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Integrative Strategies For HPV And Cervical Cancer: The Role Of Herbal Therapies And Vaccination

Vanshika Vyas[1], Shaily Chaudhary[1], Priyanshu Upadhyay[1], Priya Nayak[1], Pulin Thakur[1], Ravi Yadav[1], Raja Malakar[1], Rohit Dharwe[1], Rohit Rathore[1], Akash Yadav[2]

1. *Compfeeders Aisect College of Professional Studies, Pharmacy College, Rangwasa, Indore (M.P.), India*
2. *IPS Academy College of Pharmacy, Knowledge Village, A.B. Road, Rajendra Nagar, Indore (M.P.), India*

*Corresponding Author**
Dr. Shaily Chaudhary
Head & Professor, Compfeeders Aisect College of Professional Studies, Pharmacy College, Rangwasa, Indore (M.P.), India
Email Id: s.shailychaudhary@gmail.com

Cervical cancer is significant public health concern worldwide, particularly in developing countries. This review aims to provide an overview of the current state of cervical cancer Treatments, Preventions, and Vaccination. This review paper highlights the various treatment options available, including surgery, chemotherapy, radiation therapy and herbal therapy as well as emerging trends in targeted therapies. Furthermore, review explores prevention strategies, such as screening programs and lifestyle modification, and highlights the importance of Human Papillomavirus vaccination in reducing the burden of cervical cancer. The review also examines the challenges and opportunities in implementing effective cervical cancer control programs. This article emphasizes the need of multiple herbal therapies and vaccination for the betterment of Patients life.

Keyword Human papilloma virus, Papanicolaou test, Cervical intraepithelial lesions, DNA detection, HPV viral load, Socio-demographic, Epidemiological risk factors.

1. Introduction

Cervical cancer is a material global health issue as it's the fourth most common cancer in women worldwide and causes further than one quarter of a million deaths per time. [1]. Originally, the International Federation of Gynecology and Obstetrics (FIGO) staging of cervical cancer was primarily grounded on clinical examination[2]Cervical cancer stages range from I to IV. Cases with locally advanced or early- stage cervical cancer have access to conventional treatments, including surgery, chemotherapy, and radiotherapy. Still, no standard remedy is available for cases with metastatic cervical cancer(3)

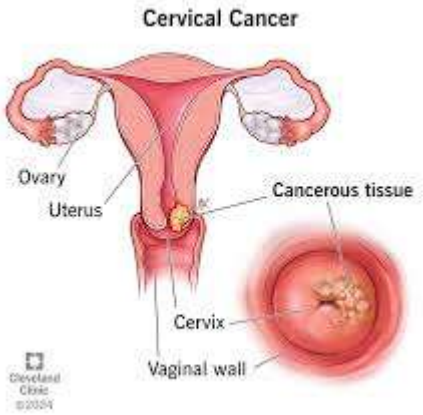

Figure 1: Anterior view cervical cancer cyst

At the same time, vaccination against the human papilloma virus (HPV) has surfaced as a pivotal tool in the forestallment of cervical cancer. HPV is responsible for around70 of cervical cancer cases and the preface of the bivalent, quadrivalent and non valent vaccines has brought new stopgap for the eradication of this complaint[4] Studies have shown that cervical cancer webbing increases with education, ranging from 5 among those with no formal education to 51 among those with a council education[5] Papilloma virus(HPV) infection is the most frequent viral infection sexually transmitted in women and the third cause of cervical cancer (6). Worldwide, 300 million people are estimated to carry HPV and among them nearly 500000 women will develop cervical cancer, substantially in underdeveloped countries (7) thus, current forestallment strategies depend on periodic Papanicolaou (Pap) testing. still, the objectification of the HPV DNA testing for cervical cancer webbing has come judicious due to the low perceptivity of Pap testing and the significance of HPV(8)

Table 1. Stages of cervical cancer

S. No.	Stages	Description
1.	Stage 0	Precancerous cell are present
2.	Stage 1	Cancer cells have grown from the surface into deeper tissues of the cervix, and possibly into the uterus and to nearby lymph nodes

3.	Stage 2	The cancer has now moved beyond the cervix and uterus, but not as far as the walls of the pelvis or the lower part of the vagina. It may or may not affect nearby lymph nodes.
4.	Stage 3	Cancer cells are present in the lower part of the vagina or the walls of the pelvis, and it may be blocking the uterus, the tubes that carry urine from the bladder. It may or may not affect nearby lymph nodes.
5.	Stage 4	The cancer affects the bladder or rectum and is growing out of the pelvis. It may or may not affect the lymph nodes. Later in stage 4, it will spread to distant organs, including the liver, bones, lungs, and lymph nodes.

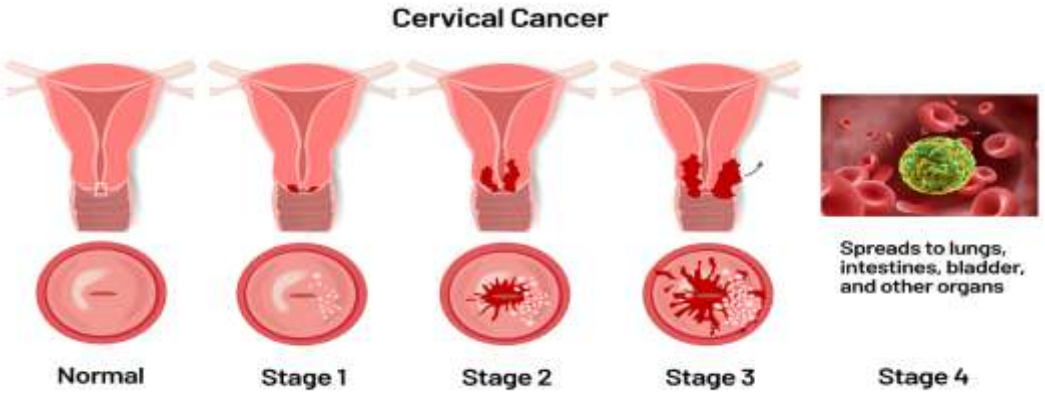

Figure 2: Different stages of cervical cancer [9]

HPV virus

HPV is transmitted through sexual contact, generally via skin – skin or skin – mucosal contact [(10)]. Further than 80 of sexually active grown-ups will be exposed to HPV in their continuances[(11).] Much more infrequently, it can be spread vertically during the perinatal period. There have also been rare reports of autoinoculation or circular infection in individualities who have no way had any sexual contact .The usual mode of vertical transmission of anogenital HPV is via sexual exertion through contact with infected cervical,

vaginal, vulvar, penile or anal epithelium presumably through bitsy scrapes inthe mucosa skin. [12,13,14,15,16,17].HPV infections can be transmitted not only through peno- vaginal intercourse, but also via other sexual practices, similar as oral coitus, peno- anal intercourse, digital – vaginal coitusand also by the use of insertive coitus toys[,18,19,20]

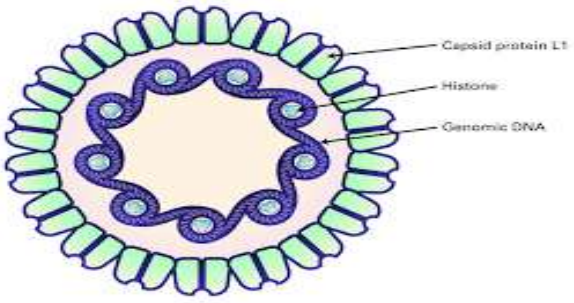

Figure 3: HPV virus cell

History of HPV virus

One of the most wide contagions in the world, the mortal Papillomavirus (HPV), has been around for generations. Further than 100 different types of HPV are allowed to live. The maturity of types are benign, but some can progress into conditions like genital knobs or cancer. Cancer- causing HPV strains are distributed as "high threat. " Two HPV kinds, HPV16 and HPV18, account for the maturity of HPV- related cancers out of the 14 high- threatHPV types presently honored. Thankfully, the HPV vaccines give a measure of defense against these dangerous strains. The question is, how did we get there? In this post, we will look at the history of HPV, from its discovery through the development of vaccines to help it. We'll also examine how wide HPV is encyclopedically[21]

Diagnosis tests for HPV

WHO presently(2021) recommends 3 webbing tests for HPV 1) Nucleic acid modification tests(NAAT) for hr- HPV types(hr- HPV DNA/ NAAT and mRNA), 2) Visual examination with acetic acid or with Lugol's iodine(VIA/ VILI) by naked eye or magnified by colposcope or camera and 3) Cytology(Conventional Pap/ Liquid- grounded cytology/ Binary staining to identifyp16 and Ki- 67).[22]

The six main possible clinical operations of HPV DNA testing are(i) triage of women with equivocal or low- grade cytological abnormalities;(ii) follow- up of women with abnormal webbing results who are negative at colposcopy/ vivisection;(iii) vaticination of the remedial outgrowth after treatment of cervical intraepithelial neoplasia(CIN);(iv) primary webbing for HPV DNA testing, alone or in combination with a Pap smear, to descry cervical- cancer precursors;(v) gain precious information on the continuity of certain HPV types and(vi) examinations of indigenous and country- grounded frequencies of type-specificHPV, to give birth values against which the global impact of HPV vaccination can be assessed in the future [,23,24,25]

Causes

HPV is spread through skin-to-skin contact, which includes oral sex, hand-to-genital contact, and sexual contact. Young age at sexual initiation, having several sexual partners, high parity, smoking, herpes simplex, HIV, co-infection with other genital infections, and using oral contraceptives are risk factors for HPV and cervical cancer.[,26,27,)]

1. Smoking

2. Human sexual activity

3. A weak immune system

4. Sexual transmitted infection

5. Combined oral contraceptive pill

Figure 4: Causes of cervical cancer

Signs and symptoms of cervical cancer

In its early stages, cervical cancer frequently has no symptoms. Symptoms that may be seen in advanced complaint include.

1. Abnormal vaginal bleeding between menstrual
2. Ages or during/ after coitus or exercise.
3. Pelvic pain.
4. Vaginal discharge.
5. Pain or discomfort during coitus.
6. Leg swelling
7. pain in lower back

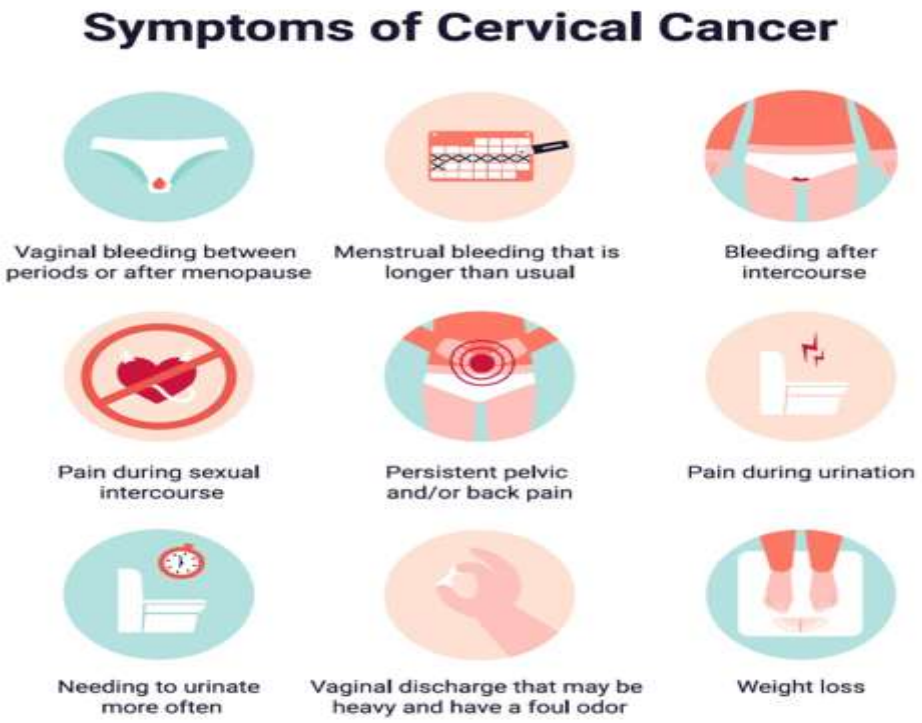

Figure 5: Sign and symptoms

Risk factors

Roughly all cervical cancer cause by HPV. The climax age of cervical cancer is about 47 periods of times. HPV generally transmit through sexual contact, it can spread without coitus, by skin- to- skin contact with infected area of body. HPV infection diagnosed in youthful women lasts from 8- 13 months

Other threat Factor

Salutary habits A diet lacking in fruits, vegetable as well as being in excess of weight, lesser than before increases threat of cervical cancer. Sexual exertion HPV infection is most common route passes through sexual contact. Particularly onset sexual exertion, high threat sexual mates. Multiple mate and failure to use condoms. Family history It's transmitted genetically from mama to her baby or to the family has 2- 3 times development of cancer is being. Smoking also increases threat of scaled cell cancer by sensational body to cancer causing chemical change and also by weakening vulnerable system. Multiple gravidity Women with 3 or further gravidity beget hormonal changes and vulnerable system is weak during period of

gestation. Diethyl stilbestol DES increases threat of adeno melanoma in cervix, especially in women whose took DES when pregnant.

Oral contraceptive

Some exploration studies recommend that useof oral contraceptives for birth control, may be connected with an raise the threat of cervical cancer [28]

Table 2. Risk factor associated to cervical

S. No.	Risk Factor	Description
1.	HPV	This is a sexually transmitted virus. More than 100 different types of HPV can occur, at least 13 of which may cause cervical cancer.
2.	Smoking	Smoking also increases risk of squamous cell cancer by sensational body to cancer causing chemical change and also by weakening immune system.
3.	Sexual activity	HPV infection is most common route passes through sexual contact. Particularly early onset sexual activity, high risk sexual partners. Multiple partner and failure to use condoms
4.	Multiple pregnancies	Women with 3 or more pregnancies cause hormonal changes and immune system is weak during period of pregnancy.
5.	Oral contraceptive	Some research studies recommend that use of oral contraceptives for birth control, may be connected with an raise the risk of cervical cancer.

Diagnosis

Assessing visible cervical lesions for invasive cancer is essential. still, as bandied over, utmost cervical cancer is asymptomatic and won't present with an overt mass in the early stages. Other possible causes of cervical lesions and/ or abnormal bleeding include STIs, cervical cystsor fibroids, and endometriosis. Opinion may bear farther evaluation of symptoms and testing to

determine whether the complaint is cervical cancer. A individual vivisection is demanded to finalize the opinion. Other pathology- determined conditions in the discrimination opinion include carcinosarcoma, epithelioid trophoblastic excrescence, placental point bump, immature scaled metaphase, and metastatic complaint from a non cervical primary excrescence. Infrequently, a routine Pap smear may identify metastatic cancer on the uterine cervix.[29]Early cervical cancer opinion improves the success of treatment. The American Cancer Society recommend Screening tests are used to find cancer before a person has any symptoms. Netting can constantly help find and treat pre-cancers and cancers beforehand, before they have a chance to spread. People whose cervix has been removed by surgery for reasons not related to cervical cancer or serious pre-cancer should n't be tested.

Figure 6: Diagnosis test for cervical cancer

People who have been vaccinated against HPV should still follow the netting recommendations for their age groups. Some individualities – because of their health history BC (HIV infection, organ transplant, DES exposure, etc.) – may need a different netting schedule for cervical cancer

Treatment of cervical cancer

Cervical cancer therapies are determined based on several factors, including the stage of the cancer, whether the cancer has metastasized to other parts of the body, the size of the tumor, and the patient's age and overall health. Treatment guidelines, recently updated by the National Comprehensive Cancer Network. [30]

There are 3 types of treatment for cervical cancer

1. Herbal treatment

2. Allopathic treatment

3. Targeted therapy

Table 3: Herbal treatment for cervical cancer

S. No.	Name	Mechanism of action	Diagram
1.	Turmeric	Curcumin has been shown to inhibit the growth of cancer cells, including cervical cancer cells, by inducing apoptosis (cell death) and arresting cell cycle progression [31]	

2.	Green tea	Inhibition of HPV-16 E6 and E7 oncogene expression: EGCG has been shown to inhibit HPV-16 E6 and E7 oncogene expression, which can help prevent cervical cancer development.(32) Modulation of HPV-related signaling pathways: EGCG has been shown to modulate HPV-related signaling pathways, including the PI3K/Akt pathway, which can help regulate cancer cell growth. (33)	
3.	Ashwagandha	.Ashwagandha has been shown to inhibit cell cycle progression and induce apoptosis in cervical cancer cells.[34]	

4.	Garlic	Allicin has been shown to inhibit cell cycle progression and induce apoptosis in cervical cancer cells.[35] Allicin has been shown to modulate Bcl-2 family proteins, which can help regulate apoptosis and prevent cancer cell growth.[36] .	
5.	Terminalia catappa	Terminalia catappa extracts have been shown to inhibit cell cycle progression and induce apoptosis in cervical cancer cells.[37].Terminalia catappa extracts have been shown to modulate Bcl-2 family proteins, which can help regulate apoptosis and prevent cancer cell growth. [38]	
6.	Astragalus	Astragalus extracts have been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development.[39]	

7.	Chelidonium majus	Chelidonium majus extracts have been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development.[40]	
8.	Lycopodium calvactum	Lycopodium clavatum has been shown to inhibit the growth of cervical cancer cells by inducing cell cycle arrest and apoptosis.[41]	
9.	Grapes	Grape extracts have been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development.[42]	

10.	Holy basil	Holy basil extracts have been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development.[43]	
11.	cruciferous veggies	ITCs have been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development.[44]	
12.	Saffron	Saffron extracts have been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development.[45]	
13.	Echinacea	Echinacea extracts have been shown to stimulate the activity of immune cells, such as natural killer cells and macrophages, which can help eliminate cancer cells.[46]	

14.	Thyme	Thyme extracts have been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development[47].	
15.	Heart-leaved moonseed	Tinospora cordifolia extracts have been shown to inhibit inflammatory pathways, including the NF-κB pathway, which can help reduce inflammation and prevent cancer cell growth[48]	

16.	Punarnava	Punarnava extracts have been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development.[49]	
17.	Combretum caffrum	Combretum caffrum extracts have been shown to inhibit the growth of cervical cancer cells by inducing cell cycle arrest and apoptosis[.50]	
18.	Hypericin	Hypericin has been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development[51]	

19.	Moringa	Moringa Tree extracts have been shown to inhibit the expression of HPV-16 E6 and E7 oncogenes, which can help prevent cervical cancer development[52]	
20.	Dong Quai's	Dong Quai's bioactive compounds, such as ferulic acid and ligustilide, have been shown to induce apoptosis in cervical cancer cells activating pro apoptotic proteins inhibiting anti apoptoticproteins[53].	

21.	Tulsi	Tulsi extracts have been shown to inhibit the expression of VEGF, a key angiogenic factor, which can help prevent the formation of new blood vessels that supply nutrients to growing tumors.[54]	
22.	Pomegranate	Pomegranate extracts have been shown to inhibit inflammatory pathways, including the NF-κB pathway, which can help reduce inflammation and prevent cancer cell growth [55]	

Allopathic treatment for cervical cancer

1. **Radiation therapy**
   Some doctors refer to radiation therapy as radiation oncology or XRT. It involves the use of beams of high-energy X-rays or radiation to destroy cancer cells. When the treating doctor aims radiation at the pelvic area, it may cause the following side effects, some of which may not emerge until after the treatment is over. Diarrhea, nausea, Upset stomach, bladder irritation ,narrowing of the vagina, Interrupted menstrual cycle, Early Menopause

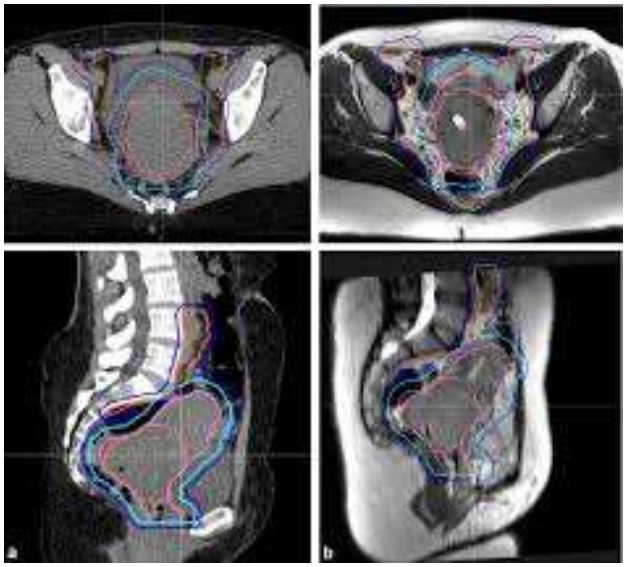

Figure 7 : Radiation therapy[56]

2. Chemotherapy

Chemotherapy is the use of chemicals (medication) to treat any disease. In this context, it refers to the destruction of cancer cells. Doctors use chemotherapy to target cancer cells that surgery cannot or did not remove, or to help the symptoms of people with advanced cancer.

Chemotherapy drugs

These are often used in advanced stages or in conjunction with radiation therapy (chemo radiation). Common chemotherapy agents include:

Cisplatin: This is the most commonly used chemotherapy drug for cervical cancer. It is often used in combination with radiation therapy for patients with locally advanced disease or as a part of combination regimens in advanced stages.

Carboplatin: Sometimes used as an alternative to cisplatin, especially in patients who cannot tolerate cisplatin due to kidney problems or other co morbidities

Paclitaxel (Taxol): Often used in combination with cisplatin or carboplatin for advanced cervical cancer. It is a chemotherapy drug that works by preventing cancer cells from dividing.

Topotecan: This drug may be used for recurrent or metastatic cervical cancer, particularly if cisplatin -based chemotherapy has not been effective.

Gemcitabine: Sometimes used in combination with cisplatin for patients with advanced or recurrent cervical cancer**.**

3. Targeted therapy

These therapies target specific molecules involved in the growth and spread of cancer cells. Some drugs in this category include:

There are some drugs which is mostly used for targeted therapy

Dabrafenib mesylate (Tafinlar), Dostarlimab-gxly (Jemperli) ,entrectinib (Rozlytrek), famtrastuzumab deruxtecan-nxki (Enhertu), larotrectinib sulfate (Vitrakvi), pembrolizumab (Keytruda), Bevacizumab

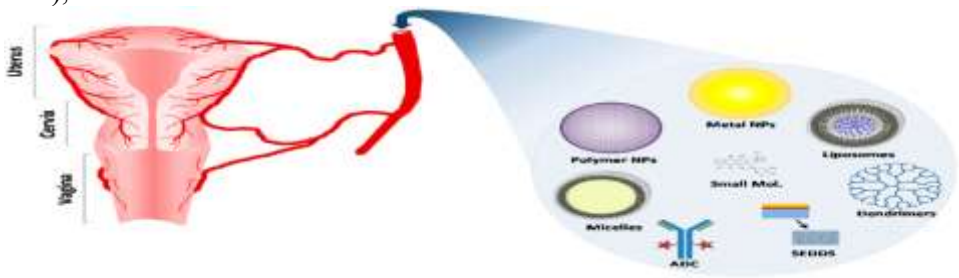

Figure 8 : Targeted therapy[57]

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