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REVIEW PAPER

# Emerging Antineoplastic Gold Nanomaterials for Cervical Cancer Therapeutics: A Systematic Review

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## Abstract

Cervical cancer, a malignant neoplasm arising from cervix cells, remains one of the leading global cause of women cancer-related deaths. The present study was aimed to conduct a comprehensive systematic review to show the anticancer activity of biological mediated gold nanoparticles (AuNPs) against cervical cancer cells. To identify the articles, a systematic search was performed through the electronic databases including Web of Science, PubMed, Scopus, Science Direct, ProQuest, Embase, and Cochrane for the articles published up to 31 August 2019. Thirty-three articles met our eligibility criteria and were entered into the present systematic review. Our finding showed that twenty-eight articles stated the biogenic AuNPs-induced cytotoxicity against cervical cancer cells, whereas five reports said no cytotoxicity. In this study, the proposed molecular mechanisms of biogenic AuNPs-induced cytotoxicity were discussed. In total, the studies suggested the induction of apoptosis and overgeneration of intracellular reactive oxygen species (ROS) through the AuNPs-treated cervical cells. The information of this study may help the researchers for translation laboratory setting studies to clinical researches. Future investigations are required to represent the efficacy of biogenic AuNPs through in vivo models alone or combination with other anticancer drugs.

**Keywords** Cancer nanotechnology · Nanotoxicity · Anticancer activity · Cervical cancer cells · Gold nanoparticles

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## Introduction

Nanotechnology encompasses the science, engineering, and technology of materials at the scale of 1 to 100 nm [1]. Nanotechnology is a multidisciplinary field of study that influences a broad area of sciences such as physics, chemistry, biology, etc. [2, 3]. Cancer nanotechnology deals with the role nanotechnology to overcome the cancers as an innovative strategy for their diagnosis and therapeutics [2, 4]. Cancer nanotechnology is an emerging and promising field of study that design smart anticancer nanomedicines to increase the efficacy, specificity, and absorption rate of anticancer drugs resulting in a significant fall in drugs systemic toxicity. The synthesis of nanocarriers to entrap the chemotherapeutic drugs for targeted drug delivery systems as well as sustained and controlled drug release systems using micelles, liposomes, dendrimers and nanoparticles (NPs) [5]. The Food and Drug Administration of United States defined nanomaterials as "materials that have at least one dimension in the range of

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approximately 1 to 100 nm and exhibit dimension-dependent phenomena" [1]. Among different kind of nanomaterials, noble NPs seem to be much more attractive for pharmaceutical and biomedical applications such as drug delivery, photothermal therapy, radiotherapy, and imaging due to their unique chemical, mechanical, optical and biological properties compared to their bulk counterparts [1, 5]. Noble NPs are prepared through biological, chemical and physical methods. It is believed that the biological approaches are much safer than chemical methods owing to the lack of toxic chemicals and also much more cost-effective than physical methods [6, 7]. The biological techniques include the use of different biological resources as reducing and stabilizing agents to change the noble metal cations to their nano-forms [8–11]. AuNPs are classified as a group of noble metal NPs with a wide range of pharmaceutical and biomedical potentials. The high bioavailability and low immunogenicity of AuNPs made them attractive for evaluation of their anticancer efficacy against different cancers alone or in combination with other anticancer drugs [5]. Recent years, the anticancer potency of biomimetic synthesized AuNPs against cervical cancer cells through in vitro investigations has been reported [12–14]. However, some of the laboratory studies have shown less or no cytotoxicity of biogenic AuNPs against cervical cancer cells [15–18]. Hence, the efficacy of biogenic AuNPs against cervical cancer cells is still unclear.

Cervical cancer is known as a malignant neoplasm originating from cervix cells. The National Cervical Cancer Coalitions estimated that developing countries are suffering from eighty percent of cervical cancer cases. World Health Organization (WHO) estimated that over 474,000 women per year would die by 2030 and an estimated over 95% will occur in low- and middle-income countries [19]. Hence, cervical cancer is considered as one of the leading cause of cancer related deaths all around the world. Human papillomavirus (HPV) infection, smoking, age, oral contraception usage, etc. are some of the considerable risk factors that are associated with cervical cancer [20]. Up to know, 216 identified subtypes of HPV have been reported among which subtypes of 16 and 18 are classified as high-risk subtypes that can infect the epithelial cells of the cervix and change the normal cellular functions by host genome alteration resulting in progression of cervical intraepithelial neoplasia [20, 21]. The current cervical cancer therapy includes surgery, radiotherapy and chemotherapy that sometimes are not successful. Paclitaxel, ifosfamide, topotecan carboplatin, and cisplatin are some of the current chemotherapeutic agents for metastatic cervical cancer, among which cisplatin seems to be more effective for advanced cervical cancer. However, neurotoxicity, neutropenia, nephrotoxicity, thrombocytopenia, etc. are some adverse effects that may occur in chemotherapy [5]. Next-generation drugs should not only decrease the cost of cancer therapy and adverse drug effects, but also increase the quality of life in the patients who have cervical cancer. To date, no comprehensive study showed the efficacy of green AuNPs against cervical cancer. It is a significant urgent to provide robust evidence from the laboratory studies whether or not green AuNPs have the anticancer activity against cervical cancer cells. This information is required for translation of laboratory setting studies to clinical researches. In this study, we aimed to conduct a systematic review of published articles to show the efficacy of biomimetic synthesized AuNPs against cervical cancer cells. The next aim of this study was to discuss the proposed molecular mechanisms of anticancer activity of biologically synthesized AuNPs against cervical cancer cells through in vitro investigations.

## Materials and Methods

The current study is a systematic review to show the efficacy of biomimetic synthesized AuNPs against cervical cancer cell lines.

### Search Strategy

To evaluate the anticancer activity of biomimetic synthesized AuNPs against cervical cancer cells, a global systematic review was performed to identify the articles published up to 31 August 2019 among the English databases including Web of Science, PubMed, Scopus, Science Direct, ProQuest, Embase, and Cochrane using a combination of keywords including "Au", "gold", and "biosynthesis", "synthesis", "fabrication", "biofabrication", "microbial", "biological", "biomimetic", "plant*", "herbal", "fungal", "bacterial", "alga*", "phyto*", "bioreduction", "myco*", "biogenic", "green", and "nanoparticle*", "nano-gold", "nanomaterial*", "colloidal", "nanostructure*", and "tumor*", "antitumor*", "cancer*", "cytotoxic", "antineoplastic", "cytotoxicity", "cell line*", "anticancer*", "cervical". To identify additional articles, the reference list of selected articles were reviewed. A protocol was devised according to PRISMA guidelines representing our literature review involving the first and second screening of articles to assess the eligibility of selected articles to enter into our systematic review [22].

### Inclusion Criteria

To assess the eligibility of articles for inclusion, the first screening was performed to include the English language original laboratory articles that their titles and abstracts represented the evaluation of biomimetic synthesized

AuNPs-induced cytotoxicity against cervical cancer cell lines through in vitro model. For the case of doubt, the entire articles were thoroughly reviewed.

### Exclusion Criteria

The exclusion criteria encompassed for the studies with the characteristics including review articles, letters, congress abstracts, editorials, articles with insufficient information, articles that reported the anticancer activity of chemically and/or physically fabricated AuNPs against cervical cancer cells, articles that evaluated the biogenic AuNPs-induced cytotoxicity against any cell lines except cervical cancer cells.

### Data Extraction and Tabulation

We designed a data extraction form to collect the following data from selected articles including first author, year of publication, a biological source with scientific name, characterization techniques, size (nm), morphology, cervical cancer cell line, dose, exposure time, cytotoxicity method, and major outcome.

## Results

### Search Results

The initial systematic search retrieved 1373 records that 642 records were found a duplicate and excluded. 731 articles were retained for first screening. During the first screening of these articles, another 642 articles were excluded according to the above-mentioned exclusion criteria. Then, 89 articles' full text was reviewed during the second screening, and finally, 33 articles met our eligibility criteria and were retained to enter into the current systematic review (Fig. 1).

### Characteristics of Included Studies

Of thirty-three studies [12–18, 23–48], twenty-four studies [12–18, 23–25, 30–37, 39, 40, 43, 44, 47, 48] reported herbal-mediated fabrication of AuNPs. Besides, algae [29, 38, 46], bacteria [26, 41, 42], cyanobacteria [45] and even animals [27, 28] were other biological sources that were used for fabrication of AuNPs. Significantly, all of the studies stated the size of AuNPs less than 100 nm. Although different morphologies were reported through the studies, most of the studies reported spherical shaped morphology for their biosynthesized AuNPs. Moreover, all of the studies used HeLa cervical cancer cell line to evaluate the anticancer activity of biogenic AuNPs, and a study [39] evaluated the biogenic AuNPs-induced cytotoxicity against both HeLa and SiHa cell lines. In total, three cytotoxic assays were used for anticancer evaluation of AuNPs including MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), WST (2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium), and MTS (3-(4,5-dimethylthiazol-2-yl)-5(3-carboxymethonyphenol)-2-(4-sulfophenyl)-2H-tetrazolium) assays. In details, thirty studies [12, 13, 15–18, 23–26, 29–48] applied MTT assay, two studies [14, 28] applied WST, and one study [27] applied MTS assay for cytotoxicity assessment. Remarkably, twenty-eight studies [12–14, 23–32, 34–48] reported significant anticancer activity of biologically fabricated AuNPs against cervical cancer cells. In contrast, five studies [15–18, 33] reported no cytotoxic influence of AuNPs against cervical cancer cells at the maximum AuNPs concentrations in their investigations.

## Discussion

### Green Chemistry: A Biosynthetic Approach for Preparation of AuNPs

Green chemistry is one of the active areas of research in nanotechnology for the synthesis of nanomaterials because of the growing need to produce environmentally safe nanomaterials [49]. The green chemistry will provide a healthy space and life to prepare nanomaterials for different applications. Green chemistry aims to overcome the drawbacks of traditional physicochemical methods by elimination of substances hazardous to the environment and human health compared to chemical processes as well as reducing the cost and energy consumption through the physical techniques [50, 51]. AuNPs have been synthesized using a wide range of natural resources with different size distributions and morphologies [52]. The present systematic review showed that the biological resources do not limit to plant extracts, algae, and microorganisms.

Interestingly, animal-mediated synthesis of AuNPs was reported in two studies indicating the unlimited potency of nature for AuNPs synthesis [27, 28]. In a study, the aqueous extract of *Nemopilema nomurai* (jellyfish) was successfully used as a green, reducing agent for the biosynthesis of AuNPs resulting in spherical shaped AuNPs with an average size of $35.2 \pm 8.7$ nm and triangular nanoplates with an average height of $70.5 \pm 30.3$ nm [27]. In another study, skate (*Dipturus chilensis*) cartilage extract was applied for the biosynthesis of AuNPs with spherical shapes and an average size of $16.7 \pm 0.2$ nm [28]. However, the present study stated that the phytosynthesis of AuNPs had received increasing attention among all biological approaches for fabrication of AuNPs.

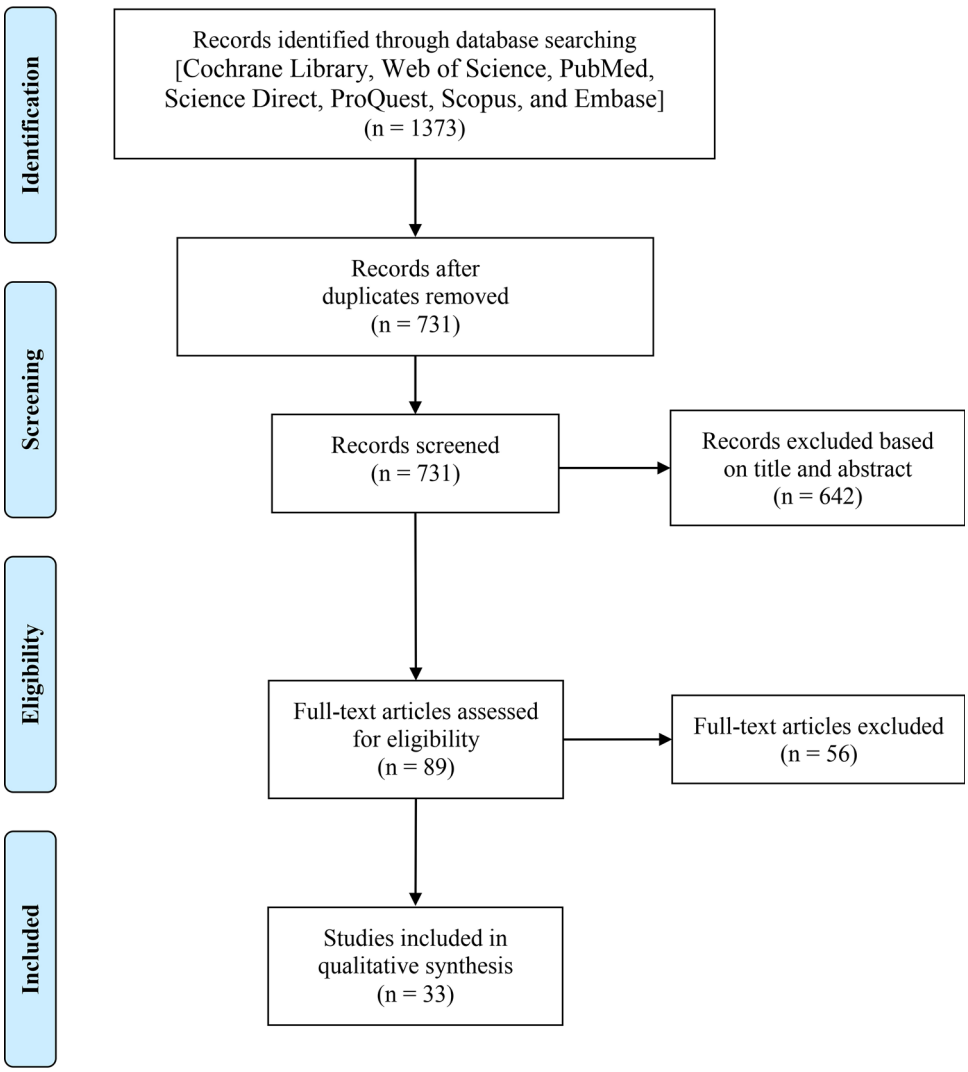


**Fig. 1** Flowchart describing the study design process

More interestingly, our systematic review revealed that all of AuNPs were bio fabricated below 100 nm through all studies. The biosynthetic approach for preparation of AuNPs is simple, energy-efficient, cost-effective, and environmentally friendly [53, 54]. It has been shown that the biomolecules and metabolites in the biological systems are responsible for converting of gold ions to AuNPs form [52, 53]. In this biosynthetic process, several parameters need to be optimized to reach monodispersed NPs such as pH, temperature, and concentration of metallic salt [7]. Although the biosynthetic approach is still at a laboratory setting, this potential exists for a biological method for large scale production with optimizing the procedures using the statistical modelling [55]. Figure 2 represented the interface of nature, nanotechnology and cervical cancer.

## Cytotoxicity of Biogenic AuNPs Against Cervical Cancer Cells

In total, the current systematic review revealed the considerable anticancer activity of biogenic AuNPs against cervical cancer cells (Table 1). However, few studies reported no AuNPs-induced cytotoxicity [15–18, 33]. The different results in biogenic AuNPs cytotoxicity responses are associated to the various parameters such as different AuNPs sizes, morphologies and surface charges as well as different biological resources that act as reducing and capping agents [56]. In a study, cellular uptake kinetics of different sizes of citrate-capped AuNPs were studied in HeLa cells. The NPs with the size of 50 nm showed optimal uptake compared to other NPs with other sizes ($50 > 30 > 14 > 74 > 100$ nm core diameter) [57]. From the pharmaceutical aspect, AuNPs may act as a nanocarrier for drug delivery systems. It was shown that the anticancer activity of AuNPs loaded with doxorubicin was much

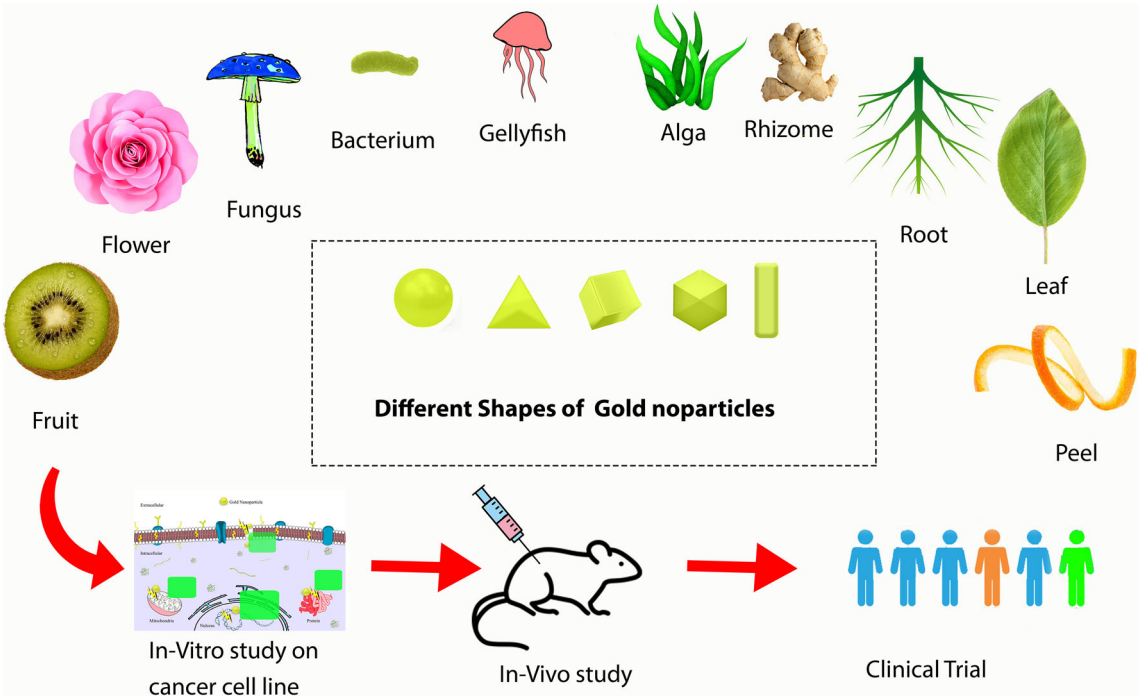


**Fig. 2** The interface of nature, nanotechnology and cervical cancer

stronger than free doxorubicin against cervical cancer cells [58].

Moreover, it was shown that AuNPs below 100 nm diameter size could be surface functionalized with as many as $1.5 \times 10^7$ molecules per square micron. This provide an opportunity to engineer the surface of AuNPs. For example, it was reported that PEGylated AuNPs would have more blood circulation time [59]. One of the potential therapeutic targets to combat cancer cells is their surface receptors. It was shown that human cervical cancer cells overexpress folate receptors. The studies revealed that the conjugation of chemotherapeutic nano-formulations with folic acid increased the specificity to cervical cancer cells [19]. Thereby, surface functionalization of biogenic AuNPs may provide a chance to design smart nanomedicines for theranostic purposes. Although we cannot expect that biogenic AuNPs only have cytotoxic influence toward cervical cancer cells without any cytotoxicity against normal cells, but we expect that biogenic AuNPs would have much cytotoxic impact against cervical cancer cells with less cytotoxicity against other normal cells. Future studies should focus on the range of biocompatibility of biogenic AuNPs toward different normal cells and provide comprehensive information about their pharmacokinetics and pharmacodynamics through in vivo investigations.

## Proposed Molecular Mechanisms of Biogenic AuNPs-induced Cytotoxicity Against Cervical Cancer Cells

It is of high importance to investigate the molecular mechanisms of anticancer activity of biogenic AuNPs against cervical cancer cells. To date, the total understanding of molecular mechanisms of biogenic AuNPs-induced cytotoxicity is limited to AuNPs-induced apoptotic pathways activation as well as overgeneration of intracellular ROS (Fig. 3). Qian et al. phytosynthesized AuNPs from aqueous leaf extract of *Alternanthera sessilis* and evaluated its anticancer activity against HeLa cells. Western blot analysis revealed that treated HeLa cells with biogenic AuNPs led to a considerable dose-dependent increase in expression of Bax and a fall in expression of Bid and Bcl-2, whereas non-treated HeLa cells showed a fall in the expression of Bax and a rise in expression of Bid and Bcl-2. Besides, caspase kit colorimetric method revealed a significant dose-dependent activity of caspases 3, 8 and 9 in AuNPs-treated HeLa cells, whereas in non-treated HeLa cells a decrease in the activity of caspases 3, 8 and 9 was observed [12]. Notably, AKT and ERK signaling pathways have a significant function through cell surviving. Ahn et al. stated that in the biogenic AuNPs-treated HeLa cells, the activation of AKT and ERK signaling pathways was blocked [27]. Kajani et al. synthesized AuNPs using *Taxus baccata* extract and stated concentration and time dependent AuNPs-induced cytotoxicity

**Table 1** The results of anticancer activity of biosynthesized AuNPs against cervical cancer cells through in vitro studies

| Author/year | Biological source/scientific name | Characterization techniques | Size (nm)/morphology | Cervical cancer cell line[a] | Dose | Exposure time (h) | Method | Major outcome | References |
|---|---|---|---|---|---|---|---|---|---|
| Qian et al. 2019 | Plant/*Alternanthera sessilis* | UV–vis, EDX, SAED, HR-TEM, AFM, FT-IR | 20–40, spherical | HeLa | 1–15 μg/mL | 24 | MTT | $IC_{50}$: 10 μg/mL | [12] |
| Patra et al. 2019 | Plant/*Piper betle*;<br>a) acetonic extract (AE)<br>b) ethanolic extract (EE) | UV–vis, HR-TEM, EDX, XRD | Average: 15–50 nm/multiple shapes | HeLa | 5–40 μg/mL | 24 | MTT | 1 mL AE + 2.5 (mM) $HAuCl_4$ led to $IC_{50}$ of > 40 μg/mL; 1 mL AE + 5.0 (mM) $HAuCl_4$ led to $IC_{50}$ of 35 μg/mL;<br>1 mL AE + 7.5 (mM) $HAuCl_4$ led to $IC_{50}$ of 30 μg/mL; 1 mL EE + 2.5 (mM) $HAuCl_4$ led to $IC_{50}$ of > 40 μg/mL; 1 mL AE + 5.0 (mM) $HAuCl_4$ led to $IC_{50}$ of 35 μg/mL;<br>1 mL EE + 7.5 (mM) $HAuCl_4$ led to $IC_{50}$ of 32 μg/mL | [13] |
| Patil et al. 2019 | Plant/*Lonicera japonica* | UV–vis, TEM, EDX, XRD, FT-IR | 10–40 nm/multiple shapes | HeLa | 100–500 μg/mL | 24 | WST-1 | $IC_{50}$: 400 μg/mL | [14] |
| Ghramh et al. 2019 | Plant/*Ricinus communis* | UV–vis, SEM, FT-IR, XRD | 40–80 nm/spherical | HeLa | 100 μg/mL | 24 | MTT | 100 μg/mL of plant extract plus 100 μg/mL of AuNPs led to around 55% cell growth inhibition | [23] |
| Elemike et al. 2019 | Plant/*Stigmaphyllon ovatum* | UV–vis, HR-TEM, XRD, Zeta potential | Average: 80 nm/triangular | HeLa | 12.5–100 μg/mL | No data | MTT | $IC_{50}$: 0.0027 μM | [24] |
| Singh et al. 2018 | Plant/*Euphrasia officinalis* | UV–vis, FE-TEM, EDX, XRD, SAED, FT-IR, DLS, Zeta potential | Average: 49.72 ± 1.2 nm/Quasi-spherical | HeLa | 1–10 μg/mL | 24 | MTT | The cell viability was reduced to 67.8 ± 1.1% at the concentration 10 μg/mL | [25] |
| Camas et al. 2018 | Bacterium/*Mycobacterium* sp. BRS2A-AR2 | UV–vis, TEM, FT-IR, DLS, Zeta potential | 5–55 nm/spherical | HeLa | 218–3500 μg/mL | 24 | MTT | $IC_{50}$: 3500 μg/mL | [26] |
| Ahn et al. 2018 | Animal/*Nemopilema nomurai* (jellyfish) | UV–vis, HR-TEM, FE-SEM, XRD | Average of 35.2 nm for spherical and 40.5 nm for triangular shaped AuNPs. | HeLa | 0.0125–0.2 mg/mL | 24 | MTS | $IC_{50}$: 0.076 mg/mL | [27] |

**Table 1** (continued)

| Author/year | Biological source/scientific name | Characterization techniques | Size (nm)/morphology | Cervical cancer cell line[a] | Dose | Exposure time (h) | Method | Major outcome | References |
|---|---|---|---|---|---|---|---|---|---|
| Ahn et al. 2018 | Animal/*Dipturus chilensis* | UV–vis, XRD, HR-TEM, DLS | Average: 16.7 ± 0.2 nm/ Spherical | HeLa | 4–126 μg/mL | 24 | WST | At concentration of 126 μg/ mL, 68% cell growth inhibition was observed | [28] |
| Vijayakumar et al. 2017 | Alga/*Fucus vesiculosus* | UV–vis, XRD, FT-IR, EDX, HR-TEM, Zeta potential | 10–100 nm/spherical and triangular | HeLa | 25–100 μg/mL | 24 | MTT | At 25 and 100 μg/mL, around 40 and 10% cell viability were observed, respectively | [29] |
| Seetharaman et al. 2017 | Plant/*Crescentia cujete* L. | UV–vis, TEM, XRD, FT-IR, DLS | Average: 32.89 nm/multiple shapes | HeLa | 62.5–1000 μg/ mL | 48 | MTT | $IC_{50}$: 316 μg/mL | [30] |
| Rajan et al. 2017 | Plant/*Elettaria cardamomum* | UV–vis, TEM, SAED, XRD, FT-IR | Average: 15.2 nm/almost spherical | HeLa | 6.25–100 μL | 24 | MTT | $IC_{50}$: 42.6 μL | [31] |
| Dutta et al. 2017 | Plant/*Syzygium jambos* L. | UV–vis, HR-TEM, SAED, XRD, FT-IR | The average size of AuNPs synthesized by bark and leaf of *S. jambos* were around 10.34 and 5.24 nm, respectively/Spherical and ellipsoidal | HeLa | No data | 24, 48, 72 | MTT | $IC_{50}$ for bark and leaf mediated synthesized AuNPs were > 250 μg/mL after 24 h of treatment<br>$IC_{50}$ for bark and leaf mediated synthesized AuNPs were 197.09 ± 3.44 and 149.02 ± 6.91 μg/mL, respectively after 48 h of treatment<br>$IC_{50}$ for bark and leaf mediated synthesized AuNPs were 154.89 ± 7.26 and 114.67 ± 10.38 μg/mL, respectively after 72 h of treatment | [32] |
| Kumar et al. 2016 | Plant/*Genipa americana* | UV–vis, XRD, DLS, TEM, SAED, FT-IR | Average: 15–40 nm/spherical | HeLa | 0.01–20 μM | 48 | MTT | No cytotoxicity | [33] |
| Kajani et al. 2016 | Plant/*Taxus baccata* | UV–vis, AFM, SEM, TEM, SAED, EDX, FT-IR | Less than 20 nm/multi shapes | HeLa | 2–20 μg/mL | 48, 72 | MTT | Dose and time dependent cytotoxicity were found. At 2 μg/mL, less than 50% cell viability was found after 48 and 72 h of treatment | [34] |

**Table 1** (continued)

| Author/year | Biological source/scientific name | Characterization techniques | Size (nm)/morphology | Cervical cancer cell line[a] | Dose | Exposure time (h) | Method | Major outcome | References |
|---|---|---|---|---|---|---|---|---|---|
| Dorosti et al. 2016 | Plant/*Dracocephalum kotschyi* | UV–vis, TEM, SEM, SAED, EDX, XRD, DLS, FT-IR, Zeta potential | 7.9–22.63 nm/spherical or nearly spherical | HeLa | 62.5–500 μg/mL | 24 | MTT | $IC_{50}$: 196.32 ± 1.02 μg/mL | [35] |
| Balashanmugam et al. 2016 | Plant/*Cassia roxburghii* | UV–vis, HR-TEM, EDX, XRD, FT-IR | 25–35 nm/predominantly spherical | HeLa | 5–100 μg/mL | 24 | MTT | $IC_{50}$: 50 μg/mL | [36] |
| Baharara et al. 2016 | Plant/*Zataria multiflora* | UV–visible, FTIR, TEM, DLS and Zeta potential | 10–42 nm/multiple shapes | HeLa | 25–400 μg/mL | 48 | MTT | $IC_{50}$: 200 μg/mL | [37] |
| Ajdari et al. 2016 | Alga/*Sargassum glaucescens* | UV–vis, TEM, SEM, EDX | 2–8 nm/spherical | HeLa | 0–100 μg/mL | 72 | MTT | $IC_{50}$: 4.75 ± 1.23 μg/mL | [38] |
| Yallappa et al. 2015 | Plant/*Mappia foetida* | UV–vis, XRD, FE-SEM, TEM, EDX | 20–50 nm/spherical | HeLa and SiHa | 10–50 μg/mL | 48 | WST-1 | $IC_{50}$: ~ 50 μg/mL for HeLa and SiHa | [39] |
| Rajan et al. 2015 | Plant/*Areca catechu* | UV–vis, TEM, XRD, FTIR | Average: 13.7 nm/spherical | HeLa | 6.25–100 μg/mL | 24 | MTT | $IC_{50}$: 25.17 μg/mL | [40] |
| Manivasagan and Oh. 2015 | Bacterium/*Streptomyces* sp. | UV–vis, XRD, FT-IR, FE-SEM, EDX, HR-TEM, SAED | 10–50 nm/spherical and truncated triangles | HeLa | 50–500 μg/mL | 24, 48 | MTT | $IC_{50}$: 350 μg/mL after 24 h<br>$IC_{50}$: 250 μg/mL after 48 h | [41] |
| Manivasagan et al. 2015 | Bacterium/*Nocardiopsis* sp. | UV–vis, XRD, TEM, DLS | 7–15 nm/spherical | HeLa | 50–400 μg/mL | 24 | MTT | $IC_{50}$: 300 μg/mL | [42] |
| Lokina et al. 2014 | Plant/*Punica granatum* | UV–vis, HR-TEM, XRD, FT-IR, SAED, TGA | 5–20 nm/triangular and spherical | HeLa | 7.8–1000 μg/mL | 48 | MTT | $IC_{50}$: 62.5 μg/mL | [43] |
| Jeyaraj et al. 2014 | Plant/*Podophyllum hexandrum* L. | UV–vis, FT-IR, XRD, TEM | 5–35 nm/spherical | HeLa | 5–50 μg/mL | 24 | MTS | $IC_{50}$: 20 μg/mL | [44] |
| Geetha et al. 2014 | Cyanobacterium/*Gloeocapsa* sp | UV–vis, SEM, TEM, FT-IR | Less than 100 nm/mostly Spherical | HeLa | 50–500 mg | 24 | WST | $IC_{50}$: 250 mg | [45] |
| Dhas et al. 2014 | Alga/*Sargassum swartzii* | UV–vis, FT-IR, HR-TEM, DLS, XRD, Zeta potential | Average: 35 nm/spherical | HeLa | 15.63–500 μg/mL | 24 | MTT | $IC_{50}$: 41.10 μg/mL | [46] |

**Table 1** (continued)

| Author/year | Biological source/scientific name | Characterization techniques | Size (nm)/morphology | Cervical cancer cell line[a] | Dose | Exposure time (h) | Method | Major outcome | References |
|---|---|---|---|---|---|---|---|---|---|
| Dharmatti et al. 2014 | Plant/*Azadirachta indica* | UV–vis, FE-SEM, FT-IR | Average: 121.7 nm/Mostly triangular | HeLa | 0.1–0.25 mM | 48 | MTT | No cytotoxicity | [15] |
| Anand et al. 2014 | Plant/*Achyranthes aspera* Linn | UV–vis, SEM, XRD | 20–30 nm/spherical | HeLa | 10–50 μg/mL | No data | MTT | At the concentration of ≥ 25 μg/mL, significant cytotoxicity was observed | [47] |
| Lin et al. 2013 | Plant/tea (Wulung tea, Gree tea and Jin-Xuan tea from Taiwan) | UV-is, TEM, SALDI-MS, FT-IR, EDX, XRD | Average: 52.2 ± 8.1 nm/nanosponges | HeLa | 0.001–0.25 nM | 24 | MTT | A dose dependent cytotoxicity was observed. Besides, at the concentration of 0.25 nM, less than 60% cell viability was observed | [48] |
| Sharma et al. 2013 | Plant/*Sapindus mukorossi* | UV–vis, HR-TEM, EDX, XRD, FT-IR, SAED, TGA | Average: 7.3 nm/ predominantly spherical and hexagonal | HeLa | 10–100 μM | 24 | MTT | No cytotoxicity | [16] |
| Das et al. 2011 | Plant/*Calotropis procera* | UV–vis, TEM, XRD, FT-IR | Average: 22 ± 10 nm/spherical | HeLa | 5–150 μM | 24 | MTT | No cytotoxicity | [17] |
| Babu et al. 2011 | Plant/*Fagopyrum esculentum* | UV–vis, HR-TEM, FT-IR, XRD, EDX, SAED | 3–20 nm/multi shapes | HeLa | 10–100 μM | 24 | MTT | No cytotoxicity | [18] |

[a]Cervical cancer cell line: HeLa (human cervical adenocarcinoma), SiHa (human cervical squamous cell carcinoma)

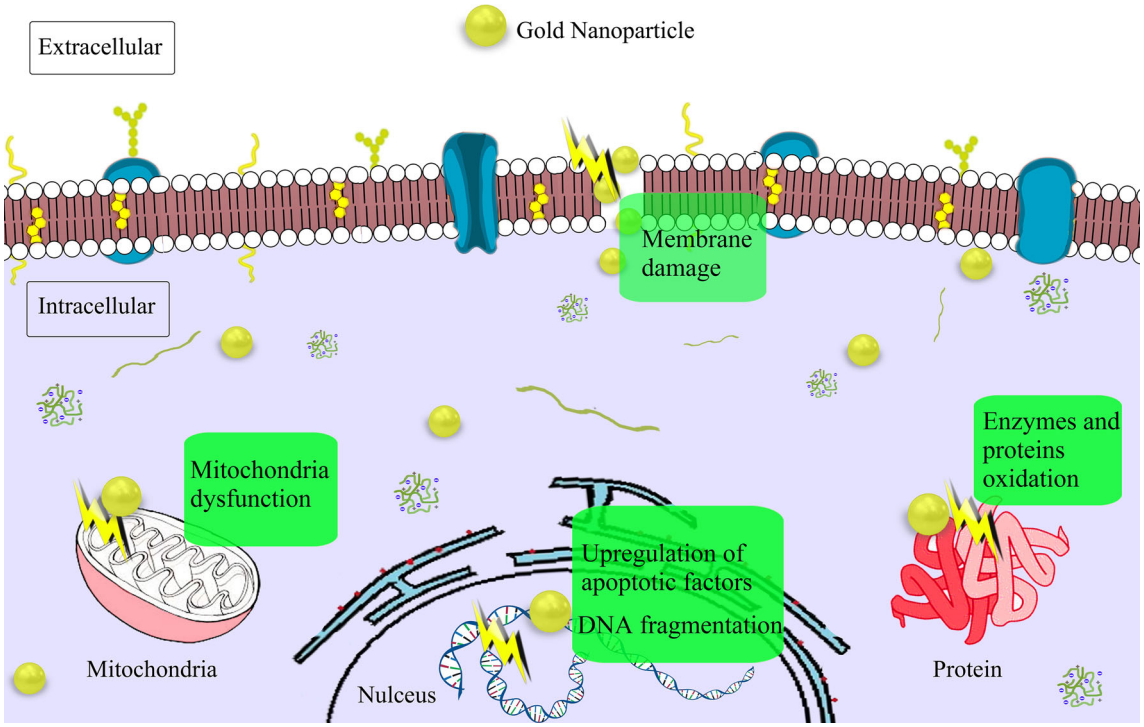


**Fig. 3** Schematic anti-cancer mechanisms of biogenic AuNPs

against HeLa cells. The results of real-time PCR stated down-regulation of anti-apoptotic Bcl-2 [34]. Baharara et al. reported the induction of apoptosis by phytosynthesized AuNPs through activation of caspases 3 and 9 in HeLa cells. They also performed flow cytometry analysis and demonstrated a time dependent apoptotic cell death in AuNPs-treated HeLa cells [37]. Ajdari et al. synthesized AuNPs using an extract of the brown seaweed *Sargassum glaucescens* and reported the induction of the intrinsic apoptotic pathway by algal-mediated AuNPs through activation of caspases 3 and 9 [38]. In a study, the western blot analysis showed the activation of caspases 3, 8 and 9 in the biogenic AuNPs-treated HeLa cells [44]. In a study, nuclear morphology analysis was performed for the AuNPs-treated HeLa cells, and the results showed fragmented DNA, apoptotic body formation as well as chromatin condensation in HeLa cells indicating apoptotic changes. The authors stated that overgeneration of ROS and activation of apoptotic pathways were responsible for these changes [41]. In another study, the ROS levels in AuNPs-treated HeLa cells were measured using 2′,7′-dichlorodihydrofluorescein (DCFHDA) method. The results showed that the intracellular ROS in the HeLa cells treated with 20 µg/mL of AuNPs were significantly higher than cisplatin-treated HeLa cells at 30 µg/mL. They also performed DNA fragmentation assay and showed AuNPs-induced fragmented DNA at the concentration of 20 µg/mL. Moreover, the results of cell cycle analysis showed cell cycle arrest in the G2/M phase [44]. Although we discussed the current proposed molecular mechanisms of anticancer activity of biogenic AuNPs, future studies may reveal other molecular mechanisms.

## Conclusion

Nanotechnology is a novel strategy to design next-generation anticancer drugs. The current trends represented a promising future for biogenic AuNPs due to their unique physicochemical properties. In the current systematic review, we had an attempt to provide comprehensive information from laboratory researches to show the efficacy of biomimetic synthesized AuNPs against cervical cancer cells. We showed a wide range of natural resources as an eco-friendly method for fabrication of AuNPs with different shapes and sizes. Besides, we introduced different molecular mechanisms of anticancer activity of biogenic AuNPs against cervical cancer cells. Although the findings of this systematic review showed the considerable anticancer potential of biogenic AuNPs against cervical cancer cells, many challenges and ambiguities should be addressed in the future studies such as the fate of these NPs in the body, their acute and chronic toxicity toward other normal tissues, genotoxicity, immunogenicity, etc.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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