***Review article***

**Natural Compounds as Promising Therapies for Cervical Cancer: Mechanisms and Synergies**

**ABSTRACT**:

**Background:**
Cervical cancer is a serious global health concern, and conventional therapies are frequently linked to significant adverse consequences. Natural substances have shown promising anticancer effects in a number of in vitro experiments, making them viable substitutes or supplements to conventional therapies in recent years.

**Objective:**
The aims of this review is to investigate the anticancer effects of various natural compounds on cervical cancer, specifically HeLa and SiHa cell lines. These compounds include carvacrol, apigenin, gallic acid, naringin, resveratrol, sesamin, piperine, ellagic acid, genistein, and thymoquinone.

**Methods:**
A extensive review of the scientific literature was assessed, emphasising on studies that examined the anticancer properties of the selected compounds in cervical cancer models. The mechanisms of action, including activation of apoptosis, the regulation of the cell cycle, and modulation of key signalling pathways, were investigated.

**Results:**
The compounds discussed exhibited various anticancer effects, such as inhibition of cell proliferation, induction of apoptosis, suppression of migration and invasion, and modulation of several cancer-associated signaling pathways (e.g., PI3K/AKT, NF-κB, mTOR/STAT3). Some compounds, such as apigenin and gallic acid, demonstrated synergistic effects when combined with conventional chemotherapies, suggesting potential for enhancing therapeutic efficacy.

**Conclusion:**
Natural bioactive compounds show significant promise as therapeutic agents for cervical cancer treatment. Although most studies are preclinical, these compounds could serve as effective adjuncts or alternatives to conventional therapies, offering benefits such as lower toxicity and enhanced efficacy. Further clinical investigations are needed to validate their therapeutic potential in vivo.

**Keywords:**
Cervical cancer, natural compounds, apoptosis, cell proliferation, signaling pathways, bioactive agents, HeLa cells, SiHa cells

BACKGROUND

Cancer that starts in the cells of the cervix is called cervical cancer. The cervix is the lower part of the uterus that connects to the vagina. According to the WHO, it is the fourth most common cancer in women worldwide, with about 604,000 new cases and 342,000 deaths in 2020. Around 90% of new cases and deaths worldwide in 2020 will occur in low- and middle-income countries [1]. Cervical cancer is caused by the human papilloma virus. This type of cancer occurs in the age group of 30 to 49 years. Thus, people in this age group only need to have a cervical cancer screening test once. WHO recommends the best age for screening is 35–45 years old [2].

Medicinal plants have been used for therapeutic purposes since the beginning of human civilization. The therapeutic effects of medicinal plants are based on the presence of various phytochemical components, or secondary metabolites. Medicinal plants have traditionally been used for various types of diseases [3].

According to the World Health Organization, a medicinal plant is a plant that contains in one or more of its organs substances that can be used for therapeutic purposes or precursors for the semi-synthesis of chemical medicines. Parts of such plants, including leaves, roots, rhizomes, stems, bark, flowers, fruits, grains, or seeds, contain chemical components with medicinal properties, as they are used to control or treat diseases. Phytochemicals, or biologically active ingredients that are not rich in nutrients, are often referred to as phytochemicals (“phyto-”, from the Greek "phyto,” meaning “plants”) or botanicals and are highly susceptible to microbial infections. It plays a role in protecting plants from invasion by insects and pests [4]. In the scientific world, there is growing interest in the therapeutic potential of drugs used in cancer from plants.

Plants are a source of promising anti-cancer drugs. However, the use of herbal active ingredients in cancer treatment can be traced back to the 1950s. The first plant-based anticancer drugs included the vinca alkaloids, vinblastine, vincristine, and the cytotoxic podophyllotoxins. The great potential of herbal drugs in the treatment and prevention of cancer is due to their safety, low cost, and oral bioavailability. However, some herbal compounds may cause side effects. These side effects can be overcome by dose-wise administration, and their use does not make them unsuitable for phytochemical research. The expensive conventional cancer treatments already available, such as chemotherapy and radiotherapy, have many side effects, such as myelosuppression, neurotoxicity, cardiotoxicity, pulmonary toxicity, and renal toxicity, which significantly reduce quality of life. Therefore, there is a need to develop treatment options that include more effective and less toxic anticancer agents compared to existing drugs. According to market statistics, about 60% of herbal anticancer drugs are available. Medicinal plants have become a popular alternative for cancer treatment in many countries around the world. Cytotoxicity screening has been performed on many plants to correlate their anticancer activity and further expand the scope of drug development. The potential benefits of herbal medicine in cancer treatment have led to its increasing use. Obtaining the anticancer effects associated with natural plant derivatives requires extensive scientific research and clinical experiments to develop improved drugs [5]. In this review, we discuss some phytoconstituents from plants used in the treatment of cervical cancer.

# PHYTOCONSTITUENT USED IN THE TREATMENT OF CERVICAL CANCER

## KAEMPFEROL

Kaempferol is a common flavonoid commonly found in a variety of plant-based foods, including fruits (gooseberries, strawberries, and blackberries), vegetables (cabbage, onions, and broccoli), and herbal medicines (barbarum and lovage). It has a very wide range of biological activities, including anti-diabetic, antioxidant, anti-inflammatory, and anti-cancer effects. Breast, prostate, bladder, colon, liver, cervix, ovary, lung, and leukemia are just some of the cancers that have anticancer properties. Yellow powder kaempferol is completely soluble in hot ethanol, ether, and alkali. It is only slightly soluble in water. Kaempferol has a melting point of 276–278 °C and an acid coefficient of 6.34 ± 0.40. It was found that kaempferol particularly inhibits the proliferation of human cervical cancer cells, such as drug-resistant HeLa, SiHa, and Multi drug resistance human cervical carcinoma cell line (KB-V1) cervical cancer cells. Kaempferol also causes cell cycle arrests at the Growth phase 2/Mitosis phase (G2/M stage) and apoptosis. These effects were linked to cyclin B1,P-glycoprotein (Pgp), Rhodamine 123 (Rh123) efflux, Cyclin dependent protein kinase-1(CDK1), Nuclear factor Kappa – B (NF- κB ), B- cell Lymphoma-2 (Bcl-2) nuclear transposition, and increased activity of Protein-53 (p53) when the mitochondrial cell membrane potential was disrupted in human telomerase reverse transcriptase (hTERT) P13K trials. Compared to the regulator group, kaempferol may effectively reduce the proliferation of triple-negative BC (TNBC) and Epithelial, human breast cancer cell line (MB-MDA-231) by impeding Growth phase 2/ Mitosis phase (G2/M) alteration and DNA destruction by upregulating ϒH2A× and cleaving caspases - 9, 3. Furthermore, kaempferol's remarkable anti-cancer properties were identified in both in vitro and in vivo settings. When kaempferol inhibits the Cyclooxygenase-2 (COX2) and Inducible nitric oxide synthase (iNOS) enzymes, the Reactive oxygen species (ROS) stage is lowered. Furthermore, it shows its protective effect by increasing anti-oxidant enzymes that can absorb free radicals and reduce infection. Nuclear blebbing, fragmentation, and the production of apoptotic bodies were confirmed in HeLa cells treated with kaempferol at doses of 40, 30, and 50 Micrometer (μM). The effect was shown to be more pronounced when absorption was raised. Agarose gel electrophoresis shows that kaempferol efficiently decreases DNA integrity, which causes DNA ladder formation in treated cells in a dose-dependent sequence, but the DNA of control cells maintains integrity. Using agarose gel electrophoresis, which demonstrated that treated cells had a DNA ladder design with sharp bands in comparison to unprocessed controls, kaempferol-mediated inter-nucleosomal disintegration was validated. By using modern flow cytometry to examine the cell cycle-regulating facts, the anti-inflammatory specialty of kaempferol was demonstrated. Studies revealed that kaempferol inhibits the G2/M cell cycle, which is the mechanism that causes its anti-cancerous effects. This happens because there is a dose-dependent increase in the percentage of cancer cells at G2/M, along with a small increase in the sub-Growth phase-1 (G1) population [6].

## SANGUINARINE

Sanguinarine (SNG) is a benzophenanthridine alkaloid mainly isolated from Sanguinaria canadensis, Chelidonium majus, and Macleaya cordata. SNGs are considered anti-tumor agents because of their cytotoxic activity against various tumors. However, the exact molecular mechanism by which SNG mediates this activity remains to be elucidated. Here we report that SNG induces human cervical cancer (HeLa) cell death through activation of two interdependent cell death pathways: apoptosis and ferroptosis. SNG-induced apoptosis is characterized by caspase activation and Poly(ADP-Ribose) polymerase (PARP) cleavage, and ferroptosis involves downregulation of solute carrier family 7 member 11 (SLC7A11), glutathione (GSH) degradation, iron accumulation, and lipid peroxidation (LPO). Interestingly, incubation with the caspase inhibitor carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone (z-VAD-fmk) not only inhibited the apoptotic features but also abolished markers of SNG-induced ferroptosis. Similarly, in addition to rescuing cells from SNG-induced ferroptosis, pretreatment with the ferroptosis inhibitor ferrostatin-1 (Fer-1) also attenuated the SNG-induced apoptotic features. Our study suggests that apoptosis and ferroptosis act in concert as partners in SNG-mediated tumor suppression in HeLa cells. Importantly, SNG increased the generation of reactive oxygen species (ROS), and ROS inhibition blocked the induction of apoptosis and ferroptosis [7].

## CAMPTOTHECIN

Camptothecin (CPT), a natural plant alkaloid, exhibits potent antitumor effects by targeting intracellular topoisomerase I. The therapeutic potential of CPT is limited by factors such as the instability of the lactone ring and water insolubility, which limits the drug's oral solubility and bioavailability in plasma. A new strategy involving pharmacological and low-dose CPT in combination with nanoparticles demonstrated potent anticancer activity in vitro and in vivo. Camptothecin (CPT), a broad-spectrum antitumor agent, was mainly isolated from Camptotheca acuminata (Family: Nyssaceae), a tree native to Tibet and China that is widely used in traditional Chinese medicine. Various CPT analogs have been used to treat colon cancer, ovarian cancer, and small-cell lung cancer. CPT works by inhibiting the enzyme topoisomerase I (Topo I). Human Topo I is a key enzyme involved in the formation of irreversible covalent Topo I-DNA complexes during DNA replication, leading to strand breaks and subsequent apoptosis induction. Research revealed that administering distinct CPT-loaded iridium sulphide with polyethylene Glycol folate nanoparticle (CPT@IrSx-PEG-FA NPs and PDA@PCPT NPs) to HeLa tumor-bearing mice resulted in the inhibition of tumor growth and progression as well as an increase in therapeutic efficacy. Furthermore, a different study showed that administering 4 mg/kg of Camptothecin based zewitterionic polymer poly carboxbetamine (CPT-PCB)-based lipoplexes to Hela tumor-bearing mice prevented the growth and progression of the tumors while also exhibiting synergistic tumor inhibition. In HeLa tumor-bearing nude mice, the synergistic effect of RNA polo-like kinase-1+Camptothecin (RLS/siPLK1+ CPT) on tumor growth suppression was assessed. According to the study's findings,Reduction-sensetive and lysosomotropic system/small interfering RLS/siPLK1+CPT shows higher anticancer efficacy than either drug alone. These findings suggest that Reduction-sensitive and Self-Crosslinking system / small interfering RNA targeting Polo-like Kinase 1 (R2SC/siPLK1) can effectively suppress the growth of tumors by apoptosing tumor cells, inhibiting the expression of the siPLK1 gene, regulating medication release, and so on. This contributes to the combined effects of siPLK1 and CPT. In a different investigation,Camptothecin-Dual nanoprobe system-Disulfide with poly ethylene glycol folate nanoparticle (CPT-DNS-DCM's) anticancer efficacy was assessed using HeLa cells that were tumor-bearing nude mice. The prodrug significantly suppressed tumor development and progression, according to the results. Furthermore, Europium and Gadolinium-sulfhydryl or disulphide-camptothecin-folic acid-Mesoporous silica nanoparticles (EuGd-SS-CPT-FA-MSN) treatment of HeLa tumor-bearing nude mice resulted in tumor eradication and decreased tumor growth and volume. A beneficial theranostic nanoplatform for preventing tumor growth in vivo may be provided by EuGd-SS-CPT-FA-MSNs. According to the findings of in vivo research, functionalized MSNs could serve as a useful platform for focused treatment [8,9].

## BERBERINE

For thousands of years, isoquinoline alkaloid berberine (BBR), a traditional Chinese phytomedicine derived from several portions of Berberis plants, has been used to treat hypertension, diabetes, hypercholesterolemia, and other conditions. Because of its strong antiproliferative, anti-inflammatory, and pro-apoptotic qualities, it has recently drawn a lot of attention from all over the world for use in the treatment of cancer. Through the modulation of many molecular and cell signaling pathways, BBR effectively promotes tumor apoptosis, replicative quiescence, and eliminates cell proliferation, epithelial mesenchymal transition, tumor neovascularization, and metastasis. Moreover, BBR has the potential to reverse drug resistance, increase tumor cell sensitivity to available cancer treatments, and greatly reduce the deleterious side effects of cytotoxic therapy. By effectively targeting the host and viral components crucial to disease development, BBR has the capacity to eradicate HPV-16-positive cervical cancer cells (SiHa cell lines) as well as HPV-18-positive cervical cancer cells (HeLa cell lines). BBR functions in these cells by (i) downregulating the production of HPV oncoproteins E6 and E7 and (ii) selectively suppressing constitutively produced Active protein-1 (AP-1) in a dose- and time-dependent manner. Moreover, BBR induces apoptosis in Hela cells by triggering the internal mitochondrial pathway, the extrinsic death receptor system through the activation of Fas, FasL, and Tumor Necrosis Factor alpha (TNF-α), and Tumor necrosis Factor receptor associated factor-1 (TRAF-1), the p53 expression pathway, and the Mitrogen activated Protein Kinase (MAPK) pathway. These cells' membrane depolarization-induced uptake of BBR also caused a number of deleterious effects, such as altered expression of p53 and disruption of the microtubule network, as well as modifications of the HPV-18 E6–E7 viral oncoproteins. Moreover, BBR inhibited Transforming Growth factor-Beta (TGF-β)-mediated epithelial-mesenchymal transition (EMT) in SiHa cells by upregulating the expression of epithelial markers, such as Epithelial-cadherin (E-cadherin), and downregulating the expression of mesenchymal markers, such as Neural-cadherin (N-Cadherin) and Snail-1. More significantly, in xenograft mouse models, BBR inhibits SiHa cell metastasis to the lungs and delays tumor neovascularization in both in vitro and in vivo settings. By (i) increasing the ratio of p53 and B-cell lymphoma protein-1 associated X/B-cell lymphoma-2 (Bax/Bcl2) proteins, (ii) producing ROS and subsequently promoting endoplasmic reticulum (ER) stress and Calcium ion

(Ca2+) release, (iii) disrupting mitochondrial membrane potential, (iv) increasing the expression of Growth arrest and DNA Damage –inducible gene-153 (GADD153), and (v) promoting caspase-3 activity, BBR causes apoptosis in CaSki cervical cancer cells in a time- and dose-dependent manner. By upregulating p53 and downregulating the levels of the Bcl-2 and COX-2 genes, BBR reduces cell growth and increases apoptosis in HeLa229 human cervical cancer cells. According to all of this research, BBR successfully prevents cervical cancer by upregulating p53 expression, encouraging tumor apoptosis, and suppressing the proliferation of the HPV 16 and HPV 18 oncoviruses [10].

## CUCURBITACIN

Cucurbitacins are a group of highly oxidized tetracyclic triterpenoids originally found in plants of the Cucurbitaceae family. B. cucumber confirmed In traditional medicine, cucurbitacin-containing plants are known for their antipyretic, analgesic, anti-inflammatory, antibacterial, and antitumor effects. Cucurbitacin has powerful pharmacological properties, including anti-tumor, anti-inflammatory, and hepatoprotective effects. Similar to other cucurbitacins, cucurbitacin-I inhibits cancer cell proliferation in in vitro and in vivo tumor models by disrupting the Janus kinase/signal transducers and activators of transcription [(JAK)/STAT3] signaling pathway. Cucurbitacin-I has been shown to be effective in a variety of human cancer cells, including glioblastoma cells, hepatocellular carcinoma, leukemia cells, nasopharyngeal carcinoma cells, and prostate cancer. Cucurbitacin-I also suppresses cancer stem cell-like properties and enhances the response to chemoradiotherapy [11]. The cucurbitacin family exhibits cytotoxicity in many types of cancer, including cervical cancer. Cucurbitacin I has been found to have antitumor activity in glioblastoma, which is supported by synergistic treatment with Chloroquine (CQ). Studies have shown that cucurbitacin I, a natural selective inhibitor of JAK2/STAT3, has potent anticancer effects against various types of cancer cells [12].

## ANTHOCYANIN

Anthocyanin-rich foods have attracted considerable attention due to their potential biological and pharmacological applications. Anthocyanins are abundant in blueberry fruits and have been shown to have various bioactive properties. Despite the potential applications of anthocyanins in the food, pharmaceutical, and cosmetic industries, their use is limited due to their relative instability. Recently, a particular family of anthocyanin derivatives, pyranoanthocyanins, has received much attention and has been reported to be more stable than the parent anthocyanins. Pyranoanthocyanidins showed the highest stability in the pH range of 3.0–9.0, while anthocyanidins showed the strongest inhibition against her HeLa cells among the three anthocyanin pigments, such as anthocyanin, anthocyanidin, and pyranoanthocyanidin. All anthocyanin dyes can effectively induce G2/M phase cell cycle arrest coupled with a significant increase in p53 protein expression. Exposure of HeLa cells to three anthocyanin dyes caused significant late-stage apoptosis, which may be involved in activation of the p38 MAPK/p53 signaling pathway. These results suggest that anthocyanidins and pyranoanthocyanidins may be more promising anticancer agents than anthocyanins [13].

## METHANOLIC NEEM

Methanolic neem is obtained from Azadirachta indica (commonly known as neem). Anticancer ability of methanolic neem stem bark extract (MNBE) against cervical cancer using HeLa and SiHa cell lines Anticancer ability of MNBE against cervical cancer by inducing cell cycle arrest and apoptosis in cervical cancer cells by regulating the expression of genes involved in cell cycle control and apoptosis. Furthermore, MNBE inhibited the migration of cervical cancer cells even at non-toxic doses, suggesting that MNBE may treat or prevent cancer metastasis. Nevertheless, further studies are required to identify and isolate the bioactive components of this extract that contribute to its anticancer effects [14].

## WITHAFERIN A(WA)

Withaferin A, a steroidal lactone, is obtained from Withania somnifera. This natural product has a wide range of pharmacological effects, including cardioprotective, anti-inflammatory, immunomodulatory, anti-angiogenic, anti-metastatic, and anti-carcinogenic properties. Withaferin A is an effective drug in the treatment of cancer. Studies in mouse models have shown promising results in breast cancer. It is also effective against pancreatic cancer, cervical cancer, lung cancer, medullary thyroid cancer, etc. It significantly downregulates the expression of HPV E6/E7 oncogenes and restores the p53 pathway, leading to apoptosis of cervical cancer cells [15]. WA induces effects on p53-dependent apoptosis in human cervical cancer cells through suppression of the HPV oncogene and upregulation of tumor suppressor proteins. WA exhibits dose-dependent anticancer activity against various cervical cell lines, such as CaSki, HeLa, SiHa, and C33a. The results of this study show that treatment with withaferin downregulates HPV oncoproteins E6 and E7, induces p53 accumulation, and activates various apoptotic markers (including Bcl2, Bax, caspase-3, and cleaved PARP). The G2/M cell cycle arrest (associated with regulation of Protein 34- cell cycle division -2 (p34-cdc2), cyclin B1, and PCNA levels) is induced by increased p21cip1/waf1 levels and interaction with proliferating cell nuclear antigen (PCNA). In vivo studies were conducted in mouse models, with results suggesting a 70% reduction in tumor size in nude mice [16].

## ARTHROSPIRA PLATENSIS

Arthrospira platensis (AP), also known as “Spirulina”, belongs to the phylum Cyanobacteria and has a distinctive photosynthetic ability [17]. Arthrospira platensis, a blue-green algae, is a popular dietary supplement with strong antioxidant properties and possible anti-carcinogenic properties [18]. Treatment with an ethanolic extract of A. platensis causes morphological changes in HeLa cells. Some of the HeLa cells shrank and separated from each other (contact inhibition), reducing their number. After observing the cell morphology, administer the MTT solution to the cells. The more formazan crystals that form, the higher the absorption measured by the Enzyme linked immuno sorbent assay (ELISA) reader, and the more cells are alive. The rate of death caused by the ethanolic extract of A. platensis in HeLa cells increases as the concentration increases. Increasing the concentration of the ethanolic extract of A. platensis also increased the rate of cell death. The cytotoxic activity of the ethanolic extract of A. platensis can be caused by chemical components such as beta-carotene, terpenoids, and flavonoids. Ethanol extracts of A. platensis may cause the accumulation of HeLa cells in the synthetic phase (S phase), resulting in the inability of HeLa cells to enter the G2/M phase. In the G2/M phase, cells are ready to divide. At this stage, the process of DNA replication and the biosynthesis of proteins and RNA necessary for cell division are complete. Barriers to the cell cycle during the G2/M phase cause regulatory errors that result in delayed or impaired cell division. Cell cycle inhibition in HeLa cells is caused by the content of β-carotene, flavonoids, and terpenoid compounds in the ethanolic extract of A. platensis. In general, beta-carotene compounds have the ability to increase p53, which recognizes cells with damaged DNA and stimulates transcription of genes such as p21 and Bax, leading to cell cycle arrest and DNA repair. You will get a chance to repair it before. Proceed to the next divisional stage. The mechanism of action of flavonoid compounds is to prevent the formation of active CDK-cyclin complexes, thereby suppressing maturation-promoting factor (MPF), which disrupts the synthetic-phase (S-phase) and G2/M-phase checkpoints. As a result, cells are no longer able to complete the cell cycle. Terpenoid compounds block the G2/M phase of the cell cycle by stabilizing mitotic spindle filaments and inhibiting the mitotic process [19].

## EMODIN WITH VINBLASTINE

Emodin (1,3,8-trihydroxy-6-methylanthraquinone), an anthraquinone derived from Chinese herbal medicine, has been shown to have antitumor effects [20].Vinblastine is one of more than 130 indole alkaloids found in periwinkle. It has strong pharmacological activity and is used in chemotherapy. Cytometry analysis showed that emodin and vinblastine induce marked cell arrest in the G2/M phase, which is characteristic of cytotoxic drugs. As the emodin concentration increased, we observed an increase in the percentage of cells blocked in the G2/M phase. Similar cell cycle changes were observed with vinblastine (10 μM), which blocked cells at the above stages. The combined effect of emodin and vinblastine increased the accumulation of cells blocked in the G2/M phase, depending on the emodin concentration. The inactivation of the anti-apoptotic protein Bcl-2 in HeLa cells is induced by both emodin and vinblastine [21].

##  CARVACROL

Carvacrol is a component of many aromatic plants that has been studied for its significant pharmacological characteristics. Although carvacrol-induced cytotoxicity has been described, no studies on human cervical cancer, HeLa, or SiHa cells have been conducted. Carvacrol was found to be a powerful anti-cancer drug, with an half maximal inhibitory concentration (IC50) of 50 mg L-1 at 48 hours eliciting growth suppression in both human cervical cancer cells. Further research using animal models may resolve carvacrol's in vivo efficacy [22].

## APIGENIN

Apigenin, a natural plant flavone abundantly found in common fruits and vegetables, is considered a bioactive flavonoid that has been shown to have anti-inflammatory, antioxidant, and anticancer properties. Epidemiological studies suggest that diets rich in flavones are associated with a reduced risk of certain cancers, particularly breast cancer, gastrointestinal cancers, skin cancer, prostate cancer, and certain hematological malignancies [23]. The PrestoBlue assays were performed on her HeLa and C33A cells, and cells were exposed to various concentrations of apigenin (0–100 μM). We observed that apigenin had a cytotoxic effect on cells and inhibited cell proliferation (thereby reducing cell viability) in a dose-dependent manner. After 24 h of treatment, 50 μM apigenin inhibited the proliferation of HeLa cells and C33A cells by 52.5–61.6% and 46.1–58.6%, respectively. The molecular mechanism of apigenin in the treatment of cervical cancer included downregulation of Focal Adhension kinase (FAK) signaling (FAK, paxillin, and integrin β1) and PI3K/AKT signaling (PI3K, AKT, and mTOR). It inactivates or activates various signaling targets such as Bcl2, Bax, p21cip1, CDK1, CDC25c, cyclin B1, fibronectin, N-cadherin, vimentin, and laminin. E-cadherin causes mitochondrial-mediated apoptosis and G2/M phase arrest, reduces EMT, and confers anticancer effects in cervical cancer [24].

## GALLIC ACID

Gallic acid (GA) is a polyhydroxyphenolic compound found in a variety of natural products, such as green tea, grapes, strawberries, bananas, and many other fruits. Many studies have demonstrated the potential anticancer activity of gallic acid and its derivatives, both in vivo and in vitro. In fact, the anticancer effects of gallic acid have been reported in various cancer cells, including human ovarian cancer cells. The anticancer effects of gallic acid have been proven to be due to its ability to inhibit cell proliferation and induce apoptosis. The combination of paclitaxel and gallic acid may be a promising protocol for the treatment of cervical cancer and may be an alternative to the currently commonly used paclitaxel/carboplatin therapy. The combination of paclitaxel and gallic acid offers many advantages over existing protocols, including higher efficacy, lower doses, and fewer side effects. More detailed mechanistic and efficacy studies are needed in cell culture, animal models, and ultimately clinical trials evaluating paclitaxel/gallic acid combination therapy [25].

## NARINGIN

Plants contain a variety of flavonoids, which are widely distributed and have important biological functions. Studies usually use citrus fruits to measure the amount of naringin in fruits, as the amount of naringin is relatively high during the ripening stage. Citrus fruits provide large amounts of flavonoids in your diet. Naringin is primarily found in the peel of grapefruit, limes, and their varieties. It has multiple biological functions and is widely used in food, cosmetics, and medicine. Naringin is a glycoside flavanone found in grapes and citrus fruits. It has been reported that grapefruit pulp contains the highest amount of naringin, followed by the membranous skin, seeds, and fruit juice [26]. In vivo studies show that Maringa exhibits significant antitumor activity in Cervical cancer cells and has low toxicity toward normal transformed cervical cells. Mechanistically, naringin promotes ER stress-associated apoptosis and promotes cell death in cervical cancer cells. Additionally, naringin attenuates the β-catenin signaling pathway by dephosphorylating serine residue at position 675 (Ser675) of β-catenin and Serine residue at position 9 (Ser9) of Glycogen synthase kinase 3-beta (GSK3β), respectively. Furthermore, naringin increases the protein expression of cell cycle checkpoint regulators (p21/Cip, p27/Kip) and shortens the cell cycle in the Gap/Growth-1 phase (G0/G1 phase) of Cervical cancer cells. Therefore, our results provide strong evidence for further consideration of the use of naringin as a potential chemotherapeutic agent in human cervical cancer [27].

## RESVERATROL

Resveratrol (3,4,5-trihydroxy-trans-stilbene) is a polyphenol stilbenoid first isolated from the roots of Veratrum grandiflorum, and Japanese knotweed (Polygonum cuspidatum) remains its main source, with high concentrations found in grapes, blueberries, plums, apples, peanuts, and red wine. Resveratrol (RSV) was first isolated by Takaoka et al. from his Veratrum grandiflorumin in 1939. RSV has been shown to have a variety of biological effects, including antioxidant, anti-inflammatory, neuroprotective, antidiabetic, and anticancer effects [28].

Treatment with resveratrol (150–250 μmol/L) for 48 hours inhibits the G1 phase in C33A (p53 mutated) and HeLa cells (HPV18 positive), as well as CaSki and SiHa cell lines (HPV16 positive). Increased cell cycle arrest. Resveratrol treatment induced apoptosis in all cell lines, especially her CaSki cells, as determined by Annexin V flow cytometry analysis. Mitochondrial membrane potential (apoptosis) was decreased in HeLa, CaSki, and SiHa cells, and lysosomal permeability (autophagy) was increased in C33A, caLo (HPV18 positive), and HeLa cell lines. Furthermore, using the IC50 of each strain, we found that resveratrol had a similar effect, suggesting that this effect is independent of resveratrol concentration. Interestingly, after resveratrol treatment, p53 expression decreased in HPV18-positive cell lines (CaLo and HeLa) and increased in HPV16-positive cell lines (CaSki and SiHa) and C33A cells. Expression of p65 (NF-κB subunit) decreased after treatment in all cell lines except SiHa cells. These results suggest that resveratrol uses different mechanisms to cause cell death in cervical cancer-derived cell lines [29].

## SESAMIN

Sesamin is the main active ingredient found in sesame seeds. Several studies have shown that sesamin has strong anti-cancer effects. Sesamin shows antiproliferative, proapoptotic, anti-inflammatory, anti-metastatic, and antibacterial effects. Pro-angiogenic and pro-autophagic activity [30]. In vitro studies show that sesamin has antiproliferative effects on cervical cancer cells, mainly through p53 activation and p53-mediated apoptosis. These results not only suggest that sesamin may be a dietary compound with potential antiproliferative activity against cervical cancer cells, but also suggest that p53/Bax may be a potential candidate for the development of new treatments for cervical cancer. It also indicates that you may be a potential target [31].

## PIPERINE

Piperine is the most important edible alkaloid found mainly in the fruits and roots of Piper nigrum L. (black pepper) and Piper longum L. (long pepper) species of the Piperaceae family. Black pepper, also known as the "king of spices", is used in Indian medicine to treat gastrointestinal and respiratory ailments. Pepper's characteristic hot, stinging taste is due to its high piperine content. Piperine has been used for many therapeutic purposes and is expected to continue to be used in the future. Pipeline has an important role in the diet due to its presence in spicy foods and its pharmacological effects (anti-inflammatory, anti-metastatic, anti-cancer, larvicidal, leishmanicidal, immunosuppressive, anti-mycobacterial, and anti-parasitic effects). It is a phytochemical [32]. In vitro results showed that piperine slowed the tumor growth of cervical cancer cells through a process caused by decreased viability, cell proliferation and colony formation, cell cycle arrest, and apoptosis. These effects were mediated by piperine through decreased expression of Extracellular signal regulated kinase (ERK), Interleukin-1 beta (IL-1β), and Interleukin-8 (IL-8). Furthermore, piperine decreased cell migration by modulating Matrix mettaloproteinases (MMP) and Tissue inhibitor mettaloproteinases (TIMP) gene and protein expression and modulating Monocyte chemoattractant protein-1 (MCP-1) secretion. Therefore, piperine suppresses tumor development in vitro by acting on the Prostaglandin endoperoxidase-2 (PTGS2) signaling pathway, thereby controlling the secretion of cytokines and the expression of MMPs, MAPKs, and TIMPs. Piperine has been shown to be an herbal medicine that may be used as an adjunctive treatment for cervical cancer. However, considering new technologies and clinical applications, functional testing is necessary [33].

## ELLAGIC ACID

Ellagic acid (EA) is a bioactive polyphenolic compound that occurs naturally as a secondary metabolite in many plant species. EA content is high in the wood and bark of pomegranate (Punica granatum L.) and some tree species. Structurally, EA is a dilactone of hexahydroxydiphenic acid (HHDP), a dimeric gallic acid derivative produced primarily by the hydrolysis of ellagitannins, a broad group of secondary metabolites. EA has attracted attention due to its antioxidant, anti-inflammatory, antimutagenic, and antiproliferative properties [34].Ellagic acid characterizes its anticancer properties. Cell proliferation, migration, and invasion are closely related to tumor progression. Therefore, inhibiting tumor cell proliferation and migration may be an important means to prevent tumor progression. Increased HeLa cell activity (proliferation, invasion, and migration) plays an important role in the development and progression of cervical cancer. EA has anti-tumor activity against her HeLa cells. significantly inhibited the proliferation, invasion, and migration of HeLa cells. We also found that the Akt/mTOR/STAT3 signaling pathway was significantly inhibited by her EA intervention. Furthermore, the effects of EA on HeLa cells may be mediated through the Akt/mTOR/STAT3 pathway. The AKT/mTOR/STAT3 signaling pathway is an important intracellular signaling pathway in tumor cell proliferation and migration. Phosphorylated AKT and mTOR are transported to the nucleus and transmit extracellular signals that regulate cell growth, differentiation, proliferation, apoptosis, and migration. STAT3 is thought to be an important regulator of cytoskeletal dynamics, transcription, cell cycle progression, and cell transformation. STAT3 activation has been shown to regulate leukemia cell migration and proliferation. Therefore, targeting the AKT/mTOR/STAT3 signaling pathway with drugs may be useful for tumor treatment. EA could inactivate her AKT/mTOR/STAT3 signaling pathway. Ellagic acid not only inhibited the proliferation and migration of HeLa cells but also directly inhibited the growth of cervical cancer. EA inhibited the migration of her HeLa cells. EA had a significant inhibitory effect on the volume of cervical cancer, which suggests that EA has a significant inhibitory effect on the growth of cervical cancer in vivo. EA could significantly inhibit the expressions of Phosphorylated-PI3k (p-PI3k),Phosphorylated-AKT (p-AKT),Phosphorylated-mTOR (p-mTOR), and Phosphorylated-STAT3 (p-STAT3) in tumor tissues. EA exhibits potent antitumor growth activity by specifically targeting the AKT/mTOR/STAT3 signaling pathway [35].

## GENISTEIN

An isoflavonoid termed genistein affects cell cycle progression, apoptosis, and metastasis [36]. .In vitro studies show that Genistein inhibited HeLa cell viability and was positively correlated with duration of action and drug dose. After 24 and 48 hours of treatment, 100 mM genistein inhibited cell proliferation, which was not evident at lower doses. This is consistent with previous studies using other cell lines. Genistein inhibited the growth of two cervical cancer cell lines, HeLa and ME-180. Genistein treatment apparently arrested ME-180 cells in their G2/M phase and most HeLa cells in their S phase. Genistein significantly inhibited cell migration. Taken together, genistein inhibited the proliferation, invasion, and metastasis of her HeLa cells. Genistein plays an antitumor role through various signaling pathways such as cell cycle arrest, mitochondrial, MAPK, and caspase pathways. However, the mechanism by which genistein suppresses cervical cancer, especially in the FAK-paxillin signaling pathway, has been little studied, as have the molecular mechanisms by which genistein affects the proliferation, migration, and invasion of HELa cells. 100 mM genistein significantly inhibited the protein phosphorylation of FAK and paxillin and significantly regulated the protein expression of β-catenin and vimentin. Therefore, genistein regulated the FAK-paxillin signaling pathway at the gene and protein levels, affecting cell migration and invasion [37].

## THYMOQUNINONE(TQ)

Thymoquinone showed considerable promise as a naturally occurring compound for the pharmaceutical industry. As a result, this key N. sativa constituent can be exploited effectively in the study areas of novel drug development to prevent cancer cell advancement. Its ability to prevent many cancer stages in humans, such as proliferation, migration, and invasion [38]*.* TQ activated unique apoptotic pathways in the human cervical squamous cell carcinomas SiHa and C33-A. TQ induces apoptosis in SiHa cells via raising p53 expression, but apoptosis in C33A cells is mostly related to the overexpression of caspase-3. The concentration of 10 µM TQ inhibited cancer metastasis, migration, and invasion in SiHa and CaSki cervical cancer cell lines by decreasing Twist1 and Zeb1 expression and promoting E-cadherin expression in a dose- and time-dependent manner. TQ reduces Twist1 and Zeb1 promoter activity, implying that Twist1 and Zeb1 are direct targets of TQ. TQ-loaded nanostructured lipid carriers (1.56 and 3.125 µM) inhibited HeLa cell line proliferation in a time- and dose-dependent manner. TQ increased apoptosis in HeLa cells by downregulating anti-apoptotic genes such as NF-kappa-B signaling and influencing the expressions of BH-3 interacting domain death agonist (BID), TNF Receptor superfamily memberane 10B (TNFRSF10B), TNF, TNF receptor super family 10A (TNFRSF10A), RELA, Tumor necrosis factor receptor associated to factor-3 (TRAF3), and RELB, while upregulating caspase-1,Bcl-2 ineracting killer (BIK), and First apoptosis signal ligand (FASL) [39].

# CONCLUSION:

Cervical cancer remains a significant global health burden, and despite advances in treatment, such as surgery, radiotherapy, and chemotherapy, these approaches often come with considerable side effects and limitations. In recent years, the exploration of natural compounds as adjuncts or alternatives to conventional therapies has garnered significant attention. The compounds discussed in this review—carvacrol, apigenin, gallic acid, naringin, resveratrol, sesamin, piperine, ellagic acid, genistein, and thymoquinone—have all shown promising anticancer properties in in vitro studies, specifically targeting human cervical cancer cell lines such as HeLa and SiHa.

These natural bioactive agents exert their effects through multiple mechanisms, including apoptosis induction, cell cycle arrest, suppression of migration and invasion, and modulation of key molecular signaling pathways. Compounds like apigenin, gallic acid, and resveratrol have demonstrated particularly potent effects in reducing cell viability and inhibiting tumor progression by interfering with critical pathways such as PI3K/AKT, NF-κB, and mTOR/STAT3. Many of these compounds also show the ability to enhance the efficacy of standard chemotherapeutic agents, providing a potential strategy to improve treatment outcomes while minimizing toxicity.

Although these findings are encouraging, most studies have been conducted in vitro or in animal models, and further research is required to determine the full clinical potential of these compounds. Future studies should focus on evaluating the pharmacokinetics, bioavailability, and safety profiles of these agents in clinical settings. If validated through rigorous clinical trials, these natural compounds could offer a promising, low-toxicity alternative or adjunct to current cervical cancer therapies, potentially improving patient outcomes and quality of life.

**ABBREVIATIONS**

|  |  |  |
| --- | --- | --- |
| S.no  | Abbreviation | EXPANSION |
|  | Akt | Protein kinase B |
|  | AP | Arthrospira platensis |
|  | AP-1 | Active Protein-1 |
|  | Bax/Bcl | B-cell lymphoma protein 2 (Bcl-2)-associated X (Bax) |
|  | BBR | Berberine |
|  | Bcl-2 | B-cell lymphoma2 |
|  | c33a | Epithelial cell |
|  | Ca2+ | Calcium ion |
|  | CaLo | cell line derived from a human cervical cancer that is positive for human papillomavirus type 18 (HPV18) |
|  | Caski | a human papillomavirus type 16 (HPV-16)-positive cell line |
|  | cdc25c | cell division cycle 25 c |
|  | CDK | cyclin-dependent kinase |
|  | CDK1 | cyclin dependent protein kinase 1 |
|  | COX2 | cyclooxygenase 2 |
|  | CPT | Camptothecin |
|  | CPT-@IrSx-PEG-FA NPs | Camptothecin @ iridium sulfide with poly ethylene glycol folate nanoparticle |
|  | CPT-DNS-DCM | Camptothecin-Dual Nanoprobe System - Disulfide Crosslinked Micelles |
|  | CPT-PCB | Camptothecin-Polymer Conjugate Block copolymer |
|  | CPT-PCB | camptothecin based zewitterionic polymer poly carboxybetamine |
|  | CQ | Chloroquine |
|  | cyclin B1 | Regulatory protein involved in mitosis |
|  | DNA | Deoxy Ribonucleic Acid |
|  | E6 and E7 | oncoprotein mediate the development of cervical cancer |
|  | EA | Ellagic Acid |
|  | E-cadherin | Epithelial cadherin |
|  | ELISA | Enzyme linked immuno sorbent assay |
|  | EMT | Epithelial mesenchymal transition |
|  | ER | Endoplasmic Reticulum |
|  | ERK | Extracellular signal regulated kinase |
|  | EuGd-SS-CPT-FA-MSN | Europium and Gadolinium - Sulfhydryl or disulphide – Camptothecin - Folic Acid - Mesoporous Silica Nanoparticle |
|  | FA | Folic Acid |
|  | FAK | Focal Adhesion kinase |
|  | fas | cell death surface receptor |
|  | FasL | Fas ligand |
|  | Fer-1 | ferrostatin |
|  | G1 | Growth 1 phase |
|  | G2/M phase | Growth phase 2/Mitosis phase |
|  | GA | Gallic Acid |
|  | GADD153 | growth arrest and DNA damage-inducible gene CHOP |
|  | GSH | Glutathione |
|  | GSK3β | glycogen synthase kinase 3 beta |
|  | HeLa | Cervical cancer cells |
|  | Hela 229 | human cervical adenocarcinoma cells that were derived from the parent HeLa cell line |
|  | HHDP | hexahydroxydiphenic acid |
|  | HPV | Human Pappilloma Virus |
|  | hTERT | Human telomerase reverse transcriptase |
|  | IC50 | half maximal inhibitory concentration |
|  | IL-1β | Interleukin 1 beta |
|  | IL-8 | Interleukin 8 |
|  | iNOS | Inducible nitric oxide synthase |
|  | JAK2/STAT3 | Activator of transcription 3 signaling pathway |
|  | KB-V1 | Multi drug resistance human cervical carcinoma cell line |
|  | LPO | Lipid peroxidation |
|  | ME-180 | Metastatic Epithelial 180 ( a cervical cancer cell line derived from a human cervical cancer that is positive for human papillomavirus type 16 (HPV16 ) |
|  | MMPs | Matrix mettaloproteinases |
|  | MNBE | Methanolic neem bark extract |
|  | MPF | maturation-promoting factor |
|  | Mtor | mechanistic target of rapamycin |
|  | N-Cadherin | Neural cadherin |
|  | p21 | Protein 21 |
|  | p21/cip | a protein that belongs to the Cip/Kip family of cyclin-dependent kinase inhibitors |
|  | p27/kip | a protein that belongs to the Cip/Kip family of cyclin-dependent kinase inhibitors |
|  | p53 | protein 53( tumor protein) |
|  | p-Akt | phophorylated protein kinase B |
|  | PARP | poly(ADP-ribose) polymerase |
|  | PCNA | Proliferating cell nuclear antigem |
|  | PDA@PCPT NPs | Polydopamine @ Polymeric Camptothecin nanoparticle |
|  | pgp | P-glycoprotein |
|  | PI3k | Phosphatidylinositol 3-kinase |
|  | p-mTor | phosphorylated mechanistic target of rapamycin |
|  | p-PI3K | phosphorylated phosphoinositide 3-kinase |
|  | p-STAT3 | phosphorylated singnal tranducer and activator of transcription 3 |
|  | R2SC/siPLK1 | Reduction-sensitive and Self-Crosslinking system / small interfering RNA targeting Polo-like Kinase 1 |
|  | Rh123 | Rhodamine 123 |
|  | RLS/siPLK1+ CPT | Replicative life-span / small interfering RNA mediated polo-like kinase 1 + camptothecin |
|  | ROS | Reactive oxygen species |
|  | RSV | Resveratrol |
|  | S phase | Synthesis Phase |
|  | ser9 | serine residue at position 9 |
|  | siHa | HPV 16 positive human cervical cancer cell line |
|  | SLC7A11 | solute carrier family 7 member 11 [ (human)] |
|  | Snail-1 | Snail Family transcriptional receptor-1(gene coding protein) |
|  | SNG | Sanguinarine |
|  | STAT3 | signal transducer and activator of transcription 3 |
|  | TIMPs | Tissue Inhibitor mettaloproteinases |
|  | TNBC | Triple negative Breast cancer |
|  | TNF-α | Tumor Necrosis factor alpha |
|  | TQ | Thymoquinone |
|  | WHO | World Health Organization |
|  | Z-VAD-FMK | Z-Val-Ala-D-fluoromethylketone, |
|  | ϒH2A× | an early cellular response to the induction of DNA double-strand breaks |

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