Effects of Genipin on Various Cancers

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Genipin is a protein cross-linking agent extracted from Gardenia (*Gardenia jasminoides* Ellis) fruits. This fruit has conventionally been used as a Chinese herbal medicine for the treatment of inflammation and jaundice and as an edible colorant in oriental countries. Uncoupling protein (UCP)-2 is a member of the family of uncoupling proteins, which are anion transporters positioned in the mitochondrial inner membrane. Genipin has been shown to have hepatoprotective activity, acting as an effective antioxidant and inhibitor of mitochondrial UCP2, and is also reported to exert significant anticancer effects.

genipin uncoupling protein-2 cancer cell metabolism reactive oxygen species

1. Effects of Genipin on Breast Cancer

Genipin inhibits the growing of cisplatin and tamoxifen-sensitive MCF-7 and T47D breast cancer cells by inhibiting UCP2 and inducing apoptosis and autophagy. The authors stated that UCP2 could be a therapeutic target in breast cancer patients treated with tamoxifen [1]. In another study, genipin modulated glucose metabolism and mitochondrial function in T47D breast cancer cells [2]. In this research, FDG uptake, glycolytic flux and mitochondrial oxidative respiration were repressed by genipin. [2]. In highly invasive triple-negative breast cancer MDA MB-231 cells, genipin induced apoptosis and repressed invasion and migration [3].

UCP2 over-expression also stimulates the growth of tumors in orthotopic xenograft models. MCF7-parental or MCF7-UCP2 over-expressing cells were inoculated orthotopically into the mammary fat pad of female nude mice two days after subcutaneous implantation of 17β-estradiol pellets. Tumor size was significantly greater in MCF-7-UCP2 over-expressing cells compared to MCF-7 parental cells [4].

In a recent study, a HER2-positive BT474 cell line showed that trastuzumab treatment induced the phosphorylation of HER2 and the overexpression of UCP2, and that the latter could be reversed by HER2 selective kinase inhibitor ONT-380. Moreover, UCP2 inhibitor genipin significantly enhanced the proliferation suppression effects of trastuzumab and markedly promoted apoptosis [5].

2. Effects of Genipin on Gastrointestinal Cancers

In AGS human gastric cancer cells, genipin repressed cell growth and induced caspase-3-dependent apoptosis [6] [7]. Genipin also reduced the p53-independent early growth response-1 (Egr1)/p21 signaling pathway in a concentration-dependent manner [6]. In a study by Kim et al., it was determined that genipin at low doses brought

nuclear factor-erythroid-2-related factor 2 (Nrf2), upregulated glutathione peroxidase, and reduced the ROS levels. However, at high doses, genipin induced cytotoxicity in the AGS cell line [8].

In Epstein–Barr virus (EBV)-associated gastric cancer SNU719 cells, genipin showed significant cytotoxicity, induced methylation on EBV C promoter and tumor suppressor gene BCL7A, arrested cell-cycle progress (S phases), upregulated EBV latent/lytic genes, stimulated EBV progeny production, activated EBV F promoter for EBV lytic activation, and suppressed EBV infection [9].

Genipin either alone or in combination with cisplatin inhibited HCT-116 colon cancer growth by suppressing UCP2-mediated proton leaks, promoted reactive oxygen species (ROS) formation, and sensitized cells to cisplatin [10].

3. Effects of Genipin on Hepatic Cancers

In Hep3B hepatocellular carcinoma (HCC) cells, genipin induced apoptosis through NADPH oxidase-ROS-cJUN NH2-terminal kinase (JNK)-dependent activation of the mitochondrial apoptotic pathway [11]. In HepG2 and MHCC97L metastatic HCC cells, genipin treatment constrained the cellular growth and proliferation, invasion, and migration by the inhibition of MMP-2 [12]. Additionally, the anti-metastatic properties of genipin have also been investigated in in vivo models. Mice with orthotopic implantation of HCC demonstrated significant tumor size reduction without any significant change in body weight. The dissected hepatic tissue showed obvious tumor cell invasion into blood vessels in the control mice, whereas no potent intrahepatic vascular invasion was observed in the genipin-treated mice [12]. In another orthotopic HCC-implantation mouse model, oral administration of genipin significantly diminished tumor size without any obvious toxic pathologic change of lung, kidney and gastrointestinal tracts [13].

In addition, the numbers of CD31- and Ki67-positive cells within HCC were decreased significantly, implying inhibitory effects of genipin on angiogenesis and cellular proliferation of cancers. Furthermore, penetration of tumor-associated macrophages (TAMs) was repressed by genipin usage, which was due to its role in inactivation of inositol-requiring 1alpha (IRE1α) proteins existing on TAMs. As IRE1α brings activation of nuclear factor kappa B (NF-κB) signaling and xbox binding protein (XBP) silencing, the administration of genipin reduces inflammation in the HCC microenvironment [13].

In HCC cells, genipin suppresses STAT3 phosphorylation and nuclear translocation, which might be attributed to the binding capacity of this compound to the Src homology-2 (SH2) domain of STAT3. In addition, the therapeutic effects of genipin in a patient-derived HCC xenograft nude mice model were demonstrated [14].

4. Effects of Genipin on Pancreatic Cancer

Interestingly, Pozza et al. revealed that UCP2 inhibition by either genipin or UCP2-specific siRNA synergistically reversed gemcitabine resistance, enhanced the activity of gemcitabine, and induced apoptosis of pancreatic cancer cells [15]. In this research, the role of UCP2 was linked for the first time to the development of chemotherapy

resistance to gemcitabine. Therefore, UCP2 can be a potential biomarker for cancer resistance [15]. In pancreatic adenocarcinoma cells, genipin or UCP2 siRNA repressed cell proliferation, induced nuclear translocation of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and increased the expression of the autophagic marker LC3-II and autophagosomes. In addition, genipin potentiated the cytotoxic activity of gemcitabine and induced autophagic cell death [16].

In another study using pancreatic cell lines, 19 proteins were recognized as differentially expressed in Panc1 and PaCa44 cells by 2D gel electrophoresis after genipin treatment. Interestingly, UCP2 sensitized pancreatic cancer cells to the glycolytic inhibitor 2-deoxy-D-glucose, and cell growth inhibition by genipin was reversed in cells transfected with siUCP2 [17].

5. Effects of Genipin on Hematologic Malignancies

Genipin was reported to abrogate the STAT3 pathway in multiple myeloma and lymphoma cells through the upregulation of Src homology2 domain-containing phosphatase 1 (SHP-1), the endogenous inhibitor of STAT3 [18][19][20][21]. Genipin was also identified to downregulate STAT3-regulated gene products like Bcl-2, Bcl-xL, surviving, cyclin D1, and vascular endothelial growth factor, and induce apoptosis in U266, U937, and MM1S cells. Furthermore, genipin increased the cytotoxic effect of the standard chemotherapeutic agents, such as bortezomib, thalidomide, and paclitaxel in U266 myeloma cells [18].

Genipin inhibited cellular proliferation of K562 leukemia cells by the activation of caspase-3 and G2/M phase cell cycle arrest [22]. In another report, genipin sensitized HL-60/MX2 multidrug-resistant leukemia cells to chemotherapeutic agents such as doxorubicin and epirubicin [23].

In a recent study, novel bacterial magnetic nanoparticles holding genipin, cytosine arabinoside (Ara-C), and poly-l-glutamic acid (PLGA) inhibited the growth of HL-60 leukemia cells and brought rapid cell death [24]. In another recent study by Long et al., genipin was mixed with poly-l-glutamic acid (PLGA) as dual crosslinkers, to which cytosine arabinoside and daunorubicin were appended to produce genipin-PLGA-modified bacterial magnetosomes. When the drug-loaded magnetosomes were administered to an in vitro model of HL-60 leukemia cells, the nanoparticles showed a potent cytotoxic effect with an inhibition rate of 96% [25].

6. Effects of Genipin on Lung Cancer

In non-small cell lung cancer H1299 cells, genipin dose-dependently induced apoptosis was related to a rise in caspase-3 and caspase-9, cytochrome c, and Bax/Bcl-2 ratio [26]. In a urethane-induced carcinogenesis animal model, the administration of 50 mg/kg genipin for eight weeks significantly decreased the incidence of pulmonary adenoma from 100% to 60% and 45% in BALB/c and C57BL/6 mice, respectively. Additionally, fewer tumors were observed in the lungs of the mice [27]. The effect of genipin could be associated to its targeting of UCP2, as demonstrated by reduced UCP staining observed in the histopathological analysis of lung tissues, supplemented by reduced complex IV (cytochrome c oxidase) staining [27]. In another study, optimized gemcitabine (Gem)-loaded

gelatin nanocarriers (GNCs) crosslinked with genipin (Gem-GNCs) showed selective cytotoxicity to H460 lung cancer cells but revealed lower cytotoxicity in A549 lung cancer cells [28]. In another study using A549 cells, genipin treatment reduced glucose consumption, increased ROS production, and decreased cellular survival. Combining genipin and elesclomol, an investigational drug that exerts potent anticancer activity through an increase in ROS, and a further reduction in glucose uptake and increased cellular and mitochondrial ROS production were observed. Co-treatment with genipin and elesclomol reduced colony forming capacity and cell survival. Suppression of cell survival by treatment with elesclomol and genipin was enhanced in the presence of an exogenous ROS inducer and attenuated by an ROS scavenger. The cytotoxic effects of combined genipin and elesclomol were accompanied by reduced mitochondrial membrane potential and occurred through apoptosis as demonstrated by the Annexin V assay and increased protein cleavage of PARP and caspase-3. In an A549 xenograft mouse model, tumor growth was only modestly retarded by treatment with elesclomol or genipin alone, but was markedly suppressed by the combination of the two drugs [29].

7. Effects of Genipin on Head and Neck Cancers

Wei et al. reported that genipin suppressed cell growth and induced apoptosis of human oral cancer cell lines. Genipin treatment upregulated the protein levels of Beclin1 and LC3II and downregulated the protein level of P62. After co-incubation with 3-MA, a kind of autophagy inhibitor, the autophagy process was lessened compared with treatment with genipin alone. Furthermore, genipin also reduced the expression of p-PI3K, p-AKT, and p-mTOR. In vivo experimentation showed that genipin significantly reduced tumor size and weight. The positive expression rate of Ki67 protein detected by immunohistochemistry was decreased, and the number of apoptotic cells measured by TUNEL assay was increased [30].

8. Effects of Genipin on Brain Tumors

In a study using U87MG and A172 glioblastoma cells, genipin moderately reduced the metabolic activity of both cell lines in a dose- and time-dependent manner. The viable cell count and colony formation ability decreased in the treated group in a concentration-dependent manner. Genipin induced apoptosis of glioblastoma cells in annexin V/PI staining assay. After genipin treatment, the expression of UCP2 and Bcl-2 was downregulated and the expression of Bax, Bak, Bik, and Cytochrome c was upregulated. The authors suggested that genipin significantly reduced the transcriptional expression of anti-apoptotic Bcl2 family members, while inducing the transcriptional expression of pro-apoptotic Bcl2 family members [31].

Zhong et al. reported that, in prolactinoma cells, genipin upregulated the expression levels of EGR1 and p21 (a downstream mediator of EGR1), with EGR1 inhibiting the proliferation, migration, and induction of prolactinoma cell apoptosis [32].

9. Effects of Genipin on Urologic Malignancies

Genipin was shown to inhibit proliferation of androgen-independent PC-3 prostate cells by suppressing UCP2, intracellular pyruvic acid, and mitochondrial succinate dehydrogenase [33].

In another study, Hong et al. stated that genipin roused mixed lineage kinase 3 (MLK3) expression in PC-3 prostate cancer cells. Furthermore, genipin-induced apoptosis was facilitated by ROS-dependent MLK3 activation [34].

In T24 and 5637 human bladder cancer cells, genipin-treated cells exhibited cell cycle arrest at the G0/G1-phase, a significant increase in the proportion of apoptotic cells, loss of MMP and Bax translocation to the mitochondria, and release of cytochrome c to the cytosol. Additionally, genipin treatment significantly reduced the phosphorylation of PI3K and Akt, significantly repressed the viability and clonogenic growing of T24 and 5637 bladder cancer cells, and inhibited the growth of T24 xenograft tumors [35].

10. Effects of Genipin on Gynecologic Malignancies

In human uterine cervix cancer HeLa cells, genipin inhibited cell proliferation and induced apoptosis dose-dependently. Apoptosis was confirmed by increase in DNA fragmentation, sub-G1 cell population, and p53 and Bax protein levels after treatment with genipin [36].

UCP2 expression in human cervical cancer cells and human ovarian serous carcinoma cells was inhibited by genipin, which it significantly augmented cisplatin sensitivity when UCP2 was repressed in vitro [37][38].

De Clercq et al. reported on the anticancer efficacy of paclitaxel-loaded genipin-crosslinked gelatin microspheres (PTX-GP-MS) for the treatment of microscopic peritoneal carcinomatosis and prevention of recurrent disease. The anticancer efficacies of IP PTX-GP-MS (PTXEtOH-GP-MS, D = 7.5 mg PTX/kg; PTXnano-GP-MS D = 7.5 and 35 mg PTX/kg), IP nanoparticular albumin-bound PTX (D = 35 mg PTX/kg), and controls (0.9% NaCl, blank GP-MS) were assessed in a xenograft mouse model with microscopic peritoneal carcinomatosis. PTXnano-GP-MS exhibited superior anticancer efficacy with significantly increased survival time and a decreased peritoneal carcinomatosis index score and ascites incidence [39][40].

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