# Honokiol

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Contributor: Yin Quan Tang , Wei Hsum Yap

Cancer is characterised by uncontrolled cell division and abnormal cell growth, which is largely caused by a variety of gene mutations. There are continuous efforts being made to develop effective cancer treatments as resistance to current anticancer drugs has been on the rise. Natural products represent a promising source in the search for anticancer treatments as they possess unique chemical structures and combinations of compounds that may be effective against cancer with a minimal toxicity profile or few side effects compared to standard anticancer therapy. Extensive research on natural products has shown that bioactive natural compounds target multiple cellular processes and pathways involved in cancer progression.

honokiol anticancer mechanism signalling pathway

## 1. Introduction

Cancer is the outcome of rampant cell division which is associated with cell cycle disorganisation [1], leading to uncontrolled cell proliferation. In addition, it also involves the dysregulation of apoptosis, immune evasion, inflammatory responses, and ultimately, metastatic spread [2]. Over the last few decades, our progressive understanding of the aetiology of cancer together with advancement of cancer treatment, detection, and prevention, have contributed towards receding cancer mortality around the world [3]. However, more than half of cancer cases were diagnosed at a later stage of cancer progression [4]. According to a study by Bray et al. [5], the worldwide estimated number of new cancer cases for the year 2018 was 18.1 million in both sexes and across all ages. Amongst all the cancer types, lung, breast, and colorectum have topped the charts with approximately 2.1 million, 2.1 million, and 1.8 million cases, respectively. On the other hand, the estimated number of deaths was approximately 9.6 million. Asia accounted for more than half of the cancer deaths (57.3%), followed by Europe (20.3%), and America (14.4%). Lung cancer has caused the highest number of deaths due to substandard prognoses. Attempts to develop the effective prevention of cancer may diminish the incidence rate for some cancers, for instance lung cancer in North America and Northern Europe. These western countries have implemented tobacco control in order to avert involuntary exposure to tobacco and minimise active smoking within the community. Unfortunately, a majority of the population are still facing an upsurge of cancer diagnosis, demanding treatment and care [5].

The common treatment regimens for cancer patients include surgery, chemotherapy, and radiotherapy [6]. Although some of these regimens represent the first-in-line options for cancer treatment, the lack of selectivity towards neoplastic cells and the development of drug toxicity has caused these therapeutic effects to recede slowly, rendering it ineffective over the years [7]. Additionally, multidrug resistance tumours pose a severe threat and have

been responsible for numerous cancer-related deaths [8]. A modern approach to target multiple cell regulating pathways is mandatory in order to provide highly efficient and targeted cancer therapy. For instance, combination therapy that targets different pathways exhibit significantly lower toxicity towards normal cells compared to mono-therapy [9]. Currently, the development of anticancer drugs possessing the capability to overcome common mechanisms of chemoresistance with minimal toxicity effects would be considered a breakthrough in cancer research [2].

Approximately 70–95% of the world population continues to use traditional medicinal herbs, plants, and fruits which contain valuable bioactive compounds with therapeutic effects to maintain health, as well as to prevent or treat physical and mental illnesses [10]. These biologically active compounds provide extensive opportunities in uncovering competent anticancer agents [2][11]. A majority of the anticancer drugs that are currently in use originate from plants, marine organisms, and microorganisms, such as the well-known plant-derived anti-cancer drugs Paclitaxel (Taxol®) and Camptothecin (CPT) [12].

The *Magnolia* genus is widely distributed throughout the world, especially in East and South-East Asia [13]. Among the *Magnolia* species, *Magnolia officinalis* and *Magnolia obovata* are commonly used in traditional Chinese (known as “Houpu”) and Japanese herbal medicine [13][14]. The traditional prescriptions named Hange-koboku-to and Sai-boku-to, which contain the *Magnolia* bark, are still used in modern clinical practice in Japan [15]. There are several potent bioactive compounds in the *Magnolia* species have been identified including honokiol, magnolol, obovatol, 4-*O*-methylhonokiol, and several other neolignan compounds [13][15][16]. This paper highlights the potential anticancer effect of a simple biphenyl neolignan found in this *Magnolia* family, namely honokiol.

# 2. Anticancer Properties of Honokiol

## 2.1. In Vitro Studies

Honokiol has been shown to exhibit antiproliferation effects against numerous cancer cells, including bone, bladder, brain, breast, blood, and colon, as shown in **Table 1**. Generally, the concentrations used for the in vitro studies are between 0–150 μM, which majority of these concentration ranges have been shown to significantly inhibit cell proliferation or cell viability of various cancer cell lines. The trend for the $IC_{50}$ values of numerous cancer cell lines were time-dependent, whereby the $IC_{50}$ values decreases as duration of the experiment increases. As seen in **Table 1**, human blood cancer Raji cells were highly susceptible to honokiol treatment ($IC_{50}$ = 0.092) compared to highly resistant human nasopharyngeal cancer HNE-1 cells ($IC_{50}$ = 144.71 μM). Interestingly, honokiol has been shown to exhibit minimal cytotoxicity against on normal cell lines, including human fibroblast FB-1, FB-2, Hs68, and NIH-3T3 cells [17][18][19][20]. The low cytotoxicity of honokiol treatment against normal cell lines should be emphasised as current chemotherapeutic regimens have a considerable amount of side effects that harm cancer patients.

Many chemotherapeutic agents have been shown to induce severe systemic toxicity and several side effects due to their deficient pharmacokinetic profiles and non-specific distribution in the body [21]. In Yang et al.’s study [22],

they have encapsulated honokiol into nanopolymers to enhance its permeability and specificity against cancer cells. They utilised the active targeting nanoparticles-loaded honokiol (ANTH) in their in vitro studies against human nasopharyngeal cancer HNE-1 cells, and this incorporation exhibited significantly lower $IC_{50}$ values compared to free honokiol treatment. As a result, the incorporation or encapsulation of honokiol in transporting vehicles can improve the anticancer effects and concurrently overcome the water solubility issue of honokiol itself. This has shown to be a promising regimen for anticancer treatment in the future.

Furthermore, it is worthy to note that honokiol can enhance the antineoplastic effects of several chemotherapeutic agents when cells are treated in combination treatment of both honokiol and the chemotherapeutic agent. In Wang et al.'s study [23], they have shown that honokiol has enhanced the in vitro cytotoxicity of paclitaxel against human cervix cancer cell lines. The combination treatment has resulted in approximately 10–60% increase of apoptotic cells and inhibition of cell viability when compared to honokiol treatment alone [23]. In another study, honokiol potentiated the apoptotic effect of both doxorubicin and paclitaxel against human liver cancer HepG2 cells. Honokiol enhanced the apoptotic effects of paclitaxel and doxorubicin by 22% and 24% respectively [24].

**Table 1.** The anticancer effects of honokiol against cancer cells in in vitro experiments.

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| Colorectal cancer | RKO | Inhibit cell proliferation Induce G1 phase cell cycle arrest Induce apoptosis ↓ Bcl-xL; ↑ Caspase-3 & caspase-9 | 0–150 μM | 46.76 μM (68 h) | [25] |
| | HCT116, HCT116-CH2, HCT116-CH3 | Inhibit cell proliferation Induce G0/G1 & G2/M phase cell cycle arrest: ↓ cyclin D1 & A1; ↑ p53 phosphorylation Induce apoptosis: ↓ Caspase-3; ↓ Bcl-2; ↑ Bax protein | 25 μM Honokiol with 2.5 or 5.0 Gy IR | N/A | [26] |
| | HT-29 | Inhibit cell growth & proliferation Induce G1 | 0–50 μM followed by 0–5 Gy IR | 23.05 μM (24 h) 13.24 μM (72 h) | [27] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | phase cell cycle arrest: ↓ Cdk1 & cyclin B1 | | | |
| | HCT116 & SW480 | Inhibit cell proliferation via Inhibition of Notch signalling: ↓ Notch1 & Jagged-1; ↓ Hey-1 & Hes1; ↓ γ-secretase complex; ↓ Skip1 Induce apoptosis: ↑ caspase-3/-7 activity; ↓ Bcl-2 & Bcl-xL; ↑ Bax protein; ↓ cyclin D1 & c-Myc; ↑ $p21^{WAF1}$ protein Inhibit primary and secondary colonosphere formation | 0–50 μM | N/A | [28] |
| | RKO & HCT116 | Inhibit cell viability Induce apoptosis: ↑ caspase-3, caspase-8 & caspase-9 activation; ↑ DR5 & cleaved PARP proteins; ↑ survivin protein; ↑ phosphorylated p53 & p53 proteins; ↓ PUMA protein | 0–60 μM | RKO: 38.25 μM (24 h) HCT116: 39.64 μM (24 h) | [29] |
| Blood cancer | B-CLL | Inhibit cell viability Induce apoptosis: ↑ caspase-3 activity; ↑ caspase-8 & | 0–100 μM | 49 μM (6 h) 38 μM (24 h) | [30] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | caspase-9 activation; ↓ caspase-9; ↑ Bax protein; ↓ Mcl-1 protein | | | |
| | Raji, Molt-4 | Inhibit cell growth: ↓ p65; ↓ NF-κB Induce apoptosis: ↑ JNK activation Increase ROS activity: ↑ Nrf2 & c-Jun protein activation | 0–2.5 μM | Raji: 3.500 μM (24 h) 0.092 μM (72 h) Molt-4: 0.521 μM (24 h) | [31] |
| Breast cancer | MCF-7, MDA-MB-231, SKBR-3, ZR-75-1, BT-474 | Inhibit cell viability and growth: ↓ EFGR; ↓ MAPK/PI3K pathway activity Induce apoptosis: ↑ PARP protein degradation; ↓ caspase-8; ↑ Bax proteins Induce G1 phase cell cycle arrest: ↓ cyclin D1; ↑ p21 & p27 | 0–100 μM | MCF-7: 40 μM (24 h) MDA-MB-231: 33 μM (24 h) SKBR-3: 29 μM (24 h) ZR-75-1: 39 μM (24 h) BT-474: 50 μM (24 h) | [32] |
| | MCF-7, MDA-MB-231 | Inhibit cell clonogenicity Inhibit cell anchorage-dependent colony formation Inhibit cell growth, migration & invasion: ↓ pS6K & 4EBP1 phosphorylation; ↑ AMPK activation; ↓ mTORC1 function; ↑ LKB1 | 1–25 μM | N/A | [33] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | & cytosolic localisation | | | |
| | MCF-7, MDA-MB-231, SUM149, SUM159 | Inhibit cell migration & invasion: ↑ AMPK phosphorylation; ↑ LKB1 Inhibit stem-like characteristics: ↓ Oct4, Nanog & Sox4 protein; ↓ STAT3; ↓ iPSC inducer mRNA | 5 μM | N/A | [34] |
| | MCF-7, MDA-MB-231, T47D, SKBR-3, Zr-75, BT-474 | Inhibit cell growth: ↓ PI3K/Akt/mTOR signalling Inhibit cell invasion Induce G0/G1 phase cell cycle arrest: ↓ cyclin D1 & cyclin E; ↓ Cdk2 & c-myc; ↑ PTEN Induce apoptosis: ↑ caspase-3, caspase-6 & caspase-9 activation | 0–40 μM | MCF7: 34.9 μM (24 h) 13.7 μM (48 h) 13.5 μM (72 h) 10.5 μM (96 h)<br><br>MDA-MB-231: 56.9 μM (24 h) 44.4 μM (48 h) 16.0 μM (72 h) 12.0 μM (96 h)<br><br>T47D: 47.7 μM (24 h) 41.6 μM (48 h) 17.6 μM (72 h) 7.1 μM (96 h)<br><br>SKBR-3: 76.1 μM (24 h) 68.1 μM (48 h) 62.7 μM (72 h) 15.7 μM (96 h)<br><br>ZR-75: 71.1 μM (24 h) 58.1 μM (48 h) 28.7 μM (72 h) 14.5 μM (96 h)<br><br>BT-474: 80.2 μM (24 h) 65.6 μM (48 h) | [35] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | | | 39.5 μM (72 h)<br>15.1 μM (96 h) | |
| | MDA-MB-231 | Inhibit cell proliferation: ↓ c-Src/EGFR-mediated signalling pathway; ↓ c-Myc protein<br>Induce G0/G1 phase cell cycle arrest: ↓ cyclin A, cyclin D1 & cyclin E; ↓ Cdk2, Cdk4 & p-$pRb^{Ser780}$; ↑ $p27^{Kip-1}$<br>Induce apoptosis: ↑ caspase-3, caspase-8 & caspase-9 cascade; ↓ Bcl-2 & Bid protein; ↑ PARP cleavage | 0–100 μM | 59.5 μM (72 h) | [36] |
| Lung cancer | A549 | Inhibit cell growth & proliferation<br>Induce G0/G1 phase cell cycle arrest: ↓ Cdk1 & cyclin B1 | 0–50 μM | 12.51 μM (24 h)<br>7.75 μM (72 h) | [27] |
| | A549, H460, H226, H1299 | Reduce invasive potential<br>Inhibit $PGE_2$-induced cell migration: ↓ $PGE_2$ production ↓ COX-2 ↑ β-catenin degradation ↓ NF-κB/p65 activity ↓ IKKα | 0–20 μM | N/A | [37] |
| | A549, H1299 | Inhibit cell viability and growth: ↓ class I | 0–60 μM | N/A | [38] |

| Cell Lines | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|
| | HDAC proteins; ↓ HDAC activity; ↑ histone acetyltransferase (HAT) activity; ↑ histone H3 & H4 Induce G1 phase cell cycle arrest: ↓ cyclin D1 & cyclin D2; ↓ Cdk2, Cdk4 & Cdk6 | | | |
| H460 & A549 | Inhibit cell proliferation Induce apoptosis: ↑ cathepsin D; ↑ cleaved PARP; ↑ caspase-3 Inhibit autophagy: ↑ p62; ↑ LC3-II | 0–60 μM | H460: ~30 μM (48 h) A549: ~40 μM (48 h) | [39] |
| Pc9-BrM3 & H2030-BrM3 (brain metastatic) | Inhibit cell proliferation and cell invasion: ↓ STAT3 protein phosphorylation; ↓ STAT-3 mediated mitochondrial respiratory function | 0–50 μM | PC9-BrM3: 28.4 μM (48 h) H2030-BrM3: 25.7 μM (48 h) | [40] |
| H23, A549 & HCC827 | Inhibit cell growth Induce G1 phase cell cycle arrest: ↓EGFR; ↓ class I HDAC; ↓ class IIb HDAC6 activity; ↑ Hsp90 acetylation & EGFR degradation | 0–40 μM | A549: 23.55 μM (24h) | [41] |
| H460, A549, H358 | Inhibit cell growth: ↓ c-RAF, ERK & AKT | 0–80 μM | H460: 30.42 μM (72 h) A549: | [42] |

| Cell Lines | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|
| | phosphorylation<br>Inhibit colony formation capacity<br>Induce apoptosis: ↑ Bax protein; ↓ Bcl-2 protein; ↑ PARP cleavage<br>Induce G1 phase cell cycle arrest: ↓ cyclin D1; ↑ p21 & p27; ↓ P70S6k kinase activity<br>Induce autophagy: ↑ LC3-I conversion to LC3-II; ↑ Sirt3 mRNA & protein; ↓ Hif-1α protein | | 50.58 μM (72 h)<br>H358:<br>59.38 μM (72 h) | |
| A549 & 95-D | Inhibit cell viability<br>Induce apoptosis: ↑ ER stress signalling pathway activation; ↑ GRP78, phosphorylation PERK & phosphorylated IRE1α; ↑ cleaved caspase-9 & CHOP; ↓ Bcl-2 protein; ↑ Bax, caspase-3 & caspase-9<br>Inhibit cell migration | 0–60 μM | N/A | [43] |
| CH27, H460 & H1299 | Inhibit cell growth<br>Induce apoptosis: ↓ Bcl-XL; ↑ mitochondrial cytochrome c release; ↑ BAD | 0–100 μM | CH27:<br>40.9 μM (24 h)<br><br>H460:<br>41.4 μM (24 h)<br><br>H1299:<br>34.7 μM (24 h) | [17] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | protein; ↑ caspase-1, caspase-2, caspase-3, caspase-6, caspase-8 & caspase-9 activity; ↑ PARP cleavage | | | |
| | MSTO-211H | Inhibit cell viability Induce apoptosis: ↑ PARP cleavage; ↑ caspase-3 activation; ↓ Bid & Bcl-xL protein; ↑ Bax protein; ↓ Mcl-1 & survivin protein; ↓ Sp1 Induce G1 phase cell cycle arrest: ↓ cyclin D1 | 0–22.5 μM | N/A | [44] |
| Skin cancer | SK-MEL2 & MeWo | Inhibit cell growth & cell proliferation Induce apoptosis via DNA degradation Induce cell death via mitochondrial depolarization | 0–100 μM | N/A | [45] |
| | A431 | Inhibit cell viability & proliferation Induce G0/G1 phase cell cycle arrest: ↓ cyclin A, cyclin D1, cyclin D2 & cyclin E; ↓ Cdk2, Cdk4 & Cdk6; ↑ p21 & p27 Induce cell apoptosis: ↑ PARP | 0–75 μM | N/A | [46] |

| Cell Lines | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|
| B16-F10 | Inhibit cell proliferation Induce cell death: ↑ Autophagosome (vacuoles) formation; ↓ cyclin D1; ↓ AKT/mTOR & Notch signalling | 0–50 μM | N/A | [47] |
| B16/F-10 & SKMEL-28 | Inhibit cell proliferation & viability: ↓ Notch signalling; ↓ TACE & γ-secretase complex proteins Inhibit clonogenicity Induce G0/G1 phase cell cycle arrest Induce autophagy: ↑ autophagosome formation; ↑ LC3B cleavage Inhibit cell stemness: ↓ CD271, CD166, Jarid1B & ABCB5 | 0–60 μM | N/A | [48] |
| UACC903 | Inhibit cell growth & proliferation | 0–50 μM | 7.45 μM (24 h) 5.10 μM (72 h) | [27] |
| SKMEL-2 | Inhibit cell proliferation & viability Induce apoptotic death: ↑ caspase-3, caspase-6, caspase-8 & caspase-9; ↑ PARP cleavage; ↓ procaspase-3, procaspase-8 & | 0–100 μM | N/A | [49] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | procaspase-9 Induce G2/M phase cell cycle arrest: ↓ cyclin B1, cyclin D1, cyclin D2 & PCNA; ↓ Cdk2 & Cdk4; ↑ p21 & p53 | | | |
| | UACC-62 | Inhibit cell proliferation & viability Induce apoptotic death: ↑ caspase-3, caspase-6, caspase-8 & caspase-9; ↑ cleaved PARP; ↓ procaspase-3, procaspase-8 & procaspase-9 Induce G0/G1 phase cell cycle arrest: ↓ cyclin B1, cyclin D1 & cyclin D2; ↓ Cdk2, Cdk4 & Cdc2p34; ↓ p21 & p27 | 0–100 μM | N/A | [49] |
| Renal cancer | A498 | Inhibit cell proliferation Inhibit colony formation capability Inhibit cell migration and invasion: ↓ Epithelial-mesenchymal transition (EMT); ↓ cancer stem cells (CSC) properties; ↑ miR-141; ↓ ZEB2 Inhibit tumoursphere formation | 0–80 μM | ~12 μM (72 h) | [50] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| Cervix cancer | KB-3-1, KB-8-5, KB-C1, KB-V1 | Inhibit cell viability: ↓ EGFR-STAT3 signalling<br>Induce mitochondria-dependent & death receptor-dependent apoptosis: ↓ Bcl-2, Mcl-1 & survivin; ↑ PARP & caspase-3 cleavage; ↑ mitochondrial release of cytochrome c; ↑ DR5<br>Enhances in vitro cytotoxicity of Paclitaxel | 0–75 μM | KB-3-1:<br>12.56 μM (72 h)<br>KB-8-5:<br>12.08 μM (72 h)<br>KB-C1:<br>11.40 μM (72 h)<br>KB-V1:<br>10.39 μM (72 h) | [23] |
| Pancreatic cancer | MiaPaCa & Colo-357 | Suppress plating efficiency of cells<br>Reduce anchorage-independent clonogenicity growth<br>Suppress migration and invasion ability | 0–5 μM | N/A | [51] |
| | MiaPaCa & Panc1 | Inhibit cell growth<br>Induce G1 phase cell cycle arrest: ↓ cyclin D1 & cyclin E; ↓ Cdk2 & Cdk4; ↑ p21 & p27<br>Induce apoptosis: ↓ Bcl-2 & Bcl-xL proteins; ↑ Bax protein; ↓ IKB-α phosphorylation; ↓ NF-κB | 0–60 μM | MiaPaCa:<br>43.25 μM (24 h)<br>31.08 μM (48 h)<br>18.54 μM (72 h)<br><br>Panc1:<br>47.44 μM (24 h)<br>34.17 μM (48 h)<br>21.86 μM (72 h) | [52] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | constitutive activation | | | |
| Thyroid cancer | ARO, WRO | Inhibit cell growth & proliferation: ↓ ERK, JNK & p37 activation and expression; ↓ mTOR & p70S6K<br>Inhibit colony formation<br>Induce apoptosis: ↑ PARP cleavage; ↑ caspase-3, caspase-8 & PARP activation; ↓ PI3K/AKT & MAPK pathways<br>Induce G0/G1 cell cycle arrest: ↓ cyclin D1; ↓ Cdk2 & Cdk4; ↑ p21 & p27<br>Induce autophagy & autophagy flux: ↑ LC3-II | ARO & WRO: 0–60 μM<br><br>SW579: 0–40 μM | ARO:<br>36.3 μM (24 h)<br>40.1 μM (48 h)<br>44.8 μM (72 h)<br><br>WRO:<br>37.7 μM (24 h)<br>31.8 μM (48 h)<br>30.7 μM (72 h)<br><br>SW579:<br>19.9 μM (24 h)<br>10.5 μM (48 h)<br>8.8 μM (72 h) | [53] |
| Nasopharyngeal cancer | HNE-1 | Inhibit cell growth<br>Induce apoptosis<br>Induce G1 phase cell cycle arrest | 0–150 μM (Honokiol & ATNH—Active targeting nanoparticles-loaded honokiol) | Honokiol:<br>144.71 μM (24 h)<br><br>ATNH:<br>69.04 μM (24 h) | [22] |
| Brain cancer | U251 | Inhibit cell growth<br>Inhibit cell proliferation<br>Induce apoptosis | 0–120 μM | 61.43 μM (24 h) | [54] |
| | T98G | Inhibit cell viability<br>Inhibit cell invasion | 0–50 μM | N/A | [55] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | Induce cell apoptosis: ↑ Bax protein; ↓ Bcl-2; ↑ Bax/Bcl-2 ratio | | | |
| | GBM8401 (Parental) & GBM8401 SP | Inhibit cell proliferation & viability Induce sub-G1 phase cell cycle arrest Induce apoptosis: ↓ Notch3/Hes1 pathway | 0–20 μM | GBM8401 (Parental): 5.30 μM (48 h) GBM8401 SP: 11.20 μM (48 h) | [29] |
| | U251 & U-87 MG | Inhibit cell viability & proliferation: ↓ PI3K/Akt & MAPK/Erk signalling pathways Inhibit cell invasion & migration: ↓ MMP2 & MMP9; ↓ NF-κB-mediated E-cadherin pathway Inhibit colony formation Induce apoptosis: ↓ Bcl-2, p-AKT & p-ERK; ↑ Bax protein; ↑ caspase-3 cleavage; ↓ EGFR-STAT3 signalling Reduce spheroid formation: ↓ CD133 & Nestin protein | 0–60 μM | U251: 54.00 μM (24 h) U-87 MG: 62.50 μM (24 h) | [56] |
| | DBTRG-05MG | Inhibit cell growth Induce | 0–50 μM | ~30 μM | [57] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | apoptosis: ↓ Rb protein; ↑ PARP & Bcl-x(S/L) cleavage<br>Induce autophagy: ↑ Beclin-1 & LC3-II | | | |
| | U87 MG (Human)<br><br>BMEC (Mouse) | Inhibit cell viability<br>Inhibit epithelial-mesenchymal transition (EMT): ↓ Snail, β-catenin & N-cadherin; ↑ E-cadherin<br>Inhibit cell adhesion & invasion: ↓ VCAM-1; ↓ phosphor-VE-cadherin-mediated BMEC permeability | 0–20 μM | U87MG:<br>22.66 μM (24 h)<br><br>BMEC:<br>13.09 μM (24 h) | [58] |
| | U87 MG | Inhibit cell viability<br>Induce G1 phase cell cycle arrest: ↑ p21 & p53; ↓ cyclin D1; ↓ Cdk4 & Cdk6; ↓ p-Rb protein; ↓ E2F1<br>Induce apoptosis: ↓ procaspase-3; ↑ caspase-8 & caspase-9 activity | 0–100 μM | 52.70 μM | [59] |
| Bone cancer | HOS & U20S | Inhibit cell proliferation<br>Inhibit colony formation<br>Induce G0/G1 phase cell cycle arrest: ↓ cyclin D1 & cyclin E; ↓ | 0–30 μM | HOS:<br>17.70 μM (24 h)<br><br>U20S:<br>21.50 μM (24 h) | [60] |

| Cell Lines | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|
| | Cdk4<br>Induce mitochondria-mediated apoptosis: ↑ caspase-3 & caspase-9 activation; ↑ PARP cleavage; ↓ Bcl-2, Bcl-xL & survivin; ↑ ERK activation; ↓ proteasome activity; ↑ ER stress and subsequent ROS overgeneration; ↑ GRP78<br>Induce autophagy: ↑ Atg7 protein activation; ↑ Atg5; ↑ LC3B-II | | | |
| SAOS-2, HOS, 143B, MG-63 M8, HU09, HU09 M132<br><br>Dunn, LM5, LM8 & LM8-LacZ (Mouse) | Inhibit cell metabolic activity<br>Inhibit cell proliferation<br>Inhibit cell migration<br>Induce rapid cell death via Honokiol-provoked vacuolation | 0–150 μM | (72 h)<br>SAOS-2: 48.38 μM<br>HOS: 51.38 μM<br>143B: 41.63 μM<br>MG-63M8: 34.88 μM<br>HU09: 59.25 μM<br>HU09M132: 31.88 μM<br><br>(72 h)<br>Dunn: 36.00 μM<br>LM5: 30.00 μM<br>LM8: 31.13 μM | [61] |
| Saos-2 & MG-63 | Inhibit cell viability<br>Induce apoptosis: ↑ | 0–100 μM | Saos-2: 37.85 μM (24 h) | [62] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | caspase-3 & PARP cleavage; ↑ Bax protein; ↓ Bcl-2; ↓ PI3K/AKT signalling pathway; ↓ miR-21 | | MG-63: 38.24 μM (24h) | |
| Oral cancer | OC2 & OCSL | Inhibit cell growth Induce G0/G1 phase cell cycle arrest: ↑ cyclin E accumulation; ↑ p21 & p27; ↓ cyclin D1, ↓ Cdk2 & Cdk4 Induce apoptosis: ↓ caspase-8 & caspase-9; ↑ caspase-3 cleavage; ↓ Bid protein Induce autophagy and autophagic flux: ↑ LC3-II; ↓ Akt/mTORC1 pathway; ↑ AMPK signalling pathway; ↑ p62 | 0–60 μM | OC2: 35.00 μM (24 h) 22.00 μM (48 h) OCSL: 33 μM (24 h) 13 μM (48 h) | [18] |
| | HN-22 & HSC-4 | Inhibit cell viability Induce apoptosis: ↓ Sp1 protein; ↑ p21 & p27; ↑ PARP & caspase-3 activation; ↓ Mcl-1 & survivin protein Induce G1 phase cell cycle arrest: ↓ cyclin D1 | 0–37.5 μM | HN-22: 26.63 μM (48 h) HSC-4: 30.00 μM (48 h) | [63] |

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| Liver cancer | HepG2 | Inhibit cell growth & proliferation: ↓ β-catenin protein Induce apoptosis: ↑ BAD protein; ↓ Bcl-2 protein Upregulation of BAD protein expression Downregulation of Bcl-2 protein level | 0–2 μM | N/A | [64] |
| | SMMC-7721 | Inhibit cell growth Induce G0/G1 phase cell cycle arrest Induce apoptosis: ↓ mitochondrial potential; ↑ ROS production; ↓ Bcl-2 protein; ↑ Bax protein | 0–37.5 μM | N/A | [65] |
| | HepG2, HUH7, PLC/PRF5, Hep3B | Inhibit cell proliferation: ↓ STAT3 activation; ↓ IL-induced Akt phosphorylation; ↓ c-Src activation; ↓ JAK1 & JAK2; ↑ SHP-1 protein Induce sub-G1 phase cell cycle arrest: ↓ cyclin D1 Downregulation of cyclin D1 level Induce apoptosis: ↓ Bcl-2 & Bcl-xL; ↓ survivin & Mcl-1 protein; ↑ caspase-3 | 0–100 μM | N/A | [24] |

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inconsequential toxicity under tested conditions when treated with a combination of honokiol and paclitaxel [23]. Indisputably, honokiol was once again proven to exhibit minor to no toxicity against normal cells.

| Cell Lines | | Mechanism of Action | Concentration Used | Efficacy/$IC_{50}$ (Exposure Time) | References |
|---|---|---|---|---|---|
| | | activation; ↑ PARP cleavage [75] | | | |
| [66] | | Enhance apoptotic effect of doxorubicin & paclitaxel | | | |
| | | [66] | | | |
| | A2780s & A2780cp | Inhibit cell growth Induce apoptosis | 0–100 μM | A2780s: 36.00 μM (48 h) A2780cp: 34.70 μM (48 h) | [66] |
| [77] | SKOV3 & Caov-3 | Inhibit cell proliferation and growth Inhibit colony formation Induce apoptosis: ↑ AMPK pathway activation; ↑ caspase-3, caspase-7 & caspase-9 activation; ↑ PARP cleavage Induce G0/G1 phase cell cycle arrest Inhibit cell migration and invasion | 0–100 μM | SKOV: 48.71 μM (24 h) Caov-3: 46.42 μM (24 h) | [20] |
| Ovarian cancer | | | | | |
| | | Inhibit cell | | SKOV3: | |

| Cancer Cell Line | Animal Model & Site of Tumour Xenograft | Dose, Duration & Route of Administration | Observation & Mechanism of Action | Efficacy on Tumour Inhibition | References |
|---|---|---|---|---|---|
| Breast cancer | | | | | |
| MDA-MB-231 cells | Both flanks of athymic nude mice | 100 mg/kg/day 28 days IP | Induce tumour growth arrest | Complete arrest of tumour growth from week 2 onwards | [32] |
| MDA-MB-231 cells | Right gluteal region of athymic nude mice | 3 mg/mouse/day Three times a week 28 days IP | Inhibit tumour progression: ↓ Ki-67; ↑ LKB1 & pAMPK; ↑ ACC phosphorylation, ↓ pS6K & 4EBP1 phosphorylation | Tumour weight of honokiol-treated group was 0.22 g compared to control group | [33] |

| Cancer Cell Line | Animal Model & Site of Tumour Xenograft | Dose, Duration & Route of Administration | Observation & Mechanism of Action | Efficacy on Tumour Inhibition | References |
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| | | | | which was 1.58 g | |
| MDA-MB-231-pLKO.1 & MDA-MB-231-LKB1$^{shRNA}$ cells | Right gluteal region of athymic nude mice | 3 mg/mouse/day Three times a week 42 days Oral gavage | Inhibit cell stemness: ↓ Oct4, Nanog & Sox2; ↓ pSTAT3 & Ki-67 Inhibit mammosphere formation | Decreased expression of Oct4, Nanog, Sox2<br><br>Reduce number of tumour cells showing Ki-67 & pStat3 expression | [34] |
| Colorectal cancer | | | | | |
| RKO cells | Axilla of BALB/c nude mice | 80 mg/kg/day Treatment on days 8–11, 14–17, 21–24, 28–31 51 days IP | Inhibit tumour growth Prolong survival of mice | 709.9% increase in tumour growth rate in honokiol-treated group compared to 1627.6% and 1408.2% in control and vehicle groups respectively | [25] |
| HCT116 cells | Flank of athymic nude mice | 200 µg/kg/day + 5 Gy irradiation Once a week 21 days IP | Inhibit tumour growth: ↓ CSC proteins → ↓ DCLK1, Sox-9, CD133 & CD44 | Significantly lower tumour weight (<800 mg) in honokiol-IR combination, (~1500 mg) in honokiol treatment group compared to (~3300 mg) in control group | [28] |
| Cervical cancer | | | | | |
| KB-8-5 cells | Athymic nu/nu nude mice (site of xenograft not stated) | 50 mg/kg Honokiol Three times a week + 20 mg/kg Paclitaxel | Suppress tumour growth: ↓ Ki-67 tissue level Induce apoptosis | Significantly lower average tumour volume for honokiol-paclitaxel combination treatment (573.9 | [23] |

| Cancer Cell Line | Animal Model & Site of Tumour Xenograft | Dose, Duration & Route of Administration | Observation & Mechanism of Action | Efficacy on Tumour Inhibition | References |
|---|---|---|---|---|---|
| | | Once a week<br>28 days<br>IP (honokiol)<br>Tail vein injection (paclitaxel) | | $mm^3$) compared to control (2585.4 $mm^3$) | |
| Lung cancer | | | | | |
| H2030-BrM3 cells | Left ventricle of NOD/SCID mice | 2 or 10 mg/kg/day<br>28 days<br>Oral gavage | Prevent metastasis of lung cancer cells to brain | 10 mg/kg: Decrease brain metastasis for >70% | [40] |
| H2030-BrM3 cells | Left lung via left ribcage of athymic nude mice | 2 or 10 mg/kg/day<br>Five days a week<br>28 days<br>Oral gavage | Decrease lung tumour growth<br>Inhibit metastasis to lymph node | 10 mg/kg: Significantly reduce incidence of mediastinal adenopathy, decrement of weight of mediastinal lymph node for >80%, only 2/6 mice have lymphatic metastasis | [40] |
| Blood cancer | | | | | |
| Raji cells | Back of BALB/c nude mice | 5 mg/20 g & 10 mg/20 g<br>Treatment on days 8–12 & 15–19<br>20 days<br>(Route of administration not specified) | Inhibit cell proliferation<br>Inhibit tumour growth | Tumour growth of honokiol-treated mice was significantly lower (~90 $cm^3$) compared to control mice (~270 $cm^3$) | [31] |
| HL60 cells | Inoculated intraperitoneally into SCID mice | 100 mg/kg/day<br>Treatment on Day 1–6<br>47 days<br>IP | Prolong survival of mice | Median survival time of honokiol-treated mice are longer (37.5 days) compared to vehicle- | [78] |

| Cancer Cell Line | Animal Model & Site of Tumour Xenograft | Dose, Duration & Route of Administration | Observation & Mechanism of Action | Efficacy on Tumour Inhibition | References |
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| | | | | treated mice (24.5 days) | |
| Pancreatic cancer | | | | | |
| MiaPaCa cells | Pancreas of immunocompromised mice | 150 mg/kg/day<br>28 days<br>IP | Suppress tumour growth<br>Inhibit metastasis:<br>↓ CXCR & SHH; ↓ NF-κB & downstream pathway<br>Inhibit desmoplastic reaction:<br>↓ ECM protein; ↓ collagen I | Significant decrease in tumour growth for honokiol-treated mice (99.6 $mm^3$) compared to vehicle-treated mice (1361.0 $mm^3$) | [51] |
| Skin cancer | | | | | |
| SKMEL-2 or UACC-62 cells | Right flank of athymic nude mice | 50 mg/kg<br>Three times a week<br>14–54 days<br>IP | Decrease tumour growth | SKMEL-2:<br>40% reduction in tumour volume<br><br>UACC-62:<br>50% reduction in tumour volume | [49] |
| Thyroid cancer | | | | | |
| ARO cells | BALB/cAnN.Cg-Foxn1nu/CrlNarl mice (site of xenograft not stated) | 5 or 15 mg/kg/mouse<br>Every three days<br>21 days<br>Oral gavage | Decrease tumour volume & tumour weight<br>Induce apoptosis & autophagy | Control: ~1000 $mm^3$; 700 mg<br>5 mg/kg Honokiol: ~600 $mm^3$; 400 mg<br>15 mg/kg Honokiol: ~400 $mm^3$; 200 mg | [53] |
| Nasopharyngeal cancer | | | | | |
| HNE-1 cells | Right dorsal aspect of right foot of BALB/c athymic nude mice | Active-targeting nanoparticles-loaded HK (ATNH), Non- | Inhibit tumour progression,<br>Induce apoptosis<br>Potential inhibitor | Efficiency in tumour delay:<br>ATNH > NATNH > Free HK | [22] |

| Cancer Cell Line | Animal Model & Site of Tumour Xenograft | Dose, Duration & Route of Administration | Observation & Mechanism of Action | Efficacy on Tumour Inhibition | References |
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| | | active-targeting nanoparticles-loaded HK (NATNH), Free Honokiol (HK)<br><br>3 mg/mouse/day Every three days Euthanise 50% mice after 12 days, rest are left to observe tumour growth & survival time up to 60 days; IV | of angiogenesis & proliferation | Median survival time: Control: 28.5 days Free HK: 34 days NATNH: 42.5 days ATNH: 57.5 days | |
| Brain cancer | | | | | |
| U21 cells | Right flank of athymic nude mice | 20 mg/kg Twice a week 27 days Caudal vein injection | Inhibit tumour growth Inhibit angiogenesis | Honokiol-treated mice have significant inhibition of tumour volume by 50.21% compared to vehicle<br><br>Significantly lower microvessel present in honokiol-treated cells | [54] |
| U-87 MG cell suspension pre-treated with honokiol or vehicle for 48h | Yolk sac of Zebrafish larvae | (Concentration N/A) 3 days Injection of cells into zebrafish | Inhibit cell proliferation Inhibit cell migration | Reduced number of cell mass compared to vehicle-treated cells | [56] |

| Cancer Cell Line | Animal Model & Site of Tumour Xenograft | Dose, Duration & Route of Administration | Observation & Mechanism of Action | Efficacy on Tumour Inhibition | References |
|---|---|---|---|---|---|
| U-87 MG cells | Right flank near upper extremity of nude mice | 100 mg/kg/day<br>Treatment at days 1–7<br>21 days<br>IP | Reduce tumour growth:<br>↓ EGFR, pSTAT3, CD133 & Nestin | Increased number of apoptotic cells in honokiol-treated tissue,<br>Significantly lower tumour volume & tumour weight in honokiol-treated mice | [56] |
| Bone cancer | | | | | |
| HOS cells | Dorsal area of BALB/c-nu mice | 40 mg/kg/day<br>7 days<br>IP | Reduce tumour growth<br>Induce apoptosis & autophagy: ↑ cleaved caspase-3; ↑ LC3B-II & phosphor-ERK (ROS/ERK1/2 signalling pathway) | Significant decrease in tumour volume & weight of honokiol-treated mice (200 $mm^3$; 0.2 g) compared to control group (~500 $mm^3$; 0.5 g)<br>Increased number of TUNEL-positive cells | [18] |
| LM8-LacZ cells | Left flank of C3H/HeNCrl mice | 150 mg/kg/day<br>25 days;<br>IP | Inhibit metastasis | Mean number of micrometastases decreased significantly by 41.4% in honokiol-treated mice compared to control mice | [61] |
| Oral cancer | | | | | |
| SAS cells | Right flank of BALB/cAnN.Cg-Foxn1nu.CrlNarl nude mice | 5 mg/kg or 15 mg/kg<br>Treatment on day 1, 4, 7, 10, 13, 16, 19, 22<br>35 days<br>Oral | Reduce tumour growth & volume | Significantly reduction in tumour growth in honokiol-treated mice<br><br>29% reduction (5 mg/kg; 21 | [18] |

| Cancer Cell Line | Animal Model & Site of Tumour Xenograft | Dose, Duration & Route of Administration | Observation & Mechanism of Action | Efficacy on Tumour Inhibition | References |
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| | | | | days), 40% reduction (15 mg/kg; 21 days)<br><br>41% reduction (5 mg/kg; 35 days), 56% reduction (15 mg/kg; 35 days) | |
| Prostate cancer | | | | | |
| C4-2 cells | Bilateral tibia of BALB/c nu/nu athymic nude mice | 100 mg/kg/day<br>42 days<br>IP | Inhibit cell proliferation:<br>↑ Ki-67<br>Induce apoptosis:<br>↑ M-31<br>Inhibit angiogenesis: ↑ CD-31 | Lower PSA value in honokiol-treated mice compared to control group | [69] |
| PC-3 cells | Left & right flanks above hind limb of nude mice | 1 or 2 mg/mice Monday, Wednesday & Friday two weeks before tumour implantation and duration of experiment after implantation<br>77 days<br>Oral gavage | Inhibit tumour growth<br>Inhibit cell proliferation<br>Inhibit neovascularisation<br>Induce apoptosis | Tumour volume of honokiol-treated mice are significantly lower (~330 $mm^3$; 1 mg), (~50 $mm^3$; 2 mg) compared to control (~400 $mm^3$) | [79] |
| Gastric cancer | | | | | |
| [83]<br>MKN45 cells | Dorsal side of BALB/c nude mice (nu/nu) | 0.5 mg/kg/day & 1.5 mg/kg/day<br>10 days<br>Injection (route not stated) | Inhibit tumour growth: ↓ GRP94 overexpression | 30% reduction in tumour volume (0.5 mg/kg)<br>60% reduction in tumour volume (1.5 mg/kg)<br><br>Decreased accumulation of GRP94 [83][84] | [80]<br>[84] |

ticellular pathway intrinsic Bax/Bak released plex [85],

which promotes the activation of caspase-9 and later caspase-3, initiating the caspase cascade, which executes cell death in a coordinated way [85]. For the extrinsic pathway, the binding of ligands such as tumour necrosis factor (TNF), Fas ligand (Fas-L), and TNF-related apoptosis-inducing ligand (TRAIL) to their respective death receptors

| Cancer Cell Line | Animal Model & Site of Tumour Xenograft | Dose, Duration & Route of Administration | Observation & Mechanism of Action | Efficacy on Tumour Inhibition | References |
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| MKN45 & SCM-1 cells | Peritoneal cavity of BALB/c nude mice | 5 mg/kg<br>Twice a week<br>28 days<br>IP | Inhibit metastasis<br>Inhibit angiogenesis | Honokiol inhibited STAT-3 signalling and VEGF signalling induced by calpain/SHP-1 | [81] |
| Ovarian cancer | | | | | |
| SKOV3 cells | Right axilla of BALB/c nude mice | 1 mg liposome-encapsulated honokiol/day<br>48 days<br>IP | Inhibit tumour growth<br>Inhibit angiogenesis | Reduction in tumour growth rate in liposome-encapsulated honokiol-treated mice by 67–70% compared to control | [66][82] |
| A2780s cells | Right flank of athymic BALB/c nude mice | 10 mg/kg Lipo-Honokiol<br>Twice a week<br>21 days<br>IV | Inhibit cancer growth<br>Prolong survival of mice<br>Increase intra-tumoural apoptosis<br>Inhibit intra-tumoural angiogenesis | Lipo-HNK treated mice have significantly smaller tumour volume ($222 \pm 71$ mm$^3$) compared to liposome-treated mice ($1823 \pm 606$ mm$^3$) and control mice ($3921 \pm 235$ mm$^3$) | [66] |
| A2780cp cells | Right flank of athymic BALB/c nude mice | 10 mg/kg Lipo-Honokiol<br>Twice a week<br>21 days<br>IV | Inhibit cancer growth<br>Prolong survival<br>Increase intra-tumoural apoptosis<br>Inhibit intra-tumoural angiogenesis | Lipo-HNK treated mice have significantly smaller tumour volume ($408 \pm 165$ mm$^3$) compared to liposome-treated mice ($2575 \pm 701$ mm$^3$) and control mice | [66] |

melanoma. Honokiol activated ER stress and down-regulated peroxisome proliferator-activated receptor-γ (PPARγ) activity resulting in PPARγ and CRT degradation through calpain-II activity in human gastric cancer cell lines [80][107][108] and human chondrosarcoma cells [14]. This was due to the ability of honokiol to upregulate and bind effectively to the glucose regulated protein 78 (GRP78) to activate apoptosis [14][109]. However, this was opposed

| Cancer Cell Line | Animal Model & Site of Tumour Xenograft | Dose, Duration & Route of Administration | Observation & Mechanism of Action | Efficacy on Tumour Inhibition | References |
|---|---|---|---|---|---|
| | | [80] | | (2828 ± 796 $mm^3$) | |

uction of

embrane

tion [110].

Besides apoptosis, honokiol has also been found to induce necrotic cell death in MCF-7 (40 µg/mL honokiol) [111], human oesophageal adenocarcinoma cells CP-A and CP-C [112], and primary human acute myelogenous leukemia HL60 [78] via p16ink4a pathway by targeting cyclophilin D to affect several downstream mechanisms. This phenomenon was also observed in transformed Barrett's and oesophageal adenocarcinoma cells when treated with honokiol (<40 µM) by targeting their STAT3 signalling pathway, thus resulting in a decrease of Ras activity and phosphorylated ERK1/2 expression [113]. The phosphorylation of Ser727 STAT3 induces translocation towards the mitochondria followed by ROS production, ultimately leading to the induction of necrosis [114]. Taken together, honokiol demonstrates the dual induction of apoptotic and necrotic cell death.

### 3.2. Cell Cycle Arrest

Cancer is attributed to uncontrolled proliferation resulting from abnormal activity of different cell cycle proteins. Therefore, cell cycle regulators are becoming attractive targets in cancer therapy. Honokiol can induce cell cycle arrest in several types of cancer cells, such as in lung squamous cell carcinoma [115], prostate cancer cells [68][116], oral squamous cancer [63], UVB-induced skin cancer [117], and more as listed in **Table 1**, by generally inducing G0/G1 and G2/M arrest. This arrest is associated with the suppression of cyclin-B1, CDC2, and cdc25C in honokiol-treated human gastric carcinoma and human neuroglioma cells [91][118][119], downregulation of cyclin dependent kinase (CDK)-2 and CDK-4, and the upregulation of cell cycle suppressors p21 and p27 in human oral squamous cell carcinoma (OSCC) cells [18][91]. In addition, the downregulation of c-Myc and class I histone deacetylases was also identified as other contributors to cell cycle arrest at the G0/G1 phase in prostate cancer cells [91][116] and acute myeloid leukemia respectively [37][95][102].

### 3.3. Autophagy

Autophagy is an evolutionary conserved catabolic process that involves the delivery of dysfunctional cytoplasmic components for lysosomal degradation [120][121]. The activation of autophagy promotes cell survival and regulates cell growth during harsh and stressful conditions via a reduction of cellular energy requirements by breaking down unnecessary components [75][121]. In cancer cells, autophagy facilitates both tumour suppression and tumourigenesis by the induction of cell death and tumour growth promotion, respectively [122][123]. The regulation of mTORC complexes mTORC1 and mTORC2 is involved in controlling the autophagic process. The activation of mTORC1 plays an important role in phosphorylation of autophagy-related protein (ATG) and subsequently inhibiting autophagy, whereas the inhibition of mTORC1 complements the autophagic process [124][125]. The inhibition of mTORC1 complex will concurrently activate Unc-51-like autophagy-activating kinase (ULK) complex, inducing localisation to the phagophore and followed by class III PI3K activation [126][127]. Beclin-1 was known to play a role in tumour suppression by recruiting several proteins associated with autophagosome elongation and maturation [128]. ATGs regulate the autophagosome elongation. For instance, ATG5-ATG12/ATG16L complexes

recruit microtubule-associated protein 1 light chain 3 (LC3), followed by conversion of pro-LC3 to active cytosolic isoform LC3 I by ATG4B [129][130]. Thereafter, the interaction with ATG3, ATG7, and phosphatidylethanolamine (PE) converts LC3 I to LC3 II. The LC3 II enables the autophagosome to bind to degraded substrates and mature autophagosomes are capable of fusing with lysosomes to selectively remove damaged organelles via autophagy [131].

Generally, there are two modes of autophagy known as conventional and alternative autophagy. Conventional autophagy (also known as Atg5/Atg7-dependent pathway) involves the activation of Atg5 and Atg7 which are core regulators of autophagy, and then leads to microtubule-associated protein 1A/1B light chain 3 (LC3) modification and translocation from cytosol to the isolation membrane. This LC3 translocation was considered as a reliable hallmark of autophagy. Contradictorily, alternative autophagy occurs independently without involving Atg5 and Atg7, as well as LC3 modification [122][123][131].

The regulation of autophagy in cancer remains controversial as it plays dual roles in tumour suppression and promotion. Autophagy is believed to contribute to the properties of cancer cells stemness, induction of recurrence, and the development of anticancer drugs. However, the actual mechanism of autophagy in cancer remains unclear. Several studies have highlighted the potential of honokiol to induce cell death via autophagy in human prostate cancer cells [70], human glioma cells [132], NSCLC cells [22], and human thyroid cancer cells [53].

The activation of Atg5/Atg7-dependent pathways through the upregulation of LC3B-II, Atg5, and Atg7 levels was observed in honokiol-treated osteosarcoma HOS and U2OS cells and leads to the accumulation of autophagic vacuoles [18]. According to a study by Chang et al. [57], the expression of two critical autophagic proteins, Beclin-1 and LC3, were found to have increased in the honokiol-treated glioblastoma multiforme cells (DBTRG-05MG cell line). Similarly, the expression of autophagosomal marker LC3-II was also increased in Kirsten rat sarcoma viral oncogene homolog (KRAS) mutated cell lines of non-small cell lung cancer (NSCLC).

Other signalling pathways are also found to be involved in honokiol-induced autophagy including the involvement of AMPK-mTOR signalling pathway which leads to autophagocytosis through the coordinated phosphorylation of Ulk1 in Kirsten rat sarcoma viral oncogene homolog (KRAS) mutant lung cancer and melanoma cells [48][53][59][91]. Besides this, the ROS/ERK1/2 signalling pathway is also believed to play a certain role in honokiol-induced autophagy though ERK activation and the generation of ROS in treated osteosarcoma cells [60][70][91]. All these recent studies have further supported the potential of honokiol in the induction of autophagy in cancer cells.

### 3.4. Epithelial-Mesenchymal Transition (EMT)

Migratory mesenchymal-like cells are involved in embryonic development, tissue repair, and regeneration, as well as several pathological processes like tissue fibrosis, tumour invasiveness, and metastasis [133][134]. These migratory mesenchymal cells originate from the conversion of the epithelial cells, and this process is known as epithelial-mesenchymal transition (EMT). This plasticity of cellular phenotypes provides a new insight into possible therapeutic interventions in cancer [134].

EMT is characterised by the loss of epithelial markers such as cytokeratins and E-cadherin, followed by an increase in mesenchymal markers such as N-cadherin and vimentin [135]. The cellular processes of EMT are composed of several key transcription factors (such as TWIST, SNAI1, SNAI2, ZEB1/2) that act in concert with epigenetic mechanisms and post-translational protein modifications to coordinate cellular alterations [133][136]. The application of gene expression signatures combining multiple EMT-linked genes has proven useful to evaluate EMT as a contributing factor in tumour development in human cancers. However, the EMT process was shown to be incomplete in tumours, venturing in between multiple translational states and expressing a mixture of both epithelial and mesenchymal genes. This hybrid in partial EMT can be more aggressive than tumour cells with a complete EMT phenotype [135]. In addition, EMT contributes to tumour metastatic progression and resistance towards cancer treatment, resulting in poor clinical outcomes [134][135].

Honokiol has been shown to block and inhibit EMT in many cancer cells such as breast cancer, melanoma, bladder cancer, human non-small cell lung cancer, and gastric cancer (**Table 1**). Honokiol reduced steroid receptor coactivator-3 (SRC-3), matrix metalloproteinase (MMP)-2, and Twist1, preventing the invasion of urinary bladder cancer cells [102][137]. In addition, honokiol was also capable of inducing E-cadherin and repressing N-cadherin expression, thus inhibiting the EMT process in J82 bladder cancer cells [102][137]. In breast cancer cells, honokiol inhibits the recruitment of Stat3 on mesenchymal transcription factor Zeb1 promoter, resulting in decreased Zeb1 expression and nuclear translocation [138]. In addition, honokiol increases E-cadherin expression via the Stat3-mediated release of Zeb1 from E-cadherin promoter [138]. Collectively, many studies have reported that honokiol effectively inhibits EMT in breast cancer cells, evidence has been found to support a cross-talk between honokiol and Stat3/Zeb1/E-cadherin axis [138]. On the other hand, EMT is inhibited by modulating the miR-141/ZEB2 signalling in renal cell carcinoma (A-498) [50].

Honokiol inhibited the EMT-driven migration of human NSCLC cells in vitro by targeting c-FLIP through N-cadherin/snail signalling as N-cadherin and snail are downstream targets of c-FLIP [139]. Twist1, a basic helix-loop-helix domain-containing transcription factor, promotes tumour metastasis by inducing EMT, and can be upregulated by multiple factors, including SRC-1, STAT3, MSX2, HIF-1α, integrin-linked kinase, and NF-κB. The capability of honokiol in targeting Twist1 can be regarded as a promising therapy for metastatic cancer [102][140].

Honokiol was found to inhibit breast cancer cell metastasis and eliminate human oral squamous cell carcinoma cell by blocking EMT through the modulation of Snail/Slug protein translation [141][142]. Honokiol markedly downregulated endogenous Snail, Slug, and vimentin expression and upregulated E-cadherin expression in MDA-MB-231, MCF7, and 4T1 breast cancer cells [142]. As primary EMT inducers, Snail and Slug dictate the induction of EMT by targeting E-cadherin and vimentin [138][142]. Furthermore, when cells were treated with honokiol, Snail and Slug expression levels were decreased from 12 h to 24 h in a time-dependent manner, suggesting that honokiol can reverse the EMT process via the downregulation of Snail and Slug in breast cancer cell lines [142]. Besides that, EMT was inhibited in human oral squamous cell carcinoma cell via the disruption of Wnt/β-catenin signalling pathway [141]. It was reported that the protein levels of mesenchymal markers such as Slug and Snail were markedly suppressed, while β-catenin and its downstream Cyclin D1 were inhibited [141]. It is known that β-catenin could mediate EMT [141][143], which plays a crucial role in cancer invasion and metastasis. The EMT markers such

as Snail and Slug are also the target genes of β-catenin [144]. Therefore, the suppression of Snail and Slug in honokiol treated human oral squamous cell carcinoma cells was believed to be due to the inhibition of Wnt/β-catenin signalling pathway [141]. Similarly, in U87MG human glioblastoma cell and melanoma cells, Snail, N-cadherin and β-catenin expression levels were decreased, whereas E-cadherin expression was increased after honokiol treatment [58][106].

### 3.5. Suppression of Migration, Invasion and Angiogenesis of Cancer Cells

Metastasis is known to be the major cause of death in cancer patients [145]. It involves the migration and invasion of tumour cells into neighbouring tissues and distant organs via intravasation into blood or lymphatic system [146][147]. The formation of invadopodium was stimulated by epidermal growth factor (EGF) and is crucial for the degradation of the extracellular matrix and remodelling membrane proteins, promoting metastasis [145]. Therefore, one of the important steps in cancer management is to control tumour cell metastasis, especially for early-stage cancer patients [147]. Various studies have reported that honokiol has the capability to suppress tumour metastasis in different types of cancer including breast cancer [33][142][148], non-small cell lung cancer [37][149] ovarian carcinoma cells [20], lung cancer [43], U251 human glioma, as well as U-87MG and T98G human glioblastoma cell [56][58][88], oral squamous cell carcinoma (OSCC) [18], bladder cancer cell [137], pancreatic cancer [51], renal cell carcinoma [150][151], and gastric cancer cells [107]. For instance, the percentage of invading urinary bladder cancer (UBC) cells was significantly reduced by 67% and 92% upon 2.4 μg/mL and 4.8 μg/mL of honokiol treatment, respectively [137]. Similarly, tumour cell migration was inhibited by 38–66% in A549 cells, by 37–62% in H1299 cells, 12% to 58% in H460 cells and 32% to 69% in H226 cells, in a concentration-dependent manner after treatment with honokiol [37].

Furthermore, honokiol also demonstrated an inhibitory effect on the expression of matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9 proteins, which play an essential role in the metastatic process of tumour cells, as well as the regulation of angiogenesis in the maintenance of tumour cell survivability [37][56][137]. MMPs are a group of extracellular matrix degrading enzymes that control various normal cellular processes, such as cell growth, differentiation, apoptosis, and migration [147]. However, MMP activity was increased in many tumour cells. The overexpression of MMP-2 and MMP-9 are associated with pro-oncogenic events such as neovascularisation, tumour cell proliferation, and metastasis because it can degrade the extracellular matrix, basement membranes, and adhesion molecules (intercellular adhesion molecule, ICAM, and vascular cell adhesion molecule) and become invasive [51][147][152].

The transition from an epithelial-to-mesenchymal (EMT) phenotype facilitates the breakdown of extracellular matrix followed by the subsequent invasion of the surrounding tissues in order to enter the bloodstream and/or lymph nodes, and travel to distant organ sites. Once cells have reached the distant organ sites, they undergo mesenchymal-to-epithelial transition and begin the establishment of distal metastasis by the surviving cancer cells followed by the outgrowth of secondary tumours [51][153]. Honokiol has been shown to inhibit the invasion of HT-1080 human fibrosarcoma cells and U937 leukemic cells by inhibiting MMP-9 [154]. In addition, honokiol also reduced the protein levels of MMP2 and MMP9 in U251 human glioma and U-87 MG human glioblastoma cell lines in a dose-dependent manner [56]. The expression of MMP-2 and MMP-9 were also found to be decreased in both

honokiol-treated A549 and H1299 cells (NSCLC cell lines), consistent with the decreased nuclear accumulation of β-catenin as both MMP-2 and MMP-9 are the downstream targets of β-catenin [37][155][156]. In the J82 bladder cancer cell, honokiol repressed the expression of SRC-3, MMP-2, and Twist1 genes which were involved in cancer cell invasion [137].

Another proposed mechanism for the inhibitory effects of honokiol on invasion and metastasis is through the liver kinase B1 (LKB1)/adenine monophosphate-activated protein kinase (AMPK) axis. Honokiol treatment increased the expression and cytoplasmic translocation of tumour-suppressor LKB1 in breast cancer cells, which led to the phosphorylation and functional activation of AMPK and resulted in the inhibition of cell invasion and metastasis [33][51]. The activation of AMPK suppresses mTOR signalling, decreasing the phosphorylation of p70 kDA ribosomal protein S6 kinase 1 (p70S6K1) and eukaryotic translation initiation factor 4E (eIF4E)-binding protein (4EBP1). This will ultimately inhibit the reorganisation of the actin cytoskeleton in cells, subsequently inhibiting cell migration [33].

In human renal carcinoma cell (RCC) 786-0, honokiol significantly upregulated the expression of metastasis suppressor gene (KISS-1), genes encoding TIMP metalloproteinase inhibitor 4 (TIMP4), and KISS-1 receptor (KISS-1R). In addition, honokiol markedly suppressed the expression of genes encoding chemokine (C-X-C motif) ligand 12 (CXCL12), chemokine (C-C motif) ligand 7 (CCL7), interleukin-18 (IL18) and matrix metalloproteinase 7 (MMP7). It was proven that honokiol significantly upregulated KISS1 and KISS1R in the 786-0 cells when treated with honokiol since recent studies showed that the activation of KISS1/KISS1R signalling by kisspeptin treatment decreases the motility and invasive capacity of conventional RCC, and overexpression of KISS1 inhibits the invasion of RCC cells Caki-1 [14][157]. In short, the activation of KISS1/KISS1R signalling by honokiol suppresses the multistep process of metastasis, including invasion and colony formation, in RCC cells 786-0 [157].

Angiogenesis is the formation of new blood vessels for supplying nutrients and oxygen to tissues and cells. In tumourigenesis, angiogenesis is important for the development and progression of malignant tumours [158]. The endothelial cells in growing cancer are active due to the release of cell growth and motility promoting proteins, creating a network of blood vessels to overcome its oxygen tension [159]. Vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF2) are among the factors that play an important role in tumour angiogenesis [147]. In human renal cancer cell lines (786-0 and Caki-1), honokiol induced down-regulation of the expression of VEGF and heme oxygenase-1 (HO-1) via the Ras signalling pathway thus inhibit angiogenesis [160][161].

In retinal pigment epithelial (RPE) cell lines, honokiol inhibited the binding of hypoxia- inducible-factor (HIF) to hypoxia-response elements present on the VEGF promoter, thereby inhibiting the secretion of VEGF protein [162][163]. This decrement of VEGF levels resulted in reduced proliferation of human retinal microvascular endothelial cells (hRMVECs) [162]. Therefore, honokiol is said to possess both anti-HIF and anti-angiogenic properties.

In the overexpression of VEGF-D Lewis lung carcinoma cell-induced tumours in C57BL/6 mice, honokiol was shown to significantly inhibit tumour-associated lymphangiogenesis and metastasis. Furthermore, a remarkable delay in tumour growth and prolonged life span in honokiol-treated mice were also observed [164]. In another study, honokiol inhibited VEGF-D-induced survival, proliferation, and microcapillary tube formation in both human

umbilical vein endothelial cells (HUVECs) and lymphatic vascular endothelial cells (HLECs). These observations are believed to be due to the inhibition in Akt and MAPK phosphorylation and downregulation of VEGFR-2 expressions in HUVECs as well as VEGFR-3 of HLECs [95][154][165]. Collectively, honokiol has been shown to exert direct and indirect effects on tumour suppression via anti-metastasis, anti-angiogenesis, and anti-lymphangiogenesis by mainly affecting HIF- and VEGF/VEGFR- dependent pathways. However, an in-depth mechanism of honokiol on the inhibition of metastatic progression and spread should be further explored in the future.

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