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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