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# Metal-Based Nanomedicine for Targeted Therapy of Cervical Cancer

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Metals, Nanomedicine, Bhasmas, Cervical cancer

**ABSTRACT:**
Chinese and Egyptian civilizations described the ample usage of metals around 2500 BC Bhasmas and Rasaushadas, a metal-based therapy for the treatment of chronic disease including malignant tumors was known to the mankind since 1500 BC through ancient India systems of medicine Ayurveda and Sidda. Nanotechnology and nanomedicine came int existance after 1990's and showing new paths and positive results in the management o metals in medicine and in particular in the treatment protocol of autoimmune diseases an cancer. The use of metals as therapeutic agents implicates that the human body can efficientl manage the metabolism as well as excretion of metals. The metals present in human body pla an important role in disease management because they exist in the form of micronutrients Cervical cancer is one of the most predominant gynecological malignancy and leading caus of death across the world mainly in developing countries. The platinum-based drug cisplati was widely recommended for locally advanced cervical cancer. There are several promisin potent metal-based drugs available for cervical cancer but lot of further research an documentation yet to be completed. Even today to reduce mortality and morbidity in cervica cancer new treatment protocols are to be worked out, one of the important new promisin treatment protocols may be metal-based nanomedicine for cervical cancer. Our review articl critically highlights the literature pertinent to the importance and status of metal-base medicine for cervical cancer.

## Introduction

Cervical cancer became a major challenging problem in gynaecological oncology field due to its resistance towards conventional therapies and high metastasis rate. [1] Worldwide cervical carcinoma comprises 12% of gynaecological malignancies and approximately 2, 74, 000 women annually die from this cancer. [2] Human papilloma virus (HPV) is the predominant risk factor for cervical cancer. [3] The treatment options like surgery, chemotherapy and radiation therapy were found to be highly invasive and nonspecific. Therefore, there is an urgent need for new therapeutic strategies development to combat cervical cancer.

## Metal-based therapy: Historical perspectives

The ample use of metals has been described in Chinese and Egyptian civilizations around 2500 B.C. Roman physician Pliny and Greek philosopher Dioscrides described the use of gold in medicine. Later, Arabic and Persian physicians used gold in their prescriptions in various forms. Besides gold, other metals like silver, arsenic, copper, iron, lead, mercury, and zinc were extensively described in various ancient systems of medicine. Ayurveda, the traditional Indian system of medicine mentioned the use of metal and mineral preparations around 1500 BC in Charakasamhita.[4] However, more systematic clinical and therapeutic applications of metallic preparations were discovered by Nagarjuna around 8th century AD. [5] According to Ayurveda, the metal-originated drugs were commonly

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called as bhasmas. Their preparation involved the conversion of metals into their corresponding oxides by a process known as bhasmikaran, in which the toxicity of the metal oxide is destroyed by inducing medicinal properties. [6] Metals were also used in the form of Parapati, Rasayoga and Sindoora.

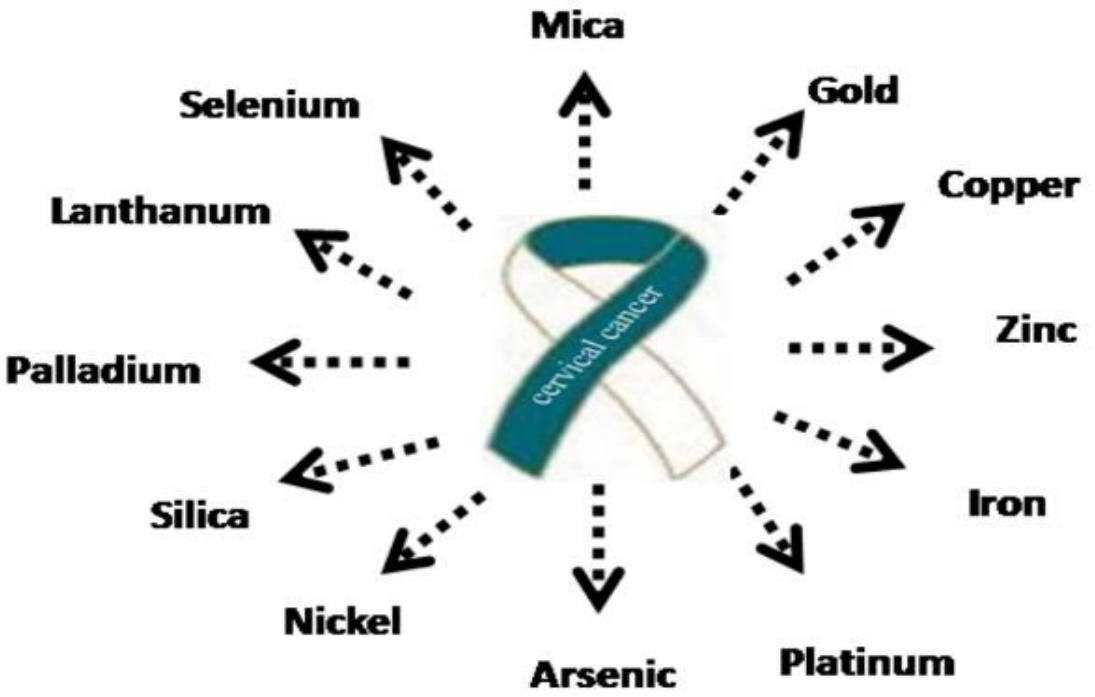


**FIGURE 1.** Metal-based therapy for cervical cancer

**Importance of metal-based therapy in cervical cancer**

Human body contains more than 70 elements and their deficiency may lead to various chronic ailments. Ayurveda described seven metals such as gold, silver, copper, iron, tin, lead and zinc as essential elements. These metals play an important role in various physiological functions. [7] The discovery of metal-based drug cisplatin in 1969, lead to tremendous progress in various cancers. [8] For locally advanced cervical cancer cisplatin-based therapy recommended widely, but dosing and scheduling yet to be determined. Metal ion equilibrium results in regulated uptake mechanism, storage and secretions because they participate in maintenance of ions across cellular compartments. [9] Any disturbances in metal ion homeostasis lead to DNA interactions and deterioration of biological macromolecules, resulting in various diseases. [10] In cancer patients elevated levels of copper, zinc, iron and selenium concentrations were reported in serum as well as tumor tissue in comparison with healthy people. Moreover, cancer patients suffering from breast, cervical, ovarian, lung, prostate, and stomach cancers also showed elevated copper levels when compared with healthy people. [11] Altered copper also be a risk factor for sustained tumor growth in cervical cancer. [12]

**Importance of metal-based nanomedicine in cervical cancer therapy**

The term nanotechnology means technology on the scale of a billionth of a meter. The extreme small size of nanoparticles, easily enter into the cells, intracellularly interact with DNA and act on receptors, proteins and enzymes. The biological events in cancer can be easily detected by nanoparticles. The metal-based bionanomaterials provided a new pathway for the diagnosis and therapy of various diseases including malignant cancers. [13] This is the first systematic review article that critically highlights the importance of metals and metal-based nano medicine in cervical cancer treatment.

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**TABLE 1:** Status of various metal-based medicine available for cervical cancer

| Ref. | Country | Formulation | Metal | Stage of Development |
|---|---|---|---|---|
| 14 | India | Abhraka Bhasma | Mica | Traditional claim |
| 15 | Singapore | Auranofin 22 | Gold | *Invitro* studies on HeLa cell lines |
| 16 | South Korea | Smart gold nanoparticles aggregated in citraconic amide surface | Gold | *Invitro* studies on HeLa cell lines |
| 17 | United Kingdom | Conjugated gold nanoparticles with a platinum analog oxaliplatin | Gold and Platinum | *Invitro* studies on HeLa cell lines |
| 18 | USA | Poly ethylene glycol (PEG) ylated gold nanoparticles with phthalocyanine photosensitizers | Gold | *Invitro* studies on HeLa cell lines |
| 19 | USA | gold nanoparticles conjugated with thiol PEGylated RNA | Gold | *Invitro* studies on HeLa cell lines |
| 20 | USA | Folate conjugated gold nanoparticles | Gold | *Invitro* studies on HeLa cell lines |
| 21 | China | gold nanoparticles coated with PEG and surface modified with 3-mercaptopropionic acid | Gold | *Invitro* studies on HeLa cell lines |
| 22 | USA | Gold nano particles conjugated with matrix metallo proteases (MMPs) | Gold | *Invitro* studies on SiHa cell lines |
| 23 | Japan | Auranofin 22 | Gold | *Invitro* studies on HeLa cell lines |
| 24 | South Korea | Zinc oxide (ZnO) nanostructures | Zinc | *Invitro* studies on HeLa cell lines |
| 25 | China | ZnO nanoparticles | Zinc | *Invitro* studies on HeLa cell lines |
| 26 | Mexico | Cisplatin<br>Carboplatin<br>Nedaplatin<br>Oxaliplatin | Platinum | Clinical trials in humans |
| 27 | China | Arsenic trioxide | Arsenic | *invitro* and *invivo* activity HeLa, SiHa, Caski cell lines |
| 28 | South Korea | Arsenic trioxide | Arsenic | *invivo* activity. |
| 29 | Australia | Arsenic trioxide | Arsenic | Clinical trials in humans |
| 30 | Korea | Arsenic trioxide, Arsenic tetraoxide | Arsenic | *Invitro* studies on HeLa cell lines |
| 32 | Turkey | Nickel oxide nanoparticles | Nickel | *Invitro* studies on HeLa cell lines |
| 33 | Poland | Palladium coumarin complex 47 | Palladium | *Invitro* studies on HeLa cell lines |
| 34 | Croatia | Quercetin/Lanthanum complex | Lanthanum | *Invitro* studies on HeLa cell lines |
| 35 | China | Selenium Nanoparticles coated with Sialic acid | Selenium | *Invitro* studies on HeLa cell lines |
| 36 | Singapore | Selenium-polypyrrole core-shell nanoparticles conjugated with transferring | Selenium | *Invitro* studies on HeLa cell lines |
| 37 | India | Tamra bhasma along with other herbs such as *Semecarpus anacardium*, *Amoora rohitaka* and *Glycyrrhiza glabra* | Copper | Clinical trials in humans |
| 38 | USA | Cetuximab, anti epidermal growth factor receptor (anti EGFR) antibody was conjugated with radio labelled copper ($^{16}$ Cu) along with biochelator 1, 4, 7, 10-tetraazacyclododecane- N, $N^{1}$, $N^{11}$, $N^{111}$- tetra acetic acid (DOTA) | Copper | *Invitro* studies on CaSki, HeLa, DoTc2 4510, C-33A, and ME-180 cell lines. |
| 39 | USA | Cisplatin combined with a copper transporter CTR1 in human cervical cancer mouse model. | Platinum and copper | *Invitro* studies on SiHa cell lines |
| 40 | India | Copper nanoparticles | Copper | *Invitro* studies on HeLa cell lines |
| 41 | USA | Copper sulfide nanoparticles | Copper | *Invitro* studies on HeLa cell lines |
| 42 | China | Complexes of copper (II) along with hesperetin, naringenin, and apigenin | Copper | *Invitro* studies on HeLa cell lines |
| 43 | Switzerland | Copper metal, Copper oxide nanoparticles and ionic Copper | Copper | *Invitro* studies on HeLa cell lines |
| 44 | China | Super paramagnetic dextran iron oxide nanoparticles (SDION) along with E1A gene | Iron | *Invitro* studies on xenograft mouse model for cervical cancer |
| 45 | Vietnam | Magnetic silica coated iron oxide nanoparticles attached to HPV18 and E Coli monoclonal antibodies | Iron | Early diagnosis of cervical cancer |
| 46 | Taiwan | Lipid coated (cationic lipid 1,2-dioleoyl-3-(trimethylammonium) propane(DOTAP) and polyethylene-glycol-2000-1,2-distearyl-3-sn-phosphatidylethanolamine (PEGDSPE) based super paramagnetic iron oxide nanoparticles (SPIOs) | Iron | *Invitro* studies on HeLa cell lines. |
| 47 | USA | Mesoporous silica coated with oligonucleotide intercalator phenanthridinium | Silica | *Invitro* studies on HeLa cell lines |
| 48 | Korea | Inorganic anionic clay layered metal hydroxide (LMH) nanoparticles | Miscellaneous | *Invitro* studies on HeLa cell lines |
| 49 | USA | Fluorescent crystals or quantum dots conjugated with anti EGFR antibodies | Miscellaneous | *Invitro* studies on HeLa cell lines |

**Mica**

In traditional system of medicine, mica possesses an important role in the form of abhraka bhasma. Abhraka contains various minerals like iron, magnesium, potassium, calcium and aluminium. Mica is a powerful cellular regenerator and used to treat various chronic diseases like cervical dysplasia, leukemia, breast cancer and human immunodeficiency virus (HIV) etc. Cellular and molecular level studies were needed to justify the use. [14]

**Gold**

The medicinal applications of gold have been known to mankind since antiquity. The gold-based compound auranofin 22 inhibited cell proliferation of cervical cancer HeLa (Human cervical carcinoma) cell lines. [15] Smart gold nanoparticles aggregated in citraconic amide

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surface with a relative size of 10nm effectively internalized into HeLa cell lines and showed an effective photo thermal destruction at a threshold intensity of 5 w/cm$^2$. [16] The conjugation of gold nanoparticles with a platinum analog without endosomal sequestration achieved efficient cystolic delivery of prodrug to bone, cervical, prostate and lung cancer cells. [17] Using 5nm Polyethylene glycol (PEG) ylated gold nanoparticles the phthalocyanine photosensitizer delivery was increased in cervical cancer cell lines. [18] 13nm gold nanoparticles conjugated with thiol PEGylated RNA (Re oxyribo nucleic acid) oligonucleotide strands and subjected to complementary siRNA (Small interface re oxyribo nucleic acid) hybridization showed greater than 2-fold increase in knockdown of target protein expression in HeLa cell lines. [19] Folate conjugated gold nanoparticles followed by photothermal treatment achieved more than 95% killing in HeLa cell lines. [20] About 3.7nm gold nanoparticles coated with PEG and surface modified with 3-mercaptopropionic acid showed improved biocompatibility and stability in HeLa cell lines. [21] Gold nanoparticles conjugated with matrix metallo proteases (MMPs) resulted in rapid internalization in cervical cancer (SiHa) cell lines. [22] Auranofin 22, a gold based supramolecular complex inhibited *invitro* proliferation of HeLa cell lines. [23]

**Zinc**

Treatment with diverse shaped Zinc oxide (ZnO) nanostructures to HeLa cell lines along with U87 (human brain tumor) and normal (HEK) cell lines by MTT [3-(4,5- dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide survival assay resulted in promising activity indicated by cell death and enhanced growth inhibition in a concentration dependent manner. The potent activity was exhibited at all effective concentrations by nanoparticles and nanosheets against HeLa and U87 cell lines and demised activity was reported in HEK cell lines. [24] The *invitro* biocompatibility evaluation of zinc oxide nanoparticles was performed on HeLa cell lines and Human mouse fibroblast (L929) cell lines using MTT assay. In case of 20nm sized at varied concentrations of ZnO both the cell proliferations were inhibited, indicates high cytotoxicity of ZnO nanoparticles and exploits the potential use of ZnO nanoparticles as anticancer agents. [25]

**Platinum**

For locally advanced cervical cancer cisplatin is widely recommended therapy. Even though cisplatin has effectiveness in cervical cancer treatment upon daily administration, large numbers of clinical trials with large number of people were required to justify the results and to overcome the side effects associated with cisplatin. Carboplatin has high degree of chemical stability when compared with cisplatin, a higher dose of carboplatin is required to obtain a comparable anticancer activity, even both possess same cytotoxicity mechanism and nephrotoxicity is reported in carboplatin. Nedaplatin is an upcoming platinum based drug developed in Japan with more anticancer activity preclinically and lack of nephrotoxicity associated with cisplatin. It also possesses similar activity along with cisplatin and carboplatin in treatment of cervical cancer. But more research to be focussed on nedaplatin to set it as new platinum based radiosensitizer. Oxaliplatin is proven as better radiosensitizer than fluorouracil in colon cancer and its efficacy should be tested along with radiation therapy in cervical cancer. [26]

**Arsenic**

Arsenic trioxide possess potent *invitro* and *invivo* activity against invasive and metastatic cervical cancer on human cervical cancer (HeLa, SiHa, Caski) cell lines, suggesting the potent therapeutic application in cervical cancer treatment in combination with induction of apoptosis and inhibition of metastasis. [27] The radiation response of cervical tumors *in vivo* was enhanced by arsenic trioxide. [28] A phase II trial of arsenic trioxide on patients suffering from stage IVB or recurrent cervical carcinoma has been reported. [29] In comparison with arsenic trioxide, arsenic tetraoxide is more effective in cervical cancer cell proliferation arrest [30] in myeloid leukaemia mitochondrial dependent apoptosis. [31]

**Nickel**

The apoptotic and cytotoxicity effects of nickel oxide nanoparticles of less than 200 nm were investigated on HeLa cell lines. The results clearly indicated that nickel oxide nanoparticles showed significant cytotoxicity in dose as well as time dependent manner. [32]

**Palladium**

High cytotoxicity was reported against A549 and HeLa cell lines with derived palladium coumarin complex 47

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when compared with standard carboplatin. This complex did not produce toxicity in other normal cell lines. [33]

**Lanthanum**

The quercetin/lanthanum complex showed highest cytotoxicity by MTT Assay on HeLa cell lines when compared with lanthanum and quercetin alone at a concentration range of 100 to 1000 mmol mL-$^{1}$. [34]

**Selenium**

The cytotoxicity of selenium nanoparticles coated with sialic acid on HeLa cell lines reported a dose dependent apoptosis via caspase-3 activation and subsequent Poly ADP ribose polymerase (PARP) cleavage. [35] Selenium polypyrrole core shell nanoparticles conjugated with transferrin were thermally highly stable with enhanced cellular uptake. These nanoparticles can be preferred for imaging and targeting human cervical cancer cells. [36]

**Copper**

Tamra bhasma, a traditional ayurvedic preparation obtained from metallic copper recommended for tumors, abdominal pains, anemia, loss of appetite and tuberculosis, since copper is important constituent in several enzymes, stimulates immune system and acts as an antioxidant. [6] Tamra bhasma had identical qualities of swarna (gold) bhasma. In a clinical trial involving 400 cancer patients the tamra bhasma along with other herbs such as *Semecarpus anacardium*, *Amoora rohitaka* and *Glycyrrhiza glabra* were tested alone or in combination with other treatment options like chemotherapy and radiation therapy for 10 years and patients were observed and found effective. [37]

The cetuximab, anti epidermal growth factor receptor (anti EGFR) antibody was conjugated with radio labelled copper ($^{16}$ Cu) along with biochelator 1, 4, 7, 10-tetraazacyclododecane- N, N$^{1}$, N$^{11}$, N$^{111}$- tetra acetic acid (DOTA) to determine the potentiality of the above conjugate in small animal PET (Positron emission tomography) imaging to estimate EGFR concentration and internalization in cervical cancer (CaSki, HeLa, DoTc2 4510, C-33A, and ME-180) cell lines. The above conjugate may be used as potential biomarker to detect EGFR expression and PET imaging in EGFR positive cervical cancer tumors. [38]

Tumor specific uptake was reported in cisplatin combined with a copper transporter CTR1 in human cervical cancer mouse model. This combination therapy enhanced SiHa cells killing in platinum drug resistant tumors. [39] The copper nanoparticles of various concentrations and 4-5 nm size exerted cytotoxicity in HeLa cell lines by apoptosis mechanism. [40] Copper sulfide nanoparticles mediated photo thermal ablation was reported in HeLa cells with respect to laser dose and nanoparticle concentration using MTT assay. Results revealed that the cytotoxic effects of copper sulfide nanoparticles were equivalent to gold nanoparticles and promising tools for photo thermal ablation of cancer. [41]

The complexes of copper (II) along with hesperetin, naringenin, and apigenin were tested on HeLa, hepatocellular cancer (HepG-2) and gastric carcinoma (SGC-7901) cell lines *invitro* by MTT assay. Complex I and II exhibited higher cytotoxicity on selected cell lines. [42]

The effect of intracellular solubility of copper metal, copper oxide nanoparticles and ionic copper cytotoxicity on Chinese hamster ovary (CHO) and HeLa cell lines was observed. The less cytotoxicity and more tolerance were observed in carbon coated copper nanoparticles. The copper oxide nanoparticles showed increased toxic response in comparision with copper in ionic form. [43]

**Iron**

The super paramagnetic dextran iron oxide nanoparticles (SDION) along with E1A gene enhanced p 53 expression, decreased the expression of Human epidermal growth factor receptor 2 (HER-2)/neu and further enhanced the radio sensitivity in xenograft mouse model for cervical cancer. [44] Magnetic silica coated iron oxide nanoparticles (29 nm to 230 nm) attached to HPV18 and E Coli monoclonal antibodies can be used as promising tools for early diagnosis of cervical cancer and diarrhoea.[45] Lipid coated (cationic lipid 1,2-dioleoyl-3-(trimethylammonium) propane (DOTAP) and polyethylene-glycol-2000-1,2-distearyl-3-sn-phosphatidylethanolamine (PEGDSPE) based super paramagnetic iron oxide nanoparticles (SPIOs) of average size 46nm had low cytotoxicity, high loading efficiency and long term image signalling in HeLa, human prostatic adenocarcinoma (PC-3), mouse neuro blastoma (Neuro-2a) and mouse colorectal adenocarcinoma (CT-26) cell lines and can be used for *invivo* cell tracking or imaging. [46]

**Silica**

Mesoporous silica coated with oligonucleotide intercalator phenanthridinium with different pore sizes 5.7 nm and 2.5 nm internalized and cause endocytosis lowering in HeLa cell lines. [47]

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**Miscellaneous**

The toxicity of inorganic anionic clay layered metal hydroxide (LMH) nanoparticles were evaluated in two A549 and normal human lung epithelial carcinoma (L-132) cell lines along with HeLa and osteosarcoma (HOS) cell lines. The LMH nanoparticles did not show cytotoxicity on the four cell lines tested and useful for designing delivery carrier for cancer targeting. [48] Fluorescent crystals or quantum dots conjugated with anti EGFR antibodies used to detect precancerous biomarkers visualized molecular changes involved in cervical cancer, which may be useful to resist photo bleaching associated with organic dyes and detecting biomarkers for cancer therapy. [49]

**Conclusion and future perspectives**

In clinical oncology, cervical cancer became a challenging problem because of high metastasis rate and resistance towards contemporary therapies. [1] Usage of metals and their respective oxides as therapeutic agents had the advantages of easy metabolism, since they were available as micronutrients and residual toxicity can be easily managed by the body. [50] The common dietary flavonoids reported cytotoxicity in cervical cancer cell lines, [23] but they are unstable upon oral administration and involved conversion into conjugated forms in gastro intestinal track. [51, 52] which made difficult to deliver them orally to achieve desired therapeutic concentration. The antioxidant activities of metal flavanoid complexes were higher than that of flavanoids alone. [53] Anti-tumor activity and binding affinity of metal flavanoid complexes were found be more when compared with free molecules. [42] We synthesized a nano copper quercetin complex, which is very effective against cervical cancer HeLa, SiHa and ME-180 cell lines. This strategy may be used as chemotherapy option for the treatment of cervical cancer after performing *invivo* experiments and clinical trials.

The metals and metal oxides treated with plant juices were used to treat cervical cancer since centuries in the form of bhasmas, the most primitive application of nanotechnology but scientific validation is still significantly lacking to validate the hidden potentials of bhasmas. Critical research is absolutely needed in this area because of the toxicity issues of metals and their oxides during their preparation. The modern metal nanoparticles and metal flavanoid complexes are more potent and stable but they were still in early developmental stages. More clinical studies with large population are in need to evaluate the potency of metal-based drugs for cervical cancer.

**Conflict of Interest**

Authors declared no conflicts

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