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Bio-Synthesized Silver Nanoparticles Using Different Plant Extracts as Anti-Cancer Agent

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Abstract

With the development of the biogenic nanotechnologies, scientists are looking new ways to design novel strategies for the treatment and diagnosis of cancer. Advances in nanotechnology have attracted many researchers to the biogenic synthesis of metallic NPs because of its advantages like, simple, fast, one pot processes, economical and biocompatibility. Medicinal plants are selected to be the best reservoirs of diverse phytochemicals for the biogenic synthesis of silver nanoparticles (AgNPs). In this review, the top point discussed is mechanistic advances in the synthesis of AgNPs from medicinal plant extracts. We have discussed the recent improvements achieved in the use of biogenic AgNPs as cancer theranostic agents. Anticipating all of the challenges in the field of cancer, we hope that biogenic AgNPs may become a potential cancer therapeutic and diagnostic agent in the near future.

Keywords: Cancer; Biogenic synthesis; Medicinal plants; Nanomedicine

Introduction

In the past era of anticancer research, very few developments have been made with regard to the practical progress towards cancer therapy. Deficiencies in the field to manage therapeutic moieties to achieve the preferred targets to cure cancer with minimal or no side effects [1]. Most importantly the acknowledgment that 1 and 10 parts per 100,000 of intravenously managed monoclonal antibodies come to their *in vivo* parenchymal focuses. There are two general, synergistic objectives that would be endeavoured to raise the efficacy of per dose of every therapeutic and secondly to provide the agents containing the therapeutic to overwhelmed biological barriers that retain it after achieving its goal. A much better therapeutic framework would be focused against clusters of cells in the initial stages of cancer [2]. Such type of framework faces many difficulties including the distinguishing proof of appropriate early markers of neoplastic infection and advancement after some time the arrangement of such markers in the early recognizing protocols and screening; and advancement in the targeted delivery of many therapeutic agents, biomarkers and for coordinated capability of avoiding biophysical and biological obstructions [3].

Nanotechnology

Nanotechnology is an emerging and multidisciplinary field, which cover enormous and various range of procedures derived from fields like biology, chemistry, physics and engineering. These devices contain nano-vectors as a carrier for anticancer drugs. Formally the definitions of nanotechnological devices feature the supplies that the device and its basic parts are man-made, and the range of the dimension must be in between 1-100 nm. In his definition of nanotechnology, George Whitesides 11 places less stringent limitations on the exact dimensions, and characterizes the 'right' size in bio-nanotechnology in an operational manner in biology [4]. Nanotechnology conveys the possibility to be applied at the molecular level to control the matter of apprehension. This is a dynamic field including biology, chemistry and physics of the nano scale objects. Remarkable research in nanotechnology has opened up new roads for drug delivery, treatment and diagnosis for cancer and many diseases other than cancer as well. Nanotechnology combined with metal nanoparticles has been effectively applied in various fields most importantly in biomedical sciences. Nanoparticles are considered suitable theranostic agents because of their shape, size and extraordinary optical and thermal characteristics [5]. These outstanding characteristics of metal based nanoparticles, which are due to a ratio of specific size and elevated surface area to volume, make them perfect for many biological applications, including therapeutic diagnostics [6].

Synthesis of Nanoparticles *via* Biological, Chemical and Physical Methods

Nanoparticles (NPs) synthesis can be carried out from various methods *via* physical, chemical and biological methods. Nonetheless, recent research shows that biological methods have assumed an awesome part in the synthesis of metal nanoparticles [7]. Micro-organisms such as fungi and bacteria can be used to synthesize nanoparticles, but on other hand the synthesis involving plants provides an eco-friendly and satisfactory approach since it is without the utilization of numerous costly, lethal and unsafe materials [8]. Among various biological resources, plants provide an ideal platform for the synthesis of NPs. Different advantages of plant derived nanoparticles contain rapid synthesis, improved stability and cost value. Furthermore, nanoparticles of numerous sizes and shapes can be produced using plants as compared with other organisms [9]. As compared to plants bacteria and fungi that require long incubation times for decrease of metal ions, the phytochemicals can do it rather rapidly and take out the need of costly and time consuming

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downstream processing. Green synthesis resources like fungi and bacteria trigger some biosafety issues, which are neutralized by using plants for green synthesis. In this manner, plants are the best applicants for green synthesis to synthesizing metal nanoparticles [9,10]. With improvements in medicinal plants research and nanotechnology, there is an expansive increment in possible treatments of diverse categories of cancer, benefitting patients economically. This interface for developed multifunctional plant derived nanoparticles has attracted many cancer treatment researchers and scientists [11]. These green synthesized nanoparticles can beat a portion of the footraces in predictable treatment and diagnostic therapies. The nanoparticles maintain a site specific and targeted activity that increases the efficacy of the drug, as the nanoparticles can avoid immune responses and cross the impermeable membranes [12] and therefore can be valuable for combating cancer. Metal nanoparticles possess surface plasmon resonance in UV-visible regions due to the coherent presence of free electrons in the conduction band, while dielectric constant, size and particle surroundings determine the band shift [13].

Importance of Metal Nanoparticles

An interesting feature of the metal nanoparticles is that absorbance of the wavelengths gives a thought regarding their shapes and sizes properties. Metal nanoparticles have been observed with enormous interest for increasing alternative therapeutics and diagnostics strategies of cancer treatment [14]. Engineered, biocompatible, functionalized and inert metal nanoparticles can be of important interest in the coming years for cancer therapeutics and diagnostics. Observing and discovery of tumours with labelled nano-crystals and targeted drug delivery with chemotherapeutic drugs have been established. Metal nanoparticles are considered among the most efficient ones for biomedical applications because to their use as an imaging resource and their multifunctional therapeutics and diagnostic abilities, for example, their antibacterial, antitumor and drug carrier properties [15]. Colloidal silver is viewed as an intense anticancer and antimicrobial operator. The chemical means of synthesis include chemical compounds to reduce Ag^+ to AgNPs; in any case, the chemical methods are often undesirable because of low biocompatibility [16]. Green synthesis, also called "biogenic synthesis", is considered an alternative approach for synthesizing the AgNPs and has given rise to a novel field: 'Phyto-nanotechnology', which deals with green synthesis of metal nanoparticles *via* exploitation of plant resources and further contains its optimization and applications. The shape and size of the AgNPs is influenced by the solvent type, stabilization and reduction [17]. The process of synthesis starts after incubation of the plant extracts with silver salts, silver nitrate is mostly used. The synthesis of noble AgNPs is a one step process that initially contains the reduction of Ag ions to Ag^+, followed by the agglomeration and stabilization that lead to the formation of oligomeric clusters of colloidal AgNPs [18,19]. The process of reduction takes place in the presence of biological catalysts. A general view to biogenic synthesis of silver NPs by the combination of plants extracts and silver nitrates salts (Figure 1).

Causes of Cancer

Cancer is caused by transformation on genotypic level that triggers a series signals on molecular level which later lead to tumor formation in cells. A state of cancer can be define, an uncontrolled cell division and subsequent invasions of healthy cells and tissues [20]. Cancer is one of the big risk factors of morbidities and mortalities everywhere throughout the world. The American Cancer Society expects that the worldwide burden of cancer will rise to 21.7 million cases by the year 2030 [21]. As indicated by a report distributed by iMShealth Institute for Healthcare Informatics in June 2016, the worldwide market for cancer treatments raised to a record level of US$107 billion in 2015, and is expected to reach US$150 billion by 2020 [22]. It is assessed that one out of eight deaths is the result of cancer and close to 70% of all cancer deaths occur in low and

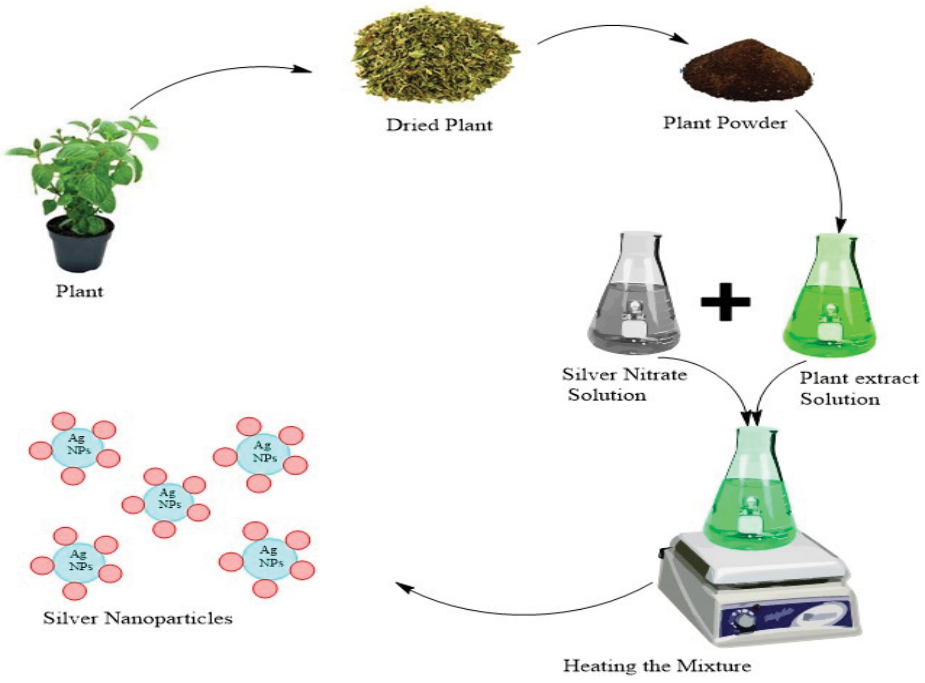

Figure 1: A schematic view of biogenic synthesis of silver nanoparticles.

middle income countries. Roughly one of every five people suffers from cancer before 75 years of age, while one out of ten in this age range is predicted to die due to cancer [23]. The increasing rates of cancer indicate that there will be a 60% increase in cancer incidence by 2030 [24]. The origins of cancer can be approximately classified as external and internal factors. External factors include chemical exposure, radiation and viruses. For example, the risk factor of cancer is high among workers frequently exposed to ionizing radiation and toxic metals [25]. Internal factors include hormones, mutations and immune conditions, which may act chronologically to trigger or promote the process of carcinogenesis [26]. Development in cells is caused by changes in qualities that trigger a movement of occasions on the atomic level, in the end prompting tumor development. Dangerous state of cancer is represented by uncontrolled cell division and ensuing attacks of solid cells and tissues [27]. Tumor is one of the actual hazard variables of morbidities and mortalities everywhere all over the world. The American Cancer Society predicts that the worldwide weight of malignancy will increase to 21.7 million crisp cases by the year 2030 [24,28]. According to a report circulated by iMShealth Institute for Healthcare Informatics in June 2016, the worldwide market for tumor medications developed to a record level of US$107 billion out of 2015, and is relied upon to achieve US$150 billion by 2020 [29]. It is surveyed that one out of eight deaths is the eventual outcome of disease, and almost 70% of all tumor deaths occur in low and centre salary nations. Around one of each five people encounters disease before 75 years of age, while one out of ten in this age run is anticipated to bite the dust because of growth. The increasing rates of malignancy demonstrate that there will be a 60% development in tumor occurrence by 2030 [24]. The reasons for malignancy can be extensively delegated outer and inside variables. Outside elements incorporate concoction presentation, radiation and infections. For instance, the danger of tumor is high among specialists often presented to ionizing radiation and poisonous metals [30]. Inner components incorporate hormones, transformations and safe conditions, which may act sequentially to trigger or improvement the technique of carcinogenesis [31].

Silver Nanoparticles Mechanism of Inhibition

The development of nanotechnology and nanomedicine revolutionized therapeutic and pharmaceutical industry. Scientists are trying to exploit nanoparticle to develop new diagnostic tools and antimicrobial agents. The use of silver nanoparticles (AgNPs) in various fields like chemistry, material science, physics and medicine on its peak [32]. An experiment reported by Asharani et al. in 2009 about the treatment of cells with AgNPs explains calcium transients. Previous studies demonstrates the linking of oxidative stress with Ca^{2+} transient that ultimately increases permeability changes of mitochondria. The process of AgNPs binding to plasma membrane receptors and Ca^{2+} signaling are rapid while the endocytosis or diffusion rate followed by the attachment with intracellular targets are comparatively slow. During the incubation period the activation of Ca^{2+} channels by the diffusion of nanoparticles are relatively high [33]. Moutin et al. in 1985 reported that the Ag^{+} and Ca^{+} or have the same site thus Regulate sarcoplasmic reticulum to release Ca^{2+}. The release of Ca^{+} from the intracellular stores can be inhibited by the high concentration of Ag^{+} as the high concentration of Ca^{+} ions that gives a specific bell shape curve. Ca^{+} ions fluctuations could be triggered by the release of Ag^{+} from AgNPs [34].

Mitochondria, Caspas 3/9 Pathways and Apoptosis by the AgNPs

Pores in mitochondrial membrane are open and then the membrane is disrupted during the apoptosis process. When cells are treated with AgNPs, they show a decrease in the red fluorescence while the green fluorescence is increased. The opening of mitochondrial membrane is controlled by two genes; one gene "Bcl-2" prevent its opening while the second gene "Bax" accelerate it [35]. Apoptosis signal are induced by the AgNPs *via* a caspas dependent pathway along with the involvement of mitochondria. Caspas 9/3 can be activated by AgNPs by time dependent manner stimulated by the disruption of mitochondrial membrane. Previous studies suggest that the process of apoptosis is stimulated by AgNPs through the presence of ROS in *in vitro* systems [36].

Signal generated by mitochondria have an important role in apoptosis and many regulators of apoptosis can induce the inhibition of the integrity of mitochondria during the apoptosis process [37]. Usually the caspas pathway is activated due to the oxidative stress caused by the release of cytochrome c from the intermembrane space of the mitochondria into the cytosol [38]. A model given below to explain the toxicity mechanism of AgNPS (Figure 2) [39].

Challenges in Cancer Nanotechnology

The foundation of the transformational progressions that leads toward malignancy would be recognized early, as a matter of normal screening, by non-invasive tools for example, the blood samples are analyzed for proteomic pattern, or the *in vivo* imaging of molecular profiles and evolving lesion contours. Biology of the host-disease relationship can be precisely determined, and manage decisions for focusing on and obstacle escaping approaches for an interposition design. Treatment effectiveness would be observed in actual time. Creating methods for *in vivo* identification and observing cancer biomarkers. Imaging technologies for clinical cancer do not hold enough spatial determination for early discovery in light of lesion anatomy. But the newly emerged field nanotechnology is expected to yield novel detecting techniques, for example which are based on the measuring its physical properties from which the contributions of the fouling molecules may be systematically decoupled by appropriate mathematical algorithms [40].

Nanoparticle advancements are under development and testing as applicant multifunctional, molecularly or physically targeted contrast agents for all clinical imaging modalities, with the goals of recognizing smaller and prior growth stage of cancer tumours, identifying molecular expressions of neoplasms and their micro-environment, and providing improved anatomical definition for lesions [41]. Weissleder and colleagues recently demonstrated that lymphotropic paramagnetic nanoparticles allow the MRI imaging of clinically occult lymph node metastases in patients with prostate cancer, which are not detectable by any other non-invasive approach. Polymeric dendrimers were utilized as gadolinium nano-carriers to image the lymphatic drainage of breast cancer in mice [42], indicating that this procedure could be used clinically instead of SENTINEL LYMPH-NODE BIOPSY. Dextran-coated, ultra-small paramagnetic iron-oxide nanoparticles were shown to outperform conventional gadolinium MRI contrast in terms of intraoperative permanence of imaging improvement, inflammatory targeting, and detectability at low magnet strength in the surgical treatment of brain tumour. Bimodal nanoparticles, carrying a near infrared optically detectable fluorochrome conjugated to an MRI

contrast agent cross-linked iron oxide were used for the preoperative, contour defining imaging of a brain tumour, and the intraoperative visualization of the lesion [43]. An alternate way to deal with molecular detection *in vivo* involves the use of implantable sensors, equipped with technology to relay sensed information extra corporeally. From many years the unsolved challenge for the clinical deployment of implantable molecular sensors remains the unwanted, non-specific adsorption of serum proteins on the sensing surfaces [44].

Silver Nanoparticles as Anti-Cancer Agent

Green synthesized colloidal biogenic AgNPs are not only subjugated for the therapy of different types of cancers, but also have promising application in diagnosis, such as bio-sensing, bio-imaging and MRI imaging, among other applications. Nano-drug particles and advancement in nano-formulations for drug delivery were examined, which includes the production, stability, characterization, formulation, and delivery [45]. Recently biogenic synthesis of nanomaterials is exposed as a practical and eco-friendly strategy, mainly because of its green chemistry principles. Apart from the eco-friendly strategy, interaction of biological compounds with noble metals will be useful for the advancement of diverse tools and devices for an extensive variety of uses in biology and medicine. Inorganic nanoparticles significantly interactive with cells and intracellular macromolecules like proteins and DNA. Cellular up-take of nanoparticles leads to era of reactive oxygen species which provoke oxidative stress. Moreover, nanoparticles easily cross the nuclear membrane and therefore they can interface with DNA specifically or indirectly although the exact mechanism for this interaction is not yet known [46]. It is clearly proven that synthesized AgNPs induces cell damage through the loss of cell membrane integrity, oxidative stress and apoptosis. AgNPs treated MCF-7 cells indicated most readily clear effect is the alteration in cell shape apparent morphological variations for example, coiling and cell shrinkage compared to control cells. Bio-synthesized AgNPs cause cellular damage in Hep-2 cell line through the formation of ROS was reported elsewhere [47].

In the future, biogenic AgNPs will be promising entities subjugated for diagnosis of cancer due to their self-fluorescence ability. The emission of bright red fluoresce inside the cancerous cell upon treatment with biogenic AgNPs clearly indicates the internalization of these nanoparticles by cells. While incubating the cells with these nanoparticles it enters inside the cell having fluorescent molecules attached during synthesis [48]. Hurdles for biogenic AgNPs as future cancer nanomedicine before testing on humans, AgNPs should be properly assessed for their potential toxicity, biocompatibility and side effects [49]. History shows widespread use of silver as a potent therapeutic agent, while silver nanoparticle has been a therapeutic agent for more than 100 years [50]. Several researchers in the last decade have experimentally proven the nontoxic status of AgNPs *in vitro* (Table 1), which varies significantly from *in vivo* condition.

The toxicological aspect of AgNPs is highly depends on factors like size, shape, morphology, surface curvature and concentration of silver nitrate salts [69]. Moreover it's very important to check interactions between biogenic AgNPs with both single molecules protein coronas like ubiquitin, bovine serum albumin, human serum albumin, tubulin and complex protein coronas like fetal bovine serum and proteins of yeast extract. Interaction of AgNPs with biological fluids leading to formation of AgNPs protein coronas can have unexpected results *in vivo*, ultimately interfering and effecting

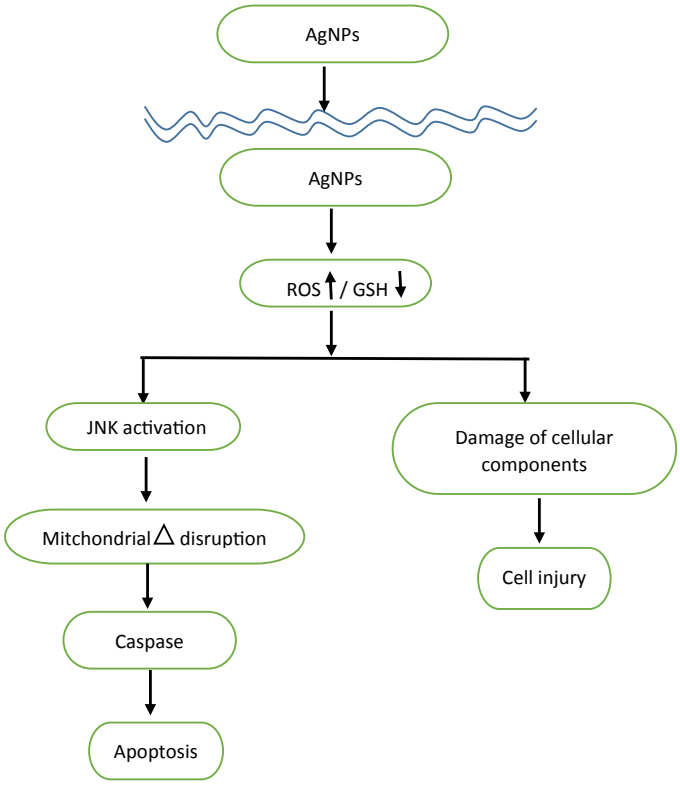

Figure 2: Apoptosis mechanism through different pathways of ROS generations, damage to cellular components and intracellular GSH depletion.

Sl. No.	Plant name	Plant part	Cell line	IC50 value	Size and shape of AgNPs	Characterization				References
						AgNO3 (Mm)	pH	Temp (C)	Incubation time	
1	*Quercus*	Fruit	MCF-7	50 µg/ml	40 nm (Spherical)	1	9	45	-	[51]
2	*Rheum emodi*	Root	MCF-7	Dose	27.5 nm (Spherical)	1	7	Room	24 h	[52]
3	*Sesbania grandiflora*	Leaf	MCF-7	20 µg/ml	22 nm (Spherical)	1	7	37	24 h	[53]
4	*Podophyllum hexandrum*	Leaf	Hela	20 µg/ml	14 nm (Spherical)	0.25–3	4.5–10	20–60	30–150 min	[54]
5	*Syzygium cumini*	Flower	Hela	Dose	<40 nm	1	Neutral	Room	6 h	[55]
6	*Rosa indica*	Petal	HCT 15	30 µg/ml	23 – 60 nm (Spherical)	1	Neutral	Room	60 min	[56]
7	*Vitex negundo L*	Leaf	HCT 15	20 µg/ml	22 nm (Spherical)	1	Neutral	37	4 h	[57]
8	*Rubus glaucus benth*	Leaf	Hep-G2	Dose	12–50 nm (Spherical)	1	Neutral	Room	48 h	[58]
9	*Suaeda monoica*	Leaf	Hep-2	500 nM	31 nm (Spherical)	1	Neutral	35	5 h	[59]
10	*Plumeria alba*	Flower	COLO 205	5.5 µg/ml	36.19 nm (Spherical)	1	Neutral	Room	30 min	[60]
11	*Achillea Biebersteinii*	Flower	MCF-7	20 µg/ml	12 nm Spherical	5	Neutral	40	3 h	[61]
12	*AlternantheraSessilis*	Aerial parts	MCF-7	3.04 µg/ml	10–30 nm Spherical	3	Neutral	Room	6 h	[62]
13	*Alternanthera sessilis*	Leaf	PC3	6.85 µg/ml	30–50 nm Spherical	3	Neutral	Room	6 h	[63]
14	*Andrographis echioides*	Leaf	MCF-7	31.5 µg/ml	68.06 nm Hexagonal	1	Neutral	Room	12 h	[64]
15	*Azadirachta indica*	Leaf	MCF-7	4.25 µg/ml	<40 nm Spherical	1	Neutral	Room	6 h	[55]
16	*Azadirachta indica*	Leaf	SiHa	Dose dependent	2–18 nm Triangular, hexagonal	1	8	Room	-	[65]
17	*Butea monosperma*	Leaf	MCF-7	Dose dependent	20–80 nm Spherical	0.1	Neutral	Room	2 h	[66]
18	*Citrullus colocynthis*	Callus	Hep-2	3.42 µg/ml	31 nm Spherical	1	Neutral	Room	24 h	[67]
19	*Cucurbita maxima*	Petal	A431	82.39 µg/ml	76 nm Spherical, cuboidal	1M	02-Oct	20-100	5-60 min	[68]
20	*Moringa oleifera*	Leaf	A431	83.57 µg/ml cuboidal	94 Spherical	1M	02-Oct	20-100	5-60 min	[68]

Table 1: Biosynthesized silver nanoparticles against human cancer cell line.

the biological activities (anticancer, antimicrobial, antifungal, etc.) of AgNPs [70]. It is of paramount importance that scientists should discover more about the formation of AgNPs and protein coronas to fully understand the *in vivo* faith of these metallic nanoparticles. Bio-synthesized AgNPs induces DNA damage in MCF-7 cells. A vital part of DNA harm is the formation free radicals (oxidative stress) mainly influences the single strand break and olive tail movement were seen in the present investigation expose that the generated ROS favours the DNA harm prompting cell demise which is exceedingly responsive hydroxyl radicals discharged by the AgNPs attack cellular components including DNA, lipids, and proteins to cause variety of oxidative damages. Besides, the outcomes were demonstrated that AgNPs were found to expand the DNA tail length in a comet test, which measures DNA strand breaks as well as alkali labile sites [71]. Furthermore, populations of nanoparticles, each with one of many different colors might be conjugated with antibodies to different molecular targets. This offers the potential advantages of readily identifying the conjugate markers, yielding specific information on their tissue distribution, introducing new protocols that include cell surface, endo-cellular and micro-environmental antigens in the same test. The use of nanoparticles as selective, enriching harvesting agents for serum proteomics has been proposed [72].

Conclusion and Recommendations

The important role of nanotechnology in the recognition of transforming different cell population early, is based on the *ex vivo* analysis or *in vivo* imaging technique. It will not only help in the appropriate combination of agents but will also avoid biological barriers in the early cancer lesions to completely eliminate issues related to health. Furthermore, biocompatibility of green synthesized AgNPs toward normal cells is beginning to a new era in the cancer diagnosis. Characterization and toxicity screening of biogenic AgNPs is strongly recommended before production at commercial scale. We hope that biogenic AgNPs might become a potential cancer nanomedicine in the near future. The rapid increase in demand of biogenic metal nanoparticles for multiple applications increases the need for their industrial production in stabilized formulations. Therefore, effort is

being exerted on biological synthesis of AgNPs as cancer nanomedicine. For optimum yield, many parameters such as pH, temperature and incubation time, salt concentration need optimization. The hidden phytochemicals compounds of plants responsible for reduction and stabilization of biogenic nanoparticles. Green synthesis of biogenic NPs for cancer diagnosis still needs a lot of research. Moreover, issues such as biocompatibility, bioavailability, toxicity and clearance of AgNPs all need to be investigated in-depth *via in vivo* trails to develop potential therapeutic and diagnostic agents for cancer.

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