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Review

Honokiol: An anticancer lignan

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ABSTRACT

Background: Honokiol ((3′,5-di-(2-propenyl)-1,1′-biphenyl-2,2′-diol), a lignan, is a promising antitumor compound, having exerted activity against a number of human cancer cell lines. Honokiol has inhibitory role on the proliferation, invasion and survival of cancer cells in in vitro as well as in vivo studies. It interferes with signaling pathways components in order to elicit the anticancer effect.

Scope and approach: In present review, the published data on the efficacy of honokiol against various cancer cell lines and tumor-bearing animal models has been presented and discussed.

Key findings and conclusions: Honokiol lowers the expression of pluripotency-factors, the formation of mammosphere, P-glycoprotein expression, receptor CXCR4 level, c-FLIP, steroid receptor coactivator-3 (SRC-3), Twist1, matrix metalloproteinases, class I histone deacetylases, H3K27 methyltransferase among numerous other anticancer functions. It increases bone morphogenetic protein 7 (BMP7), Bax protein, among others. It does so by interfering with the major checkpoints such as nuclear factor kappa B (NF-κB), and activator of transcription 3 (STAT3), mammalian target of rapamycin (m-TOR), epidermal growth factor receptor (EGFR), Sonic hedgehog (SHH). It promotes the efficacy of several anticancer drugs and radiation tolerance. The derivatization of honokiol results in compounds with interesting attributes in terms of cancer control. This review will shed light on the scopes and hurdles in the relevance of the bioactive lignan honokiol in cancer management.

1. Introduction

Honokiol (3,5-di-(2-propenyl)-1,1-biphenyl-2,2-diol) is a phenylpropanoid molecule, a biaryl-type lignan, present in the genus *Magnolia* [1,2]. It is present in all parts of the *Magnolia* genus such as bark, phloem, wood, leaf blades, and petioles. It has been detected in the species *M, obovata*, *M. officinalis*, *M. grandiflora*, and *M. dealbata*. In *M. officinalis* powder, the amount of honokiol ranged from 17 to 19 mg/g.

Magnolia bark extracts have been in usage as traditional herbal medicines in Korea, China and Japan, among other countries [3]. Wide-ranging pharmacological activities of honokiol are emerging. Honokiol has neuroprotective function [4]. It suppressed the production of prostaglandin E2 and cyclooxygenase-2 (COX-2) level in the brain of mice, ameliorating neuroinflammatory processes [5]. Neonatal rats, when injected with honokiol (10 mg/kg), acute pain response was subdued [6]. It exerted anti-inflammatory effect by targeting Lyn kinase in human neutrophils [7]. Honokiol inhibited collagen-induced arthritis by negating pro-inflammatory cytokines and matrix metalloproteinases and blocking oxidative tissue damage [8]. A study found that honokiol inhibits the replication, viral gene expression, and endocytotic process of dengue virus (DENV-2) [2]. The application of 25 mg/kg honokiol to guinea pig models lowered the testosterone level as compared with letrozole [9].

Its apoptosis induction and malignancy control role has received much attention in recent times.It has shown various degree of efficacy towards pancreatic cancer, prostate cancer gastric cancer, oral cancer, glioblastoma or brain cancer, skin cancer, ovarian cancer, bone cancer/osteosarcoma [10], chondrosarcoma, lung cancer, nasopharyngeal and thyroid cancer, blood caner, liver cancer, colon cancer, bladder cancer.

Honokiol reduced tumor growth in SKMEL-2 and UACC-62

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melanoma xenografts in mice [11]. Honokiol pretreatment of cervix squamous carcinoma A431 cells induced apoptosis and DNA fragmentation. At 50 μmol/L dose, G0/G1 cell cycle arrest occurred [12]. Honokiol inhibited the migration of urinary bladder cancer cells [13]; oral squamous cell carcinoma cells [14]; bladder tumor [15]; colon cancer [16]; and thyroid cancer [17]. Mice glioma could be treated with honokiol-induced autophagy [18].

2. Anticancer mechanisms of honokiol

Cancer is an heterogenous disease, manifesting in multiple subtypes. The initiation and progression of cancer is found associated both with epigenetic as well as genetic aberrations, which dysregulate key cell signaling pathways. Be that melanoma, glioma, renal cancer, hepatic cancer or any other tissue-specific cancer, the problem is the same. Oxidative stress and high inflammation l [19] lead to acidosis [20–22] and hypoxia [23]. As a result, aromatase enzyme goes into an overdrive [24], and excess estrogen is produced [25]. Excess expression of estrogen receptors result to capture the estrogen. So, honokiol's response towards any of those cancers is mediated by the same mechanisms. The selected anticancer pathways of honokiol has been discussed below.

Honokiol scavenges superoxide as well as peroxyl radicals. This antioxidative property is responsible for antitumor response, as NF-κβ (nuclear factor kappaB) is stimulated by reactive oxygen species (ROS) [26]. NF-κβ activation creates a gamut of inflammatory components such as MMP-9, TNF-α, IL-8, ICAM-1 and MCP-1, among others [27,28]. Metastatic role of the proteolytic enzymes MMP-9 and the proangiogenic factors IL-8 is well-validated [29]. So, carcinogenesis can be prevented in its absence. Honokiol suppressed NF-kB activation, by inhibiting the nuclear translocation and phosphorylation of p65 subunit. Also, it enhanced TNF-α -induced apoptotic cell death [27]. Honokiol can reduce hypoxia-inducible factor-1α (HIF-1α) protein level and suppressing the hypoxia-related signaling pathway. HIF-1α is a key mediator of for the adaptation of cancer cells to low oxygen levels [30]. As hypoxia promotes tumor, anticancer role of honokiol is understandable [31].

Honokiol significantly inhibited the calcineurin inhibitor cyclosporine A-induced survival of renal cancer cells, by downregulating VEGF (vascular endothelial growth facto) and HO-1 (heme oxygenase-1) [32]. VEGF is an angiogenic factor and is up-regulated in tumors for mediating autocrine signaling pathways [33]. Receptor tyrosine kinase c-Met can promote cancer growth by inducing differentiation, proliferation, cell cycle, motility, and apoptosis, through the regulation of HO-1 [34]. HGF (hepatocyte growth factor) is a ligand for c-Met, and excess c-Met expression in gastric cancer and lung cancer has been observed [35,36]. So, honokiol is likely to be interfering with the kinase function. Honokiol's role in inhibition of STAT3 (signal transducers and activators of transcription 3) activation in hepatocellular carcinoma (HCC) cells by the interference of upstream kinases such as c-Src, Janus-activated kinase 1 (JAK 1), and Janus-activated kinase 2 (JAK 2) is well-known [37]. Constitutively activated STAT3 levels are correlated with cellular transformation and aggressive cancer forms [38]. c-Src kinase over-expression transforms cell phenotypes imparting anchorage-independent growth and tumorigenicity [39]. The interaction of honokiol with another oncogenic transcription factor FOXM1 and subsequent inhibition has been explained to result in anticancer effect [40]. The induction and overexpression of FoxM1 by Ras, results in malignancies [41].

Honokiol is capable of suppressing high-glucose-induced inflammatory responses of human renal mesangial cells [42]. The abnormal glucose metabolism, hyperglycemia, and cancer link has been proven [43]. Persistent hyperglycemic condition fuels NF-κβ activation which leads to the expression of a number of cytokines, chemokines and cell adhesion molecules [44].

Honokiol also reduces the effect of extracellular signal-regulated kinase (ERK) activation, protects mitochondrial respiratory chain (ETC) enzyme, and inhibits protein kinase C (PKC) and NADPH oxidase activities. It leads to the accumulation of cells in the G2/M phase of the cell cycle and elevates the level of caspases and Poly (ADP-ribose) polymerase (PARP). Honokiol induced the apoptosis of hepG2 human hepatocellular carcinoma cells by activating p38 MAPK pathway and subsequent caspase-3 [45]. It down-regulates the expression of cyclin D1, cyclin D2, Cdk2, Cdk4 and Cdk6 proteins and up-regulates the expression of Cdk's inhibitor proteins p21 and p27 [12].

It prevented the invasion of urinary bladder cancer cell by the downregulation of steroid receptor coactivator-3 (SRC-3), matrix metalloproteinase (MMP)-2 and Twist1 [13]. So, it suppressed epithelial-mesenchymal transition (EMT) by the induction of E-cadherin and repression of N-cadherin [13]. Honokiol inhibited EMT-driven migration of human NSCLC cells in vitro by targeting c-FLIP [46]. Twist1, a basic helix-loop-helix domain-containing transcription factor, promotes tumor metastasis, by inducing EMT. Twist1 is upregulated by multiple factors including SRC-1, STAT3, MSX2, HIF-1α, integrin-linked kinase, NF-κB [47], and it uses PDGFRα as its transcriptional target [48]. Modulators of Twist1 are regarded as promising therapy for metastatic cancer, and honokiol merits investigation in this context.

When applied to neuro-2a cells, honokiol selectively induced DNA fragmentation and cell apoptosis by increasing the expression of the proapoptotic Bax protein and its translocation from the cytoplasm to mitochondria. It induced the activation of caspases-9, -3, and -6, which led to the apoptosis of neuroblastoma cells [49]. Honokiol induced autophagy of glioma cells (human glioma U87 MG) and neuroblastoma cells through the ROS-mediated regulation of the p53/cyclin D1/CDK6/CDK4/E2F1-dependent pathway, p53/PI3K/Akt/mTOR signaling pathway and endoplasmic reticular stress/ERK1/2 signaling pathways and suppressing cell migration [18,50,51]. Autophagy markers such as Beclin-1 and LC3-II have been observed after the lignan treatment. Beclin-1, the macroautophagy protein, forms part of the phosphatidylinositol-3 kinase complexes which tag membranes for autophagosome generation, and subsequent union with lysosomes [52]. Blood-brain barrier (BBB) integrity is important for nervous system homeostasis. Cancer cells often escape the drugs by exploiting this barrier. Honokiol's ability to traverse the BBB is emerging [51]. If the drug can also cross the BBB, it can inhibit the cancer [53]. Honokiol suppresses the migration of highly metastatic renal cell carcinoma (RCC) through the activation of RhoA/ROCK (Rho-associated protein kinase)/MLC (phosphorylated myosin light chain) signaling [54].

This lignan can control bladder tumor growth by suppressing oncoprotein EZH2 (Enhancer of zeste homolog 2), a histone H3K27 methyltransferase [15]. Histone modification can lead to the change in the chromatin architecture, affect transcriptional regulation and cause cancer [55]. It also induces caspase-dependent apoptosis in B-cell chronic lymphocytic leukemia (B-CLL) cells [56]. This lignan down-regulates c-FLIP (cellular-FLICE inhibitory protein), an anti-apoptotic regulator, by increasing its degradation by ubiquitin/proteasome-mediated mechanism, which modulates the death receptor-induced apoptosis [57]. c-FLIP can inhibit cell death mediated by the death receptors Fas, DR4, DR5, and TNF-R1 [58]. So, honokiol might be exploited to inhibit c-FLIP, the apoptosis inhibitor. Honokiol might be a potential treatment for t(8;21) translocation leukemia as it can target AML1-ETO oncoprotein, a chromosomal translocation product, by increasing the expression of UbcH8, an E2-conjugase [59]. The t(8;21)-encoded AML1-ETO chimeric product leads to anomalous hematopoietic cell proliferation [60]. So, the abolition of this fusion product by honokiol holds prospect for leukemia therapy.

Honokiol upregulates the expression of bone morphogenetic protein 7 (BMP7) in colon cancer cells, which plays role in the activation of p53 [16]. BMP7 are transforming growth factor-beta superfamily cytokines secreted by bone stromal cells and are involved in Smad signaling [61]. These proteins can lead to vascular calcification, and control gastric cancer progression [62]. They can prevent recurrent metastatic disease like prostate cancer stem-like cells on bones [63]. BMP7's role in cancer

inhibition is via the activation of p38 mitogen-activated protein kinase, increased expression of the cell cycle inhibitor p21, and the metastasis suppressor gene NDRG1 (N-myc downstream-regulated gene 1) [63]. Also, honokiol targets SW480 colon cancer stem cells by inhibiting the γ-secretase complex and the Notch signaling pathway [64]. Honokiol induces cell cycle arrest and apoptosis induction on acute myeloid leukemia by inhibiting class I histone deacetylases [65].

Honokiol markedly decreased the expression of cyclins (D1 and E) and cyclin-dependent kinases (Cdk2 and Cdk4), increased Cdk inhibitors, p21 and p27, enhanced of Bax/Bcl-2 and Bax/Bcl-xL ratios in pancreatic cancer cells [66]. Honokiol-treated pancreatic cancer had retarded tumor growth and metastasis due to the downregulation of CXCR4 and SHH (Sonic hedgehog) by the lignan, causing muted tumor-stromal cross-talk [67]. CXCR4 is a G protein-coupled receptor (GPCR) for CXCL12 chemokine, and it mediates the proliferation, survival, migration, and homing of cancer cells [68]. HER2 (human epidermal receptor 2) enhances the expression of CXCR4 by stimulating CXCR4 translation and attenuating CXCR4 degradation [69]. It is increasingly being acknowledged that the molecules targeting CXCR4 can be cancer therapeutics. Chemotherapy resistance is a major obstacle in successful oncotherapy, which is largely due to abundant efflux protein expression on the cancer cell membranes. Honokiol downregulated the expression of P-glycoprotein in MCF-7, leading to drug accumulation, and increased sensitivity of cancer cells [70]. Low extracellular pH, due to intracellular calcium levels and inhibition of PKC, enhance the higher expression of P-glycoprotein [71]. The lignan lowering the drug efflux pump expression might be dose- and variable-dependent, and the result might not replicate in vivo. The administration of honokiol with poor soluble P-glycoprotein substrate sirolimus for oral delivery is being considered [72]. SHH plays role in the formation of desmoplasia in pancreatic cancer [73], and SHH signaling pathway is involved in medulloblastomas [74]. Honokiol acts as the agonist of both retinoid X receptor (RXR) and peroxisome proliferator-activated receptor gamma (PPARγ) [75].

Honokiol acts as a radio-sensitizing agent for colorectal cancers [76]. Radiosensitizers enhance the sensitivity of hypoxic, tumor cells to the lethal effect of radiations. The lignan might be modulating the milieu, so that selective absorption of the radiation by the cancer cells occur. In fact, a number of phytochemicals has been attributed to improve radiation therapy outcomes, by either acting as radiosensitizer to tumor cells or as radioprotector to normal cells [77]. A plant phenol thymol protected Chinese hamster lung fibroblast (V79) cells from radiation-induced oxidative stress, and lipid peroxidation, promoting cell viability [78]. Honokiol is assumed to prevent radiation-induced damage by the same antioxidative mechanism, common to several phenolic compounds [79].

All the above discussed cancer perspectives are summarized along with their most probable mechanism of action in Table 1. Fig. 1 presents the structure and biological activities of honokiol.

3. Scopes and hurdles

Honokiol enhances the anticancer effect of oxaliplatin in colon cancer cells [80]. Honokiol raise the efficacy of anticancer drug imatinib against human leukemia cells [81]; lapatinib against HER-2 overexpressed breast cancer cells [82]; adriamycin (doxorubicin) against 4T1 cells [83]; paclitaxel and doxorubicin against HCC cells [37], among others. When combined with rosiglitazone had superior growth inhibitory effect on SK-Hep1 hepatoma cells, which occurred via the G0/G1 phase-related proteins p21, cyclin D1, cyclin E1, and Rb [75]. While it is encouraging result, the risk of drug-herb adverse reaction is there. If the lignan hampers or modifies the intended effect of the drugs need to be probed.

4. Efficacy enhancement of Honokilol

Honokiol is a lipophilic compound. While patient tolerance of honokiol is its merit, its water insolubility compromises its efficacy. Also, pharmacokinetics of honokiol in rats has been studied by intravenous injection of this lignan, and subsequent blood analysis, which showed quick distribution and rapid decrease [84]. From another rat model study, it came forth that the elimination of honokiol in liver, kidney and brain was more rapid than in plasma [85]. In another pharmacokinetics study on nude mice bearing RKO-incubated tumor, honokiol was absorbed quickly following intraperitoneal injection, and was maintained in plasma for more than 10 h [86]. To enhance the stability and bioavailability of honokiol, it is processed as honokiol-in-HP-β-CD-n-liposome. So, pegylated liposome (PEGL) is used to encapsulate honokiol. PEGylated liposomal honokiol improves the solubility, and drug concentration in plasma, while reducing clearance rate [87]. Pharmacokinetic study has revealed that honokiol-in-HP-β-CD-in-liposome has longer residence time in circulating system than the untreated honokiol [87]. Honokiol-loaded polymeric nanoparticles was tested against nasopharyngeal carcinoma [88]. The co-delivery of paclitaxel and honokiol by pH-responsive polymeric micelles for the suppression of multidrug resistance (MDR) and metastasis of breast cancer cells was studied [89]. Liposomal honokiol combined with cisplatin synergistically target colon cancer models [90] as well as ovarian carcinoma [91].

Structural modification of honokiol to develop more effective analogues to control cancer has been studied, confirming a structure-activity connection [92]. Honokiol derivative 5-formylhonokiol possesses strong inhibitory activity against K562 (human myelogenous leukemia), A549 (human lung adenocarcinoma) and SPC-A1 (human lung adenocarcinoma) tumor cell lines [93]. On several tumor cell lines, 5-formylhonokiol exerted better anti-angiogenesis capacity than honokiol, by the downregulation of the ERK signal pathway [94]. Some other honokiol derivatives include 3′,5-Diallyl-2,4′-dihydroxy-[1,1′-biphen-yl]-3,5′-dicarbaldehyde, butyrate ester derivative of honokiol with unsubstituted phenol group, 4′-O-methylhonokiol, honokiol position isomers. Table 2 presents the honokiol derivatives and their therapeutic potential.

5. Discussion

Irrespective of the heterogeneity and tissue specific-behavior, most cancers are resultant of acidosis, hypoxia, inflammation, enzyme activation, and estrogen dominance. Cancer mitigation lies in raising the pH and lowering the estrogen level. From literature review of different in vitro paradigms, it was clear that honokiol mediates cancer inhibition via the same ERK, Akt/mTOR, p38, and JNK pathways.

The in vitro-derived results on the cancer control ability of honokiol are promising but biased interpretations. It is increasingly being acknowledged that it is the milieu which regulates the fate of cancer. If the enzyme is aberrant activated and endocrine system is disrupted, cancer turns aggressive. In the in vitro system, there is no effect of immune system, so the results are more likely to be positive, yet misleading. But, in in vivo or human system, there are numerous enzymes to metabolize honokiol, rendering it ineffective. Even if honokiol is effective on certain cancer, it is mostly by its structural similarity to estrogen. So, this phenol might be acting as agonist or antagonist of estrogen. In fact, reports exist to conform that lignans inhibit aromatase enzyme activity in human pre-adipose cell culture system [95]. Also, it is biochemically a lignan. Lignan from soy, flaxseed, and sesame are often considered phytoestrogen [96]. Dietary lignans are metabolized by gut flora into enterolactone and enterodiol. Secoisolariciresinol, matairesinol, lariciresinol and pinoresinol are some of the enterolignan precursors [96]. Plant lignans have been considered as SERM (selective estrogen receptor modulators), to tame excess estrogen, the cause of carcinogenesis. So, the role of lignans in cancer is dual and conflicting.

Table 1
Anticancer perspectives of honokiol.

Cancer types	Mechanisms
Breast	Inhibited tumor growth rate, induced apoptosis, and decreased microvasculature density
	Increased LKB1 expression, and suppressed individual cell-motility Reduced expression of pluripotency-factors, formation of mammosphere, and aldehyde dehydrogenase activity
	Activated the AMP-dependent protein kinase (AMPK)
	Inhibited the expressions of pluripotency factors (Nanog, Oct4, and Sox2)
	Suppressed the STAT3-phosphorylation
	Induced apoptosis, inhibited cell growth, and caused cell cycle arrest
	Suppressed the epithelial-mesenchymal-transition, and mammosphere-formation
	Decreased levels of Oct4, stemness factors, and Nanog
	Enhanced the expression and cytoplasmic-localization of LKB1 Increased miR-34a in LKB1-dependent manner
	Inhibited EMT, nuclear-localization and Zeb1 expression, expression of stemness factors and mammosphere-formation
	Inhibited TNF-α-induced Nur77 mRNA expression
	Inhibited the expression level of Mucin 1 and multidrug resistance proteins
Pancreatic	Reduced the desmoplasia, and expression of C-X-C chemokine receptor type 4 and sonic hedgehog
	Lowered the levels of cyclins D1, E and cyclin-dependent kinases (Cdk2 and Cdk4)
	Decreased the phosphorylation of kappa B alpha (IκB-α) inhibitor
Prostate	Decreased levels of mRNA expression and phosphorylated c-Myc protein1
	Lowered Cyclin D1 and increase Zeste Homolog 2
	Inhibited the cell viability, androgen receptor signaling
	Suppressed the androgen receptor stimulation
	Down regulated AR protein
	Decreased expressions of Bcl-xL as well as Mcl-1 proteins
	Induced apoptosis, apoptotic DNA fragmentation
Gastric	Down regulated the expressions of cdc25C, CDC2, and Cyclin B1, Increased Bax expressions, and up regulated p-cdc25c, p 21 & 53, and p-CDC2 expressions
	Activated the endoplasmic reticulum (ER) stress and down regulated the peroxisome proliferator-activated receptor-γ (PPARγ) activity
	Enhanced cytokeratin-18, endoplasmic reticulum (ER) stress, and E-cadherin
	Lowered vimentin, and Snail expressions
	Decreased the vessel density, reversed epithelial-to-mesenchymal transition
	Inactivated nuclear factor kappa-light-chain-enhancer of activated B cell
Oral	Inhibited Akt, JAK2/STAT3, and Erk signaling pathways
	Suppressed tumor growth and IL-6 level
	Lowered the levels of PCNA and endothelial marker CD31
	Decreased levels of EGFR, and mTOR
	Suppressed tumor growth, and decreased expressions of Cdks and cyclins
	Suppressed transcription factor specificity protein 1 (Sp1)
	Up regulated p21 and p27, and reduction of anti-apoptotic proteins including surviving and Mcl-1 were reported after supplementation of honokiol
Skin	Inhibited COX-2 activity, PGE2 production, and suppressed UVB-induced DNA hypermethylation
	Attenuated protein kinase B, and activated AMP-activated protein kinase (AMPK) signaling
	Lowered tumor multiplicity, and induced apoptosis
	Decreased cell viability, cell growth, & survival rate
	Modulated cell cycle regulatory proteins
	Decreased the production of expressions of IL-1α and IL-8
Glioblastoma	Inhibited cell migration, and activated PI3K/Akt/mTOR and endoplasmic reticular stress/ERK1/2 signaling pathways
	Down regulated the expressions of Hes1 and Notch3
	Reduced cell viability, and induced apoptosis
	Induced G1 cell cycle arrest and increased phosphorylation levels of p21 and p53
	Down regulated cyclin D1, E2F1, and phosphorylated (p)RB, CDK4, and CDK6
	Induced apoptosis, reduced the cell viability, triggered intracellular Ca ($^{2+}$) concentration ([Ca(2+)]i)
	Lowered mitochondrial membrane potential, activated caspase-9/caspase-3, and released cytochrome c
Ovarian	Altered Bcl-2 members and caspase-3
Bone	Decreased the number of macrometastases
	Up regulated Bax and Bak, and enhanced expression and activities of glucose-regulated protein 78 (GRP78)
Renal	Activated the signaling of phosphorylated myosin light chain
	Down-regulated Ras activation and c-Met phosphorylation
	Inhibited the expression of calcineurin inhibitor (CNI)-induced HO-1, promoted apoptosis
Lung	Induced endoplasmic reticulum (ER) stress and autophagy
	Protected from the increment of migration, c-FLIP, N-cadherin (a mesenchymal marker), snail (a transcriptional modulator), p-Smad2/3 expression
	Induced autophagy and up regulated the Sirt3
Blood	Lowered the activity of histone deacetylases, and suppressed the clonogenic activity of hematopoietic progenitors
	Induced caspase-dependent cell death, and activated caspase-3, -8, and -9
	Up-regulated the Bcl2-associated protein (Bax)
Liver	In SK-Hep1 hepatoma cells, honokiol has been found to activate PPARγ, induce cell cycle arrest in the G0/G1 phase, exhibit growth inhibition, decrease cyclin D1, E1, and Rb expressions, and increases p21 level (Chen et al., 2016).
	Suppressed Janus-activated kinase 1, upstream kinases c-Src, and Janus-activated kinase 2
Colon	Up regulated the expression of bone morphogenetic protein 7 (BMP7)
	Decreased prostaglandin E2 (PGE2) and vascular endothelial growth factor (VEGF) levels
	Inhibited expressions of COX-2, AKT/p-AKT, VEGF, extracellular signal-related kinase (ERK)1/2/p-ERK1/2
	Reduced endothelial cell density (CD31 staining), and elevated levels of apoptosis (TUNEL staining)
Bladder	Suppressed the epithelial-mesenchymal transition
	Induced E-cadherin and repressed N-cadherin
	Down regulated the cell invasion-associated genes, MMP-2, steroid receptor coactivator-3 (SRC-3), and Twist1

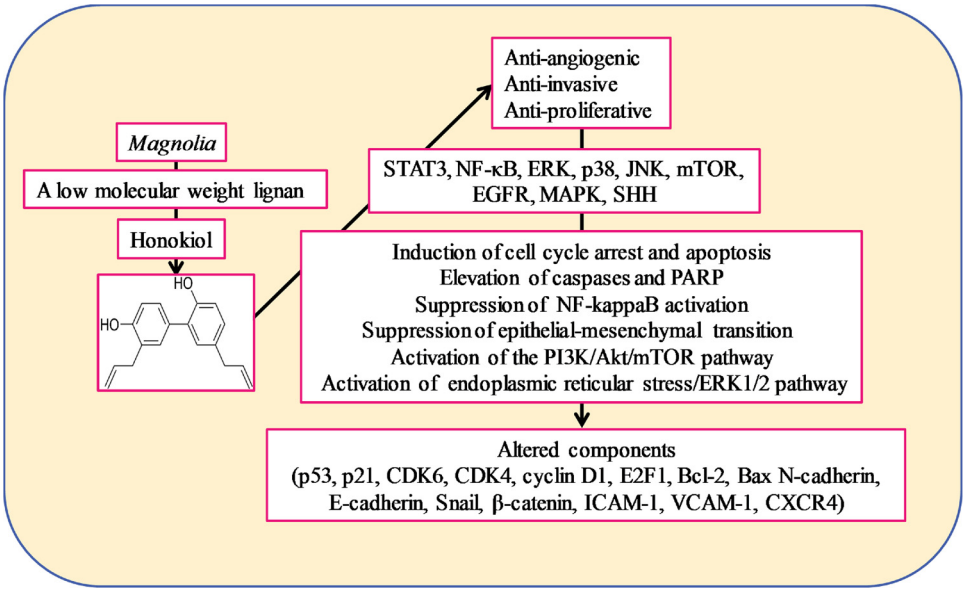

Fig. 1. The structure and biological activities of honokiol.

Table 2
Honokiol derivatives and their therapeutic potential.

S. No	Compound	Therapeutic potential
1	5-Formylhonokiol 3'- Formylhonokiol 3', 5-Diformylhonokiol	Showing strongest inhibitory activity against K562 (human myelogenous leukemia), A549 (human lung adenocarcinoma) and SPC-A1 (human lung adenocarcinoma) tumor cell lines
2	3′,5-Diallyl-2,4′-dihydroxy-[1,1′-biphen-yl]-3,5′-dicarbaldehyde	inhibit the newly-grown segmental vessels from the dorsal aorta of zebrafish exhibit more potent growth inhibitory effects on human umbilical vein endothelial cells (HUVECs), A549, HepG2, and LL/2
3	A butyrate ester derivative of honokiol with unsubstituted phenol group	Play a vital role in the antiproliferative activity and identified an interesting pharmacological lead against hepatocellular carcinoma
4	4'-*O*-methylhonokiol (MH)	Cannabinoid-(CB2) receptor selective antiosteoclastogenic scaffold
5	Honokiol position isomers	Antitumor and antiviral activities, with minimal cytotoxicity

Apart from honokiol, *M. officinalis* produces another biphenolic compound magnolol, isomer of honokiol, known to possess antioxidant and anti-inflammatory properties [97]. Lignan mixture (wikstromal, matairesinol and benzylbutyrolactol) from *Cedrus deodara* has apoptosis-inducing effect towards several cancer cell lines [98]. *Podophyllum hexandrum* [99] and *Linum album* [100] have an aryltetralin lactone lignan podophyllotoxin. Podophyllotoxin is an anticancer agent and it used to semisynthetically derive anticancer drugs etoposide, teniposide and etopophose [99]. All the lignans with anticancer potential act by shrinking the tumor, and lowering the expression of estrogen, insulin growth factor, VEGF and MMP enzymes, but enhancing caspase-3 [101].

Other plant phenol such as eugenol has breast cancer treatment potential, via the interference with E2F1/surviving [102]. So, a number of plant phenols exert cancer anti-proliferation by the same pathways. Ellagic acid activates cdk inhibitory protein p21, causing cell cycle arrest at G phase, in cervical carcinoma (CaSki) cells [103]. So, most plant phenols reduce oxidative stress, and mitigate inflammation, lowering cancer risk. Studies have shown that α-santalol, when combined with honokiol and magnolol can inhibit skin cancer. So, not only honokiol, but plant phenols from different origins can exert anticancer effect [104]. The therapeutic potential lies in their ring structure, which is related to estrogen. Apart from lignans, other class of plant secondary metabolites such as alkaloids, glucosides, terpene, terpenoids, flavones, coumarins have also intervene in carcinogenesis by acting as different steps of the same cancer propagation pathways [105].

The dosage and the administration route play important role in the therapeutic efficacy of almost all therapeutic agents, including honokiol. Because drugs are toxic, and they must tread the fine balance between efficacy and safety. Further, there is no universal dosage for all patients, as age, gender, comorbidity and other medical history must be taken care of. Additional studies on human subjects can shed light on its potential for health care. There are abundant bioactive phytochemicals, but the real challenge lies in retaining their stability. Also, the promising results might be the resultant of poorly-designed studies. As long as the inflammatory agents are not eliminated, and hormonal imbalance is not corrected, a phytochemical ca not resolve a complex disease like honokiol.

6. Conclusion

Honokiol has attracted research and clinical attention for its immune elicitation and cancer regulation properties. It intervenes the critical pathways as STAT3, NF-κB, mTOR, EGFR, MAPK, SHH among several others. It induces apoptosis, suppresses the proliferation, expression of cancer stem cell marker protein, P-glycoprotein number reduction, and radiosensitization. Its implication in cancer therapy is still in budding stage, and clinical trials on this lignan ought to be pursued. Further research undertakings can shed light on the mechanistic pathways of cancer inhibition.

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