Turk J Pharm Sci 2017;14(3):324-334
DOI: 10.4274/tjps.49368

REVIEW

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

Jinekolojik Kanser Tedavisinde Sekonder Metabolitlerin Rolü: Bazı Yolaklar ve Mekanizmalar

Mürşide Ayşe DEMİREL[1], İpek SÜNTAR[2]*

[1]Gazi University, Faculty of Pharmacy, Laboratory Animals Breeding and Experimental Research Center, Ankara, Turkey
[2]Gazi University, Faculty of Pharmacy, Department of Pharmacognosy, Ankara, Turkey

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

ÖZ

Jinekolojik kanserler insanlarda ve hayvanlarda en yaygın görülen kanserler arasındadır. Tedavi başarısı tanıdaki evre, tümör tipi, orijini ve metastazı içeren birçok faktöre bağlıdır. Günümüzde bu kanserlerin tedavisinde, cerrahi müdahale, kemoterapi ve radyoterapi uygulanmaktadır. Ancak, birçok anti-karsinojenik ilaç ciddi yan etkilere neden olabilir ve ayrıca tedaviye beklenen yanıt alınamayabilir. Son yıllarda yapılan çalışmalarda kanser ve inflamasyon arasındaki ilişkinin önemi vurgulanmıştır. Ve bununla birlikte, inflamatuvar yolaklara karşı yararlı biyoaktif etkiler gösteren birçok fitokimyasalın jinekolojik kanser tedavisi için antikarsinojenik potansiyele sahip olduğu kanıtlanmıştır. Bu derlemede, jinekolojik kanserlerdeki inflamatuvar yolaklar ve bu yolaklarda etkili sekonder metabolitlerin tedavideki rolü özetlenmektedir.

Anahtar kelimeler: Jinekolojik kanserler, yolak, sekonder metabolitler, bitkisel bileşenler, inflamasyon

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[1,2]; approximately 1 in 6 deaths is due to cancer.[2] Cancer is commonly diagnosed in domestic animals as it is in humans.[3] Mammary gland tumors, skin tumors, osteosarcomas, and hemopoietic tumors are the most prevalent malignant tumors which cause mortality in dogs and cats.[4,5]

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.[6,7] 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.[8] 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.[9,10] In this study,

*Correspondence: E-mail: ipesin@gazi.edu.tr, ORCID-ID: orcid.org/0000-0003-4201-1325
Received: 15.12.2016, Accepted: 19.07.2017

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.[11-13] 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.[14] 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.[13]

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.[15] Primary ovarian tumors and uterine tumors are rarely observed in domestic animals.[16-18] The clinical signs of these tumors are generally less obvious than those of other cancers and are realized incidentally during laparatomy or ultrasonographic examination. These tumors mainly have benign character and can be treated by removing the relevant organ along with the tumor.[4,17]

Canine transmissible venereal tumor, also known as infectious sarcoma, venereal granuloma, and transmissible lymphosarcoma Sticker tumor, is a benign reticuloendothelial tumor that effects the external genitalia in both sexes, but is occasionally observed in the internal genitalia, other organs, conjunctiva mucosae, 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.[19,20]

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.[21,22] On the other hand, mammary tumors are rare in livestock.[23] 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.[4,24]

Breast cancer is the most frequent cancer in women and diagnosed in approximately 25% of all cancer types.[25] 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.[26,27]

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.[28]

Acute inflammation is the protective response of organisms against tissue destruction. Inflammation heals spontaneously after improving the tissue. However, continuation of the infection and immun 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" exibited the origin of cancer in the chronic inflammatory region.[29] 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.[30,31] TNF is a cell-signaling protein produced chiefly by effective macrophages, which are involved in systemic inflammation. It is the main mediator of binary hipaloptic apoptosis. 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.[32]

COX enzymes are bi-functional membrane-bound enzymes that are responsible for the formation of prostanoids, 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 spesific 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.[7,33,34] 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.[35]

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.[36,37] 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.[38] 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.[39] 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.[40]

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.[41] 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.[6]

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 (bortezomib) 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 additon, 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 therapeutical 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[42] 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.[43]

Effects of phytochemicals against gyecological cancers

High risk of cancers is associated with environmental factors

and unhealthy lifestyle behaviors. According to epidemiologic evidence, dietary behavior notably affects cancer prevalence.[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.[45] A number of natural compounds that have been reported to exhibit beneficial biologic effects in gynecologic cancer therapy are presented in Figure 1.

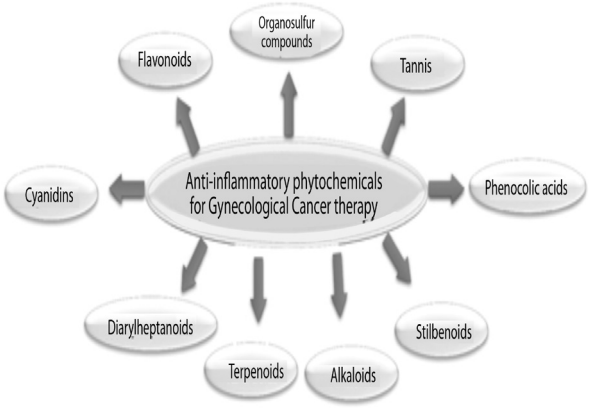

Figure 1. Secondary metabolite groups exhibiting beneficial effects in gynecologic cancer therapy

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.[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.[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.[46,48] Apigenin, a flavone-type compound widely found in fruits and vegetables, is a bioactive constituent with anti-inflammatory, antioxidant, and anticancer activities.[47] The anti-inflammatory action of apigenin was shown to supress downstream events by binding to COX-2, and to regulate mitogen-activated protein kinase (MAPK) pathways in endometrial cancer cells through its selective effect on AP-1.[13,49] Supression of procarcinogen-activating enzyme over-expression, which causes DNA mutations and induction of apoptosis through the p53-related pathway, as well as inhibition of tumor cell growth by acting as as a cytochrome P450 (CYP)-1 family enzyme inhibitor, were previously shown for apigenin treatment.[47,50] A previous study reported that apigenin showed cytotoxic action on Michigan Cancer Foundation (MCF)-7 breast cancer cell lines.[7] In addition, the anti-proliferative action of apigenin in human epidermal growth factor receptor 2 over-expressed breast cancer cells by inhibition of phosphatidylinositide 3-kinase (PI3K) activity and Akt kinase activity was also demonstrated.[51] Another study showed that intrinsic and extrinsic apoptotic pathways were involved in the induction of apoptosis by apigenin in malondialdehyde (MDA)-MB-453 human breast cancer cells.[52] Apigenin was demonstrated to down-regulate cyclin D1, D3, and cyclin-dependent kinase (CDK)4 levels, and increased p27 protein levels in breast cancer cells.[53] Through suppression of AP-1 activity, 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.[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[55], and to inhibit E2-induced DNA synthesis in MCF-7 cells.[56,57] Anti-estrogenic effects mediated through estrogen receptor (ER)-binding dependent and independent mechanisms were also revealed.[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[60], and exerted an anti-proliferative effect against SiHa human cervical cancer cells.[61] Apigenin was shown to play a beneficial role in the treatment of endometrial cancer in postmenopausal women.[46]

Luteolin, a flavonoid-type compound, possesses multiple biologic characteristics including anti-inflammatory and antioxidant properties, and displays cancer chemopreventive effect.[13] 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).[62] It was shown to have the ability to inhibit protein kinase Cε and Src kinase in the oncogenic signaling pathway.[13,63] 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.[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.[7,65-67] Fisetin inhibited the invasion and migration of cervical cancer cells by dose-dependently supressing 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.[68] Fisetin was found to display anti-inflammatory activity in lipopolysaccharide (LPS)-induced acute pulmonary inflammation, and anti-carcinogenesis action.[69,70] Fisetin demonstrated an inhibitory effect on Wnt signaling by modulating the expression of beta-catenin[71,72], and the reducing effect on NF-κB and AP-1.[7,73]

A citrus flavonoid, tangeretin, displayed inhibitory action on the growth and invasive properties of human mammary 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.[7,77] 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.[13,79] In two cisplatin-resistant ovarian cancer cell lines, namely OVCAR-3 and A2780/CP70, 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 cyle, 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], and inhibits angiogenesis. A number of studies demonstrated the protective effects of genistein against ovarian cancer.[89-91] 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 migratin 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.[7,95]

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.[96] 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/wt[97], 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[7], and markedly inhibited ovarian cancer cell proliferation by downregulating the expression of Mucin4 in HO-8910PM cells.[101] 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.[102]

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 NFκB 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.[7,107]

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 IκB-α phosphorylation and induction of caspase-3 activation.[7,108] It was also shown to possess a potent growth-inhibitory effect against various human cancer cells. In a previous study, resveratrol supressed 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.[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.[111]

Phenethyl isothiocyanate is an effective constituent obtained from plants from the Brassicaceae family.[112] Its chemopreventive potential against breast cancer cells[113,114] and cervical cancer[115] was investigated previously. Phenethyl isothiocyanate was found to have an apoptosis induction effect in chemotherapeutic drug-resistant cell lines. Phenethyl isothiocyanate enhanced death receptor (DR)4 and DR5 and cleaved caspase-3 expression, induced caspase-8, and supressed ERK1/2 and MEK phosphorylation in cervical cancer cells.[7,115] 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 supression. 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.[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.[112]

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.[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.[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.[119] It was also recently shown that diindolylmethane possessed higher activity than indole-3-carbinol in *in vitro* studies.[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.[88] Diindolylmethane and indole-3-carbinol induced *HO-1* and *SOD1* genes and exhibited synergistic action with isothiocyanates, such as phenethyl isothiocyanate and sulforaphane.[121]

Triterpenic compounds are a broad group of trepenoids including cucurbitanes, dammaranes, ergostanes, friedelanes, lanostanes, limonoids, lupanes, oleananes, tirucallanes, and ursanes. *In vitro* and *in vivo* studies indicated their chemopreventive and therapeutical 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, IκB 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.[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.[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.[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.[125] Crocetin displayed proapoptotic action in MCF-7 breast cancer cells through the caspase-dependent pathway by enhancing Bax protein expression.[126] Crocetin analogues were shown to decrease colony formation and cellular RNA and DNA synthesis[127], as well as viability of HeLa cells.[128] Besides cell growth reduction, crocetin-derived compounds including crocin, safranal, and picrocrocin, displayed apoptotic activity.[123,129]

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.[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 IκB-α phosphorylation and NF-κB nuclear translocation.[130-132]

Curcuminoids are the main phytoconstituents of the popular Indian plant, *Curcuma longa* L., one of the species from the family Zingiberaceae.[7] An *in vivo* study revealed that curcumin prevented chemoresistance to paclitaxel treatment by downregulating NF-κB, MAPK, and Akt pathways.[133] 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.[134,135] 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.[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.[136] Curcumin was shown to dose-dependently inhibit Bcl-2 and P53 protein expressions, reduce NF-κB expression, and enhance caspase-3 expression.[137] The cell growth suppression effect was supported with another type of human ovarian cancer cells (Ho-8910).[138,139] Curcumin was shown to possess an mTOR inhibitory effect[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.[141]

Hirsutenone, a diarylheptanoid-type component of *Alnus hirsuta* (Spach) Rupr. (Betulaceae) barks, was demonstrated to sensitize cisplatin-resistant ovarian and cervical cancer cells.[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.[142]

Previous studies revealed that piperlongumine, an alkaloid-type compound from *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.[13,110,142,143]

CONCLUSION

Gynecologic cancers occur as a result of the disruption of multicellular targets and survival signaling.[13] Inflammatory pathways have been found to possess important roles during this stage. According to *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.[7,43] According to several scientific reports, combination therapy of plant-based drugs with commercially used anticarcinogenic drugs has been presented as an effective approach.[144] 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.

Conflict of Interest: No conflict of interest was declared by the author.

REFERENCES

1. Dalkic E, Wang X, Wright N, Chan C. Cancer-drug associations: a complex system. PLoS One. 2010;5:e10031.
2. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1659-1724.
3. Thamm D, Dow S. How companion animals contribute to the fight against cancer in humans. Vet Ital. 2009;45:111-120.
4. Morris J, Dobson J. Small Animal Oncology. 1st ed. Blackwell Science; United Kingdom; 2001.
5. Cannon CM. Cats, cancer and comparative oncolog. Vet Sci. 2015;2:111-126.
6. Kisielewski R, Tołwińska A, Mazurek A, Laudański P. Inflammation and ovarian cancer current views. Ginekol Pol. 2013;84:293-297.
7. Wang H, Khor TO, Shu L, Su ZY, Fuentes F, Lee JH, Kong AN. Plants vs. cancer: a review on natural phytochemicals in preventing and treating cancers and their druggability. Anticancer Agents Med Chem. 2012;12:1281-1305.
8. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62:220-241.
9. Prabhu A, Venkat P, Gajaraj B, Kılıngar Nadumane V. Induction of apoptosis in the cervical cancer cell line HeLa by a novel metabolite extracted from the fungus Aspergillus japonicus Saito. Turk J Biol. 2014;38:922-929.
10. Birudu RB, Naik MJ. Anticancer properties of secondary metabolites of medicinal plants in carcinoma. Br Med Bull. 2014;2:662-668.
11. Benedet JL, Bender H, Jones H 3rd, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet. 2000;70:209-262.
12. Amant F, Van Calsteren K, Halaska MJ, Beijnen J, Lagae L, Hanssens M, Heyns L, Lannoo L, Ottevanger NP, Vanden Bogaert W, Ungar L, Vergote I, du Bois A. Gynecologic cancers in pregnancy: guidelines of an international consensus meeting. Int J Gynecol Cancer. 2009;19(Suppl 1):1-12.
13. Farrand L, Oh SW, Song YS, Tsang BK. Phytochemicals: a multitargeted approach to gynecologic cancer therapy. Biomed Res Int. 2014:2014:890141.
14. Hacker NF, Eifel PJ, van der Velden J. Cancer of the vagina. Int J Gynaecol Obstet. 2015;131(Suppl 2):84-87.
15. Lyman GH. Risk factors for cancer. Primary Care. 1992;19:465-479.
16. Gülçubuk A, Altun ED, Bozkurt ER, Sontaş BH, Haktanır D. Ovarian teratoma in a dog. Turk J Vet Anim Sci. 2012;36:573-576.
17. Demirel MA, Ergin I. Unilateral typical type serous borderline ovarian tumor in a Pointer dog. Med Weter. 2016;72:321-323.
18. Serin G, Aydogan A, Yaygingul R, Tunca R. Uterine leiomyosarcoma in a dog: a case report. Vet Med. 2010;55:405-408.
19. Mello Martins MI, Ferreira de Souza F, Gobello C. The canine transmissible venereal tumor: etiology, pathology, diagnosis and treatment. In: Concannon PW, England G, Verstegen III J, Linde-Forsberg C, eds, Recent Advances in Small Animal Reproduction, International Veterinary Information Service, Ithaca NY (www.ivis.org), 2005: A1233.0405.

20. Lopes PD, dos Santos ACAA, Silva JES. Canine transmissible venereal tumor in the genital area with subcutaneous metastases in the head - case report. RPCV. 2015;110:120-123.

21. Moulton JE. Tumours of mammary gland. In: Moulton JE. eds, Tumours in Domestic Animals. 3rd edn. Berkeley and Los Angeles; University of California Press; 1990:518-552.

22. Sleeckx N, de Rooster H, Veldhuis Kroeze EJ, Van Ginneken C, Van Brantegem L. Canine mammary tumours, an overview. Reprod Domest Anim. 2011;46:1112-1131.

23. Prpar Mihevc S, Dovč P. Mammary tumors in ruminants. Acta Agric Slov. 2013;102:83-86.

24. Port Louis LR, Varshney KC, Nair MG. An immunohistochemical study on the expression of sex steroid receptors in canine mammary tumors. ISRN Vet Sci. 2012;2012:378607.

25. Maeda S, Saimura M, Minami S, Kurashita K, Nishimura R, Kai Y, Yano H, Mashino K, Mitsuyama S, Shimokawa M, Tamura K; Kyushu Breast Cancer Study Group. Efficacy and safety of eribulin as first- to third-line treatment in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. Breast. 2017;32:66-72.

26. Robertson FM, Bondy M, Yang W, Yamauchi H, Wiggins S, Kamrudin S, Krishnamurthy S, Le-Petross H, Bidaut L, Player AN, Barsky SH, Woodward WA, Buchholz T, Lucci A, Ueno NT, Cristofanilli M. Inflammatory breast cancer: the disease, the biology, the treatment. CA Cancer J Clin. 2010;60:351-375.

27. Yeh ED, Jacene HA, Bellon JR, Nakhlis F, Birdwell RL, Georgian-Smith D, Giess CS, Hirshfield-Bartek J, Overmoyer B, Van den Abbeele AD. What radiologists need to know about diagnosis and treatment of inflammatory breast cancer: a multidisciplinary approach. Radiographics. 2013;33:2003-2017.

28. Macciò A, Madeddu C. Inflammation and ovarian cancer. Cytokine. 2012;58:133-147.

29. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357:539-545.

30. Li-Weber M. Targeting apoptosis pathways in cancer by Chinese medicine. Cancer Lett. 2013;332:304-312.

31. Bai L, Wang S. Targeting apoptosis pathways for new cancer therapeutics. Annu Rev Med. 2014; 65:139-155.

32. Wajant H. The Fas signaling pathway: more than a paradigm. Science. 2002;296:1635-1636.

33. Maturu P, Jones D, Ruteshouser EC, Hu Q, Reynolds JM, Hicks J, Putluri N, Ekmekcioglu S, Grimm EA, Dong C, Overwijk WW. Role of Cyclooxygenase-2 Pathway in Creating an Immunosuppressive Microenvironment and in Initiation and Progression of Wilms' Tumor. Neoplasia. 2017;19:237-249.

34. Verdoodt F, Kjaer SK, Friis S. Influence of aspirin and non-aspirin NSAID use on ovarian and endometrial cancer: Summary of epidemiologic evidence of cancer risk and prognosis. Maturitas. 2017;100:1-7.

35. de M Souza CH, Toledo-Piza E, Amorin R, Barboza A, Tobias KM. Inflammatory mammary carcinoma in 12 dogs: clinical features, cyclooxygenase-2 expression, and response to piroxicam treatment. Can Vet J. 2009;50:506-510.

36. Nelson DE, Ihekwaba AE, Elliott M, Johnson JR, Gibney CA, Foreman BE, Nelson G, See V, Horton CA, Spiller DG, Edwards SW, McDowell HP, Unitt JF, Sullivan E, Grimley R, Benson N, Broomhead D, Kell DB, White MR. Oscillations in NF-kappaB signaling control the dynamics of gene expression. Science. 2004;306:704-708.

37. Escárcega RO, Fuentes-Alexandro S, García-Carrasco M, Gatica A, Zamora A. The transcription factor nuclear factor-kappa B and cancer. Clin Oncol (R Coll Radiol). 2007;19:154-161.

38. Hoesel B, Schmid JA. The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer. 2013;12:86.

39. Karin M. NF-kappaB as a critical link between inflammation and cancer. Cold Spring Harb Perspect Biol. 2009;1:a000141.

40. Huber MA, Azoitei N, Baumann B, Grünert S, Sommer A, Pehamberger H, Kraut N, Beug H, Wirth T. NF-kappaB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. J Clin Invest. 2004;114:569-581.

41. Freedman RS, Deavers M, Liu J, Wang E. Peritoneal inflammation - A microenvironment for Epithelial Ovarian Cancer (EOC). J Transl Med. 2004;2:23.

42. Aherne SA, O'Brien NM. Dietary flavonols: chemistry, food content, and metabolism. Nutrition. 2002;18:75-81.

43. Johannot L, Somerset SM. Age-related variations in flavonoid intake and sources in the Australian Population. Public Health Nutr. 2006;9:1045-1054.

44. Cheung ZH, Leung MC, Yip HK, Wu W, Siu FK, So KF. A neuroprotective herbal mixture inhibits caspase-3-independent apoptosis in retinal ganglion cells. Cell Mol Neurobiol. 2008;28:137-155.

45. McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.). Phytother Res. 2006; 20: 519-530.

46. Shukla S, Gupta S. Apigenin: a promising molecule for cancer prevention. Pharm Res. 2010;27:962-978.

47. Sung B, Chung HY, Kim ND. Role of Apigenin in Cancer Prevention via the Induction of Apoptosis and Autophagy. J Cancer Prev. 2016;21:216-226.

48. Brusselmans K, Vrolix R, Verhoeven G, Swinnen JV. Induction of cancer cell apoptosis by flavonoids is associated with their ability to inhibit fatty acid synthase activity. J Biol Chem. 2005;280:5636-5645.

49. Frigo DE, Duong BN, Melnik LI, Schief LS, Collins-Burow BM, Pace DK, McLachlan JA, Burow ME. Flavonoid phytochemicals regulate activator protein-1 signal transduction pathways in endometrial and kidney stable cell lines. J Nutr. 2002;132:1848-1853.

50. Jagadeeshan S, Kunnumakkara AB, Ramachandran I, Nair SA. Anticancer aktivities of fruits and vegetables against gynecological cancers. In: Kunnumakkara AB. eds. Anticancer Properties of Fruits and Vegetables: A Scientific Review. World Scientific; Singapore; 2014:131-160.

51. Way TD, Kao MC, Lin JK. Degradation of HER2/neu by apigenin induces apoptosis through cytochrome c release and caspase-3 activation in HER2/neu-overexpressing breast cancer cells. FEBS Lett. 2005;579:145-152.

52. Choi EJ, Kim GH. Apigenin induces apoptosis through a mitochondria/caspase-pathway in human breast cancer MDA-MB-453 cells. J Clin Biochem Nutr. 2009;44:260-265.

53. Way TD, Kao MC, Lin JK. Apigenin induces apoptosis through proteasomal degradation of HER2/neu in HER2/neu-overexpressing breast cancer cells via the phosphatidylinositol 3-kinase/Akt-dependent pathway. J Biol Chem. 2004;279:4479-4489.

54. Lindenmeyer F, Li H, Menashi S, Soria C, Lu H. Apigenin acts on the tumor cell invasion process and regulates protease production. Nutr Cancer. 2001;39:139-147.

55. Choi EJ, Kim GH. Apigenin causes G(2)/M arrest associated with the modulation of p21(Cip1) and Cdc2 and activates p53-dependent apoptosis pathway in human breast cancer SK-BR-3 cells. J Nutr Biochem. 2009;20:285-290.

56. Wang C, Kurzer MS. Phytoestrogen concentration determines effects on DNA synthesis in human breast cancer cells. Nutr Cancer. 1997;28:236-247.

57. Wang C, Kurzer MS. Effects of phytoestrogens on DNA synthesis in MCF-7 cells in the presence of estradiol or growth factors. Nutr Cancer. 1998;31:90-100.

58. Collins-Burow BM, Burow ME, Duong BN, McLachlan JA. Estrogenic and antiestrogenic activities of flavonoid phytochemicals through estrogen receptor binding-dependent and -independent mechanisms. Nutr Cancer. 2000;38:229-244.

59. Long X, Fan M, Bigsby RM, Nephew KP. Apigenin inhibits antiestrogen-resistant breast cancer cell growth through estrogen receptor-alpha-dependent and estrogen receptor-alpha-independent mechanisms. Mol Cancer Ther. 2008;7:2096-2108.

60. Zheng PW, Chiang LC, Lin CC. Apigenin induced apoptosis through p53-dependent pathway in human cervical carcinoma cells. Life Sci. 2005;76:1367-1379.

61. Wu C, Chen F, Rushing JW, Wang X, Kim HJ, Huang G, Haley-Zitlin V, He G. Antiproliferative activities of parthenolide and golden feverfew extract against three human cancer cell lines. J Med Food. 2006;9:55-61.

62. Lin Y, Shi R, Wang X, Shen HM. Luteolin, a flavonoid with potential for cancer prevention and therapy. Curr Cancer Drug Targets. 2008;8:634-646.

63. Byun S, Lee KW, Jung SK, Lee EJ, Hwang MK, Lim SH, Bode AM, Lee HJ, Dong Z. Luteolin inhibits protein kinase C(epsilon) and c-Src activities and UVB-induced skin cancer. Cancer Res. 2010;70:2415-2423.

64. Ham S, Kim KH, Kwon TH, Bak Y, Lee DH, Song YS, Park SH, Park YS, Kim MS, Kang JW, Hong JT, Yoon DY. Luteolin induces intrinsic apoptosis via inhibition of E6/E7 oncogenes and activation of extrinsic and intrinsic signaling pathways in HPV-18-associated cells. Oncol Rep. 2014;31:2683-2691.

65. Gábor M, Eperjessy E. Antibacterial effect of fisetin and fisetinidin. Nature. 1966;212:1273.

66. Maher P, Dargusch R, Ehren JL, Okada S, Sharma K, Schubert D. Fisetin lowers methylglyoxal dependent protein glycation and limits the complications of diabetes. PLoS One. 2011;6:e21226.

67. Arai Y, Watanabe S, Kimira M, Shimoi K, Mochizuki R, Kinae N. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J Nutr. 2000;130:2243-2250.

68. Chou RH, Hsieh SC, Yu YL, Huang MH, Huang YC, Hsieh YH. Fisetin inhibits migration and invasion of human cervical cancer cells by down-regulating urokinase plasminogen activator expression through suppressing the p38 MAPK-dependent NF-κB signaling pathway. PLoS One. 2013;8:e71983.

69. Geraets L, Haegens A, Brauers K, Haydock JA, Vernooy JH, Wouters EF, Bast A, Hageman GJ. Inhibition of LPS-induced pulmonary inflammation by specific flavonoids. Biochem Biophys Res Commun. 2009;382:598-603.

70. Lim DY, Park JH. Induction of p53 contributes to apoptosis of HCT-116 human colon cancer cells induced by the dietary compound fisetin. Am J Physiol Gastrointest Liver Physiol. 2009;296:1060-1068.

71. Teiten MH, Gaascht F, Dicato M, Diederich M. Targeting the wingless signaling pathway with natural compounds as chemopreventive or chemotherapeutic agents. Curr Pharm Biotechnol. 2012;13:245-254.

72. Syed DN, Afaq F, Maddodi N, Johnson JJ, Sarfaraz S, Ahmad A, Setaluri V, Mukhtar H. Inhibition of human melanoma cell growth by the dietary flavonoid fisetin is associated with disruption of Wnt/β-catenin signaling and decreased Mitf levels. J Invest Dermatol. 2011;131:1291-1299.

73. Liao YC, Shih YW, Chao CH, Lee XY, Chiang TA. Involvement of the ERK signaling pathway in fisetin reduces invasion and migration in the human lung cancer cell line A549. J Agric Food Chem. 2009;57:8933-8941.

74. Bracke ME, Depypere HT, Boterberg T, Van Marck VL, Vennekens KM, Vanluchene E, Nuytinck M, Serreyn R, Mareel MM. Influence of tangeretin on tamoxifen's therapeutic benefit in mammary cancer. J Natl Cancer Inst. 1999;91:354-359.

75. Luo H, Rankin GO, Li Z, Depriest L, Chen YC. Kaempferol induces apoptosis in ovarian cancer cells through activating p53 in the intrinsic pathway. Food Chem. 2011;128:513-519.

76. Yang JH, Kondratyuk TP, Jermihov KC, Marler LE, Qiu X, Choi Y, Cao H, Yu R, Sturdy M, Huang R, Liu Y, Wang LQ, Mesecar AD, van Breemen RB, Pezzuto JM, Fong HH, Chen YG, Zhang HJ. Bioactive compounds from the fern Lepisorus contortus. J Nat Prod. 2011;74:129-136.

77. An G, Gallegos J, Morris ME. The bioflavonoid kaempferol is an Abcg2 substrate and inhibits Abcg2-mediated quercetin efflux. Drug Metab Dispos. 2011;39:426-432.

78. Lin Z, Bazzaro M, Wang MC, Chan KC, Peng S, Roden RB. Combination of proteasome and HDAC inhibitors for uterine cervical cancer treatment. Clin Cancer Res. 2009;15:570-577.

79. Jung SK, Lee KW, Byun S, Lee EJ, Kim JE, Bode AM, Dong Z, Lee HJ. Myricetin inhibits UVB-induced angiogenesis by regulating PI-3 kinase in vivo. Carcinogenesis. 2010;31:911-917.

80. Huang H, Chen AY, Ye X, Li B, Rojanasakul Y, Rankin GO, Chen YC. Myricetin inhibits proliferation of cisplatin-resistant cancer cells through a p53-dependent apoptotic pathway. Int J Oncol. 2015;47:1494-1502.

81. Kasiske BL, O'Donnell MP, Lee H, Kim Y, Keane WF. Impact of dietary fatty acid supplementation on renal injury in obese Zucker rats. Kidney Int. 1991;39:1125-1134.

82. Lee MM, Gomez SL, Chang JS, Wey M, Wang RT, Hsing AW. Soy and isoflavone consumption in relation to prostate cancer risk in China. Cancer Epidemiol Biomarkers Prev. 2003;12:665-668.

83. Lee HP, Gourley L, Duffy SW, Estéve J, Lee J, Day NE. Dietary effects on breast-cancer risk in Singapore. Lancet. 1991;337:1197-1200.

84. Magee PJ, Rowland IR. Phyto-oestrogens, their mechanism of action: current evidence for a role in breast and prostate cancer. Br J Nutr. 2004;91:513-531.

85. Peeters PH, Keinan-Boker L, van der Schouw YT, Grobbee DE. Phytoestrogens and breast cancer risk. Review of the epidemiological evidence. Breast Cancer Res Treat. 2003;77:171-183.

86. Pike AC, Brzozowski AM, Hubbard RE, Bonn T, Thorsell AG, Engström O, Ljunggren J, Gustafsson JA, Carlquist M. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. EMBO J. 1999;18:4608-4618.

87. Myung SK, Ju W, Choi HJ, Kim SC; Korean Meta-Analysis (KORMA) Study Group. Soy intake and risk of endocrine-related gynaecological cancer: a meta-analysis. BJOG. 2009;116:1697-1705.

88. Banerjee S, Kong D, Wang Z, Bao B, Hillman GG, Sarkar FH. Attenuation of multi-targeted proliferation-linked signaling by 3,3'-diindolylmethane (DIM): from bench to clinic. Mutat Res. 2011;728:47-66.

89. Andres S, Abraham K, Appel KE, Lampen A. Risks and benefits of dietary isoflavones for cancer. Crit Rev Toxicol. 2011;41:463-506.

90. Kim MK, Kim K, Han JY, Lim JM, Song YS. Modulation of inflammatory signaling pathways by phytochemicals in ovarian cancer. Genes Nutr. 2011;6:109-115.

91. Lee JY, Kim HS, Song YS. Genistein as a Potential Anticancer Agent against Ovarian Cancer. J Tradit Complement Med. 2012;2:96-104.

92. Hussain A, Harish G, Prabhu SA, Mohsin J, Khan MA, Rizvi TA, Sharma C. Inhibitory effect of genistein on the invasive potential of human cervical cancer cells via modulation of matrix metalloproteinase-9 and tissue inhibitors of matrix metalloproteinase-1 expression. Cancer Epidemiol. 2012;36:387-393.

93. Markovits J, Linassier C, Fossé P, Couprie J, Pierre J, Jacquemin-Sablon A, Saucier JM, Le Pecq JB, Larsen AK. Inhibitory effects of the tyrosine kinase inhibitor genistein on mammalian DNA topoisomerase II. Cancer Res. 1989;49:5111-5117.

94. López-Lazaro M, Willmore E, Austin CA. Cells lacking DNA topoisomerase II beta are resistant to genistein. J Nat Prod. 2007;70:763-767.

95. Gopalakrishnan A, Xu CJ, Nair SS, Chen C, Hebbar V, Kong AN. Modulation of activator protein-1 (AP-1) and MAPK pathway by flavonoids in human prostate cancer PC3 cells. Arch Pharm Res. 2006;29:633-644.

96. Yesil-Celiktas O, Sevimli C, Bedir E, Vardar-Sukan F. Inhibitory effects of rosemary extracts, carnosic acid and rosmarinic acid on the growth of various human cancer cell lines. Plant Foods Hum Nutr. 2010;65:158-163.

97. Berdowska I, Zieliński B, Fecka I, Kulbacka J, Saczko J, Gamian A. Cytotoxic impact of phenolics from Lamiaceae species on human breast cancer cells. Food Chem. 2013;141:1313-1321.

98. Xu Y, Jiang Z, Ji G, Liu J. Inhibition of bone metastasis from breast carcinoma by rosmarinic acid. Planta Med. 2010;76:956-962.

99. Tai J, Cheung S, Wu M, Hasman D. Antiproliferation effect of Rosemary (Rosmarinus officinalis) on human ovarian cancer cells in vitro. Phytomedicine. 2012;19:436-443.

100. Hossan MS, Rahman S, Bashar ABMA, Jahan R, Al-Nahain A, Rahamatullah M. Rosmarinic acid: A review of its anticancer action. World J Pharm Pharm Sci. 2014;3:57-70.

101. Zeng L, Gao J, Zhang R. [Study on anti-tumor effect of cyanidin-3-glucoside on ovarian cancer]. Zhongguo Zhong Yao Za Zhi. 2012;37:1651-1654.

102. Chen PN, Chu SC, Chiou HL, Chiang CL, Yang SF, Hsieh YS. Cyanidin 3-glucoside and peonidin 3-glucoside inhibit tumor cell growth and induce apoptosis in vitro and suppress tumor growth in vivo. Nutr Cancer. 2005;53:232-243.

103. Gu JW, Makey KL, Tucker KB, Chinchar E, Mao X, Pei I, Thomas EY, Miele L. EGCG, a major green tea catechin suppresses breast tumor angiogenesis and growth via inhibiting the activation of HIF-1α and NFκB, and VEGF expression. Vasc Cell. 2013;5:9.

104. Qiao Y, Cao J, Xie L, Shi X. Cell growth inhibition and gene expression regulation by (-)-epigallocatechin-3-gallate in human cervical cancer cells. Arch Pharm Res. 2009;32:1309-1315.

105. Leone M, Zhai D, Sareth S, Kitada S, Reed JC, Pellecchia M. Cancer prevention by tea polyphenols is linked to their direct inhibition of antiapoptotic Bcl-2-family proteins. Cancer Res. 2003;63:8118-8121.

106. Cherbonnel-Lasserre C, Dosanjh MK. Suppression of apoptosis by overexpression of Bcl-2 or Bcl-xL promotes survival and mutagenesis after oxidative damage. Biochimie. 1997;79:613-617.

107. Lambert JD, Yang CS. Mechanisms of cancer prevention by tea constituents. J Nutr. 2003;133:3262-3267.

108. Jeong WS, Kim IW, Hu R, Kong AN. Modulatory properties of various natural chemopreventive agents on the activation of NF-kappaB signaling pathway. Pharm Res. 2004;21:661-670.

109. Stakleff KS, Sloan T, Blanco D, Marcanthony S, Booth TD, Bishayee A. Resveratrol exerts differential effects in vitro and in vivo against ovarian cancer cells. Asian Pac J Cancer Prev. 2012;13:1333-1340.

110. Farrand L, Byun S, Kim JY, Im-Aram A, Lee J, Lim S, Lee KW, Suh JY, Lee HJ, Tsang BK. Piceatannol enhances cisplatin sensitivity in ovarian cancer via modulation of p53, X-linked inhibitor of apoptosis protein (XIAP), and mitochondrial fission. J Biol Chem. 2013;288:23740-23750.

111. Ko HS, Lee HJ, Kim SH, Lee EO. Piceatannol suppresses breast cancer cell invasion through the inhibition of MMP-9: involvement of PI3K/AKT and NF-κB pathways. J Agric Food Chem. 2012;60:4083-4089.

112. Satyan KS, Swamy N, Dizon DS, Singh R, Granai CO, Brard L. Phenethyl isothiocyanate (PEITC) inhibits growth of ovarian cancer cells by inducing apoptosis: role of caspase and MAPK activation. Gynecol Oncol. 2006;103:261-270.

113. Hahm ER, Singh SV. Bim contributes to phenethyl isothiocyanate-induced apoptosis in breast cancer cells. Mol Carcinog. 2012;51:465-474.

114. Moon YJ, Brazeau DA, Morris ME. Dietary phenethyl isothiocyanate alters gene expression in human breast cancer cells. Evid Based Complement Alternat Med. 2011;2011:462525.

115. Huong le D, Shim JH, Choi KH, Shin JA, Choi ES, Kim HS, Lee SJ, Kim SJ, Cho NP, Cho SD. Effect of β-phenylethyl isothiocyanate from cruciferous vegetables on growth inhibition and apoptosis of cervical cancer cells through the induction of death receptors 4 and 5. J Agric Food Chem. 2011;59:8124-8131.

116. Zhang L, Hao Q, Bao L, Liu W, Fu X, Chen Y, Wu H. Phenethyl isothiocyanate suppresses cervical carcinoma metastasis potential and its molecular mechanism. Mol Med Rep. 2014;10:2675-2680.

117. Li Y, Zhang T, Korkaya H, Liu S, Lee HF, Newman B, Yu Y, Clouthier SG, Schwartz SJ, Wicha MS, Sun D. Sulforaphane, a dietary component of broccoli/broccoli sprouts, inhibits breast cancer stem cells. 2010;16:2580-2590.

118. Chaudhuri D, Orsulic S, Ashok BT. Antiproliferative activity of sulforaphane in Akt-overexpressing ovarian cancer cells. Mol Cancer Ther. 2007;6:334-345.

119. Acharya A, Das I, Singh S, Saha T. Chemopreventive properties of indole-3-carbinol, diindolylmethane and other constituents of cardamom against carcinogenesis. Recent Pat Food Nutr Agric. 2010;2:166-177.

120. Bradlow HL, Zeligs MA. Diindolylmethane (DIM) spontaneously forms from indole-3-carbinol (I3C) during cell culture experiments. In Vivo. 2010;24:387-391.

121. Saw CL, Cintrón M, Wu TY, Guo Y, Huang Y, Jeong WS, Kong AN. Pharmacodynamics of dietary phytochemical indoles I3C and DIM: Induction of Nrf2-mediated phase II drug metabolizing and antioxidant

genes and synergism with isothiocyanates. Biopharm Drug Dispos. 2011;32:289-300.

122. Bishayee A, Ahmed S, Brankov N, Perloff M. Triterpenoids as potential agents for the chemoprevention and therapy of breast cancer. Front Biosci (Landmark Ed). 2011;16:980-996.
123. Gutheil WG, Reed G, Ray A, Anant S, Dhar A. Crocetin: an agent derived from saffron for prevention and therapy for cancer. Curr Pharm Biotechnol. 2012;13:173-179.
124. Nam KN, Park YM, Jung HJ, Lee JY, Min BD, Park SU, Jung WS, Cho KH, Park JH, Kang I, Hong JW, Lee EH. Anti-inflammatory effects of crocin and crocetin in rat brain microglial cells. Eur J Pharmacol. 2010;648:110-116.
125. Chryssanthi DG, Lamari FN, Iatrou G, Pylara A, Karamanos NK, Cordopatis P. Inhibition of breast cancer cell proliferation by style constituents of different Crocus species. Anticancer Res. 2007;27:357-362.
126. Mousavi SH, Tavakkol-Afshari J, Brook A, Jafari-Anarkooli I. Role of caspases and Bax protein in saffron-induced apoptosis in MCF-7 cells. Food Chem Toxicol. 2009;47:1909-1913.
127. Abdullaev FI, Frenkel GD. Effect of saffron on cell colony formation and cellular nucleic acid and protein synthesis. Biofactors. 1992;3:201-204.
128. Tavakkol-Afshari J, Brook A, Mousavi SH. Study of cytotoxic and apoptogenic properties of saffron extract in human cancer cell lines. Food Chem Toxicol. 2008;46:3443-3447.
129. Escribano J, Alonso GL, Coca-Prados M, Fernandez JA. Crocin, safranal and picrocrocin from saffron (Crocus sativus L.) inhibit the growth of human cancer cells in vitro. Cancer Lett. 1996;100:23-30.
130. Rhode J, Fogoros S, Zick S, Wahl H, Griffith KA, Huang J, Liu JR. Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells. BMC Complement Altern Med. 2007;7:44.
131. Lee HS, Seo EY, Kang NE, Kim WK. [6]-Gingerol inhibits metastasis of MDA-MB-231 human breast cancer cells. J Nutr Biochem. 2008;19:313-319.
132. Oyagbemi AA, Saba AB, Azeez OI. Molecular targets of [6]-gingerol: Its potential roles in cancer chemoprevention. Biofactors. 2010;36:169-178.
133. Sreekanth CN, Bava SV, Sreekumar E, Anto RJ. Molecular evidences for the chemosensitizing efficacy of liposomal curcumin in paclitaxel chemotherapy in mouse models of cervical cancer. Oncogene. 2011;30:3139-3152.
134. Bachmeier BE, Mohrenz IV, Mirisola V, Schleicher E, Romeo F, Höhneke C, Jochum M, Nerlich AG, Pfeffer U. Curcumin downregulates the inflammatory cytokines CXCL1 and -2 in breast cancer cells via NFkappaB. Carcinogenesis. 2008;29:779-789.
135. Aggarwal BB, Shishodia S. Suppression of the nuclear factor-kappaB activation pathway by spice-derived phytochemicals: reasoning for seasoning. Ann NY Acad Sci. 2004;1030:434-441.
136. Kumar SS, Surianarayanan M, Vijayaraghavan R, Mandal AB, MacFarlane DR. Curcumin loaded poly(2-hydroxyethyl methacrylate) nanoparticles from gelled ionic liquid in vitro cytotoxicity and anti-cancer activity in SKOV-3 cells. Eur J Pharm Sci. 2014;51:34-44.
137. Ganta S, Amiji M. Coadministration of Paclitaxel and curcumin in nanoemulsion formulations to overcome multidrug resistance in tumor cells. Mol Pharm. 2009; 6:928-939.
138. Crist KA, Zhang Z, You M, Gunning WT, Conran PB, Steele VE, Lubet RA. Characterization of rat ovarian adenocarcinomas developed in response to direct instillation of 7,12-dimethylbenz[a]anthracene (DMBA) coated suture. Carcinogenesis. 2005;26:951-957.
139. Hamam F. Curcumin: New weapon against cancer. Food and Nutrition Sciences. 2014;5:2257-2264.
140. Beevers CS, Chen L, Liu L, Luo Y, Webster NJ, Huang S. Curcumin disrupts the Mammalian target of rapamycin-raptor complex. Cancer Res. 2009;69:1000-1008.
141. Ravindran J, Prasad S, Aggarwal BB. Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? Aaps J. 2009;11:495-510.
142. Farrand L, Kim JY, Byun S, Im-aram A, Lee J, Suh JY, Lee KW, Lee HJ, Tsang BK. The diarylheptanoid hirsutenone sensitizes chemoresistant ovarian cancer cells to cisplatin via modulation of apoptosis-inducing factor and X-linked inhibitor of apoptosis. J Biol Chem. 2014;289:1723-1731.
143. Farrand L, Kim JY, Im-Aram A, Suh JY, Lee HJ, Tsang BK. An improved quantitative approach for the assessment of mitochondrial fragmentation in chemoresistant ovarian cancer cells. PLoS ONE. 2013;8:e74008.
144. Kma L. Roles of plant extracts and constituents in cervical cancer therapy. Asian Pacific J Cancer Prev. 2013;14:3429-3436.