REVIEW ARTICLE

Role Silver and Bimetallic Nano Particles Synthesized by Green Chemical Methods for their Therapeutic Potential for Cancer: A Review

Hayder D. Saleem[1], Thulfeqar A. Hamza[2], Samar E. Izzat[3]*, Doaa A. Hamad[4], Mahmood J. Abdulhasan[5], Ayat H. Adhab[6]

[1]*Al-Manara College For Medical Sciences, Maysan, Iraq*
[2]*Department of Medical Laboratory Techniques, Al-Mustaqbal University College, Babylon, Iraq*
[3]*Al-Nisour University College, Baghdad, Iraq*
[4]*Department of Nursing, Hilla University College, Babylon, Iraq.*
[5]*Environmental Research Group, Scientific Research Center, Al-Ayen University, Thi-Qar, Iraq*
[6]*Department of Pharmacy, Al-Zahrawi University College, Karbala, Iraq*

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ABSTRACT

Cancer is one of the critical public health challenges in the world. All cancer therapies have been used without the best choice due to these therapies being limited in activities with many side effects representing new problems. With time researchers have tried to find an advanced strategy for more activity with less toxicity and fewer side effects. Nanomaterials witness very large success as drags for many diseases and hold a promising future in complex, incurable diseases such as cancer. Bio-synthesized or what we name green chemistry of metallic nanoparticles, which shown promising results, encourage cancer use before using as drug delivery systems. This review highlights an overview of the materials that could be used as reduction reagents to synthesize AgNPs and bimetalic Ag: AuNPs and Ag: PtNPs by using them as nano-therapeutics for cancer with less side effect.

Keywords: AgNPs, Bimetallic, Bio-synthesis, Cancer, Reduction agents.

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INTRODUCTION

Cancer is a disease with an enormous worldwide impact. Cancer and antibiotic resistance may be the reason behind killing about 1.5 million people, giving real and series indicators '' antibiotics and current chemotherapeutics are not as effective as they were in the past''. This fact highlights how to solve this problem or reduce it completely.[1] Currently, the advances in nanotechnology significantly influence human health, mainly represented by two parameters: the first, increase the drug solubility and sensitivity with selectivity. The best suggestion for this problem is to use nanomaterials as the therapeutic agent for different medical materials.[2] The second parameter was the administration route, low localization effects, and related drug resistance limit the further utilization of antibiotics, which is 12 types as reported[3] in Figure 1. As potential broad-spectrum antibiotic agents, Nanoparticles have a better response over evolved resistance to conventional antibiotics or Superbugs. Their large surface area to volume ratio provides a large area to interact with surrounding microorganisms.[4] Nanoparticles

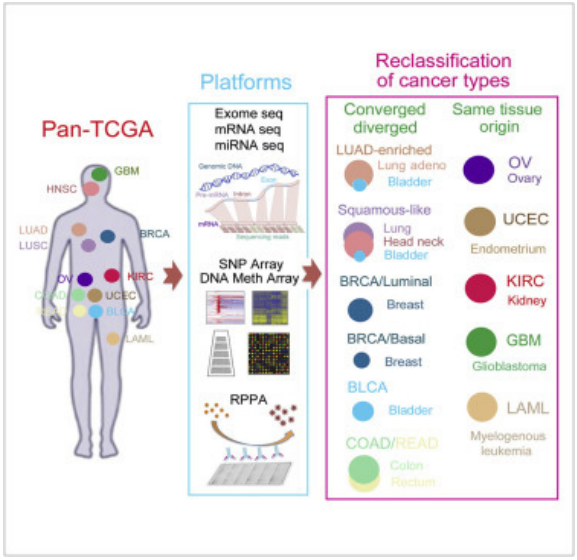

Figure 1: Typical skim for classification of cancer according to the tissues origin

Author for Correspondence: samar.e.anesth@nuc.edu.iq

(NPs) can be functionalized with diverse molecules for targeting, stealth, or payload delivery features to the NPs of 1–100 nm size range.

A new eco-friendly chemical strategy for preparing nanomedicine represents a critical requirement to face the problem of preventing exposure to cancer or trying to reduce its influence. The best choice can be related to the use of green chemistry due to is non-toxic, cheap and environmentally friendly.[5] One of the most important solutions for this problem was the development opportunity nanomedicine and by using metallic NP such Ag with depend on green chemical synthesis such as natural plant extracts.[6]

Green synthesis could be a replacement choice for simple, cheap and environmentally friendly, without side effect, an alternative approach for the synthesis of AgNPs. The synthesized nano materials were characterized using techniques such as UV-visible, Raman spectroscopy, transmission electron microscopy, Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), and energy dispersive X-ray.[7] Mostly, the anti-bacterial activities were estimated by measuring minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and minimum fungal concentration (MFC). In this review, we review samples for some green synthesis of AgNPs in pristine and hybridization with ether metal which tested as anti-bacterial for cancer therapy under spontaneous and triggered anti-bacterial action. The review highlights the sources that could be used as reduction agents to convert Ag in precursor in micro-scale to Ag in Nanoscale by testing the inhibition activities for synthesized AgNPs in two cases alone and with hybridization metals.

Yeast and Fungus for Pristine AgNPs

Figure 2 includes images for Rhizopus stolonifer yeast, *Trichoderma viride* fungus, light micrograph and the lower photos for fungus *T. viride* were extracted the reduction reagents. Extraction of yeast was used by Skóra *et al.*[8] to synthesize AgNPs with different concentrations of AgNO3 as a source of silver and exist of a reduction agent. Antimicrobial tests for AgNPs showed inhibit activities against the bacteria growth, without impact on fungi growth high inhibitory potential of bacteria biofilm formation but also eradication for established biofilms. The four mammalian normal and cancer cell lines were tested on the cytotoxic effect of the NPs through the metabolic activity, cell viability, and wound-healing assays simultaneously, which showed potential as the material for root-end filling with deep penetration to the root canal.

Rhizopus stolonifer was used from Banu *et al.*[9] to snthesized AgNPs isolated from local soil samples and inoculated by an appropriate amount of malt glucose yeast peptone broth and behave as reduction agent to convert $AgNO_3$ to AgNPs. The synthesized AgNPs were spherical, 3-D nanoparticles ranging between 5 to 50 nm. The biologically testing for synthesized nanoparticles and efficacy on cancer cells was investigated on two cancer cell lines, HT-29 (colon cancer) and EAC. Anticancer activity was assessed using an MTT assay, which shows AgNPs had excellent anti-cancer activity against both tested cells.

Kulandaivelu and Gothandam[10] used fungus *T. viride,* as shown in Figure 3, for the extracellular biosynthesis for AgNPs from AgNO3. The *in-vitro* cytotoxic effect of AgNPs against MCF-7 cancer cell lines was assessed, which could significantly acting as an inhibition agent in a time and concentration-dependent manner by MTT assay. Various concentrations of AgNPs were used to test cytotoxic effects by, ranging from 1 to 100 µg/mL. The maximum concentration of AgNPs makes significant cytotoxic effects and the apoptotic features were confirmed through caspase-3 activation and DNA. The study results show that biologically synthesized silver NPs might be effective in treating breast cancer and could be a new potential adjustment chemotherapeutic and chemo-preventive culture supernatant of *Nocardiopsis sp.* MBRC-1.

Manivasagan *et al.*[11] used culture supernatant of *Nocardiopsis sp.* MBRC-1 as a reduction reagent for the simple and cost-effective green synthesis of silver nanoparticles from AgNO3 at room temperature. The synthesized AgNPs also looked spherical in shape with an average particle size of 45 ± 0.15 nm. The analysis with FTIR shows that the protein

Figure 2: The images for *Rhizopus stolonifer* yeast, *T. viride* fungus, light micrograph and the lower photos for fungus *T. viride*

Figure 3: The images of summer Savory and *S.ovatum* leaf

component in the form of enzyme nitrate reductase may cause reduction and as capping agents. The prepared AgNPs behaves with strong antimicrobial activity against bacteria and fungi, and the cytotoxicity of AgNPs against vitro human cervical cancer cells showed a dose-response activity with IC50 value was 200 micro g/mL of AgNPs against the cell.

Summer Savory and *Stigmaphyllon ovatum* leaf

Figure 3 shows two types of summer savory and *S. ovatum* leaf extracted to produce reduction agents. Shahram *et al*.[12] used the biosynthesis method when using extract of summer savory to prepare AgNPs from AgNO3 and that was hexagonal structure with a size ranging from 10 to 100 nm. The anti-cancerous performance for AgNPs was evaluated, which showed MTT assay demonstrated exceptional anticancer effects against K-562 and MCF-7 human cancer cell lines with IC50 values 50 and 200 mg/ml, respectively. The antimicrobial properties of the synthesized AgNPs were examined by MIC, MBC, and MFC against five microbial strains included *Klebsiella pneumonia, Escherichia coli, Enterococcus faecalis, Staphylococcus aureus*, and *Saccharomyces cerevisiae* which showed active behavior.

Gudikandula *et al*.[13] successfully synthesized AgNPs from AgNO3 using the culture filtrate of *Ganoderma enigmaticum* and *Trametes ljubarskyi* white-rot fungi materials at room temperature. The activity of AgNPs was tested in cytotoxic effect in disposing of the human lung cancer cell line (A549) and human breast cancer cell (MCF-7) by using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay after treatment for 24 h. The results for improving concentrations of AgNPs (40–120 µg/mL) at 24 h reduced viability of cancer cell lines and substantial cytotoxic effects toward the treated cells were shown at 120 µg/mL concentration.

***Padina tetrastromatica* Seaweed Extract**

P. tetrastromatica seaweed, as shown in Figure 4 is used as a source for reducing synthesized NPs. Clara *et al*.[14] depend on using marine sources represented by Padina tetrastromatica seaweed extract, to synthesize AgNPs due to the presence of active components. The medical applications were made by cytotoxicity against breast cancer MCF-7 cells of the inhibitory concentration (IC50) was found for AgNPs at 24 h incubation.

The Walnut Green Husk and Fruit of *Diospyros malabarica*

Khorrami *et al*.[15] used walnut green husk reported with *D. malabarica* in Figure 5 as a reducing and stabilizing agent for synthesized AgNPs.

The synthesized NPs high stability behavior significantly improved the cytotoxicity, and antioxidant activity of the green synthesized AgNPs against a cancerous cell line compared with the walnut green husk extract and a commercial silver nanoparticle. The new activity may relate to a synergistic effect of the synthesized AgNPs and its biological coating.

Bharadwaj *et al*.[16] studied *D. malabarica* fruit and the potential of forming AgNPs. They analyzed its anti-bacterial and anti-cancer activity, a rapid, single-step, cost-effective and eco-friendly method for synthesizing AgNPs at room temperature. The TEM analysis shows that the average size of AgNPs, was 17.4 nm.

Pathogenic microorganism strains of *S. aureus* and *E. coli* were used to test the anti-bacterial activity of the silver nanoparticles by the well-diffusion method. The results of inhibiting the growth of bacteria with an average zone area of (8.4 ± 0.3 mm and 12.1 ± 0.5 mm) and (6.1 ± 0.7 mm and 13.1 ± 0.5 mm) at 500 and 1000 µg/mL concentrations of AgNPs, respectively. The anti-cancer effect of the AgNPs was also confirmed with MTT assay using the U87-MG (human primary glioblastoma) cell line, which shows IC50 value equal to 58.63 ± 5.74 µg/mL.

Bio-metallic Nanoparticles with AgNPs

Hybridization of AgNPs was done with Au and Pt, which used extracted materials from leaves and root of some plants.

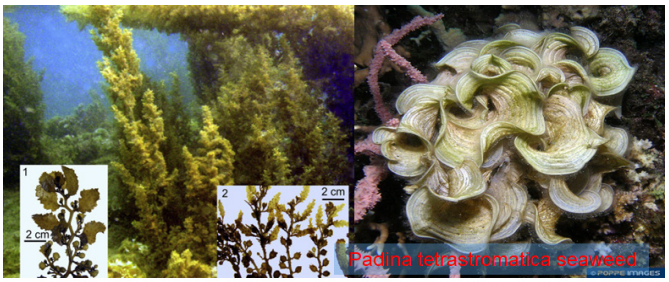

Figure 4: The external appearance for some of *P. tetrastromatica* seaweed

Figure 5: External images for walnut green husk and *D. malabarica*

Figure 6: Images for *S. ovatum* leaf

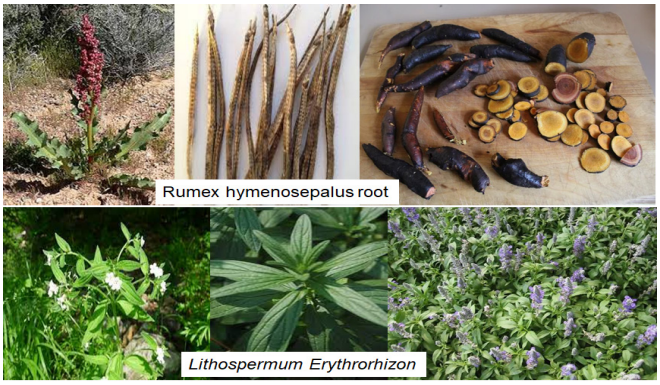

Figure 7: Photograph images for *R. Hymenosepalus* root and *Lithospermum Erythrorhizon*

Abdel Hamid *et al*.[17] used an aqueous extract of sago pondweed (*Potamogeton pectinatus* L.) as a reduction agent to synthesize bimetallic Nano particles Ag:AuNPs, which looks spherical in shape, with some nanotriangles and hexagons. Alloy-type Au–Ag nanoparticles could be synthesized at pH 12. Then those NPs were kept stable over 3 weeks. The outcomes show that the proteins and flavones of plant extract cause synthesis and stabilization of the NPs.

S. ovatum leaf extract was used by Elias *et al*.[18] to synthesize AgNPs, AuNPs, and Ag:AuNPs in an aqueous medium with Particle sizes 24, 80, and 15 nm, respectively. The concentration values of Ag:AuNPs, AgNPs and AuNPs, were 5.75×10^{-16}, 9.1×10^{-9}, and 0.0027 µM, respectively, representing the best for the maximum cytotoxity toward the growth of the carcinoma cells with the IC50 (Figure 6).

Rumex hymenosepalus root extract also used by Villalobos *et al*.[19] for synthesizing Au:AgNPs bimetallic nanoparticles core@shell structure by sequential *R. hymenosepalus* root extract as redactor agent. the particle morphology for NPs was quiz spherical and size 36 ± 11, 24 ± 4, 13 ± 3 nm for Au:AgNPs, AuNPs and AgNPs respectively which analyzes by TEMs images. A growth kinetics study was performed using the Gompertz model for microorganisms exposed to NPs, which refers to the best response for Au@AgNPs and AgNPs with Au@AgNPs hamper the growth rate and also the phase of *E. coli* and *Candida albicans* inder a dose-dependent manner.

L. erythrorhizon and *R. hymenosepalus* roots were reported in Figure 7. Shkryl *et al*.[20] Used green chemistry for the rapid and easy biological synthesis of AgNPs, AuNPs, and Ag-AuNPs by the callus extract of Lithospermum erythrorhizon as a reducing agent. The results showed the formation of spherical and non-spherical crystalline shapes, with the reduction agent's product.

CONCLUSION

Green chemistry does not synthesize many materials without any harmful byproduct for the environment but also finds substitution materials for different reactions. Leaves and roots or bacteria can be used successfully as a reduction agent responsible for converting Ag precursors to AgNPs in easy, simple and cheap methods and are commonly used as an inhibition for cancer with different types. The testing of activities of AgNPs in pristine or hybridization with AuNPs or PtNPs in bimetallic NPs were confirmed by assessment the value of IC50 by assay MTT. Generally AgNPs in binary systems Ag:AuNP and Ag:PtNPs behave higher activities than Ag:NPs. The synthesis of bimetallic not only increases the activities of AuNPs but also increases the sensitivities and selectivity without any toxicity for cells of bodies which is important requirement to prevent side effect.

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