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PHYTO THERAPEUTIC AGENT CAPPED Ag-NPs COATED WITH HUMAN SERUM ALBUMIN ACTS AS A DRUG DELIVERY AGAINST BREAST CANCER

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ABSTRACT

Researchers in the field of nanomedicine have recently paid more attention to drug delivery systems based on nanotechnology because they can achieve ideal drug release and biodistribution. Serum albumin-based nano vehicles have been extensively created and studied due to their notable biological properties and many other materials that are utilized to prepare drug delivery vehicles for efficient cancer treatment. One of these is human serum albumin that is a remarkable promising carrier as an anti-cancer agent. HSA enjoys advantages such as long half-life, repeated recycling, and specific accumulation. HSA includes a number of binding pockets where different ligands, including fatty acids and ions, can bind, giving medications the choice of non-covalent binding sites. Moreover, HSA has lengthened the half-life of medications, lessen renal drug clearance and aid in drug accumulation in particular tumour tissues. HSA offers a promising chance to distribute well-known drugs in a novel method. Brucine is a plant alkaloid compound that was extracted from a fresh leaf of Wrightia tinctoria. Silver nano particles were synthesized by adding silver nitrate with brucine solution. Characterization of nano particles were done by using UV-vis Spectrophotometer, SEM and FTIR. Bioconjugation of HSA with Phyto therapeutic agent capped Ag-NPs were performed and studied in this review. Human serum albumin as a drug delivery vehicle against MCF-7 breast cancer cell line was performed and analysed in ex-vivo method. The results suggest that Phyto therapeutic agent capped Ag-NPs coated with HSA can be employed as a practical drug delivery system in cancer treatment.

KEYWORDS: Human serum albumin, Nanoparticles, Bioconjugation, Drug delivery.

1. INTRODUCTION

Small chemical compounds make up the majority of the medications that are now on the market and are used to treat a variety of human ailments. However these small-molecule medications frequently have drawbacks, including quick breakdown, brief circulation times, quick renal clearance, non-specific distribution, and hazardous buildup in particular organs or in particular tissues(Wang et al., 2020). Serum albumin, a naturally occurring ligand carrier that circulates for a long time in the blood and is highly concentrated, has demonstrated incredible promise as a delivery system for anti-cancer drugs. Albumin has the ability to extend the half-life of medications that are typically removed quickly from circulation and, more crucially, to encourage their accumulation within tumors(Hoogenboezem & Duvall, 2018). One class of effective drug delivery systems uses serum albumin as a well-behaved carrier material to encapsulate or conjugate therapeutic compounds for delivery of drugs that are targeted to tumors(Elzoghby et al., 2012). The most prevalent protein in plasma, human serum albumin that regulates plasma colloidal osmotic pressure and transports endogenous substances. The primary reason for selecting albumin protein as drug delivery cargo is its excellent biocompatibility, biodegradability, and non-immunogenicity (An & Zhang, 2017). Researchers' attention and enthusiasm for developing novel applications of nanotechnology to cure various types of cancer have been captured by the effective therapeutic benefits of cancer treatment assisted by nanomaterials that have appeared in recent decades(Barreto et al., 2011, Nazir et al., 2014). In that, AgNPs are extensively used in in-vitro and ex-vivo studies using various cancer cell models due to their inherent anticancer effect, some recent scientific studies have sought to exploit AgNPs in conjunction with anticancer pharmaceuticals(Morais et al., 2020). The tremendous anticancer potential of AgNPs has led to a breakthrough in the metastatic cancer treatment. Also, we evaluated the most current studies on the toxicological action of AgNPs at the cellular level, which portrays it as a powerful anticancer agent with clear therapeutic efficacy(Jabeen et al., 2021). Analytical methods such as UV-visible spectrophotometer, FT-IR and SEM analysis are used to characterize chemical nature and morphology of the synthesized AgNPs(Revathy et al., 2022). HSA conjugates have the ability to localise pharmaceuticals at specific sites and regulate drug release. HSA is therefore viewed as a viable option for the delivery of drugs in the treatment of cancer(Taheri et al., 2011). AgNPs application is recommended in transportation of conjugated drug molecules as it has no adverse effect on serum proteins. Since HSA is present in the circulatory system, it may be possible to use AgNPs in a variety of biomedical applications(Hazarika & Jha, 2020). However, the fundamental cause−effect relationships are still ill-defined so that a better understanding of the NP−protein interactions is essential in order to develop new functional and safe NPs that is

one of the most pressing areas of collaborative study in materials science and biology(Goy-López et al., 2012). After bioconjugation, cell line activities were studied. Breast cancer is a common malignancy that causes 14% of all cancer deaths and accounts for 23% of all cancer occurrences. For this study, Michigan Cancer Foundation-7 (MCF7) cells are utilised(Rao & Deeba, 2020). The human breast cancer cell line Michigan Cancer Foundation-7 (MCF7) is frequently employed in experimental investigations because the mammary epithelium of the breast cancer patient, like the MCF7 cell line, has individual characteristics. Hence, this cell line is a widely used research tool in the study of cancer(Holliday & Speirs, 2011). With these evidences, here we investigated human serum albumin as a targeted drug delivery vehicle using Phyto therapeutic agent capped Ag-NPs and its anti- cancer activity against Michigan Cancer Foundation-7 cell line for ex-vivo studies.

2. ALBUMIN AND ITS FUNCTIONAL STUCTURE

Human serum albumin (HSA) is a single chain of 609 amino acids and a molecular weight of 66.5 kDa. It contains the active albumin (585 amino acids) as well as signal peptides (1–18) and pro-peptides (19–24)(Larsen et al., 2016). The primary structure of HSA consists of one N-terminus, one C-terminus and three homologous domains such as domain I, II, and III. Each of the domains has two helical subdomains (IA and IB, IIA and IIB, IIIA and IIIB) respectively. Each of these subdomains consists of 4 to 6 α-helices(Sand et al., 2015a). Other blood proteins are glycosylated, while HSA is not. Moreover, because of its negatively charged surface and ability to diffuse in and out of blood arteries, HSA has a half-life of around 19 days in blood and is highly stable(Bern et al., 2015; Foss et al., 2016). HSA and BSA share 76% identity in the sequence(Huang et al., 2004)whereas serum albumins from different origins have an average sequence identity of over 62%(Majorek et al., 2012). HSA is a globular, heart-shaped protein contains repeating series of six helical subdomains(He & Carter, 1992; Sugio et al., 1999). HSA displays its excellent capacity to carry various ligands mainly due to its hydrophobic packets, providing potential applications in drug delivery. In the 3D structure of an albumin, there are two key regions—Sudlow site I and Sudlow site II—that serve as the protein's primary drug-binding sites(Sand et al., 2015).

3. MECHANISM OF HSA SERVES AS A DRUG DELIVERY VEHICLE

The primary role of albumin is derived from its contribution to the transport and oncotic pressure of plasma colloid. Albumin contains hormones, enzymes, drugs, and poisons in addition to stabilizing blood volume in circulation. In addition to maintaining the integrity of the capillary membrane, other physiological processes include antioxidant characteristics, free radical scavenging, and others(Zunszain et al., 2003). Many endogenous and external targets exist for this medication. Additionally, human albumin binds and transports a wide range of hydrophobic molecules, including endogenous (such as cholesterol, fatty acids, bilirubin, and thyroxine) and exogenous (such as drugs and toxins) substances, transition metal ions, and gas (nitric oxide NO), with implications for their solubilization, transport, metabolism, and detoxification(Neumann et al., 2010). Human serum albumin used as a potential drug delivery vehicle based on its properties like long half-life and accumulation in cancer tissues. It has a characteristics such as ease-of-diffusion towards epithelia,. Basically the tumor containing blood vessels are not well-organized, immature and leaky. Through leaky tumor blood vessels albumin can carry anti-cancer agents to tumor sites(Hoogenboezem & Duvall, 2018; Sand et al., 2015). There are many strategy for HSA to deliver drugs, including covalent linking drugs to the albumin are with chemical techniques, fusing peptide or protein using recombinant technology, non-covalently binding drugs to albumin and drug carrying albumin nano particle(An & Zhang, 2017). With notable benefits such abundance in blood, high concentration in tumor areas, superior binding efficacy with a variety of ligands, and an extension of circulatory half life, human serum albumin (HSA) has proven its adaptable and functional capabilities(Larsen et al., 2016; Sand et al., 2015b; Toh et al., 2020). They forecast that HSA via non-covalently binding, covalently binding, and genetic fusion techniques could generally function as a good drug delivery vehicle. In fact, a number of HSA-based or HSA-binding medications, including Albiglutide, Semaglutide, Abraxane, and Levemir, have been developed and successfully used in clinical settings(Hoogenboezem & Duvall, 2018b).

4. MATERIALS AND METHODS

Silver Nitrate

Nanoparticles (NPs) are used for drug encapsulation and delivery because they are more biocompatible than conventional treatments(X. Wang et al., 2008). Over the years, it has been emphasized that NP size reduction is crucial for increasing their bioavailability and suitability for therapeutic applications in conditions like cancer(Kim et al., 2007). Silver nanoparticles (AgNPs) have a great deal of potential for treating cancer because they selectively disrupt the mitochondrial respiratory chain, which produces ROS and prevents ATP synthesis, both of which result in DNA damage(AshaRani et al., 2009; Morones et al., 2005). The use of plants for the synthesis of AgNPs is justified since it is not only straightforward, quicker, and easier, but also because the synthesized particles were more reliable,

stable, and affordable than those produced by other traditional methods(Mohanpuria et al., 2008). With these evidences, here we investigated the green synthesis of AgNPs using aqueous extract obtained from leaf of Wrightia tinctoria and its cytotoxicity against ex-vivo MCF-7 cell line.

MCF 7 cell line

Glucocorticoid, progesterone, and estrogen receptors are present in the human breast cancer cell line MCF-7. It was created in 1970 by Dr. Soule of the Michigan Cancer Foundation in Detroit, Michigan, from the pleural effusion of a 69-year-old White woman who had metastatic breast cancer (adenocarcinoma). MCF-7 cells are beneficial for in vitro breast investigations because they retained a number of desirable traits unique to mammary epithelium, such as processing estrogen via estrogen receptors (ER) in the cell cytoplasm to produce estradiol. It is the first breast cancer cell line to respond to hormones(Electroporation-Based Therapies for Cancer, 2014). Our work has revealed that silver nitrate has a high cytotoxic potential at low concentrations on MCF7 human breast carcinoma cells and the apoptosis proportion of cells was increased by treatment of silver nitrate in MCF7 human breast carcinoma cells depolarizing mitochondrial membrane potential. These findings demonstrate that silver nitrate could be used as a pharmaceutical agent against breast cancers(Kaplan & Mehtap Kutlu, 2020).

Synthesis of AgNPs

Briefly, 1g of leaf extract powder (Brucine) was weighed and dissolved in 3ml of ethanol and mixed in 17ml of distilled water. This, plant aqueous extract solution was used in further studies. Then, 0.022g of silver nitrate was taken and dissolved in 100ml of distilled water(Song et al., 2009). Briefly, 5ml of prepared leaf extract aqueous solution was added to 95ml of 1mM aqueous silver nitrate solution separately for the reduction of Ag^{+} ions. The effect of temperature on synthesis rate and particle size/ shape of the prepared AgNPs was studied by carrying out the reaction in a water bath at 95^{0}C for 20 mins. Thus, the solution obtained was purified by repeated centrifugation at 3500rpm for 30 mins at room temperature, followed by resuspended of the pellet in distilled water to remove unwanted biological molecules. To ensure better separation of free entities from metal nanoparticles, the process of centrifugation and resuspension in sterile deionized water was repeated three times. By doing this, we can get rid of any uncoordinated biological compounds(Sukirtha et al., 2012).

Preparation of bioconjugates

HSA was purified by liquid chromatography using a Superdex 75 column that had been pre-equilibrated with 0.01 M phosphate before use. In order to completely cover the surface of a specific volume of HSA coated Ag-NP solution, 1 mL of an HSA stock solution with a concentration 10 times in excess to a defined volume of Ag NP solution(10^{12} NPs/mL) was added. Spectrophotometric analysis was used to measure the protein concentration using a molar absorption value of 35 219 M^{-1} cm^{-1} at 280nm(Pace et al., 1995). In order to track the development of protein adsorption on the NP surfaces, protein-NP bioconjugates were incubated for varying lengths of time (between 0 and 48 h) with slow stirring. After incubation, the bioconjugate samples were centrifuged between 8000 and 16000rpm for 20 min (the larger the size, the lower the speed) and then the sample was resuspended in protein-free water solution, and then centrifuged again to remove any excess unbound or loosely bound protein molecules to the NP surfaces(Capule & Yang, 2012; Casals et al., 2011). Then, the bioconjugates were determined by Dynamic Light Scattering method.

5. BIOMEDICAL APPLICATION

One of the biggest causes of death and illness in the globe is cancer. Radiation therapy, chemotherapy, and surgery are currently the most widely used cancer treatments(Urruticoechea et al., 2010). However, their drawbacks, such as renal toxicity, liver toxicity, or decreased drug availability at the target location, outweigh their advantages(Lomis et al., 2016). A target-specific and biocompatible drug delivery method, such as human serum albumin, can be used to solve these issues(Abbasi et al., 2012; Jeong et al., 2016; Satya Prakash, 2010). The properties of HSA-NPs include biocompatibility, biodegradability and non-immunogenicity(Satya Prakash, 2010). By enhancing the increased permeability and retention (EPR) effect rather than administering free medicines, this has improved tumour targeting(Maeda et al., 2000).

6. CONCLUSION

Human serum albumin (HSA) has demonstrated its adaptability and functionality with major advantages including abundance in blood, high concentration in tumor areas, superior binding efficacy with a range of ligands, and an extension of circulatory half life. They predicted that HSA may generally serve as an effective drug delivery vehicle by non-covalently binding, covalently binding, and genetic fusion approaches. Albiglutide, Semaglutide, Abraxane, and Levemir are only a few of the HSA-based or HSA-binding medicines that have been created and utilised successfully in clinical settings. To conclude, the present study documented the first ever synthesis, characterization

and cytotoxicity of biosynthesized AgNPs from Wrightia tinctoria against ex-vivo MCF-7 cell line with human serum albumin. Collectively, our data suggests that AgNPs possess superior cytotoxic activity compared to the Wrightia tinctoria aqueous extract. With little uncovered mechanism in the current study, there is a wide scope for detailed investigation in the future for the application of AgNPs in cancer therapy. Human serum albumin as a drug delivery vehicle against MCF-7 breast cancer cell line was performed and analysed in ex-vivo method. The results suggest that Phyto therapeutic agent capped Ag-NPs coated with HSA can be employed as a practical drug delivery system in cancer treatment

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