Nutrition and Cancer

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hnuc20

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To cite this article: Sayeh Mottaghi & Hassan Abbaszadeh (2021): Natural Lignans Honokiol and Magnolol as Potential Anticarcinogenic and Anticancer Agents. A Comprehensive Mechanistic Review, Nutrition and Cancer, DOI: 10.1080/01635581.2021.1931364

To link to this article: https://doi.org/10.1080/01635581.2021.1931364

Published online: 28 May 2021.

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2021.1931364

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REVIEW

Natural Lignans Honokiol and Magnolol as Potential Anticarcinogenic and Anticancer Agents. A Comprehensive Mechanistic Review

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ABSTRACT

Plant lignans constitute an important group of polyphenols, which have been demonstrated to significantly induce cancer cell death and suppress cancer cell proliferation with minimal toxicity against non-transformed cells. Numerous epidemiological studies have shown that the intake of lignans is associated with lower risk of several cancers. These natural compounds have the potential to inhibit carcinogenesis, tumor growth, and metastasis by targeting various signaling molecules and pathways. Growing evidence indicates that honokiol and magnolol as natural lignans possess potent anticancer activities against various types of human cancer. The aim of present review is to provide the reader with the newest findings in understanding the cellular and molecular mechanisms mediating anticancer effects of honokiol and magnolol. This review comprehensively elucidates the effects of honokiol and magnolol on the molecular targets and signal transduction pathways implicated in cancer cell proliferation and metastasis. The findings of current review indicate that honokiol and magnolol can be considered as promising carcinopreventive and anticancer agents.

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; EMT: epithelial-mesenchymal transition; ERK: extracellular signal-regulated kinase; 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; PARP: poly-(adenosine 5′-diphosphate-ribose) polymerase; 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; TNF-α: tumor necrosis factor-alpha; TRAIL-R: Trail receptor; VEGF: vascular endothelial growth factor

ARTICLE HISTORY
Received 2 October 2020
Accepted 6 May 2021

Introduction

Cancer and Plant Lignans

Cancer disease has become a growing threat to the world with 18.1 million new cases and 9.6 million deaths in 2018, which represents one of the most important health issues (1, 2). Cancer is a complex disease driven by genetic and epigenetic changes that cause cells to overproliferate and avoid mechanisms that topically control their survival, growth, and migration (3). Carcinogenesis is recognized as a multistep and multipath process in which distinct molecular and cellular alterations occur, consisting of three stages: initiation, promotion, and progression (4). In cancer cells, there is a dysregulation of cell-cycle and disruption of processes, which cause cell death such as apoptosis (3). The toxicities and severe systemic side effects of chemotherapeutic drugs have prompted scientists to develop and discover novel phytochemicals for cancer therapy (5). Many studies have indicated that polyphenolic compounds possess potent anticancer activities (6). Polyphenols constitute one of the largest and most important groups of plant secondary metabolites found abundantly in fruits, vegetables, flowers, grains, spices, soy, tea, and wine (7). The chemical structures of polyphenolic compounds are very diverse and complex,

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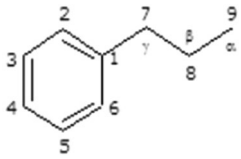

Figure 1. Phenylpropane unit.

with molecular weights ranging from 500 to 3000 Da (6). Polyphenols possess one or more aromatic rings directly attached to several hydroxyl groups, which can be classified into several major groups, including flavonoids, phenolic acids, stilbenes, and lignans (6, 8). Plant lignans are a complex group of phenolic compounds that are present in higher levels in sesame and flax seeds and in lower levels in various seeds, grains, fruits, and vegetables (9, 10). In 1936, the term lignan was first described by Haworth as phenylpropanoid dimers composed of two phenylpropane units (C6–C3) attached by their central carbon (C8) (11), as shown in Figure 1. Lignans, as non-flavonoid polyphenols, are mostly found in nature in the free form, while their conjugated form as glycosides are only a minor form (12). Numerous studies indicate that plant lignans possess various biological and pharmacological effects such as antioxidant, anti-inflammatory, antiallergic, antihyperlipidemic, antithrombotic, antibacterial, antiviral, antiprotozoal, antiangiogenic, and anticancer effects (10, 13–16). Natural lignans have the potential to suppress different stages of carcinogenesis, including initiation, promotion, and progression by targeting various signaling molecules and pathways (17). Many epidemiological studies have revealed the beneficial effects of dietary lignans on prevention of several types of malignant tumors (18). These natural compounds have shown to have potent anticancer activities against various human cancers In Vitro and In Vivo (19, 20). Studies indicate that anticancer effects of lignans are associated with the modulation of a wide range of molecular targets such as protein tyrosine kinases, pro-apoptotic and anti-apoptotic proteins, transcription factors, membrane receptors, chemokines, cell surface adhesion molecules, cell cycle proteins, and cell signaling pathways (20, 21). Natural lignans have attracted much attention because of their potent anticancer effects such as the antiproliferative effects of podophyllotoxin and its derivatives (etoposide and teniposide) (22). There is much evidence indicating that plant lignans with potent anticancer effects could be developed as effective anticancer agents (20, 23). Indeed, several natural lignans have been investigated in the phase I and II clinical trials as anticancer agents (24). Honokiol and magnolol as natural lignans have been reported to have remarkable biological effects such as anticancer activities (19, 25, 26). Numerous experimental studies have demonstrated that honokiol and magnolol possess potent anticancer activity against various cancer cell lines. The present review aimed to provide a comprehensive overview of the cellular and molecular mechanisms by which honokiol and magnolol exert their anticancer effects against different types of human cancer.

Overview of Plant Lignans Honokiol and Magnolol

Honokiol (5,3′-Diallyl-2,4′-dihydroxybiphenyl) and magnolol (5,5′-diallyl-2,2′-dihydroxybiphenyl) are bioactive natural compounds extracted from the bark of *Magnolia officinalis*, which possesses a wide variety of pharmacological properties (Figure 2) (27). *Magnolia officinals* bark extract has been employed for centuries in Chinese and Japanese traditional medicines (28). Herbal preparations and supplements containing *Magnolia* bark are still widely used for treatment of thrombotic stroke, gastrointestinal disturbances, anxiety, nervous disorders, allergic and inflammatory diseases, and malignant tumors (28, 29). The safety and toxicity of *Magnolia* extract have been extensively evaluated (30). *Magnolia* bark extract has been found to be a safe natural compound with little toxicity (30, 31). In Vitro and In Vivo genotoxicity investigations demonstrate that *magnolia* bark extract has no genotoxic and mutagenic properties (32). In recent years, *Magnolia officinals* bark extract has attracted considerable attention due to its potent anticancer activities. Honokiol and magnolol are the major constituents responsible for the anticancer effects of the *magnolia* bark extract (30). Honokiol is characterized by a chemical structure similar to its isomer, magnolol. In fact, the only difference between their chemical structures is the position of one hydroxyl group (33). In the last

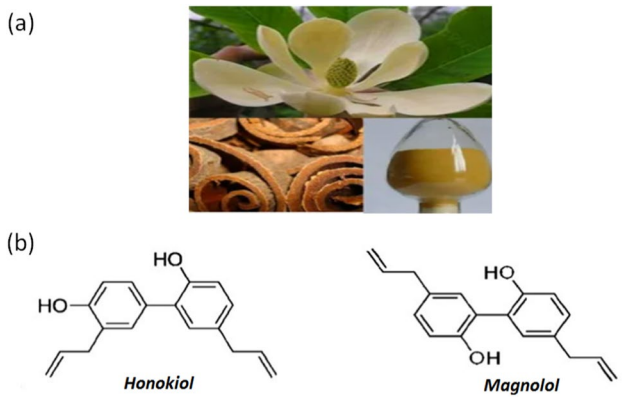

Figure 2. Chemical structures of honokiol and magnolol.

decade, honokiol and magnolol have been shown to possess a wide range of biological and pharmacological properties, including neuroprotective, antidepressant, antithrombotic, antiviral, antimicrobial, anti-inflammatory, antioxidant, and anticancer effects (34–36). In the past few years, many studies have focused on antiproliferative effects of honokiol and magnolol on various types of cancer. Numerous In Vitro and In Vivo studies indicate that honokiol and magnolol have potent anticancer activities. These natural compound exert their anticancer effects by modulating a variety of molecular targets and signal transduction pathways (37, 38). It has been reported that co-treatment with honokiol and magnolol exerts synergistic anticancer effects. Honokiol and magnolol synergistically inhibit cancer cell proliferation and induce cancer cell death (39). Several studies have demonstrated the selective cytotoxicity of honokiol and magnolol against various cancer cell lines. Theses plant lignans have the potential to inhibit cancer cell proliferation with low toxicity against normal cells (40–42).

Major Signaling Molecules and Pathways Implicated in Anticancer Effects of Honokiol and Magnolol

Apoptosis Signaling Pathways and Anticancer Effects of Honokiol and Magnolol

Apoptosis is a tightly regulated process of programmed cell death that plays a pivotal role in both physiological and pathological conditions. In mammalian cells, apoptosis can be triggered through two major pathways, including the extrinsic cell death pathway and the intrinsic cell death pathway (43). The Bcl-2 family proteins play a key role in the intrinsic mitochondrial pathway, which are stratified into two functional subgroups: the anti-apoptotic members (Bcl-2, Bcl-xl, and MCL-1) and pro-apoptotic members (Bax, Bad, Bak, and Bid) (8, 44). BCL-2 family members can facilitate or prevent the release of cytochrome c from mitochondria into cytosol and regulate the formation of the apoptosome (45). The anti-apoptotic Bcl-2 proteins act through direct interaction with pro-apoptotic proteins, resulting in the inhibition of their activity and apoptosis. Pro-apoptotic proteins such as Bax directly trigger mitochondrial outer membrane permeabilization, which leads to the release of cytochrome c during apoptosis (46). It is well known that the Pro-apoptotic protein Bax serves as the major transcriptional target of P53. During p53-mediated apoptosis, tumor suppressor protein p53 directly affect the pro-apoptotic protein Bax, leading to the activation of Bax protein (47). The extrinsic pathway initiates apoptosis in response to the activation of death receptors such as Fas (also known as CD95), TRAIL receptor (TRAIL-R) or tumor necrosis factor receptor 1 (TNFR1). The activated death receptors can initiate apoptosis directly, via the activation of initiator and effector caspases or indirectly, by potentiating the death receptor signal via the activation of the mitochondrial pathway (43). Many studies indicate that honokiol and magnolol have the ability to potently cause cancer cell death by inducing apoptosis through different cellular and molecular mechanisms (20, 23) (Figure 3). Honokiol has been found to have potent anticancer effects by activating caspase-dependent apoptotic pathways in various cancer cells (21, 26). Honokiol causes apoptosis in bladder cancer cells via a mitochondrial apoptosis pathway. This plant lignan leads to the ROS generation, collapse of mitochondrial membrane potential, and activation of caspase-3 and -7 in bladder cancer cells (48). Honokiol can lead to caspase-mediated apoptosis in KRAS mutant lung cancer cells by upregulating the expression of pro-apoptotic protein Bax and downregulating the expression of anti-apoptotic protein Bcl-2 (49). Honokiol has the potential to significantly induce apoptosis in ovarian carcinoma cells via the activation of caspase-9, -3, and -7 and cleavage of PARP (40). Honokiol triggers apoptosis in human gastric carcinoma cells via upregulation of the pro-apoptotic Bax and downregulation of anti-apoptotic Bcl-2 (50). Honokiol activates intrinsic apoptosis pathway in osteosarcoma cells through downregulation of Bcl-2, Bcl-xl, and survivin and activation of caspase-9 and -3 and cleavage of PARP (37). It has been reported that honokiol-induced apoptosis in glioblastoma multiforme (GBM) cells is associated with the suppression of Rb protein and cleavage of PARP and Bcl-x (S/L) (51). Magnolol has been found to activate mitochondrial apoptotic pathway in gallbladder cancer cells. Magnolol treatment leads to the upregulation of p53 and Bax, downregulation of Bcl-2, loss of MMP, release of cytochrome c, activation of caspase-9 and -3 and cleavage of PARP in gallbladder cancer cells (52). Magnolol has been shown to cause apoptotic cell death in esophagus cancer KYSE-150 cells by downregulating the protein expression of Bcl-2 and upregulating the protein expression of caspase-3, caspase-9, and Bax (53). It has been reported that the mitochondrial dysfunction is involved in Magnolol-mediated apoptosis in MCF-7 human breast cancer cells. Magnolol triggers apoptosis in MCF-7 cells through ROS production, upregulation of p53 and Bax, downregulation of Bcl-2, collapse of MMP,

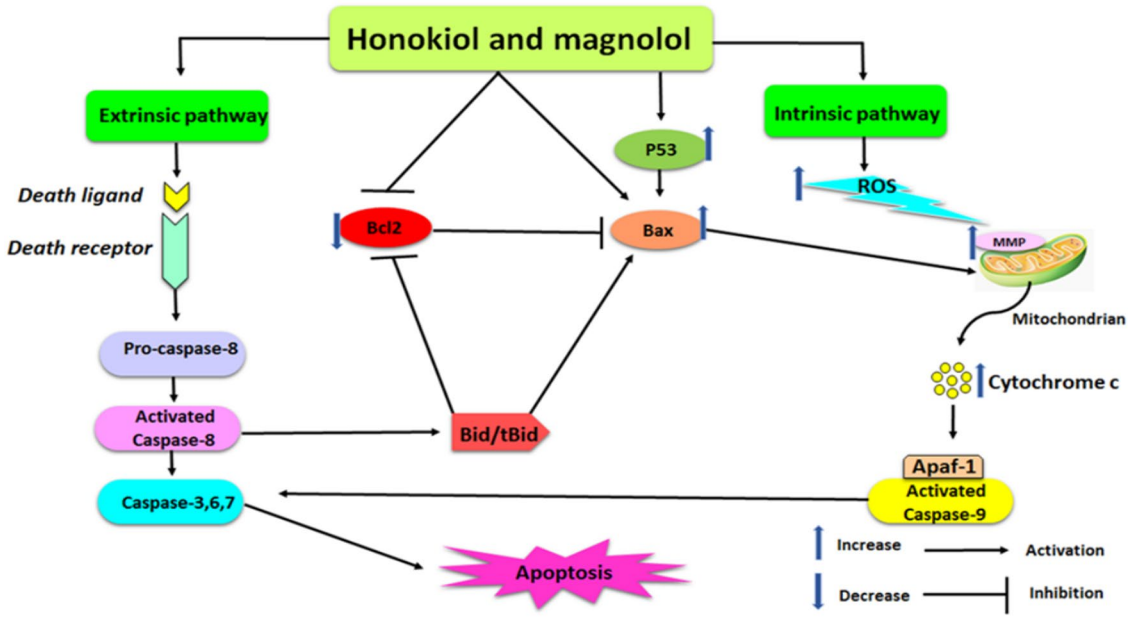

Figure 3. Schematic illustration of honokiol and magnolol effects on apoptosis signaling pathways. Plant lignans honokiol and magnolol induce apoptotic cell death in various human cancer cells by activating intrinsic mitochondrial and extrinsic death receptor pathways.

and release of cytochrome c and apoptosis inducing factor (AIF) from mitochondria into the cytosol (19). Magnolol significantly induces apoptotic cell death in human leukemia cells through disruption of MMP, release of cytochrome c into the cytosol, activation of caspase-9, -3 and -2, and cleavage of PARP (54). Magnolol is able to cause apoptotic cell death in human lung squamous carcinoma CH27 cells via downregulation of Bcl-X_L protein, upregulation of Bad and Bcl-X_S, release of cytochrome c and activation of caspase-9, -3 and -6 (55). The studies indicate that magnolol-induced apoptosis in MG-63 and 143B osteosarcoma cells is associated with the upregulation of p53 and activation of mitochondrial apoptotic pathway (56). Magnolol treatment can lead to apoptotic cell death in HCT-116 colon cancer cells by decreasing the expression of Bcl2 and increasing the expression of p53, Bax, caspase-3, the active forms of PARP, and cytosolic cytochrome c (57). Magnolol has the potential to remarkably upregulate the expression of Bax and cleaved PARP-1, downregulate the expression of Bcl-2, and induce the collapse of MMP and release of cytochrome c from mitochondria into the cytosol in human hepatocellular carcinoma HepG2 cells (58). Magnolol significantly promotes apoptosis in thyroid carcinoma cells by releasing cytochrome-c into cytosol and increasing the levels of activated caspase-9 and -3 and cleaved PARP (59). Honokiol and magnolol also have the ability to induce apoptosis in cancer cells by targeting the extrinsic pathway. These plant lignans activate death receptor pathway, which leads to the activation of caspase-8, caspase-3 and apoptotic cell death (60–64) (Table 1).

ROS Generation and Anticancer Effects of Honokiol and Magnolol

Reactive oxygen species (ROS), a group of highly reactive molecules containing oxygen, are generated as natural by-products of cellular metabolism (65). It is well accepted that ROS play a major role in the regulation of intracellular signaling pathways. Studies have provided evidence that excessive ROS production can result in the apoptotic cell death (66). ROS-induced apoptosis can be initiated via intrinsic and extrinsic pathways. (67). Enhanced generation of ROS induces a rapid depolarization of mitochondrial membrane potential, which results in the release of cytochrome c from the mitochondria into the cytosol. After release, it activates caspase-9 and subsequently activates downstream caspase-3 (68). ROS at elevated levels can also lead to the activation of death receptors and caspases-8 and -10. Activated caspases-8 and -10 directly cleave and activate downstream effector caspases such as caspases-3, -6, and -7, resulting in apoptotic death (67). Honokiol and magnolol have been found to exert their anticancer activities through intracellular ROS production. These natural lignans significantly induce the generation of ROS in cancer cells, which results in the activation of apoptotic

signaling pathway (69, 70). Honokiol has the potential to induce ROS-dependent apoptosis in bladder cancer cells. This plant lignan causes a significant ROS accumulation and collapse of MMP in bladder cancer cells, leading to the activation of caspase-3 and -7 and apoptotic cell death (48). Honokiol has been reported to enhance the generation of intracellular ROS in human osteosarcoma U2OS and HOS cells, which plays an important role in the upstream pathway of honokiol-induced apoptosis in osteosarcoma cells (69). Magnolol has been reported to induce cancer cell death in renal carcinoma 786-O and OS-RC-2 cells, which is associated with increased ROS generation, loss of MMP, release of cytochrome c, activation of caspases and apoptotic cell death (56). Magnolol causes the accumulation of intracellular ROS in MCF-7 human breast cancer cells, which leads to the decreased $\Delta\Psi m$, release of cytochrome c and AIF from mitochondria into the cytosol, and induction of apoptosis (70) (Table 1).

Cell Cycle Arrest and Anticancer Effects of Honokiol and Magnolol

Cell cycle is a highly organized and regulated process by which cells grow and divide (71). The progression of cell cycle is regulated through cyclins that control the activities of CDKs and play a key role in cell cycle regulation (71, 72). There are at least four major classes of cyclins (A, B, D, and E) that are clearly involved in cell-cycle control. 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 is a mitotic cyclin, which is essential to take cells into mitosis (73). CDK inhibitors (CDKi), such as p15, p16, p21, p27, p53, and retinoblastoma tumor suppressor protein (RB) have shown to negatively regulate the cell cycle, which can result in the inhibition of cell proliferation by cell cycle arrest (74). Alterations in the expression of cell cycle regulatory proteins, which lead to the loss of normal cell-cycle control are a hallmark of many malignant tumors. (75). Cell cycle arrest is one of the major molecular mechanisms that contributes to the anticancer activities of plant lignans (76, 77). Honokiol and magnolol have shown to modulate a number of cell-cycle regulatory proteins such as cyclins, CDKs, and CDKi in cancer cells, consequently leading to cell cycle arrest (38, 78) (Figure 4). Honokiol has been found to cause G0/G1 phase cell cycle arrest in oral squamous cell carcinoma cells via upregulation of CDK inhibitors, p21 and p27 and downregulation of

Table 1. Anticancer cellular and molecular mechanisms of honokiol and magnolol.

Lignan	Type of cancer	Anticancer cellular and molecular mechanisms
Honokiol	Lung, breast, ovarian, prostate, bladder, skin, pancreatic, and thyroid cancers, glioblastoma, osteosarcoma, gastric carcinoma, squamous cell carcinoma, glioma, and fibrosarcoma	Induction of apoptosis (by upregulating Bax, downregulating Bcl-2, Bcl-xl, and survivin, activating caspase-3, -7, and -9 and cleaving PARP, and also by targeting extrinsic death receptor pathway, leading to a sequential activation of caspase-8 and -3) ROS production Induction of cell cycle arrest (by upregulating p53, p21, and p27, downregulating cyclin D1, cyclin D2, cyclin B1, cyclin E, CDK2, CDK4, and CDK6, and inhibiting the phosphorylated retinoblastoma protein) Induction of autophagy (via activation of AMPK and ERK 1/2 pathways and suppression of PI3K/Akt/mTOR pathway) Inhibition of angiogenesis (by suppressing the PI3K/Akt/mTOR and MAPK phosphorylation, and downregulating the expression of VEGFR-2 and VEGFR-3, HIF-1α, and VEGF) Inhibition of cancer cell migration and invasion (by modulating the AMPK/mTOR signaling pathway, downregulating the expression of MMP-2, MMP-9, N-cadherin, Twist1, snail, slug, and vimentin and inhibiting EMT by targeting Stat3/Zeb1/E-cadherin axis) Inhibition of NF-κB signaling pathway Modulation of MAPK signaling pathway (via activation of p38 and ERK1/2 and also by reducing the phosphorylation of ERK1/2) Suppression of PI3K/Akt/mTOR signaling pathway
Magnolol	Gallbladder, breast, colon, esophagus, liver, lung, thyroid, prostate, and ovarian cancers, leukemia, epidermoid carcinoma, fibrosarcoma, and osteosarcoma,	Induction of apoptosis (by upregulating p53, Bax, Bad, and Bcl-X_S, downregulating Bcl-2 and Bcl-XL, activating caspase-3, -7, and -9 and cleaving PARP, and also by activating extrinsic death receptor pathway, leading to a sequential activation of caspase-8 and -3) ROS generation Induction of cell cycle arrest (via upregulation of the expression levels of p53, p21, and p27 and downregulation of the expression levels of cyclin D1, cyclin B1, cyclins E, cyclin A2, CDC25A, CDK2, CDK1, CDK4, and Cdc2) Induction of autophagy (via inhibition of PI3K/Akt/mTOR pathway and activation of ERK 1/2 pathway) Inhibition of angiogenesis (by inhibiting VEGFR2 and PI3K/Akt/mTOR/ p70s6k and Ras-dependent MAPK pathways and downregulating the expression of HIF-1α and VEGF) Inhibition of cancer cell migration and invasion of (by upregulating the expression of E-cadherin, ZO-1, and claudin, downregulating the expression of MMP-2 and MMP-9, N-cadherin, TWIST1, Slug, and Snail, and suppressing TGF-β-induced EMT) Inhibition of NF-κB signaling pathway Modulation of MAPK signaling pathway (via activation of JNK, inactivation of ERK1/2 and by inducing the phosphorylation of p38 and ERK1/2) Suppression of PI3K/Akt/mTOR signaling pathway

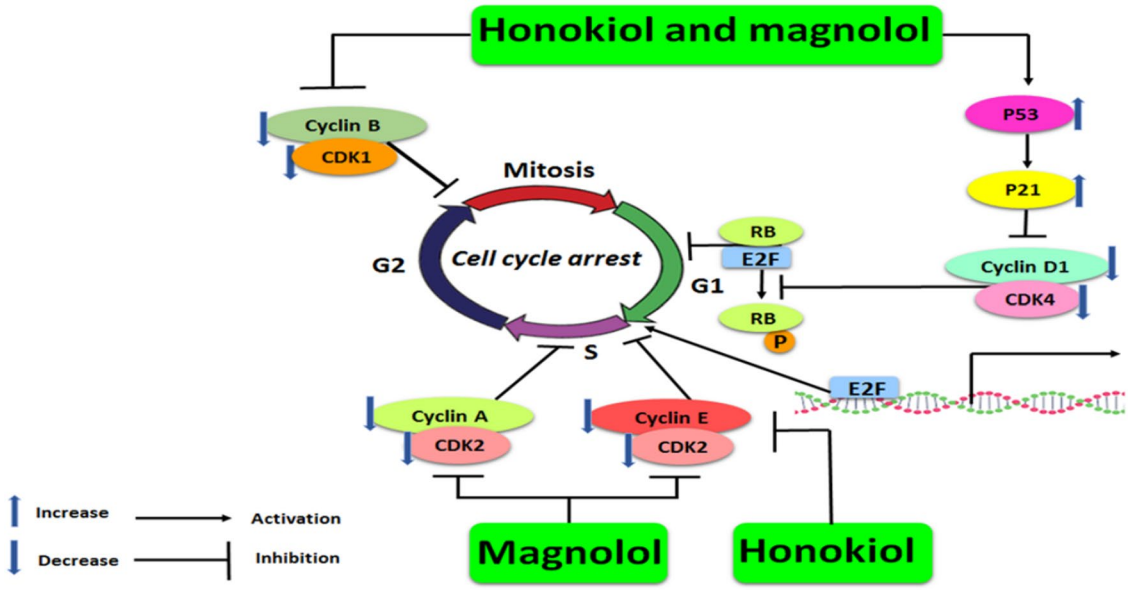

Figure 4. Schematic diagram showing honokiol and magnolol effects on cell cycle. Honokiol and magnolol induce cell cycle arrest in human cancer cells by targeting various cell cycle regulatory proteins, leading to the inhibition of cancer cell proliferation.

cyclin D1, CDK2, and CDK4 (37). Honokiol has the potential to inhibit UV-induced skin tumor development by increasing the expression of p21 and p27 and decreasing the expression of cyclin E, cyclin D1, cyclin D2, CDK2, CDK4, and CDK6 in UVB-induced skin cancer (79). Honokiol arrests the progress of cell cycle at G2/M in human gastric carcinoma MGC-803 cells by increasing the expression of P53 and p21 and decreasing the expression of cyclin B1 (50). Honokiol has the ability to inhibit human prostate cancer cell proliferation by inducing cell cycle arrest at G0/G1 phase, which is associated with increase in the protein expression of p53 and p21, decrease in the protein expression of cyclin D1, CDK4, CDK6, and cyclin E, and suppression of phosphorylated retinoblastoma protein (78). Honokiol treatment leads to G0/G1 phase cell cycle arrest in KRAS mutant lung cancer cells by increasing the protein levels of p21 and p27 and decreasing the protein level of cyclin D1 (49). Magnolol is able to affect cell cycle progression of human prostate cancer cells by inhibiting the expression of cyclin A, cyclin B1, cyclin D1, cyclin E, CDK2 and CDK4, resulting in the cell cycle arrest at G2/M-phase (80). Magnolol has been reported to suppress cell cycle progression at G2/M phase in non-small cell lung cancer cells by upregulating the expression levels of p21 and p27 and downregulating the expression levels of cyclin A2, cyclin D1, CDK1, and CDK4 (38). The studies indicate that G0/G1phase arrest induced by magnolol in gallbladder cancer cells is associated with the upregulation of p53 and p21 and downregulation of cyclin D1 and CDK2 (52). Magnolol treatment significantly causes cycle arrest at G0/G1 phase in human glioblastoma cells by increasing the expression of p21 and decreasing the expression of cyclin A and cyclin D1 (81). Magnolol triggers cell cycle arrest at G2/M phase in epidermoid carcinoma cells by upregulating the expression of p21 and downregulating the expression of cyclin A, cyclin B1, CDK4, and Cdc2 (82). It has been reported that the inhibitory effects of magnolol on the proliferation of MCF-7 human breast cancer cells is associated with the cell cycle arrest at G2/M phase. This plant lignan remarkably increases the expression of p53 and p21 and decreases the expression of cyclin B1 and CDK1 in MCF-7 cells (19) (Table 1).

Autophagy Signaling Pathway and Anticancer Effects of Honokiol and Magnolol

Autophagy is a tightly regulated lysosomal system that digests cytoplasmic material and organelles (83). Autophagy is well known as type II programmed cell death (PCD-type II) that can be described as a type of caspase independent cell death (84). During the autophagic process, cytoplasmic components are engulfed by the autophagosome (a double membrane-bound vesicle) and transported to the lysosome for degradation (85, 86). Simultaneously, a soluble form of LC3 (LC3-I) is converted to LC3-phosphatidylethanolamine conjugate (LC3-II), which is localized in autophagosomal membranes.

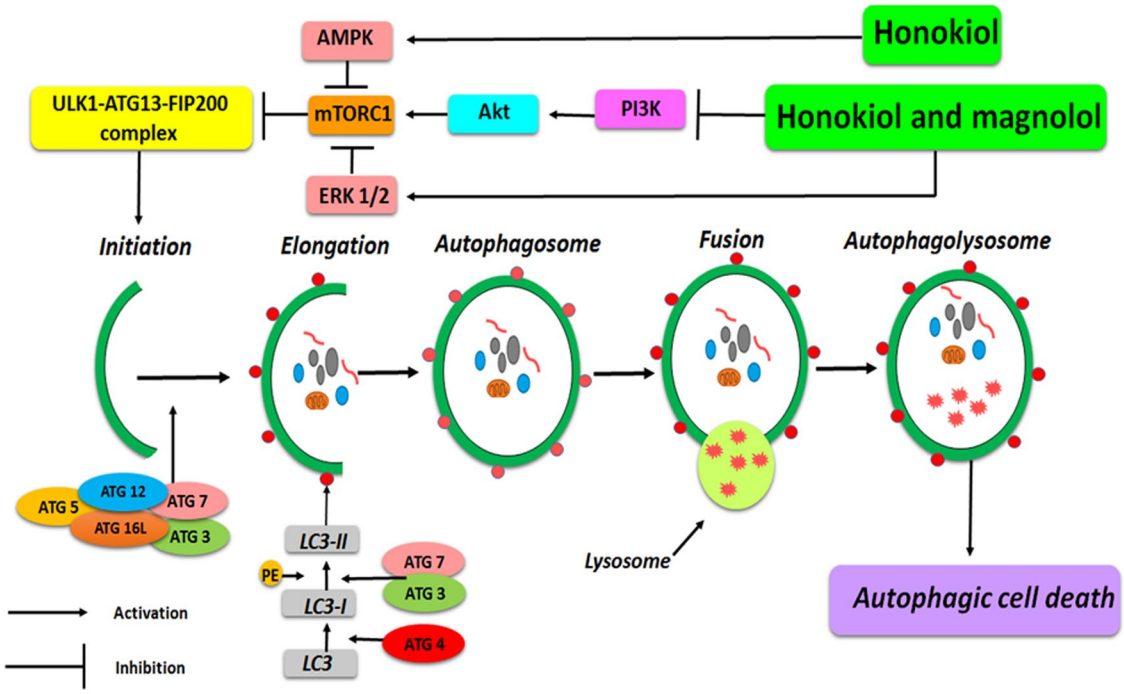

Figure 5. Schematic illustration of honokiol and magnolol effects on autophagy pathway. Honokiol and magnolol can lead to autophagy induction in human cancer cells via suppression of PI3K/AKT/MTOR pathway and activation of AMPK and ERK 1/2 pathways.

LC3-II is an important autophagosome marker for monitoring autophagy activity (87). A set of autophagy-related genes (ATGs) has been found to initiate and form autophagosomes (88, 89). Autophagy induction is regulated by the cellular ATP and energy level, which are detected by the energy-sensing kinase, adenosine monophosphate–activated protein kinase (AMPK) (90). Activated AMPK is known to suppress activity of the mammalian target of rapamycin 1 (mTORC1). mTOR inactivation has been reported to be essential for the induction of autophagy via activation of ULK1-ATG13-FIP200 complex (91). In cancer cells, autophagy activation can cause cell death and suppress cell survival, which lead to the inhibition of carcinogenesis (86, 92). The natural lignans honokiol and magnolol have been found to remarkably induce cancer cell death not only by activating the apoptosis pathway, but also through induction of autophagy pathway (37, 38) (Figure 5). In the present review, autophagy signaling pathways involved in anticancer potentials of honokiol and magnolol have been described. Honokiol has been found to upregulate the level of autophagy markers in human glioblastoma multiforme DBTRG-05MG cells. This plant lignan significantly increases the expression levels of autophagy-related proteins, Beclin-1 and LC3 in human glioblastoma multiforme cells (51). Honokiol has been reported to trigger autophagy in KRAS mutant lung cancer cells by targeting the AMPK-mTOR signaling pathway. This natural lignan increases the level of phospho-AMPK and inhibits mTOR phosphorylation, which result in the autophagocytosis in non-small cell lung cancer (NSCLC) cell lines harboring KRAS mutations (49). Honokiol causes autophagic cell death in human oral squamous cell carcinoma by activating the AMPK signaling molecule and suppressing the Akt/mTORC1 pathway (37). Honokiol can lead to the autophagy induction in human prostate cancer cells via suppression of mTOR and AKT phosphorylation and ROS generation (93). Honokiol has been found to significantly induce autophagy-dependent cell death in human thyroid cancer cells by inhibiting the Akt/mTOR pathway (94). Honokiol treatment activates autophagy pathway in human osteosarcoma cells by affecting the ROS/ERK1/2 signaling pathway. This plant lignan induces phosphorylation of ERK1/2 and enhances ROS generation in osteosarcoma cells (69). Studies indicate that honokiol and magnolol have the potential to synergistically provoke autophagy in glioblastoma cells. The combination of honokiol and magnolol significantly increases the expression of p-ERK in glioblastoma cells (39). It has been reported that autophagic cells death induction by magnolol in human non-small lung cancer H460 cells is associated with the suppression of PI3K/Akt pathway (95). Magnolol has the ability to trigger autophagy in A549 and NCI-H1299 non-small

cell lung cancer cells by suppressing the Akt/mTOR pathway, which leads to cell death (38) (Table 1).

Angiogenesis Inhibition and Anticancer Effects of Honokiol and Magnolol

Angiogenesis, the generation of new blood vessels from preexisting vessels, plays a pivotal role in both physiological processes such as wound healing, reproductive function, and embryonic development and pathological states such as tumor growth, invasion, and metastasis (96, 97). Matrix degradation, endothelial cell proliferation, migration, sprouting, and recruitment of mural cells occur during this process (98). Angiogenesis is a complex and multistage process, which is tightly regulated by angiogenic factors, cytokines, angiogenic enzymes, adhesion molecules, and endothelial cell receptors (99). Vascular endothelial growth factor (VEGF) has been described as a key and specific angiogenic factor, which plays a fundamental role in the generation of new blood vessels (100). VEGF interacts with specific receptors (VEGFR) on endothelial cells to initiate the intracellular processes necessary for proliferation, adhesion, and migration of these cells, thus promoting angiogenesis (97). Under hypoxia condition, hypoxia-inducible factor 1 (HIF-1) acts as an angiogenic factor (101). HIF-1 is known as a primary regulator of VEGF during hypoxic conditions (102). Inhibition of angiogenesis is considered to be an effective approach to suppress tumor progression (96). Studies indicate that plant lignans have the potential to significantly inhibit angiogenesis in several standard models of angiogenesis (103, 104). Honokiol and magnolol have been found to have potent antiangiogenic activities. These natural lignans have the ability to inhibit new blood vessels formation via direct inhibitory effects on angiogenesis process (105, 106). The data presented in this review reveals the mechanisms of action underlying the antiangiogenic influences of honokiol and magnolol (Figure 6). Honokiol has been found to have potent inhibitory effects on endothelial cell proliferation, migration, and tube formation by inhibiting the HIF pathway, which suppresses the secretion of VEGF protein (107). Honokiol potently suppresses lymphangiogenesis in Lewis lung carcinoma model. This natural lignan inhibits endothelial cell survival, proliferation, and tubule formation by suppressing the phosphorylation of Akt and MAPK and attenuating the expression of VEGFR-2 and VEGFR-3 in HUVECs and human lymphatic vascular endothelial cells (HLECs), respectively (106). Honokiol is known to significantly suppress endothelial cell proliferation and growth of aggressive angiosarcoma by inhibiting the phosphorylation of VEGFR-2, Akt, and MAPK (108). Magnolol has been reported to have potent antiangiogenic activities In Vitro and In Vivo. This natural lignan potently inhibits VEGFR2 receptors, which subsequently inactivates Akt/mTOR/p70s6k signaling pathway in hypoxic human bladder cancer cells and tumor tissues. Magnolol inhibits HUVEC tube formation and blood vessels generation in chicken

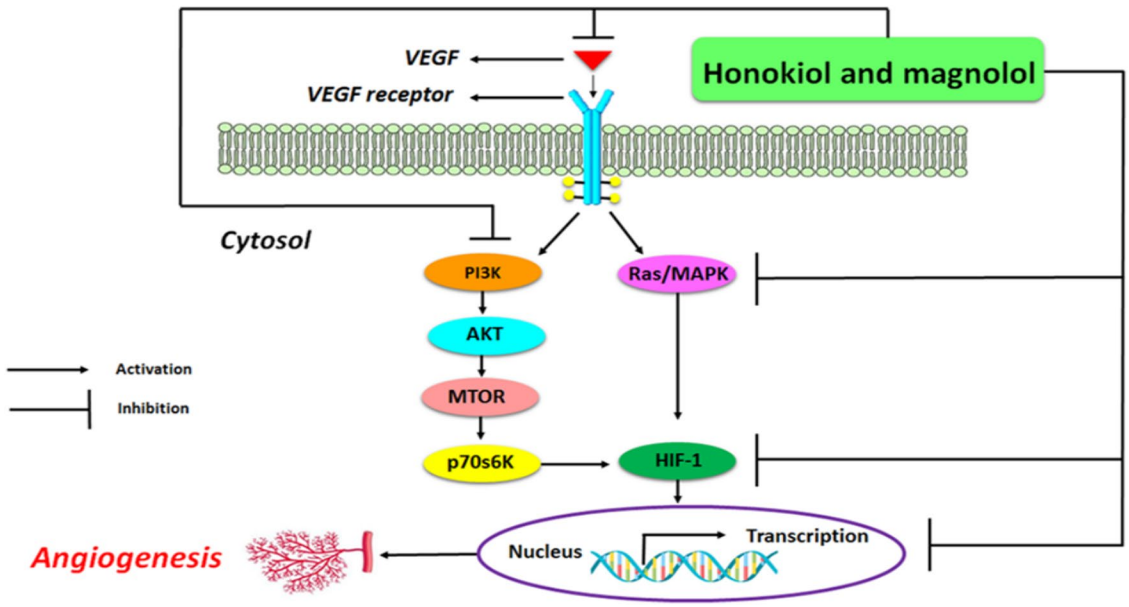

Figure 6. Molecular mechanisms by which honokiol and magnolol inhibit angiogenesis process. Natural lignans honokiol and magnolol block tumor angiogenesis by inhibiting VEGF receptors and Ras-dependent MAPK and PI3K/AKT/MTOR signaling pathways and downregulating the expression of VEGF and HIF-1α.

chorioallantoic membrane and matrigel plug by suppressing the protein expression of HIF-1α and VEGF (109). Magnolol has the potential to inhibit endothelial cell proliferation, migration, and tubulogenesis as well as the microvessel sprouting in Ex Vivo model by inhibiting Ras-dependent MAPK and PI3K/Akt signaling pathways (105) (Table 1).

Inhibition of Cancer Cell Migration and Invasion and Anticancer Effects of Honokiol and Magnolol

Cell migration and invasion are involved in the pathophysiology of many diseases such as cancer (110). Several molecules have been shown to play key roles in the signaling processes associated with cell migration (111). Matrix metalloproteinases (MMPs) are calcium- and zinc-dependent endopeptidases, which are capable of degrading the extracellular matrix (ECM) (112). Overexpression of MMPs has been found to be implicated in the processes of cancer invasion and metastasis (113). It is well known that the expression of MMPs is mainly regulated by multiple signaling pathways, including AMPK/MTOR, MAPK, PI3K/Akt/MTOR, NF-κB, and JAK/STAT signaling cascades (114–116). Studies have revealed that the suppression of MMPs activity is associated with the inhibition of cancer cell invasion and migration (117). Therefore, MMPs can serve as the potential molecular targets for treatment of cancer (118). Epithelial-mesenchymal transition (EMT) is a complex and critical process during development by which epithelial cells obtain the features of invasive mesenchymal cells (119). EMT has been found to be involved in cancer invasiveness and metastasis (120). EMT is characterized by upregulation of mesenchymal markers, N-cadherin followed by downregulation of epithelial surface marker, E-cadherin (121). This process is regulated by a complex network of signaling pathways and transcription factors. During EMT, downregulation of E-cadherin is mediated by its transcriptional repression via the binding of EMT transcription factors (EMT-TFs) such as TWIST, SNAIL, and SLUG to the E-cadherin promoter (122). The studies demonstrate that honokiol and magnolol are able to modulate a variety of molecular and cellular targets such as MMPs to inhibit cancer cell migration and invasion (123, 124). Honokiol and magnolol have the potential to target EMT pathways, which are implicated in cancer metastasis (125, 126). Numerous studies indicate that honokiol has the ability to significantly inhibit invasion and metastasis of various types of cancer. This plant lignan suppresses glioma cell migration and invasion by downregulating the expression of epidermal growth factor receptor, MMP-2, and MMP-9 (126). Honokiol has been found to suppress the migration of non-small cell lung cancer cells via down-regulation of matrix metalloproteinases MMP-2 and MMP-9 (127). Honokiol remarkably inhibits EMT in bladder cancer cells by upregulating E-cadherin and downregulating N-cadherin. This natural lignan blocks bladder cancer cell migration and invasion by decreasing the expression of steroid receptor coactivator-3 (SRC-3), MMP-2, and Twist1 (128). Honokiol has been found to suppress migration of human non-small cell lung cancer cells by inhibiting EMT. This natural lignan downregulates the expression levels of N-cadherin, Snail, and c-FLIP induced by TNF-α + TGF-β1 in human non-small cell lung cancer cells (129). Honokiol is able to suppress breast cancer cell metastasis by inhibiting EMT. This natural lignan significantly upregulates the expression level of E-cadherin and downregulates the expression levels of Snail, Slug, and vimentin in breast cancer cells (130). Honokiol potently inhibits EMT in breast cancer cells by targeting Stat3/Zeb1/E-cadherin axis. Honokiol enhances the expression of E-cadherin by releasing Zeb1 from E-cadherin promoter (131). Honokiol treatment effectively suppresses migration and invasion of ovarian cancer cells by targeting the AMPK/mTOR signaling pathway. This natural compound significantly activates the AMPK in ovarian cancer cells, leading to the inhibition of mTOR/4EBP1 (40). Honokiol and magnolol have been reported to inhibit the invasiveness of human fibrosarcoma HT-1080 cells by suppressing the activity of MMP-9 (124). Magnolol significantly suppresses the migration of human colorectal cancer cells via inhibition of EMT. This plant lignan enhances the expression of epithelial markers E-cadherin, claudin, and ZO-1 and attenuates the expression of mesenchymal markers N-cadherin, Slug, Snail, and TWIST1 in human colorectal cancer cells (125). Magnolol is found to inhibit the invasion and metastasis of breast cancer cells by suppressing the expression of MMP-9 through inactivation of the NF-κB pathway (19). Magnolol has the ability to inhibit migration and invasion of PC-3 human prostate cancer cells by enhancing the expression levels of MMP-2 and MMP-9 in a concentration-dependent manner (123) (Table 1).

NF-κB Signaling Pathway and Anticancer Effects of Honokiol and Magnolol

NF-κB signaling pathway plays a fundamental role in cancer development and progression (132). NF-κB resides in the cytosol of resting cells in an inactive form, bound to a family of inhibitory proteins called

IκB (inhibitors of κB) such as IκB-α (133). Activation of NF-κB has been found to be associated with several cellular processes in malignant tumors (134). Numerous studies have revealed the activation of NF-κB-regulated genes in many hematologic and solid malignancies (135). NF-κB activation mediates cancer cell proliferation, inhibits apoptosis, and induces angiogenesis (136). NF-κB also triggers epithelial mesenchymal transition, which promotes cancer cell migration and invasion (137). Inhibition of NF-κB signaling pathway in cancer cells can lead to the tumor suppression, making this pathway a potential therapeutic target for cancer (138). Many plant lignans have indicated to inhibit NF-κB pathway in cancer cells. The suppression of NF-κB activity by these natural compounds induces apoptotic cell death and inhibits cancer cell proliferation, migration, and invasion (139, 140). Honokiol and magnolol have been reported to significantly suppress the NF-κB signaling pathway in cancer cells (60, 141) (Figure 7). Honokiol has the potential to inhibit NF-κB activation and NF-κB-dependent gene expression in cancer cells by suppressing the IκB kinase activity in cancer cells. This plant lignan exerts anticancer effects by inhibiting the nuclear translocation and phosphorylation of NF-κB (60). The studies demonstrate that honokiol is able to block invasion and migration of non-small cell lung cancer cells through the inhibition of NF-κB/p65 activity (127). Honokiol significantly suppresses the transcriptional activity of NF-κB in pancreatic MIA PaCa-2 and PANC-1 cancer cells. Honokiol increases cytoplasmic accumulation of NF-κB with a reduction in nuclear NF-κB in pancreatic cancer cells (142). Magnolol is found to inhibit the migration and invasion of MDA-MB-231 cells by suppressing NF-κB transcriptional activity, which leads to the downregulation of MMP-9 expression (19). Magnolol has the potential to inhibit the proliferation, migration, and invasion of cholangiocarcinoma cells by suppressing the NF-κB activity (141) (Table 1).

MAPK Signaling Pathway and Anticancer Effects of Honokiol and Magnolol

Mitogen-activated protein kinase (MAPK) cascades are crucial signal transduction pathways that regulate several important cellular processes, including cell proliferation, differentiation, and migration as well as apoptosis and angiogenesis (143). The MAPK pathway consists of four major cascades, including the extracellular signal-regulated kinase (ERK)1/2), the p38 MAPK, the c-Jun N-terminal kinase (JNK), and the ERK5 (144). It has been reported that ERK pathway is mostly activated by growth factors. In contrast, the p38 and JNK are potently activated by stress signals such as tumor necrosis factor (TNF), interleukin (IL)-1β, ultraviolet radiation, and ROS and respond weakly to growth factors. (145). MAPK signaling

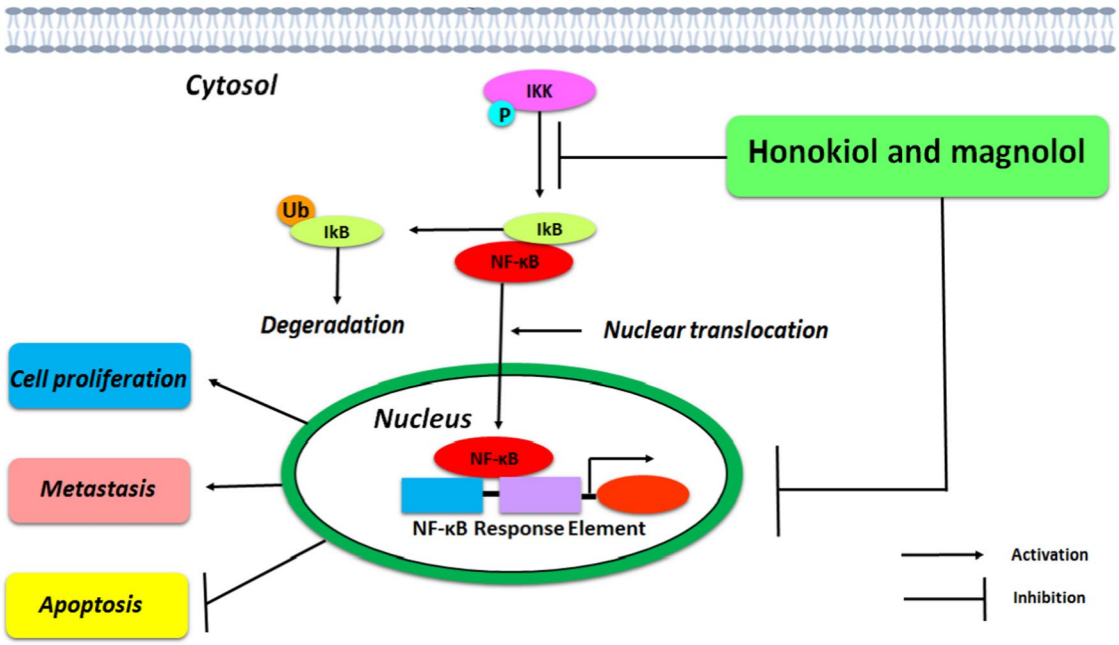

Figure 7. Honokiol and magnolol exert anticancer effects through inhibition of transcriptional activity of NF-κB in cancer cells. These plant lignans inhibit the IκB kinase (IKK) activity and the nuclear translocation of NF-κB, which result in the induction of apoptosis and inhibition of cancer cell proliferation and metastasis.

pathways regulate the expression of genes controlling apoptosis process through various cellular mechanisms. Indeed, the modulation of apoptosis by MAPKs is highly complex. MAPKs can play a dual role in the regulation of apoptosis. Depending on the type of stimulus and cell, MAPKs can activate or inhibit apoptosis pathway (146). The MAPK signaling pathway has been found to play an important role in apoptosis induced by lignans honokiol and magnolol in cancer cells (37, 42). The studies indicate that honokiol has the potential to modulate the MAPK signaling pathway in glioblastoma U87 cells. Honokiol induces apoptosis in glioblastoma cells by reducing the phosphorylation of ERK1/2 and increasing the activation of p38 (64). Honokiol potently causes apoptotic and autophagic cell death in human osteosarcoma cells through the activation of ERK (37). Magnolol is capable of inducing apoptosis in non-small cell lung cancer cells through the activation of p38 and JNK (42). The studies demonstrate that magnolol triggers apoptosis in human lung squamous carcinoma CH27 cells through the inactivation of ERK1/2 and the activation of JNK (55). Magnolol is found to provoke apoptosis in esophagus cancer KYSE-150 cells by targeting the MAPK signaling pathway. This plant lignan significantly upregulates the phosphorylation of p38 and ERK1/2 in esophagus cancer cells (53) (Table 1).

PI3K/Akt/mTOR Signaling Pathway and Anticancer Effects of Honokiol and Magnolol

Phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway is an important intracellular pathway, which plays a pivotal role in regulating cell survival, proliferation, differentiation, and migration in physiological and pathological conditions (147). The activation of PI3K/Akt/mTOR signaling pathway is achieved through multiple distinct mechanisms (148). The PI3K/Akt/mTOR pathway is activated in response to the binding of a ligand to a tyrosine kinase receptor (149). The PI3K/AKT/mTOR pathway has been identified to be one of the most frequently dysregulated signaling cascades almost in all human cancers (147). The dysregulation of this pathway has been associated with a various types of cancer hallmarks such as uncontrolled proliferation, genomic instability, and metabolic reprogramming in cancer cells (150, 151). The activation of PI3K/Akt/mTOR pathway can lead to the development of cancer, metastasis, and resistance to anticancer agents (152). This makes PI3K/Akt/mTOR pathway a key signaling cascade involved in the development and progression of cancer (153). Suppression of PI3K/AKT/mTOR pathway can contribute to decreased cancer cell proliferation and increased cancer cell death (147). PI3K/AKT/mTOR pathway inhibition is being studied as a promising target to develop novel therapeutic agents for the management of cancer (147). Honokiol and magnolol have been found to exert their anticancer effects by suppressing the PI3K/Akt/mTOR signaling pathway (154, 155). Honokiol provokes autophagic and apoptotic cell death in human osteosarcoma MG63 cells through inhibition of the PI3K/Akt/mTOR signaling pathway. This plant lignan remarkably reduces the protein levels of PI3K, p-Akt, and p-mTOR in MG-63 cells (155). Honokiol treatment has the ability to trigger apoptosis and inhibit migration and invasion of ovarian carcinoma SKOV3 and Caov-3 cells by targeting the AMPK/mTOR signaling pathway. It significantly activates the AMPK signaling pathway in ovarian carcinoma cells, leading to the downregulation of p-mTOR (40). Honokiol has the potential to cause ROS-induced autophagic cell death in glioma cells by modulating the p53/PI3K/Akt/mTOR signaling pathway. It significantly attenuates the protein expression of PI3K, p-Akt, and p-mTOR in glioma cells (156). Honokiol has been reported to exert anticancer effects on breast cancer cells by downregulating the PI3K/Akt/mTOR signaling pathway (157). Honokiol treatment causes autophagy-dependent cell death in human prostate cancer PC-3 and LNCaP cells by suppressing the mTOR and Akt phosphorylation (93). Honokiol induces autophagy in neuroblastoma cells by affecting the PI3K/Akt/mTOR signaling pathway. This natural lignan significantly attenuates the amount of PI3K and downregulates the phosphorylation of protein kinase B (Akt) and mTOR in neuro-2a cells (158). The studies indicate that magnolol anticancer effects against ovarian cancer cells are attributed to the inhibition of the HER2 downstream PI3K/Akt/mTOR signaling pathway in HER2-overexpressing ovarian cancer cells (159). Magnolol is found to trigger apoptotic cell death in human prostate cancer cells by suppressing the EGFR/PI3K/Akt signaling pathway (154) (Table 1).

Conclusions and Future Perspectives

In oncology, plant-derived bioactive constituents such as polyphenols have a long-term history of promising and encouraging preliminary results, especially considering them as safe compounds. In recent years, lignans as natural polyphenolic compounds have interested many researcher with evidence supporting potent

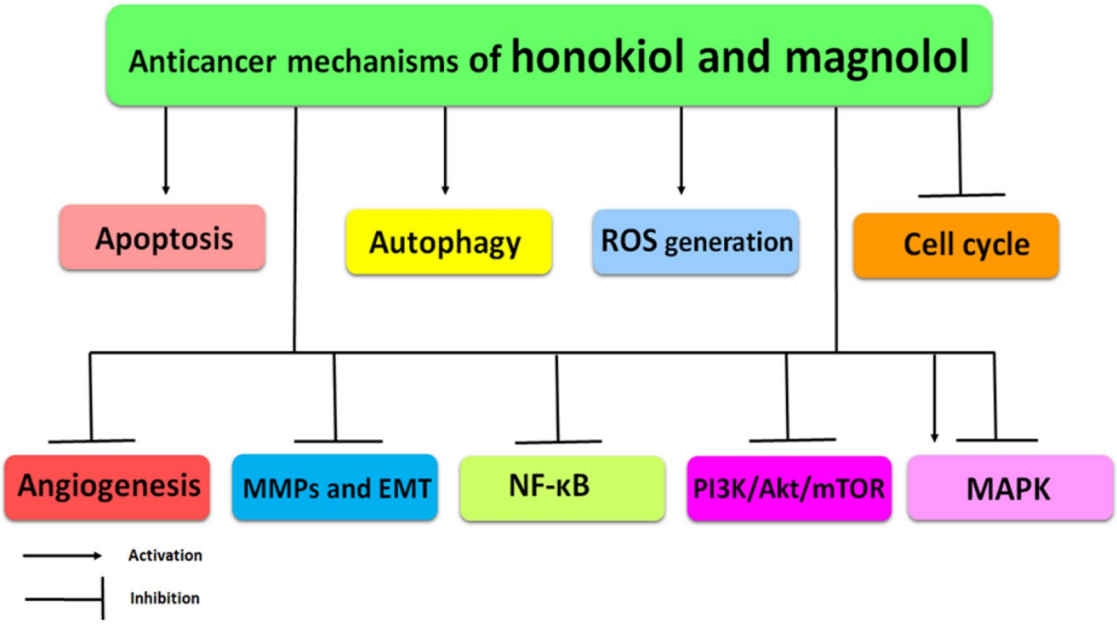

Figure 8. Mechanisms of action underlying anticancer effects of honokiol and magnolol.

antiproliferative activities of these natural compounds. Since a detailed mechanistic insight into the anticancer effects of plant lignans can contribute to the development of new compounds with potent and selective anticarcinogenic and anticancer effects, therefore, the major goal of this review is to mechanistically provide detailed information on the anticancer effects of honokiol and magnolol. Natural lignans honokiol and magnolol have been reported to modulate multiple molecular mechanisms involved in cancer initiation and progression. The current review demonstrates that honokiol and magnolol have the potential to significantly affect many various signaling molecules and pathways in cancer cells, including apoptosis, ROS levels, cell cycle, autophagy, angiogenesis, MMPs, EMT, and NF-κB, MAPK, and PI3K/Akt/mTOR signaling pathways (Figure 8). Because cellular and molecular mechanisms underlying anticancer activity of honokiol and magnolol are still not fully known, therefore, further studies are needed to characterize the detailed mechanisms involved in anticancer effects of these plant lignans. In addition, despite the promising results obtained from In Vitro and In Vivo studies, the real applicability of honokiol and magnolol is still debated, since the In Vitro and In Vivo results have not been transferred to human clinical trials. Therefore, clinical researches are essential to be conducted to provide more reliable evidence. Studies have revealed that one of the most important drawbacks of polyphenolic compounds is their low bioavailability, which restricts their clinical use (8). Honokiol and magnolol have been found to have poor oral bioavailability, which is associated with their poor water-solubility, extensive first-pass metabolism, and low absorption (160). Therefore, the bioavailability of honokiol and magnolol is needed to be improved for clinical use. So far, several nanocarrier-based strategies have been utilized to enhance the oral bioavailability and anticancer activities of honokiol and magnolol (141, 160–162). Studies have reported that nanoparticles, as great drug delivery systems, can improve the absorption and bioavailability of honokiol and magnolol, thereby enhancing their anticancer potency in clinical practice (141, 160–162). However, more studies are needed to be conducted to explore more efficient nano delivery systems for enhancement of the oral bioavailability of honokiol and magnolol. In conclusion, this review presents comprehensive In Vitro and In Vivo evidence supporting the bright future of honokiol and magnolol for prevention and treatment of cancer disease, as these natural lignans have shown potent antiproliferative effects with minimal toxicity against non-tumorigenic cells. Since plant lignans honokiol and magnolol have the ability to synergistically act against cancer cells, therefore, the combination of these natural compounds can be an effective approach for prevention and treatment of malignant tumors.

Author Contributions

Sayeh Mottaghi and Hassan Abbaszadeh equally contributed to the manuscript. Both authors contributed

to designing the work, collecting data, writing the paper, preparing the figures and reviewing the manuscript.

Disclosure Statement

The authors declare no conflicts of interest

Funding

This study was supported by Ahvaz Jundishapur University of Medical Sciences.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA. 2018;68(6):394–424. doi:10.3322/caac.21492
2. Nagai H, Kim YH. Cancer prevention from the perspective of global cancer burden patterns. J Thorac Dis. 2017;9(3):448. doi:10.21037/jtd.2017.02.75
3. Sever R, Brugge JS. Signal transduction in cancer. Cold Spring Harbor Perspectives in Medicine. 2015;5(4):a006098. doi:10.1101/cshperspect.a006098
4. Siddiqui IA, Sanna V, Ahmad N, Sechi M, Mukhtar H. Resveratrol nanoformulation for cancer prevention and therapy. Ann NY Acad Sci. 2015;1348(1):20–31. doi:10.1111/nyas.12811
5. Cragg GM, Pezzuto JM. Natural products as a vital source for the discovery of cancer chemotherapeutic and chemopreventive agents. Med Princ Pract. 2016;25(2):41–59. doi:10.1159/000443404
6. Amawi H, Ashby CR, Samuel T, Peraman R, Tiwari AK. Polyphenolic nutrients in cancer chemoprevention and metastasis: role of the epithelial-to-mesenchymal (EMT) pathway. Nutrients. 2017;9(8):911. doi:10.3390/nu9080911
7. Angeloni C, Maraldi T, Milenkovic D, Vauzour D. Dietary polyphenols and their effects on cell biochemistry and pathophysiology 2014. Oxid Med Cell Longevity. 2015;2015:1–2. doi:10.1155/2015/782424
8. Abbaszadeh H, Keikhaei B, Mottaghi S. A review of molecular mechanisms involved in anticancer and antiangiogenic effects of natural polyphenolic compounds. Phytother Res. 2019;33(8):2002–14. doi:10.1002/ptr.6403
9. Landete J. Plant and mammalian lignans: a review of source, intake, metabolism, intestinal bacteria and health. Food Res Int. 2012;46(1):410–24. doi:10.1016/j.foodres.2011.12.023
10. Marcotullio MC, Curini M, Becerra JX. An Ethnopharmacological, phytochemical and pharmacological review on lignans from Mexican Bursera spp. Molecules. 2018;23(8):1976. doi:10.3390/molecules23081976
11. Sainvitu P, Nott K, Richard G, Blecker C, Jérôme C, et al. Structure, properties and obtention routes of flaxseed lignan secoisolariciresinol, a review. BASE. 2012;16(1):115–24.
12. Saleem M, Kim HJ, Ali MS, Lee YS. An update on bioactive plant lignans. Nat Prod Rep. 2005;22(6):696–716. doi:10.1039/b514045p
13. Teponno RB, Kusari S, Spiteller M. Recent advances in research on lignans and neolignans. Nat Prod Rep. 2016;33(9):1044–92. doi:10.1039/c6np00021e
14. Xin H, Kong Y, Wang Y, Zhou Y, Zhu Y, et al. Lignans extracted from Vitex negundo possess cytotoxic activity by G2/M phase cell cycle arrest and apoptosis induction. Phytomedicine. 2013;20(7):640–7. doi:10.1016/j.phymed.2013.02.002
15. Zanwar A, Hegde M, Bodhankar S. Cardioprotective effect of flax lignan concentrate and omega-3-fatty acid alone and in combination in ischemia/reperfusion injury in isolated rat heart. Atherosclerosis. 2014;235(2):e251. doi:10.1016/j.atherosclerosis.2014.05.751
16. Zanwar AA, Hegde MV, Rojatkar SR, Sonawane KB, Rajamohanan PR, Bodhankar SL. Isolation, characterization and antihyperlipidemic activity of secoisolariciresinol diglucoside in poloxamer-407-induced experimental hyperlipidemia. Pharm Biol. 2014;52(9):1094–103. doi:10.3109/13880209.2013.877492
17. De Silva SF, Alcorn J. Flaxseed lignans as important dietary polyphenols for cancer prevention and treatment: chemistry, pharmacokinetics, and molecular targets. Pharmaceuticals. 2019;12(2):68. doi:10.3390/ph12020068
18. Rodríguez-García C, Sánchez-Quesada C, Toledo E, Delgado-Rodríguez M, Gaforio JJ. Naturally lignan-rich foods: a dietary tool for health promotion?Molecules. 2019;24(5):917. doi:10.3390/molecules24050917
19. Liu Y, Cao W, Zhang B, Liu Y-q, Wang Z-y, et al. The natural compound magnolol inhibits invasion and exhibits potential in human breast cancer therapy. Sci Rep. 2013;3:3098. doi:10.1038/srep03098
20. Ong CP, Lee WL, Tang YQ, Yap WH. Honokiol: a review of its anticancer potential and mechanisms. Cancers. 2019;12(1):48. doi:10.3390/cancers12010048
21. Banik K, Ranaware AM, Deshpande V, Nalawade SP, Padmavathi G, et al. Honokiol for cancer therapeutics: a traditional medicine that can modulate multiple oncogenic targets. Pharmacol Res. 2019;144:192–209. doi:10.1016/j.phrs.2019.04.004
22. Pusztai R, Abrantes M, Sherly J, Duarte N, Molnar J, et al. Antitumor-promoting activity of lignans: inhibition of human cytomegalovirus IE gene expression. Anticancer Res. 2010;30(2):451–4.
23. Dai X, Yin C, Guo G, Zhang Y, Zhao C, et al. Schisandrin B exhibits potent anticancer activity in triple negative breast cancer by inhibiting STAT3. Toxicol Appl Pharmacol. 2018;358:110–9. doi:10.1016/j.taap.2018.09.005
24. Luo J, Hu Y, Kong W, Yang M. Evaluation and structure-activity relationship analysis of a new series of arylnaphthalene lignans as potential anti-tumor agents. PLOS One. 2014;9(3):e93516. doi:10.1371/journal.pone.0093516
25. Lee Y-S, Choi S-S, Yonezawa T, Teruya T, Woo J-T, Kim HJ, Cha B-Y. Honokiol, magnolol, and a combination of both compounds improve glucose metabolism in

high-fat diet-induced obese mice. Food Sci Biotechnol. 2015;24(4):1467–74. doi:10.1007/s10068-015-0189-6
26. Rauf A, Patel S, Imran M, Maalik A, Arshad MU, et al. Honokiol: an anticancer lignan. Biomed Pharmacother. 2018;107:555–62. doi:10.1016/j.biopha.2018.08.054
27. Shen J-L, Man K-M, Huang P-H, Chen W-C, Chen D-C, et al. Honokiol and magnolol as multifunctional antioxidative molecules for dermatologic disorders. Molecules. 2010;15(9):6452–65. doi:10.3390/molecules15096452
28. Poivre M, Duez P. Biological activity and toxicity of the Chinese herb Magnolia officinalis Rehder & E. Wilson (Houpo) and its constituents. J Zhejiang Univ Sci B. 2017;18(3):194–214. doi:10.1631/jzus.B1600299
29. Lee Y-J, Lee YM, Lee C-K, Jung JK, Han SB, et al. Therapeutic applications of compounds in the Magnolia family. Pharmacol Ther. 2011;130(2):157–76. doi:10.1016/j.pharmthera.2011.01.010
30. Sarrica A, Kirika N, Romeo M, Salmona M, Diomede L. Safety and toxicology of magnolol and honokiol. Planta Med. 2018;84(16):1151–64. doi:10.1055/a-0642-1966
31. Liu Z, Zhang X, Cui W, Zhang X, Li N, et al. Evaluation of short-term and subchronic toxicity of magnolia bark extract in rats. Regul Toxicol Pharm. 2007;49(3):160–71. doi:10.1016/j.yrtph.2007.06.006
32. Li N, Song Y, Zhang W, Wang W, Chen J, et al. Evaluation of the in vitro and in vivo genotoxicity of magnolia bark extract. Regul Toxicol Pharm. 2007;49(3):154–9. doi:10.1016/j.yrtph.2007.06.005
33. Fried LE, Arbiser JL. Honokiol, a multifunctional antiangiogenic and antitumor agent. Antioxid Redox Signal. 2009;11(5):1139–48. doi:10.1089/ars.2009.2440
34. Cho Y-Y, Jeong H-U, Kim J-H, Lee HS. Effect of honokiol on the induction of drug-metabolizing enzymes in human hepatocytes. Drug Des Devel Ther. 2014;8:2137. doi:10.2147/DDDT.S72305
35. Yang C, Zhi X, Xu H. Advances on semisynthesis, total synthesis, and structure-activity relationships of honokiol and magnolol derivatives. Mini Rev Med Chem. 2016;16(5):404–26. doi:10.2174/1389557516666151120115558
36. Zhang J, Chen Z, Huang X, Shi W, Zhang R, et al. Insights on the multifunctional activities of magnolol. BioMed Res Int. 2019;2019:1–15. doi:10.1155/2019/1847130
37. Huang KJ, Kuo CH, Chen SH, Lin CY, Lee YR. Honokiol inhibits in vitro and in vivo growth of oral squamous cell carcinoma through induction of apoptosis, cell cycle arrest and autophagy. J Cell Mol Med. 2018;22(3):1894–908. doi:10.1111/jcmm.13474
38. Shen J, Ma H, Zhang T, Liu H, Yu L, et al. Magnolol inhibits the growth of non-small cell lung cancer via inhibiting microtubule polymerization. Cell Physiol Biochem. 2017;42(5):1789–801. doi:10.1159/000479458
39. Cheng Y-C, Hueng D-Y, Huang H-Y, Chen J-Y, Chen Y. Magnolol and honokiol exert a synergistic anti-tumor effect through autophagy and apoptosis in human glioblastomas. Oncotarget. 2016;7(20):29116. doi:10.18632/oncotarget.8674
40. Lee JS, Sul JY, Park JB, Lee MS, Cha EY, et al. Honokiol induces apoptosis and suppresses migration and invasion of ovarian carcinoma cells via AMPK/mTOR signaling pathway. Int J Mol Med. 2019;43(5):1969–78. doi:10.3892/ijmm.2019.4122
41. Songjang W, Jiraviriyakul A. Honokiol and magnolol induce apoptosis and cell cycle arrest in human ovarian cancer cells. PJ. 2019;11(5):1114–23. doi:10.5530/pj.2019.11.174
42. Tsai J-R, Chong I-W, Chen Y-H, Hwang J-J, Yin W-H, et al. Magnolol induces apoptosis via caspase-independent pathways in non-small cell lung cancer cells. Arch Pharmacal Res. 2014;37(4):548–57. doi:10.1007/s12272-013-0232-1
43. Green DR, Llambi F. Cell death signaling. Cold Spring Harb Perspect Biol. 2015;7(12):a006080. doi:10.1101/cshperspect.a006080
44. Popgeorgiev N, Jabbour L, Gillet G. Subcellular localization and dynamics of the Bcl-2 family of proteins. Front Cell Dev Biol. 2018;6:13. doi:10.3389/fcell.2018.00013
45. Gillies LA, Kuwana T. Apoptosis regulation at the mitochondrial outer membrane. J Cell Biochem. 2014;115(4):632–40. doi:10.1002/jcb.24709
46. Czabotar PE, Lessene G, Strasser A, Adams JM. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. Nat Rev Mol Cell Biol. 2014;15(1):49–63. doi:10.1038/nrm3722
47. Aubrey BJ, Kelly GL, Janic A, Herold MJ, Strasser A. How does p53 induce apoptosis and how does this relate to p53-mediated tumour suppression? Cell Death Differ. 2018;25(1):104–13. doi:10.1038/cdd.2017.169
48. Hsiao C-H, Yao C-J, Lai G-M, Lee L-M, Whang-Peng J, Shih P-H. Honokiol induces apoptotic cell death by oxidative burst and mitochondrial hyperpolarization of bladder cancer cells. Exp Ther Med. 2019;17(5):4213–22. doi:10.3892/etm.2019.7419
49. Luo L-X, Li Y, Liu Z-Q, Fan X-X, Duan F-G, et al. Honokiol induces apoptosis, G1 arrest, and autophagy in KRAS mutant lung cancer cells. Front Pharmacol. 2017;8:199. doi:10.3389/fphar.2017.00199
50. Yan B, Peng Z-Y. Honokiol induces cell cycle arrest and apoptosis in human gastric carcinoma MGC-803 cell line. Int J Clin Exp Med. 2015;8(4):5454.
51. Chang KH, Yan MD, Yao CJ, Lin PC, Lai GM. Honokiol-induced apoptosis and autophagy in glioblastoma multiforme cells. Oncol Lett. 2013;6(5):1435–8. doi:10.3892/ol.2013.1548
52. Li M, Zhang F, Wang X, Wu X, Zhang B, et al. Magnolol inhibits growth of gallbladder cancer cells through the p53 pathway. Cancer Sci. 2015;106(10):1341–50. doi:10.1111/cas.12762
53. Chen Y, Huang K, Ding X, Tang H, Xu Z. Magnolol inhibits growth and induces apoptosis in esophagus cancer KYSE-150 cell lines via the MAP kinase pathway. J Thorac Dis. 2019;11(7):3030. doi:10.21037/jtd.2019.07.46
54. Zhong W-B, Wang C-Y, Ho K-J, Lu F-J, Chang T-C, et al. Magnolol induces apoptosis in human leukemia cells via cytochrome c release and caspase activation. Anti-Cancer Drugs. 2003;14(3):211–7.
55. Yang SE, Hsieh MT, Tsai TH, Hsu SL. Effector mechanism of magnolol-induced apoptosis in human lung squamous carcinoma CH27 cells. Br J Pharmacol. 2003;138(1):193–201. doi:10.1038/sj.bjp.0705024

56. Wen H, Zhou S, Song J. Induction of apoptosis by magnolol via the mitochondrial pathway and cell cycle arrest in renal carcinoma cells. Biochem Biophys Res Commun. 2019;508(4):1271–8. doi:10.1016/j.bbrc.2018.12.087
57. Park JB, Lee MS, Cha EY, Lee JS, Sul JY, et al. Magnolol-induced apoptosis in HCT-116 colon cancer cells is associated with the AMP-activated protein kinase signaling pathway. Biol Pharm Bull. 2012;35(9):1614–20. doi:10.1248/bpb.b12-00352
58. Wang Y-D, Sun X-J, Yang W-J, Li J, Yin J-J. Magnolol exerts anticancer activity in hepatocellular carcinoma cells through regulating endoplasmic reticulum stress-mediated apoptotic signaling. OncoTargets Ther. 2018;11:5219. doi:10.2147/OTT.S168887
59. Huang SH, Chen Y, Tung PY, Wu JC, Chen KH, et al. Mechanisms for the magnolol-induced cell death of CGTH W-2 thyroid carcinoma cells. J Cell Biochem. 2007;101(4):1011–22. doi:10.1002/jcb.21100
60. Tse AK-W, Wan C-K, Shen X-L, Yang M, Fong W-F. Honokiol inhibits TNF-α-stimulated NF-κB activation and NF-κB-regulated gene expression through suppression of IKK activation. Biochem Pharmacol. 2005;70(10):1443–57. doi:10.1016/j.bcp.2005.08.011
61. Xu H, Tang W, Du G, Kokudo N. Targeting apoptosis pathways in cancer with magnolol and honokiol, bioactive constituents of the bark of Magnolia officinalis. Drug Discov Ther. 2011;5(5):202–10. doi:10.5582/ddt.2011.v5.5.202
62. You Q, Li M, Jiao G. Magnolol induces apoptosis via activation of both mitochondrial and death receptor pathways in A375-S2 cells. Arch Pharmacal Res. 2009;32(12):1789–94. doi:10.1007/s12272-009-2218-6
63. Raja SM, Chen S, Yue P, Acker TM, Lefkove B, et al. The natural product honokiol preferentially inhibits cellular FLICE-inhibitory protein and augments death receptor–induced apoptosis. Mol Cancer Ther. 2008;7(7):2212–23. doi:10.1158/1535-7163.MCT-07-2409
64. Zhang Y, Ren X, Shi M, Jiang Z, Wang H, et al. Downregulation of STAT3 and activation of MAPK are involved in the induction of apoptosis by HNK in glioblastoma cell line U87. Oncol Rep. 2014;32(5):2038–46. doi:10.3892/or.2014.3434
65. Abdal Dayem A, Hossain M, Lee S, Kim K, Saha S, Yang G-M, Choi H, Cho S-G. The role of reactive oxygen species (ROS) in the biological activities of metallic nanoparticles. IJMS. 2017;18(1):120. doi:10.3390/ijms18010120
66. Hafezi K, Hemmati AA, Abbaszadeh H, Valizadeh A, Makvandi M. Anticancer activity and molecular mechanisms of α-conidendrin, a polyphenolic compound present in Taxus yunnanensis, on human breast cancer cell lines. Phytother Res. 2020;34(6):1397–408. doi:10.1002/ptr.6613
67. Redza-Dutordoir M, Averill-Bates DA. Activation of apoptosis signalling pathways by reactive oxygen species. Biochim Biophys Acta. 2016;1863(12):2977–92. doi:10.1016/j.bbamcr.2016.09.012
68. Orrenius S, Gogvadze V, Zhivotovsky B. Calcium and mitochondria in the regulation of cell death. Biochem Biophys Res Commun. 2015;460(1):72–81. doi:10.1016/j.bbrc.2015.01.137
69. Huang K, Chen Y, Zhang R, Wu Y, Ma Y, Fang X, Shen S. Honokiol induces apoptosis and autophagy via the ROS/ERK1/2 signaling pathway in human osteosarcoma cells in vitro and in vivo. Cell Death Dis. 2018;9(2):1–17. doi:10.1038/s41419-017-0166-5
70. Zhou Y, Bi Y, Yang C, Yang J, Jiang Y, et al. Magnolol induces apoptosis in MCF-7 human breast cancer cells through G2/M phase arrest and caspase-independent pathway. Die Pharmazie. 2013;68(9):755–62.
71. Bai J, Li Y, Zhang G. Cell cycle regulation and anticancer drug discovery. Cancer Biol Med. 2017;14(4):348.
72. Hydbring P, Malumbres M, Sicinski P. Non-canonical functions of cell cycle cyclins and cyclin-dependent kinases. Nat Rev Mol Cell Biol. 2016;17(5):280. doi:10.1038/nrm.2016.27
73. Duronio RJ, Xiong Y. Signaling pathways that control cell proliferation. Cold Spring Harbor Perspect Biol. 2013;5(3):a008904. doi:10.1101/cshperspect.a008904
74. Law ME, Corsino PE, Narayan S, Law BK. Cyclin-dependent kinase inhibitors as anticancer therapeutics. Mol Pharmacol. 2015;88(5):846–52. doi:10.1124/mol.115.099325
75. Mikhail S, Albanese C, Pishvaian MJ. Cyclin-dependent kinase inhibitors and the treatment of gastrointestinal cancers. Am J Pathol. 2015;185(5):1185–97. doi:10.1016/j.ajpath.2015.01.008
76. Chen Y, Li H, Zhang W, Qi W, Lu C, et al. Sesamin suppresses NSCLC cell proliferation and induces apoptosis via Akt/p53 pathway. Toxicol Appl Pharmacol. 2020;387:114848. doi:10.1016/j.taap.2019.114848
77. Jeong JB, Hong SC, Jeong HJ, Koo JS. 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 Immunopharmacol. 2011;11(10):1573–7. doi:10.1016/j.intimp.2011.05.016
78. Hahm E-R, Singh SV. Honokiol causes G0-G1 phase cell cycle arrest in human prostate cancer cells in association with suppression of retinoblastoma protein level/phosphorylation and inhibition of E2F1 transcriptional activity. Mol Cancer Ther. 2007;6(10):2686–95. doi:10.1158/1535-7163.MCT-07-0217
79. Vaid M, Sharma SD, Katiyar SK. Honokiol, a phytochemical from the Magnolia plant, inhibits photocarcinogenesis by targeting UVB-induced inflammatory mediators and cell cycle regulators: development of topical formulation. Carcinogenesis. 2010;31(11):2004–11. doi:10.1093/carcin/bgq186
80. McKeown BT, McDougall L, Catalli A, Hurta RA. Magnolol causes alterations in the cell cycle in androgen insensitive human prostate cancer cells in vitro by affecting expression of key cell cycle regulatory proteins. Nutr Cancer. 2014;66(7):1154–64. doi:10.1080/01635581.2014.951736
81. Chen L-C, Liu Y-C, Liang Y-C, Ho Y-S, Lee W-S. Magnolol inhibits human glioblastoma cell proliferation through upregulation of p21/Cip1. J Agric Food Chem. 2009;57(16):7331–7. doi:10.1021/jf901477g
82. Chilampalli C, Guillermo R, Zhang X, Kaushik RS, Young A, et al. Effects of magnolol on UVB-induced skin cancer development in mice and its possible

mechanism of action. BMC Cancer. 2011;11(1):456. doi:10.1186/1471-2407-11-456
83. Chun Y, Kim J. Autophagy: an essential degradation program for cellular homeostasis and life. Cells. 2018;7(12):278. doi:10.3390/cells7120278
84. Linder B, Kögel D. Autophagy in cancer cell death. Biology. 2019;8(4):82. doi:10.3390/biology8040082
85. Lu Z, Cao S, Zhou H, Hua L, Zhang S, Cao J. Mechanism of arctigenin-induced specific cytotoxicity against human hepatocellular carcinoma cell lines: Hep G2 and SMMC7721. PLOS One. 2015;10(5):e0125727. doi:10.1371/journal.pone.0125727
86. Yun CW, Lee SH. The roles of autophagy in cancer. IJMS. 2018;19(11):3466. doi:10.3390/ijms19113466
87. Yoshii SR, Mizushima N. Monitoring and measuring autophagy. IJMS. 2017;18(9):1865. doi:10.3390/ijms18091865
88. Bednarczyk M, Zmarzły N, Grabarek B, Mazurek U, Muc-Wierzgoń M. Genes involved in the regulation of different types of autophagy and their participation in cancer pathogenesis. Oncotarget. 2018;9(76):34413. doi:10.18632/oncotarget.26126
89. Su T, Li X, Yang M, Shao Q, Zhao Y, et al. Autophagy: an intracellular degradation pathway regulating plant survival and stress response. Front Plant Sci. 2020;11:164. doi:10.3389/fpls.2020.00164
90. Kim J, Kundu M, Viollet B, Guan K-L. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol. 2011;13(2):132–41. doi:10.1038/ncb2152
91. Yang X, Yu D-D, Yan F, Jing Y-Y, Han Z-P, et al. The role of autophagy induced by tumor microenvironment in different cells and stages of cancer. Cell Biosci. 2015;5(1):14. doi:10.1186/s13578-015-0005-2
92. Bishop E, Bradshaw TD. Autophagy modulation: a prudent approach in cancer treatment?Cancer Chemother Pharmacol. 2018;82(6):913–22. doi:10.1007/s00280-018-3669-6
93. Hahm ER, Sakao K, Singh SV. Honokiol activates reactive oxygen species-mediated cytoprotective autophagy in human prostate cancer cells. Prostate. 2014;74(12):1209–21. doi:10.1002/pros.22837
94. Lu C-H, Chen S-H, Chang Y-S, Liu Y-W, Wu J-Y, et al. Honokiol, a potential therapeutic agent, induces cell cycle arrest and program cell death in vitro and in vivo in human thyroid cancer cells. Pharmacol Res. 2017;115:288–98. doi:10.1016/j.phrs.2016.11.038
95. Li H-b, Yi X, Gao J-m, Ying X-x, Guan H-q, Li J-c. Magnolol-lnduced H460 cells deathvia autophagy but not apoptosis. Arch Pharm Res. 2007;30(12):1566–74. doi:10.1007/BF02977326
96. Rajabi M, Mousa SA. The role of angiogenesis in cancer treatment. Biomedicines. 2017;5(4):34. doi:10.3390/biomedicines5020034
97. Abbaszadeh H, Ebrahimi SA, Akhavan MM. Antiangiogenic activity of xanthomicrol and calycopterin, two polymethoxylated hydroxyflavones in both in vitro and ex vivo models. Phytother Res. 2014;28(11):1661–70. doi:10.1002/ptr.5179
98. Jabłońska-Trypuć A, Matejczyk M, Rosochacki S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. J Enzyme Inhib Med Chem. 2016;31(sup1):177–83. doi:10.3109/14756366.2016.1161620
99. Yoo SY, Kwon SM. Angiogenesis and its therapeutic opportunities. Mediators Inflamm. 2013;2013:1–11. doi:10.1155/2013/127170
100. Duffy AM, Bouchier-Hayes DJ, Harmey JH. Vascular endothelial growth factor (VEGF) and its role in non-endothelial cells: autocrine signalling by VEGF. In: Madame Curie bioscience database [Internet]. Austin, TX: Landes Bioscience; 2013.
101. Fallah A, Sadeghinia A, Kahroba H, Samadi A, Heidari HR, et al. Therapeutic targeting of angiogenesis molecular pathways in angiogenesis-dependent diseases. Biomed Pharmacother. 2019;110:775–85. doi:10.1016/j.biopha.2018.12.022
102. Zimna A, Kurpisz M. Hypoxia-inducible factor-1 in physiological and pathophysiological angiogenesis: applications and therapies. BioMed Res Int. 2015;2015:1–13. doi:10.1155/2015/549412
103. Gu Y, Scheuer C, Feng D, Menger MD, Laschke MW. Inhibition of angiogenesis: a novel antitumor mechanism of the herbal compound arctigenin. Anti-Cancer Drugs. 2013;24(8):781–91. doi:10.1097/CAD.0b013e328362fb84
104. Jiang Z, Wu M, Miao J, Duan H, Zhang S, et al. Deoxypodophyllotoxin exerts both anti-angiogenic and vascular disrupting effects. Int J Biochem Cell Biol. 2013;45(8):1710–9. doi:10.1016/j.biocel.2013.04.030
105. Kim KM, Kim NS, Kim J, Park J-S, Yi JM, et al. Magnolol suppresses vascular endothelial growth factor-induced angiogenesis by inhibiting Ras-dependent mitogen-activated protein kinase and phosphatidylinositol 3-kinase/Akt signaling pathways. Nutr Cancer. 2013;65(8):1245–53. doi:10.1080/01635581.2013.828082
106. Wen J, Fu A, Chen LJ, Xie XJ, Yang GL, et al. Liposomal honokiol inhibits VEGF-D-induced lymphangiogenesis and metastasis in xenograft tumor model. Int J Cancer. 2009;124(11):2709–18. doi:10.1002/ijc.24244
107. Vavilala DT, Ponnaluri VC, Kanjilal D, Mukherji M. Evaluation of anti-HIF and anti-angiogenic properties of honokiol for the treatment of ocular neovascular diseases. PLOS One. 2014;9(11):e113717. doi:10.1371/journal.pone.0113717
108. Bai X, Cerimele F, Ushio-Fukai M, Waqas M, Campbell PM, et al. Honokiol, a small molecular weight natural product, inhibits angiogenesis in vitro and tumor growth in vivo. J Biol Chem. 2003;278(37):35501–7. doi:10.1074/jbc.M302967200
109. Chen M-C, Lee C-F, Huang W-H, Chou T-C. Magnolol suppresses hypoxia-induced angiogenesis via inhibition of HIF-1α/VEGF signaling pathway in human bladder cancer cells. Biochem Pharmacol. 2013;85(9):1278–87. doi:10.1016/j.bcp.2013.02.009
110. Pijuan J, Barceló C, Maiques O, Moreno DF, Sisó P, et al. In vitro cell migration, invasion and adhesion assays: from cell imaging to data analysis. Front Cell Dev Biol. 2019;7:107. doi:10.3389/fcell.2019.00107
111. Guan X. Cancer metastases: challenges and opportunities. Acta Pharmaceutica Sinica B. 2015;5(5):402–18. doi:10.1016/j.apsb.2015.07.005

112. Singh D, Srivastava SK, Chaudhuri TK, Upadhyay G. Multifaceted role of matrix metalloproteinases (MMPs). Front Mol Biosci. 2015;2:19. doi:10.3389/fmolb.2015.00019
113. Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez VE, et al. Role of matrix metalloproteinases in angiogenesis and cancer. Front Oncol. 2019;9:1370. doi:10.3389/fonc.2019.01370
114. Fanjul-Fernández M, Folgueras AR, Cabrera S, López-Otín C. Matrix metalloproteinases: evolution, gene regulation and functional analysis in mouse models. Biochim Biophys Acta. 2010;1803(1):3–19. doi:10.1016/j.bbamcr.2009.07.004
115. Guo Y, Liu N, Liu K, Gao M. Capsaicin inhibits the migration and invasion via the AMPK/NF-κB signaling pathway in esophagus sequamous cell carcinoma by decreasing matrix metalloproteinase-9 expression. Biosci Rep. 2019;39(8):1–12. doi:10.1042/BSR20190819
116. Xu F, Na L, Li Y, Chen L. Roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours. Cell Biosci. 2020;10(1):1–12. doi:10.1186/s13578-020-00416-0
117. Merchant N, Nagaraju GP, Rajitha B, Lammata S, Jella KK, et al. Matrix metalloproteinases: their functional role in lung cancer. Carcinogenesis. 2017;38(8):766–80. doi:10.1093/carcin/bgx063
118. Cathcart J, Pulkoski-Gross A, Cao J. Targeting matrix metalloproteinases in cancer: bringing new life to old ideas. Genes Dis. 2015;2(1):26–34. doi:10.1016/j.gendis.2014.12.002
119. Son H, Moon A. Epithelial-mesenchymal transition and cell invasion. Toxicol Res. 2010;26(4):245–52. doi:10.5487/TR.2010.26.4.245
120. Savci-Heijink CD, Halfwerk H, Hooijer GKJ, Koster J, Horlings HM, Meijer SL, van de Vijver MJ. Epithelial-to-mesenchymal transition status of primary breast carcinomas and its correlation with metastatic behavior. Breast Cancer Res Treat. 2019;174(3):649–59. doi:10.1007/s10549-018-05089-5
121. Loh C-Y, Chai J, Tang T, Wong W, Sethi G, Shanmugam M, Chong P, Looi C. The E-cadherin and N-cadherin switch in epithelial-to-mesenchymal transition: signaling, therapeutic implications, and challenges. Cells. 2019;8(10):1118. doi:10.3390/cells8101118
122. Serrano-Gomez SJ, Maziveyi M, Alahari SK. Regulation of epithelial-mesenchymal transition through epigenetic and post-translational modifications. Mol Cancer. 2016;15(1):18. doi:10.1186/s12943-016-0502-x
123. Hwang E-S, Park K-K. Magnolol suppresses metastasis via inhibition of invasion, migration, and matrix metalloproteinase-2/-9 activities in PC-3 human prostate carcinoma cells. Biosci Biotechnol Biochem. 2010;74(5):961–7. doi:10.1271/bbb.90785
124. Nagase H, Ikeda K, Sakai Y. Inhibitory effect of magnolol and honokiol from Magnolia obovata on human fibrosarcoma HT-1080 invasiveness in vitro. Planta Med. 2001;67(08):705–8. doi:10.1055/s-2001-18345
125. Chei S, Oh H-J, Song J-H, Seo Y-J, Lee K, et al. Magnolol suppresses TGF-β-induced epithelial-to-mesenchymal transition in human colorectal cancer cells. Front Oncol. 2019;9:752. doi:10.3389/fonc.2019.00752
126. Pucci C, Martinelli C, Ciofani G. Innovative approaches for cancer treatment: current perspectives and new challenges. Ecancermedicalscience. 2019;13:1–26. doi:10.3332/ecancer.2019.961
127. Singh T, Katiyar SK. Honokiol inhibits non-small cell lung cancer cell migration by targeting PGE2-mediated activation of β-catenin signaling. PLOS One. 2013;8(4):e60749. doi:10.1371/journal.pone.0060749
128. Shen L, Zhang F, Huang R, Yan J, Shen B. Honokiol inhibits bladder cancer cell invasion through repressing SRC-3 expression and epithelial-mesenchymal transition. Oncol Lett. 2017;14(4):4294–300. doi:10.3892/ol.2017.6665
129. Lv X-q, Qiao X-r, Su L, Chen S-z. Honokiol inhibits EMT-mediated motility and migration of human non-small cell lung cancer cells in vitro by targeting c-FLIP. Acta Pharmacol Sin. 2016;37(12):1574–86. doi:10.1038/aps.2016.81
130. Wang W-d, Shang Y, Li Y, Chen S-z. Honokiol inhibits breast cancer cell metastasis by blocking EMT through modulation of Snail/Slug protein translation. Acta Pharmacol Sin. 2019;40(9):1219–27. doi:10.1038/s41401-019-0240-x
131. Avtanski DB, Nagalingam A, Bonner MY, Arbiser JL, Saxena NK, et al. Honokiol inhibits epithelial–mesenchymal transition in breast cancer cells by targeting signal transducer and activator of transcription 3/Zeb1/E-cadherin axis. Mol Oncol. 2014;8(3):565–80. doi:10.1016/j.molonc.2014.01.004
132. Xia L, Tan S, Zhou Y, Lin J, Wang H, et al. Role of the NFκB-signaling pathway in cancer. OncoTargets Ther. 2018;11:2063. doi:10.2147/OTT.S161109
133. Avtanski D, Poretsky L. Phyto-polyphenols as potential inhibitors of breast cancer metastasis. Mol Med. 2018;24(1):29. doi:10.1186/s10020-018-0032-7
134. Aggarwal BB, Sung B. NF-κB in cancer: a matter of life and death. Cancer Discov. 2011;1(6):469–71. doi:10.1158/2159-8290.CD-11-0260
135. Basseres D, Baldwin A. Nuclear factor-κ B and inhibitor of κ B kinase pathways in oncogenic initiation and progression. Oncogene. 2006;25(51):6817–30. doi:10.1038/sj.onc.1209942
136. Hoesel B, Schmid JA. The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer. 2013;12(1):1–15. doi:10.1186/1476-4598-12-86
137. Xia Y, Shen S, Verma IM. NF-κB, an active player in human cancers. Cancer Immunol Res. 2014;2(9):823–30. doi:10.1158/2326-6066.CIR-14-0112
138. Letícia de Castro Barbosa M, Alves da Conceicao R, Guerra Manssour Fraga A, Dias Camarinha B, Cristina de Carvalho Silva G, Gilcler Ferreira Lima A, Azevedo Cardoso E, de Oliveira Freitas Lione V. NF-κB signaling pathway inhibitors as anticancer drug candidates. ACAMC. 2017;17(4):483–90. doi:10.2174/1871520616666160729112854
139. Harikumar KB, Sung B, Tharakan ST, Pandey MK, Joy B, et al. Sesamin manifests chemopreventive effects through the suppression of NF-κB–regulated cell survival, proliferation, invasion, and angiogenic gene products. Mol Cancer Res. 2010;8(5):751–61. doi:10.1158/1541-7786.MCR-09-0565
140. Maxwell T, Chun S-Y, Lee K-S, Kim S, Nam K-S. The anti-metastatic effects of the phytoestrogen arctigenin on human breast cancer cell lines regardless of the

status of ER expression. Int J Oncol. 2017;50(2):727–35. doi:10.3892/ijo.2016.3825
141. Yang B, Ni X, Chen L, Zhang H, Ren P, et al. Honokiol-loaded polymeric nanoparticles: an active targeting drug delivery system for the treatment of nasopharyngeal carcinoma. Drug Deliv. 2017;24(1):660–9. doi:10.1080/10717544.2017.1303854
142. Arora S, Bhardwaj A, Srivastava SK, Singh S, McClellan S, Wang B, Singh AP. Honokiol arrests cell cycle, induces apoptosis, and potentiates the cytotoxic effect of gemcitabine in human pancreatic cancer cells. PLOS One. 2011;6(6):e21573. doi:10.1371/journal.pone.0021573
143. Peng Q, Deng Z, Pan H, Gu L, Liu O, et al. Mitogen-activated protein kinase signaling pathway in oral cancer. Oncol Lett. 2018;15(2):1379–88.
144. Guo YJ, Pan WW, Liu SB, Shen ZF, Xu Y, et al. ERK/MAPK signalling pathway and tumorigenesis. Exp Ther Med. 2020;19(3):1997–2007. doi:10.3892/etm.2020.8454
145. Lee S, Rauch J, Kolch W. Targeting MAPK signaling in cancer: mechanisms of drug resistance and sensitivity. IJMS. 2020;21(3):1102. doi:10.3390/ijms21031102
146. Yue J, López JM. Understanding MAPK signaling pathways in apoptosis. IJMS. 2020;21(7):2346. doi:10.3390/ijms21072346
147. Yang J, Nie J, Ma X, Wei Y, Peng Y, et al. Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer. 2019;18(1):26. doi:10.1186/s12943-019-0954-x
148. Hassan B, Akcakanat A, Holder AM. Meric-Bernstam F. Targeting the PI3-kinase/Akt/mTOR signaling pathway. Surg Oncol Clin. 2013;22(4):641–64. doi:10.1016/j.soc.2013.06.008
149. Yip PY. Phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin (PI3K-Akt-mTOR) signaling pathway in non-small cell lung cancer. Transl Lung Cancer Res. 2015;4(2):165.
150. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74. doi:10.1016/j.cell.2011.02.013
151. Lien EC, Dibble CC, Toker A. PI3K signaling in cancer: beyond AKT. Curr Opin Cell Biol. 2017;45:62–71. doi:10.1016/j.ceb.2017.02.007
152. Hillmann P, Fabbro D. PI3K/mTOR pathway inhibition: opportunities in oncology and rare genetic diseases. IJMS. 2019;20(22):5792. doi:10.3390/ijms20225792
153. Ortega MA, Fraile-Martínez O, Asúnsolo Á, Buján J, García-Honduvilla N, et al. Signal transduction pathways in breast cancer: the important role of PI3K/Akt/mTOR. J Oncol. 2020;2020:1–11. doi:10.1155/2020/9258396
154. Lee DH, Szczepanski MJ, Lee YJ. Magnolol induces apoptosis via inhibiting the EGFR/PI3K/Akt signaling pathway in human prostate cancer cells. J Cell Biochem. 2009;106(6):1113–22. doi:10.1002/jcb.22098
155. Li Z, Dong H, Li M, Wu Y, Liu Y, et al. Honokiol induces autophagy and apoptosis of osteosarcoma through PI3K/Akt/mTOR signaling pathway. Mol Med Rep. 2018;17(2):2719–23.
156. Lin C-J, Chen T-L, Tseng Y-Y, Wu G-J, Hsieh M-H, et al. Honokiol induces autophagic cell death in malignant glioma through reactive oxygen species-mediated regulation of the p53/PI3K/Akt/mTOR signaling pathway. Toxicol Appl Pharmacol. 2016;304:59–69. doi:10.1016/j.taap.2016.05.018
157. Liu H, Zang C, Emde A, Planas-Silva MD, Rosche M, et al. Anti-tumor effect of honokiol alone and in combination with other anti-cancer agents in breast cancer. Eur J Pharmacol. 2008;591(1–3):43–51. doi:10.1016/j.ejphar.2008.06.026
158. Yeh P-S, Wang W, Chang Y-A, Lin C-J, Wang J-J, et al. Honokiol induces autophagy of neuroblastoma cells through activating the PI3K/Akt/mTOR and endoplasmic reticular stress/ERK1/2 signaling pathways and suppressing cell migration. Cancer Lett. 2016;370(1):66–77. doi:10.1016/j.canlet.2015.08.030
159. Chuang T-C, Hsu S-C, Cheng Y-T, Shao W-S, Wu K, et al. Magnolol down-regulates HER2 gene expression, leading to inhibition of HER2-mediated metastatic potential in ovarian cancer cells. Cancer Lett. 2011;311(1):11–9. doi:10.1016/j.canlet.2011.06.007
160. Lin H-L, Cheng W-T, Chen L-C, Ho H-O, Lin S-Y, et al. Honokiol/magnolol-loaded self-assembling lecithin-based mixed polymeric micelles (lbMPMs) for improving solubility to enhance oral bioavailability. Int J Nanomed. 2021;16:651. doi:10.2147/IJN.S290444
161. Wang Y-J, Chien Y-C, Wu C-H, Liu D-M. Magnolol-loaded core–shell hydrogel nanoparticles: drug release, intracellular uptake, and controlled cytotoxicity for the inhibition of migration of vascular smooth muscle cells. Mol Pharmaceutics. 2011;8(6):2339–49. doi:10.1021/mp200257y
162. Wu W, Wang L, Wang L, Zu Y, Wang S, et al. Preparation of honokiol nanoparticles by liquid antisolvent precipitation technique, characterization, pharmacokinetics, and evaluation of inhibitory effect on HepG2 cells. Int J Nanomed. 2018;13:5469. doi:10.2147/IJN.S178416