

A review on nanoparticles targeting cervical and endometrial cancer

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Abstract

The two most frequent gynecological cancers in women globally are cervical and endometrial cancers. Despite the fact that a variety of medications have been created for treatment, they frequently result in a number of negative side effects, toxicity, and multidrug resistance (MDR). Despite the fact that surgery and chemo radiotherapy can cure 80–95 percent of women with early-stage cancer, recurring and metastatic disease remains a leading cause of cancer death. To address this, scientists have taken advantage of the benefits afforded by nano systems, such as nanocarriers in the fields of tumor targeting, increased drug accumulation in tumors, and so on. The major characteristics of this system include biodegradability, biocompatibility, non-toxicity, prolonged circulation, and a large payload range of a therapeutic drug. Anticancer treatment side effects can be decreased by encapsulating the drug and delivering it directly to the cancer site. Drug release at cancer locations using stimuli responsive nanocarriers is effective for achieving target-specific delivery. When compared to the conventional system, these methods exhibit improved ability to target malignant cells without harming healthy cells and offer the promise for advanced cancer therapy. Recent breakthroughs in intrinsic and extrinsic-stimulus sensitive nanomaterial systems for drug administration in cancer therapy, as well as other polymeric nano particles employed in cancer therapy, are discussed in this study.

Keywords: Cervical cancer; Endometrial cancer; Drug resistance; Nano medicine; Tumor targeting

1. Introduction

The key distinguishing feature of malignant tumors is unregulated and continual cell proliferation. Majority of the deaths in world are caused by cancer [1,2]. Cervical and endometrial cancers are two common gynecological cancers in women around the world [3-6]. Cervical cancer most prevalent type in women. In 2015, over 90% of the 270 000 cervical cancer fatalities occurred in low- and middle-income countries (LMICs), where mortality is 18 times greater than in developed countries[7]. Cervical cancer is caused mostly by sexually transmitted diseases (STDs), as well as the human papillomavirus (HPV), often HPV-16 and HPV-18[8]. In India, around 432.2 million women under the age of 15 are diagnosed with cancer[9-11]. Endometrial carcinoma (EC) is a cancer that arises from the uterine cavity's epithelial lining. It is the most frequent type of female pelvic cancer, with a life-time incidence of 4% [12, 13]. Obesity is one of the

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most major risk factors for this disease, and as obesity rates have raised, so has the incidence of endometrial cancer. Endometrial cancer surgery has improved in recent years, and now includes sentinel lymph-node mapping in addition to the conventional, minimally invasive removal of the uterus, fallopian tubes, and ovaries. The Cancer Genome Atlas (TCGA) project has improved our understanding of endometrial cancer's biologic heterogeneity [14-16]. Surgery, targeted therapy, chemotherapy, and radiation therapy are among the therapeutic options used to extend a patient's life and improve their quality of life [1, 2]. Multidrug resistance is a major issue in antitumor chemotherapy (MDR) [17-20]. The distribution of available chemotherapeutic medicines to target-specific locations is a big difficulty [21-23]. The development of nano phytochemicals and nanoparticles in the treatment of cancer involved reducing the negative effects caused by conventional medications used for cancer treatment. Several studies have found that a variety of herbal and medicinal plants have anti-cancer properties [24, 25]. Due to their low aqueous solubility, the high dose required, and poor oral pharmacokinetics, these phytochemicals use as therapeutic agents is limited [26]. Recent advances in the realm of nanomaterials have been extensively investigated in the field of imaging and treatment of different diseases, including cancer [27-31]. Nanoparticles have the potential to enhance imaging and conventional therapy [29, 32]. Because of their gradual rate of release into the blood stream; NPCs have better bioavailability and absorption. Another benefit is that they are only needed in little quantities, lowering overall treatment costs. As a result, using NPCs alone or in combination with established therapeutic regimens may significantly improve treatment outcomes and lengthen the lives of cervical and endometrial cancer patients.

1.1. Etiology of cervical cancer

The sexually transmitted HPV causes the majority of cervical cancer cases. The virus that causes genital warts is HPV. There are over 100 distinct HPV strains. Cervical cancer is caused by only a few strains, the two most frequent of which are HPV-16 and HPV-18. Being infected with an HPV strain that causes cancer [8].

1.2. Etiology of endometrial cancer

The most distinguishing pathologic trait of EC is its reliance on hormones. Endometrioid adeno carcinoma of the endometrium, also known as type-I EC, accounts for 85-90% of all ECs and is usually triggered by lengthy estrogen irradiation [33]. Chronic oestrogen exposure combined with a relative progesterone shortage causes endometrial hypertrophy. Oestrogen excess can be caused by either endogenous or external factors [34].

1.3. Risk Factors for Cervical Cancer

HPV infection is connected to several cervical cancer risk factors [35, 36]. The intrusive cancer growth process could sustain up to 21 years from the genesis lesion driven by sexually transmitted HPV [37]. However, there are numerous risk factors including sexual contact at early ages, multiple sexual partners, smoking, and a low standard of life [38, 39].

1.4. Sexually transmitted infections (STI)

The infection is spread by sexual contact and results in squamous intraepithelial lesions. Due to immunological action, most of them disappear by 6–12 months. A low fraction of them, however, persist and may lead to cancer [36].

1.5. Human immunodeficiency virus

In women with HIV, the chance of being infected from high-risk HPV strains is greater [40]. HIV-positive women are more likely to contract HPV at a young age and have a higher risk of this cancer. HIV-positive women with cervical cancer are diagnosed at a younger age than non-infected women [41].

2. Reproductive and sexual factors

2.1. Sexual partners

Cervical cancer has also been linked to factors related to sexual behavior. According to one study, people who have several sexual partners had a higher chance of cervical cancer [42]. Furthermore, studies reported that women who have multiple sexual partners are more likely to contract HPV and develop cervical cancer [43, 44]. According to the meta-analysis, those who have several sexual partners have a much higher risk of cervical diseases than people who have fewer partners [45].

2.2. Oral contraceptive pills

OC tablets have been linked to a higher risk for cervical cancer. The relative risk of cervical cancer in current users raised as the length of OC usage increased in an international study. The usage of OC for 5 years or more has been shown to scale up the risk of cancer [46, 47].

2.3. Risk factors for endometrial cancer

Age, obesity, anovulatory cycles- PCOs, perimenopause, null parity, diabetes mellitus and ovarian tumors- granulosa cell tumors are some of the risk factors for endometrial hyperplasia [48, 49]. It can also be caused by immune suppression (in renal graft recipients) and infection [50-52] Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, puts women at a higher risk of endometrial hyperplasia [53, 54].

2.4. Conventional Approaches for Cervical and Endometrial Cancer Treatment

Treatment options are determined by several parameters, including the patient's age, illness stage, and histological type of tumor, type of metastases, grade of tumor (grade-G), size, development pattern, and overall health. Three therapy techniques are now in use: Surgery, radiation, and hormone treatment are all options [55].

3. Strategies for vaginal medication administration for targeted therapy

3.1. Suppositories

They are simple and affordable to make and administer, but their dwelling duration is brief, necessitating frequent drug delivery. In addition, a phase-II clinical trial found that a rod-shaped bleomycin suppository containing witepsol base caused early, common acute reactions [56].

3.2. Sponge

Because of its unique features, including robustness, capacity to bind fluids and natural acidity, the collagen sponge was first used in contraception. The side effects are minimal, and the vaginal toxicity was moderate but acceptable [57, 58].

3.3. Patch

For the therapy of CIN, a bio adhesive patch with 5-fluorouracil is used. A drug-loaded film is formed having Carbopol * 981, used in the patch's bilaminar design. This adhered directly to a polyvinyl chloride emulsion backing layer [59, 60].

3.4. Insertable devices

Chemo radiation is the most often used therapy, but it is often coupled with side effects from intravenous chemotherapeutic injection for radio sensitization [61]. For cervical cancer treatment, insertable cisplatin-loaded poly (ethylene-co-vinyl acetate) (EVAc) intra-vaginal rings were developed, which could be easily and inexpensively manufactured and were simple to use and administer [62].

3.5. Semi-solid cream or gel

It is one of the most commonly used vaginal formulations, having benefits such as acceptance, feasibility, and low cost. However, it has certain drawbacks, such as messy administration, leakage, and non-uniform distribution. Nanogel was found to extend retention time *in vivo* research [63].

3.6. Vaginal tablets

Vaginal tablets are commonly used to treat vaginitis because of their quick-dissolving, dispersion, disintegration in the vaginal cavity, and subsequent medication release [64].

3.7. Hormone replacement therapy (HRT)

Hormones are used to treat cancer in this sort of treatment HRT, which is used to treat menopausal symptoms, is not the same thing (menopausal hormone therapy). It is mostly used to treat advanced endometrial cancer. Chemotherapy is frequently combined with hormone therapy.

4. Side Effects of Conventional Approaches

4.1. Short term

Chemotherapy treatments can have a variety of negative effects like fatigue, pain, mouth and throat sores, diarrhea, nausea and vomiting, constipation, blood disorders, sexual and reproductive issues, appetite loss, hair loss, heart issues and nervous system effects.

4.2. Long term

The majority of side effects subside following treatment. Some, on the other hand, continue, return, or evolve afterward. Some forms of chemotherapy, for example, can harm the heart, lungs, liver, nephrons, or reproductive system permanently [65].

4.3. Drug Delivery Systems by Nanotechnology

Nanotechnology has made significant research achievements, particularly in medicinal nanotechnology. Pharmaceutical and materials research leads to drug delivery innovation, which improves pharmacological activity, reduces toxicity, and improves physicochemical properties to increase drug solubility and stability [66-69]. In recent years, it has evolved in treating cancer, allowing for higher retention of medications included in nanocarriers, reducing toxic effects, and targeted delivery, hence increasing drug bioavailability [70-71]. The enhanced permeability and retention (EPR) effect describes how nanocarriers of different sizes tend to collect in tumor site [72-76]. The general explanation for this occurrence is that tumor cells must induce the formation of blood vessels in the tumor microenvironment to proliferate [77, 78]. Furthermore, tumor tissues are frequently devoid of adequate lymphatic outflow [79].

5. Strategies of drug delivery in nanotechnology

5.1. Delivery of drugs that is sensitive to intrinsic triggers

5.1.1. pH sensitive system

pH sensitive polymeric materials gained popularity among a variety of fields, including medication delivery, insulin therapy and gene transporters [80-83]. Proton intensity is a unique technique and a trigger that has endogenous/intrinsic variability in pathology and structural variances, resulting in a pH-responsive drug delivery system. This delivery system is capable of sensing the macro and microenvironments in which tissue, organs, and cells exist [84-86]. Acids and bases with Log P values ranging 3-10 are commonly used as pH-sensitive materials. Carboxylic, sulfonate, primary, or tertiary amines are functional groups that ionize as a function of pH. Polymer cross linked from N, N-dimethyl aminoethyl methacrylate, maleic anhydride (MAN) is classic examples (MAA). The pictorial depiction of the pH sensitive system is represented in (Fig. 1).

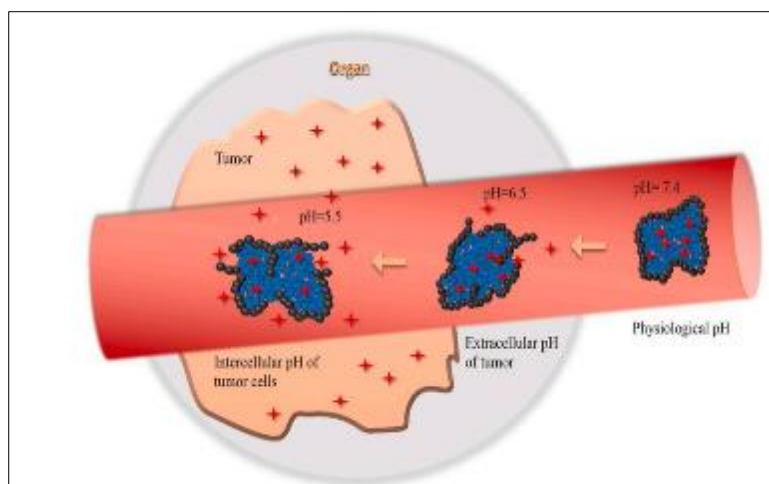


Figure 1 Pictorial depiction of the pH sensitive system

5.1.2. Enzyme sensitive system

Enzymes are a type of protein which plays an important role in biochemical processes. They have the distinct feature of displaying specific activities, similar to a lock and key system [87]. Due to the varied needs of cancerous cells in terms of multiplication, development, and invading for metastasis to various areas, cancer cells over express a few enzymes that differentiate them from normal cells. As a result, an enzyme-responsive system can be built that takes benefit which are up regulated in cancer cells. Enzymes may be employed to stimulate drug release from a nano formulation, allowing for stimuli-sensitive delivery of drugs [88]. Enzyme responsive systems have been studied less than other stimuli-responsive systems, although they have a lot of potential for target-specific action [89-90]. Metalloproteinases (MMPs) are found in the extracellular matrix and are primarily expressed in cancer tissue [91]. The pictorial depiction of the enzyme sensitive system is represented in (Fig. 2).

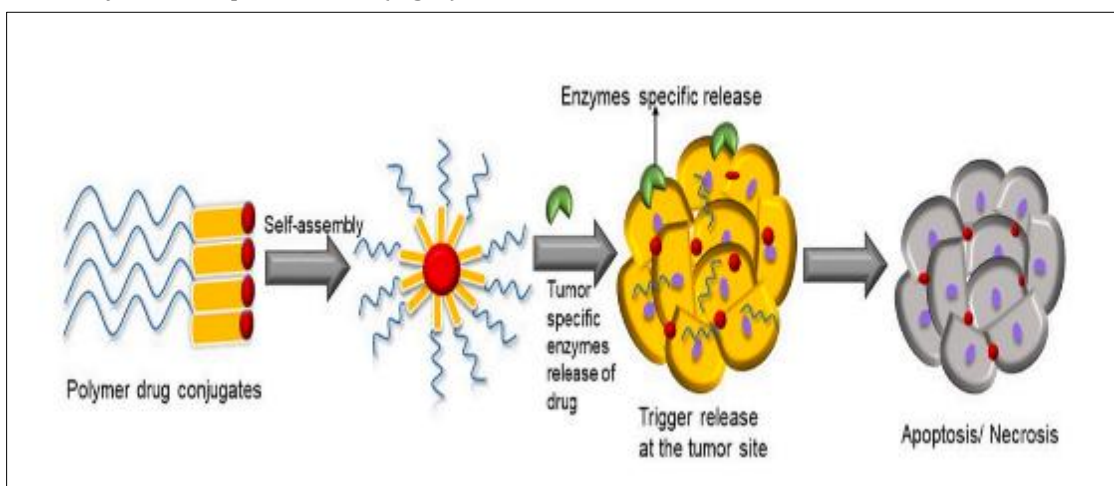


Figure 2 Pictorial depiction of the enzyme sensitive system

5.2. Delivery of drugs that is sensitive to extrinsic triggers

5.2.1. Temperature sensitive system

Temperature-sensitive polymeric materials have physical properties which vary dramatically and abruptly as a function of temperature [92, 93]. Temperature is a variable which may be exploited to induce and regulate drug release at the lesion site; hence these are intensively investigated in stimuli-sensitive studies [94-95]. Hyperthermia increases tumor vascular permeability, which improves chemotherapeutic delivery to the target region [96]. The pictorial depiction of the temperature sensitive system is represented in (Fig. 3).

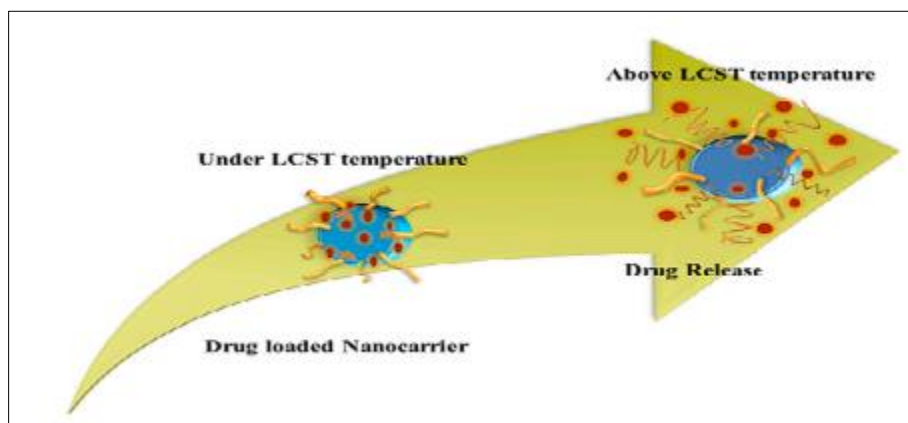


Figure 3 Pictorial depiction of the temperature sensitive system

5.2.2. Magnetic sensitive system

Magnetic sources have attracted researchers' attention as a non-invasive technique for cancer treatment [97]. The benefit involved is; it can be used for tumor focusing and projecting. The body generally does not absorb frequencies

below 400 Hz, but it led the magnetic nanoparticle to the desired site [98, 99]. For using magnetic power in a cancer-tracking system, it must be magnetized, either by introducing the magnetite or through the direct modification by biocompatible polymeric materials [100]. Magnetic nanoparticles (MNPs) are microscopic particles which can induce heat and behave like transducer when exposed to a magnetic field. The primary goal is to raise MNP concentration in the tumor area, resulting in slowed elimination from the body, diminished intracellular contact and increased cellular absorption, all of which led to cancer cell death [101-105]. The pictorial depiction of the magnetic sensitive system is represented in (Fig. 4).

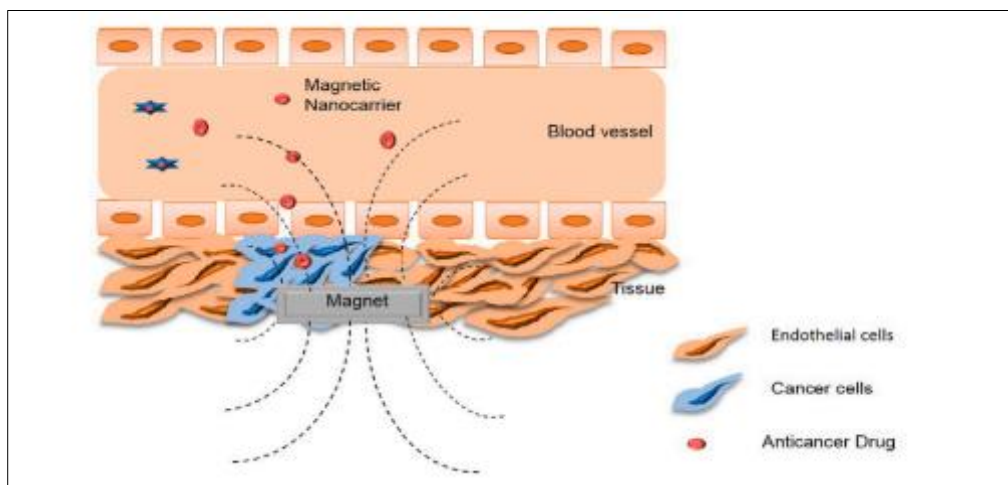


Figure 4 Pictorial depiction of the magnetic sensitive system

6. Nanocarriers in Cervical and Endometrial Cancer Treatment

6.1. Lipid-based nanocarriers

They are nanocarriers that have a lot of potential for dissolving, engulfing, and delivering pharmaceuticals. They can help with bioavailability and adverse effects by improving medication absorption [106-108]. The most common materials employed in the manufacture of these nanocarriers are biocompatible lipids having biocompatibility and biodegradability.

6.2. Solid lipid nanoparticles

In the early 1990s, solid lipid nanoparticles (SLNs) emerged as a class of colloidal drug transporters [109, 110] with a wide range of applications in clinical medicine [111-113]. Alba wax, carnauba wax, saturated glycerol esters, palmitic palmitate, and glyceryl di behenate are among these solid lipids [114, 116]. The benefits of using these include increased medication solubility, decreased dose, and improved stability [108, 117]. Because of the drug's modest loading capacity and premature ejection during storage, this type of device has limitations [118, 119].

6.3. Liposomes

Liposomes are spherical vesicles with a central aqueous cavity and two lipid membranes made up of natural phospholipids, synthetic phospholipids and cholesterol [120]. Liposomes can be made using a variety of phospholipids and excipients, resulting in flexible systems that can be easily changed in the formulation [121].

6.4. Inorganic nanoparticles

These nanoparticles are biocompatible. Inorganic NPs were developed as multifunctional nanoplatforams for a variety of biomedical applications. It also improved antitumor medication site-specific delivery, increased permeability, and reduced toxicity and side effects [122].

6.5. Carbon tubes (CNTs)

CNTs have the potential to be used as a bio-therapeutic carrier system for both diagnosis and treatment. It is a nanomaterial that is non-toxic and has a high capacity for attaching medicinal agents and other components [123]. Carbon nanotubes are classified into two types based on their structure: single-wall and multi-wall carbon nanotubes

(SWCNTs and MWCNTs). SWCNTs are formed up of tube-shaped carbon benzene rings, whereas MWCNTs are made up of multiple layers of carbon nanotubes.

6.6. Dendrimers

Dendrimers are monodispersed systems made up of low-molecular-weight polyenes with a specified structure resembling tree branches or arms [124-126]. Small molecules can be incorporated into dendrimers via electrostatic or hydrophobic interactions [127, 128], polar interchanges like amine and carboxyl groups can be used to attach medicines to their surfaces. Surface groups are covalently changed in some situations and sugar and medicines are added [129, 130] Because of their biocompatibility, they are being used in medical and biotechnological applications [131, 132]. Due to their promise in malignant cells treatment, they are used in anti-cancer medications [133, 134].

The list of various drugs delivered through nanocarriers in cervical and endometrial cancers is listed in the (Table 1).

Table 1 Drugs delivered through nanocarriers in cervical and endometrial cancers

Nanocarrier	Drug	Tumour targeted	Advantages
Solid-lipid nanoparticles	Docetaxel, paclitaxel	Cervical cancer	lowering toxicity while increasing therapeutic efficacy
Liposomes	Paclitaxel(PTX), Doxorubicin, Liposome-protamine-DNA(LPD) nanoparticle	Cervical cancer	Anti-tumoraction has been improved.
Inorganic nanoparticles	Bleomycin, doxorubicin	Cervical cancer, Endometrial cancer	improved the antitumor drug's site-specific delivery
Carbon tubes	Methotrexate, cisplatin, paclitaxel, doxorubicin,	Cervical cancer, Endometrial cancer	Excellent drug entrapment and inherent stability
Dendrimers	Methotrexate, 5-FU, cisplatin, doxorubicin	Cervical cancer, Endometrial cancer	The controlled release can be obtained

7. Conclusion

In conclusion, this study found that advances in nanotechnology led to the development of several nanocarrier delivery methods, which reduced the negative effects of chemotherapy and other therapies on cancer patients. The use of active and passive targeting in conjunction with nanocarrier drug delivery has been shown to improve cancer patient survival rates. Stimuli sensitive nanocarrier systems have emerged as a reliable way for aiding in imaging, diagnosis, and improving therapy efficacy by delivering and releasing drugs and genes to oncological cells. The fundamental trigger for the release of payloads via modifying the polymeric layer integrated into NP carriers is intrinsic stimuli in the biological system such as redox state, pH, and enzyme. External stimuli such as thermo-responsive and magnetic release the therapy at the designated region via a remote-control method. This type of nanocarrier technology has been shown to lessen cell toxicity while also lowering doses.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declared that they have no conflict of interest.

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