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ROLE OF MEDICINAL PLANTS IN PREVENTION OF CERVICAL CANCER: A REVIEW

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Abstract:

Cervical cancer is a malignant carcinoma type of cancer. It originates from the cervix region and joins the narrow portion of the uterus where it joins the top of the vagina. There are two types of cells which cover the cervix the one is squamous epithelial cells and the other is glandular cells. About 80% - 90% of cervical cancers are squamous cell carcinomas and the remaining types are caused due to adenocarcinomas which are developed from the gland cells. The last 20 years Adenocarcinomas are found to be most common among people. The squamous and adenocarcinomas commonly known as adenosquamous carcinomas or mixed carcinomas are rarely found or least commonly present. Cervical cancers are more common in younger women's than the elders. Cervical cancer is characterized by Pelvic pain, bleeding after the menopause, abnormal vaginal bleeding, bleeding after sexual intercourse. For diagnose Screening methods like Pap test and biopsy is used. The research has been done worldwide to seek out the effective treatment for cancer with the help of active constituents present in the plant. In this session of review article the plants having anti-oxidants, anti-cancer properties and there important role in reducing the side effects caused due to chemotherapy and radiotherapy was discussed.

Keywords: Cervical cancer, squamous epithelial cells, Adenocarcinomas, Anti-oxidants, Anti-cancer.

INTRODUCTION:

The human papilloma viruses (HPVs) are the primary etiologic agents of cervical cancer, which represents the main cause of cancer-related death in women in developing countries and the third leading cause of cancer-related death among women worldwide.[1].Every year, 470,000

cases of cervical cancer are diagnosed [2]. A picture of normal cervical cells and a cancerous cervical cell has been represented in (Figure 1).

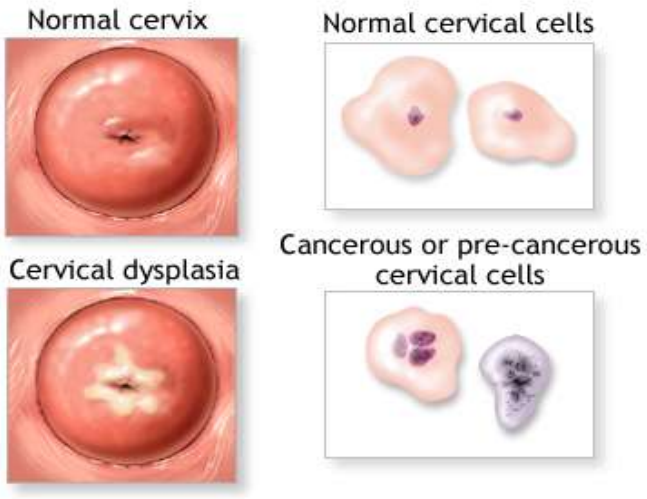


Figure: 1

A prophylactic vaccine against HPV is now available (GARDASILTM, Merck) but, due to the long latency period between infection and onset of cancer, the benefits of prophylactic vaccination will not be visible for decades[3]. So a therapeutic vaccine, which is targeting againstinfected individuals, is also required. Successful immunotherapy should induce specific cell-mediated immunity that would rapidly clear an established infection and provide protection against future exposure. Treatment of HPV- diseases will benefit from therapies that boost natural immune-mediated tumor defense mechanisms and that focus the immune response on the relevant tumor antigens. HPV-6 and HPV-8 are low risk HPVs, whereas HPV-16 and HPV-18 are at high risk.

The HPV16 oncoproteins (E5, E6 and E7) are responsible for the onset and maintenance of the transformedstate and, therefore, represent appropriate targets for therapeutic vaccinesE7-based vaccine formulations have been tested in animal models and some have advanced into phase II and III clinical trials. In this study plant-produced fusions of E7 and the

E7 mutant E7GGG to Clostridium thermocellum-1, 3-1, 4-glucanase (LicKM) were assessed in mice. Due to its reduced transformation potential, E7GGG has been proposed as asafer candidate than E7 for vaccine development.[5]

DIAGNOSIS:

It can be diagnosed by some methods:

- VISIBLE LESION:
  - By EUA
  - Urinalysis
  - Rectosigmoidoscopy
  - Lymph angiogram
  - Optional: MRI, PET, CT, US.
  - Biopsy
  - Colposcopy
  - Pap test.

PAP TEST:

A Pap test is a commonly used procedure to collectcells from the surface of thecervix and vagina. A piece of cotton, a brush, or a small wooden stick is used to gently scrape cells from the cervix and vagina. Then the cells are viewed under a microscope to find out the abnormal. This procedure is also called a Pap smear. A new method of collecting and viewing cells has been developed. In that method the cells are placed into a liquid before being placed on a slide. The diagrammatic representation of paptest has been shown in (figure 2).

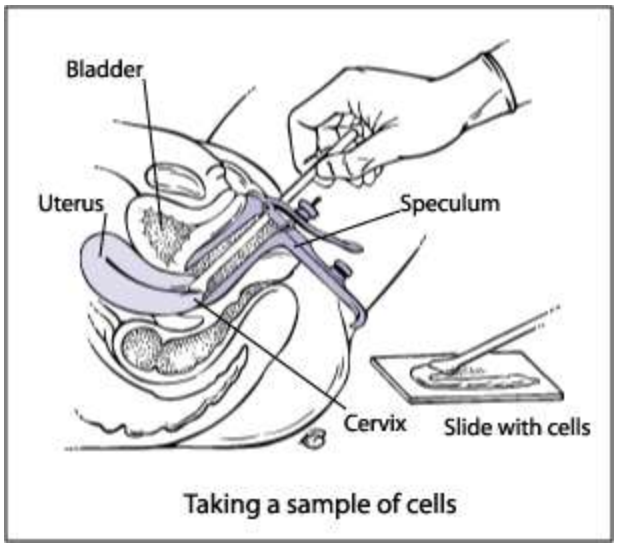


Figure 2: pap test

A speculum is inserted into the vagina to widen it. Then, a brush is inserted into the vagina to collect cells from the cervix. The collected cells are checked under a microscope for signs of disease.

BIOPSY:A cervical biopsy is usually done after an abnormality has been found during a routine pelvic exam or Pap smear. Abnormalities can include the presence of the human papillomavirus (HPV), or cells that are precancerous. Certain types of HPV can put you at risk for developing cervical cancer.

Types of Cervical Biopsies:

Three different methods are used to remove tissue from the cervix:

- Punch biopsy: In this method, small pieces of tissue are taken from the cervix with an instrument called "biopsy forceps." Cervix is stained with a dye to make it easier for the

examiner to see any abnormalities. A picture of punch biopsy has been represented in (Figure 3).

Figure: 3

- Cone biopsy: This surgery uses a scalpel or laser to remove large, cone-shaped pieces of tissue from the cervix. A general anesthesia is given during this biopsy.

LYMPHANGIOGRAM: Lymph node plays an important role in immune system. It helps to store white blood cells that fight infections. They also trap cancer cells. Lymph nodes and lymph vessels don't normally show up on X -ray, so a special procedure called LYMPHANGIOGRAM is used. A sample of lymph node is collected to check the cancer cells.

OPTIONAL TESTS:

- MRI SCAN (magnetic resonance imaging): This uses magnetism to build up a picture of body.

- CT (computerized tomography): This uses x- ray to build up a three dimensional picture of body.

- PET/CT (Positron emission tomography): This uses low dose radiation to identify the areas of cancer

- EUA (EXAMINATION UNDER ANAESTHETIC): This allows the examiner to examine the vagina and cervix while under general anesthetics.

STAGES OF CERVICAL CANCER:

The stages of cervical cancer are described in four stages:

- Stage 0
- Stage 1
- Stage 2
- Stage 3
- Stage 4

➢ **Stage 0:**

The cancer is found only in the first layer of the cells lining the cervix not in the deeper tissues.

➢ **Stage 1:**The cancer has spread from the cervix lining to the deeper tissues but is still found in the uterus. It has not spread to the lymph nodes and the other parts of the body (T1, N0, and M0). Where T is a tumor, N is a node and M is a metastasis.

This stage is further more described as:

Stage Ia: T1a, N0, M0

T1a: Invasive carcinoma was diagnosed only by microscopy which is viewing the cervical cancer.

N0: The tumor has not spread to the regional lymph nodes.

M0: There is no distant metastasis.

Stage Ia1: T1a1, N0, M0

T1a1: There is cancerous area in 3mm or a smaller depth, and 7mm or smaller length.

Stage Ia2: T1a2, N0, M0

T1a2: There is a cancerous area larger than 3mm but not larger than 5mm in depth and 7mm are smaller in length.

Stage Ib: T1b, N0, M0

T1b: In this stage the doctor can see the lesions only on the cervix. The cancer may have been found because of physical examination, laparoscopy or by other imaging methods.

Stage Ib1: T1b1, N0, M0

T1b1: The tumor is 4 cm or smaller.

Stage Ib2: T1b2, N0, M0

T1b2: The tumor is larger than 4 cm.

- **Stage II:** The cancer has spread beyond the cervix to the nearby areas, such as vagina or tissues near the cervix, but still inside the pelvic area.it has not been spread to the lymph and other parts of the body.

Stage IIa: T2a, N0, M0

T2a: The tumor has not spread to the tissues next to the cervix, also called as parametrial area.

Stage IIa1: T2a1, N0, M0

T2a1: The Tumor is 4cm or smaller.

Stage IIa2: T2a2, N0, M0

T2a2*:* The tumor is larger than 4cm

Stage IIb: T2b, N0, MO

T2b: The tumor has spread to the parametrial area (tissues surrounding the uterus).

- **Stage III:**

The cancer is spread outside the cervix and vagina but not to the lymph nodes or other parts of the body. (T3, N0, MO)

T3: The tumor extends to the pelvic wall, and involves the lower third of the vagina which leads to hydronephrosis (swelling of the kidney) or a non-functioning kidney.

Stage IIIa: The Tumor has spread to the lower parts of the vagina.

T3a: The tumor involves the lower third of the vagina, but it has not grown into the pelvic wall.

Stage IIIb: The cancer may have spread as far as the pelvic wall and to lymph nodes

T3b: The tumor has grown into the pelvic wall and/or causes hydronephrosis or nonfunctioning kidneys.

- **Stage IVa:** The cancer has spread to the bladder or rectum and may or may not have spread to the lymph nodes.

T4: The tumor has spread to the mucosa (lining) of the bladder or rectum and grown beyond the pelvis. The diagrammatic representation has been explained in (figure 4).

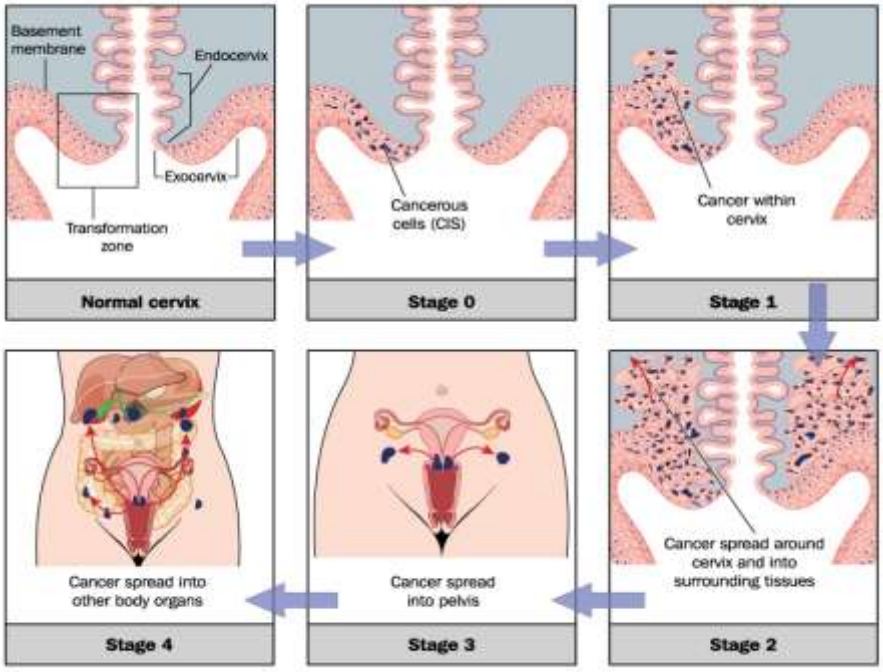


Figure: 4 Stages Of Cervical Cancer [Normal To Stage 4]

Statistical Data Of Cervical Cancer:

Survival rate on different stages has been represented in (figure 5).

5-Year Survival Rate	Stage
93%	0
93%	IA
80%	IB
63%	IIA
58%	IIB
35%	IIIA
32%	IIIB
16%	IVA
15%	IVB

Figure: 5 Survival Rate On Different Stages

PATHOGENESIS OF CERVICAL CANCER:

Transmission of HPV occurs primarily by skin-to-skin contact. Basal cells of stratified squamous epithelium may be infected by HPV. Other cells types appear to be relatively resistant. It is assumed that the HPV replication cycle begins with entry of the virus into the cells of the basal layer of the epithelium.

- MOLECULAR BIOLOGY :

Cervical cancer is one of the best understood examples, How the viral infection can lead to malignancy.In high-grade intraepithelial neoplasias and invasive cancers, HPV-DNA generally is integrated into the host genome. Integration of HPV-DNA disrupts or deletes the E2 region, which interferes with the function of E2, which normally down-regulatesof the E6 and E7 genes, and leads to an increased expression of E6 and E7 genes.The function of the E6 and E7 in HPV infection is to subvert the cell growth-regulatory pathways and modify the cellular environment which multiplies viral replication [6]. The E6 and E7 gene products deregulate the host cell growth cycle by binding and inactivating two tumor suppressor protein (p53) and the retinoblastoma gene product (pRb). P53gene when binds to HPV E6 gene a rapid degeneration takes place. [7]. The Normal activities of p53 govern

the G1 arrest, apoptosis, and DNA repair are abrogated. Low-risk HPV E6 proteins do not bind p53 at detectable levels and have no effect p53 stability in vitro. The Human papilloma virus (HPV) E7 gene product binds to pRb and this binding disrupts the complex between pRb and the cellular transcription factor E2F-1,which results in the liberation of E2F-1, and which allows the transcription of genes required for the cell to enter the S phase of the cell cycle [8]. The E7gene reacts with other mitotically interactive cellular proteins such as cyclin E, resulting in stimulation of cellular DNA synthesis and cell proliferation. The E7 protein from low-risk HPV types binds pRb with decreased affinity. Next, on the E5 gene product induces an increase in mitogen-activated protein kinase activity, thereby enhancing cellular responses to growth and differentiation factors. This results in continuous proliferation and delayed differentiation of t4he host cell. The inactivation of p53 and pRb proteins can give rise to an increased proliferation rate and genomic instability. As a consequence, the host cell accumulates more and more damage DNA that cannot be repaired, leading to transformed cancerous cells [9].The diagrammatic representation of Molecular biology has been explained in figure 6.

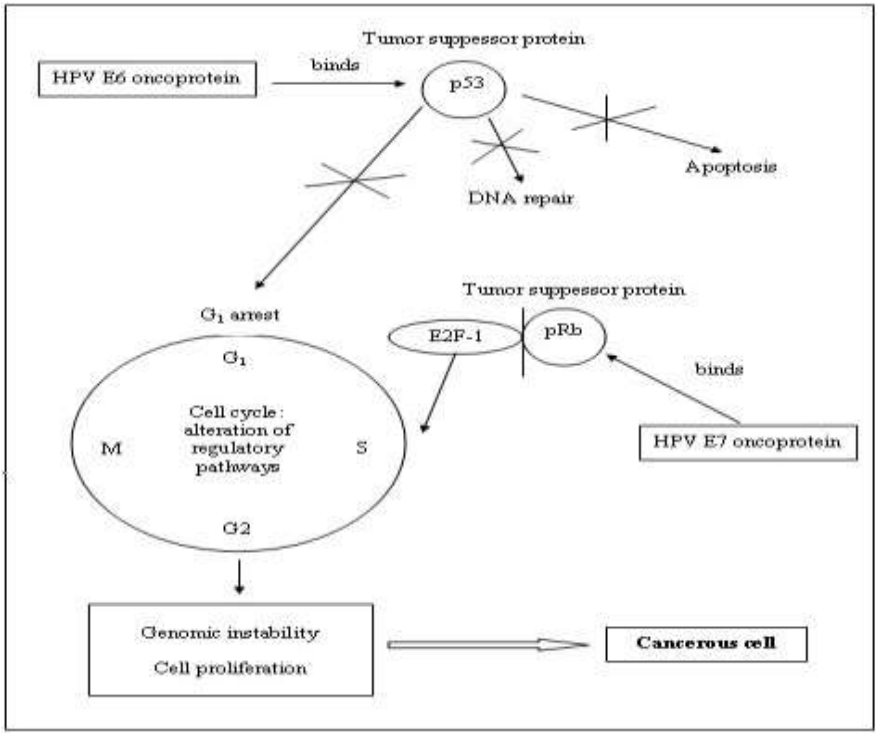
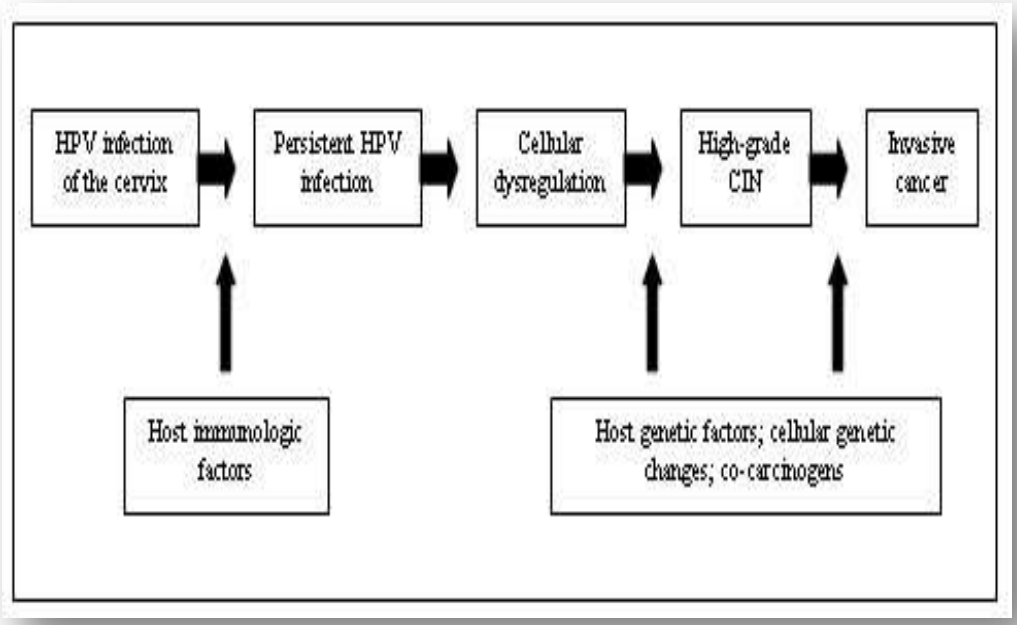


Figure: 6 molecular Mechanism of Oncogenic Hpv Infection

- DEVELOPMENT OF CERVICAL CANCER: The progression from HPV infection to cervical cancer may take from 5 to 15 years it can be summarized into 4 key stages:
    - HPV transmission
    - HPV infection
    - Viral persistence and development of a precancerous lesion
    - Invasion through the basement membrane of the epithelium.

The diagrammatic representation has been explained in figure 7.

FIGURE: 7 DEVELOPMENT OF CERVICAL CANCER



SYMPTOMS:

In early stages (in precancerous stage) cervical cancer does not show any symptoms. On later stages one or more symptoms are noticed.

- Abnormal vaginal bleeding caused between the regular menstrual periods and after sexual intercourse or a pelvic exam.

PLANTS	PARTSUSED	MECHANISM OF ACTION	CHEMICAL CONSTITUENTS	USES
Aerva lanata (Amarantheceae) 	Whole plant of *Aerva lanata* is used.	Inhibition of cellular levels of NADH and glucose levels	Alkaloids, palmitic acid, tannins, coumestrol, beta-sitosterol	It is a diuretic which helps in promoting the proper flow of urine. It also treats kidney stone.
Anisomles malabarica (Lamiaceae) 	Whole plant of *Anisomles malabarica*	Leaves have anti-epileptic potential acts against both MES and PTZ convulsion models	It contains secondary metabolite such as anisomelic acid, betasitosterol and betulinic acid which has the cytotoxic effect on a cancer cells.	Infusion of leaves used in dyspepsia and fever. Decoction of the plant or its essential oil is used in rheumatism. In traditional medicine it is as an anti-cancer agent.
Bidens pilosa(Asteraceae) 	The whole plant was used.[11]	Have an anti-diabetic activity The mechanism of action of cytopilene and probably its polyene derivatives in type 1 diabetics include inhibition of T-cell proliferation and the cell differentiations and partial depletion of TH cells, and protection of B.pancreatic islets	Linoleic acid, leuteolin, ethyl caffeate	The compounds have anti-tumor, anti-oxidant, anti-inflammatory, anti-malarial activities. It is also used as vasodilators and anti-ulcerative.

Campthotheca acuminate: (Corneaceae) 	Barks and stems of *Campthotheca acuminata* were used.[12,13]	Inhibition of topoisomerase I	Campthotheca acuminata contain the alkaloid campthothicin. camptothecin are used as the drugs for cancer treatment, which includes irinotecan, topotecan, and rubitecan	Pentacyclicquinolinecampthothecin and 10 hydroxy - campthothecin which inhibits the DNA topoisomerase I and very effective against cancer cells. The extracts of C.acuminata are mainly used for brain tumors, liver cancer in the GIT and other cancers.
Cassia tora *(*Fabaceae) 	Seeds, roots and leaves of the plant was used	Methanolic extract of C.tora leaves inhibits the oedma causing inflammation	Cinnamaldehyde, tannins,and coumarin. It also contains resins.	Seeds and leaves are used for skin disease. Seed as laxative property.
Gardenia gummifera (Rubiaceae)	Root part of the plant is used	The medicinal value of plants lies in some chemical substances usually in secondary metabolite which produces a definite physiological action on the cancer cells	It contains 89% resins and 0.1% of volatile oil the coloring agent gardenia.	It is used as an anthelmintic, anti-spasmodic, Carminative and also used as a cardio tonic, anti-oxidant and anti-hyperlipidemia.
Xylopiaaethiopica *(*Annonaceae) 	Fruits of *Xylopia* was used	Anti –proliferative, anti-oxidant and have cytotoxic effect on cancer cell lines.	Anonaceine is the alkaloid present in the fruits of the X.aethiopica.[14]	Anti-bacterial and anti-fungal and the essential oil extracted from the fruit is used as an anti-proliferative in the cell lines.

Menstrual periods may be heavier and may last longer. Women in their menopause may experience bleeding.

- Increased vaginal discharge and Pain in the pelvic area
- Pain during sex

Other symptoms are:

- Difficulty urinating or defecating
- Swelling of one or both legs
- Fatigue and Weight loss

TABLE 1: HERBAL PLANTS USAGE IN CERVICAL CANCER:

- Some of the herbal plants used in the treatment of cervical cancer are:

CONCLUSION:

Due to the increased adverse effect caused by chemotherapy in treatment of cervical cancer, herbal plants can be replaced. [15]The medicinal plants contain many anti-oxidants, carotenoids and flavonoids, enzyme and minerals. Researches states that the anti-oxidant contains remarkable anti-tumor activity and anti-cancer activity along with the secondary metabolites. Hence ethno medicinal plants having remarkable anti-cancer activity with through clinical trials can be tried for curing cancer.

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