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REVIEW

Role of the Phytochemicals in Cervical Cancer: Current Understanding of Pharmacological Actions and Associated Molecular Mechanisms

Dinesh Kumar Patel

Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Uttar Pradesh, India

ABSTRACT

Natural products have been used as an important biological resource for drug discovery for the last fifty years. Cancer is one of the main causes of death globally. Patients' quality of life is negatively impacted by the severe side effects of conventional cancer treatments. Although there have been significant advancements in the field of cancer therapy, the utilization of chemotherapeutic approaches is severely limited by issues such as drug resistance, distant metastases, toxicity, and related side effects. Cervical cancer (CC) is the third most frequent malignancy in women and the fourth most dangerous disease worldwide. Research on natural products has broadened to include compounds other than conventional anticancer drugs due to their chemoprotective and chemosensitizing qualities. Examining the available scientific data on their use in the treatment of CC is the goal of this study. The terms cancer, cervical cancer, phytochemical, pharmacological, and herbal medicine were used to gather the scientific data for this review from PubMed, Scopus, Science Direct, and Google. The current review article's scientific findings outline the biological potential of phytochemicals: α-mangostin, 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC), 10-gingerol (10-G), sesamol, gallic acid, punicalagin, resveratrol, indole-3-carbinol (I3C), γ-tocotrienol, caffeic acid, naringin, quercetin, curcumin, chrysin, plumbagin, alloimperatorin, calycopterin, engeletin, moscatilin, and chamaejasmine in medicine. The biological significance of phytochemicals for treating CC was indicated by the scientific findings presented in this review article. Additionally, this review article also discussed their different molecular mechanisms. Scientists studying the medicinal properties of herbal products will find this article's scientific content useful for the treatment of CC.

Keywords: Cancer, cervical cancer, herbal medicine, phytochemical

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INTRODUCTION

Traditional medicine has been used extensively in Asian nations to treat human illnesses and associated secondary complications for more than 5,000 years.[1] Around the world, herbal therapy is continuously the most widely used complementary and alternative medicine modality.[2] Numerous plants, herbs, and their byproducts, such as pure plant phytocompounds, were used to make herbal medications.[3] Over 80% of people still get their primary medical care from medicinal plants in most regions of the world.[4] Because of their therapeutic efficacy and medicinal worth, plant-based medications are becoming more and more necessary worldwide.[5] Many different kinds of human health issues have been treated with medicinal plants in both industrialized and developing nations. The food and pharmaceutical sectors use plants and plant-derived products as raw materials.[6–9] For millennia, medicinal plants have been utilized as a source of food and medicine, and they also play a significant role in the human health care system. The medical systems of China, Japan, India, and Korea all deeply rely on medicinal herbs.[10–12] One of the leading causes of death worldwide is cancer. Conventional cytotoxic chemotherapeutics are gradually being replaced by more targeted, mechanism-based chemopreventive agents. A diet rich in fruits and vegetables is linked to a lower risk of cancer-related death and may help prevent a variety of human cancers, according to a wealth of epide-

Address for Correspondence: Dinesh Kumar Patel, Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Uttar Pradesh, India
E-mail: dkp.itbhu@gmail.com **ORCID ID:** 0000-0001-8138-6379

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miological evidence. Various phases of carcinogenesis are effectively suppressed by dietary polyphenols.[13] The number of cancer cases worldwide is currently rising dynamically. According to the epidemiological data presented, female genital malignancies continue to pose a significant public health risk. Antiangiogenic agents, poly (ADP-ribose) polymerase (PARP) inhibitors, tumor-intrinsic signaling pathway inhibitors, selective estrogen receptor downregulators, and immune checkpoint inhibitors are examples of novel, promising targeted agents with potential anticancer effects. These agents target the primary causes of cancer development. Human papillomavirus (HPV) is thought to be the primary cause of lower genital tract cancers in women. Cervical, endometrial, and ovarian malignancies are the most prevalent gynecological cancers.[14] Cancer is treated using a range of methods, such as radiation therapy, chemotherapy, and surgery. All of them, nevertheless, have certain drawbacks. Conventional chemicals have toxicities and adverse consequences. Herbal medicine has emerged as a highly accessible, non-toxic, and safe source of chemicals that cure cancer.[15]

Approximately 9.6 million people die from cancer each year, making it the second most common cause of death worldwide. The use of chemotherapeutic techniques is hampered by severe constraints such as medication inefficacy, drug resistance, distant metastases, related side effects, and toxicity, despite the notable advancements in the field of cancer therapy. Antioxidant-rich natural substances have been shown to activate many survival pathways and shield healthy cells from the negative effects of anticancer treatments. Furthermore, numerous preclinical and clinical investigations have demonstrated that a number of these dietary components either directly or indirectly improve the activities of numerous chemotherapeutic medications, hence increasing their therapeutic potential.[16] In poor and underdeveloped countries, lung, colon, breast, and melanoma cancers are prevalent.[17] According to reports, an alternate technique of suitable food adjustment could prevent over 30% of human cancers. Numerous studies have been conducted recently to look into the possible chemopreventive effects of natural phytochemicals, especially dietary polyphenols, on cancer.[18] Recently, there has been a lot of interest in natural compounds that might have anti-cancer properties as possible alternatives to conventional chemotherapy. These compounds, which originate from microorganisms, plants, and marine life, have been shown to influence angiogenesis, immune response, cell proliferation, and survival, among other aspects of cancer biology. Examples of naturally occurring compounds with potent therapeutic effects and potential as anti-cancer medications include terpenoids, phenols, flavonoids, and alkaloids.[19] According to clinical studies, epigallocatechin-3-gallate can prevent malignancies of the ovary, cervical, endometrial, breast, testicular, and prostate systems in both men and women.[20] The development of anticancer drugs has gained impetus due to growing interest in plant-derived therapeutic agents against cancer and research into the anti-proliferative effectiveness of these compounds.[21]

CERVICAL CANCER

Cervical cancers can have a major impact on global health issues, especially for women. It is the third most commonly diagnosed cancer and the fourth most common cause of cancer-related deaths in women globally, according to the World Health Organization.[21] 12,990 cases of uterine cervical cancer (CC) are among the approximately 105,890 new cases of genital cancer in women in the United States. The cause of 4,120 of the 30,890 deaths is CC. In terms of death rate, ovarian cancer has the highest death rate (63.9%), followed by uterine cervix (31.7%), vagina (20.5%), and vulva cancer (18.6%). Thyroid, vaginal, and breast cancers are very common in young women under 50. The most widely used treatment for CC is chemotherapy, which mixes specific cytotoxic medications with methotrexate agents like doxorubicin and cisplatin and anti-metabolites such as deoxyribonucleic acid (DNA)-interactive agents.[20] CC is the third most frequent malignancy in women worldwide. More than 99% of cervical malignancies are linked to HPV infection, and some HPV strains can cause cancer in people. With a 70% progression-free survival rate, radiotherapy is the preferred treatment for patients with locally advanced CC.[22] In contrast to other malignancies, about 90% of CC deaths take place in underdeveloped nations. CC usually affects women early in their reproductive years, and its frequency increases between the ages of 30 and 34 before peaking between the ages of 50 and 65. About 132,000 new cases and 74,000 deaths from CC occur in India each year, making up one-third of all deaths from CC globally. Geographical differences in the population and prevalence of HPV, the primary risk factor for cervical cancer, are responsible for the disease's incidence and death. The use of hormonal contraceptives, high parity, high sexual activity, co-infection with HIV, and smoking are some of the many co-factors that increase the risk in females infected with HPV. More than 70% of CC occurrences worldwide are caused by the HPV 16 and 18 genotypes, with HPV 16 accounting for about 50–60% of instances.[23]

One of the most common neoplasias detected in women worldwide is still cervical cancer. Persistent infection with high-risk HPV subtypes is the main risk factor for cervical

cancer. These subtypes are found in almost 99% of cervical malignant lesions, with HPV 16 and HPV 18 accounting for at least 60% and 15% of all cases, respectively. The two main HPV oncogenes, E6 and E7, work together to maintain HPV DNA replication, apoptosis evasion, genomic instability, and cell immortalization, which is fully responsible for the onset and progression of CC.[24] Nowadays, radiotherapy, immunotherapy, local targeted therapy, and surgical resection are the primary treatments for cervical cancer. Traditional treatments are useful for CC in its early stages, but because of their severe side effects, drug resistance, numerous recurrences, and metastasis, they are not as helpful for CC that is locally advanced and metastatic. Natural remedies made from plants have emerged as the most promising options for cancer treatments in recent years. Flavonoids, terpenoids, alkaloids, and phenols are among the many plant-derived natural products that have been found to have antitumor properties. These products can suppress angiogenesis, induce apoptosis, decrease telomerase activity, inhibit tumor-cell proliferation, enhance immunological function, and reverse multidrug resistance.[25] Cisplatin, a platinum-based anticancer agent, is a chemotherapeutic drug used to treat epithelial cancers such as testicular, cervical, lung, and ovarian cancers. Cisplatin mostly alters DNA at the guanosine N7 site, which results in intra- and inter-strand cross-links and apoptosis. By reducing toxicity to healthy cells, the application of phytochemicals in cancer treatment may improve the effectiveness of chemotherapy. As a result, using phytochemicals in addition to cisplatin may lessen the negative consequences of using cisplatin alone.[26]

PHARMACOLOGICAL ACTIVITIES OF PHYTOCHEMICALS

α-Mangostin

This study assessed how α-mangostin affected tumor growth in xenografted mice, as well as cell proliferation, cell cycle distribution, and gene expression. The most susceptible cell lines were those with the highest number of HPV16 copies, and α-mangostin suppressed cell growth in a concentration-dependent manner. Furthermore, α-mangostin caused cell death in SiHa and HeLa cells and increased G1-cell cycle arrest in CaSki cells, indicating that it is a viable adjuvant for the treatment and prevention of CC.[24]

2',4'-Dihydroxy-6'-Methoxy-3',5'-Dimethylchalcone

A natural substance obtained from *Syzygium nervosum* A. Cunn. ex DC, 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC), was examined for its ability to inhibit several cancer cell lines. In this study, it was examined how DMC and three human CC cell lines (C-33A, HeLa, and SiHa) were affected by the CC medications 5-fluorouracil, cisplatin, and doxorubicin. In C-33A, HeLa, and SiHa cells, DMC demonstrated antiproliferative CC activity. It was further examined that DMC showed stronger antiproliferative cancer action in HeLa cells. DMC treatment increased DNA damage in cancer cells, suggesting that it is a potential anticancer drug. DMC was a chemical that caused the HeLa CC cell line to undergo apoptosis. DMC is a phytochemical agent that may be a good option for developing a medication to treat CC.[27]

10-Gingerol

10-Gingerol (10-G) was isolated and identified from "Tongling white ginger" in order to assess its anti-cancer properties against HeLa cells. 10-G prevented HeLa cells from proliferating, causing changes in cell shape, increased cytotoxicity, and inhibition in the G0/G1 phase of the cell cycle. Following a large decline in the majority of cell cycle-related genes and protein expression, cyclin B1 and cyclin E1 (protein) showed only minor declines. Apoptosis markers (caspase family) were markedly activated and upregulated by both death receptors. Additionally, there were notable alterations in markers of the mitochondria-dependent pathway, which resulted in cell death.[28]

Sesamol

Ephrin type-A receptor 2 (EPHA2) was knocked down in the SiHa cell line in this work, and the alterations in molecular markers linked to autophagy, mitophagy, and mitochondrial dynamics were assessed. The findings showed that EPHA2 knockdown (EPHA2-KD) decreased mitochondrial fission, mitophagy, and autophagy while increasing mitochondrial fusion. Additionally, the effects of treating CC with EPHA2-KD and sesamol on making it more sensitive to cisplatin treatment were examined. According to the data, treatment with EPHA2-KD and sesamol considerably raises cellular susceptibility to cytotoxicity caused by cisplatin. Furthermore, a decrease in EPHA2 expression levels after sesamol therapy indicates that sesamol effectively targets EPHA2, pointing to potential therapeutic approaches to reduce chemoresistance.[29]

Gallic Acid

The purpose of this study was to create a medication delivery system by conjugating gallic acid with gold nanoparticles (GNPs). Normal Vero kidney cells, CC cells infected with HPV type 16 (CaSki) or 18 (HeLa), and uninfected (C33A) CC cells were all used in the investigation. The findings demonstrated that gallic acid caused apoptosis, which stopped cancer cells from proliferating. Gallic acid was delivered to cancer

cells using 15-nm spherical GNPs in order to increase the effectiveness of its anticancer activity. GNPs-gallic acid was not harmful to normal cells, but it was less effective than gallic acid at inhibiting the proliferation of CC cells. In order to lessen the negative effects of chemotherapy and radiation therapy, GNPs may be employed as phytochemical delivery systems for alternative cancer treatments.[22]

Punicalagin

By examining the expression of Bcl-2 family proteins, caspases, and the cell cycle regulatory proteins p53 and NF-κB signaling in human CC cells, this study aimed to investigate the effectiveness of punicalagin on cell viability and investigate the molecular basis of punicalagin-stimulated apoptosis. Additionally, the morphological changes in CC cells were examined by the TUNEL assay, reactive oxygen species (ROS) production, mitochondrial membrane depolarization, and AO/EtBr analysis. This study also showed that, via inhibiting nuclear factor kappa B (NF-κB), punicalagin promoted cell apoptosis and inhibited CC cell multiplication. According to a study, punicalagin is a traditional option for anticancer drug design since it shows opposing activities on NF-κB signaling networks to stop the progression of cancer cells.[21]

Resveratrol

This study examined the kind of cell death that resveratrol caused in a number of CC cell lines. In C33A (with p53 mutation), HeLa (HPV18 positive), and CaSki and SiHa (HPV16 positive) cell lines, resveratrol administration (150–250 μmol/l) for 48 hours increased cell cycle arrest at the G1 phase. Resveratrol administration caused apoptosis in all cell lines, but especially in CaSki cells. HeLa, CaSki, and SiHa cells showed a drop in mitochondrial membrane potential (apoptosis), while C33A, CaLo (HPV18 positive), and HeLa cell lines showed an increase in lysosomal permeability (autophagy). Moreover, resveratrol had a comparable impact, indicating that it is independent of resveratrol concentration. After treatment, all cell lines except SiHa cells showed a decrease in the expression of p65, an NF-κB component. According to these findings, resveratrol causes cell death in cell lines originating from CC via a variety of methods.[30]

Indole-3-Carbinol

Determining PTEN expression during CC development and whether indole-3-carbinol (I3C) influenced PTEN expression *in vivo* were the objectives of this investigation. In a mouse model of cervical cancer, the K14HPV16 transgenic mice stimulated with estrogen showed decreased PTEN expression as low-grade cervical dysplasia progressed to high-grade cervical dysplasia in humans. Furthermore, the transgenic mouse cervical epithelium showed higher PTEN expression in response to dietary I3C. This finding implies that I3C elevation of PTEN is one way it prevents the development of CC.[31]

γ-Tocotrienol

This study examined γ-tocotrienol capacity to induce apoptosis and halt the proliferation of human cervical carcinoma HeLa cells, as well as the mechanism underlying these outcomes. The findings showed that a concentration of γ-tocotrienol over 30 μM significantly reduced the expression of proliferative cell nuclear antigen (PCNA) and Ki-67 and inhibited the proliferation of HeLa cells, with a 50% inhibitory concentration (IC_{50}) of 46.90±3.50 μM at 24 hours. γ-tocotrienol decreased the S phase and stopped the cell cycle in the G0/G1 phase in HeLa cells, according to DNA flow cytometric analysis. HeLa cells underwent apoptosis in response to γ-tocotrienol in a dose- and time-dependent manner. These findings showed that γ-tocotrienol might cause apoptosis in human CC HeLa cells via the mitochondrial apoptotic pathway and dramatically suppress cell proliferation through G0/G1 cell cycle arrest.[18]

Caffeic Acid

The current study examined the mechanism of action and efficacy of cisplatin and caffeic acid in combination on four human CC cell lines, comparing them to the normal kidney Vero cell line of *Chlorocebus sabaeus*. The sulforhodamine B assay was used to assess cell viability. HeLa and CaSki cell lines were tested for caspase activation in response to cisplatin and caffeic acid together using Caspase-Glo assay kits, which measure the activity of caspases-3, -7, -8, and -9. The findings showed that cisplatin and caffeic acid by themselves inhibited the growth of HeLa, CaSki, SiHa, and C33A cell lines. Vero cells showed no discernible cytotoxicity after caffeic acid treatment. When combined with cisplatin, caffeic acid, a potential anticancer drug, may improve its therapeutic effectiveness.[26]

Naringin

This study assesses the mechanism of naringin-induced cell death and its antiproliferative action on CC cells. The findings showed that naringin significantly reduced cell viability and that its IC_{50} values against C33A, SiHa, and HeLa cells are 745, 764, and 793 μM, respectively. Immunoblotting analysis and Annexin V-FITC show that cells exposed to greater concentrations of naringin exhibit a significant increase in apoptosis. Naringin mechanistically causes CC cells to undergo cell death linked to endoplasmic reticulum (ER) stress. In addition to activating the apoptosis-associated protein CHOP and other related proapoptotic proteins (PARP1

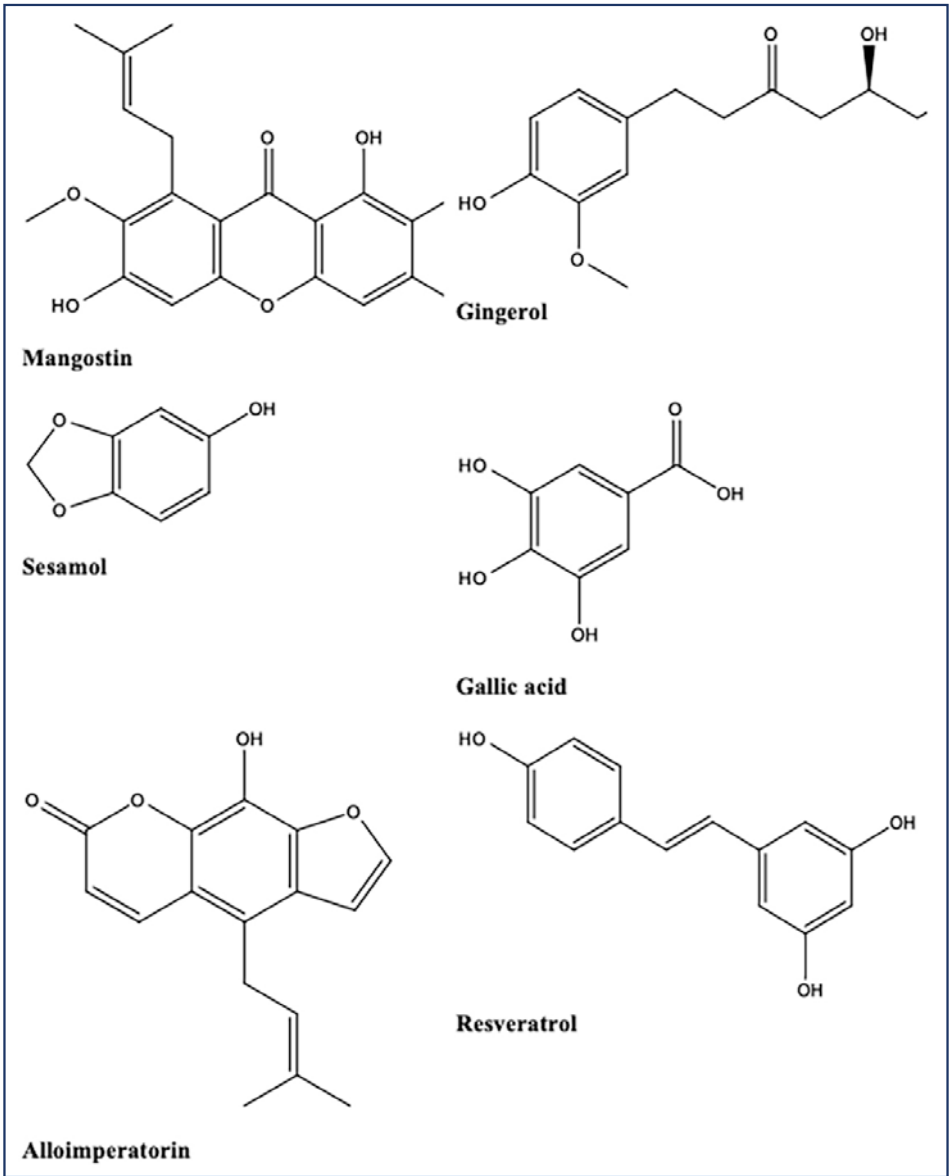

Figure 1. Chemical structure of phytochemicals having potential against cervical cancer

and caspase-3), naringin phosphorylates eIF2α and enhances the protein production of ER stress sensors. Interestingly, the apoptotic effect of naringin is reversed when an ER stress inhibitor (salubrinal) is administered prior to treatment. In CC cells, naringin causes ER stress-induced apoptosis and inhibits Wnt/β-catenin signaling at the same time, which ultimately results in cell cycle arrest at the G0/G1 phase.[32]

Quercetin

The purpose of this study was to examine quercetin potential as a phytochemical that modulates epigenetic pathways for anticancer treatments in HeLa cells treated with quercetin. It was discovered that quercetin reduces the activity of DNA methyltransferases (DNMTs), histone deacetylases (HDACs), and histone methyltransferases (HMTs) in a dose-dependent way and modifies the expression of several chromatin modifiers. When their expression was restored, the examined tumor suppressor genes (TSGs) displayed a sharp dose-dependent decrease in promoter methylation. [33] Examining the expression of Bcl-2 family proteins (Bcl-2, Bcl-xL, Mcl1, Bax, Bad, p-Bad), cytochrome C, Apaf-1, caspases, and survivin, as well as the cell cycle regulatory proteins (p53, p21, cyclin D1) and NF-κB family members (p50, p65, IκB, p-IκB-α, IKKβ, and ubiquitin ligase) in human CC (HeLa) cells, the current study was conducted to assess the impact of quercetin on cell viability and to identify the molecular mechanism of querce-

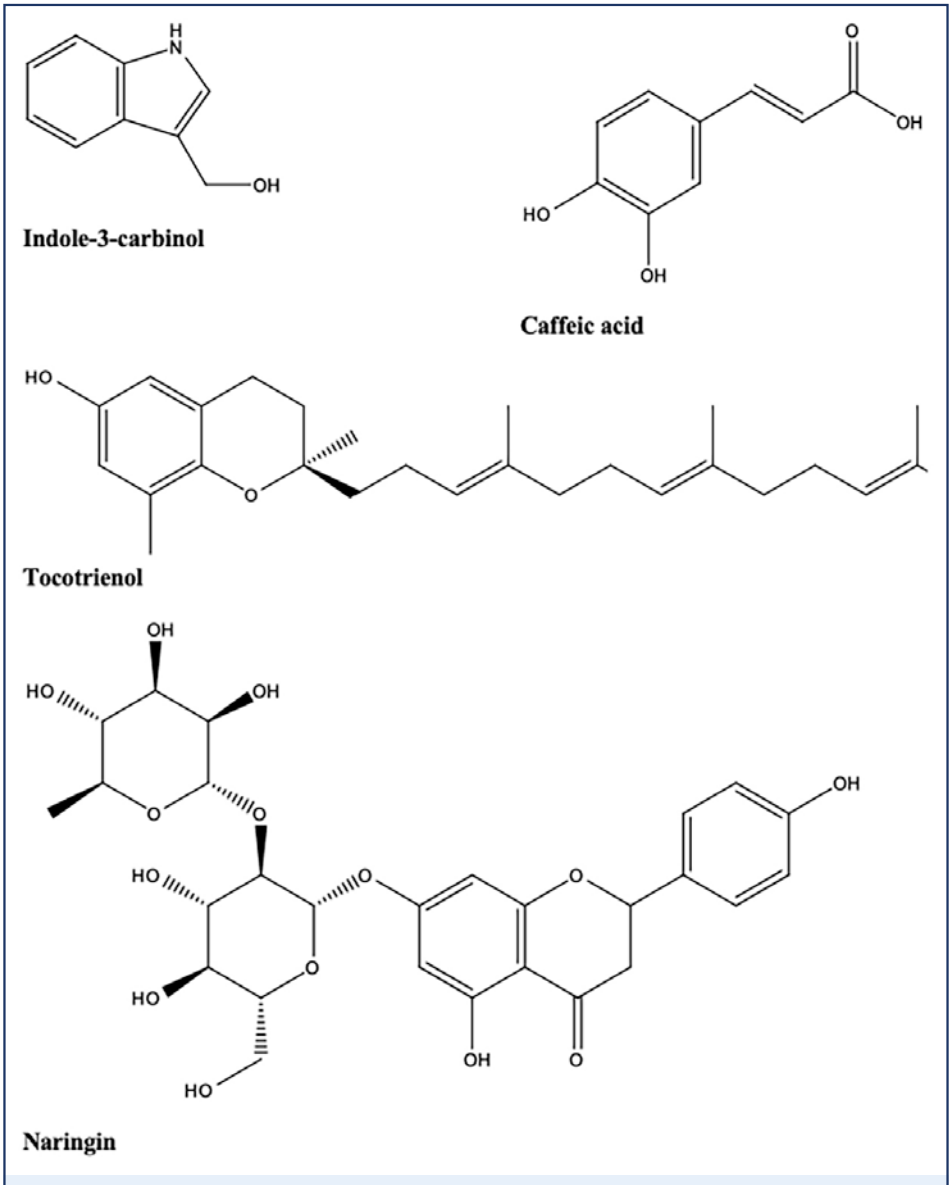

Figure 2. Chemical structure of phytochemicals having potential against cervical cancer

tin-induced cell death. A classic option for anticancer drug design is quercetin, which inhibits the growth of cancer by exerting opposing effects on many signaling networks.[34] The anti-cancer properties of the common phytochemical quercetin have been investigated employing comet assay, DNA fragmentation, nuclear morphology, colony formation, cell viability assay, and flow cytometry. Additionally, a number of genes implicated in metastasis, cell cycle regulation, apoptosis, and distinct signal transduction pathways were subjected to qPCR investigation. Quercetin causes DNA damage, promotes apoptosis, inhibits colony formation, lowers cell viability, and triggers G2-M cell cycle arrest. Quercetin causes apoptosis. Through docking experiments, quercetin may inhibit anti-apoptotic proteins. Moreover, quercetin inhibits the WNT, MAPK, and PI3K pathways. Molecular biology research confirmed quercetin anticancer activity in cell-based experiments and provided useful mechanistic insights.[13]

Curcumin

Two well-known phytochemicals, curcumin and ellagic acid, were tested in HeLa CC cells for possible anticancer and anti-HPV properties. Ellagic acid, a polyphenol present in walnut, raspberry, and strawberry fruits, and curcumin, a naturally occurring substance, are both found in the roots of the *Curcuma longa* plant. The 2,5-diphenyl-2H-tetrazolium bromide (MTT) assay demonstrated that the combination of

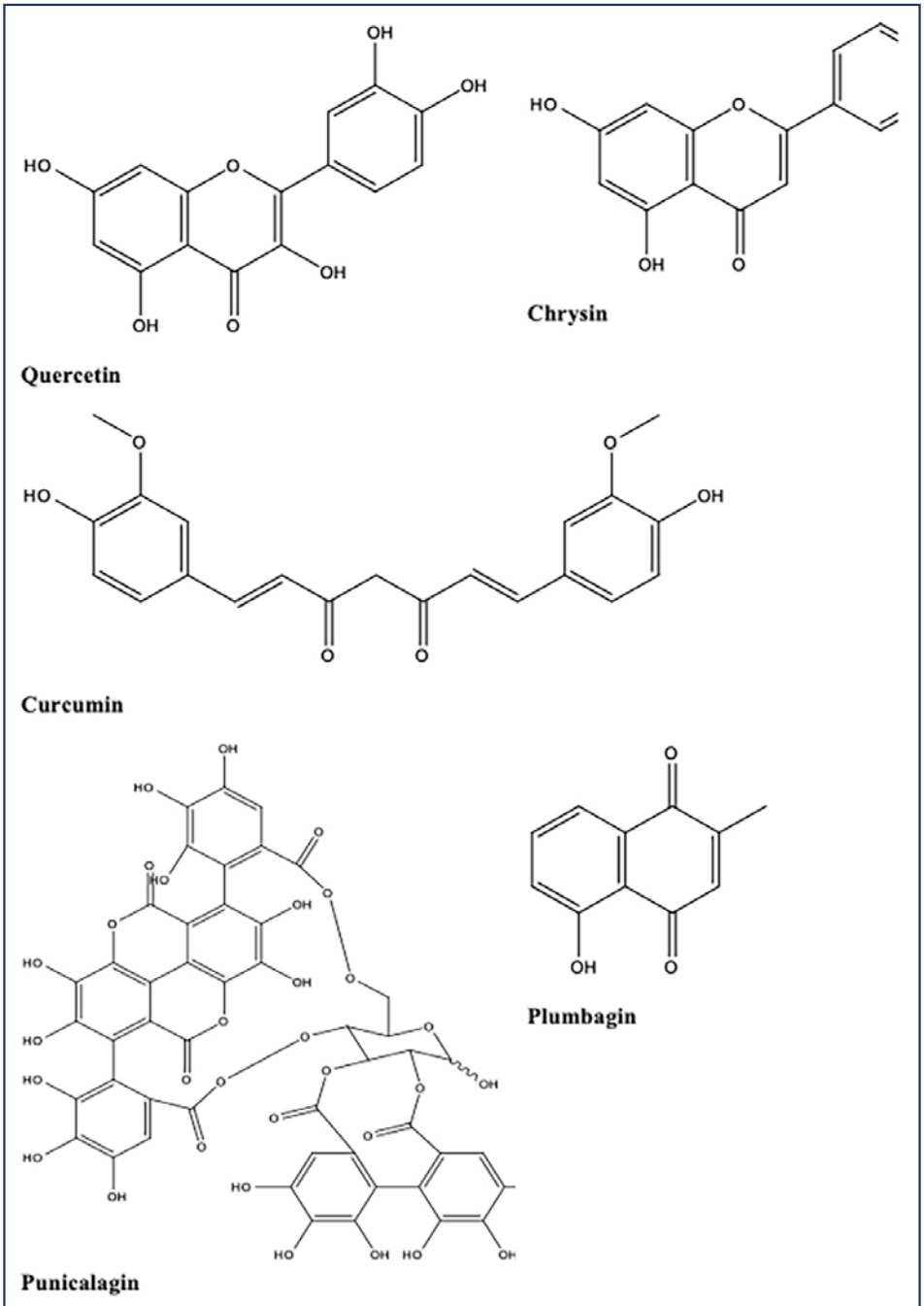

Figure 3. Chemical structure of phytochemicals having potential against cervical cancer

curcumin and ellagic acid at different doses had superior anticancer activities compared to either medication when taken alone. In addition, curcumin and ellagic acid cause DNA damage, ROS production, and p53 restoration.[35]

Chrysin

Chrysin-mediated epigenetic changes in HeLa cells have been investigated in the current work. The methylation status of the CpG promoters of several TSGs and the expression of these TSGs at the transcript and protein levels were investigated using colony formation and migration tests, which were followed by methylation-specific PCR. Additionally, following chrysin treatment, analyses of H3 and H4 histone modification marks, global DNA methylation, the biochemical activities of DNMTs, HMTs, histone deacetylases (HDACs), and HATs, as well as the expression analysis of chromatin-modifying enzymes, were

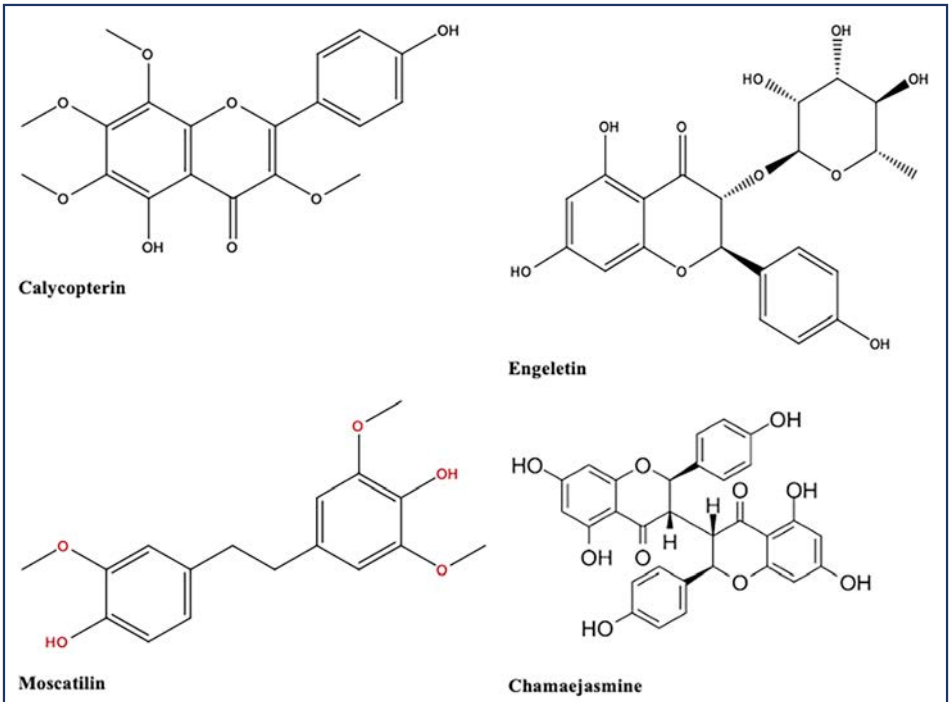

Figure 4. Chemical structure of phytochemicals having potential against cervical cancer

conducted. Chrysin administration decreases the ability of HeLa cells to migrate and promotes cytostatic behavior in a dose- and time-dependent way. According to the study's findings, chrysin merits more experimental validation as a possible epigenetic modulator for the treatment of cancer.[36]

Plumbagin

The molecular changes linked to plumbagin-mediated suppression of human CC SiHa and HeLa cell proliferation, survival, and epithelial-to-mesenchymal transition have been examined. After 24 and 48 hours, plumbagin (1–4 μM) significantly reduced the viability of SiHa and HeLa cells and increased cell death. In SiHa and HeLa cells, plumbagin also resulted in severe G2/M and S-G2/M phase cell cycle arrest, respectively. After 24 and 48 hours, the mRNA and protein expression levels of CDK1 and 2, as well as cyclin B1, A, and E2, declined. Plumbagin also modifies MMP-2, 9, E-cadherin, N-cadherin, β-catenin, and vimentin, in addition to having an anti-metastatic impact at non-cytotoxic levels. When combined, plumbagin effectively inhibits the growth and spread of human CC cells.[23]

Alloimperatorin

The current work examined the molecular mechanism and biological potential of alloimperatorin-induced CC cell apoptosis. The cytotoxicity of alloimperatorin on HeLa, SiHa, and MS-751 cells was assessed using cholecystokinin octapeptide. Alloimperatorin-induced apoptosis was evaluated using flow cytometry. Western blotting, fluorescence polymerase chain reaction (PCR), and mitochondrial membrane potential were used to confirm the apoptotic process. The study's findings demonstrated that alloimperatorin decreased HeLa cell activity. Alloimperatorin decreased the mitochondrial membrane potential of HeLa cells and accelerated their rate of apoptosis in comparison to the control group. According to the findings, alloimperatorin can cause HeLa cell death via extrinsic and mitochondrial apoptotic pathways.[37]

Calycopterin

Calycopterin was isolated and identified through phytochemical analysis of *Cleome iberica* aerial parts. Additionally, the dried extract's levels of total flavonoids and total phenolics were found to be 90.7 and 39.6 mg/g, respectively. The acetone extract and several isolated compounds showed significant cytotoxicity against the CC cell line (HeLa) in the MTT assay, whereas the studied compounds demonstrated poor activity in antimicrobial assessment. Of them, calycopterin was determined to be the most potent, with an IC_{50} of 5.1 μM.[38]

Engeletin

Engeletin biological potential in controlling CC has been studied along with its underlying molecular mechanisms.

Table 1. Molecular mechanism of phytochemicals having potential against cervical cancer

S. no	Phytochemical	Molecular mechanism	Reference
1.	α-mangostin	*In vitro* and *in vivo*, α-mangostin-dependent reductions in E6, E7, and KCNH1 gene expression were observed, along with changes in cytokine expression, Ki-67, and tumor growth inhibition.	[24]
2.	2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC)	After DMC therapy, the cell cycle assay revealed a higher proportion of cells in the G0/G1 phase. Additionally, apoptotic cell death brought on by DMC treatment was roughly three to four times greater than that of the untreated group.	[27]
3.	10-gingerol (10-G)	10-G caused AMPK activation and PI3K/AKT inhibition, which caused HeLa cells to undergo mTOR-mediated cell death.	[28]
4.	Sesamol	Targeting EPHA2 with knockdown or sesamol therapy increases the sensitivity of cervical cancer to cisplatin by modifying autophagy, mitophagy, and mitochondrial dynamics.	[29]
5.	Gallic acid (GA)	Targeting EPHA2 with knockdown or sesamol therapy increases the sensitivity of cervical cancer to cisplatin by modifying autophagy, mitophagy, and mitochondrial dynamics.	[22]
6.	Punicalagin	Punicalagin stimulated mitochondrial mediated apoptosis, which in turn suppressed the viability of cervical cancer cells in a dose-dependent manner.	[21]
7.	Resveratrol	Following resveratrol therapy, HPV18-positive cell lines (CaLo and HeLa) showed a decrease in p53 expression, while HPV16-positive cell lines (CaSki and SiHa) and C33A cells showed an increase.	[30]
8.	Indole-3-carbinol (I3C)	In the transgenic mouse's cervical epithelium, dietary I3C boosted PTEN expression. This finding implies that I3C's elevation of PTEN is one way it prevents the growth of cervical cancer.	[31]
9.	γ-Tocotrienol	When γ-tocotrienol caused HeLa cells to undergo apoptosis, Bcl-2 was down-regulated, Bax was up-regulated, cytochrome was released from the mitochondria, caspase-9 and caspase-3 were activated, and poly (ADP-ribose) polymerase (PARP) was cleaved.	[18]
10.	Caffeic acid	HeLa and CaSki cell lines' ability to proliferate was markedly suppressed by cisplatin (CDDP) and caffeic acid (CFC). A combination index <1 for CDDP and CFC in HeLa and CaSki cell lines showed synergistic growth inhibition; the two also markedly elevated caspase-3, -7, and -9 expression.	[26]
11.	Naringin	By reducing the phosphorylation and protein expression of β-catenin (Ser576) and GSK-3β (Ser9), naringin inhibits the β-catenin pathway. At the same time, it causes cell cycle arrest at a G0/G1 phase by upregulating the expression of cell cycle checkpoint proteins p21/cip and p27/kip.	[32]
12.	Quercetin	According to molecular docking experiments, quercetin may engage with residues in the catalytic cavity of a number of DNMTs and HDACs to operate as a competitive inhibitor. Quercetin decreased levels of global DNA methylation in a way that was dependent on both time and dose. The findings show that quercetin caused G2/M phase cell cycle arrest and mitochondrial death via a p53-dependent mechanism, thereby suppressing the survival of HeLa cells in a dose-dependent manner.	[33,34]
13.	Curcumin	The HPV E6 oncoprotein on HeLa cells decreased, indicating that curcumin and ellagic acid have anti-HPV activity, according to a mechanistic research.	[35]
14.	Chrysin	Chrysin reactivates tumor-suppressor genes at the mRNA and protein levels by decreasing their methylation. In addition to H3 and H4 histone modification marks being altered, it was discovered that the expression levels of several chromatin-modifying enzymes, including DNMTs, HMTs, HDACs, and HATS, were reduced. After chrysin treatment, there was also a decrease in global DNA methylation.	[36]
15.	Plumbagin	Apoptosis was highly promoted by plumbagin, which also caused cleavage of caspase 3, 9, and PARP and an increase in the Bax:Bcl2 ratio. When pre-treated with N-acetyl cysteine, plumbagin significantly increased the formation of reactive oxygen species, which triggered cell death.	[23]
16.	Alloimperatorin	While Bax apoptotic proteins decrease the expression of PARP, procaspase3, 8, 9, and BCL-2 proteins as well as the production of cyt-c in the mitochondria, alloimperatorin increases the expression of caspase3, 8, and 9.	[37]

Table 1. Cont.

S. no	Phytochemical	Molecular mechanism	Reference
17.	Calycopterin	In the MTT assay, calycopterin demonstrated significant cytotoxicity against the HeLa cervical cancer cell line.	[38]
18.	Engeletin	In cervical cancer cells linked to the inhibition of the nuclear factor-κB (NF-κB) signaling pathway, evertin markedly decreased the expression of chemokine (C-C motif) ligand 2 (CCL2). Additionally, nngeletin inhibited NF-κB, which was implicated in the inhibition of angiogenesis.	[39]
19.	Moscatilin	Both intrinsic and extrinsic apoptotic signaling pathways are linked to mosaicin-mediated apoptosis. Furthermore, the JNK signaling pathway promoted the apoptosis produced by moscatilin.	[40]
20.	Chamaejasmine	The inhibition of PI3K/Akt signaling cascades may be the mechanism by which chamaejasmine causes HeLa cells to undergo apoptosis.	[41]

Treatments with engeletin decreased CC cell proliferation in a dose-dependent manner. Engeletin also inhibited the CC epithelial-to-mesenchymal transition (EMT) pathway, as seen by the markedly decreased invasion and migration. Treatments with engeletin decreased the expression of vascular endothelial growth factor-A (VEGFA) in C cells, which helped to inhibit angiogenesis. Engeletin administration successfully decreased the tumor weight and volume in the xenograft model, along with phosphorylated NF-κB, CCL2, and VEGFA expression. Engeletin may therefore be a viable therapeutic approach for the management of CC.[39]

Moscatilin

To determine its mode of action, the biological potential of moscatilin, which was isolated from *Dendrobii Herba*, has been studied in the FaDu human pharyngeal squamous carcinoma cell line. Moscatilin mediated apoptosis to cause FaDu cell death. Five μM moscatilin treatments enhanced the expression of apoptosis-related proteins and PARP. Moscatilin may be employed as a chemotherapeutic treatment to treat squamous cell carcinoma of the head and neck.[40]

Chamaejasmine

To clarify the underlying molecular pathways, the biological potential of chamaejasmine, a bioactive component of *Stellera chamaejasme* L., on CC cells has been studied. Both *in vitro* and *in vivo*, chamaejasmine exhibits strong anticancer effects on CC cell lines. Mechanistic research revealed that chamaejasmine could cause HeLa cells to undergo apoptosis. This effect could be mediated by inhibiting PI3K/Akt signaling cascades, which not only suggests that chamaejasmine may be used therapeutically for CC but also offers important information about how it works.[41]

CONCLUSION

In order to determine the possible health benefits of phytochemicals in medicine, this study aims to examine all the available scientific data on phytochemicals regarding their application in the treatment of cervical cancer. This review examines and discusses the specific pharmacological actions of phytochemicals. The terms cancer, cervical cancer, phytochemical, pharmacological, and herbal medicine were used to gather the scientific data for this review from PubMed, Scopus, Science Direct, and Google. The current review article's scientific findings outline the biological significance and therapeutic efficacy of phytochemicals in the treatment of cervical cancer. The biological potential of α-mangostin, 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC), 10-G, sesamol, gallic acid, punicalagin, resveratrol, indole-3-carbinol (I3C), γ-tocotrienol, caffeic acid, naringin, quercetin, curcumin, chrysin, plumbagin, alloimperatorin, calycopterin, engeletin, moscatilin, and chamaejasmine (Figs. 1-4) for their therapeutic effectiveness on CC was indicated by the scientific findings presented in this review article. Additionally, this review article discussed the molecular mechanisms of these phytochemicals (Table 1). Scientists studying biology will find this article's scientific content useful in order to understand the therapeutic potential of phytochemicals for the treatment of cervical cancer. In order to elucidate the biological potential of phytochemicals in medicine, this review article also explains their molecular mechanisms and specific pharmacological activity. Thus, the objective of this article is to present scientific data regarding the pharmacological activity, biological significance, and associated molecular mechanisms of phytochemicals that may be used in medicine to treat CC in the future. The scientific evidence presented in this article indicated the possibility

for treatment of CC in medicine from natural phytochemicals. Even though scientific data analysis showed that phytochemicals have pharmacological activity that may help treat cervical cancer, more scientific investigation should be done in order to find out where these phytochemicals come from naturally. Although phytochemicals offer a lot of biological potential for their uses in medicine, scientists should also investigate how well they work for other secondary human complications. Furthermore, we must ascertain these phytochemicals' plasma profiles through different clinical research in order to assess their safety parameters in medicine. The construction of novel therapeutic compounds from these phytochemicals ought to be pursued in the future based on their documented biological activity.

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