Honokiol

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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.

Keywords: 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 phase cell cycle arrest: ↓ Cdk1 & cyclin B1	0–50 μM followed by 0–5 Gy IR	23.05 μM (24 h) 13.24 μM (72 h)	[27]
	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 & caspase-9 activation; ↓ caspase-9; ↑ Bax protein; ↓ Mcl-1 protein	0–100 μM	49 μM (6 h) 38 μM (24 h)	[30]
	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]

Cell Lines		Mechanism of Action	Concentration Used	Efficacy/IC_{50} (Exposure Time)	References
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 & cytosolic localisation	1–25 μM	N/A	[33]
	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) MDA-MB-231: 56.9 μM (24 h) 44.4 μM (48 h) 16.0 μM (72 h) 12.0 μM (96 h) T47D: 47.7 μM (24 h) 41.6 μM (48 h) 17.6 μM (72 h) 7.1 μM (96 h) SKBR-3: 76.1 μM (24 h) 68.1 μM (48 h) 62.7 μM (72 h) 15.7 μM (96 h) ZR-75: 71.1 μM (24 h) 58.1 μM (48 h) 28.7 μM (72 h) 14.5 μM (96 h) BT-474: 80.2 μM (24 h) 65.6 μM (48 h) 39.5 μM (72 h) 15.1 μM (96 h)	[35]

Cell Lines	Mechanism of Action	Concentration Used	Efficacy/IC_{50} (Exposure Time)	References
MDA-MB-231	Inhibit cell proliferation: ↓ c-Src/EGFR-mediated signalling pathway; ↓ c-Myc protein Induce G0/G1 phase cell cycle arrest: ↓ cyclin A, cyclin D1 & cyclin E; ↓ Cdk2, Cdk4 & p-pRb^{Ser780}; ↑ $p27^{Kip-1}$ Induce apoptosis: ↑ caspase-3, caspase-8 & caspase-9 cascade; ↓ Bcl-2 & Bid protein; ↑ PARP cleavage	0–100 μM	59.5 μM (72 h)	[36]

Cell Lines		Mechanism of Action	Concentration Used	Efficacy/IC_{50} (Exposure Time)	References
Lung cancer	A549	Inhibit cell growth & proliferation Induce G0/G1 phase cell cycle arrest: ↓ Cdk1 & cyclin B1	0–50 μM	12.51 μM (24 h) 7.75 μM (72 h)	[27]
	A549, H460, H226, H1299	Reduce invasive potential 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 HDAC proteins; ↓ HDAC activity; ↑ histone acetyltransferase (HAT) activity; ↑ histone H3 & H4 Induce G1 phase cell cycle arrest: ↓ cyclin D1 & cyclin D2; ↓ Cdk2, Cdk4 & Cdk6	0–60 μM	N/A	[38]
	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 phosphorylation Inhibit colony formation capacity Induce apoptosis: ↑ Bax protein; ↓ Bcl-2 protein; ↑ PARP cleavage Induce G1 phase cell cycle arrest: ↓ cyclin D1; ↑ p21 & p27; ↓ P70S6k kinase activity Induce autophagy: ↑ LC3-I conversion to LC3-II; ↑ Sirt3 mRNA & protein; ↓ Hif-1α protein	0–80 μM	H460: 30.42 μM (72 h) A549: 50.58 μM (72 h) H358: 59.38 μM (72 h)	[42]
	A549 & 95-D	Inhibit cell viability Induce apoptosis: ↑ ER stress signalling pathway activation; ↑ GRP78, phosphorylation PERK & phosphorylated IRE1α; ↑ cleaved caspase-9 & CHOP; ↓ Bcl-2 protein; ↑ Bax, caspase-3 & caspase-9 Inhibit cell migration	0–60 μM	N/A	[43]

Cell Lines	Mechanism of Action	Concentration Used	Efficacy/IC_{50} (Exposure Time)	References
CH27, H460 & H1299	Inhibit cell growth Induce apoptosis: ↓ Bcl-XL; ↑ mitochondrial cytochrome c release; ↑ BAD protein; ↑ caspase-1, caspase-2, caspase-3, caspase-6, caspase-8 & caspase-9 activity; ↑ PARP cleavage	0–100 μM	CH27: 40.9 μM (24 h) H460: 41.4 μM (24 h) H1299: 34.7 μM (24 h)	[17]
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]

Cell Lines		Mechanism of Action	Concentration Used	Efficacy/IC_{50} (Exposure Time)	References
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]
	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 & procaspase-9 Induce G2/M phase cell cycle arrest: ↓ cyclin B1, cyclin D1, cyclin D2 & PCNA; ↓ Cdk2 & Cdk4; ↑ p21 & p53	0–100 μM	N/A	[49]
	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]

Cell Lines		Mechanism of Action	Concentration Used	Efficacy/IC_{50} (Exposure Time)	References
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]
Cervix cancer	KB-3-1, KB-8-5, KB-C1, KB-V1	Inhibit cell viability: ↓ EGFR-STAT3 signalling Induce mitochondria-dependent & death receptor-dependent apoptosis: ↓ Bcl-2, Mcl-1 & survivin; ↑ PARP & caspase-3 cleavage; ↑ mitochondrial release of cytochrome c; ↑ DR5 Enhances in vitro cytotoxicity of Paclitaxel	0–75 μM	KB-3-1: 12.56 μM (72 h) KB-8-5: 12.08 μM (72 h) KB-C1: 11.40 μM (72 h) KB-V1: 10.39 μM (72 h)	[23]
Pancreatic cancer	MiaPaCa & Colo-357	Suppress plating efficiency of cells Reduce anchorage-independent clonogenicity growth Suppress migration and invasion ability	0–5 μM	N/A	[51]
	MiaPaCa & Panc1	Inhibit cell growth Induce G1 phase cell cycle arrest: ↓ cyclin D1 & cyclin E; ↓ Cdk2 & Cdk4; ↑ p21 & p27 Induce apoptosis: ↓ Bcl-2 & Bcl-xL proteins; ↑ Bax protein; ↓ IKB-α phosphorylation; ↓ NF-κB constitutive activation	0–60 μM	MiaPaCa: 43.25 μM (24 h) 31.08 μM (48 h) 18.54 μM (72 h) Panc1: 47.44 μM (24 h) 34.17 μM (48 h) 21.86 μM (72 h)	[52]
Thyroid cancer	ARO, WRO	Inhibit cell growth & proliferation: ↓ ERK, JNK & p37 activation and expression; ↓ mTOR & p70S6K Inhibit colony formation Induce apoptosis: ↑ PARP cleavage; ↑ caspase-3, caspase-8 & PARP activation; ↓ PI3K/AKT & MAPK pathways Induce G0/G1 cell cycle arrest: ↓ cyclin D1; ↓ Cdk2 & Cdk4; ↑ p21 & p27 Induce autophagy & autophagy flux: ↑ LC3-II	ARO & WRO: 0–60 μM SW579: 0–40 μM	ARO: 36.3 μM (24 h) 40.1 μM (48 h) 44.8 μM (72 h) WRO: 37.7 μM (24 h) 31.8 μM (48 h) 30.7 μM (72 h) SW579: 19.9 μM (24 h) 10.5 μM (48 h) 8.8 μM (72 h)	[53]
Nasopharyngeal cancer	HNE-1	Inhibit cell growth Induce apoptosis Induce G1 phase cell cycle arrest	0–150 μM (Honokiol & ATNH—Active targeting nanoparticles-loaded honokiol)	Honokiol: 144.71 μM (24 h) ATNH: 69.04 μM (24 h)	[22]

Cell Lines		Mechanism of Action	Concentration Used	Efficacy/IC_{50} (Exposure Time)	References
Brain cancer	U251	Inhibit cell growth Inhibit cell proliferation Induce apoptosis	0–120 μM	61.43 μM (24 h)	[54]
	T98G	Inhibit cell viability Inhibit cell invasion Induce cell apoptosis: ↑ Bax protein; ↓ Bcl-2; ↑ Bax/Bcl-2 ratio	0–50 μM	N/A	[55]
	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 apoptosis: ↓ Rb protein; ↑ PARP & Bcl-x(S/L) cleavage Induce autophagy: ↑ Beclin-1 & LC3-II	0–50 μM	~30 μM	[57]
	U87 MG (Human) BMEC (Mouse)	Inhibit cell viability Inhibit epithelial-mesenchymal transition (EMT): ↓ Snail, β-catenin & N-cadherin; ↑ E-cadherin Inhibit cell adhesion & invasion: ↓ VCAM-1; ↓ phosphor-VE-cadherin-mediated BMEC permeability	0–20 μM	U87MG: 22.66 μM (24 h) BMEC: 13.09 μM (24 h)	[58]
	U87 MG	Inhibit cell viability Induce G1 phase cell cycle arrest: ↑ p21 & p53; ↓ cyclin D1; ↓ Cdk4 & Cdk6; ↓ p-Rb protein; ↓ E2F1 Induce apoptosis: ↓ procaspase-3; ↑ caspase-8 & caspase-9 activity	0–100 μM	52.70 μM	[59]

Cell Lines		Mechanism of Action	Concentration Used	Efficacy/IC_{50} (Exposure Time)	References
Bone cancer	HOS & U20S	Inhibit cell proliferation Inhibit colony formation Induce G0/G1 phase cell cycle arrest: ↓ cyclin D1 & cyclin E; ↓ Cdk4 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 Induce autophagy: ↑ Atg7 protein activation; ↑ Atg5; ↑ LC3B-II	0–30 μM	HOS: 17.70 μM (24 h) U20S: 21.50 μM (24 h)	[60]
	SAOS-2, HOS, 143B, MG-63 M8, HU09, HU09 M132 Dunn, LM5, LM8 & LM8-LacZ (Mouse)	Inhibit cell metabolic activity Inhibit cell proliferation Inhibit cell migration Induce rapid cell death via Honokiol-provoked vacuolation	0–150 μM	(72 h) SAOS-2: 48.38 μM HOS: 51.38 μM 143B: 41.63 μM MG-63M8: 34.88 μM HU09: 59.25 μM HU09M132: 31.88 μM (72 h) Dunn: 36.00 μM LM5: 30.00 μM LM8: 31.13 μM	[61]
	Saos-2 & MG-63	Inhibit cell viability Induce apoptosis: ↑ caspase-3 & PARP cleavage; ↑ Bax protein; ↓ Bcl-2; ↓ PI3K/AKT signalling pathway; ↓ miR-21	0–100 μM	Saos-2: 37.85 μM (24 h) MG-63: 38.24 μM (24h)	[62]
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 activation; ↑ PARP cleavage Enhance apoptotic effect of doxorubicin & paclitaxel	0–100 μM	N/A	[24]
Ovarian cancer	A2780s & A2780cp	Inhibit cell growth Induce apoptosis	0–100 μM	A2780s: 36.00 μM (48 h) A2780cp: 34.70 μM (48 h)	[66]
	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]
	SKOV3, COC1, Angelen & A2780	Inhibit cell proliferation Induce cell apoptosis: ↓ Bcl-xL; ↑ BAD protein; ↑ caspase-3 activation Induce G1 phase cell cycle arrest	0–93.75 μM	SKOV3: 62.63 μM (24 h) COC1: 73.50 μM (24 h) Angelen: 61.50 μM (24 h) A2780: 55.85 μM (24 h)	[67]

Cell Lines		Mechanism of Action	Concentration Used	Efficacy/IC_{50} (Exposure Time)	References
Prostate cancer	PC-3 & LNCaP	Inhibit cell viability Induce G0/G1 phase cell cycle arrest: ↓ cyclin D1 & cyclin E; ↓ Cdk2, Cdk4 & Cdk6; ↑ p21 & p53; ↓ Rb & E2F1 proteins; ↓ Rb phosphorylation at $Ser^{807/811}$; ↑ ROS generation	0–60 μM	N/A	[68]
	PC-3, LNCaP & C4-2	Inhibit cell growth Induce apoptosis: ↑ caspase-3, caspase-8 & caspase-9 activation; ↑ PARP cleavage Induce apoptosis via DNA fragmentation: ↑ Bax & Bak proteins; ↓ Mcl-1 protein	0–75 μM	18.75–37.50 μM (24 h)	[69]
	PC-3, LNCaP	Inhibit cell viability Induce autophagy: ↑ LC3-BII protein; ↓ mTOR pathway Induce apoptosis via DNA fragmentation: ↑ ROS generation	0–40 μM	N/A	[70]
Head & neck squamous cancer	Cal-33 & MD-1483	Inhibit cell growth Induce cell apoptosis and cell cycle arrest: ↓ EGFR signalling pathway; ↓ STAT3 signalling pathway; ↓ Bcl-xL & cyclin D1; ↓ phosphorylation p42/p44 MAPK & phosphorylated Akt	0–100 μM	Cal-33: 3.80 μM (72 h) 1483: 7.44 μM (72 h)	[71]
Neuroblastoma	Neuro-2a	Induce apoptosis via DNA fragmentation: ↑ caspase-3, caspase-6 & caspase-9 activation; ↑ Bax protein; ↓ mitochondrial membrane potential; ↑ cytochrome c releaseInduce sub-G1 phase cell cycle arrest	0–100 μM	63.3 μM (72 h)	[72]
	Neuro-2a & NB41A3	Inhibit cell viability Induce autophagy: ↑ LC3-II; ↑ PI3K/Akt/mTOR signalling pathway; ↑ Grp78; ↑ ROS generation; ↑ ERK1/2; ↑ p-ERK1Induce apoptosis via DNA fragmentation Inhibit cell migration	0–100 μM	Neuro-2a: ~50 μM (72 h)	[73]
Bladder cancer	T24 & 5637	Inhibit cell viability and induce apoptosis: ↑ Bax protein; ↑ PARP cleavage; ↓ Bcl-2 protein Inhibit clonogenicity Induce G1 phase cell cycle arrest: ↓ cyclin D1; ↑ p21 & p27 Inhibit sphere formation capacity Inhibit cell migration & invasion: ↓ EZH2 gene expression; ↓ MMP9 Inhibit cell stemness: ↓ EZH2 gene expression; ↓ CD44 & Sox2; ↑ miR-143 overexpression	0–72 μM	N/A	[74]

2.2. In Vivo Studies

Based on the in vivo studies, honokiol possessed the capability to inhibit tumour growth, metastasis, and angiogenesis using different animal models, as shown in **Table 2**. The degree of tumour inhibition was shown to be significantly effective against each distinct cancer cell line, ranging from 0–150 mg/kg via various delivery methods of honokiol

between oral gavage or injection (intraperitoneal, caudal vein, or intravenous). Honokiol was shown to downregulate the expression of Oct4, Nanog, and Sox2 which were known to be expressed in osteosarcoma, breast carcinoma and germ cell tumours [34]. According to Wang et al.'s study, they have found that the average tumour size was significantly lower than the control group without affecting their body weight, suggesting 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.

Over the years, the development of chemo-resistance in ovarian cancer cells has hindered the outcome of treatment regimen towards ovarian cancer [75]. Despite the effectiveness of honokiol to inhibit cancer cell proliferation, delivering effective concentration towards the tumour site was deemed challenging due to its water insolubility [66]. The encapsulation of honokiol in liposome, namely Lipo-HNK by Luo and his team has displayed substantial efficacy against cisplatin-resistance ovarian cancer cell line A2780cp. The tumour volume for Lipo-HNK treated mice was 408 ± 165 mm^3 compared to liposome-treated mice and control mice were 2575 ± 701 mm^3 and 2828 ± 796 mm^3 respectively after 21 days [66]. In addition, Lipo-HNK was also shown to prolong survival and induce intra-tumoral apoptosis in vivo. The promising in vivo properties of honokiol should consolidate its importance as a potential anticancer agent for future researches.

Zebrafish (*Danio rerio*) model has emerged as a newly important cancer model that complements against traditional cell culture assays and mice model due to its small size, heavy brood, and rapid maturation time. Importantly, its transparent body wall enables visibility of tumour progression and the ease of experimentation [76][77]. It was known that juvenile zebrafish (*Danio rerio*) or zebrafish embryos have the competency to study cancer cell invasion, metastasis, tumour-induced angiogenesis. Honokiol reduced U-87 MG human glioma/glioblastoma cell proliferation and migration in zebrafish yolk sac and in vivo xenograft nude mouse model [56]. These observations are associated with a reduction in EGFR, phosphorylated STAT3, CD133 and Nestin levels, thus highlighting the regulation of honokiol in EGFR-mediated STAT3/JAK signalling pathway to induce anti-tumour and anti-metastasis.

The subsections below will further discuss the mechanism of anticancer actions of honokiol including the induction of cancer cell death, inhibition of cell cycle progression, induction of autophagy, prevention of epithelial–mesenchymal transition (EMT), as well as the suppression of migration, invasion, and angiogenesis of cancer cells.

Table 2. The antitumour effect of honokiol in in vivo tumour bearing animal models.

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 which was 1.58 g	[33]
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 Reduce number of tumour cells showing Ki-67 & pStat3 expression	[34]
Colorectal cancer					

Cancer Cell Line	Animal Model & Site of Tumour Xenograft	Dose, Duration & Route of Administration	Observation & Mechanism of Action	Efficacy on Tumour Inhibition	References
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 Once a week 28 days IP (honokiol) Tail vein injection (paclitaxel)	Suppress tumour growth: ↓ Ki-67 tissue level Induce apoptosis	Significantly lower average tumour volume for honokiol-paclitaxel combination treatment (573.9 mm^3) compared to control (2585.4 mm^3)	[23]
Lung cancer					
H2030-BrM3 cells	Left ventricle of NOD/SCID mice	2 or 10 mg/kg/day 28 days 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 Five days a week 28 days Oral gavage	Decrease lung tumour growth 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 Treatment on days 8–12 & 15–19 20 days (Route of administration not specified)	Inhibit cell proliferation 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 Treatment on Day 1–6 47 days IP	Prolong survival of mice	Median survival time of honokiol-treated mice are longer (37.5 days) compared to vehicle-treated mice (24.5 days)	[78]
Pancreatic cancer					

Cancer Cell Line	Animal Model & Site of Tumour Xenograft	Dose, Duration & Route of Administration	Observation & Mechanism of Action	Efficacy on Tumour Inhibition	References
MiaPaCa cells	Pancreas of immunocompromised mice	150 mg/kg/day 28 days IP	Suppress tumour growth Inhibit metastasis: ↓ CXCR & SHH; ↓ NF-κB & downstream pathway Inhibit desmoplastic reaction: ↓ 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 Three times a week 14–54 days IP	Decrease tumour growth	SKMEL-2: 40% reduction in tumour volume UACC-62: 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 Every three days 21 days Oral gavage	Decrease tumour volume & tumour weight Induce apoptosis & autophagy	Control: ~1000 mm^3; 700 mg 5 mg/kg Honokiol: ~600 mm^3; 400 mg 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-active-targeting nanoparticles-loaded HK (NATNH), Free Honokiol (HK) 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	Inhibit tumour progression, Induce apoptosis Potential inhibitor of angiogenesis & proliferation	Efficiency in tumour delay: ATNH > NATNH > Free HK Median survival time: Control: 28.5 days Free HK: 34 days NATNH: 42.5 days ATNH: 57.5 days	[22]
		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 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 Treatment at days 1–7 21 days IP	Reduce tumour growth: ↓ EGFR, pSTAT3, CD133 & Nestin	Increased number of apoptotic cells in honokiol-treated tissue, 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 7 days IP	Reduce tumour growth 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) Increased number of TUNEL-positive cells	[18]
LM8-LacZ cells	Left flank of C3H/HeNCrl mice	150 mg/kg/day 25 days; 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 Treatment on day 1, 4, 7, 10, 13, 16, 19, 22 35 days Oral	Reduce tumour growth & volume	Significantly reduction in tumour growth in honokiol-treated mice 29% reduction (5 mg/kg; 21 days), 40% reduction (15 mg/kg; 21 days) 41% reduction (5 mg/kg; 35 days), 56% reduction (15 mg/kg; 35 days)	[18]
Prostate cancer					
C4-2 cells	Bilateral tibia of BALB/c nu/nu athymic nude mice	100 mg/kg/day 42 days IP	Inhibit cell proliferation: ↑ Ki-67 Induce apoptosis: ↑ M-31 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 77 days Oral gavage	Inhibit tumour growth Inhibit cell proliferation Inhibit neovascularisation 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					

Cancer Cell Line	Animal Model & Site of Tumour Xenograft	Dose, Duration & Route of Administration	Observation & Mechanism of Action	Efficacy on Tumour Inhibition	References
MKN45 cells	Dorsal side of BALB/c nude mice (nu/nu)	0.5 mg/kg/day & 1.5 mg/kg/day 10 days Injection (route not stated)	Inhibit tumour growth: ↓ GRP94 overexpression	30% reduction in tumour volume (0.5 mg/kg) 60% reduction in tumour volume (1.5 mg/kg) Decreased accumulation of GRP94	[80]
MKN45 & SCM-1 cells	Peritoneal cavity of BALB/c nude mice	5 mg/kg Twice a week 28 days IP	Inhibit metastasis 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 48 days IP	Inhibit tumour growth 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 Twice a week 21 days IV	Inhibit cancer growth Prolong survival of mice Increase intra-tumoural apoptosis Inhibit intra-tumoural angiogenesis	Lipo-HNK treated mice have significantly smaller tumour volume (222 ± 71 mm^3) compared to liposome-treated mice (1823 ± 606 mm^3) and control mice (3921 ± 235 mm^3)	[66]
A2780cp cells	Right flank of athymic BALB/c nude mice	10 mg/kg Lipo-Honokiol Twice a week 21 days IV	Inhibit cancer growth Prolong survival Increase intra-tumoural apoptosis Inhibit intra-tumoural angiogenesis	Lipo-HNK treated mice have significantly smaller tumour volume (408 ± 165 mm^3) compared to liposome-treated mice (2575 ± 701 mm^3) and control mice (2828 ± 796 mm^3)	[66]

3. Mechanism of Action of Honokiol

3.1. Dual Induction of Apoptotic and Necrotic Cell Death

Apoptosis is a normal physiological process that maintains the homeostatic cellular balance in multicellular organisms [83]. Generally, apoptosis can be classified into two central pathways, namely the intrinsic pathway (mitochondrial-mediated pathway) and extrinsic pathway (death receptor-mediated pathway) [84]. The intrinsic pathway is associated with changes in mitochondrial membrane permeability that lead to imbalance in Bax/Bak ratio and release of cytochrome *c* and other mitochondrial proteins into cytosol [83][84]. The released cytochrome *c* interacts with apoptosis protease-activating factor 1 (Apaf1) and forms an apoptosome complex [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 (type 1 TNF receptor (TNFR1), Fas (also called CD95/Apo-1) and TRAIL receptors will turn procaspase-8 into active caspase-8 to induce apoptosis [85][86][87].

Honokiol has been shown tp initiate caspase-dependent apoptotic pathways in different types of cancer (**Table 1**). Chen et al. [14] found that JJ012 human chondrosarcoma cells lose their mitochondrial membrane potential when treated at 10 μM of honokiol, thus leading to apoptosis. Other studies have also shown that honokiol markedly disrupted the balance of

Bax/Bcl-2 ratio [13][79][26][56][88][89][90][91]. The increasing ratio of proapoptotic to antiapoptotic Bcl-2 family proteins (Bax/Bcl-2) will induce the release of cytochrome *c* and other apoptogenic proteins through the mitochondrial membrane to the cytosol, subsequently leading to the activation of caspase cascade and apoptosis [26]. Furthermore, honokiol downregulated the expression of several other anti-apoptosis mRNA and proteins such as Bcl-xL [13][79][17][57], survivin [60][92], and MCL-1 [79], as well as upregulated other pro-apoptotic proteins such as BAD, BAX, and BAK proteins [79][17].

Moreover, honokiol has been shown to effectively induce apoptosis in p53-deficient cancer cells, such as MDA-MD-231 breast cancer cells, as well as lung and bladder cancer cell lines by inhibiting the activation of ras-phospholipase D [32][93][94]. Besides p53, other tumour suppressor genes that will be activated in honokiol treatment include p21 [46], p21/waf1 [95], p27 [46], p38 MAPK [96][97], and p62 [18][39].

Besides the intrinsic pathway, honokiol is capable of targeting death receptors TNF-related apoptosis-inducing ligand (TRAIL) receptors and tumour necrosis factor receptors (TNFR) resulting in a sequential activation of caspase-8 and -3, which cleaves target proteins and then leads to apoptosis [98][99][100]. Activation of the death receptor mediated apoptotic pathway is primarily inhibited by cellular-caspase-8/FADD-like IL-1β-converting enzyme (FLICE) inhibitory protein (c-FLIP), which inhibits caspase-8 activation by preventing the recruitment of caspase-8 to the death inducing signalling complex [100]. However, honokiol was able to downregulate c-FLIP through the ubiquitin/proteasome-mediated mechanism, resulting in the sensitisation of non-small cell lung cancer cells to TRAIL-mediated apoptosis [101][102].

Other than intrinsic and extrinsic pathways, honokiol can also induce apoptosis by the endoplasmic reticulum (ER) stress-induced mechanism. A variety of ER stresses result in unfolded protein accumulation responses [103][104]. For survival, the cells induce ER chaperone proteins to increase protein aggregation, temporarily halt translation, and activate the proteasome machinery to degrade misfolded proteins. However, under severe and prolonged ER stress, an unfolded protein response activates unique pathways that lead to cell death through apoptosis [105]. According to a study by Zhu et al. [43], honokiol can upregulate the expressions of ER stress-induced apoptotic signalling molecules such as GRP78, phosphorylated PERK, phosphorylated eIF2α, CHOP, Bcl-2, Bax, and cleaved caspase-9 in human lung cancer cells. Chiu et al. [106] found that honokiol also led to an increase in ER stress activity in melanoma cell lines B16F10 (mouse), human malignant melanoma, and human metastatic 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 by another study where treatment of various human gastric cancer cells with honokiol led to the induction of GRP94 cleavage but did not affect GRP78 [80].

Necrosis is known as unprogrammed cell death whereby cell swelling and destabilisation of the cell membrane results in the leakage of cellular cytoplasmic contents into the extracellular space, thus causing inflammation [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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