Plant-Derived Natural Products in the Treatment of Cancer

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Cervical cancer is the second most common gynecological malignancy globally; it seriously endangers women's health because of its high morbidity and mortality. Conventional treatments are prone to drug resistance, recurrence and metastasis. Therefore, there is an urgent need to develop new drugs with high efficacy and low side effects to prevent and treat cervical cancer. In recent years, plant-derived natural products have been evaluated as potential anticancer drugs that preferentially kill tumor cells without severe adverse effects. A growing number of studies have shown that natural products can achieve practical anti-cervical-cancer effects through multiple mechanisms, including inhibition of tumor-cell proliferation, induction of apoptosis, suppression of angiogenesis and telomerase activity, enhancement of immunity and reversal of multidrug resistance. This paper reviews the therapeutic effects and mechanisms of plant-derived natural products on cervical cancer and provides references
for developing anti-cervical-cancer drugs with high efficacy and low side effects.

Flavonoids cancer

1. Flavonoids

Flavonoids are phenolic phytochemicals that are commonly found in fruits, vegetables and plant-based beverages (e.g., green tea and wine) [1]. More than 8000 species have been identified and isolated from plants. Their structures consist of C_6-C_3-C_6 skeletons labeled with A, B and C rings, which can be classified into flavones, flavanones, flavonols, flavanols, isoflavones and anthocyanidins based on their structural diversity [2][3]. Many studies have reported that flavonoids have a significant role in tumor prevention and treatment attributed to their wide range of biological activities, such as anti-inflammatory, antioxidant, anti-hyperlipidemic, anti-fatigue, anti-aging, etc. [4][5][6]. In addition, they can induce apoptosis of tumor cells by inhibiting various pro-cancer pathways and genes in tumor cells.

2. Flavones in the Treatment of Caner

Scutellaria baicalensis is one of the versatile herbs traditionally and has been used in China to treat inflammatory diseases, hypertension, cardiovascular diseases, bacterial and viral infections. A large amount of evidence suggests that *S. baicalensis* also has potent anticancer activity, and its main bioactive components are baicalein, Wogonin, and baicalin [7][8]. Baicalein is a flavonoid derived from the roots of *S. baicalensis* and has a variety of

pharmacological activities, which can inhibit cell proliferation and migration; induce apoptosis and cell-cycle arrest [9]. Cyclin D1 is a potential therapeutic target for cervical cancer. Baicalein inhibits cyclin D1 overexpression and arrests the cell cycle at G0/G1 phase through Wnt/β-catenin and protein kinase B/glycogen synthase kinase-3β (AKT/GSK-3β) signaling pathways to suppress proliferation and induce apoptosis of human cervical cancer HeLa and SiHa cells [10][11]. According to reports, baicalein inhibited tumor necrosis factor alpha (TNF-α)-induced the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the expression of apoptosis protein 1 (cIAP-1), cIAP-2, FLIP, B-cell lymphoma 2 (Bcl-2), matrix metalloproteinase 2 (MMP2), MMP9, first apoptosis signal receptor (Fas), FasL, caspase 8 and vascular endothelial factor (VEGF) in a dose-dependent manner to suppress HeLa cell invasion and migration. On the other hand, baicalein blocked TNF-α-induced nuclear translocation of p65 through inhibiting the phosphorylation and degradation of the inhibitory subunit of NF-κB (IκBα), activated caspase 8 and promoted the cleavage of poly (ADP-ribose) polymerase (PARP) expression to induce apoptosis in HeLa cells. In addition, baicalein had strong anti-inflammatory activity by inhibiting the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2) and p38, which reduced the expression of the inflammatory cytokines, including interleukin 8 (IL-8) and monocyte chemoattractant protein 1 (MCP1) [12][13][14]. Moreover, baicalein inactivated the AKT/mammalian target of rapamycin (mTOR) pathway by targeting the circHIAT1/miR-19a-3p axis to inhibit the proliferation of cervical cancer cells [15]. Another study illustrated that baicalin significantly suppressed cervical cancer xenograft tumor growth and metastasis in vivo through intraperitoneally injecting 10 mg/kg/d baicalin for four weeks. It was also reported that baicalein downregulated the expression of long non-coding RNA (lncRNA) in a dose- and time-dependent manner and named baicalein down-regulated long non-coding RNA (BDLNR). As it physically bound itself to Y-box binding protein 1 (YBX1), recruited YBX1 to the PIK3CA promoter, and it mediated the anti-cancer effects of baicalein in cervical cancer via activating PI3K/Akt pathway [16]. It is suggested that BDLNR may be a potential therapeutic target to enhance the anticancer effect of baicalein.

Wogonin is a natural monoflavonoid with the potential for selective tumor therapy in vitro and in vivo [17]. Wogonin could decrease the expression of HPV oncoproteins E6 and E7 and induce apoptosis in SiHa and CaSki cells through the mitochondria-mediated pathway, thus reducing mitochondrial membrane potential (MMP); elevating the Bcl-2-associated X protein (Bax)/Bcl-2 expression ratio; leading to cytochrome c (Cyt c) release; and triggering the cleavage of caspase 3, caspase 9 and PARP [18]. Wogonin also inhibited HeLa cell proliferation by inducing G1-phase cell-cycle arrest and apoptosis via decreasing the expression of cyclin D1, cyclin-dependent kinase 4 (CDK 4), pRb and nuclear transcription factor E2F-1, as well as increasing the expression of cyclin-dependent kinase inhibitor 1A/CDK-interacting protein 1(p21cip1) at the mRNA and protein levels through a p53-dependent mechanism [19]. Moreover, wogonin can enhance the effect of cisplatin on the induction of cancer cell apoptosis through reactive oxygen species (ROS)-dependent mechanism [20]. The results indicate that wogonin is a potential anticancer agent.

Apigenin is an edible natural flavonoid found in various dietary plant foods, such as vegetables and fruits [21]. It has a strong inhibitory effect on tumor-cell viability in vivo and in vitro. Its derivative apigenin 7-glucoside has anti-inflammatory, antioxidant and anticancer activities [22]. Apigenin 7-glucoside significantly suppressed the proliferation of HeLa cells, and the IC_{50} value at 48 h was 47.26 μmol/L. It induced apoptosis in HeLa cells through

the death receptor pathway and the mitochondrial pathway, which effectively increased the expression of ROS, Fas, FasL, TNF-α, TNF-r1, Fas-associated death domain (FADD), TNF receptor-associated death domain (TRADD), caspase 3 and caspase 9 and decreased the expression of pro-caspase 8, caspase 10, Bcl-2 and Bcl-2 extra-large protein (Bcl-xl). Additionally, apigenin 7-glucoside treatment increased p16 INK4A expression and reduced Cyclin (A, D, E) and CDK2/6 expression. Meanwhile, it inhibited HeLa cell migration by targeting the phosphatase and tensin homolog (PTEN)/PI3K/AKT pathway [23]. Some studies reported that apigenin showed selective sensitivity for human cervical cancer HeLa, SiHa, CaSki and C33A cells with IC_{50} values of 10, 68, 76 and 40 μmol/L, respectively. Apigenin also induced mitochondrial redox damage, decreased MMP and lipid peroxidation and inhibited the migration and invasion of cervical cancer cells [24]. Zhang et al. found that Apigenin suppressed cervical tumor growth in vivo by attenuating histamine-induced abnormal estrogen receptor signaling by increasing the estrogen receptor β/estrogen receptor α (ERβ/ERα) ratio when tumor model mice were administered intraperitoneally with 100 mg/kg apigenin +1 mg/kg histamine every 3 d. Moreover, apigenin induced autophagy and apoptosis in HeLa cells through the PI3K/AKT/mTOR signaling pathway [25]. Consequently, apigenin and its derivatives may prevent the development and progression of cervical cancer and represent promising drugs for cervical cancer therapy.

Luteolin is a common plant flavonoid found in various plants, including fruits, vegetables and medicinal herbs. Luteolin-rich plants have been used to treat multiple diseases, such as hypertension, cancer and inflammation [26] [27]. Luteolin could dose-dependently reduce the proliferation of HeLa cells with IC_{50} value of 21.8 μmol/L. Luteolin induced apoptosis and G2/M phase cell-cycle arrest in HeLa cells by downregulating UHRF1 and DNA methyltransferase 1 (DNMT1) with a reduction of overall DNA methylation and upregulating p16 INK4A expression [28]. On the other hand, luteolin promoted apoptosis by inhibiting TNF-α-induced NF-κB activation, downregulating A20 and c-IAP1 gene expression and enhancing c-Jun N-terminal kinase (JNK) activity [29]. It was also reported that luteoloside inhibited HeLa cell proliferation by endogenous and exogenous pathways, which increased the ratio of Bax/Bcl-2 to reduce MMP and release Cyt c, upregulated Fas expression and activated caspase 8 and caspase 3. At the same time, luteoloside inhibited mTOR and activated p38 mitogen-activated protein kinase (MAPK) signaling pathways to exert anti-cervical-cancer effects [30]. In addition, luteolin combined with TNF-related apoptosis-inducing ligand (TRAIL) synergistically induced apoptosis in HeLa cells through upregulation of death receptor 5 (DR5) and Bid cleavage, and activation of caspase-8 [31]. These data suggest that luteolin may serve as a new therapeutic strategy for cervical cancer.

3. Flavanones

Citrus fruits are rich in flavonoids and are known for their health-promoting and chemopreventive properties. Naringin, a flavonoid glycoside, can be isolated from citrus fruits, such as orange, tangerine, lemon and lime, and has several pharmacological activities [32]. Naringin can significantly reduce cancer cell viability and proliferation without toxicity to normal tissue cells [33]. The IC_{50} values of naringin for HeLa, SiHa and C33A cells after 24-h treatment were 793, 764 and 745 μmol/L, respectively, and showed a dose-dependent relationship. Naringin increased the level of endoplasmic reticulum (ER) stress sensors, phosphorylated eIF2α and activated the

apoptosis-related protein CHOP and other associated pro-apoptotic proteins (PARP1). Importantly, naringin also blocked the β-catenin signaling pathway by decreasing β-catenin (Ser576) and GSK-3β (Ser9) protein expression and phosphorylation and induced cell-cycle arrest at G0/G1 phase by increasing the expression of cell-cycle checkpoint proteins p21/cip and p27/kip to trigger apoptosis in cervical cancer cells [34]. Another study reported that naringin promoted the expressions of caspases (3, 8 and 9), p53, Bax, Fas death receptor and its adaptor protein FADD to induce apoptosis in HeLa cells through the death receptor pathway and the mitochondrial pathway. The activation of the exogenous pathway was associated with increased caspase 8, which activated the death receptor by cleaving Bid into tBid and the crosstalk between the death receptor and mitochondrial pathways [35]. Moreover, naringin also induced growth inhibition and apoptosis in HeLa cells by decreasing the expression of NF-κBp65, COX-2 and caspase 1 [36]. The results suggest that naringin is a potentially effective drug for treating human cervical cancer.

Hesperidin is a citrus flavonoid and has various functions, including antioxidation, antitumor and anti-angiogenesis functions, which can protect mitochondrial membranes from free radical attack and inhibit tumor-cell migration and invasion [37][38]. Hesperetin inhibited the cell viability of SiHa cells in a dose- and time-dependent manner with IC_{50} values of 650 μmol/L. Hesperetin induced cell-cycle arrest at G2/M phase and apoptosis in SiHa cells by death receptor and mitochondrial pathways, characterized by depolarizing MMP and increasing the expression of caspase 3, caspase 8, caspase 9, p53, Bax, Fas and FADD [39]. In addition, hesperidin inhibited HeLa cell proliferation and induced apoptosis through ER stress and mitochondria-mediated pathways via decreasing the expression of cyclin D1, cyclin E1 and CDK2, promoting Cyt c release, and activating the expression of apoptosis-inducing factor (AIF), GADD153/CHOP and glucose-regulated protein of 78 kDa (GRP78) [40]. Hesperidin has potential in preventing and treating cervical cancer and may open new avenues for cancer treatment.

Silibinin is a bioactive polyphenolic flavonoid isolated from the fruits and seeds of *silybum marianum*. It has been used to treat various diseases, especially the liver, gallbladder and kidney [41][42]. *Silibinin* inhibited the growth of Hela and SiHa cells in a dose- and time-dependent manner, with IC_{50} values of 332 and 275 μmol/L for HeLa cells, and 250 and 195 μmol/L for SiHa cells at 48 h and 72 h, respectively. It reduced ATP content, mtDNA copy number and MMP, activated the dynamin-related protein 1(Drp1)-mediated mitochondrial fission pathway, induced G2/M cell-cycle arrest through reducing the expression of CDK1, cyclin B1 and Cdc25C [43]. S*ilibinin* also suppressed angiogenesis and promoted apoptosis in HeLa cells through inhibiting the mTOR/p70S6K/4E-BP1 signaling pathway and decreasing the accumulation and transcriptional activity of hypoxia-inducible factor-1α (HIF-1α) and the release of VEGF. Moreover, the anti-angiogenic ability of s*ilibinin* was enhanced by blocking AKT activation through PI3K/AKT inhibitor LY294002 [44]. At the same time, s*ilibinin* induced apoptosis in HeLa cells through the mitochondrial pathway and the death-inducing pathway, resulting in decreased expression of CDK1 and CDK2 proteins and increased ratio of Bax/Bcl-2, followed by Cyt c release and activation of caspase 9, as well as increased expression of Fas and FasL and activation of caspase 8 [45]. The evidence has shown that hydroxyl radical (-OH) is the main form of s*ilibinin*-induced ROS [46]. S*ilibinin* inhibits HeLa cell growth by activating apoptotic vesicles and caspase 3, and promoting the phosphorylation of p53 and JNK in a dose-dependent manner. p53 subsequently interferes with mitochondrial function through the p53-upregulated modulator of apoptosis (PUMA) pathway, which upregulates the Bax/Bcl-2 ratio, reduces MMP and increases ROS production. Then ROS induces

autophagy and apoptosis in HeLa cells. Furthermore, p53-mediated glutathione (GSH) depletion significantly enhanced the cytotoxicity of NO in HeLa cells [47][48]. It may be a classical candidate for the design of anticancer drugs.

4. Flavonols

Kaempferol is a natural flavonol and widely distributes in many plant families. The growing evidence has shown that kaempferol is a potential cancer therapeutic agent with potent antitumor, anti-inflammatory and antioxidant properties [49]. It inhibited SiHa cell growth and proliferation in a dose- and time-dependent manner, and promoted SiHa cell apoptosis by disrupting MMP and elevating intracellular free Ca^{2+} concentration, which caused shrinkage of spindle-shaped SiHa cells and damage of their microtubule networks [50]. Another study showed that Kaempferol inhibited HeLa cell growth in a time- and concentration-dependent manner and the IC_{50} value was 10.48 μmol/L at 72 h, while it had weak toxicity for normal cells with IC_{50} value of 707 μmol/L at 72 h. It induced apoptosis and senescence in HeLa cells by inhibiting PI3K/AKT pathway and human telomerase reverse transcriptase (hTERT) expression and promoting the p53 pathway [51]. Telomerase is considered a new and potentially selective target for tumor therapy. Telomerase inhibition by kaempferol may provide a safe and effective approach for the treatment of cervical cancer. Additionally, overexpression of P-glycoprotein (P-gp) causes efflux of chemotherapeutic drugs from cells and is considered to be one of the crucial mechanisms of multidrug resistance (MDR) in cancer [52]. It was reported that kaempferol significantly decreased the activity and function of P-gp in MDR human cervical cancer KB-V1 cells in a dose-dependent manner, reduced drug efflux, improved sensitivity to chemotherapeutic drugs vinblastine and paclitaxel as well as cytotoxicity, which in turn induced apoptosis and reversed MDR in KB-V1 cells [53]. Kaempferol might be a potential candidate for the prevention and treatment of cancer due to its safety and low-cost advantages.

Quercetin is a dietary polyphenolic compound with wide distribution in vegetables and fruits and has various activities, including anti-allergic, anti-inflammatory and antitumor activities [54][55]. Quercetin can suppress tumor-cell proliferation and induce apoptosis, cell-cycle arrest and DNA damage through intrinsic apoptosis pathway, which involved in PI3K, MAPK and Wnt [56]. Priyadarsini et al. showed that quercetin could target both opposing signaling pathways, p53 and NF-κB to inhibit the proliferation of HeLa cells [57]. Quercetin induced apoptosis of HeLa and SiHa cells by blocking the interaction of E6/E6AP complex, reactivating p53 and upregulating the expression of transcriptional target p21 [58]. Further, quercetin promoted apoptosis and reduced migration of HeLa cells within 18 h by downregulating the expression of AKT and Bcl-2, and blocked the cell cycle at the G2/M phase. The accumulation of ROS increased Cyt c release and MMP depolarization and activated caspase 3, which in turn exhibited significant anti-proliferative and pro-apoptotic effects on HeLa cells [59]. Interestingly, the combination of quercetin with other chemical agents effectively enhanced the antitumor effect. Quercetin inhibited the viability of HeLa and SiHa cells in a dose- and time-dependent manner, with an IC_{50} of 30 μmol/L for HeLa cells at 24 h and 50 μmol/L for SiHa cells at 48 h. Treatment with cisplatin or quercetin alone did not reduce the expression of MMP2 protein in cervical cancer cells but their combination significantly decreased MMP2 expression, which inhibited the migration and invasion of cervical cancer cells. Meanwhile, quercetin enhanced the chemosensitivity of cervical

cancer cells by downregulating the expression of P-gp and methyltransferase-like 3 (METTL3), which mediated HeLa cell proliferation and apoptosis [60]. Quercetin also increased the sensitivity of HeLa cells to cisplatin by inhibiting the expression of the multidrug resistance-associated protein (MRP) and heat shock protein Hsp72, which induced apoptosis and reversed cellular resistance [61]. These studies provided the experimental basis for the treatment of cisplatin-resistant patients.

Fisetin is a natural flavonols found in vegetables, fruits and nuts and has antitumor, anti-invasive, anti-angiogenic, antidiabetic, cardioprotective and neuroprotective activities [62][63]. Fisetin suppressed urokinase-type plasminogen activator (u-PA) expression by blocking the phosphorylation of p38 MAPK and the nuclear translocation of NF-κB, which inhibited the migration and invasion of SiHa cells. Moreover, the addition of the p38 MAPK inhibitor SB203580 further enhanced the inhibitory effect of fisetin on u-PA activity and expression [64]. It was also reported that fisetin not only promoted apoptosis protease activating factor-1 (Apaf-1) expression and Cyt c release to activate caspase 3 and caspase 9 but also inhibited ERK1/2 phosphorylation, COX-2 expression and prostaglandin E2 (PGE2) production by blocking the NF-κB/p300 signaling pathway, which in turn promoted HeLa cell apoptosis [65]. Furthermore, fisetin significantly inhibited the growth rate of tumors with inhibition rates of 82.65% and 92.62% in a mouse model of HeLa cell line injection without significant side effects [66]. It was also experimentally proven that fisetin combined with sorafenib could activate the DR5-mediated death receptor pathway and mitochondria-dependent pathway, which upregulated Bax/Bcl-2 ratio and promoted MMP depolarization, caspase 3/caspase 8 activation and PARP cleavage to induce apoptosis in HeLa cells [67]. Fisetin is expected to be an anticancer drug for the clinical treatment of cervical cancer.

5. Flavanols

Green tea (*Camellia sinensis*) is one of the most commonly used herbs globally and is widely known for its effectiveness in preventing chronic diseases and tumors. This is mainly attributed to the biologically active catechin compounds in green tea, such as (−)-epigallocatechin gallate (EGCG), (−)epigallocatechin 3-gallate (ECG), (−)epigallocatechin (EGC) and (+) catechin. Among them, EGCG is the main component of catechins and has substantial antioxidative, antitumor and anti-angiogenic effects [68][69]. After treatment with 150 and 300 μg/mL of catechin for 72 h, apoptosis rates of SiHa cells reached 31.62% and 34.8%, with an IC_{50} value of 196.07 μg/mL. In addition, catechin inhibited the proliferation and induced apoptosis of SiHa cells partly by regulating TP53 and caspase 3, caspase 8 and caspase 9 [70]. EGCG concentration- and time-dependently inhibited HeLa cell proliferation with an IC_{50} value of 20 μg/mL. EGCG inhibited the activation of AKT and NF-κB by blocking the phosphorylation and degradation of the inhibitory κBα and κBβ subunits to result in the downregulation of COX-2 expression. Furthermore, EGCG treatment led to mitochondrial dysfunction through increasing ROS production, p53 and Bax/Bcl-2 ratios to promote Cyt c release and activation of caspase cascade, which induced apoptosis in HeLa cells [71]. Recently, one study indicated that EGCG inhibited transforming growth factor-β (TGF-β)-induced epithelial-mesenchymal transition (EMT) in Hela and SiHa cells via the ROS/Smad signaling pathway to inhibit cell migration and invasion [72]. Besides, EGCG can be used as an anti-angiogenic agent in the treatment of cervical cancer. EGCG significantly suppressed hypoxia and serum-induced accumulation of HIF-1a protein, as well as the

expression of VEGF by blocking PI3K/Akt/mTOR and ERK1/2 signaling pathways, thereby inhibiting HeLa cell angiogenesis [73]. Meanwhile, EGCG enhances the sensitivity of cisplatin to cervical cancer cells by inhibiting the mTOR signaling pathway and the levels of p-p70S6K1 and p-4E-BP1, which in turn inhibits cell viability and induces apoptosis in HeLa cells [74]. It has also been shown that EGCG can induce apoptosis in HeLa cells by inhibiting telomerase activity [75]. It is suggested that telomerase inhibition may be one of the critical mechanisms of EGCG treatment.

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