in vivo imaging indicates AgZE as a theranostic agent with potential applications in future research.

2. Mechanism behind Anticancer Activity of AgZE

Earlier reports explain the idea behind the anticancer activity of silver nanoparticles to release of silver ions [8][13][32]. In one such report, Lu et al. exhibited the generation of silver ions and superoxide radical following the silver nanoparticle dissolution in dissolved oxygen as per the following reaction [33]:

$AgNPs + O_2$ (dissolved oxygen) $\quad Ag^+$ (silver ion) $+ O_2$ (superoxide radical)

Previous literature on silver nanoparticles has demonstrated the release of more silver ions (both chemically and biosynthesized silver nanoparticles) in acidic environment as compared to the normal environment [13][32][34]. Following this, the silver ions are released more in the acidic microenvironment of tumor cells than in the normal cells, causing increased cytotoxicity. Therefore, the cell viability MTT assay using AgZE on various normal and cancer cell lines corroborates with the earlier reports of illustrating more cytotoxicity towards cancer cell lines [13][32]. The cell uptake study also reveals increased uptake of AgZE by cancer cell (U-87) in 24 h as compared to the normal cell line (HEK-293T).

Henceforth, the increased incorporation, as well as anticancer activity of the AgZE, is due to: (i) enhanced uptake of AgZE by the cancer cells due to their upregulated cellular metabolic rate, cell proliferation rate, and overexpression of receptors [32][35][36], (ii) enhanced permeability and retention effect (EPR) due to the leaky vasculature of tumor [37], and (iii) nanoparticles/drugs behave differently with cancer cells than normal cells due to cell type behavior [5][38]. It has been also reported that curcumin (an anticancer agent) exhibits neuronal restoration at low doses despite their anticancer activity [39].

3. Preclinical Approach and Future Perspective

The translation of the nanomedicine for preclinical trials needs to address several critical issues. Firstly, target specificity of the nanoparticles and drugs to the desired site of the tumor tissues is a difficult challenge. A survey reported that less than 1% of the nanoparticles being injected reach the desired site of a tumor [40]. In the current study, the AgZE acts as both a therapeutic and diagnostic agent. The cell uptake studies indicated increased uptake of AgZE by 24 h as per the ICPOES data, showing the enhanced diffusion or internalization of the nanoparticles within cancer cells without any targeting agent or chemotherapeutic drug. Secondly, the production cost, toxicity, and the therapeutic efficiency regarding nanoparticles affect the translational use of nanomedicine in the market. The development and production of AgZE is cost effective, hence it is economical in nature and can be afforded widely if clinically approved in the near future after proper biosafety evaluation in large animals. The AgZE are even non-toxic in nature, established by both in vitro (cell viability in normal cells) and in vivo (hemolytic assay). The AgZE are stable and show good dispersibility due to their even pellet dispersion. Thirdly, the other issues associated with the nanoparticles are cell penetration, immunogenicity, long term toxicity, excretion, biodegradability, administration route and dosage, pharmacokinetics, and pharmacodynamics. Taking into account all the above-mentioned issues, AgZE has the potential to be a promising cancer therapeutic, as well as diagnostic agent, in the near future after evaluating its biosafety.

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