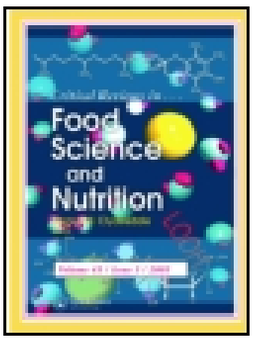

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Sayeh Mottaghi & Hassan Abbaszadeh (2021): A comprehensive mechanistic insight into the dietary and estrogenic lignans, arctigenin and sesamin as potential anticarcinogenic and anticancer agents. Current status, challenges, and future perspectives, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1913568

To link to this article: https://doi.org/10.1080/10408398.2021.1913568

Published online: 27 Apr 2021.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1913568

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REVIEW

A comprehensive mechanistic insight into the dietary and estrogenic lignans, arctigenin and sesamin as potential anticarcinogenic and anticancer agents. Current status, challenges, and future perspectives

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ABSTRACT

A large body of evidence indicates that lignans as polyphenolic compounds are beneficial against life-threatening diseases such as cancer. Plant lignans have the potential to induce cancer cell death and interfere with carcinogenesis, tumor growth, and metastasis. Epidemiological studies have revealed that the intake of lignans is inversely associated with the risk of several cancers. Moreover, numerous experimental studies demonstrate that natural lignans significantly suppress cancer cell proliferation with minimal toxicity against non-transformed cells. Dietary lignans arctigenin and sesamin have been found to have potent antiproliferative activities against various types of human cancer. The purpose of this review is to provide the reader with a deeper understanding of the cellular and molecular mechanisms underlying anticancer effects of arctigenin and sesamin. Our review comprehensively describes the effects of arctigenin and sesamin on the signaling pathways and related molecules involved in cancer cell proliferation and invasion. The findings of present review show that the dietary lignans arctigenin and sesamin seem to be promising carcinopreventive and anticancer agents. These natural lignans can be used as dietary supplements and pharmaceuticals for prevention and treatment of cancer.

KEYWORDS

Arctigenin; sesamin; lignans; anticarcinogenic effects; anticancer effects; molecular mechanisms

Introduction

Overview of cancer and natural lignans

Cancer has become one of most serious health threats worldwide with about 9.6 million deaths in 2018 (Nagai and Kim 2017) (Bray et al. 2018). Cancer is a heterogeneous disease, in which many signal transduction pathways are affected (Pereira, Billaud, and Almeida 2017). The processes of initiation, promotion, and progression are necessary for the development and invasiveness of malignant tumors (Siddiqui et al. 2015). In cancer cells, there is a disrupted cell cycle, uncontrolled cell proliferation, and dysregulated pathways associated with cell death such as apoptosis (Sever and Brugge 2015). The severe toxic effects of currently used chemotherapeutic drugs have prompted scientists to discover novel phytochemicals for cancer chemoprevention and treatment (Cragg and Pezzuto 2016). Many epidemiological, preclinical, and clinical studies have reported that polyphenols possess chemopreventive and anticancer effects (Amawi et al. 2017). Polyphenols are a wide variety of phytochemicals and plant metabolites found abundantly in fruits, vegetables, spices, soy, nuts, tea, and wine (Angeloni et al. 2015). The chemical structures of this group of natural products are highly diverse and complex (Amawi et al. 2017). Based on the number of aromatic rings and the interconnection of these rings, polyphenols can be categorized into four major groups, including flavonoids, phenolic acids, stilbenes, and lignans (Abbaszadeh, Keikhaei, et al. 2019; Amawi et al. 2017). Plant lignans are bioactive compounds, which are biosynthetically derived from phenylpropanoids (Marcotullio, Curini, and Becerra 2018). These natural compounds are found in a variety of plant foods such as sesame seeds, flax seeds, whole grains, fruits, and vegetables (Landete 2012) . Many studies demonstrate that natural lignans possess a variety of biological properties such as antioxidant, antiallergic, anti-inflammatory, antithrombotic, antihyperlipidemic, antibacterial, antiprotozoal, antiviral, antiangiogenic, and anticancer effects (Marcotullio, Curini, and Becerra 2018; Teponno, Kusari, and Spiteller 2016; Xin et al. 2013; Zanwar, Hegde, and Bodhankar 2014; Zanwar, Hegde, and Bodhankar 2014). Lignans have been reported to have in vivo and in vitro antiproliferative activities against a variety of human cancer cell lines (De Silva and Alcorn 2019; Ezzat et al. 2018). These natural compounds can inhibit various phases of carcinogenesis, including initiation, promotion, and progression by modulating different signaling pathways (De Silva and Alcorn 2019). Inhibitory effects of natural lignans on cancer cell proliferation could be attributed to various molecular mechanisms, including modulation of a wide variety of transcription factors,

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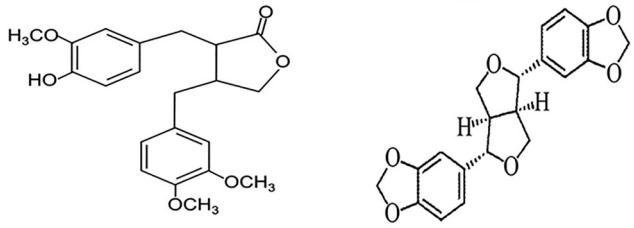

Figure 1. Chemical structures of arctigenin and sesamin.

receptor tyrosine kinases, cell surface adhesion molecules, membrane receptors, and cell signaling pathways (Ong et al. 2019). Cancer chemoprevention with natural compounds is a promising approach to reverse, suppress or prevent one or more of the biological events, leading to the development of malignant tumors (Wang et al. 2012). Many human epidemiological studies have indicated the potential effects of dietary lignans on the prevention of several types of cancer (Rodríguez-García et al. 2019). The consumption of dietary lignans has been shown to be associated with a reduced risk of different types of cancer (Hedelin et al. 2006; Lin et al. 2012; Zamora-Ros et al. 2014). Plant lignans have drawn the attention of many researchers due to their potent antiproliferative effects such as the anticancer activities of podophyllotoxin and its derivatives (etoposide and teniposide) (Pusztai et al. 2010). Indeed, anticancer effects of several plant lignans have been evaluated in phase I and II clinical trials (Luo et al. 2014). To further explore the lignans with potent anticarcinogenic and anticancer effects, it is necessary to have a deeper understanding of their anticancer cellular and molecular mechanisms. To the best of our knowledge, among dietary lignans with anticancer activities, only antiproliferative effects of dietary lignans arctigenin and sesamin have been widely studied so far. Therefore, the current study aimed at providing a comprehensive review to mechanistically elucidate the anticancer activities of arctigenin and sesamin. In the past few years, numerous studies have focused on in vivo and in vitro antiproliferative effects of dietary lignans arctigenin and sesamin on various malignant tumors (Figure 1). Many experimental studies demonstrate that arctigenin and sesamin have the ability to potently act against various types of human cancer (He et al. 2018; Majdalawieh, Massri, and Nasrallah 2017).

Overview of dietary lignans arctigenin and sesamin

Natural lignan arctigenin is the major bioactive constituent of Arctium lappa (Burdock), which has long been consumed as a popular vegetable in North and South America, Europe, and Asia, especially in China because of its remarkable health benefits (Maxwell et al. 2017). Arctium lappa has widely been employed in traditional medicine for treatment of hepatitis, hypertension, gout, and inflammatory diseases (Predes et al. 2011). Recent studies have indicated that Arctium lappa possesses potent anticancer effects against various types of human cancer cells (Agha et al. 2020; Don and Yap 2019). Arctigenin as a natural lignan has been reported to be responsible for beneficial effects of Arctium lappa (Gao, Yang, and Zuo 2018; Wu et al. 2014). This plant lignan has attracted much attention due to its promising therapeutic effects. Arctigenin has demonstrated to possess a range of bioactive properties in vivo and in vitro such as anti-oxidant, anti-inflammatory, antiviral, neuroprotective, immune modulatory, and anticancer effects (Lu et al. 2018). Sesamin is one of the most abundant lignans in seeds of sesame (Sesamum indicum), which has been used as a dietary supplement (nutrient-rich food) with beneficial effects on human health for thousands of years in almost all the countries in the world (Nagendra Prasad et al. 2012). Sesame seed as a source of nutritional and bioactive constituents, is known to have remarkable antioxidant, antihypertensive, anti-inflammatory, antihyperlipidemic, and anticancer effects (Hsu and Parthasarathy 2017; Lin et al. 2014; Wichitsranoi et al. 2011). Sesamin, as the major component of sesame, has been found to have a variety of biological and pharmacological effects, including anti-oxidative, anti-inflammatory, antihypertensive, neuroprotective, hypocholesterolemic, antidiabetic, immunomodulatory, and anticancer effects (Ahmad et al. 2016; Guo et al. 2015; Harikumar et al. 2010; Hong et al. 2013; Zhang et al. 2013). In the past few years, numerous studies have focused on the antiproliferative effects of dietary lignans arctigenin and sesamin on various types of cancer. Many in vitro and in vivo studies demonstrate that arctigenin and sesamin possess potent anticancer effects (Hsieh et al. 2014; Majdalawieh, Massri, and Nasrallah 2017). These natural lignans exert their anticancer effects by targeting a variety of molecular targets and signaling pathways (Hsieh et al. 2014; Majdalawieh, Massri, and Nasrallah 2017).

Methods

Search strategy

In this review, the relevant literature was collected by using arctigenin, sesamin, lignans, anticarcinogenic effects, anticancer effects and molecular mechanisms as the keywords from multiple scientific databases, including PubMed, Web of Science, Science Direct, Google Scholar, Wiley, ACS Publications, Springer, Europe PMC and Taylor & Francis up to November 2020.

Inclusion/exclusion criteria

In the present review, the following criteria were applied for inclusion: (1) cellular and animal studies with anticancer and antiproliferative effects of arctigenin and sesamin; (2) studies reporting molecular targets and signaling pathways involved in the anticancer activities of arctigenin and sesamin; (3) studies showing pharmacological and biological effects of arctigenin and sesamin; (4) studies indicating safety, selective toxicity, and natural sources of arctigenin and sesamin; (5) studies reporting molecular mechanisms underlying anticarcinogenic and anticancer effects of natural lignans. Studies with anticancer effects and molecular

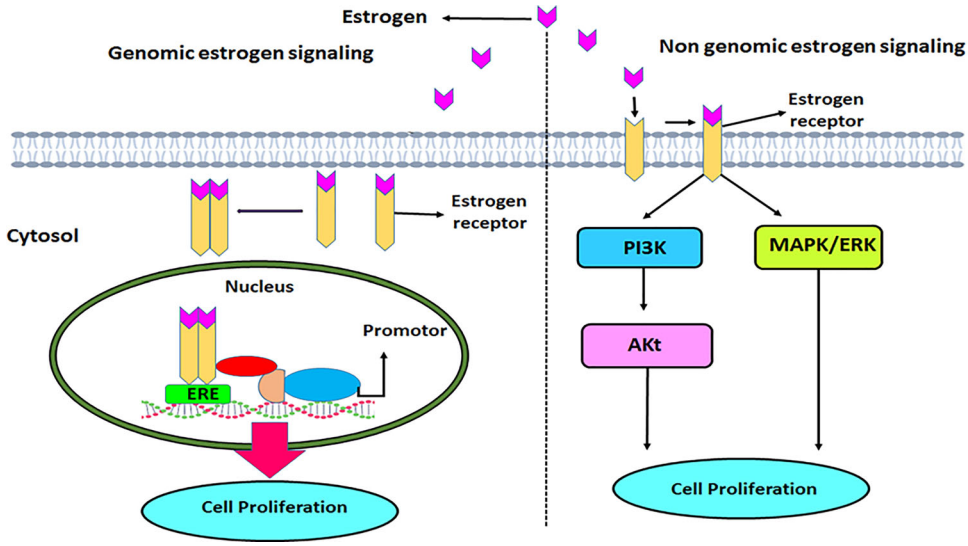

Figure 2. Simplified diagram of genomic and non-genomic signaling pathways of estrogen receptors. In the genomic pathway, estrogen binds to its receptor, which then dimerizes and translocates to nucleus and binds to estrogen response element (ERE) and regulates estrogen responsive genes. In the non-genomic pathway, estrogen interact with membrane-bound classical estrogen receptors (ERs), leading to the activation of MAPK or other cytoplasmic signaling pathways and rapid changes in protein function.

mechanisms of non-polyphenolic compounds or other bioactive compounds were excluded.

Selective cytotoxicity of arctigenin and sesamin

Several studies have demonstrated the selective cytotoxicity of arctigenin and sesamin against various cancer cell lines. Theses plant lignans have the potential to inhibit cancer cell proliferation with little or no toxicity against normal cells (Akl et al. 2013; He et al. 2018). Sesamin has been reported to have no toxic effect on human skin fibroblasts cells (Lin et al. 2019). Moreover, sesamin tratment (up to 100 µM) has shown no effect on the viability of human aortic endothelial cells (HAECs) (Wu et al. 2010). Studies have indicated that arctigenin has no significant toxicity against lung fibroblast cells and normal mammary epithelial cells (Hsieh et al. 2014). This dietary lignan has also exhibited no toxicity toward normal colon cance cells (Han et al. 2016). Arctigenin has been found to have low toxicity on normal hepatic cells (Lu et al. 2015).

In vitro studies

Major molecular targets and signaling pathways involved in anticancer effects of dietary lignans, arctigenin and sesamin

Estrogen receptors and anticancer activities of arctigenin and sesamin

Estrogens are a group of steroid hormones derived from cholesterol, which are implicated in several physiological processes by acting on different tissues (Capper, Rae, and Auchus 2016). At the cellular level, estrogens have been found to affect multiple cellular processes, including cell survival, proliferation, and differentiation (Lecomte et al. 2017). Estrogens exert their influences by binding to two estrogen receptors, ERα and ER*β*, which are found in the cytoplasm and in the nucleus (Fuentes and Silveyra 2019). ERα is greatly expressed in female reproductive tissues (Ovaries, uterus, and mammary glands). ER*β* is strongly expressed in ovaries but weakly expressed in the mammary gland. In men, ERα is mostly found in the testicle (Leydig cells and gubernaculum), whereas ER*β* is expressed in the prostate, germinal cells, and epididymis (Lecomte et al. 2017). In response to estrogens, estrogen-ER complex translocates into the nucleus and interacts with specific DNA sequences known as estrogen response elements (EREs), leading to the transactivation of gene expression (Le Dily and Beato 2018; Lecomte et al. 2017). In contrast to the genomic action, the non-genomic actions of estrogens involve cytoplasmic signaling pathways, which occur rapidly and lead to the activation of multiple intracellular signaling pathways such as MAPK (mitogen activated protein kinase) or PI3K (Lecomte et al. 2017) (Figure 2). Many natural compounds present in vegetables and plants called phytoestrogens, possess estrogenic or antiestrogenic activities with potential antiproliferative activities that provide considerable nutritional or pharmacological benefits (Rietjens, Louisse, and Beekmann 2017). Phytoestrogens are non-steroidal phenolic compounds, which have a structural or functional similarity to endogenous estradiol. These plant compounds exert estrogenic or antiestrogenic effects by interacting with the estrogen receptors (Basu and Maier 2018). Phytoestrogens can competitively bind to estrogen receptors (ERs) α and *β*, preventing more potent endogenous estrogen and estrogen metabolites from binding to estrogen receptors (Lecomte et al. 2017). In many breast cancers, the proliferative effect due to ERα activation is counteracted by the presence of ER*β*, which exerts an antiproliferative effect (Chang et al. 2006). The activation of ER*β* has been found to induce apoptosis and cell cycle arrest (Lecomte et al. 2017). It is well documented that phytoestrogens exhibit higher affinity for ER-*β* compared to ER-α and act as agonists, partial agonists, and antagonists (Paterni et al. 2014). The two major

Table 1. Anticancer cellular and molecular mechanisms of arctigenin and sesamin (In vitro studies).

Lignan	Type of cancer	Anticancer molecular mechanisms
Arctigenin	breast, ovarian, lung, liver , colorectal, gastric, and prostate cancers	Induction of apoptosis (via up-regulation of Bax, Fas/FasL, and TNF-α, down-regulation of Bcl-2, activation of caspase-9 ,8 and −3 and p38 MAPK, and suppression of the iNOS/NO/STAT3/survivin signaling) Induction of autophagy (by activating the AMPK signaling molecule and suppressing the mTOR pathway) Induction of cell cycle arrest (via downregulation of cyclin A, cyclin E, cyclin D1 , CDK2, and CDK4, suppression of Rb protein phosphorylation, and upregulation of p53 and p21) Inhibition of angiogenesis (by inhibiting the Akt signaling pathway and reducing the expression of VEGF receptor 2) ROS generation Anti-estrogenic effects Inhibition of migration and invasion of cancer cells (via downregulatinon of the expression of MMP-2 and MMP-9 and suppression of EMT) Inhibition of PI3K/Akt/mTOR signaling pathway Suppression of NF-κB signaling pathway Activation of p38 MAPK pathway Inhibition of the phosphorylation of ERK 1/2 and JNK 1/2
Sesamin	Liver, breast, lung, colorectal, prostate, and cervical cancers and leukemia	Induction of apoptosis (via upregultion of Bax/Bcl-2 ratio, down-regulation of Bcl-2 and Bcl-xL, activation of caspase-3 ,inhibition of the pAkt PI3K signaling pathway, and induction of ER stress) Induction of autophagy (by activating IRE1α/JNK pathway and increasing the levels of unphosphorylated -EphA1 and -EphB2 receptor tyrosine kinases) Induction of cell cycle arrest (through upregulation of p53 and p21 and downregulation of cyclin A , cyclin B cyclin E1, cyclin D1 and CDK2, and inhibition of Akt activity,) Inhibition of angiogenesis (via downregulation of MMP-2 gene expression and suppression of TNF-alpha and VEGF expression) Anti-estrogenic effects Inhibition of migration and invasion of cancer cells (by suppressing the expression of MMP-9 protein via the p38-MAPK and NF-κB signaling pathways, and inhibition of EMT) Inhibition of the pAkt-PI3K signaling pathway Suppression of NF-κB signaling pathway Suppression of P-p38 MAPK and p-JNK1/2

groups of phytoestrogens are isoflavones (eg., daidzein and genistein) and lignans (Talaei and Pan 2015). A number of plant lignans have been found to modulate estrogen signaling pathways (Kiyama 2016; Talaei and Pan 2015; Zhu, Kawaguchi, and Kiyama 2017). Dietary lignans arctigenin and sesamin have shown to have anti-estrogenic effects (Hsieh et al. 2014; Pianjing et al. 2011; Truan, Chen, and Thompson 2012; Zhu, Kawaguchi, and Kiyama 2017). These plant lignans can participate in both estrogenic and antiestrogenic effects by activating or blocking estrogen receptors, which lead to the inhibition of breast cancer cell proliferation (Lecomte et al. 2017) (Table 1).

Apoptosis pathway and anticancer activities of arctigenin and sesamin

Apoptosis constitutes a highly conserved molecular process of programmed cell death that occurs in physiological and pathological conditions. Apoptosis can be mediated through the activation of two pathways: the extrinsic cell death pathway and the intrinsic cell death pathway (Green and Llambi 2015; Hafezi et al. 2020). The intrinsic or mitochondrial pathway is regulated by the B cell lymphoma (Bcl-2) family proteins (Hardwick and Soane 2013). Bcl-2 family proteins are important regulators of cell death and survival, which are divided into two major categories: the anti-apoptotic members (Bcl-2, Bcl-xl, and MCL-1) and pro-apoptotic members (Bax, Bad, Bak, and Bid) (Abbaszadeh, Keikhaei, et al. 2019; Popgeorgiev, Jabbour, and Gillet 2018). These proteins regulate programmed cell death by modulating the outer mitochondrial membrane permeabilization (Gillies and Kuwana 2014). The anti-apoptotic Bcl-2 proteins directly inhibit the activity of pro-apoptotic proteins, which leads to the suppression of apoptosis. Pro-apoptotic proteins such as Bax directly enhances the mitochondrial outer membrane permeabilization that leads to the release of cytochrome c into the cytosol during apoptosis (Czabotar et al. 2014). Bax is known to be the major transcriptional target of p53, which is transactivated in a number of systems during p53-mediated apoptosis (Aubrey et al. 2018). The extrinsic apoptotic pathway is initiated by binding of cytokine ligands to death receptors (DR) such as Fas (also known as CD95), TRAIL receptor (TRAIL-R) or tumor necrosis factor receptor 1 (TNFR1). Both pathways induce cell death by activating caspase cascade (Green and Llambi 2015). Many studies carried out across the world have demonstrated that dietary lignans arctigenin and sesamin have the potential to significantly cause cancer cell death by inducing apoptosis through several molecular mechanisms (Deng et al. 2013; Hsieh et al. 2014) (Figure 3). Natural lignan arctigenin has been found to induce apoptosis in various cancer cells such as breast (Feng et al. 2017), ovarian (Huang et al. 2014), liver (Lu et al. 2015), and colon cancers (Li et al. 2016) via different signaling pathways. Studies demonstrate that arctigenin triggers apoptosis in breast cancer cells through caspase-dependent apoptosis by activating caspase- 9 and −3 (Feng et al. 2017). Arctigenin is able to significantly provoke apoptosis in ovarian cancer cells, which is associated with suppression of the iNOS/NO/STAT3/survivin signaling (Huang et al. 2014) . This dietary lignan also has the potential to trigger apoptosis in Hep G2 and SMMC7721 cells through a mitochondrial apoptosis pathway. Arctigenin treatment leads

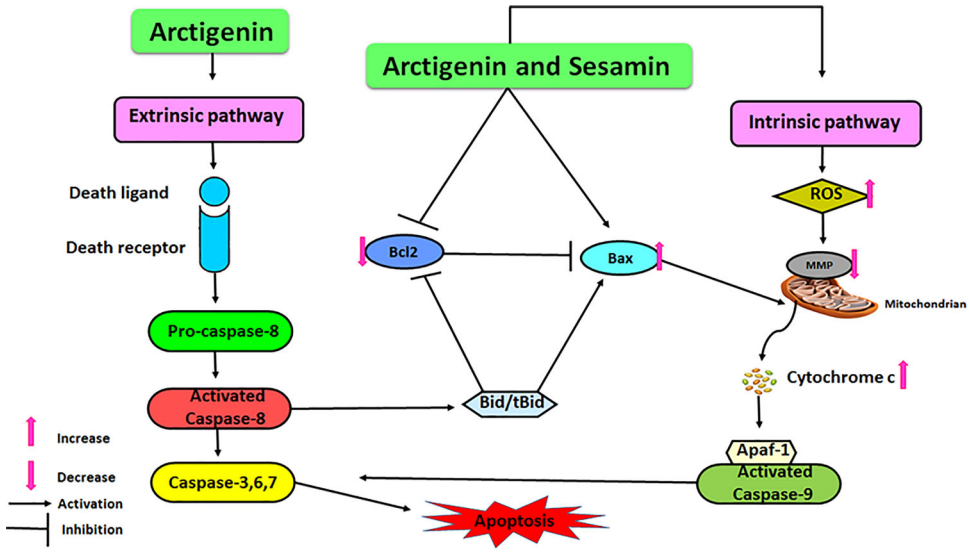

Figure 3. Schematic representation of arctigenin and sesamin effects on apoptosis. The natural lignan arctigenin executes cancer cells by inducing apoptosis via intrinsic mitochondrial and extrinsic death receptor pathways. The dietary lignan sesamin triggers apoptotic cell death in various human cancer cells by activating intrinsic mitochondrial pathway.

to the collapse of mitochondrial membrane potential, up-regulation of Bax, down-regulation of Bcl-2, release of cytochrome c, activation of caspase-9 and −3 and cleavage of poly (ADP-ribose) polymerase (PARP) in Hep G2 and SMMC7721 cells. Arctigenin activates caspase-8 and enhances the expression levels of Fas/FasL and TNF-α, suggesting that the Fas/FasL pathway is also implicated in apoptosis induced by arctigenin in hepatocellular carcinoma cell lines (Lu et al. 2015). Arctigenin has been found to promote apoptosis in HT-29 colon cancer cell line via ROS production, loss of mitochondrial membrane potential (MMP), activation of p38 MAPK, caspase-9, and −3 (Li et al. 2016). Sesamin has been found to induce apoptosis in HepG2 cells via downregulation of Bcl-2 and Bcl-xL (Deng et al. 2013). This plant lignan inhibits the pAkt-PI3K signaling pathway by downregulating the expression of COX-2, leading to increased apoptosis in lung cancer cells (Fang et al. 2019). Sesamin significantly triggers apoptosis in HeLa cells through ER stress by regulating the IRE1α/JNK pathway (Dou et al. 2018). It also induces apoptosis in human breast cancer MCF-7 cells by enhancing the expression levels of Bax and caspase-3 (Siao et al. 2015). Sesamin has the potential to trigger apoptotic death in human leukemia cells by enhancing the ROS generation and activating the intrinsic mitochondrial pathway (Banjerdpongchai, Yingyurn, and Kongtawelert 2010) (Table 1).

Autophagy pathway and anticancer activities of arctigenin and sesamin

Autophagy is a lysosome-mediated degradation and recycling pathway, which plays a fundamental role in cell survival, proliferation, and differentiation (Chun and Kim 2018). Although autophagy is well known as a cell survival process that promotes tumor development, it can also be described as a caspase independent form of programmed cell death (PCD) called autophagy induced cell death or autophagy-associated cell death (type II PCD) (Linder and Kögel 2019). During autophagy, an isolation membrane engulfs cytoplasmic components to form a double-membraned structure called an autophagosome. The outer membrane of an autophagosome then fuses with the membrane of lysosomes to form an autolysosome, allowing lysosomal enzymes to digest the sequestered cytoplasmic components (Lu et al. 2015; Yun and Lee 2018). Simultaneously, a cytosolic form of LC3 (LC3-I) is converted to LC3-phosphatidylethanolamine conjugate (LC3-II), which is localized in both the outer and inner membranes of the autophagosome. LC3-II is used as most important indicator of autophagy to monitor autophagy activity (Yoshii and Mizushima 2017). Autophagy process is regulated by several key factors, including autophagy-related genes (ATG) and their proteins and signaling complexes (Bednarczyk et al. 2018). Beclin-1 protein also named Atg 6, is considered to be one of the essential components of ATG proteins (Toton et al. 2014). It is well known that the induction of autophagy is regulated by the level of cellular ATP and energy, which are detected by adenosine monophosphate–activated protein kinase (AMPK) – a cellular energy sensor (Kim et al. 2011). AMPK is activated in response to the low ratio of ATP/AMP and nutrient deprivation through its upstream kinase, liver kinase BQ (LKB1kinase) (Hardie, Ross, and Hawley 2012). AMPK is known to directly suppress the activity of the mammalian target of rapamycin 1 (mTORC1). Inactivated mTOR has been found to be involved in autophagy induction by activating the ULK1-ATG13-FIP200 complex (Yang et al. 2015). Autophagy induction has the potential to prevent tumor initiation and increase anti-tumor immune responses. In cancer cells, autophagy activation can induce cell death and inhibits cell survival, which lead to the suppression of tumorigenesis (Bishop and Bradshaw 2018). Lignans as natural compounds have been found to significantly induce cancer cell death not only by affecting the apoptosis pathway, but also via activation of autophagy

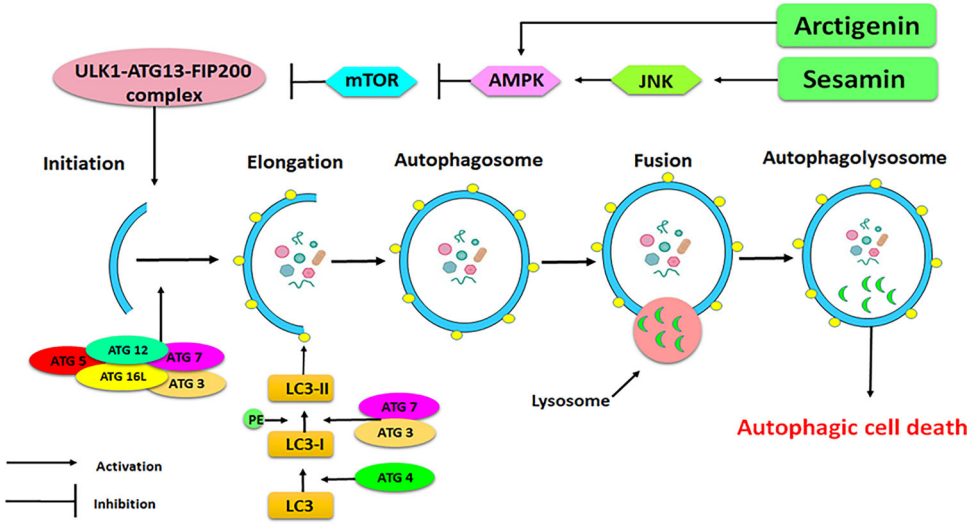

Figure 4. Role of the plant lignans arctigenin and sesamin in the modulation of autophagy in cancer cells. These dietary lignans induce autophagy process in cancer cells by regulating signaling pathways such as MTOR and AMPK pathways.

pathway (Ong et al. 2019) In this review, we will describe the effects of dietary lignans arctigenin and sesamin on autophagy signaling pathway, which is involved in their anticancer potentials (Figure 4). Arctigenin has the potential to significantly activate autophagy pathway in MCF-7 cells by activating the AMPK signaling molecule and suppressing the mTOR pathway (Maxwell et al. 2018). Sesamin has been found to remarkably induce autophagic death in cervical cancer cells (HeLa) by activating IRE1α/JNK pathway (Dou et al. 2018). Sesamin treatment also triggers autophagy in colon cancer HT-29 cells by increasing the levels of unphosphorylated -EphA1 and -EphB2 receptor tyrosine kinases (Tanabe et al. 2011) (Table 1).

Cell cycle and anticancer activities of arctigenin and sesamin

Cell growth and division are tightly regulated by a conserved biological process: the cell cycle (Bai, Li, and Zhang 2017) . The progression of cell cycle from one phase to another is controlled through various cyclins and cyclin-dependent kinases (CDK), by phosphorylating the target proteins (Hydbring, Malumbres, and Sicinski 2016). The cyclins control the activities of CDKs and play an essential role in cell cycle regulation (Bai, Li, and Zhang 2017). As cells proceed through a sequence of phases in cell cycle, four major classes of cyclins are generated sequentially (D, E, A, and B), which activate CDKs. Entry into S-phase is regulated by the activation of the cyclin E and D (cyclins D1, D2, and D3), and progression through S phase requires cyclin A. Cyclin B has been identified as a mitotic cyclin, which is essential to take cells into mitosis (Duronio and Xiong 2013). During tumorigenesis, there is an imbalance between the action of cell cycle progression proteins and cell cycle arrest proteins, leading to the marked cell division and proliferation (Otto and Sicinski 2017). A number of CDK inhibitors (CDKi) such as p15, p16, p21, p27, p53, and retinoblastoma tumor suppressor protein (RB) have been found to suppress cell cycle progression and induce cell cycle arrest (Law et al. 2015). Numerous lignans-treated cancer cells have shown downregulation of cyclins and CDKs as well as upregulation of CDKi, consequently resulting in cell cycle arrest (Hahm and Singh 2007; Jeong et al. 2011). Dietary lignans arctigenin and sesamin have the ability to induce cell cycle arrest in cancer cells by targeting a variety of cell cycle regulatory proteins (Deng et al. 2013; Maimaitili et al. 2017) (Figure 5). It has been reported that arctigenin treatment results in the cell cycle arrest at the G0/G1 phase in glioma cells by increasing the expression levels p53, p21, and retinoblastoma proteins and decreasing the expression levels of cyclin D1 and CDK4 proteins (Maimaitili et al. 2017). Arctigenin has the potential to induce cell cycle arrest at the G2/M1 via downregulation of cyclin A, cyclin E, and CDK2 in CT26 cells (Han et al. 2016). This natural lignan causes cell cycle arrest at the G0/G1 phase by targeting the cell cycle regulatory proteins in human gastric adenocarcinoma cell lines SNU-1 and AGS. Arctigenin results in a significant accumulation of cells in the G0/G1 phase by inhibiting the phosphorylation of Rb protein, upregulating the expression of p21 and p15 and downregulating the expression of cyclin D1, cyclin E, CDK2, and CDK4 in SNU-1and AGS cells (Jeong et al. 2011). Treatment with sesamin triggers cell cycle arrest at G1 phase via inhibition of Akt activity, upregulation of p53, and downregulation of cyclin D1 and CDK2 expression in non-small-cell lung carcinoma A549 and H1792 cells (Chen, Chen, et al. 2020). Sesamin has been found to inhibit the proliferation of HepG2 cells by inducing G2/M phase arrest via suppression of signal transducer and activator of transcription 3 (STAT3) signaling in HepG2 cells, leading to upregulation of p53 and p21 and downregulation of cyclin A and cyclin B (Deng et al. 2013). The studies indicate that the inhibition of COX-2 expression in lung cancer cells-treated with sesamin is associated with the downregulation of cyclin E1 and cell cycle arrest (Fang et al. 2019) (Table 1).

Angiogenesis and anticancer activities of arctigenin and sesamin

Angiogenesis, the process leading to the generation of new blood vessels from preexisting vessels, plays a fundamental

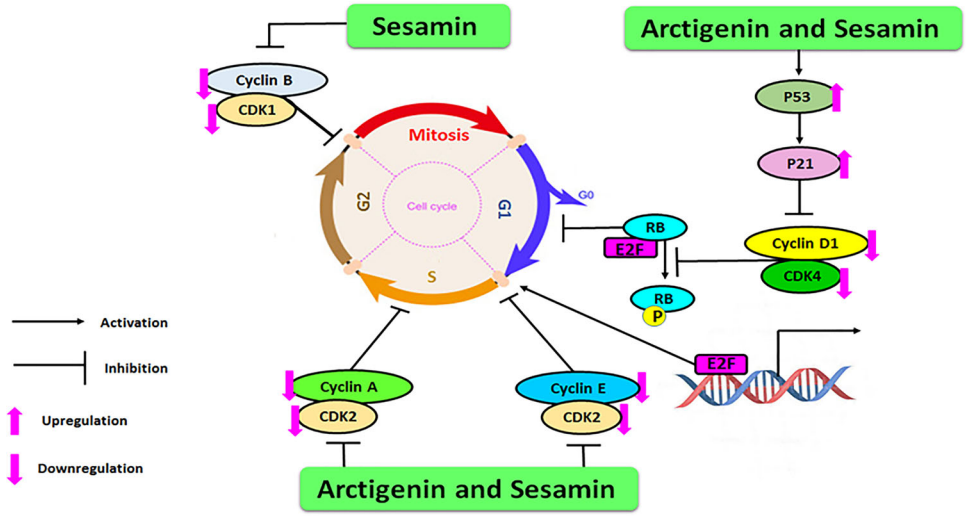

Figure 5. Schematic illustration of arctigenin and sesamin effects on cell cycle. These natural lignans trigger cell cycle arrest and inhibit cancer cell proliferation by modulating various cell cycle regulatory proteins.

role in organogenesis in the embryo as well as in physiological tissue remodeling and pathological states such as tumorigenesis and metastasis (Abbaszadeh, Ebrahimi, and Akhavan 2014; Rajabi and Mousa 2017). Matrix degradation, endothelial cell proliferation, migration, sprouting and recruitment of mural cells occur during this process (Jabłońska-Trypuć, Matejczyk, and Rosochacki 2016). A complex network of angiogenic growth factors, cytokines and adhesion molecules is involved in the regulation of angiogenesis process. These angiogenic proteins trigger angiogenesis through various molecular signaling mechanisms (Yoo and Kwon 2013). The most important angiogenic growth factors regulating the angiogenesis process, including vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), placental growth factor (PGF), epidermal growth factor (EGF), transforming growth factor-beta (TGF-β), and platelet-derived growth factor (PDGF) (Mousa and Davis 2017; Rajabi and Mousa 2017). Hypoxia-inducible factor 1 (HIF-1) is known to act as an angiogenic factor during hypoxic conditions. HIF activates a signaling pathway, which leads to the upregulation of VEGF expression (Fallah et al. 2019). Lignans have been shown to have potent antiangiogenic influences. Studies demonstrate that these natural compounds suppress angiogenesis via direct inhibitory effects on angiogenesis process in multiple standard models of angiogenesis (Liu et al. 2013; Xiang et al. 2014). The information presented in this review reveals the potential mechanism of action underlying the anti-angiogenic activity of dietary lignans arctigenin and sesamin (Figure 6). It has been reported that arctigenin treatment inhibits Akt signaling pathway, reduces the expression of VEGF receptor 2, and proliferating cell nuclear antigen (PCNA) and suppresses vascular sprouting from aortic rings. This natural lignan inhibits the vascularization and tumor growth in a murine dorsal skinfold chamber model (Liu et al. 2013). The anti-angiogenic effects of arctigenin have been shown by the chick embryo chorioallantoic membrane (CAM) assay. The generation of new blood vessels is significantly inhibited in arctigenin-treated CAM (Lou et al. 2017). Sesamin is known to suppress the expression of gene products implicated in angiogenesis. It significantly inhibits TNF-induced the expression of VEGF in human KBM-5 myeloid leukemia cells (Harikumar et al. 2010). Sesamin has the potential to inhibit the proliferation and capillary tube formation of HUVECs. This plant lignan suppresses the VEGF-induced HUVEC migration through the downregulation of MMP-2 gene expression. Sesamin also significantly suppresses the VEGF expression in invasive CL1-5 cells (Tsai et al. 2006) (Table 1).

ROS generation and anticancer activities of arctigenin and sesamin

Reactive oxygen species (ROS) are oxygenic reactive compounds, which are generated as natural by-products of cellular metabolism (Abdal Dayem et al. 2017). It is well documented that ROS at high levels act as intracellular signaling molecules to trigger apoptosis (Hafezi et al. 2020). ROS-mediated apoptosis can be initiated via intrinsic mitochondrial and extrinsic death receptor pathways (Redza-Dutordoir and Averill-Bates 2016). Increased generation of ROS depolarizes the mitochondrial membrane and releases cytochrome c from the mitochondria into the cytosol. Cytochrome c can activate caspase-9 by nucleotide binding to apoptotic protein-activating factor 1 (APAF-1), which results in the activation of caspase-3 (Orrenius, Gogvadze, and Zhivotovsky 2015). Elevated ROS levels have also been found to be involved in the activation of death receptors and caspases-8 and −10. Activated caspases-8 and −10 can directly activate caspases-3, −6, and −7 and trigger apoptotic cell death (Redza-Dutordoir and Averill-Bates 2016). A desirable characteristic of some ROS-enhancing agents is to selectively induce cell death in cancer cells but not non-transformed cells (Adams et al. 2013). Several natural lignans have been shown to exert their anticancer effects via intracellular ROS generation. Lignans induce the ROS generation in cancer cells, which plays an upstream role in the activation of apoptosis pathway (Banjerdpongchai, Yingyurn,

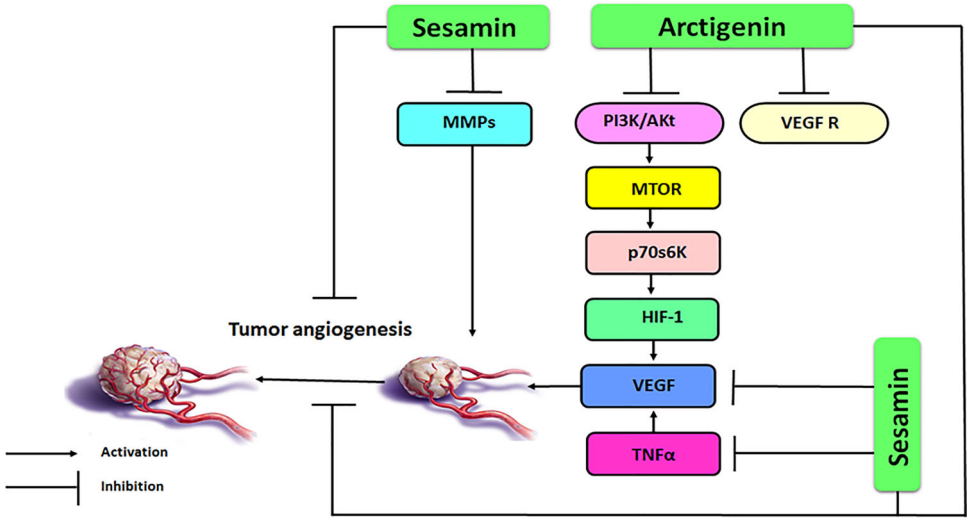

Figure 6. Schematic representation of arctigenin and sesamin effects on angiogenesis process. These plant lignans inhibit tumor angiogenesis by affecting multiple molecular targets and signaling pathways.

and Kongtawelert 2010; Huang et al. 2018). It has been shown that the elevated ROS can activate the MAPK, which lead to the cell death. Arctigenin is found to induce apoptosis in estrogen receptor-negative breast cancer cells by activating the p38 MAPK in a ROS-dependent manner (Hsieh et al. 2014). Arctigenin exerts potent anticancer effects on acidity-tolerant prostate cancer PC-3AcT cells via ROS-induced mitochondrial damage. This natural lignan significantly increases the ROS levels and decreases the mitochondrial membrane potential in PC-3AcT cells (Lee, Oh, and Lee 2018). Arctigenin has the potential to trigger apoptosis in colon cancer cells by targeting the ROS/p38 MAPK pathway. It significantly enhances the generation of ROS and activation of p38 MAPK in HT-29 cells (Li et al. 2016). Sesamin has been found to promote apoptosis in human leukemia MOLT-4 and HL-60 cells via the generation of ROS and activation of intrinsic mitochondrial pathway (Banjerdpongchai, Yingyurn, and Kongtawelert 2010) (Table 1).

Cancer cell migration and invasion and anticancer activities of arctigenin and sesamin

Cell migration and invasion are fundamental processes involved in many physiological conditions such as morphogenesis, embryonic development, angiogenesis, neurogenesis, and inflammation (Pijuan et al. 2019). However, cell migration and invasion are also involved in pathogenic processes of many diseases such as cancer (Pijuan et al. 2019). The metastatic process could be stratified into five major stages, (1) detachment of cancer cells from the primary tumor site, (2) intravasation into blood or lymphatic system, (3) survival in the circulation, (4) spread into distant tissue and finally, and (5) colonization at secondary tumor sites (Martin et al. 2013). Several molecules have been found to play important roles in the signaling processes, leading to cell migration (Guan 2015). Matrix metalloproteinases (MMPs) are an important family of calcium-dependent zinc-containing endopeptidases, which are able to degrade extracellular matrix (ECM) proteins (Singh et al. 2015). There is strong evidence for a positive correlation between overexpression of MMPs and cancer invasion and metastasis (Quintero-Fabián et al. 2019). It is well known that the overexpression of MMPs can be induced by growth factors such as EGFs and receptor tyrosine kinases (RTKs) such as EGF receptor (EGFR). RTKs have been found to regulate a variety of downstream signaling pathways such as MAPK, PI3K/Akt, and JAK/STAT signaling cascades (Butti et al. 2018). Studies have indicated that the suppression of MMPs activity results in the inhibition of cancer cell invasiveness (Merchant et al. 2017). Therefore, MMPs can be considered as viable molecular targets for cancer therapy (Cathcart, Pulkoski-Gross, and Cao 2015). It is well documented that MMPs activities are suppressed by tissue inhibitors of metalloproteinases (TIMPs) (Wang et al. 2012). Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type-1 (PAI-1) have been reported to have an essential role in tumor invasion and metastasis (Lampelj et al. 2015). The uPA system catalyzes the inactive plasminogen to the active plasmin, which is able to directly or indirectly degrade the BM and ECM by activating pro-MMPs to MMPs, which finally leads to the cancer metastasis (Mali et al. 2017). Epithelial-mesenchymal transition (EMT) is described as a complex process that allows epithelial cells to acquire the features of invasive mesenchymal cells (Son and Moon 2010). EMT has been reported to be implicated in cancer invasiveness and metastasis (Savci-Heijink et al. 2019). The hallmark features of EMT are the downregulation of epithelial surface marker, E-cadherin and the upregulation of mesenchymal markers, including N-cadherin and vimentin (Loh et al. 2019). The downregulation of E-cadherin during EMT is induced via suppression of its transcriptional activity by binding of EMT transcription factors (EMT-TFs) such as TWIST, SLUG, and SNAIL to the E-cadherin promoter (Serrano-Gomez, Maziveyi, and Alahari 2016). The evidence indicates that the dietary lignans arctigenin and sesamin have the potential to modulate a number of molecular and cellular targets such as MMPs to reduce cancer cell

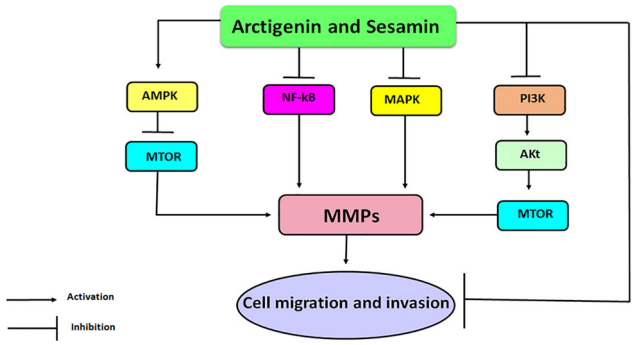

Figure 7. Schematic diagram showing the effects of arctigenin and sesamin on cancer cell migration and invasion. These dietary lignans suppress MMPs activity by modulating a number of molecular and cellular targets and signaling pathways, leading to the inhibition of cancer cell invasiveness.

migration and invasion (Lou et al. 2017; Xu et al. 2015) (Figure 7). Arctigenin and sesamin have been reported to affect EMT pathways, which are involved in cancer metastasis (Kong et al. 2014; Lu et al. 2019) (Figure 8). Arctigenin inhibits migration and invasion of colorectal cancer cells by downregulating the expression levels of MMP-2 and MMP-9, N-cadherin, vimentin, β-catenin, and Snail and upregulating the expression level of E-cadherin. This natural lignan considerably suppresses lung metastasis of colorectal cancer CT26 cells in an experimental model of metastasis (Han et al. 2016). Arctigenin has the potential to suppress migration and invasion of human breast cancer cells by downregulating the expression of MMP-2, MMP-9, and uPA (Lou et al. 2017; Maxwell et al. 2017). Arctigenin exerts anti-metastasis and invasion effects against hepatocellular carcinoma by suppressing epithelial-mesenchymal transition. This dietary lignan significantly increases the expression of E-cadherin and decreases the expression of N-cadherin and vimentin in hepatocellular carcinoma cells by inhibiting the GSK3β-dependent Wnt/β-Catenin signaling pathway (Lu et al. 2019). Arctigenin inhibits TGF-β-induced epithelial mesenchymal transition in human lung cancer cells by downregulating the expression of smad2/3, N-cadherin, snail and upregulating the expression of E-cadherin (Xu, Lou, and Lee 2017). Sesamin has been found to inhibit invasion of prostate cancer cells by suppressing the expression of MMP-9 protein via the p38-MAPK and NF-κB signaling pathways in a concentration-dependent manner (Xu et al. 2015). Sesamin is able to suppress cell migration and invasion of human head and neck squamous cell carcinoma by inhibiting the expression of MMP-2 (Chen, Chen, et al. 2020). Dietary lignan sesamin has the potential to inhibit epithelial-mesenchymal transition in cancer stem-like SP cells from gallbladder cancer by suppressing the NF-κB activity. This natural lignan significantly upregulates the expression of E-cadherin and downregulates the expression of Twist and Vimentin in cancer stem-like SP cells (Kong et al. 2014) (Table 1).

PI3K/Akt/mTOR signaling pathway and anticancer activities of arctigenin and sesamin

Phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway is known to play a vital role in the regulation of cell proliferation, differentiation, migration, and survival as well as angiogenesis and cellular metabolism (Chamcheu et al. 2019). The activation of PI3K/Akt/mTOR signaling pathway occurs via multiple molecular mechanisms (Hassan et al. 2013). This pathway is activated upon the ligand binding to the tyrosine kinase receptors such as VEGFR, EGFR, PDGFR, IGF-1R, and HER2/neu, leading to the recruitment of class IA PI3Ks to the cell membrane where they enhance the conversion phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3) (Yip 2015). Dysregulation of PI3K/Akt/mTOR signaling pathway is found to be associated with genetic/epigenetic alterations, resulting in the activation of downstream oncogenic signaling pathways (Chamcheu et al. 2019). It has been documented that the hyperactivation of PI3K/Akt/mTOR signaling is associated with numerous human malignancies (Hillmann and Fabbro 2019). The suppression of PI3K/Akt/mTOR signaling pathway has been reported to sensitize resistant cancer cells to chemotherapeutic agents (Deng et al. 2019). Inhibition of this signaling pathway has been a focus of recent therapeutic studies (Syed et al. 2013). Several natural lignans have been reported to exert their anticancer effects by targeting the PI3K/Akt/mTOR signaling pathway (Lee, Szczepanski, and Lee 2009; Rauf et al. 2018). Dietary lignans arctigenin and sesamin have the potential to significantly inhibit PI3K/Akt/mTOR signaling cascade in cancer cells. Arctigenin is found to induce apoptosis in hepatocellular carcinoma cells through deactivation of PI3K/Akt signaling pathway (Lu et al. 2015). Arctigenin attenuates the expression level of survivin, Bcl-xL, and Mcl-1 and the phosphorylation of mTOR and S6K, through suppression of PI3K/Akt signaling, which results in apoptotic cell death in hepatocellular carcinoma cells (Li et al. 2015). Arctigenin potently exerts anticancer effects against acidity-tolerant prostate carcinoma PC-3 cells by suppressing the PI3K/Akt/mTOR pathway (Lee, Oh, and Lee 2018). The estrogenic lignan arctigenin has the ability to inhibit mTOR pathway in MCF-7 human breast cancer cells, which leads to the autophagic cell death (Maxwell et al. 2018). Sesamin has been indicated to induce G1 phase cell cycle arrest and apoptosis in non-small cell lung cancer (NSCLC) cells by modulating Akt/p53 pathway. This plant lignan significantly suppresses Akt activity and upregulates p53 expression in NSCLC cells (Chen, Chen, et al. 2020). Sesamin also suppresses the pAkt-PI3K signaling pathway by attenuating the expression of COX-2, which lead to cell cycle arrest and apoptosis in lung cancer cells (Fang et al. 2019) (Table 1).

NF-κB signaling pathway and anticancer activities of arctigenin and sesamin

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling is an important signaling pathway, which plays a fundamental role in the regulation of cell proliferation, differentiation, and apoptosis as well as cellular immunity and inflammation (Dąbek, Kułach, and Gąsior 2010). It is well known that the NF-κB exists in the cytosol of resting cells in an inactive form bound to a family of

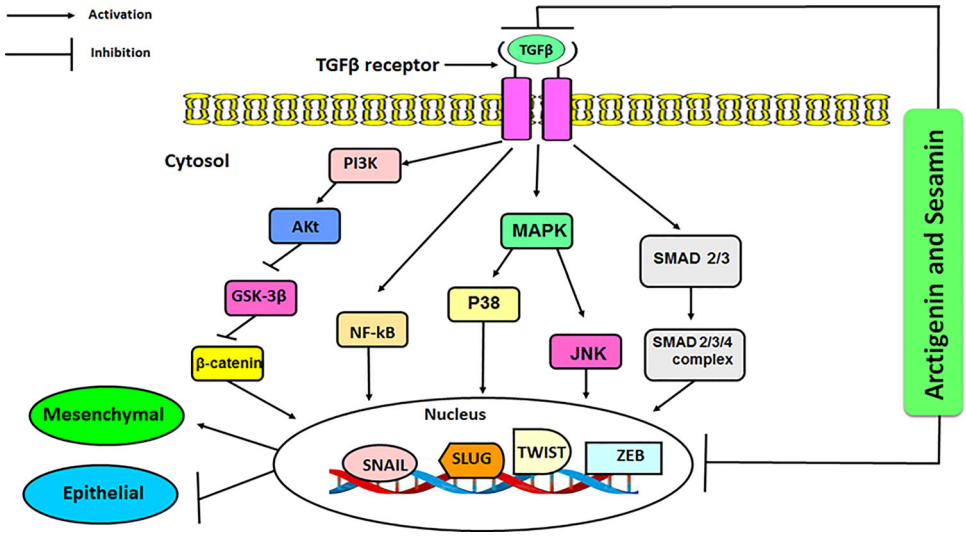

Figure 8. Proposed mechanisms by which dietary lignans arctigenin and sesamin inhibit EMT and cancer metastasis. The most important signaling pathway are shown, which promote the epithelial to mesenchymal transition by binding to TGF-β receptors and activating specific EMT-inducing transcription factors (snail,slug, Zeb, and twist). Arctigenin and sesamin can inhibit cancer cell migration by suppressing EMT-inducing transcription factors.

inhibitory proteins known as IκB (inhibitors of κB) such as IκB-α, IκB-β, IκB-γ, IκB-ε, and IκB-ζ (Avtanski and Poretsky 2018). Upon activation, the inhibitory IκBα protein is phosphorylated by the IκB kinase (IKK) complex, leading to degradation of IκBα and release of NF-κB. The free NF-κB translocates to the nucleus and activates the transcription of genes controlling cell cycle, apoptosis, angiogenesis, and metastasis (Hoesel and Schmid 2013). It is well documented that NF-κB has an essential role in pathogenesis and treatment of cancer. The important role of NF-κB in cancer development, progression, and resistance to treatment has attracted much attention (Huang et al. 2014). Hyperactivation of the NF-κB signaling pathway has been involved in various tumor tissues. An altered NF-κB signaling pathway is often found in solid and hematologic malignancies (Rauf et al. 2018). Activation of NF-κB in cancer cells has been reported to promote cell proliferation, inhibit apoptosis, and induce angiogenesis. NF-κB activity is also associated with the induction of epithelial-mesenchymal transition, which facilitates distant metastasis (Xia, Shen, and Verma 2014). Inhibition of NF-κB pathway can cause cancer cells to stop proliferating, which makes the NF-κB pathway a potential target for cancer therapy (Letícia de Castro Barbosa et al. 2017). Numerous NF-κB inhibitors have indicated promising anticancer activities in preclinical studies (Rauf et al. 2018). Lignans have been found to negatively regulate the NF-κB signaling pathway. These natural compounds have the potential to suppress the phosphorylation and degradation of IκBα and the nuclear translocation of NF-κB. Through inhibition of NF-κB activity, lignans induce apoptosis and inhibit cancer cell proliferation and invasion (Arora et al. 2011; Harikumar et al. 2010). Dietary lignans arctigenin and sesamin have been reported to exert potent anticancer effects by suppressing NF-κB signaling pathway (Harikumar et al. 2010; Maxwell et al. 2017) (Figure 9). Arctigenin as a natural lignan has the potential to exert anti-metastatic activity against breast cancer cells by suppressing NF-κB signaling pathway, which results in the inhibition of MMP-9 and uPA (Maxwell et al. 2017). Sesamin has been found to have anticancer effects against leukemia KBM-5 cells via the suppression of NF-κB signaling pathway. This plant lignan reduces NF-κB activation by inhibiting the phosphorylation and degradation of IκBα, leading to the suppression of NF-κB p65 subunit phosphorylation and nuclear translocation in leukemia cells (Harikumar et al. 2010). Sesamin has the ability to suppress prostate cancer cell proliferation and invasion by inhibiting the NF-κB signaling pathway (Xu et al. 2015) (Table 1).

MAPK signaling pathway and anticancer activities of arctigenin and sesamin

Mitogen-activated protein kinase (MAPK) cascades are important signaling pathways involved in cancer cell survival, proliferation, apoptosis, angiogenesis, and metastasis (Peng et al. 2018). The MAPK pathway consists of four major cascades, including the extracellular signal-regulated kinase (ERK)1/2) cascade, the c-Jun N-terminal kinase (JNK) cascade, the p38 cascade, and the ERK5 cascade (Guo et al. 2020). ERK cascade is mostly activated by growth factors such as epidermal growth factor, whereas the JNK and p38 cascades are activated by a variety of stress signals, including ultraviolet radiation, ROS and inflammatory cytokines such as TNF-α and interleukin (IL)-1β (Lee, Rauch, and Kolch 2020). MAPK signaling cascades have been found to regulate apoptosis process through several cellular mechanisms. MAPKs have a dual action in the regulation of apoptosis. These signaling cascades can act as activators or inhibitors of apoptosis, depending on the type of stimulus and cell (Yue and López 2020). Several lignans have been identified to exert their anticancer effects by regulating the MAPK signaling pathway (Huang et al. 2018; Tsai et al. 2014). Dietary lignan arctigenin has been found to trigger apoptosis in colon cancer cells via activation of p38 MAPK pathway (Li et al. 2016). Arctigenin exerts anti-metastatic effects against human breast cancer cells by inhibiting the

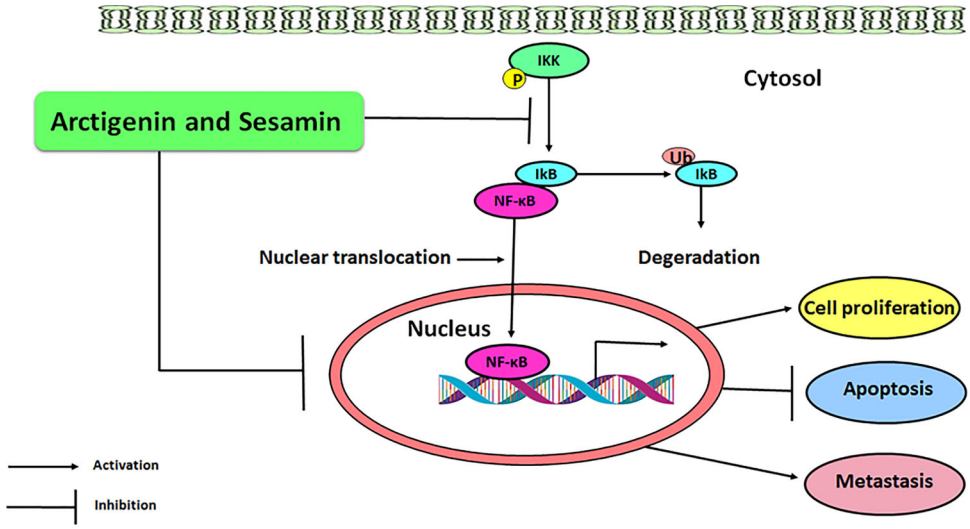

Figure 9. Inhibition of NF-κB signaling pathway by dietary lignans arctigenin and sesamin. These natural compounds inhibit the phosphorylation and degradation of IκBα and the nuclear translocation of NF-κB, which lead to the induction of apoptosis and inhibition of cancer cell proliferation and invasion.

phosphorylation of ERK 1/2 and JNK 1/2 (Maxwell et al. 2017). This natural lignan promotes apoptosis in breast cancer cells by enhancing the activation of p38 MAPK (Hsieh et al. 2014). Arctigenin is able to trigger apoptotic cell death in primary effusion lymphoma cells by inhibiting the ERK and p38 MAPK signaling (Baba et al. 2018). The studies indicate that sesamin has the potential to inhibit the proliferation and invasion of prostate cancer cells by suppressing the phosphorylation of p38-MAPK protein (Xu et al. 2015). Sesamin suppresses the migration of oral cancer cells by targeting the MAPK signaling pathway. This dietary lignan remarkably reduces the expression of P-p38 and p-JNK1/2 in oral cancer cells (Chen, Chen, et al. 2020) (Table 1).

In vivo studies

To date, theres is no study on the in vivo anticancer effcts of sesamin. In vivo anticancer effects of arctigenin have been indicated in several xenograft animal models. Arctigenin has the potential to significantly prevent several types of cancer in vivo such as liver, breast, prostate, and pancreatic cancers by modulating multiple molecular targets . Arctigenin has been found to have a marked suppressive impact on the growth of liver cancer in mice . This natural lignan can prevent liver tumor growth by attenuating the expression of gankyrin and enhancing the C/EBPα binding to the gankyrin promoter (Sun et al. 2018). Arctigenin remarkably suppresses breast tumor growth in nude mice by downregulating the expressinon of pSTAT3 and its downstream genes cyclin D1 and Mcl-1 (Feng et al. 2017). Arctigenin has been reported to have a considerable inhibitory effect on the prostate tumor growth in tumor-bearing mice. This dietary lignan potently suppresses prostate tumor growth by reducing circulating free fatty acids (FFAs), downregulating the expression of androgen receptor (AR), and Ki67, and pro-angiogenic factors, including IGF-1, VEGF, and monocyte chemoattractant protein (MCP)-1, upregulating the expression of prostate tumor suppressor gene Nkx3.1, and inhibiting angiogenesis (Hao et al. 2020) . Arctigenin has been reported to potently inhibit pancreatic tumor growth in xenograft mouse models by suppressing the phophorylation of Akt (Awale et al. 2006) (Table 2).

Current challenges and future perspectives

One of the main drawbacks of natural lignans is their poor bioavailability due to their poor water-solubility, which restricts their use as chemopreventive and anticancer agents. Therefore, the bioavailability of dietary lignans arctigenin and sesamin should be enhanced for clinical use. Numerous studies have discovered strategies to enhance the bioavailability of lignans such as chemical modifications, combination with other compounds, inhibition of intestinal cell transportsand and use of nanoformulations. The modification of dietary lignans arctigenin and sesamin using nanoparticles can be a good solution to improve their absorption and bioavailability, which leads to the increased their clinical anticancer efficacies. Because the cellular and molecular mechanisms involved in anticarcinogenic and anticancer activities of dietary lignans arctigenin and sesamin are still not sufficiently characterized, therefore, further efforts are needed to elucidate the exact mechanisms by which these natural compounds act against cancer cells. Despite the promising results obtained from in vitro cellular studies, there are no in vivo studies on the anticancer effects of sesamin and there are only a few in vivo studies about the anticancer activities of arctigenin. Moreover, there are also no clinical trials indicating the anticancer effects of plant lignans arctigenin and sesamin. Therefore, in vivo and clinical studies are needed to be conducted to provide more reliable evidence.

Conclusions

Lignans as natural polyphenols are potent bioactive molecules with antitumorigenic and anticancer activities. In recent years, special attention has been paid to the effects of lignans on the prevention and treatment of cancer with

Table 2. In vivo anticancer effects and molecular mechanisms of arctigenin.

Type of cancer and animal models	Dosage and duration of treatment	Effects and mechanisms of action
Liver cancer Subcutaneous injection of HepG2 cells into the left flank of female BALB/c nude mice (6–8 weeks old)	The nude mice were treated with arctigenin (1 mg/kg or 10 mg/kg) by subcutaneous injection for 30 days	Inhibition of liver tumor growth by attenuating the expression of gankyrin and enhancing the C/EBPα binding to the gankyrin promoter
Breast cancer Subcutaneous injection of human breast cancer MDA-MB-231 cells into the right flank of female nude mice (6–8 weeks old)	The nude mice were treated with arctigenin (15 mg/kg) by intraperitoneal injection for 4 times per week	Suppression of breast tumor growth via downregulation of pSTAT3 and its downstream genes cyclin D1 and Mcl-1
Prostate cancer Subcutaneous injection of androgen-sensitive LAPC-4 human prostate cancer cells into the male severe combined immunodeficiency (SCID) mice (5–7 weeks old)	The SCID mice were treated with arctigenin (50 mg/kg) by oral adminestration for 6-weeks	Inhibition of prostate tumor growth through reduction of circulating free fatty acids (FFAs), downregulation of androgen receptor (AR), and Ki67, and pro-angiogenic factors, including IGF-1, VEGF, and monocyte chemoattractant protein (MCP)-1, upregulation of prostate tumor suppressor gene Nkx3.1, and suppression of angiogenesis
Pancreatic cancer Subcutaneous injection of PANC-1 cells into the right side of female SPF/VAF BALB/cAn Ncrj-nu/nu mice (5 weeks old)	The nude mice were treated with arctigenin (50 μg/mouse) by intraperitoneal injection from the 15th day (on 6 days of the week) until 64th day	Suppression of pancreatic tumor growth via inhibition of Akt phophorylation

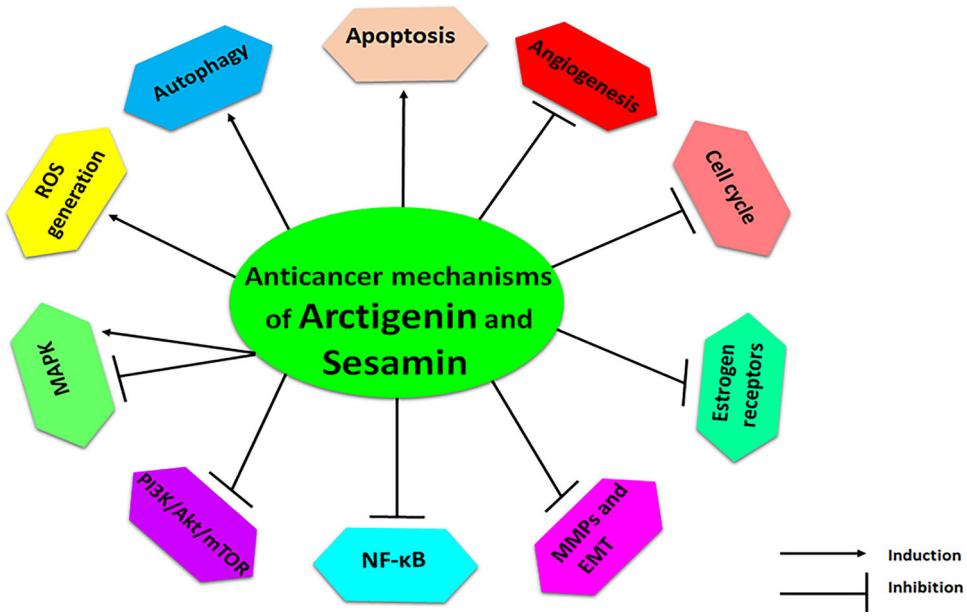

Figure 10. Molecular mechanisms involved in anticancer activities of natural lignans arctigenin and sesamin.

evidence supporting potent antiproliferative effects of these natural compounds. Since a deeper understanding of molecular mechanisms underlying the anticancer effects of lignans can contribute to the development of new compounds with potent and selective antiproliferative effects, therefore, this review aims to provide detailed information on the anticancer mechanisms of dietary lignans arctigenin and sesamin. Many studies demonstrate that lignans influence numerous molecular targets and signaling pathways associated with the development and progression of cancer. The present review indicates that estrogenic lignans arctigenin and sesamin have the potential to modulate many various cellular and molecular events in cancer cells such as apoptosis, autophagy, cell cycle, angiogenesis, ROS levels, estrogen receptors, MMPs, EMT, and signaling pathways such as NF-κB, PI3K/Akt/mTOR, and MAPK, which play crucial roles in antiproliferative and anti-invasive effects of these dietary lignans (Figure 10). Collectively, the current review presents experimental data, supporting the bright future of dietary and estrogenic lignans arctigenin and sesamin as chemopreventive and chemotherapeutic agents. The intake of natural lignans arctigenin and sesamin as dietary supplements can be associated with low risk of various types of cancer. The therapeutic applications of arctigenin and sesamin in cancer seem to be promising, as these natural compounds have demonstrated potent anticancer effects with low toxicity against non-tumorigenic cells.

Conflicts of interest

The authors declare no conflicts of interest.

Abbreviations:

AMPK adenosine monophosphate-activated protein kinase
APAF-1 apoptotic protein-activating factor 1
Bcl-2 B-cell lymphoma 2

CAM	chorioallantoic membrane
CDK	cyclin-dependent kinases
CDKi	CDK inhibitors
DR	Death receptors
ECM	extracellular matrix
EGF	epidermal growth factor
EMT	epithelial-mesenchymal transition
ERK	extracellular signal-regulated kinase
FGFs	fibroblast growth factors
HIF-1α	hypoxia-inducible factor-1alpha
HUVECs	human umbilical vein endothelial cells
JNK	c-Jun N-terminal kinase
MAPK	mitogen-activated protein kinases
MMP	mitochondrial membrane potential
MMPs	matrix metalloproteinases
mTOR	mammalian target of rapamycin
NF-κB	nuclear factor kappa B
NSCLC	non-small cell lung cancer
PAI-1	plasminogen activator inhibitor type-1
PARP	poly-(adenosine 5′-diphosphate-ribose) polymerase
PDGF	platelet-derived growth factor = PGF = placental growth factor
PI3K	phosphatidylinositol 3-kinase
PTEN	phosphatase and tensin homolog
ROS	Reactive oxygen species
RTKs	receptor tyrosine kinases
STAT3	signal transducer and activator of transcription 3
TGF-β	transforming growth factor-beta
TIMPs	tissue inhibitors of metalloproteinases
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor-alpha
TRAIL-R	Trail receptor
uPA	urokinase plasminogen activator
VEGF	vascular endothelial growth factor

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