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Arctigenin, an anti-tumor agent; a cutting-edge topic and up-to-the-minute approach in cancer treatment

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ABSTRACT

Today, herbal-derived compounds are being increasingly studied in cancer treatment. Over the past decade, Arctigenin has been introduced as a bioactive dibenzylbutyrolactone lignan which is found in Chinese herbal medicines. In addition to anti-microbial, anti-inflammatory, immune-modulatory functions, Arctigenin has attracted growing attention due to its anti-tumor capabilities. It has been shown that Arctigenin can induce apoptosis and necrosis and abolish drug resistance in tumor cells by inducing apoptotic signaling pathways, caspases, cell cycle arrest, and the modulating proteasome. Moreover, Arctigenin mediates other anti-tumor functions through several mechanisms. It has been demonstrated that Arctigenin can act as an anti-inflammatory compound to inhibit inflammation in the tumor microenvironment. It also downregulates factors involved in tumor metastasis and angiogenesis, such as matrix metalloproteinases, N-cadherin, TGF-β, and VEGF. Additionally, Arctigenin, through modulation of MAPK signaling pathways and stress-related proteins, is able to abolish tumor cell growth in nutrient-deprived conditions. Due to the limited solubility of Arctigenin in water, it is suggested that modification of this compound through amino acid esterification can improve its pharmacogenetic properties. Collectively, it is hoped that using Arctigenin or its derivates might introduce new chemotherapeutic approaches in future treatment.

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1. Introduction

Chemotherapy is the primary way of cancer treatment. It typically helps to prevent the growth, division, and invasion of cancer cells. Chemotherapy has a more substantial effect on cancer cells because these cells generally develop and divide quicker than normal cells. Nature is a plentiful source of diverse and biologically active compounds. Nowadays, nature-derived products encompass a large part of currently-used chemotherapeutic agents. According to Newman et al. study, in the time frame 1981 to 2014, from the 174 approved anticancer agents, only 23% of the total number were classified into the absolutely synthetic category, and the remaining (77%) were either natural or mimicked natural products, indicating that many anti-cancer drugs are somehow naturally-derived drugs (Newman and Cragg, 2016). Therefore, Over the past decades, natural compounds such as polyphenols have been used for several malignancies. A growing body of studies has confirmed the significance of phytochemicals in cancer treatment (Lin et al., 2020).

A large group of polyphenols is found in plants, especially vegetables, whole grains, and seeds. These compounds, which act as antifeedants in plants, are considered precursors to phytoestrogens (Korkina et al., 2011). Lignans are phenolic compounds that are broadly found in plants, including Linum, Sesamum, Forsythia, and Podophyllum genera. Lignan precursors (e.g., lariciresinol, pinoresinol, matairesinol, and secoisolariciresinol) are metabolized and converted into lignans, enterolactone, and enterodiol. Except for podophyllotoxins which are cytotoxic lignans and have clinical importance in cancer therapy, other lignans in human nutrition are present mainly in some nuts, oilseeds, and cereal bran (e.g., wheat and oat) and many barriers. Lignan products are built by coupling two phenylpropane units (i.e., C6C3), where two C6C3 units are linked by a bond between C8 and C8' (Solyomváry et al., 2017).

Lignans are almost highly soluble in organic solvents, whereas they are almost insoluble or sparingly soluble in water. These compounds are composed of eight classes, including furan, furofuran, dibenzylbutyrolactone, dibenzylbutane, arylnaphthalene, aryltetralin, dibenzylbutyrolactol, and dibenzocyclooctadiene (Umezawa, 2003). Although most lignans are derived from plants, many of them are metabolized by mammalian gut microbiota, which are called enterolignans (Heinonen et al., 2001). Sesame seed and flaxseed, among food sources, contain a higher amount of lignans than other foods. Cereals (e.g., wheat, rye, oat, and barley), cruciferous vegetables (e.g., broccoli and cabbage), soybeans, and some fruits, especially strawberries and apricots, are the other sources (Landete, 2012).

Arctigenin is a bioactive dibenzylbutyrolactone lignan found in herbal medicines, including *Arctium lappa* L. *Ipomea cairica*, *Saussurea medusa,* Forsythia suspensa Vahl, *and Torreya nucifera (*Cho et al., 2002*)*. Two plant species, allowing the isolation of an extraordinarily high amount of arctigenin, are *Serratula tinctoria* and *Jurinea mollis* (Könye et al., 2016; Sólyomváry et al., 2015b). Arctigenin has shown various therapeutic properties, including anti-viral, anti-bacterial, anti-inflammatory, immune-modulatory, and anti-tumor activities. Lately, Arctigenin has been studied extensively for its anti-tumor properties. It has shown that Arctigenin, through involvement in various molecular mechanisms and signaling pathways, exerts anti-tumor activities. Hence, we aimed to overview the effects of Arctigenin on cancer in this study.

2. Cancer and arctigenin

Tumorigenesis is the process of cancer formation, whereby normal cells are converted to highly proliferative cancer cells. This process results from changes at the genetic, epigenetic, and cellular levels, leading to abnormal cell division. A set of cellular and molecular events has been involved in cancer development. Generally, tumorigenesis has been divided into a three-step process, including tumor initiation, tumor promotion, and tumor progression. During cancer development, tumor cells acquire six central properties: self-reliant proliferation, evasion of apoptosis, insensitivity to anti-proliferative signals, unrestricted replicative and proliferative potential, the maintenance of vascularization and angiogenesis, and, in case of malignancy, invasion and metastasis into tissues (Hanahan and Weinberg, 2000). In addition to the changes in the cancer cells, alteration in the microenvironment, as well as external signals, are required to develop cancer. Acrtigenin, as a natural product from plants, has been shown to be involved in tumor regression. Therefore we have discussed the mechanisms whereby Arctigenin can inhibit tumor growth in the following (Fig. 1 and Table 1).

2.1. Arctigenin induces anti-inflammatory responses

Inflammation prompts cancer development and promotes all steps of tumorigenesis. Over the last few decades, immune system and inflammation's contribution to cancer development has regained enormous interest. Regardless of its occurrence in the course of chronic inflammatory disease, inflammation has a significant effect on the composition of the tumor microenvironment, which influences anti-cancer immune responses and mediates tumor progression. Proinflammatory cytokines and chemokines such as TNF-α and IL-1β, through multiple mechanisms and signaling pathways, can directly affect pre-malignant and malignant cells by enhancing their proliferation and resistance, hence directly encouraging tumor growth (Greten and Grivennikov, 2019; Shabgah et al., 2021a, 2021b).

Inflammasomes are multicomplex proteins which upon activation, mediate inflammation via production of IL-1β. NLRP3, as a member of inflammasomes, is a complex protein that has been involved in colitis and colorectal cancer (Zaki et al., 2010). The activation of NLRP3 leads to the progression of colitis to colorectal cancer, which is called colitis-associated cancer. Conversely, blockade of NLRP3 inflammasome is

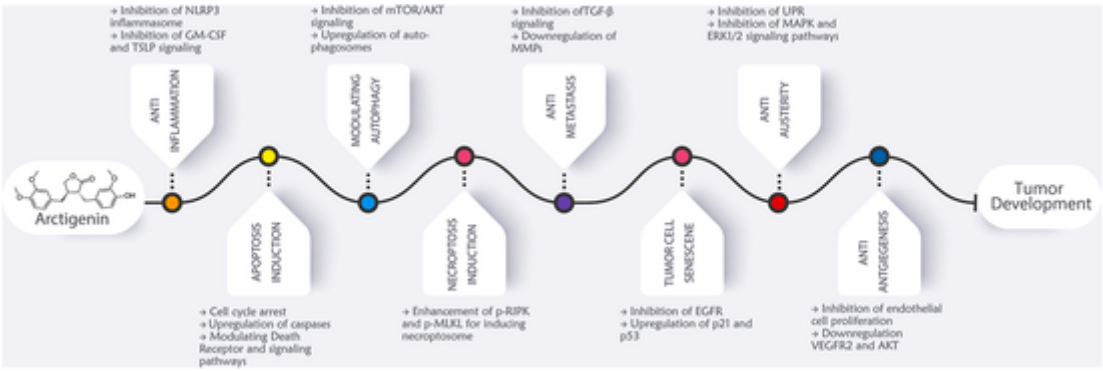

Fig. 1. Anti-tumor effects of Arctigenin. Arctigenin, by inducing apoptosis, inhibition of inflammation, metastasis, angiogenesis, and modulation of several cellular signalings, suppresses tumor development.

Table 1
Summarized anti-tumor properties of Arctigenin in several studies.

Cancer Type	Effect on Cancer	Mechanism of Action	Model of Study	Reference
Glioblastoma	Anti-proliferation Anti-metastasis	induced autophagy through inhibition of AKT/mTOR pathway	in vitro (U87MG and T98G cells)	Jiang et al. (2020)
Breast Cancer	Anti-proliferation	suppressed GM-CSF, TSLP, MMP3, MMP9 expression through inhibition of NF-κB inhibited COX2 through suppression of MAPK/AP-1	in vitro (4T1 and MDA-MB-231 cells) in vivo 4T1 murine model	(Lee et al., 2020a; Lou et al., 2017; Maxwell et al., 2017; Shi et al., 2020)
	Anti-metastasis Anti-stemness			
	Anti-metastasis	inhibited metastasis through activation of PP2A and downregulation of CIP2A and AKT dephosphorylation	in vitro (MDA-MB-231 and MDA-MB-468 cells)	Huang et al. (2017)
	Anti-proliferation Anti-inflammation	inhibited STAT3 binding to DNA downregulated cyclin D1 and Mcl-1	in vitro (MDA-MB-231) in vivo MDA-MB-231 murine model	Feng et al. (2017)
	Cell cycle arrest	degraded cyclin D1 in an Akt/GSK3β-dependent manner downregulated cyclin D1 through inhibiting β-catenin	in vitro (BT474 and MCF7 cells)	(Lee et al., 2017; Zhu et al., 2020)
Colitis-associated Cancer	Anti-inflammation	downregulated NLRP3 activation and fatty acid oxidation	in vivo murine model	Qiao et al. (2020)
Gallbladder Cancer	promoting cell senescence	downregulated EGFR and inhibited RAF/MEK/ERK signaling pathway	in vitro (GBC-SD and NOZ cells) ex vivo (human gallbladder cancer tissues)	Zhang et al. (2017)
Colorectal Cancer	Anti-proliferation Anti-drug resistance	abolished cisplatin-resistance through upregulation of pro-apoptotic proteins, autophagy, and MDR1 downregulation	in vitro (SW480 SW620 cells)	Wang et al. (2019)
	Cell cycle arrest Anti-metastasis	induced intrinsic apoptotic pathway through inhibiting MAPK pathway downregulated MMP2, MMP9, N-cadherin, vimentin, β-catenin, and Snail	in vitro (CT26 cells) in vivo CT26 murine model	Han et al. (2016)
	Anti-drug resistance	inhibited etoposide resistance through inhibiting degradation of topoisomerase IIα and reducing GRP78	in vitro (HT29 cells)	Yoon and Park (2019)
	Anti-austerity	blocked expression of UPR target genes including PERK, ATF4, CHOP, and GRP78 enhanced phosphorylation of eIF2α	in vitro (HT29 cells) in vivo HT29 xenograft murine model	Kim et al. (2010)
	Anti-angiogenesis	decreased proliferation of human dermal microvascular endothelial cells decreased AKT phosphorylation and downregulation of VEGF1 and suppressed vascularization	in vitro (HDMEC cells) in vivo CT26 murine model	Gu et al. (2013)
Hepatocellular Carcinoma	Anti-proliferation Anti-autophagy	inhibited starvation-induced autophagy	in vitro (HepG2 cells)	Okubo et al. (2020)
	Anti-proliferation	induced intrinsic and extrinsic apoptotic pathway through inducing ROS and inducing JNK and p38 MAPK pathways	in vitro (HepG2 cells) in vivo HepG2-bearing mice	Lu et al. (2020)
	Anti-proliferative	induced apoptosis through activating caspase −3, −7 and −8	in vitro (HuH7 cells)	Naoe et al. (2019)
Prostate Cancer	Anti-proliferation	induced necroptosis through activation of oxidative stress and CCN1 upregulation	in vitro (PC3AcT and PC3 cells)	Lee et al. (2020b)
	Anti-austerity Anti-drug resistance	induced ROS and intrinsic apoptotic pathway through inhibition of PI3K/Akt/mTOR pathway	in vitro (PC3 cells)	Lee et al. (2018)
	Anti-proliferation	decreased adipokines and cytokines including IGF-1, VEGF, and MCP-1 decreased androgen receptor	in vitro (LNCaP cells) in vivo LAPC-4 murine model	Hao et al. (2020)
Pancreatic Cancer	Anti-drug resistance	increased slightly survival time and progression free in gemcitabine-resistant patients	phase I clinical trial	Ikeda et al. (2016)
Lymphoma	Anti-proliferation Anti-austerity	triggered intrinsic apoptotic pathway through inhibiting ERK and p38 MAPK signaling	in vitro (BC3 PEL cells)	Baba et al. (2018)
Ovarian Cancer	Anti-proliferation	inhibited STAT3 phosphorylation, and downregulated survivin and iNOS expression	in vitro (OVCAR3 and SKOV3 cells)	Huang et al. (2014)
Lung Cancer	Anti-proliferation Anti-migration	inhibited TMEM16A gene through inhibiting MAPK pathway	in vitro (LA795 cells) in vivo LA795 murine model	Guo et al. (2020)
	Anti-drug resistance Cell cycle arrest	induced apoptosis through caspase-3 cleavage downregulated Survivin expression	in vitro (H460 cells)	Wang et al. (2014)

(*continued on next page*)

Table 1 (*continued*)

Cancer Type	Effect on Cancer	Mechanism of Action	Model of Study	Reference
	Anti-metastasis Cell cycle arrest	inhibited EMT through repressing TGF-β-induced phosphorylation of SMAD2/3, and downregulated Snail and N-cadherin inhibited ERK/β-catenin pathway decreased cyclin H, cyclin E, CDK2, and CDK7	in vitro (A549 cells)	(Susanti et al., 2013; Xu et al., 2017)
Retinoblastoma	Anti-proliferation	induced apoptosis through Bax upregulation downregulated JAG1 expression inhibited Notch1 signaling	in vitro (Y79 cells)	Ke et al. (2019)
Bladder Cancer	Cell cycle arrest	decreased cyclin D1 expression through decreasing ERK1/2 phosphorylation and activated p38 phosphorylation	in vitro (T24 cells)	Yang et al. (2012)
Gastric Cancer	Cell cycle arrest	blocked phosphorylation of Rb through downregulation of cyclin D1/CDK4 and cyclin E/CDK2	in vitro (SNU-1 and AGS cells)	Jeong et al. (2011)

beneficial for cancer regression (Qiao et al., 2020). Arctigenin has inhibited NLRP3 in macrophages which consequently decreased the production of IL-1β and IL-18 in colitis-associated cancer. Further analysis has shown that Arctigenin inhibited the assembly of NLRP3 complex without any impact on its mRNA expression or macrophage viability (Qiao et al., 2020). Since carnitine palmitoyltransferase 1 (CPT1) plays a pivotal role in NLRP3 assembly in macrophage and its overexpression correlated to IL-1β expression, tumor size, tumor load, and tumor number, it has been speculated that Arctigenin downregulated CPT1 expression and CPT1 was considered as Arctigenin target in colorectal cancer (Qiao et al., 2020). These results indicated that Arctigenin exerts hindering effects on colorectal carcinogenesis in vivo.

Tumor-derived growth factors influence the tumor microenvironment and play crucial roles in tumor development. These cytokines, in the inflammatory microenvironment, mediate tumor colonization and cell proliferation via several mechanisms (Smith and Kang, 2013). Tumor-derived cytokines such as thymic stromal lymphopoietin (TSLP) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been confirmed to be involved in cancer progression (Quail et al., 2017; Ragonnaud et al., 2019). NF-κB interaction with the promoter of GM-CSF and TSLP genes mediates the expression of these cytokines. Arctigenin has been shown to inhibit translocation of NF-κB into the nucleus, hence suppressing proliferation, invasion, and stemness of breast tumor cells (4T1 and MDA-MB-231 cell lines) (Shi et al., 2020). Subsequent to TSLP and GM-CSF signaling, STAT3 is activated which its crosstalk with β-catenin signaling plays an important role in cancer cell stemness (Shi et al., 2020; Takebe et al., 2015). Arctigenin, by decreasing GM-CSF and TSLP expression, has also been involved in inhibiting STAT3/β-catenin signaling and breast cancer cell stemness (Shi et al., 2020).

2.2. Arctigenin promotes apoptosis and inhibits drug resistance

Apoptosis is a vital process to maintain cellular balance so that its disruption leads to uninhibited tumor cell growth, making this phenomenon a target for the therapeutic strategy to fight against cancer. Hence, apoptosis has been considered the main molecular mechanism by which chemotherapeutic drugs perform their anti-cancer functions (Son et al., 2011). Therefore, drug resistance is regarded as a key feature for cancer which continues to be a limiting factor in achieving treatment. Since most standard treatment regimens, including chemotherapy and radiotherapy, induce apoptosis and death in cancer cells, resistance to apoptosis is known to be one of the mechanisms involved in cancer drug resistance (Nik et al., 2019). Defects in specific apoptotic pathways lead to cancer development and progression. Therefore, cancer drug resistance can originate from alteration in the normal pathways of apoptosis-induced cell death (Kaufmann and Vaux, 2003). In the following sub-sections, we reviewed the mechanisms concerning Arctigenin-induced tumor growth inhibition.

2.2.1. Pro-apoptotic effects of Arctigenin on apoptosis-associated signaling pathways

Arctigenin exerts anti-proliferative functions on HT29 cells (a colorectal cancer cell line) via enhancing caspase-3 and caspase-9 activities. The proposed mechanism for this Arctigenin-induced apoptosis in HT29 cells relies on stimulation of ROS production to induce p38/MAPK signaling pathway and intrinsic apoptotic pathway (Li et al., 2016). Also, Arctigenin imposed anti-proliferative effects on MDA-MB-231 (a breast cancer cell line) through induction of $p22^{phox}$ interaction with NADPH oxidase 1 to trigger ROS production to activate p38/MAPK. Subsequent to p38/MAPK induction, Arctigenin induced mitochondrial apoptosis pathway through alteration in Bax/Bcl-2 ratio. It has also been shown that pro-apoptotic effects of Arctigenin on MDA-MB-231 were independent of death receptors (Hsieh et al., 2014). In PC-3 cells (a prostatic cancer cell line), Arctigenin also increased ROS production and inhibited PI3K/Akt/mTOR signaling pathway to induce mitochondrial apoptotic pathway (Lee et al., 2018). Other than mentioned in vitro studies, Lu et al., in Hep-G2-bearing mice, have shown that Arctigenin also induced ROS-dependent tumor cell apoptosis by inducing the JNK/p38 MAPK signaling pathway (Lu et al., 2020). Collectively, these studies have indicated that ROS is a major mediator in Arctigenin-induced apoptosis in cancer cells, indicating the importance of the mitochondrial pathway in this issue.

Expression of anti-apoptotic proteins such as Bcl-2, Mcl-1, cIAP2, c-Myc, and cyclin D also proposed another mechanism involved in apoptosis-dependent cancer drug resistance (Yao et al., 2011). STAT3 signaling pathway has lately been demonstrated to endow apoptosis resistance to tumor cells. In this regard, STAT3 dimerization, phosphorylation, and nuclear translocation activate the expression of the aforementioned anti-apoptotic proteins (Yao et al., 2011). Arctigenin administration specifically suppressed IL-6-induced STAT3 phosphorylation and nuclear translocation in a time- and dose-dependent manner without statistically significant effect on STAT3 expression in HepG2 cells (an HCC cell line). The effect of Arctigenin on STAT3 phosphorylation was reversible (Yao et al., 2011). Moreover, Arctigenin inhibited phosphorylation of STAT3's activator tyrosine kinases, including Src, JAK1, JAK2, Akt, and ERK1/2, with no impact on their expression levels (Yao et al., 2011). In contrast, protein tyrosine phosphatase such as SHP2, which inhibits JAK/STAT3 pathway, has also been upregulated by Arctigenin (Yao et al., 2011). Collectively, Arctigenin inhibited the expression of anti-apoptotic proteins, including cIAP2, Mcl-1, cyclin D1, Bcl-2, and C-myc via suppression of JAK/STAT3 pathway, leading to apoptosis and cell cycle attest at sub-G1 phase (Yao et al., 2011). In Arctigenin-receiving TNBC (MDA-MB-231 cells)-xenografted nude mice, it has been shown that p-STAT3 was downregulated. Subsequent to p-STAT downregulation, the expression of cyclin D1 and Mcl-1 mRNA expression was also reduced, indicating anti-tumor efficiency of Arctigenin in vivo (Feng et al., 2017).

2.2.2. Pro-apoptotic effects of Arctigenin on cancer via cell cycle arrest

Estrogen receptor (ER)-positive breast cancer is best known for higher expression of cyclin D1 (Perou et al., 2000). Cyclin D1 coupling with cyclin-dependent kinase (CDK)4 or CDK6 initiates cell cycle entry through phosphorylation and inactivation of retinoblastoma (Rb) and subsequent release of E2F transcription factor (Kato et al., 1993). Arctigenin induced cell cycle arrest in ER + breast cancer cells (BT474 and MCF-7 cell lines) in a way other than caspase-dependent apoptosis. It has been shown that Arctigenin suppressed expression of cyclin D1 in these cells post-transcriptionally via proteasomal degradation. Mechanistically, Arctigenin induces GSK3 (via a reduction in phospho-Akt and phospho-GSK3β as inhibitors of GSK3) for phosphorylation and ubiquitination of cyclin D1 to further proteasomal degradation (Mervai et al., 2015) (Zhu et al., 2020). Collectively, Arctigenin induced ER + breast cancer cell cycle arrest at G1 phase via post-transcriptional regulation of cyclin D1 without affecting apoptosis (Zhu et al., 2020). Other than breast cancer cells, Arctigenin also arrested colon cancer cell cycle. Arctigenin-treated CT26 colon cells have been arrested at G2/M phase. Arctigenin-mediated cell cycle arrest in this regard has been implemented through reducing mRNA expression of cyclin A, E, and CDK2 (Han et al., 2016). Another mechanism proposed for Arctigenin involvement in cell cycle arrest has been focused on nuclear protein of the ataxia telangiectasia locus (NPAT). NPAT contributes to histone biosynthesis, and its inhibition impedes expression of all histone subtypes. NPAT phosphorylation by CDK2/cyclin E has led to its association with histone gene promoters. Arctigenin likely inhibits cyclin E/CDK2 to downregulate NPAT and histone subtypes. Consequently, this results in A549 cell cycle arrest at the G1/S phase (Susanti et al., 2013).

As a member of the inhibitor of apoptosis proteins (IAPs) family and a cell cycle promoter protein, Survivin is involved in the regulation of proliferation and cell survival through inhibition of caspase activation (Sah et al., 2006). This protein, which is almost expressed in the G2/M phase of the cell cycle, confers resistance to chemotherapeutic agents such as cisplatin. Since Arctigenin has been shown to be involved in sensitization of H460 cells (a lung cancer cell line) to cisplatin, it was speculated that Arctigenin might be involved in inhibition and downregulation of Survivin (Wang et al., 2014). However, the mechanism underlying Survivin inhibition by Arctigenin in lung cancer is needed to be elucidated. In ovarian cancer cells, Arctigenin effects on Survivin have implied on iNOS/STAT3 signaling pathway. It has been confirmed that Arctigenin treatment of OVCAR3 and SKOV3 cells leads to downregulation of iNOS and subsequently decrease in NO production. Subsequent to the decrease in NO production, it is postulated that STAT3 inactivation was implemented, which per se resulted in Survivin suppression (Huang et al., 2014). Moreover, β-catenin has also been shown to regulate the expression of Survivin in colon cancer cells (SW480 cell line). Yoo et al. have confirmed that Arctigenin reduced expression of β-catenin and facilitated degradation of this transcription factor by mediating its phosphorylation. Arctigenin-dependent downregulation of β-catenin has been linked to the reduction of Survivin in SW480 cells (Yoo et al., 2010). Collectively, Arctigenin inhibits Survivin, leading to cell cycle arrest at G2/M and S phases.

2.2.3. Pro-apoptotic effects of Arctigenin via modulating death receptor

Induction and activation of the extrinsic pathway of apoptosis are initiated through binding of ligands to the death receptors, including Fas 9/10, tumor necrosis factor receptor (TNFR)1, TNF-related apoptosis-inducing ligand (TRAIL) receptor (Holler et al., 2000; Wang and El-Deiry, 2003). After the interaction of ligands with these receptors, TNF-receptor-associated death domain (TRADD) is recruited to the cell survival complex (Complex I), which comprises ubiquitin E3 ligase and RIPK1. In this complex, deubiquitination of RIPK1 dissociates this protein from TRADD and forms other complexes, which consequently leads to the activation of caspase-8. On the other hand, if Fas receptor-related apoptosis occurs, caspase-9 will be the initiator of cell death (Naoe et al., 2019). Administration of Arctigenin to the hepatoblastoma cells (HUH6 cells) has led to activation of TNFR1-related activation of apoptosis through inducing caspase 8/3/7 cascade rather than caspase 9/3/7 (Naoe et al., 2019).

2.2.4. Pro-apoptotic effects of Arctigenin via affecting Notch receptor

Notch signaling is one of the conserved signaling pathways, which regulates cell apoptosis, viability, and migration. This pathway can promote cancer development, especially in retinoblastoma. Ligation of Notch ligand (e.g., jagged-1) to Notch receptor gives rise to release of its intracellular domain (NICD) from the cell membrane into the nucleus to act as a transcription factor and activate downstream gene expression. Treatment of Y79 cells (a human retinoblastoma cell line) with Arctigenin has markedly decreased jagged-1, NICD, HES1, and HES5 expression and subsequently affected cell viability. However, the underlying mechanism regarding Arctigenin effects on retinoblastoma should be elucidated (Ke et al., 2019).

2.2.5. Pro-apoptotic effects of Arctigenin via affecting proteasome

Upon microenvironmental stress conditions, the accumulation of multi-catalytic protease complex (i.e., proteasomes) leads to degradation of a series of proteins such as topoisomerases IIα (the etoposide target) in cancer cells. Consequently, this process results in cancer cell resistance to etoposide due to the loss of this drug target. It has been shown that Arctigenin inhibited proteasomal degradation of topoisomerase IIα and induced downregulation of 78-kDa glucose-regulated protein (GRP78; a microenvironmental stress-induced chaperone and a tumor cell protective factor against death and apoptosis). Therefore, administration of Arctigenin can be helpful against etoposide resistance in H19 cells (Yoon and Park, 2019).

2.3. Arctigenin manipulates autophagy mechanisms in cancer cells

Arctigenin has also been shown to inhibit proliferation of cisplatin-resistant colorectal cancer cells (SW480 and SW620 cells) dose-dependently. The molecular analysis of Arctigenin-induced cell death has revealed that Arctigenin triggers autophagy in cisplatin-resistant cells. LC3 (1A/1B-light chain 3) proteins are key proteins involved in the formation of autophagosomes and subsequent initiation of the autophagy process (Tanida et al., 2008). Arctigenin has upregulated the expression of LC3-II and p65 proteins and downregulated LC3-I expression, resulting in autophagy induction (Wang et al., 2019). In addition to autophagy induction, Arctigenin decreased IC50 of cisplatin, doxorubicin, oxaliplatin, and paclitaxel and mRNA expression of MDR1 (multidrug resistant 1) in resistant colorectal cancer cells (Wang et al., 2019).

In ER + breast cancer cells (e.g., MCF-7), Arctigenin also resulted in neither cell cycle arrest nor caspase-mediated apoptosis and even necroptosis. Further examination has shown that Arctigenin treatment inhibited the mTOR signaling pathway and mTOR downstream autophagy-inhibitory S6K and S6 proteins (inhibitors of LC3-II and LC3-I). Therefore, Arctigenin-dependent inhibition of mTOR signaling suppressed autophagy-inhibitory mechanisms, leading to degrade produced proteins. Amidst degraded proteins, ERα was also degraded by the autophagy system, resulting in reduced signal transduction from estrogen receptors and subsequently inhibited tumor growth (Maxwell et al., 2018). In glioblastoma cell lines (U87MG and T98G cells), Arctigenin also induced autophagy through inhibition of mTOR/AKT signaling pathway and induction of LC3-II and p62 proteins (Jiang et al., 2020).

Although induction of autophagy may suppress tumor development, evidence in murine models shows that autophagy inhibition can limit the growth of established tumors and improve efficacy of treatments (Yang et al., 2011). It has been shown that cancer cells degrade themselves to provide energy and sustain core cellular processes in nutrient starvation experience. Despite mentioned Arctigenin-induced au-

tophagy in cancer cells, Okubo et al. have shown that Arctigenin inhibited autophagy in HepG2 cells through induction of p62 accumulation (Okubo et al., 2020).

2.4. Arctigenin mediates necroptosis in cancer cells

Necroptosis, a programmed and regulated form of necrosis, is begun by ripoptosome formation through autophosphorylation and transphosphorylation of receptor-interacting serine/threonine-protein kinase (RIPK)1 and the recruitment of RIPK3. The ripoptosome phosphorylates and activates MLKL oligomerization to permeabilize organelle's plasma membranes (Linkermann and Green, 2014). Lee et al. have shown that Arctigenin can induce necroptosis in prostate cancer cells in lactic acidosis conditions (a cancer-specific metabolism). Arctigenin induced cell death through enhancement of phosphorylated (p)-RIPK and p-MLKL without any change in cleaved caspase3 and apoptosis. Mechanistically, it was postulated that Arctigenin upregulated CCN1 (cellular communication network factor 1) to promote necroptosis and necroptosome formation (Lee et al., 2020b).

2.5. Arctigenin exerts inhibitory roles in inhibition of metastasis

Metastasis is an intricate process in which cancer cells detach from a primary organ site and form tumors at distant organ sites. In primary tumors, loss of cell-matrix and cell-cell adhesion leads to cell motility and initiation of tumor invasion and metastasis. The epithelial-mesenchymal transition (EMT) is the most important cellular process for tumor metastasis. In this process, cancer cells lose their epithelial-like markers, such as E-cadherin, and acquire mesenchymal properties, including expression of N-cadherin. During this process, several cytokines, factors, and molecular mechanisms are involved. TGF-β is the most well-known EMT stimulator, which its ligation to its receptor induces formation of SMAD2/3/4 complex to bind SMAD response element (SRE) on the promoter of target genes. Arctigenin has been shown to inhibits TGF-β-induced SMAD2/3 phosphorylation and downregulates E-cadherin, and concomitantly upregulates N-cadherin expression in A549 cells. In addition to the SMAD pathway, it has been shown that Arctigenin inhibits non-SMAD TGF-β downstream signaling pathways. In this regard, Arctigenin inhibited TGF-β-dependent phosphorylation of ERK as well as transcriptional activity of β-catenin (Xu et al., 2017).

The next step in cancer cell migration and metastasis is to cross the physical barriers, including extracellular matrix and basement membranes. This process necessitates the presence of protease enzymes such as matrix metalloproteases (MMPs). The gelatinase, also called MMP9, is a highly expressive enzyme in invasive breast cancers. Treatment of MCF-7 and MDA-MB-231 cell lines with Arctigenin showed inhibitory effects on MMP9 transcription and protein levels. Moreover, Arctigenin downregulated the expression of urokinase-type plasminogen activator (uPA), which is the activator and facilitator of MMP9 release. Mechanistically, it has been shown that Arctigenin inhibited Akt/NF-κB and MAPK/AP-1 pathways as two main regulatory pathways for MMP9 expression in vitro. The inhibition of MMP9 synthesis at the transcription level and decreased proteolytic activity of MMP9 have led to impairment of cell migration (Lou et al., 2017; Maxwell et al., 2017). In addition to MMP9 inhibition, Arctigenin attenuated MMP3 and cyclooxygenase-2 (COX2) transcript through inhibition of ERK, JNK, and nuclear translocation of AP-1 in the 4T1-grafted mice (Lee et al., 2020a).

An oncoprotein called cancerous inhibitor of protein phosphatase 2A (CIP2A) inhibits a tumor-suppressor protein named serine/threonine protein phosphatase 2A (PP2A). PP2A per se regulates various important oncogenic proteins, including ERK, Akt, c-Myc, and p70S6K. Upon PP2A inhibition by CIP2A, dephosphorylation of these oncoproteins was abrogated, resulting in anchorage-independent tumor formation and cell growth in vivo. Therefore, PP2A restoration, which leads to inhibition of CIP2A, can decrease tumor aggressiveness. In triple-negative breast cancer (TNBC), including MDA-MB-231 and MDA-MB-468, Arctigenin downregulated CIP2A transcription and even promoted its proteolysis. Also, Arctigenin increased activation of phosphorylated (p)-Akt. Further examinations have revealed that Arctigenin-related inhibition of TNBC aggressiveness is also in a PP2A-dependent manner so that PP2A inhibition abrogated Arctigenin inhibitory effects on TNBCs (Huang et al., 2017).

2.6. Arctigenin promotes senescence of tumor cells

Cellular senescence is a process in which cell division is ceased. The physiological importance of this phenomenon has been attributed to the inhibition of carcinogenesis. In addition to above mentioned anti-tumor effects of Arctigenin, it has also been shown that this compound can induce senescence in tumor cells. Epidermal growth factor receptor (EGFR) and its following signaling (i.e., RAF/MEK/ERK) is one of the inhibitors of cellular senescence in gallbladder cancer. Treatment of gallbladder cancer cells (GBC-SD and NOZ cells) with Arctigenin inhibited expression of EGFR and upregulated p21 and p53, which consequently induced cellular senescence in these cells. These data were also confirmed in the murine model of cancer (Zhang et al., 2017).

2.7. Arctigenin affects microtubular system

Microtubules are a vital part of eukaryotic cells, which are involved in several cellular processes. These molecules contribute to the formation of cell cytoskeleton, development and maintenance of cell shape, intracellular transport, cell signaling, and cell division (miosis or mitosis). Microtubules are assembled through polymerization of α- and β-tubulins in a dynamic equilibrium. Since microtubules play crucial roles in cell division, their targeting in cancers might be promising in inhibiting tumor cell growth (Jordan and Wilson, 2004). In this regard, Arctigenin has also been proved to be involved in inhibiting the microtubular system. In Arctigenin-treated SW480 cells, it has been shown that Arctigenin influenced microtubular dynamics and induced β-tubulin synthesis, which has led to increased levels of free tubulins and disequilibrium in the ratio of tubulins. Consequently, this process might be involved in the formation of multinuclear giant SW480 cells (Sólyomváry et al., 2015a). However, it is needed to be elucidated the precise underlying mechanism.

2.8. Arctigenin abolishes tumor growth in nutrient-deprived conditions

Cancer cells are capable of surviving even under extreme conditions, including low oxygen supply and nutrient deprivation. This is mainly confirmed for highly invasive tumors, especially pancreatic cancer. According to angiographic investigations, most pancreatic cancers are hypovascular in terms of tumor vessel number (Hahnfeldt et al., 1999). It is hypothesized that this tolerance to nutrient starvation might be a biological response to the inadequate blood supply. Therefore, it has been assumed that abolishing cancer cells' tolerance to nutrition starvation is acknowledged as anti-austerity in cancer treatment (Magolan and Coster, 2010). Deprivation of nutrients, especially glucose, triggers a signaling pathway known as the unfolded protein response (UPR), which increases cell survival by inducing stress proteins. Upon glucose deprivation, UPR target genes including p-PERK, CHOP, ATF4, and GRP78 are activated. Inhibition of UPR leads to apoptosis through the mitochondrial pathway and activating caspase-3 and -9, leading to suppressing tumor growth in colon cancer HT-29 xenografts (Kim et al., 2010). It has been shown that Arctigenin exhibits preferential cytotoxicity against nutrient- and glucose-deprived tumor cells. Since nutrient deprivation rarely occurs in non-cancerous tissues, it might be considered that the anti-austerity ability of Arctigenin is specific to tumor cells (Awale et al., 2006). Mechanistically, Akt/PKB signaling pathway has been introduced as the main regulator of cellular

respiration under nutrient starvation (Izuishi et al., 2000). Hence, Arctigenin, by inhibiting phosphorylation of Akt, might be responsible for preferential cytotoxicity against nutrient-deprived tumor cells (Awale et al., 2006).

In addition to pancreatic cells, Arctigenin also exerted anti-tumor effects on primary effusion lymphoma (PEL) cells under glucose deprivation. In this regard, Arctigenin, by decreasing ATP levels, has shown to be involved in mitochondrial disruption in glucose-starved PEL cells, which consequently disrupted mitochondrial membrane can induce caspase-9-mediated apoptosis (Baba et al., 2018). Also, in glucose-deprived PEL cells, Arctigenin suppressed activation (i.e., phosphorylation) of p38 MAPK and ERK1/2 signaling pathways which are involved in cell viability and proliferation (Baba et al., 2018). Another mechanism proposed for Arctigenin involvement in glucose-deprived PEL cell inhibition is attributed to downregulation of endoplasmic reticulum (ER) stress-related molecules. These molecules, including GRP78 and activating transcription factor (ATF)6α, play a pivotal role in cellular stress. Arctigenin by p38 MAPK inhibition leads to decreased promoter activity of GRP78 and ATF6α genes, resulting in severe ER stress and then apoptosis through inhibition of unfolded protein response (UPR) activation (Baba et al., 2018).

2.9. Anti-angiogenic properties of Arctigenin in cancer

Angiogenesis in the tumor microenvironment is a highly dynamic procedure that mediates development of new blood vessels. During this process, endothelial cells were stimulated, then proliferated, and subsequently migrated by growth factors (e.g., VEGF) and signaling pathways (such as AKT) to be reorganized into new capillaries (Laschke et al., 2006). Arctigenin has been shown to inhibit the viability of human dermal microvascular endothelial cells (HDMECs). Although Arctigenin couldn't suppress migration of HDMECs, it inhibited vascular sprouting in vivo in a dose-dependent manner. Regarding the expression of angiogenesis-promoting factors, Arctigenin reduced expression of VEGFR2 and p-AKT. Finally, the vascularization and growth of CT26 were suppressed by Arctigenin in vivo. Collectively, this natural compound inhibits colon tumor growth via inhibiting angiogenesis (Gu et al., 2013).

3. Anti-tumor effects of Arctigenin derivates

According to a few studies, Arctigenin has shown different pharmacokinetic patterns. Pharmacokinetic studies proposed that the extensive first-pass metabolism of Arctigenin after oral administration would hinder its in vivo and clinical efficacy. The tissue levels of Arctigenin peaked at 30 min following oral administration of 70 mg/kg in rats and were rapidly removed within 4 h, and maximum Arctigenin levels were reported in the spleens, followed by the liver and other organs. To optimize the clinical and in vivo efficacy of Arctigenin, alternative administration routes other than oral administration such as sublingual or buccal routes are suggested (He et al., 2013). Due to the substantial first-pass metabolism of Arctigenin, most Arctigenin is expected to be rapidly metabolized after oral administration as a single or as an active component in herbal formulations (Gao et al., 2018). He et al. have shown that after intravenous (i.v.) injection of Arctigenin to piglets, the distribution half-life and volume of Arctigenin was short and low, respectively, indicating that the distribution of Arctigenin was rapid, but its distribution into tissues was very low. According to this study, Arctigenin is mainly distributed in the extracellular fluids and blood. Moreover, elimination half-time was also relatively short, resulting in rapid elimination of Arctigenin after i.v. injection (He et al., 2019). According to Gao et al. study, data showed that Arctigenin exhibited a higher absorption rate in rats and strong elimination ability. It was also shown that Arctigenin hydrolyzed rapidly in the plasma of rats (Gao et al., 2014). Collectively, it has been shown that Arctigenin is very insoluble to be absorbed by the body, hence limiting its clinical applications.

Due to the aforementioned reasons, it was suggested that Arctigenin should be modified by either biological or chemical methods to form derivates with a higher bioavailability and better solubility. One of the Arctigenin modifications is esterification with valine amino acid, which is called Arctigenin valine ester (ARG-V). This valine ester derivative (ARG-V) exhibited vividly improved pharmacological activity and showed a rapid absorption phase and a slow elimination phase compared to Arctigenin. In terms of anti-tumor efficacy, ARG-V showed better antiproliferative effects on the growth of H_{22} hepatoma transplanted tumors compared to Arctigenin (Cai et al., 2018a). Also, ARG-V administration has minor damage to immune organs (Cai et al., 2018b). In addition to the anti-tumor activity of Arctigenin derivates, it has also been shown that these derivates can be promising against anti-austerity in pancreatic cancer. In this regard, monoethoxy, diethoxy, and triethoxy derivatives of Arctigenin showed more potent cytotoxicity under nutrient-deprived conditions than Arctigenin in vitro. Also, triethoxy derivate revealed anti-tumor effects slightly more than Arctigenin in vivo (Kudou et al., 2013).

Modification of Arctigenin can also improve nitrite-scavenging (i.e., anti-oxidant activity) effects, immune responses and decrease damages to the liver and kidney (Cai et al., 2018a). In a study, six derivates of Arctigenin, including crotonate, furoate, naphthoate, laurate, palmitate, and β-indolylacetate, were synthesized. In terms of nitrite scavenging, almost all derivates were active than Arctigenin, in which the β-indolylacetate derivate is the strongest in this regard. Concerning anti-tumor (such as apoptosis induction), immune responses effectiveness (IL-2, IL-6, and IFN-γ levels), β-indolylacetate form also has the highest function, which also has shown the fewest side effect on the organs (especially the liver, kidney, spleen, and thymus) in H_{22} tumor-bearing mice (Chen et al., 2016). Collectively, Arctigenin monoester derivates with little toxicity and high anti-tumor activity might show promising practical progress in clinical trials and improve the application of Arctigenin.

4. Arctigenin combination therapy with other agents

In addition to structural modification and producing derivates, Arctigenin can also be used in combination with other natural or chemotherapeutic agents to enhance its effectiveness in cancer treatment. Quercetin is a flavonoid that is abundantly found in fruits and vegetables and has anti-inflammatory, anti-oxidant, and anti-proliferative properties. Additionally, quercetin possesses anti-carcinogenic properties, especially in prostate cancer, through multiple mechanisms, including inhibition of androgen receptors and modulating PI3K/Akt/mTOR pathways (Cimino et al., 2012). Since quercetin is extensively glucuronidated, sulfated, and methylated upon uptake, hence these modifications may decrease its bioactivity and limit its bioavailability in vivo. Because of being common in inhibiting androgen receptors with Arctigenin, therefore it is suggested that Arctigenin and quercetin are ideal candidates for being combined to augment the anti-tumor effects through an amplified inhibition of either androgen receptor or PI3K/Akt pathways at low concentrations. Arctigenin and quercetin combination therapy showed stronger anti-proliferative and powerful androgen receptor signaling inhibitory impacts in LAPC-4 and LNCaP cells (prostate cancer cell lines) than Arctigenin or quercetin treatment alone. Moreover, this combination reduced expression of oncogenic miRNAs, including miR-19b, miR21, and miR-148a in LAPC-4 cells. Enhanced inhibition of migration of LAPC-4 and LNCaP cells was also demonstrated by Arctigenin plus quercetin combination. Collectively, these data suggest that quercetin is a suitable drug to be combined in prostate cancer treatment (Wang et al., 2015).

5. Clinical trials evaluating anti-tumor effectiveness of arctigenin

Since several bodies of evidence confirmed the vigorous anti-tumor effects of Arctigenin, researchers have concluded to evaluate the efficacy of this herbal compound in a clinical trial. For instance, in a phase I clinical trial involving 15 advanced pancreatic cancer patients refractory to gemcitabine, GBS-01 (an extract rich in Arctigenin from the fruit of *Arctium lappa* L.) was prescribed orally at escalating doses from 3 g to 12 g. Results regarding dose-limiting toxicities indicated that none of the patients at any doses showed any toxicity signs. Although being mild, hyperglycemia, elevated γ-glutamyl transpeptidase, and increased serum bilirubin were the main adverse events. The suggested GBS-01 dose for favorable clinical responses was 12 g. The overall survival and median progression-free of patients were 5.7 and 1.1 months, respectively. Collectively, the possible benefit and clinical safety of GBS-01 monotherapy were confirmed in these patients, and it has been shown that GBS-01 is capable of alleviating tumor cell tolerance to nutrient starvation (Ikeda et al., 2016).

6. Concluding remarks and future directions

Arctigenin, as a bioactive lignan, is mainly found in Chinese herbal medicine called *Arctium lappa* L. This natural compound exerts several functions such as anti-inflammation, anti-microbial, and anti-tumorigenesis. Arctigenin, via inhibition of inflammation, cell proliferation, metastasis, and angiogenesis, plays its anti-tumor functions in several cancers. It has been proposed several advantages of using Arctigenin over the common chemotherapeutic agents, including alkylating agents, anti-metabolism drugs, platinum, and hormones. These drugs may have serious side effects such as vomiting, diarrhea, hair loss, liver damage, jaundice, limb numbness, difficulty in breathing, heart failure, and throat cramps (Guo et al., 2020). In comparison with common anticancer drugs, the side effects of Arctigenin were negligible (Guo et al., 2020). Since Arctigenin has low solubility in water, its modification to produce new derivates, including amino acid ester derivates, can solve this problem to use in vivo. Consequently, the modification of Arctigenin to improve its efficacy, bioavailability, and pharmacokinetic properties might be one of the future directions. Most studies regarding the anti-tumor activity of Arctigenin have been experienced in vitro and limited in vivo studies. Therefore, it is necessary to examine its function in vivo. Also, due to the lack of more clinical trials and even animal studies, Arctigenin efficacy in cancer treatment has not been fully elucidated. Hence, future direction concerning the anti-tumor effect of Arctigenin should be more pronounced in vivo. Although a body of evidence from in vitro studies demonstrates a promise of Arctigenin administration in cancer treatment, translation of these studies to clinical ones is limited. It is hoped that the clinical translation of these studies would provide a promising and potent therapeutic approach for cancer treatment regimens.

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Declaration of competing interest

None.

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References

Awale, S., Lu, J., Kalauni, S.K., Kurashima, Y., Tezuka, Y., Kadota, S., Esumi, H., 2006. Identification of arctigenin as an antitumor agent having the ability to eliminate the tolerance of cancer cells to nutrient starvation. Canc. Res. 66, 1751–1757.

Baba, Y., Shigemi, Z., Hara, N., Moriguchi, M., Ikeda, M., Watanabe, T., Fujimuro, M., 2018. Arctigenin induces the apoptosis of primary effusion lymphoma cells under conditions of glucose deprivation. Int. J. Oncol. 52, 505–517.

Cai, E., Guo, S., Yang, L., Han, M., Xia, J., Zhao, Y., Gao, X., Wang, Y., 2018a. Synthesis and antitumour activity of arctigenin amino acid ester derivatives against H22 hepatocellular carcinoma. Nat. Prod. Res. 32, 406–411.

Cai, E., Song, X., Han, M., Yang, L., Zhao, Y., Li, W., Han, J., Tu, S., 2018b. Experimental study of the anti-tumour activity and pharmacokinetics of arctigenin and its valine ester derivative. Sci. Rep. 8, 3307.

Chen, Q., Yang, L., Han, M., Cai, E., Zhao, Y., 2016. Synthesis and pharmacological activity evaluation of arctigenin monoester derivatives. Biomed. Pharmacother. 84, 1792–1801.

Cho, M.K., Park, J.W., Jang, Y.P., Kim, Y.C., Kim, S.G., 2002. Potent inhibition of lipopolysaccharide-inducible nitric oxide synthase expression by dibenzylbutyrolactone lignans through inhibition of I-kappaBalpha phosphorylation and of p65 nuclear translocation in macrophages. Int. Immunopharm. 2, 105–116.

Cimino, S., Sortino, G., Favilla, V., Castelli, T., Madonia, M., Sansalone, S., Russo, G.I., Morgia, G., 2012. Polyphenols: key issues involved in chemoprevention of prostate cancer. Oxid Med Cell Longev 2012, 632959.

Feng, T., Cao, W., Shen, W., Zhang, L., Gu, X., Guo, Y., Tsai, H.I., Liu, X., Li, J., Zhang, J., Li, S., Wu, F., Liu, Y., 2017. Arctigenin inhibits STAT3 and exhibits anticancer potential in human triple-negative breast cancer therapy. Oncotarget 8, 329–344.

Gao, Q., Yang, M., Zuo, Z., 2018. Overview of the anti-inflammatory effects, pharmacokinetic properties and clinical efficacies of arctigenin and arctiin from Arctium lappa L. Acta Pharmacol. Sin. 39, 787–801.

Gao, Q., Zhang, Y., Wo, S., Zuo, Z., 2014. Elucidation of arctigenin pharmacokinetics after intravenous and oral administrations in rats: integration of in vitro and in vivo findings via semi-mechanistic pharmacokinetic modeling. AAPS J. 16, 1321–1333.

Greten, F.R., Grivennikov, S.I., 2019. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity 51, 27–41.

Gu, Y., Scheuer, C., Feng, D., Menger, M.D., Laschke, M.W., 2013. Inhibition of angiogenesis: a novel antitumor mechanism of the herbal compound arctigenin. Anti Canc. Drugs 24, 781–791.

Guo, S., Chen, Y., Shi, S., Wang, X., Zhang, H., Zhan, Y., An, H., 2020. Arctigenin, a novel TMEM16A inhibitor for lung adenocarcinoma therapy. Pharmacol. Res. 155, 104721.

Hahnfeldt, P., Panigrahy, D., Folkman, J., Hlatky, L., 1999. Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy. Canc. Res. 59, 4770–4775.

Han, Y.H., Kee, J.Y., Kim, D.S., Mun, J.G., Jeong, M.Y., Park, S.H., Choi, B.M., Park, S.J., Kim, H.J., Um, J.Y., Hong, S.H., 2016. Arctigenin inhibits lung metastasis of colorectal cancer by regulating cell viability and metastatic phenotypes. Molecules 21.

Hanahan, D., Weinberg, R.A., 2000. The hallmarks of cancer. Cell 100, 57–70.

Hao, Q., Diaz, T., Verduzco, A.D.R., Magyar, C.E., Zhong, J., Elshimali, Y., Rettig, M.B., Henning, S.M., Vadgama, J.V., Wang, P., 2020. Arctigenin inhibits prostate tumor growth in high-fat diet fed mice through dual actions on adipose tissue and tumor. Sci. Rep. 10, 1403.

He, B., Zhang, H.-J., Yang, W.-H., Shao, Z.-Y., Wu, L.-J., Chen, X.-B., Chen, J., Liu, W., Ran, Z.-P., Jin, R.-G., Cao, J.-Y., 2019. Pharmacokinetics of arctigenin and fructus Arctii powder in piglets. Frontiers in Veterinary Science 6, 235.

He, F., Dou, D.Q., Hou, Q., Sun, Y., Kang, T.G., 2013. Pharmacokinetic study of arctigenin in rat plasma and organ tissue by RP-HPLC method. Nat. Prod. Res. 27, 903–906.

Heinonen, S., Nurmi, T., Liukkonen, K., Poutanen, K., Wähälä, K., Deyama, T., Nishibe, S., Adlercreutz, H., 2001. In vitro metabolism of plant lignans: new precursors of mammalian lignans enterolactone and enterodiol. J. Agric. Food Chem. 49, 3178–3186.

Holler, N., Zaru, R., Micheau, O., Thome, M., Attinger, A., Valitutti, S., Bodmer, J.L., Schneider, P., Seed, B., Tschopp, J., 2000. Fas triggers an alternative, caspase-8-independent cell death pathway using the kinase RIP as effector molecule. Nat. Immunol. 1, 489–495.

Hsieh, C.J., Kuo, P.L., Hsu, Y.C., Huang, Y.F., Tsai, E.M., Hsu, Y.L., 2014. Arctigenin, a dietary phytoestrogen, induces apoptosis of estrogen receptor-negative breast cancer cells through the ROS/p38 MAPK pathway and epigenetic regulation. Free Radic. Biol. Med. 67, 159–170.

Huang, K., Li, L.A., Meng, Y.G., You, Y.Q., Fu, X.Y., Song, L., 2014. Arctigenin promotes apoptosis in ovarian cancer cells via the iNOS/NO/STAT3/survivin signalling. Basic Clin. Pharmacol. Toxicol. 115, 507–511.

Huang, Q., Qin, S., Yuan, X., Zhang, L., Ji, J., Liu, X., Ma, W., Zhang, Y., Liu, P., Sun, Z., Zhang, J., Liu, Y., 2017. Arctigenin inhibits triple-negative breast cancers by targeting CIP2A to reactivate protein phosphatase 2A. Oncol. Rep. 38, 598–606.

Ikeda, M., Sato, A., Mochizuki, N., Toyosaki, K., Miyoshi, C., Fujioka, R., Mitsunaga, S., Ohno, I., Hashimoto, Y., Takahashi, H., Hasegawa, H., Nomura, S., Takahashi, R., Yomoda, S., Tsuchihara, K., Kishino, S., Esumi, H., 2016. Phase I trial of GBS-01 for advanced pancreatic cancer refractory to gemcitabine. Canc. Sci. 107, 1818–1824.

Izuishi, K., Kato, K., Ogura, T., Kinoshita, T., Esumi, H., 2000. Remarkable tolerance of tumor cells to nutrient deprivation: possible new biochemical target for cancer therapy. Canc. Res. 60, 6201–6207.

Jeong, J.B., Hong, S.C., Jeong, H.J., Koo, J.S., 2011. Arctigenin induces cell cycle arrest by blocking the phosphorylation of Rb via the modulation of cell cycle regulatory proteins in human gastric cancer cells. Int. Immunopharm. 11, 1573–1577.

Jiang, Y., Liu, J., Hong, W., Fei, X., Liu, R., 2020. Arctigenin inhibits glioblastoma proliferation through the AKT/mTOR pathway and induces autophagy. BioMed Res. Int.

2020, 3542613.
Jordan, M.A., Wilson, L., 2004. Microtubules as a target for anticancer drugs. Nat. Rev. Canc. 4, 253–265.
Kato, J., Matsushime, H., Hiebert, S.W., Ewen, M.E., Sherr, C.J., 1993. Direct binding of cyclin D to the retinoblastoma gene product (pRb) and pRb phosphorylation by the cyclin D-dependent kinase CDK4. Genes Dev. 7, 331–342.
Kaufmann, S.H., Vaux, D.L., 2003. Alterations in the apoptotic machinery and their potential role in anticancer drug resistance. Oncogene 22, 7414–7430.
Ke, N., Liu, Q., Pi, L., Fang, J., Chen, L., Chen, X., 2019. The antitumor function of arctigenin in human retinoblastoma cells is mediated by jagged-1. Mol. Med. Rep. 19, 3642–3648.
Kim, J.Y., Hwang, J.H., Cha, M.R., Yoon, M.Y., Son, E.S., Tomida, A., Ko, B., Song, S.W., Shin-ya, K., Hwang, Y.I., Park, H.R., 2010. Arctigenin blocks the unfolded protein response and shows therapeutic antitumor activity. J. Cell. Physiol. 224, 33–40.
Könye, R., Ress, Á.E., Sólyomváry, A., Tóth, G., Darcsi, A., Komjáti, B., Horváth, P., Noszál, B., Molnár-Perl, I., Béni, S., Boldizsár, I., 2016. Enzyme-hydrolyzed fruit of Jurinea mollis: a rich source of (-)-(8R,8′R)-Arctigenin. Natural Product Communications 11 1934578X1601101011.
Korkina, L., Kostyuk, V., De Luca, C., Pastore, S., 2011. Plant phenylpropanoids as emerging anti-inflammatory agents. Mini Rev. Med. Chem. 11, 823–835.
Kudou, N., Taniguchi, A., Sugimoto, K., Matsuya, Y., Kawasaki, M., Toyooka, N., Miyoshi, C., Awale, S., Dibwe, D.F., Esumi, H., Kadota, S., Tezuka, Y., 2013. Synthesis and antitumor evaluation of arctigenin derivatives based on antiausterity strategy. Eur. J. Med. Chem. 60, 76–88.
Landete, J.M., 2012. Plant and mammalian lignans: a review of source, intake, metabolism, intestinal bacteria and health. Food Res. Int. 46, 410–424.
Laschke, M.W., Harder, Y., Amon, M., Martin, I., Farhadi, J., Ring, A., Torio-Padron, N., Schramm, R., Rücker, M., Junker, D., Häufel, J.M., Carvalho, C., Heberer, M., Germann, G., Vollmar, B., Menger, M.D., 2006. Angiogenesis in tissue engineering: breathing life into constructed tissue substitutes. Tissue Eng. 12, 2093–2104.
Lee, J., Imm, J.Y., Lee, S.H., 2017. β-Catenin mediates anti-adipogenic and anticancer effects of arctigenin in preadipocytes and breast cancer cells. J. Agric. Food Chem. 65, 2513–2520.
Lee, M.G., Lee, K.S., Nam, K.S., 2020a. Anti-metastatic effects of arctigenin are regulated by MAPK/AP-1 signaling in 4T-1 mouse breast cancer cells. Mol. Med. Rep. 21, 1374–1382.
Lee, Y.J., Nam, H.S., Cho, M.K., Lee, S.H., 2020b. Arctigenin induces necroptosis through mitochondrial dysfunction with CCN1 upregulation in prostate cancer cells under lactic acidosis. Mol. Cell. Biochem. 467, 45–56.
Lee, Y.J., Oh, J.E., Lee, S.H., 2018. Arctigenin shows preferential cytotoxicity to acidity-tolerant prostate carcinoma PC-3 cells through ROS-mediated mitochondrial damage and the inhibition of PI3K/Akt/mTOR pathway. Biochem. Biophys. Res. Commun. 505, 1244–1250.
Li, Q.C., Liang, Y., Tian, Y., Hu, G.R., 2016. Arctigenin induces apoptosis in colon cancer cells through ROS/p38MAPK pathway. J buon 21, 87–94.
Lin, S.-R., Chang, C.-H., Hsu, C.-F., Tsai, M.-J., Cheng, H., Leong, M.K., Sung, P.-J., Chen, J.-C., Weng, C.-F., 2020. Natural compounds as potential adjuvants to cancer therapy: preclinical evidence. Br. J. Pharmacol. 177, 1409–1423.
Linkermann, A., Green, D.R., 2014. Necroptosis. N Engl J Med 370, 455–465.
Lou, C., Zhu, Z., Zhao, Y., Zhu, R., Zhao, H., 2017. Arctigenin, a lignan from Arctium lappa L., inhibits metastasis of human breast cancer cells through the downregulation of MMP-2/-9 and heparanase in MDA-MB-231 cells. Oncol. Rep. 37, 179–184.
Lu, Z., Zhou, H., Zhang, S., Dai, W., Zhang, Y., Hong, L., Chen, F., Cao, J., 2020. Activation of reactive oxygen species-mediated mitogen-activated protein kinases pathway regulates both extrinsic and intrinsic apoptosis induced by arctigenin in Hep G2. J. Pharm. Pharmacol. 72, 29–43.
Magolan, J., Coster, M.J., 2010. Targeting the resistance of pancreatic cancer cells to nutrient deprivation: anti-austerity compounds. Curr. Drug Deliv. 7, 355–369.
Maxwell, T., Chun, S.Y., Lee, K.S., Kim, S., Nam, K.S., 2017. The anti-metastatic effects of the phytoestrogen arctigenin on human breast cancer cell lines regardless of the status of ER expression. Int. J. Oncol. 50, 727–735.
Maxwell, T., Lee, K.S., Kim, S., Nam, K.S., 2018. Arctigenin inhibits the activation of the mTOR pathway, resulting in autophagic cell death and decreased ER expression in ER-positive human breast cancer cells. Int. J. Oncol. 52, 1339–1349.
Mervai, Z., Sólyomváry, A., Tóth, G., Noszál, B., Molnár-Perl, I., Baghy, K., Kovalszky, I., Boldizsár, I., 2015. Endogenous enzyme-hydrolyzed fruit of Cirsium brachycephalum: optimal source of the antiproliferative lignan trachelogenin regulating the Wnt/β-Catenin signaling pathway in the SW480 colon adenocarcinoma cell line. Fitoterapia 100, 19–26.
Naoe, A., Tsuchiya, T., Kondo, Y., Uga, N., Watanabe, S., Yasui, T., Hara, F., Suzuki, T., 2019. Arctigenin induces apoptosis in human hepatoblastoma cells. Pediatr. Surg. Int. 35, 723–728.
Newman, D.J., Cragg, G.M., 2016. Natural products as sources of new drugs from 1981 to 2014. J. Nat. Prod. 79, 629–661.
Nik, M.E., Momtazi-Borojeni, A.A., Zamani, P., Navashenaq, J.G., Iranshahi, M., Jaafari, M.R., Malaekeh-Nikouei, B., 2019. Targeted-nanoliposomal combretastatin A4 (CA-4) as an efficient antivascular candidate in the metastatic cancer treatment. J. Cell. Physiol. 234, 14721–14733.
Okubo, S., Ohta, T., Shoyama, Y., Uto, T., 2020. Arctigenin suppresses cell proliferation via autophagy inhibition in hepatocellular carcinoma cells. J. Nat. Med. 74, 525–532.
Perou, C.M., Sørlie, T., Eisen, M.B., van de Rijn, M., Jeffrey, S.S., Rees, C.A., Pollack, J.R., Ross, D.T., Johnsen, H., Akslen, L.A., Fluge, Ø., Pergamenschikov, A., Williams, C., Zhu, S.X., Lønning, P.E., Børresen-Dale, A.-L., Brown, P.O., Botstein, D., 2000. Molecular portraits of human breast tumours. Nature 406, 747–752.
Qiao, S., Lv, C., Tao, Y., Miao, Y., Zhu, Y., Zhang, W., Sun, D., Yun, X., Xia, Y., Wei, Z., Dai, Y., 2020. Arctigenin disrupts NLRP3 inflammasome assembly in colonic macrophages via downregulating fatty acid oxidation to prevent colitis-associated cancer. Canc. Lett. 491, 162–179.
Quail, D.F., Olson, O.C., Bhardwaj, P., Walsh, L.A., Akkari, L., Quick, M.L., Chen, I.C., Wendel, N., Ben-Chetrit, N., Walker, J., Holt, P.R., Dannenberg, A.J., Joyce, J.A., 2017. Obesity alters the lung myeloid cell landscape to enhance breast cancer metastasis through IL5 and GM-CSF. Nat. Cell Biol. 19, 974–987.
Ragonnaud, E., Moritoh, K., Bodogai, M., Gusev, F., Garaud, S., Chen, C., Wang, X., Baljinnyam, T., Becker, K.G., Maul, R.W., Willard-Gallo, K., Rogaev, E., Biragyn, A., 2019. Tumor-derived thymic stromal lymphopoietin expands bone marrow B-cell precursors in circulation to support metastasis. Canc. Res. 79, 5826–5838.
Sah, N.K., Khan, Z., Khan, G.J., Bisen, P.S., 2006. Structural, functional and therapeutic biology of survivin. Canc. Lett. 244, 164–171.
Shabgah, A.G., Al-qaim, Z.H., Markov, A., Yumashev, A.V., Ezzatifar, F., Ahmadi, M., Gheibihayat, S.M., Navashenaq, J.G., 2021a. Chemokine CXCL14; a double-edged sword in cancer development. Int. Immunopharm. 97, 107681.
Shabgah, A.G., Qasim, M.T., Mostafavi, S.M., Zekiy, A.O., Ezzatifar, F., Ahmadi, M., Haftcheshmeh, S.M., Navashenaq, J.G., 2021b. CXC chemokine ligand 16: a Swiss army knife chemokine in cancer. Expet Rev. Mol. Med. 23.
Shi, H., Zhao, L., Guo, X., Fang, R., Zhang, H., Dong, G., Fu, J., Yan, F., Zhang, J., Ning, Z., Ma, Q., Li, Z., Li, C., Dai, J., Si, C., Xiong, H., 2020. Arctigenin Attenuates breast cancer progression through decreasing GM-CSF/TSLP/STAT3/β-Catenin signaling. Int. J. Mol. Sci. 21.
Smith, H.A., Kang, Y., 2013. The metastasis-promoting roles of tumor-associated immune cells. J. Mol. Med. (Berl.) 91, 411–429.
Solyomváry, A., Beni, S., Boldizsar, I., 2017. Dibenzylbutyrolactone lignans - a review of their structural Diversity, biosynthesis, occurrence, identification and importance. Mini Rev. Med. Chem. 17, 1053–1074.
Sólyomváry, A., Mervai, Z., Tóth, G., Ress, Á.E., Noszál, B., Molnár-Perl, I., Baghy, K., Kovalszky, I., Boldizsár, I., 2015a. A simple and effective enrichment process of the antiproliferative lignan arctigenin based on the endogenous enzymatic hydrolysis of Serratula tinctoria and Arctium lappa fruits. Process Biochem. 50, 2281–2288.
Sólyomváry, A., Tóth, G., Komjáti, B., Horváth, P., Kraszni, M., Noszál, B., Molnár-Perl, I., Boldizsár, I., 2015b. Identification and isolation of new neolignan and sesquineolignan species: their acid-catalyzed ring closure and specific accumulation in the fruit wall of Cirsium eriophorum (L.) Scop. Process Biochem. 50, 853–858.
Son, Y., Cheong, Y.-K., Kim, N.-H., Chung, H.-T., Kang, D.G., Pae, H.-O., 2011. Mitogen-activated protein kinases and reactive oxygen species: how can ROS activate MAPK pathways?. J Signal Transduct 2011 792639-792639.
Susanti, S., Iwasaki, H., Inafuku, M., Taira, N., Oku, H., 2013. Mechanism of arctigenin-mediated specific cytotoxicity against human lung adenocarcinoma cell lines. Phytomedicine 21, 39–46.
Takebe, N., Miele, L., Harris, P.J., Jeong, W., Bando, H., Kahn, M., Yang, S.X., Ivy, S.P., 2015. Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update. Nat. Rev. Clin. Oncol. 12, 445–464.
Tanida, I., Ueno, T., Kominami, E., 2008. LC3 and autophagy. Methods Mol. Biol. 445, 77–88.
Umezawa, T., 2003. Diversity in lignan biosynthesis. Phytochemistry Rev. 2, 371–390.
Wang, H.Q., Jin, J.J., Wang, J., 2014. Arctigenin enhances chemosensitivity to cisplatin in human nonsmall lung cancer H460 cells through downregulation of survivin expression. J. Biochem. Mol. Toxicol. 28, 39–45.
Wang, P., Phan, T., Gordon, D., Chung, S., Henning, S.M., Vadgama, J.V., 2015. Arctigenin in combination with quercetin synergistically enhances the antiproliferative effect in prostate cancer cells. Mol. Nutr. Food Res. 59, 250–261.
Wang, S., El-Deiry, W.S., 2003. TRAIL and apoptosis induction by TNF-family death receptors. Oncogene 22, 8628–8633.
Wang, Y., Lina, L., Xu, L., Yang, Z., Qian, Z., Zhou, J., Suoni, L., 2019. Arctigenin enhances the sensitivity of cisplatin resistant colorectal cancer cell by activating autophagy. Biochem. Biophys. Res. Commun. 520, 20–26.
Xu, Y., Lou, Z., Lee, S.H., 2017. Arctigenin represses TGF-β-induced epithelial mesenchymal transition in human lung cancer cells. Biochem. Biophys. Res. Commun. 493, 934–939.
Yang, S., Ma, J., Xiao, J., Lv, X., Li, X., Yang, H., Liu, Y., Feng, S., Zhang, Y., 2012. Arctigenin anti-tumor activity in bladder cancer T24 cell line through induction of cell-cycle arrest and apoptosis. Anat. Rec. 295, 1260–1266.
Yang, Z.J., Chee, C.E., Huang, S., Sinicrope, F.A., 2011. The role of autophagy in cancer: therapeutic implications. Mol. Canc. Therapeut. 10, 1533–1541.
Yao, X., Zhu, F., Zhao, Z., Liu, C., Luo, L., Yin, Z., 2011. Arctigenin enhances chemosensitivity of cancer cells to cisplatin through inhibition of the STAT3 signaling pathway. J. Cell. Biochem. 112, 2837–2849.
Yoo, J.H., Lee, H.J., Kang, K., Jho, E.H., Kim, C.Y., Baturen, D., Tunsag, J., Nho, C.W., 2010. Lignans inhibit cell growth via regulation of Wnt/beta-catenin signaling. Food Chem. Toxicol. 48, 2247–2252.
Yoon, S.B., Park, H.R., 2019. Arctigenin inhibits etoposide resistance in HT-29 colon cancer cells during microenvironmental stress. J. Microbiol. Biotechnol. 29, 571–576.
Zaki, M.H., Boyd, K.L., Vogel, P., Kastan, M.B., Lamkanfi, M., Kanneganti, T.D., 2010. The NLRP3 inflammasome protects against loss of epithelial integrity and mortality during experimental colitis. Immunity 32, 379–391.
Zhang, M., Cai, S., Zuo, B., Gong, W., Tang, Z., Zhou, D., Weng, M., Qin, Y., Wang, S., Liu, J., Ma, F., Quan, Z., 2017. Arctigenin induced gallbladder cancer senescence through modulating epidermal growth factor receptor pathway. Tumour Biol 39 1010428317698359.
Zhu, L., Shen, X.B., Yuan, P.C., Shao, T.L., Wang, G.D., Liu, X.P., 2020. Arctigenin inhibits proliferation of ER-positive breast cancer cells through cell cycle arrest mediated by GSK3-dependent cyclin D1 degradation. Life Sci. 256, 117983.