IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

"Review on Cervical Cancer and Phytoconstituent for the Treatment"

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Abstract –

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem. The practice of monitoring the effects of medical drugs after they have been licensed for use, especially in order to identify and evaluate previously unreported adverse reactions.

Cervical Cancer is a form of cancer that begins in the cervix Most cervical cancers are caused by different strains of the human papillomavirus (HPV), a sexually transmitted infection. In a small percentage of people, the virus survives for years, contributing to the process by which some cervical cells develop into cancer cells. Cervical cancer usually has no symptoms in early stages. The stage of cancer determines by examining the tumor and determining whether the cancer has spread to other parts of the body cancer stages are I, II, III and IV stages they are further divided into subtypes. Diagnosis of cancer stages is performing using screening tests, visual examination, staging test, colposcopy and biopsy tests. For treatment of cervical cancer plants are used like Mangifera indica, croton lechery, zingiber, solanum nigrum, citrus grandis, etc. to avoid surgery and various side effects of treatment, plants are used.

Keyword – Pharmacovigilance, toxicology, cervical cancer, human papillomavirus, plant, therapy

Introduction:

Pharmacovigilance is the science and activities relating to the detection , assessment, understanding, and prevention of adverse effects or any othermedicine / vaccine rated problem for patients safety.

Objectives:

1. Improve patient care & safety
2. Improve public health & safety
3. Benefit risk analysis
4. Encourage safe, rational and appropriate use of drug.

5. Improvement of patient care and safety in relation to the use of medicines with medical and paramedical interventions remains to be an important parameter.
6. To promote understanding, education and clinical training.
7. To contribute to the assessment of benefit, harm, effectiveness and risk of medicines.

Types of Pharmacovigilance:

There are four important methods in pharmacovigilance such as-

1. Passive Surveillance
2. Active Surveillance
3. Cohort Event Monitoring
4. Targeted Clinical Investigation

❖ Passive Surveillance:

Spontaneous adverse effect reported by health care professional to companies.

It involves the uses of spontaneous adverse event reports voluntarily send by health care professionals or patients to the marketing authorization holder or regulatory authority.

Here, Data related to the reporter remains anonymous, but patient related details like country, age, gender and pre-existing combeites can recovered forms.

❖ Active Surveillance:

Toxicity and safety monitoring during process of manufacturing. This method aims to monitor certain specific drug related adverse events and seek to ascertain the number of adverse drug reaction entirely through a pre-planned process.

It is commonly known as toxicity monitoring or safety monitoring.

❖ Cohort Event Monitoring:

Cohort event monitoring (CEM) is an intensive method of post-marketing surveillance foe medicines safety. The method is best on prescription event monitoring, which began in the 1970s, and has since been adopted by WHO for monitoring the safety of medicines used in Public Health Programmes.

❖ Targeted Clinical Investigation:

When significant risks are identified from pre-approval clinical trial, further clinical studies might be called into evaluate the mechanism of action for adverse reaction.

In some instances, pharmacodynamics and pharmacokinetic studies might be conducted to define where a particular dosing instruction can put patient at an increased risk of adverse events.

Role of Pharmacovigilance

Pharmacovigilance has been widely accepted to possess a significant role in early observation of the risk associated with the drug. All the medicines are tested on a small ratio of the population concerned before it is approved for post marketing surveillance.

The pharmacovigilance has been known to possess various roles like, identification, quantification and documentation of drug-related problems; contribution towards reducing the risk of drug-related problems in healthcare systems; and enhancement of knowledge and understanding of factors and mechanisms which are responsible for drug related injuries.

However, in order to fulfil various roles of pharmacovigilance, the interactions and influence of many stakeholders in society with decision-making powers has been required, which include, politicians at national, regional and local levels; healthcare administrators; drug regulatory authorities; pharmaceutical companies; healthcare professionals like physicians, dentists, pharmacists and nurses; academic institutions; media representatives; health insurance companies; lawyers; and patient group.

Components of pharmacovigilance:

Pharmacovigilance delivers four primary capabilities to pharmaceutical companies

A. Adverse event case management including expediate reporting.

B. Aggregate reporting

C. Signal intelligence

D. Risk Management

A. Adverse event case management including expediate reporting

An adverse event is any upward medical occurrence in a patient administered a medical product which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable or unintended sign (e.g. - an abnormal laboratory finding) symptoms, or disease temporarily associated with the use of a medical product, or not considered related to this medical product.

B. Aggregate reporting

Aggregate reporting is the process that reviews the cumulative safety information from wide range of sources, on a periodic basic and submits the findings to regulate worldwide.

The aggregate safety reports are presented to regulator as soon as the medicine is marketed anywhere in the world and enables understanding of risk and benefit profile of the product over of period of time.

Example: -

Periodic safety update reports (PSUR) / Periodic benefit risk evaluation reports (PBRER): -

It is a pharmacovigilance document intended to provide an evaluation of the risk benefit balance of a medicinal product for submission by marketing authorization holders at defined time points during the post authorization phase.

− Sources of safety information
− Active surveillance system
− Clinical trial data
− Competent authorization updates & website publications

− Nonclinical studies update
− Post authorization use in special population
− Table of content is PSUR: -

1. Introduction
2. Worldwide marketing authorization status
3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information.
5. Data in summary tabulations
6. Summaries of significant findings from clinical trials during the reporting intervals
7. Finding from interventional studies
8. Information from other sources
9. Nonclinical data
10. Literature
11. Other periodic reports
12. Signal & risk evaluation
13. Benefit evaluation
14. Conclusion & actions
15. Appendices to PSUR

C. Signal intelligence: -

Pharmacovigilance signal intelligence practice is focused on adopting DPA algorithms. SRS data for constituting hypotheses of signal drug in combination that needed further investigation to establish evidence-based medicine to confirm casualties associated between those pairs. Then regulatory actions may be taken to protect public health.

D. Risk management: -

✓ Steps of risk management: -

1. Identify the risk -
a. Preclinical studies
b. Harms identified in clinical trials & meta-analysis
c. Formal mortality & morbidity studies

2. Understand the risk-
a. Rigorous case definition
b. Case series analysis
c. Clear description in label

3. Monitor the risk-
a. Post marketing surveillance
b. Database analysis
c. Prospective cohort studies & registries

✓ Risk minimization & communication: -

1. Communicate the risk: -
a. Advice on label (not enough to communicate specific risk minimization activities or change behavior's)
b. Partnership with regulators
c. Education of physicians, patients, company staff

2. Act to reduce the risk: -

a. Limited distribution
b. Limited prescribing rights
c. Contraindicate for certain groups, indications, routes of administration
d. Advice for high-risk groups

✓ Risk management legal framework: -

1. ICH-E2E – pharmacovigilance planning (Nov. 2004)
2. EMA – Guideline on risk management system for medicinal products for human use (EMEA/CHMP/96268/2005)
3. GMP – ANNEX20 quality risk management (Feb. 2008)

Clinical Trials: -

Clinical trial is systemic investigation in human subjects for evaluating the safety and efficacy of any new drug. Clinical trial is conducted only when satisfactory report information has been gathered on the quality pf the non-clinical safety.

Protocol designing for clinical trials: -

1. General & background information
2. Objective & justification
3. Trial design
4. Selection & withdrawal of subject
5. Ethical consideration
6. Treatment / study design
7. Safety assessment
8. Quality control
9. Record keeping

Protocol & Amendments: -

Components: -

1. Assessment of efficacy
2. Assessment of safety statistics
3. Data handling & management
4. Quality control & quality assurance
5. Finance & insurance
6. Publication policy
7. Evaluation
8. Supplementary & appendices

What are the Benefits of a Clinical Trial?

- You may get a new treatment for a disease before it is available to everyone.
- You play a more active role in your own health care.
- Researchers may provide you with medical care and more frequent health check-ups as part of your treatment.
- You may have the chance to help others get a better treatment for their health problems in the future.

- You may be able to get information about support groups and resources.

What are the Potential Risks of a Clinical Trial?

- The new treatment may cause serious side effects or be uncomfortable.
- The new treatment may not work, or it may not be better than the standard treatment.
- You may NOT be part of the treatment group (or experimental group) that gets the new treatment—for example, a new drug or device. Instead, you may be part of the control group, which means you get the standard treatment or a no-treatment placebo.
- The clinical trial could inconvenience you. For example, medical appointments could take a lot of time. You might need to travel to the study site several times or stay in the hospital.
- How is the Safety of Clinical Trial Participants Protected?
- The history of clinical research is not perfect. Based on many years of experience and learning, Congress has passed laws to protect study participants. Today, every clinical investigator is required to monitor and make sure that every participant is safe. These safeguards are an essential part of the research. Research abuses like the Tuskegee Syphilis Experiment, which began in 1932, before safeguards were in place, will NOT happen again.
- Researchers are required to follow strict rules to make sure that participants are safe. These rules are enforced by the Federal Government. Each clinical trial also follows a careful study plan or protocol that describes what the researchers will do. The principal investigator, or head researcher, is responsible for making sure that the protocol is followed.
- An Institutional Review Board, or IRB, at each study site must approve every clinical trial in the United States. The IRB is made up of doctors, scientists, and lay people, like yourself, who are dedicated to making sure that the study participants are not exposed to unnecessary risks. The people on the IRB regularly review the study and its results. They make sure that risks (or potential harm) to participants are as low as possible.
- Along with the IRB, many clinical trials are closely supervised by a Data and Safety Monitoring Committee. The Committee is made up of experts in your condition who periodically look at the results of the study as it is in progress. If they find that the experimental treatment is not working or is harming participants, they will stop the trial right away.
- The informed consent process also helps protect participants. Before joining a clinical trial, you will be told what to expect as a participant and all the things that might happen. For example, someone from the research team will explain possible side effects or other risks of the treatment. As part of the informed consent process, you will have a chance to ask questions about the trial.
- After getting all this information, you can think about whether or not you want to participate. If you decide to join the trial, you will be given an informed consent form to sign. By signing the form, you show that you have been told all the details and want to be part of the study. The informed consent form is NOT a contract. You can leave the trial at any time and for any reason without being judged or put in a difficult position regarding your medical care.

Bevacizumab

Bevacizumab, sold under the brand name Avastin among others, is a medication used to treat a number of types of cancers and a specific eye disease. For cancer, it is given by slow injection into a vein and used for colon cancer, lung cancer, glioblastoma, and renal-cell carcinoma.

Brand Name - Avastin

CAS ID: 216974-75-3

Target: VEGF-A

Source: Humanized (from mouse)

AHFS/Drugs.com: Monograph

Bioavailability: 100% (IV only)

Elimination half-life: 20 days (range: 11–50 days)

Possible serious side effects

- GI perforation. A hole that develops in your stomach or intestine. ...
- Abnormal passage in the body. ...
- Wounds that don't heal. ...
- Serious bleeding. ...
- Severe high blood pressure.
- Infusion-related reactions. ...
- Severe stroke or heart problems.

Side effects seen most often

In clinical studies across different types of cancer, some patients experienced the following side effects:

- High blood pressure
- Too much protein in the urine
- Nosebleeds
- Bleeding
- Back pain
- Headache
- Taste change
- Dry skin
- Inflammation of the skin
- Inflammation of the nose
- Watery eyes

Avastin is not for everyone

Talk to your doctor if you are:

- Undergoing surgery. Avastin should not be used for 28 days before or after surgery and until surgical wounds are fully healed
- Pregnant or think you are pregnant. Data have shown that Avastin may harm your unborn baby. Use birth control while on Avastin. If you stop Avastin, you should keep using birth control for 6 months before trying to become pregnant
- Planning to become pregnant. Taking Avastin could cause a woman's ovaries to stop working and may impair her ability to have children
- Breastfeeding. Breastfeeding while on Avastin may harm your baby, therefore, women should not breastfeed during and for 6 months after taking Avastin

Mechanism of Action

As demonstrated in preclinical models: Avastin directly binds vascular endothelial growth factor (VEGF) to inhibit angiogenesis

- While expressed in normal tissues, VEGF is also present at physiologically relevant levels in tumours
- A VEGF ligand binds to receptors on endothelial cells to help drive angiogenesis

Pregnancy warning

- Based on the mechanism of action and animal studies, Avastin may cause fetal harm
- Advise female patients that Avastin may cause fetal harm, and to inform their healthcare provider of a known or suspected pregnancy
- Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose of Avastin
- Advise nursing women not to breastfeed during treatment with Avastin and for 6 months following their last dose of treatment
- Avastin may impair fertility

Most common adverse reactions

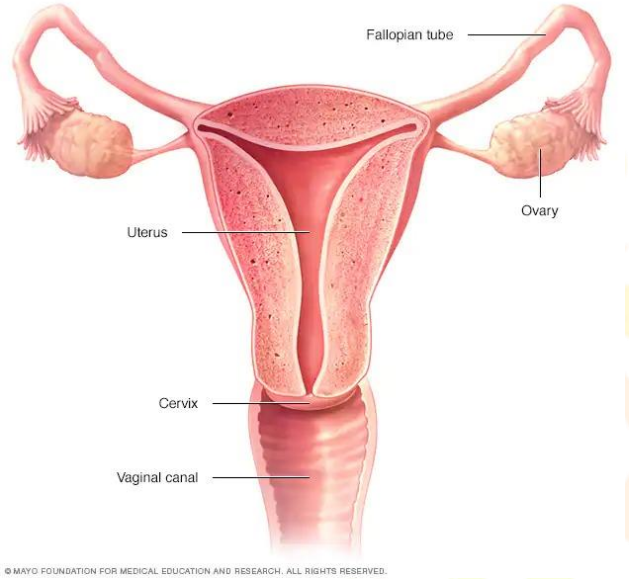
- Across studies, the most common adverse reactions observed in Avastin patients at a rate >10% were:
  - Epistaxis
  - Headache
  - Hypertension
  - Rhinitis
  - Proteinuria
  - Taste alteration
  - Dry skin
  - Haemorrhage

Cervical Cancer

Introduction -

Cervical cancer is a type of cancer that begins in the cervix. The cervix is a hollow cylinder that connects the lower part of a woman's uterus to her vaginal opening. Cells on the cervix's surface are the origin of the majority of cervical cancers. (1)

Cervical cancer is caused by different strains of the HPV, a sexually transmitted infection..



When the body is exposed to HPV, the immune system usually prevents the virus from causing harm. However, in a small percentage of people, the virus survives for years, contributing to the process by which some cervical cells develop into cancer cells. (2)

SYMPTOMS –

Cervical cancer that is in its early stages usually has no symptoms. Cervical cancer in its advanced stages manifests as the following signs and symptoms:

1.Vaginal bleeding after a sexual encounter, between periods, or after menopause

2.Vaginal discharge that is watery, bloody, and has a foul odor.

3.Pelvic pain or discomfort during intercourse. (2)

Cancer can cause the following symptoms after it has spread:

1.Pelvic ache

2.Having difficulty peeing

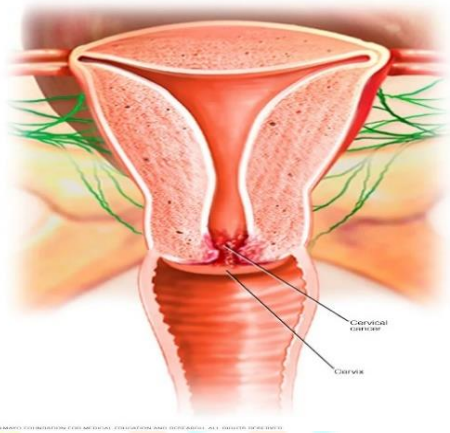
3.Leg swelling

4.Failure of the kidneys

5.Bone ache

6.Loss of appetite and weight loss

7.Fatigue (3)



Stages of cancer -

Doctors determine the stage of cancer by examining the tumor and determining whether the cancer has spread to other parts of the body.

Staging is determined by the results of a physical exam, imaging scans, and biopsies.

stage I: The cancer has spread from the cervix lining into deeper tissue but is still contained within the uterus. It hasn't spread to the rest of the body. This stage may be subdivided into smaller groups to better describe the cancer (see below).

Stage IA: The cancer is only detected by examining cervical tissue or cells under a microscope. Tumor size can also be determined through imaging tests or tissue sample evaluation.

Stage IA1: A cancerous area measuring less than 3 millimeters (mm) in depth exists.

Stage IA2: A cancerous area ranging in depth from 3 mm to less than 5 mm.

Stage IB: The tumor has grown in size but is still confined to the cervix. There is no far-reaching spread.

Stage IB1: The tumor is 5 mm or more deep and less than 2 centimeters (cm) wide. A centimeter is roughly the width of a standard pen or pencil.

Stage IB2: The tumor is 2 cm or more deep and less than 4 cm wide.

Stage IB3: The tumor is 4 cm or larger in width.

Stage II: The cancer has spread outside the uterus to nearby areas such as the vagina or tissue near the cervix, but it is still contained within the pelvic area. It hasn't spread to the rest of the body. This stage may be subdivided into smaller groups to better describe the cancer (see below).

Stage IIA: The tumor has spread to the top two-thirds of the vagina. It has not spread to the tissue surrounding the cervix, known as the parametrial area.

Stage IIA1: The tumor is less than 4 cm wide.

The Stage IIA2: tumor is 4 cm or larger in width at this stage.

Stage IIB: The tumor has spread to the parametrial area at this stage. The tumor never makes it to the pelvic wall.

Stage III: The tumor has spread to the pelvic wall and/or has involved the lower third of the vagina; causes kidney swelling, known as hydronephrosis; prevents a kidney from functioning; and/or involves regional lymph nodes. Lymph nodes are small bean-shaped organs that aid in infection resistance. There is no far-reaching effect.

Stage IIIA: The tumor has spread to the lower third of the vaginal wall but has not yet spread to the pelvic wall.

Stage IIIB: The tumor has invaded the pelvic wall and/or is affecting a kidney.

Stage IIIC: The tumor has spread to the lymph nodes in the surrounding area. Imaging tests and pathology can both detect this. The addition of a lowercase "r" indicates that imaging tests were performed to confirm lymph node involvement. The use of a lowercase "p" denotes that pathology results were used to determine the stage.

Cancer has spread to lymph nodes in the pelvis at stage IIIC1.

The cancer has spread to the para-aortic lymph nodes at stage IIIC2. Lymph nodes are located in the abdomen near the base of the spine and near the aorta, which is a major artery that runs from the heart to the abdomen.

Stage IVA: The cancer has spread to the bladder or rectum but not to the rest of the body.

Stage IVB indicates that the cancer has spread to other parts of the body. (4)

DIAGONSIS -

1) Screening tests can help detect cervical cancer and precancerous cells that may one day develop into cervical cancer. Screening tests include: Pap test, HPV DNA test.

2) Staging If your doctor determines that you have cervical cancer, you'll have further tests to determine the extent (stage) of your cancer. Your cancer's stage is a key factor in deciding on your treatment.

Staging exams include: Imaging tests. Tests such as X-ray, CT, MRI and positron emission tomography (PET) help your doctor determine whether your cancer has spread beyond your cervix.

3) Visual examination of your bladder and rectum. Your doctor may use special scopes to see inside your bladder and rectum.

4) Colposcopy. The doctor may do a colposcopy to check the cervix for abnormal areas. Colposcopy can also be used to help guide a biopsy of the cervix. During a colposcopy, a special instrument called a colposcope is used.

5) Biopsy. A biopsy is the removal of a small amount of tissue for examination under a microscope. Other tests can suggest that cancer is present, but only a biopsy can make a definite diagnosis. (4)

Plants for treating cervical cancer-

Plants have always been a very good source of drugs and many beneficial uses of medicinal plants are extensively. The plant standardized extracts they are complex mixtures needed further to clarify the effective constituents and to elucidate the roles that these different components play in cytotoxicity observed when used alone or in combination. In addition, the synergistic effect of the individual active components of these extracts and molecular mechanisms involved need further investigation in order to evaluate the potential of these compounds as anticancer agents. The phytochemicals are pure compounds. Although some bioactive components with anti-cervical cancer potential have been identified, many others remain unknown and/or untested. The protective effects of natural products have been related to the presence of phytochemicals, bioactive non-nutrient plant compounds which commonly have complementary and overlapping mechanisms of action, including free radical scavenging, antimutagenics. induction of apoptosis in cancer cell lines, among

others. (5)

The extracts from different plants with anti-cervical cancer activity -:

Sr. No.	Botanical Plant	Family	Extract	Part	Cell Type	Activity	Mechanism Of Action
1	Zingiber officinale	Zingiberaceae	Aqueous extract	Rhizome	Hela	Induction of apoptosis Antiproliferation	inhibition of microtubule structure and functions and increase of cell population in sub-G0/G1 phase
2	Croton lechleri	Euphorbiaceae	methanol	Leaf	Hela	Cytotoxicity	Not investigated
3	Mangifera indica	Anacardiaceae	Ethanol	peel	Hela	induction of apoptosis Antiproliferation	Down regulation of anti-apoptotic Bcl-2 expression, increase of cell population in the sub-G1 phase, activation of caspase-3, 7, 8, and 9 and degradation of PARP protein
4	Citrus grandis	Rutaceae	Chloroform	Leaf	Hela	Induction of apoptosis	Downregulation of Bcl-2 expression, activation of caspases and degradation of PARP protein
5	Solanum nigraum	solanaceae	Aqueous	Whole plant	U14	AntiproliferationInduction of apoptosisInhibition of tumor growth	Modulated immune response of tumor-bearing mice, caused G0/G1 phase cell cycle arrest and induced apoptosis
6	Cinnamomic cassia	lauraceae	Aqueous	Bark	SiHa	Induction of apoptosis	Increase of intracellular calcium signaling as well as loss of mitochondrial membrane potential, and downregulation of MMP-2 expression to reduce migration potential

7	Artemisia afra	Composita	Ethanol	leaf	Hela	Antiproliferation Induction of apoptosis	Induction of caspase activation and cell cycle arrest in the G2/M phase
8	Ficus hirta	moraceae	Aqueous ,ethyl ,alcohol	Root	hela	Antiproliferation	Inhibition of cell viability, induction of morphology changes and increase of sub-G1 phase
9	Cassia tora	Leguminosae	Methanol	Leaf	Hela	Induction of apoptosis Antiproliferation	Reduction of DNA content and caspase -3 activity
10	Quercetin			Flavonoids	Hela	Antiproliferation Induction of apoptosis	Induction of G2/M phase cell cycle arrest, upregulation of proapoptotic Bcl-2 family proteins, cytochrome c, Apaf-1 and caspases and downregulation of anti-apoptotic Bcl-2 proteins

11	Agrimonia eupatoria	Rosaceae	Aqueous ,methanol	Leaf stem flower	Hela	Antiproliferation	Not investigated
12	Boswellia serrata	Burseraceae	Hydroalcoholic	Plant		Anti inflammatory ,induce apoptosis in cancer cell	Induce apoptosis in cancerous cell .and plant causes death of cervical cancer cell
13	Anisomeles malabarica	Lamiaceae	Chloroform	Whole Plant	Hela ,SiHa	Inhibit proliferation ,antipyretic	induce death in human papillomaviruses (HPV) 16-positive cervical cancer cells by apoptosis and necrosis
14	Kaffir lime (citrus hysteric)	Citrus	chloroform	Leaf	hela	reduce HeLa cell viability. ,anti inflammatory	reduced the viability of cervical cancer cells in micromolar
15	Leea indica	Vitaceae	Methanolic	Leaves	Cancer cell	antitumor activity against Ehrlich ascites carcinoma cell	- the activation and release of mitochondrial pro-apoptotic proteins known as caspases under the control of Bcl-2 family of proteins or upregulated expression of

							pro-apoptotic receptors on cancer cells
16	Xylopia aethiopica or African guinea prpper	Annonaceae	Methanolic	Fruit	Cancer cell	Anticancer ,antifungal	Inhibit the cell proliferation and also included apoptosis cell cycle arrest in C-33A cells.

CONCLUSION-

The action targets involved using natural plants with anti-cervical cancer potential include telomerase, tubulin and microtubule, DNA topoisomerase, p53 and NF-KB and TRAIL. The mechanisms of action are associated with induction of apoptosis, cell cycle arrest and anti-migration and/or anti-invasion against the HPV disease. This paper has presented the lists of the extracts, constituents and formulations from various medicinal plants, vegetables and fruits used in the treatment to cervical cancer. Although many drugs of natural origin have been discovered, it is still necessary to search for novel anticancer agents with more effectively and reduce mortality as well as serious side effects involved makes natural products ideal candidates for exerting synergism and attenuation effects on anticancer drugs. Some novel natural compounds sometimes have more potent anti-cervical cancer. plants may have the potential to reduce the risk and improve survival probability of patients with cancer.

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