The Role of Secondary Metabolites on Gynecologic Cancer Therapy: Some Pathways and Mechanisms

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ABSTRACT

Gynecologic cancers are among the most common cancers in humans and animals. Treatment success depends on several factors including stage at diagnosis, tumor type, origin and metastasis. Currently, surgery, chemotherapy, and radiotherapy are preferred in the treatment of these cancers. However, many anticarcinogenic drugs can cause severe adverse effects and also the expected response to treatment may not be obtained. In recent studies, the importance of the relationship between cancer and inflammation has been emphasized. Therefore, several phytochemicals that exhibit beneficial bioactive effects towards inflammatory pathways were proven to have anticarcinogenic potential for gynecologic cancer therapy. This review summarizes the role of inflammatory pathways in gynecologic cancers and effective secondary metabolites for cancer therapy.

Key words: Gynecologic cancers, pathway, secondary metabolites, phytoconstituents, inflammation

INTRODUCTION

Cancer is a complex disease in which cells in a specific tissue are no longer fully responsive to the signals within the tissue that regulate cellular differentiation. The disease is characterized by abnormal cell growth spread through the blood and lymph systems to other tissues in the body. It is globally the second leading cause of death for both men and women, approximately 1 in 6 deaths is due to cancer. Cancer is commonly diagnosed in domestic animals as it is in humans. Mammary gland tumors, skin tumors, osteosarcomas, and hemopoietic tumors are the most prevalent malignant tumors which cause mortality in dogs and cats. It has been demonstrated that the activation of the inflammatory pathways including cytokines, nuclear factor kappa B, (NF-κB) prostaglandins, cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), free radicals, inducible nitric oxide synthase (iNOS), and signal transducers and activators of transcription (STAT)-3 lead to the development of various malignant tumors. As chronic inflammation has been recognized as a potential risk factor for cancer progression, targeting inflammatory pathways could be beneficial for preventing the development of gynecologic cancers. The goal of cancer therapy includes both prolonging survival and preserving a high quality of life. However, many drugs used in the treatment of cancer can cause adverse effects such as fatigue, nausea, vomiting, malaise, diarrhea, and headaches. Most novel drugs are still under research because gynecologic cancers are common and show a low survival rate, as in ovarian and breast cancer especially. Due to the adverse effects of many synthetic drugs, secondary metabolites of medicinal plants have attracted attention for scientific research such that they may be used as proven beneficial anticancer agents. In this study,
we aimed to review the inflammatory pathways related to gynecologic cancers and effective plant secondary metabolites as anti-inflammatory agents for cancer management in both humans and animals.

**Overview on gynecological cancers in humans and animals**

Gynecologic cancers, the fourth most common type of cancers in women, affect the tissue and organs of the female reproductive system including the ovaries, uterus, cervix, and vulva-vagina.\(^1^\)\(^2\)\(^3\) Vulvar and vaginal cancers include only about 2% of malignant neoplasms of the genital tract in women. Vaginal cancers are caused by primary tumors of the vagina or metastasis of other gynecologic cancers. Primary vaginal cancer is rare, seen in approximately 1 in every 1100 women. Treatment success depends on the origin of the tumor.\(^4\) Because endometrial and cervical cancers can generally be diagnosed at the preinvasive stage, treatment success is higher. However, ovarian cancer is one of the deadliest cancer types because diagnosis is frequently in the late stage due to the lack of obvious symptoms.\(^5\)

Gynecologic cancers in animals occur as a consequence of many carcinogenic factors such as genetic, immune, and hormonal changes due to endogenous or exogenous factors, ionized radiation, chemical agents, and oncogenic viruses.\(^6\) Primary ovarian tumors and uterine tumors are rarely observed in domestic animals.\(^7\)\(^8\)\(^9\) The clinical signs of these tumors are generally less obvious than those of other cancers and are realized incidentally during laparotomy or ultrasonographic examination. These tumors mainly have benign character and can be treated by removing the relevant organ along with the tumor.\(^4\)\(^7\)

Canine transmissible venereal tumor, also known as infectious sarcoma, venereal granuloma, and transmissible lymphosarcoma Sticker tumor, is a benign reticuloendothelial tumor that affects the external genitalia in both sexes, but is occasionally observed in the internal genitalia, other organs, conjunctiva mucosa, the oral and nasal cavities. Transmissible venereal tumor is usually transmitted to genital organs during coitus. Some treatment protocols including surgical resection, radiotherapy, immunotherapy, biotherapy, and chemotherapy have been administered for transmissible venereal tumor. However, chemotherapy without surgical intervention has been determined to be the most effective and practical therapy with vincristine sulfate, vinblastine, doxorubicin, and cyclophosphamide as single agents or in combination.\(^8\)\(^9\)\(^10\)

Mammary tumors, the frequency of which varies according to the animal species, is recognized as one of the gynecologic cancer types in veterinary medicine. Dogs are the most frequently affected by mammary tumors among domestic species.\(^11\)\(^12\)\(^13\) On the other hand, mammary tumors are rare in livestock.\(^13\) Steroid hormones play an important role in the hyperplasia and neoplasia of mammary gland tissue. There are estrogen and/or progesterone receptors in mammary tumor cells in animals; these receptors may influence the pathogenesis of tumor and response to hormone therapy. The treatment of malignant mammary tumors should include surgery and chemotherapy.\(^4\)\(^14\) Breast cancer is the most frequent cancer in women and diagnosed in approximately 25% of all cancer types.\(^2\) Inflammatory breast cancer, a subtype of breast cancer, is rare (2-5%). The 5-year survival rate is low. Appropriate therapy including chemotherapy, mastectomy, and radiation therapy improve prognosis of breast cancer. Despite improvements in treatment modalities, high-grade or metastatic breast cancer cannot generally be treated. The main purpose of treatment is to improve the quality of life and prolong survival.\(^2\)\(^6\)\(^7\)

**Inflammatory response in cancer**

Several inflammatory mediators are responsible for the formation of cancer. Various anticancer drugs exhibit action directly on pro-inflammatory cytokines such as interleukin (IL)-6 or tumor necrosis factor (TNF)-α. Furthermore, reactive oxygen species (ROS) and reactive nitrogen species lead to carcinogenesis by causing a cellular redox imbalance in miscellaneous cancer cells. In addition to STAT3, the Ras protein can also be activated in response to IL-6.\(^2\)\(^8\)

Acute inflammation is the protective response of organisms against tissue destruction. Inflammation heals spontaneously after improving the tissue. However, continuation of the infection and immune system deficiency could result in chronic inflammation, which may lead to tissue damage and finally carcinogenesis. It was first mentioned in 1863 by Rudolf Virchow that leucocytes in neoplastic tissues serve the possible relationship between inflammation and cancer. He observed that the “lymphoreticular infiltrate” exhibited the origin of cancer in the chronic inflammatory region.\(^2\)\(^9\) It was hypothesized that angiogenesis was one of the molecular actions that provided a connection between chronic inflammation and cancer, and tumors have been called “wounds that do not heal.” Chronic inflammation has been demonstrated to be a key factor in the pathogenesis of malignant tumors such as with human papilloma virus infection, which causing cervical cancer.\(^6\)

Apoptosis is a process of programmed cell death that appears in multicellular organisms. Therefore, inadequate apoptosis causes uncontrolled cell proliferation. Chemotherapeutic agents prevent tumor cell proliferation and even kill tumor cells through apoptotic pathways. Therefore, apoptosis plays an important role in chemotherapy. The process of apoptosis includes contraction and membrane blebbing and nuclear fragmentation. The execution of apoptosis involves the signal transmission pathway.\(^2\)\(^8\)\(^3\)\(^1\) TNF is a cell-signaling protein produced chiefly by effective macrophages, which are involved in systemic inflammation. It is the main mediator of binary anti-apoptotic. Inflammatory responses are initiated by the binding of TNF to its receptor. Fas ligand (FasL) is a cytotoxic type II transmembrane protein of the TNF family. The engagement of FasL with its receptor (apoptosis antigen 1 or cluster of differentiation 95) initiates death-inducing signaling complex formation, which includes accessory molecules, the Fas-associated death domain protein, caspase-8, and -10.\(^3\)\(^2\)

COX enzymes are bi-functional membrane-bound enzymes that are responsible for the formation of prostanooids, including thromboxane and prostaglandins. COX-1, which is...
stably expressed in cells and tissues, is generally involved in housekeeping functions. COX-3 is only expressed from specific tissue such as brain and spinal cord. COX-2 is generally found at low levels in cells, whereas it significantly increases in tissue with tumor cells. It has been considered that this situation could be due to the cross-talk between inflammatory mediators such as ILs and cytokines (i.e., IL-1, IL-6, and TNF-α). The association between COX-2 expression in cancers and tumor size has been reported. The prevention of COX-2 expression may inhibit cancer formation because COX-2 is a pro-inflammatory mediator that can be stimulated even in the very early stages of carcinogenesis. COX-2 transcriptional activation is mediated by transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), specificity protein 1 transcription factor, and activator protein (AP)-1. COX-2 over-expression is related to high grade of tumor, metastasis, recurrence, and survival rates in canine mammary carcinomas. Furthermore, the highest levels of COX-2 were reported to be expressed in inflammatory mammary carcinoma.

The transcription factor NF-κB is a nuclear factor that binds to the enhancer element of the immunoglobulin kappa light-chain of activated B cells. Negative regulators of some signaling pathways of NF-κB are up-regulated by NF-κB. This situation generally results in the deactivation of NF-κB in acute inflammation. The persistent stimulus of NF-κB in chronic inflammation appears to exceed inhibitory feedback circuits, which leads to an increased constitutive activity of NF-κB. There is a two-way relationship between inflammation and NF-κB in cancer. NF-κB is a part of the immune defense that eliminates transformed cells. Therefore, activation of NF-κB is contributed by effectiveness of cytotoxic immune cells against tumor cells. Accordingly, NF-κB, which has a variety of pro-tumorigenic functions, is mainly activated in tissue with tumor. The anti-tumorigenic function of the immune system with NF-κB has been known as tumor-immunosurveillance. The immune defense against cancer cells is not adequate to eliminate abnormal cells; these may proceed onto "escape phase" and "equilibrium phase" in which the immune system has the ability to control tumor progression. These phases are characterized by chronic inflammation with increased levels of NF-κB. It has been considered that the activity of NF-κB with a pro-tumorigenic effect is similar in immune-suppressed patients and patients with chronic inflammatory diseases. The antiapoptotic genes that provide cell survival mechanisms are up-regulated by NF-κB activation. NF-κB stimulates cytokines such as TNF-α, IL-1, IL-6, and IL-8, which regulate the immune response, as well as induce adhesion molecules, which provide migration of leukocytes to sites of inflammation. Generally, the contribution of inflammation and NF-κB to cancer induction and progression is complicated. NF-κB signaling has been reported to cause cancer progression by epithelial-mesenchymal transition because NF-κB is associated with an up-regulation of matrix metalloproteinases and VEGF and its receptors.

Ovarian cancer originates mainly from the ovarian surface epithelium. Ovarian epithelial cells are exposed to several pro-inflammatory mediators such as cytokines, ILs, growth factors, prostaglandins and eicosanoids. Therefore, the ovulation process can be considered as a potential inflammation period due to the rise of pro-inflammatory mediator production, which leads to oxidative stress. Moreover, ovarian cancer occurs due to the activation of collagenase, an enzyme that destroys the extracellular matrix. The recurring period of cellular damage and repair in high oxidation conditions disrupt DNA replication.

**Therapeutic approach to gynecologic cancers**

For the determination of cancer stage and therefore appropriate treatment strategies, histopathologic evaluation should be carried out as the initial step to detect the differentiation of neoplastic lesions. On the treatment procedure, extirpation of the tumor and application of chemotherapeutic agents, particularly including paclitaxel and cisplatin-based derivatives, are generally preferred. Endometrial cancers are successfully treated by hysterectomy. Contrary to expectations, high-grade endometrial tumors could only be appropriately removed in 44-72% of patients. Nevertheless, neoadjuvant chemotherapy can sometimes be effective after removing the mass. Likewise, the effect of radiotherapy has not been fully identified. Cervical cancers are frequently squamous cell carcinomas originating from the epithelial cells lining the cervix. Radical therapy on cervical cancers includes surgery and application of chemotherapeutics such as a combination of histone deacetylase inhibitor (vorinostat) and proteasome inhibitor (bortezomid) as well as radiotherapy. However, treatment success is dependent on clinical factors such as age, histologic type and grade. Radiotherapy is regarded as a beacon of hope in high-grade cervical cancer. On the other hand, as the first-line therapy in ovarian cancer, cisplatin and its derivatives are applied following surgical removal tumors. However, in some cases, ovarian cancer can progress or recur despite chemotherapy, which is known as chemoresistance and has a poor prognosis. Chemoresistance occurs due to the dysregulation of signaling factors which are responsible for the induction of cell death. In addition, these chemotherapeutic agents can cause infertility and serious side effects. For this reason, new therapeutic approaches to cure cancer with fewer adverse effects, as well as to overcome chemoresistance, are needed in all gynecologic cancer types.

Bioactive secondary metabolites derived from botanical sources may represent a promising therapeutic strategy for both cancer management and chemosensitivity enhancement. Recently, several studies revealed that different types of phytoconstituents had diverse potential applications in signaling pathways associated with cancer by inhibiting factors that are dysregulated in malignant cells, either individually or by enhancing the effects of conventional therapy. One of the most important advantages of phytochemicals over synthetic drugs is their high tolerability. Moreover, plant extracts, which contain thousands of phytochemicals, have been shown to be potentially active on multiple targets within various oncogenic signaling pathways.

**Effects of phytochemicals against gynecological cancers**

High risk of cancers is associated with environmental factors...
and unhealthy lifestyle behaviors. According to epidemiologic evidence, dietary behavior notably affects cancer prevalence.\textsuperscript{44} It is known that diets rich in fruits and vegetables provide a reduction in cancer risk, which is attributable to the effects of phytochemicals.\textsuperscript{45} A number of natural compounds that have been reported to exhibit beneficial biologic effects in gynecologic cancer therapy are presented in Figure 1.

**Figure 1.** Secondary metabolite groups exhibiting beneficial effects in gynecologic cancer therapy

According to previous epidemiologic research, a diet rich in flavonoid-containing foods is associated with a decreased risk of cancers including breast, digestive system, skin, and prostate.\textsuperscript{46} These compounds have the capacity to inhibit cancer development via different biologic activity mechanisms including suppression of inflammation and angiogenesis, regulation of the cellular response to oxidative stress and DNA damage, retardation of cell proliferation, and induction of apoptosis.\textsuperscript{47} Studies have demonstrated that flavonoids can induce apoptosis in human breast cancer cells by inhibiting the activity of fatty acid synthase, which catalyzes the synthesis of long-chain fatty acids.\textsuperscript{46,48} Apigenin, a flavone-type compound widely found in fruits and vegetables, is a bioactive constituent that apigenin showed cytotoxic action on Michigan Cancer Foundation (MCF)-7 breast cancer cell lines.\textsuperscript{46} In addition, apigenin inhibited phorbol 12-myristate 13-acetate-mediated cell survival and tumor cell invasion in the estrogen-insensitive breast tumor cell line MDA-MB-231.\textsuperscript{46,54} By CDK1 and cyclin-dependent kinase inhibitor 1 p21 (Cip1) pathway regulation, apigenin treatment was shown to induce G(2)/M phase cell cycle arrest in SK-BR-3 cells. Moreover, apigenin was reported to cause activation in MDA-MB-468 cells with extracellular signal-regulated kinase (ERK)/MAPK phosphorylation,\textsuperscript{25} and to inhibit E2-induced DNA synthesis in MCF-7 cells.\textsuperscript{54,57} Anti-estrogenic effects mediated through estrogen receptor (ER)-binding dependent and independent mechanisms were also revealed.\textsuperscript{58,59} Apigenin inhibited the growth of human cervical carcinoma HeLa cells through an apoptotic pathway induced by a p53-dependent increase in p21/waf1 protein expression\textsuperscript{52} and exerted an anti-proliferative effect against SiHa human cervical cancer cells.\textsuperscript{61} Apigenin was shown to play a beneficial role in the treatment of endometrial cancer in postmenopausal women.\textsuperscript{66} Luteolin, a flavonoid-type compound, possesses multiple biologic characteristics including anti-inflammatory and antioxidant properties, and displays cancer chemopreventive effect.\textsuperscript{71} The anticancer potential of luteolin could be related to its anticancer activity, which is also provided by inhibition of cell proliferation, metastasis and angiogenesis, and induction of apoptosis. In addition, luteolin suppresses cell survival pathways including PI3K/Akt, NF-κB, and the X-linked inhibitor of apoptosis protein (XIAP).\textsuperscript{62} It was shown to have the ability to inhibit protein kinase Cε and Src kinase in the oncogenic signaling pathway.\textsuperscript{72,63} Luteolin was demonstrated to have a notable cytotoxic activity in human papillomavirus (HPV)-positive cervical cancer cells in a dose-dependent manner. HPV E6 and E7 oncogene expressions were suppressed and caspase cascades were activated. Luteolin also inhibited the expression of Bcl-2 and Bcl-xL.\textsuperscript{64} Fisetin, 3,3',4',7-tetrahydroxyflavone, from Fabaceae plants such as *Acacia greggii* A. Gray, and *Acacia berlandieri* Benth., was shown to possess anti-proliferative activity and display anticarcinogenic potential by inducing apoptosis.\textsuperscript{73,65-67} Fisetin inhibited the invasion and migration of cervical cancer cells by dose-dependently suppressing the expression and activity of urokinase plasminogen activator and decreased p38 MAPK phosphorylation. Fisetin affected the nuclear translocation of NF-κB and inhibited tTPA (tetradecanoylphorbol-13-acetate)-enhanced migration and invasion.\textsuperscript{68} Fisetin was found to display anti-inflammatory activity in lipopolysaccharide (LPS)-induced acute pulmonary inflammation, and anti-carcinogenesis action.\textsuperscript{69,70} Fisetin demonstrated an inhibitory effect on Wnt signaling by modulating the expression of beta-catenin\textsuperscript{71,72} and the reducing effect on NF-κB and AP-1.\textsuperscript{73} A citrus flavonoid, tangeretin, displayed inhibitory action on the growth and invasive properties of human mammmary cancer cells when co-administered with tamoxifen *in vitro*. However, it was reported that tangeretin exhibit no inhibitory activity on...
tumor growth, moreover, it completely neutralized tamoxifen’s inhibitory action in vivo.74

A common flavonol compound, kaempferol, was reported to induce apoptosis in ovarian cancer cells through p53 activation.75 Yang et al.76 reported that kaempferol inhibited quinine reductase 2 by blocking NF-κB activity. Kaempferol was shown to act as a breast cancer resistance protein (Bcrp, Abcg2) inhibitor in Madin-Darby canine kidney cell monolayers.77 Kaempferol inhibited VEGF expression, induced the phosphorylation of Akt, and modulated p53, Bad, Bax and Bcl-xl genes, all of which induce apoptosis in ovarian cancer cells.50,78

Another flavonol, myricetin, which is commonly present in fruits and vegetables, was found to exhibit an anti-angiogenic effect through the inhibition of PI3K and the suppression of matrix metalloproteinases responsible for vascular growth.137 In two cisplatin-resistant ovarian cancer cell lines, namely OVCAR-3 and A2780/CPT0, myricetin exerted a higher cytotoxic effect than cisplatin. On the other hand, it was found to be less cytotoxic to the normal ovarian cell line IOSE-364. Therefore, due to its potential cytotoxic effect and selectivity against cisplatin-resistant cancer cells, myricetin could be beneficial in overcoming cancer chemoresistance.80

According to epidemiologic studies, soy products, which are rich in isoflavonoids namely genistein, daidzein, and glycitein, have important roles in decreasing the incidence and mortality rates of breast cancer, especially by acting as natural selective ER modulators.81–86 In ER-positive breast cancer, it has been reported that estrogen receptors are over-expressed by approximately 70%. By binding ER, estrogen induces mammary cell proliferation and cell division, as well as DNA replication, and disrupts the cell cycle, apoptosis, and DNA repair, which results in tumor formation.7 Due to estrogen-antagonistic activities, these compounds decrease the risk of hormone-dependent tumors.87 Genistein regulates genes related to the cell cycle and apoptosis,88,89 and inhibits angiogenesis. A number of studies demonstrated the protective effects of genistein against ovarian cancer.89,90 Dose- and time-dependent growth inhibitory action was detected in HeLa cells treated with genistein. This activity was found to be mediated by apoptosis and cell cycle arrest at the G2/M phase. Moreover, genistein induced mitogen inibition by regulating matrix metallopeptidase (MMP)-9 and tissue inhibitors of metalloproteinases 1 expression.92 Genistein was shown to function as an inhibitor on tyrosine kinase by exerting its effect via DNA topoisomerase II inhibition.93,94 Moreover, genistein was suggested to be involved in the c-Jun N-terminal kinase (JNK) pathway in inducing the effect of AP-1.

According to several in vitro and in vivo studies, Rosmarinus officinalis L. (Lamiaceae) extracts were reported to have important roles as anti-inflammatory, anti-tumorogenic, and anti-proliferative agents.7 Anticarcinogenic activities of the extracts prepared from R. officinalis were shown in MCF-7 and MDA-MB-231 cell lines.95 As the main metabolite of the plant, rosmarinic acid displayed cytotoxic effects against two human breast cancer cell lines, adriamycin-resistant MCF-7/Adr and wild-type MCF-7/wt17, and inhibited bone metastasis from breast carcinoma through the NF-κB ligand (RANKL)/ RANK/osteoprotegerin pathway by the suppression of IL-8 expression.98 Rosmarinic acid was also reported to exert DNA methyltransferase inhibition activity, which is an important potential therapeutic feature against cancer. Co-administration of rosmarinic acid with cisplatin provided sensitivity against chemoresistant-human ovarian cancer cell lines by blocking the cell cycle and resulting in inhibition of cell proliferation and apoptosis.99,100

Cyanidins are a group of compounds from red berries including grapes, blackberry, cranberry, raspberry and red cabbage. Cyanidin-3-glucoside was reported to block ethanol-induced ErbB2/cSrc/FAK pathway activation in breast cancer cells and prevented metastasis,101 and markedly inhibited ovarian cancer cell proliferation by downregulating the expression of Mucin4 in HO-8910PM cells.102 Studies have shown that peonidin-3-glucoside and cyanidin-3-glucoside exhibited strong inhibitory activity on cell growth of breast cancer cells HS578T through G2/M arrest, regulated protein levels of CDks, and induced caspase-3 activation, chromatin condensation, as well as cell death.103

Epigallocatechin gallate (EGCG), a major catechin found in green tea, was reported to be effective in the treatment of breast cancer through the inhibition of hypoxia-inducible factor 1α and NFXB activation, as well as VEGF expression in cultured E0771 cells. In an in vivo study in mice, EGCG remarkably decreased tumor weight, tumor CD and tumor VEGF expression, but displayed no apparent activity on body and heart weight, and angiogenesis and VEGF expression in the heart and skeletal muscle.103 EGCG was also reported to be beneficial in treating cervical cancer.104 Studies that investigated the molecular mechanisms revealed that EGCG exhibited its effect by inhibiting the anti-apoptotic protein Bcl-xl.105,106 The inhibitory effect on MAPK, CDK, growth factor-related cell signaling, and induction of AP-1 and NF-κB, topoisomerase I, and matrix metalloproteinases are among the other pathways on which EGCG acts.107

Resveratrol is a stilbenic compound found mainly in red grape skin and peanuts. It was shown to have chemopreventive potential through the activation of LPS-induced NF-κB-luciferase activity at lower doses, but inhibition at higher doses through the reduction of LPS-induced κB-α phosphorylation and induction of caspase-3 activation.108 It was also shown to possess a potent growth-inhibitory effect against various human cancer cells. In a previous study, resveratrol suppressed the in vitro cellular invasion of NuTu-19 ovarian cancer cells; however, the effect was not observed in vivo.109

A metabolite derived from resveratrol, piceatannol (3,3’,4,5’-tetrahydroxy-trans-stilbene), was reported to be a potent cisplatin sensitivity enhancer in OvCA. Piceatannol induced the expression of p53-mediated pro-apoptotic protein NOXA, caspase-3 activation, and enhanced XIAP degradation through the ubiquitin-proteasome pathway, which is related to the induction of dynamin-related protein
(Drp) 1-dependent mitochondrial fission, which results in more effective apoptosis induction. In a xenograft mouse model, reduction in tumor size was recorded with the combination treatment of cisplatin and piceatannol.\textsuperscript{110} Anti-invasive, anti-adhesive, and anti-migration activity mechanisms of piceatannol in MDA-MB-231 cells were found to occur through the inhibition of MMP-9 involved in PI3K/AKT and NF-κB pathways.\textsuperscript{111} Phenethyl isothiocyanate is an effective constituent obtained from plants of the Brassicaceae family.\textsuperscript{122} Its chemopreventive potential against breast cancer cells\textsuperscript{133} and cervical cancer\textsuperscript{126} was investigated previously. Phenethyl isothiocyanate was found to have an apoptosis induction effect in chemotherapeutic drug-resistant cell lines. Phenethyl isothiocyanate enhanced death receptor (DR4 and DR5 and cleaved caspase-3 expression, induced caspase-8, and suppressed ERK1/2 and MEK phosphorylation in cervical cancer cells.\textsuperscript{115} Phenethyl isothiocyanate was also reported to exert an inhibitory effect on the adhesion and invasion of HeLa cells by G2/M phase arrest induction and CDK1, MMP2/9, CD44, intercellular adhesion molecule 1 suppression. It was considered to act via the transforming growth factor (TGF)β/Smad2 pathway, evident by increasing TGFβ, IL6, and IL8 production and Smad2 phosphorylation.\textsuperscript{116} In another study, phenethyl isothiocyanate was demonstrated to have cytotoxic potential against OVCAR-3 cells by its anti-proliferative effect in a dose-dependent manner. Apoptosis induction was through caspase-3 and -9 activation. Activation of Akt, ERK1/2, and the expression of transcription factor c-Myc were inhibited and pro-apoptotic p38 and JNK1/2 were activated by phenethyl isothiocyanate treatment.\textsuperscript{118}

Sulforaphane is an organosulfur component of cruciferous plants. Sulforaphane was demonstrated to enhance tumor suppression protein transcription. Sulforaphane also suppressed the Wnt/β-catenin self-renewal pathway in breast cancer stem cells.\textsuperscript{117} It exerted potent antiproliferative activity in the human ovarian cancer cell line SKOV3, and mouse ovarian cancer cell lines C3 and T3, through down-regulation of cell cycle transition regulators cyclin D1, CDK4, and CDK6, and identifying the Akt pathway as a target.\textsuperscript{118} Indole-3-carbinol, a constituent from Brassica sp., and its digestion metabolite, diindolylmethane, were demonstrated to have anti-cancer activities against hormone responsive cancers such as breast and ovarian cancers.\textsuperscript{119} It was also recently shown that diindolylmethane possessed higher activity than indole-3-carbinol in in vitro studies.\textsuperscript{120} It was revealed that diindolylmethane affected the NF-κB/Wnt/Akt/mTOR pathways, modulated key cytochrome CYPs enzymes, regulated angiogenesis, invasion, and metastasis, and the epigenetic behavior of cancer cells.\textsuperscript{58} Diindolylmethane and indole-3-carbinol induced HO-1 and SOD1 genes and exhibited synergistic action with isothiocyanates, such as phenethyl isothiocyanate and sulforaphane.\textsuperscript{121}

Triterpenic compounds are a broad group of triterpenoids including cucurbitanes, dammaranes, ergostanes, friedelanes, lanostanes, limonoids, lupanes, oleananes, tirucallanes, and ursanes. In vitro and in vivo studies indicated their chemopreventive and therapeutic effects on breast cancer through apoptosis, nitric oxide (NO), DR4, DR5, caspase-3/7, caspase 8, Bax, JNK, MAPK, p38 induction, and phosphor-STAT3, poly polymerase cleavage, COX-2, IL-1β, NF-κB, IkB kinase α/β, cyclin D1, cyclin A, cyclin B1, Erα protein and mRNA, human epidermal growth factor receptor 2 phosphorylation, caveolin-1, Akt, Janus Kinase 1, STAT3, Bcl2, c-Jun, c-Fos, JNK, the mechanistic target of rapamycin (mTOR) suppression, as well as cell cycle blockage.\textsuperscript{122}

Saffron is a spice from the dry stigmas of the plant Crocus sativus L., which has been traditionally used as a remedy for several problems such as cancer by ancient Arabian, Indian, and Chinese cultures. Crocetin is a carotenoid-type component of saffron, and has been demonstrated to have remarkable activity as an anti-tumor agent in in vitro and in vivo studies. Crocetin inhibits the growth of cancer cells through the inhibition of nucleic acid synthesis, induction of the antioxidative system, apoptosis, and hindering growth factor signaling pathways.\textsuperscript{123} Crocetin was shown to inhibit LPS-induced nitric oxide release, reduce the levels of TNF-α, IL-1β, and intracellular ROS, activate the NF-κB pathway, and prevent LPS-induced hippocampal cell death.\textsuperscript{124} Crocetin and its derivatives were found to have anti-proliferative effect in MCF-7 and MDA-MB-231 breast cancer cells in a dose-dependent manner.\textsuperscript{125} Crocetin displayed proapoptotic action in MCF-7 breast cancer cells through the caspase-dependent pathway by enhancing Bax protein expression.\textsuperscript{126} Crocetin analogues were shown to decrease colony formation and cellular RNA and DNA synthesis,\textsuperscript{127} as well as viability of HeLa cells.\textsuperscript{128} Besides cell growth reduction, crocetin-derived compounds including crocin, safranal, and picrocrocin, displayed apoptotic activity.\textsuperscript{129,130}

Previous studies demonstrated that Zingiber officinale Roscoe (Zingiberaceae) as one of the important plant species that possessed an inhibitory effect on ovarian cancer cell growth through the inhibition of NF-κB activation, and reduced VEGF and IL-8 secretion.\textsuperscript{130} Gingerol is the active secondary metabolite of Z. officinale. The anticarcinogenic potential of gingerol was also investigated against breast and ovarian cancers and was reported to exhibit antioxidant, anti-inflammatory, and antitumor activities by diminishing iNOS and TNF-α expression via suppression of IkB-α phosphorylation and NF-κB nuclear translocation.\textsuperscript{130,132}

Curcuminoids are the main phytoconstituents of the popular Indian plant, Curcuma longa L., one of the species from the family Zingiberaceae.\textsuperscript{7} An in vivo study revealed that curcumin prevented chemo resistance to paclitaxel treatment by downregulating NF-κB, MAPK, and Akt pathways.\textsuperscript{131} The anticancer activity of curcumin was attributed to its capacity to induce apoptosis in cancer cells without showing cytotoxic action on healthy cells. The interaction of curcumin with NF-κB indicates a relationship between its anti-inflammatory and anticarcinogenic effects.\textsuperscript{132,133} When co-administered with paclitaxel, curcumin exhibited a synergistic decrease in tumor volume and incidence in a xenograft model in nonobese diabetic/
severe combined immunodeficiency mice. Furthermore, pre-administration of curcumin to cervical cancer cells enhanced sensitivity to paclitaxel.\textsuperscript{13} The inhibitory activity of curcumin was demonstrated on ovarian tumor cell (A2780) growth using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay.\textsuperscript{136} Curcumin was shown to dose-dependently inhibit Bcl-2 and PS3 protein expressions, reduce NF-κB expression, and enhance caspase-3 expression.\textsuperscript{137} The cell growth suppression effect was supported with another type of human ovarian cancer cells (Ho-8910).\textsuperscript{138,139} Curcumin was shown to possess an mTOR inhibitory effect\textsuperscript{140} and modulatory activity on tumor cell growth via multiple cell signaling pathway regulation including cyclin D1, c-Myc, Bcl-2, Bcl-x, cFLIP, XIAP, c-IAP1, caspase-8, 3, 9, p53, p21, DR4, DR5, JNK, Akt and 5′ adenosine monophosphate-activated protein kinase.\textsuperscript{141}

Hirsutenone, a diarylheptanoid-type component of \textit{Alnus hirsuta} (Spach) Rupr. (Betulaceae) barks, was demonstrated to sensitize cisplatin-resistant ovarian and cervical cancer cells.\textsuperscript{13} Hirsutenone activated p53 through phosphorylation at Ser 15 in cells with wild-type p53, and affected p53-null and p53-mutant cell lines. These actions were reported to be partially regulated by Akt, linking hirsutenone-dependent PI3K inhibition.\textsuperscript{142}

Previous studies revealed that piperlongumine, an alkaloid-type compound from \textit{Piper longum} L., significantly and dose-dependently induced cell apoptosis, G2/M phase arrest, and intracellular ROS accumulation. Furthermore, combination therapies of low-dose piperlongumine/cisplatin or paclitaxel provided an anti-growth effect on human ovarian cancer cells. Piperlongumine also enhanced cisplatin-induced apoptosis via increased levels of Drp 1-dependent mitochondrial fission.\textsuperscript{13,203,423,43}

CONCLUSION

Gynecologic cancers occur as a result of the disruption of multicellular targets and survival signaling.\textsuperscript{13} Inflammatory pathways have been found to possess important roles during this stage. According to \textit{in vitro} and preclinical cancer prevention and treatment studies, plant extracts and their constituents have been proven to be effective such that they may be potential agents in gynecologic cancer therapy by exhibiting beneficial activities on multiple targets within various oncogenic signaling pathways including inflammation.\textsuperscript{7,143} According to several scientific reports, combination therapy of plant-based drugs with commercially used anticarcinogenic drugs has been presented as an effective approach.\textsuperscript{134} Flavonoids, cyanidins, tannins, phenolic acids, stilbenoids, organosulfur compounds, terpenoids, diarylheptanoids, and alkaloids can be counted among the phytoconstituents that exhibit anticarcinogenic effects by regulating inflammatory pathways, and could be further evaluated as novel drug candidates after clinical studies have been completed.

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