Honokiol: a novel natural agent for cancer prevention and therapy

Sumit Arora[1], **Seema Singh**[1], **Gary A. Piazza**[1,2], **Carlo M. Contreras**[3], **Jayanth Panyam**[4], and **Ajay P. Singh**[1,2,#]

[1]Department of oncologic Sciences, Mitchell Cancer Institute, University of South Alabama, Mobile, Alabama, USA

[2]Department of Biochemistry and Molecular Biochemistry, College of Medicine, University of South Alabama, Mobile, Alabama, USA

[3]Department of Surgery, College of Medicine, University of South Alabama, Mobile, Alabama, USA

[4]Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, USA

Abstract

Honokiol ((3',5-di-(2-propenyl)-1,1'-biphenyl-2,2'-diol) is a bioactive natural product derived from *Magnolia spp*. Recent studies have demonstrated anti-inflammatory, anti-angiogenic, anti-oxidative and anti-cancer properties of honokiol *in vitro* and in preclinical models. Honokiol targets multiple signaling pathways including nuclear factor kappa B (NF-κB), signal transducers and activator of transcription 3 (STAT3), epidermal growth factor receptor (EGFR) and mammalian target of rapamycin (m-TOR), which have great relevance during cancer initiation and progression. Furthermore, pharmacokinetic profile of honokiol has revealed a desirable spectrum of bioavailability after intravenous administration in animal models, thus making it a suitable agent for clinical trials. In this review, we discuss recent data describing the molecular targets of honokiol and its anti-cancer activities against various malignancies in pre-clinical models. Evaluation of honokiol in clinical trials will be the next step towards its possible human applications.

Keywords

Honokiol; chemoprevention; chemotherapy; natural agent

1.0. Introduction

Honokiol is a bioactive compound obtained from several species of the genus *Magnolia* (*officinalis, obovata*, and *grandiflora*) of Magnoliaceae family (1). The *Magnolia* genus is distributed throughout the world with main center in east and south-east Asia. The bark, cones, and leaves from *Magnolia officinalis* plant have long been used in traditional Chinese medicine, where it is known as "houpa". In Japan, *Magnolia obovata* has been used in a similar manner and is known as "koboku". Recent studies in animals and *in vitro* models

[#]To whom correspondence should be addressed: Ajay P. Singh, Ph.D. Department of Oncologic Sciences Mitchell Cancer Institute University of South Alabama 1660 Springhill Avenue Mobile, AL 36604-1405, U.S.A. Phone: 251-445-9843; Fax: 251-460-6994 asingh@usouthal.edu.

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have demonstrated multiple biological properties of honokiol including anti-arrhythmic (2), anti-inflammatory (3), anti-thrombocytic (4), anti-angiogenesis (5, 6), anti-tumor (7, 8), anxiolytic (9), anti-oxidative (10) activities. Honokiol has also been found to exert potent broad-spectrum antimicrobial (11), antifungal (12) and anti-HIV (human immunodeficiency viruses) activities (13).

Cancer is major health problem world-wide. It is the second-leading cause of disease-related deaths in the United States after the heart disease (14). While the mortality from heart disease continues to decrease both in younger and older patients, not much improvement in life expectancy has been achieved in patients diagnosed with cancer (15). To make significant progress in fight against cancer, advances in cancer diagnosis and development of effective preventive and therapeutic strategies are needed. As exemplified by other agents from aspirin to taxol, the use of natural products has been successful approach towards managing, this devastating health problem. The present review discusses the accumulating literature on the anti-tumor activity of honokiol against various malignancies, its mechanism of action, pharmacokinetics and safety aspects for possible human applications.

2.0. Honokiol and its anti-tumor derivatives

Honokiol is a small bi-phenolic lignan with molecular formula $C_{18}H_{18}O_2$ and molecular weight of 266 g/mole (Figure 1). It consists of a para-allyl-phenol and an ortho-allyl-phenol that are linked together through ortho-, para-C-C-coupling. Previously, it has been shown that, ether derivative and 3,3′-diallyl derivative also have significant growth inhibitory activity against Hep-G2 cells (human hepatocellular carcinoma), suggesting that the 3′-allyl group of honokiol plays an important role in inducing cytotoxicity (16). The 4′-hydroxy and the 5-allyl groups are responsible for honokiol-mediated neurite growth-promoting activity (1). Three novel anti-tumor derivatives of honokiol namely 3'- formylhonokiol, 5-formylhonokiol and 3', 5-diformylhonokiol have also been developed (Figure 1) (17). Out of these derivatives, 3'- formyl-honokiol and 5-formyl-honokiol are actually isomers with latter possessing the strongest inhibitory activity against K562 (human myelogenous leukemia), A549 (human lung adenocarcinoma) and SPC-A1 (human lung adenocarcinoma) tumor cell lines (17). The formyl group at C-5 position poses the enhanced inhibitory effect through formation of intra-molecular hydrogen bond, whereas a formyl group at C-3 position decreases anti-tumor activity. In a recent study, a derivative of honokiol namely, 3′, 5-diallyl-2,4′-dihydroxy-[1,1′-biphen-yl]-3,5′-dicarbaldehyde was found to suppress the newly-grown segmental vessels from the dorsal aorta of zebrafish, and to prevent inappropriate vascularisation as well as exhibit more potent growth inhibitory effects on human umbilical vein endothelial cells (HUVECs), A549, HepG2, and LL/2 (mouse Lewis lung carcinoma) cells as compared to honokiol (18). The above structure–activity relationship (SAR) studies suggest that the presence of hydroxyl and allylic groups on a biphenolic moiety of honokiol are responsible for growth inhibitory effect of honokiol (18, 19)

3.0. Molecular targets and mechanisms of action

Cancer progresses through a series of genetic and epigenetic aberrations that cause dysregulation of key cell signaling pathways involved in growth, malignant behavior and therapy-resistance (20). Studies have shown that honokiol is able to target many such pathologically relevant pathways. While novel modes of honokiol action continue to emerge, we discuss some of the important molecular targets of honokiol (Figure. 2), with emphasis on its translational relevance in cancer prevention and therapy.

3.1. Nuclear factor kappa B (NF-κB) and signal transducers and activator of transcription (STAT3)

NF-κB and STAT3 are two ubiquitously expressed transcription factors controlling the expression of a wide array of genes involved in numerous physiological processes including development, differentiation, immunity, metabolism and cancer (21). Aberrant activation of these transcription factors is common in many malignancies, and is pathologically significant in early and late developmental steps of cancer (21). Some of the gene targets are common, while others are unique to these transcription factors. For example, both NF-κB and STAT3 upregulate the expression of proteins that regulate apoptosis (Bcl-xL, Bcl-2, c-IAP2), cell cycle (cyclins D and B) and proliferation *c-Myc, Cox2*) (22, 23) On the other hand, A1/Bfl-1(Bcl-2 family member) and c-FLIP are mostly NF-κB-dependent, whereas Mcl-1 and Survivin are STAT3-dependent (21, 22). Both NF-κB and STAT3 are also shown to be involved in regulation of HIF1α and VEGF gene expression, involved in invasion and angiogenesis, respectively (24). Some of these genes, in fact, require transcriptional cooperation between STAT3 and NF-κB (21). All these observations clearly suggest that targeting of NF-κB and STAT3 could yield preventive and therapeutic effects in cancer.

Honokiol has been shown to inhibit NF-κB activation through suppression of Akt and activation of IKK (inhibitor kinase), which then leads to phosphorylation and subsequent IκBα degradation (21, 22). IκBα keeps NF-κB sequestered in the cytoplasm in an inactive state and its degradation leads to nuclear translocation of NF-κB and transcriptional activation (22, 24). STAT3, among various STAT proteins, is constitutively activated in many human cancer cells (21) and can be inhibited by honokiol (25). Honokiol suppresses STAT3 activity induced by IL-6, one of the many growth factors that activate STAT3 (25). Furthermore, STAT3 inhibition by honokiol has also been correlated with the repression of upstream protein tyrosine kinases c-Src, JAK1 and JAK2 (26). Although not yet demonstrated, suppression of STAT3 and NF-κB activation by honokiol could also be inter-linked. The p65 subunit of NF-κB has been shown to interact with STAT3 (27) and it is reported that STAT3 prolongs NF-κB nuclear retention through acetylation (28). Activation of both STAT3 and NF-κB in tumor cells by factors in tumor microenvironment (interleukins and chemokines) and release of cytokines and chemokines by tumor cells as a response (21, 28) also suggest their role in mediating the cross-talk between tumor and its microenvironment. All these observations clearly imply that NF-κB and STAT3 inhibition by honokiol can have a multifaceted impact on the growth and spread of the tumor cells.

3.2. Epidermal growth factor receptor (EGFR) and downstream signaling

EGFR or ErbB1 is one of the four members of ErbB receptor tyrosine kinase family (29). EGFR activation occurs upon binding to its ligands, which then leads to its homo- or hetero-dimerization with other members of the ErbB family, and subsequent activation of downstream signaling cascades. There are multiple ligands reported for EGFR including epidermal growth factor (EGF), transforming growth factor-a (TGF-a), amphiregulin, epiregulin, betacellulin and heparin-binding epidermal growth factor (HB-EGF) (29). EGFR is overexpressed in a variety of cancers and its aberrant activation is shown to promote cell survival and proliferation through induction of phosphatidyl-inositol 3-kinase (PI3K)/Akt, mitogen-activated protein kinase (MAPK), and STAT3 (30). EGFR can also be activated in a ligand-independent manner by cellular Src (c-Src), a non-receptor tyrosine kinase. c-Src is also upregulated in many human malignancies and promotes activation of mitogenic signaling through EGFR (30). An earlier study reported that the growth inhibitory effect of honokiol was associated with downmodulation of EGFR signaling in human breast cancer cells (31). Honokiol has been shown to downregulate the expression and phosphorylation of both c-Src and EGFR, causing reduced activation of downstream signaling molecules. Honokiol also inhibited EGFR signaling in head and neck squamous cell carcinoma cells

(HNSCC) (32). Furthermore, honokiol also promoted the growth inhibitory activity of the EGFR-inhibiting agents erlotinib and lapatinib in HNSCC and Her-2 over-expressing breast cancer cells, respectively (32, 33). These observations provide clear evidence for the suppressive effects of honokiol on EGFR and its downstream signaling in cancer cells.

3.3. Mammalian target of rapamycin (m-TOR)

The mammalian target of rapamycin (mTOR) is a protein kinase that is centrally involved in the control of cell metabolism, growth and proliferation (34). Aberrant activation of mTOR in most cancer cells is primarily caused by PI3K–Akt pathway, which is activated through a variety of mechanisms (34). mTOR controls translational initiation of many survival proteins via activating p70 S6 kinase (S6K) and inhibition of eIF4E inhibitor 4E-BP1(35). mTOR signaling pathway is dysregulated in premalignant or early malignant human tissues and is highly implicated in the carcinogenic process(35). Honokiol suppresses the activation of mTOR and its signaling mediators (4E-BP1 and p70 S6 kinase) by inhibiting ERK and Akt pathways (31) or by upregulation of PTEN (Phosphatase and Tensin homolog) expression (33). Combination of honokiol with the mTOR inhibitor rapamycin resulted in synergistic apoptosis induction in breast cancer cells (33). Furthermore, honokiol decreased PI3K/mTOR pathway mediated immunoresistance of glioma, breast and prostate cancer cell lines without affecting proinflammatory T cell functions (36).

4.0. Chemopreventive/ chemotherapeutic effects of honokiol in various malignancies: preclinical studies

4.1. Skin cancer

Importance of skin cancer can be judged from its incidence, which is almost equal to incidence of cancers in all other organs in the United States (37). Moreover, its incidence is expected to increase substantially, because of continuous depletion of the ozone layer that allows more solar ultraviolet (UV) radiation to reach to the earth's surface, and changing life style and dietary behavior (38). Solar UV radiations particularly UVB (290-320 nm), can induce both direct and indirect biological effects including DNA damage, cancer and premature aging signs (38). In a recent study, effect of honokiol was assessed on ultraviolet (UV) radiation-induced skin tumorigenesis using the SKH-1 hairless mouse (a model for dermatological studies) (39). It was found that honokiol treatment (3 mg per mouse applied topically) resulted in 80% reduction in tumor size and 62% reduction in malignant progression of papillomas to carcinomas in UVB-irradiated mice as compared to untreated group. At molecular level, honokiol was found to inhibit UVB-induced expression of cyclooxygenase-2, prostaglandin E2, proliferating cell nuclear antigen and pro-inflammatory cytokines, such as TNF-α, interleukin (IL)-1β and IL-6 in the skin as well as in skin tumors (39). Chilampalli and colleagues also reported the reduction (45%) in tumor multiplicity by honokiol treatment one hour prior to UVB irradiation in SKH-1 mice (39). They observed the release of caspases-3, -8 and -9as well as poly (ADP-ribose) polymerase (PARP) cleavage and p53 activation upon honokiol treatment that led to DNA fragmentation and apoptosis. Cytotoxicity of honokiol was also associated with translocation of cytochrome c to cytosol in human melanoma cell lines (SK-MEL2 and MeWo) (40). Altogether, these studies indicate that honokiol is a promising candidate for the development of new strategies for the prevention of UV radiation-induced skin cancers in humans by targeting inflammatory mediators, cell cycle regulators, and cell survival signals in UVB-exposed skin.

4.2. Lung cancer

In both economically developed and developing countries, lung cancer is the most frequently diagnosed cancer and the leading cause of cancer related deaths (14). Honokiol was tested for its radio-sensitization potential in lung carcinoma (6). Lewis lung carcinoma cells (LL/2) treated with liposomal honokiol for 24 h showed a higher radiation enhancement ratio (~ two-fold) as compared to the radiation alone, indicating increased sensitivity to radiation-induced cytotoxicity when co-treated with honokiol. In an animal model (Lewis lung carcinoma-bearing C57BL/6 mice), combination treatment (radiation and honokiol) caused greater reduction in tumor volume (78%) as compared to radiation alone (42%). In another study, it was shown that honokiol alone had antitumor activity in A549 lung cancer xenograft model and the combination of honokiol with cisplatin reduced the tumor volume (3.59-fold) as compared to cisplatin alone on day 40 (41).

4.3. Breast cancer

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death among females in the United States (14). It accounts for nearly 23% of the total cancer cases and 14% of the cancer deaths in females (14). In many research studies, honokiol has been evaluated for its anti-cancer potential against breast cancer (31, 42-44). Honokiol was shown to inhibit the growth in breast cancer cell lines (MDA-MB-231, SK-BR-3, MDA-MB-436, ZR-75-1and T47-D, MCF-7, 4T1) in a dose dependent manner regardless of their HR, HER2 or p53 status (31, 43, 44). Furthermore, in 4T1 bearing-BALB/c mice, systemic administration of liposomal honokiol (20 mg/kg) and adriamycin (5 mg/kg) was more effective as compared to adriamycin alone increasing the life span of animals by 8 days (42). Growth inhibitory effects of honokiol in breast cancer were shown to occur through arrest of cell cycle at the G0/G1 phase and induction of apoptosis (33, 42, 44). Honokiol also caused suppression of Ras activation induced by EGFR in and Ras dependent PLD (phospholipase D) activity in MDA-MB-231 breast cancer cells suggesting that it can serve as a valuable therapeutic agent for all those cancers that depend on Ras and PLD (42). Furthermore, it was shown that growth inhibitory effect of honokiol was mediated, in part, by downmodulation of c-Src/EGFR-mediated signaling (31). Inhibition of NF-κB, COX-2 and PGE2 was also observed in breast cancer after treatment with honokiol. Honokiol also sensitized the cancer cells for drug therapy by downregulating the expression of P-glycoprotein. These studies indicate that honokiol could be used, alone or in combination with other drugs, for breast cancer therapy.

4.4. Ovarian cancer

Studies in a variety of ovarian cell lines (SKOV3, COC1, Angelen and A2780) have demonstrated the cytotoxicity of honokiol *in vitro* with IC_{50} reported to be in the range of 14 - 20 μg/mL after 24 h treatment (45). Administration of honokiol into tumor-bearing animals (xenograft model of SKOV3 cells in BALB/c mice) decreased microvessel density and inhibited tumor growth (~ 70%) as compared to the control (45). The anti-tumor activity of liposomal honokiol was also evaluated in nude mice bearing human ovarian cancer cells viz. A2780s (cisplatin-sensitive) and A2780cp (cisplatin-resistant). Administration of liposomal honokiol (10 mg/kg, intravenously twice per week) was shown to cause significant inhibition (84–88% relative to controls) in the growth of both A2780s and A2780cp tumor xenografts and prolong the survival of the treated mice (46). In another study, combination of pegylated liposomal honokiol and cisplatin produced synergistic growth-inhibitory effects in human ovarian carcinoma mouse xenograft model of SKOV3 cells (47). The combination treatment inhibited tumor growth by 91% as compared to either pegylated honokiol (66%) or Cisplatin (52%) alone. The mechanism responsible for anticancer effects of honokiol in ovarian cancer was suggested to be the induction of apoptosis and inhibition of angiogenesis.

4.5. Prostate cancer

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer related death in males in economically developed countries (14). Therefore, novel cancer prevention and therapeutic approaches are required to have an impact on the incidence and mortality from prostate cancer. In an earlier study, honokiol was shown to induce apoptosis in human prostate cancer cells irrespective of their androgen responsiveness or p53 status (48). The study used PC-3 (an androgen-independent cell line lacking functional p53), LNCaP (an androgen responsive cell line with wild-type p53), and C4-2 (an androgen-independent variant of the LNCaP cell line) (48). Suppression of growth by honokiol administration (2 mg/mouse thrice a week) in PC-3 xenograft mouse model correlated with induction of apoptosis (TUNEL positive apoptotic bodies) and decrease in proliferation index (PCNA staining)(48). Interestingly, honokiol was found to be more effective in inhibiting the growth of cancer-associated stromal fibroblasts as compared to that associated with normal/benign-disease (48). In mouse (BALB/c nude) xenograft model of C4-2 cells, honokiol alone (100 mg/kg/day for 6 weeks i.p.) and honokiol with docetaxel (5 mg/kg once a week), showed a significant decrease of serum PSA (prostate-specific antigen) in comparison with the control group after 6 weeks treatments (49). Therefore, honokiol may be effective in prevention and therapy of prostate cancer.

4.6. Gastrointestinal cancers

Honokiol has also been shown to be effective in three types of gastro-intestinal cancers viz., colorectal, gastric and pancreatic. Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females in developed countries (14). Usefulness of honokiol against colorectal carcinoma has been shown in two independent studies. In the first study, honokiol was shown to impart anti-proliferative effect against RKO (Human colorectal carcinoma cells) with an IC_{50} of 12.47 µg/mL after 68 h treatment (50). Furthermore, a similar effect of honokiol was also observed *in vivo in* xenograft model of RKO cells in BALB/c nude mice. The mean survival time increased to 50.9 days in honokiol-treated group (i.p. injection, 80 mg/kg body weight/day) with significant inhibition of tumor growth as compared to that for vehicle treated group which had an average survival time of 29.7 days. In the second study, human colorectal carcinoma cell lines, RKO, SW480 and LS180, were treated with various doses of honokiol (51). Honokiol inhibited the growth with an IC_{50} of 10.33, 12.98, 11.16 µg/mL in RKO, SW480 and LS180 cells, respectively, after 68 h treatment.

Honokiol was also shown to be effective against gastric cancer cells. Honokiol induced apoptosis and downregulated the expression of peroxisome proliferator-activated receptor-gamma (PPAR-γ) and COX-2 in gastric cancer cells (AGS, MKN45, N87 and SCM-1) (52). In another study, honokiol markedly decreased the levels of glucose-regulated protein (GRP94) in a dose (5-40 µM) – and time- (0.5-18 h) dependent manner in various gastric cancer cells (AGS, N87, MKN45 and SCM-1) (53). Significant anti-tumor activity was associated with decreased accumulation of GRP94 in tumors (xenograft model of MKN45 cells in BALB/c mice) after i.v. administration of honokiol (0.5 and 1.5 mg/kg body weight every day for 10 days).

In a recent study from our group, honokiol was shown to exhibit growth-inhibitory effects against two human pancreatic cancer cell lines (MiaPaCa and Panc1) (54). Honokiol altered the expression of many cell-cycle associated and survival proteins, in part, through inhibition of constitutively active NF-κB. Furthermore, we showed that honokiol potentiated the cytotoxic effect of gemcitabine by restricting gemcitabine-induced nuclear localization of NF-κB. As constitutive activation of NF-κB is reported in majority of pancreatic cancer

cases and implicated in early and late development of the disease (54), honokiol could serve as a novel natural agent for pancreatic cancer prevention and therapy.

4.7. Other cancers

Honokiol has also proven its therapeutic potential as anti-cancer agent for various other solid and hematological malignancies. One category of such cancers is malignant gliomas, which accounts for approximately 70% of the malignant primary brain tumors that are diagnosed in adults in the United States each year (55). Brain tumors are particularly hard to treat, because the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) limit the delivery of both conventional and targeted therapeutics. Interestingly, it was recently shown that honokiol could effectively cross BBB and BCSFB and inhibit brain tumor growth (7). In this study, two *in vivo* model systems viz. Rat 9L (intracerebral gliosarcoma model in Fisher 344 rats) and human U251 xenograft glioma model in nude mice were used. Intravenous injection of honokiol (twice a week for 3 weeks) caused significant reduction in tumor volume (52% and 50% in rat 9L intracerebral gliosarcoma model and human U251 xenograft glioma model, respectively). It was shown that approximately 10% of honokiol in plasma crossed BCSFB and entered into cerebrospinal fluid (CSF). This study is indicative of the potential of honokiol as a novel therapeutic candidate for treatment of gliosarcoma. In another study, honokiol was shown to repress PI3K/mTOR pathway- mediated immunoresistance in glioma cell lines (U87 and U251) without affecting critical proinflammatory T cell functions (36). Thus, honokiol may also be a candidate to overcome immunoresistance in glioma, without interfering with T cell functions.

Dose- and time- dependent cytotoxic effects of honokiol were also observed in oral sqamous carcinoma cells (HSC-3 and HSC-4) (56). Furthermore, growth inhibitory effects of honokiol have also reported in human head and neck squamous cell carcinoma (HNSCC) cell lines (Cal-33, Cal-1483, 686LN and 686LNR30 cells (32). These effects were associated with inhibition of EGFR and its downstream effectors, including mitogen-activated protein kinase, Akt, and signal transducer and activator of transcription 3 (STAT3), and reduced expression of target genes, Bcl-XL and cyclin D1. In these studies, honokiol was also shown to inhibit growth of erlotinib-resistant HNSCC cells.

With regard to hematological malignancies, honokiol has been shown to be effective in leukemia cell lines viz. B-CLL and Molt 4B (57-59). Honokiol also induced apoptosis in human multiple myeloma cell lines including dexamethasone-sensitive (MM.1S) and dexamethasone-resistant (MM.1R, RPMI-8226, U266 and SU-DHL-4) cells and in tumor cells collected from patients with relapsed refractory multiple myeloma (60). Honokiol also enhanced doxorubicin accumulation by 24% in human doxorubicin-resistant uterine sarcoma cells (MES-SA/Dx5), thus indicating its usefulness as an adjuvant (60, 61). Honokiol also inhibited the growth of chondrosarcoma cell lines, JJ012 and SW1353, with an IC_{50} of 27 μM and 27.3 μM, respectively (62). Furthermore, honokiol led to a reduction in tumor volume (~53%) in BALB/c nude mouse xenograft model of JJ012 cells (1.5 mg/kg body weight i.p. every day for 21 days) (62). Honokiol also exhibited growth inhibitory effects against primary human endothelial cells, fibroblasts, mouse endothelium cells (SVR) and anti-tumor effects in SVR bearing tumor model in BALB/c mice (5). Honokiol inhibited the migration of human fibrosarcoma cells (HT-1080) at 100 μM (63). All these studies indicate that honokiol could be an effective therapeutic agent against multiple cancer types.

5.0. Pharmacokinetics of honokiol

Pharmacokinetics includes the study of **a**bsorption, **d**istribution, **m**etabolism and **e**xcretion of the administered drug (ADME). Honokiol demonstrates a biphasic kinetic profile, consisting of a rapid distribution phase followed by a slower elimination phase (elimination

$t_{1/2}$ = 49.2 and 56.2 min for 5 and 10 mg of honokiol, respectively) following intravenous (i.v.) administration (64). In another study, elimination $t_{1/2}$ was found to be 526.6 min after a single oral dose of honokiol in Houpu decoction (a compound prescription of honokiol; 5g/ Kg body weight) in Wistar rats. This study suggested that rhubarb and immature orange fruit extract in the decoction influenced the absorption, distribution and elimination of honokiol (65). The maximal plasma concentration of honokiol following rectal administration of Houpo extract at a dose of 245 mg/ kg (equivalent to 13.5 mg/kg of honokiol) in Wistar rats was approximately six times to that administered orally at an identical dose (66) indicating that rectal dosing avoids first-pass metabolism to some extent. Honokiol was shown to undergo metabolism through glucuronidation and sulfation in liver before elimination in humans and rats (67).

Due to the concerns about poor aqueous solubility, liposomal formulations of honokiol have been developed and tested for their pharmacokinetics. PEGylated (polyethylene glycol coated) liposomal honokiol was shown to enhance the serum honokiol concentration and decreased clearance. PEGylated liposomal honokiol had higher $t_{1/2\beta}$ (time it takes for plasma levels of the drug to decrease to half) ratio (26 min) as compared to free honokiol (13 min) after single i.v. administration (20 mg/kg body weight) in Balb/c mice (68). Approximately, 60-65% honokiol was protein-bound as revealed by equilibrium dialysis. In another comparative study, plasma honokiol concentrations was maintained above 30 and 10 μg/mL for 24 and 48 hours, respectively, in liposomal honokiol-treated mice, whereas it fell quickly (less than 5 μg/mL) by 12 hours in free honokiol-treated mice bearing A549 xenograft tumors (41). In a recent study, organ distribution of honokiol was revealed to be in the following order: lungs > plasma > liver > brain > kidney > heart > spleen, following treatment of animal models (rat 9L intracerebral gliosarcoma model in Fisher 344 rats and human U251 xenograft glioma model in nude mice) (7). This study also demonstrated that honokiol crossed blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) after i.v. administration. Pharmacokinetics of honokiol (Figure 3) can be summarized as: free honokiol has poor GIT absorption, bio-transformed in liver to mono-glucuronide honokiol and sulphated mono-hydroxyhonokiol, ~ 50% is secreted in bile, ~ 60-65% plasma protein bound with elimination half life of ($t_{1/2}$) of 49.05 – 56.24 minutes.

6.0. Safety issues

Although most natural products are generally considered to be safe, it is important to establish the toxicological profile of honokiol before its use in humans. There has been only one direct toxicological study on honokiol, while other studies have been conducted on Magnolia bark extract (containing honokiol and magnalol as active compounds) or Magnolol alone (biologically active structural isomer of honokiol). Toxicity of honokiol was evaluated in rats by i.v. administration in the dose range of 20-80mg/Kg body weight, once a day for 14 days in Sprague-Dawley rats. No significant differences were observed in body weight, mean daily food intake, hematological values, serum biochemical values and tissue pathologic changes between honokiol-treated group and vehicle-treated group (7) suggesting potential safety of honokiol. The potential genotoxic effects of Magnolia bark extract were evaluated in Chinese hamster ovary cells (CHO) and in Chinese hamster lung cells (V79) using chromosomal aberration assays (69). No mutagenic activity was observed, indicating that honokiol is not genotoxic. Furthermore, Magnolia bark extract treatment also did not affect the proportions of immature to total erythrocytes, nor did it increase the number of micronuclei in the immature erythrocytes of Swiss albino mice. In a short-term toxicity study, magnolia bark extract was shown to produce no clinically significant changes (macroscopic or microscopic hematological, clinical chemistry, urinalysis, organ and total body weight) in Sprague-Dawley rats after oral administration (70). Sub-chronic toxicity studies by the same group for 90-days indicated no mortality, ophthalmic abnormalities or

treatment related changes in hematology, coagulation or organ weight. In fact, in another study, Magnolol was shown to inhibit mutagenicity induced by several indirect mutagens (71). These studies suggest that honokiol either alone or as a part of magnolia bark extract does not induce toxicity in animal models and thus could be clinically safe.

7.0. Conclusions

Honokiol has generated an extensive interest due to its various beneficial pharmacological properties. Besides its potent anti-inflammatory effects, honokiol has shown promising activities against multiple malignancies. Honokiol inhibits the production of numerous cytokines, inducible enzymes, and adhesion molecules associated with tumor initiation, promotion, progression, metastasis and therapy-resistance. Therefore, it has significant potential to serve as a novel agent for cancer prevention and therapy. Among the important chemopreventive and therapeutic target pathways are NF-κB, STAT3, EGFR, mTOR and MAPK. Honokiol, however, has poor aqueous solubility, which adversely affect its intestinal absorption. This limitation has been addressed by developing liposomal formulations. Biologically effective serum concentrations of honokiol can be achieved following intravenous administration; glucuronidation and sulfation are the main metabolic pathways for its clearance. Toxicological studies on honokiol and Magnolia bark extract have not shown any pathologic changes in the liver, lung, kidney, spleen, brain, heart, pancreas, intestines, or bone marrow after systemic or oral administration, suggesting its safety. Future studies are warranted to further broaden our understanding of the mechanistic basis of honokiol's biological action. Nonetheless, honokiol appears to be a promising natural agent for cancer prevention and therapy, and its evaluation in human clinical trials will be the next step towards its possible human applications.

Acknowledgments

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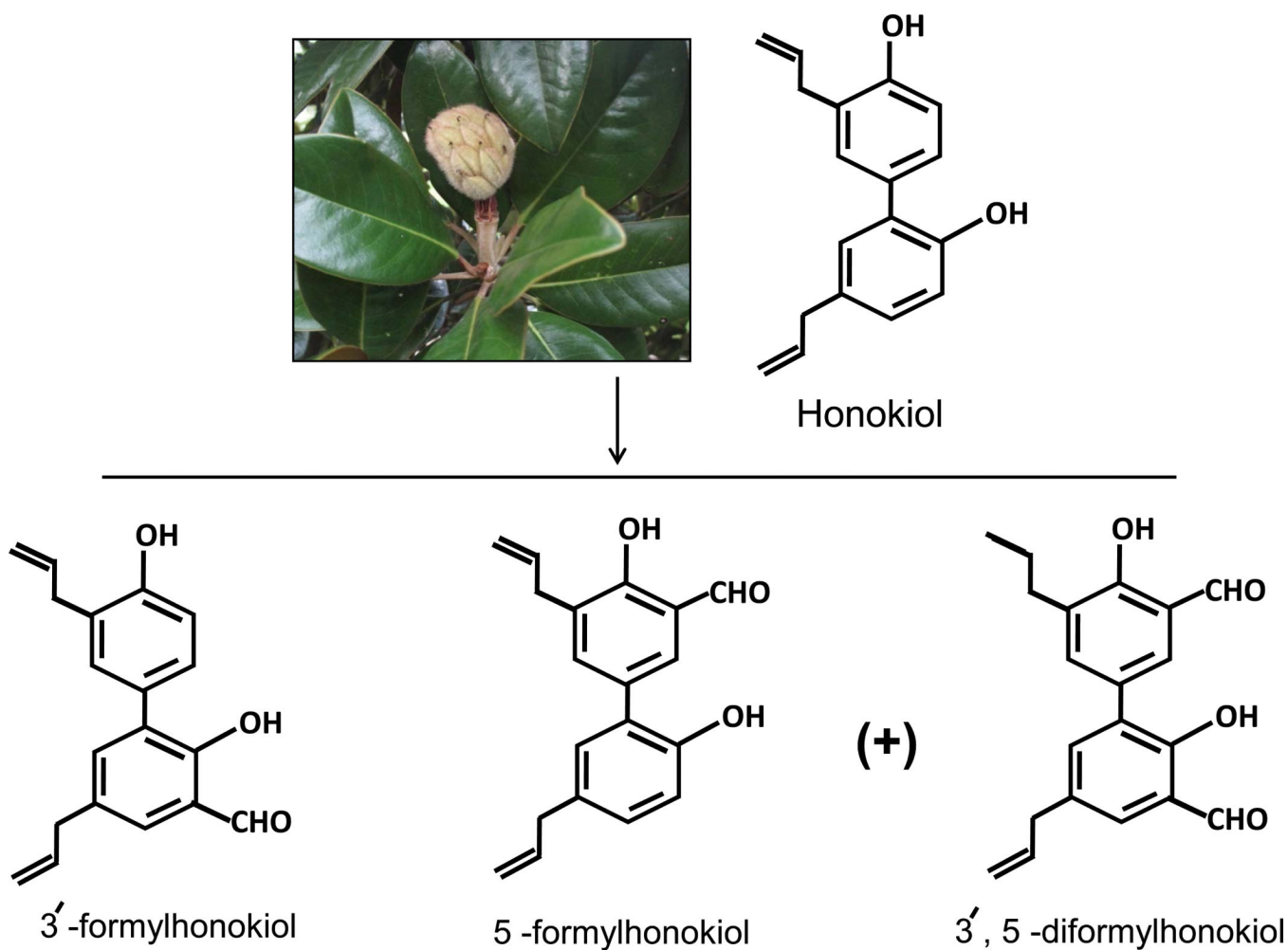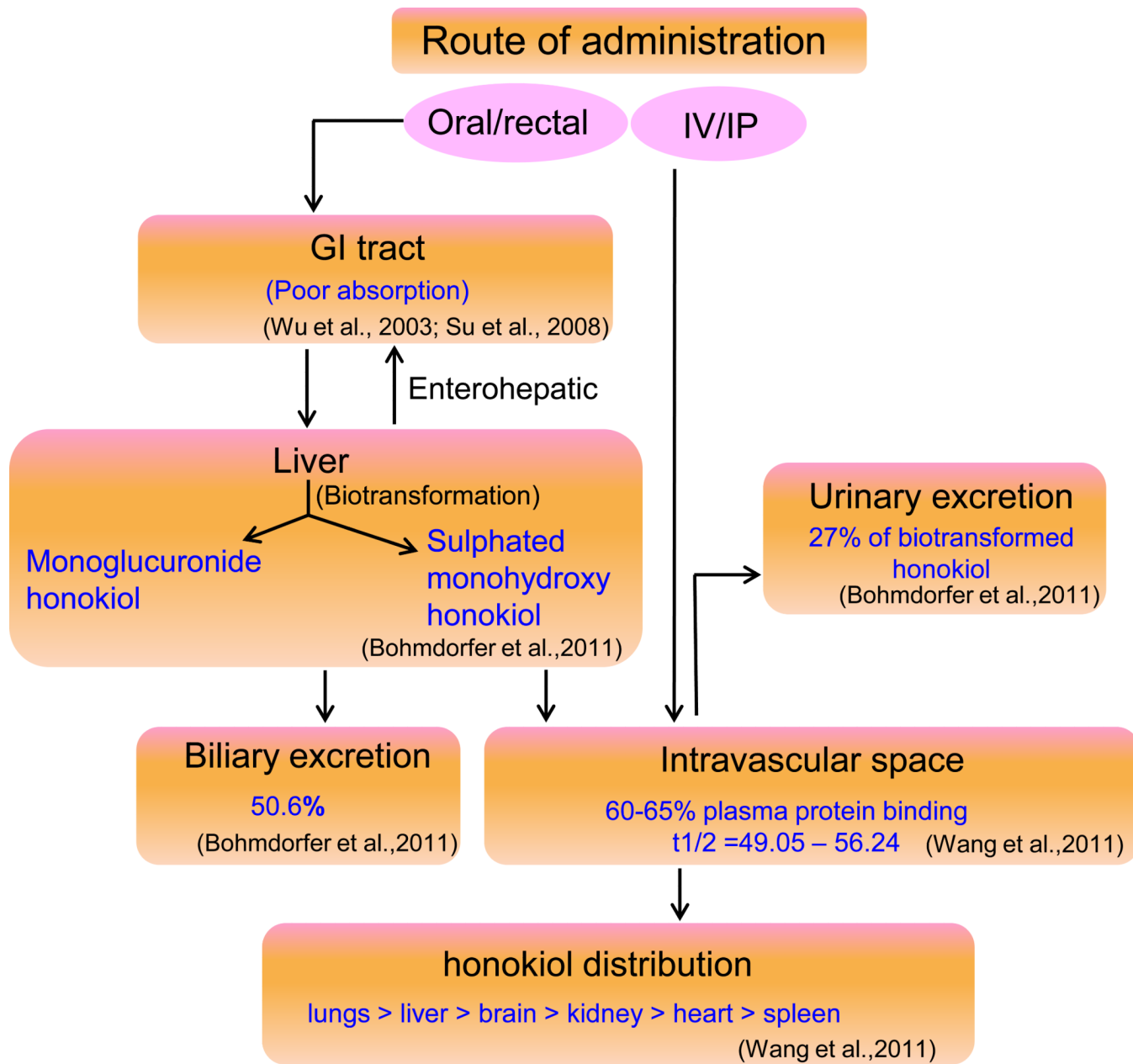
Figure 1.
Honokiol and its derivatives. Three novel anti-tumor derivatives of honokiol namely 3'-formylhonokiol, 5-formylhonokiol and 3', 5-diformylhonokiol are prepared after treating the honokiol with chloroform in 35% sodium hydroxide solution in presence of tetrabutyl ammonium bromide as phase transfer catalyst under 50 °C for 3 h. Out of these derivatives 3'- formylhonokiol and 5-formylhonokiol are isomers. Among honokiol and its three C-formylation derivatives, 5-formylhonokiol displayed the strongest inhibitory ability on tumor cell lines.
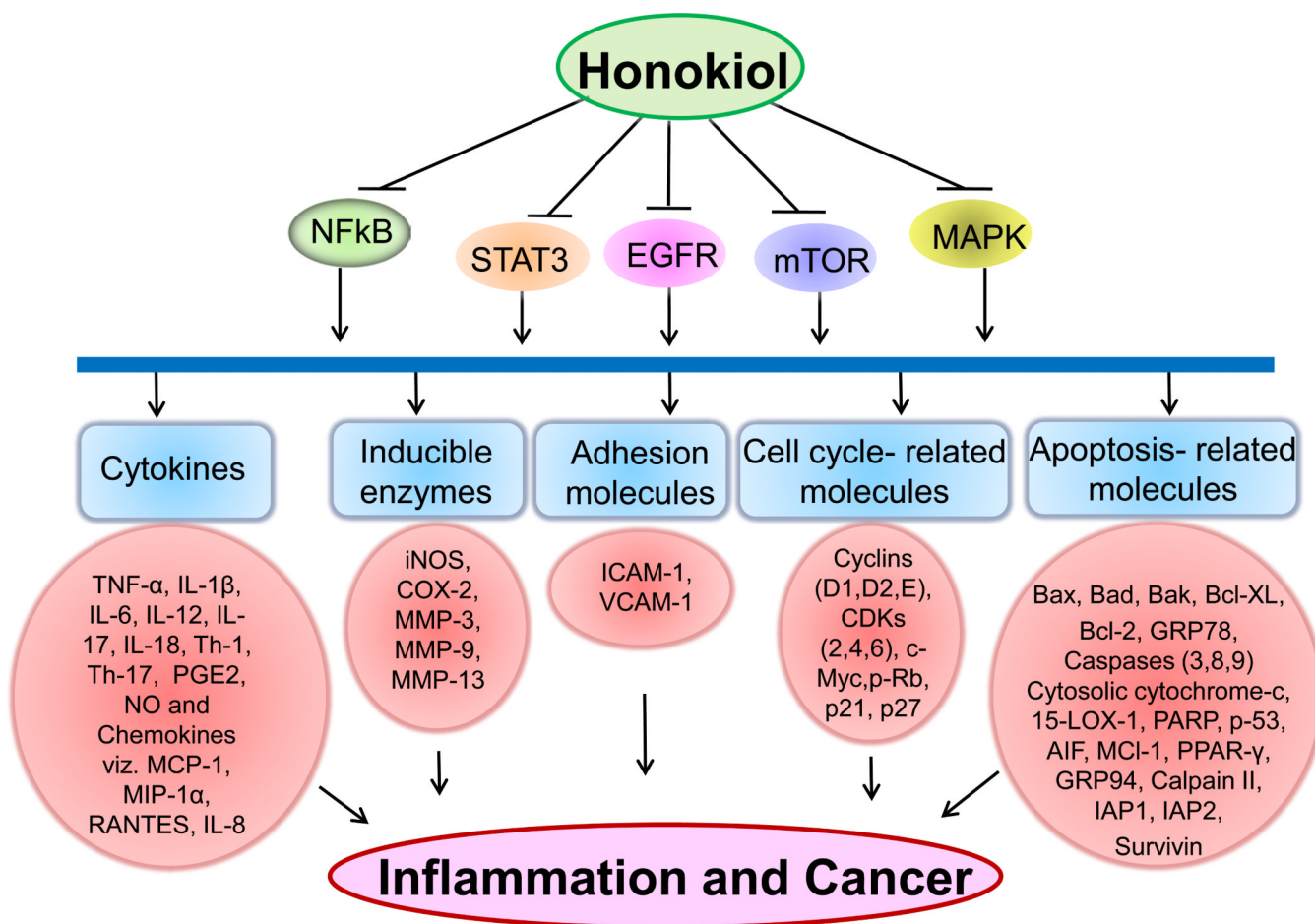
Figure 2.
A schematic diagram depicts the mechanism of action of honokiol through various molecular targets that results in chemopreventive and chemotherapeutic activity. Honokiol inhibits nuclear factor-κB (NF-κB), signal transducers and activator of transcription (STAT-3), epidermal growth factor receptor (EGFR), mammalian target of rapamycin (m-TOR) or Mitogen-activated protein kinases (MAPK) followed by downstream inhibition of cytokines, inducible enzymes, adhesion molecules, cell cycle and apoptosis-related molecules involved in inflammation, proliferation, angiogenesis, invasion and metastasis.

Figure 3.
Schematic representation of pharmacokinetic profile of honokiol. Honokiol has poor GIT absorption, bio-transformed in liver to mono-glucuronide honokiol and sulphated mono-hydroxyhonokiol, ~ 50% is secreted in bile, ~ 60-65% plasma protein bound and ~ 27% is excreted in the urine with elimination half life of (t1/2) of 49.05 – 56.24 minutes.