Pharmacological Research 144 (2019) 192–209

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Honokiol for cancer therapeutics: A traditional medicine that can modulate multiple oncogenic targets

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ARTICLE INFO

Keywords:
Honokiol
Cancer
Phytochemicals
Molecular target
Traditional Chinese Medicine

ABSTRACT

In spite of billions of dollars expended on cancer research every year, the incidence rate and the mortality rate due to this widespread disease has increased drastically over the last few decades. Recent reports from the World Health Organization advocate that overall global cancer burden and deaths due to cancer are expected to double by the next decade. Synthetic drugs developed as chemotherapeutics have repeatedly shown adverse side effects and development of chemoresistance. Cancer is basically a multifactorial disease that necessitates the modulation of multiple targets and oncogenic signaling pathways. Honokiol ($C_{18}H_{18}O_2$) is a biphenolic natural compound isolated from the leaves and barks of *Magnolia* plant species and has been extensively studied for its beneficial effects against several chronic diseases. Honokiol is capable of efficiently preventing the growth of wide variety of tumors such as those of brain, breast, cervical, colon, liver, lung, prostate, skin, and hematological malignancies. Recent work has shown that this phytochemical can modulate various molecular targets such as activation of pro-apoptotic factors, suppression of anti-apoptotic proteins and different transcription factors, downregulation of various enzymes, chemokines, cell surface adhesion molecules, and cell cycle proteins, and inhibition of activity of protein tyrosine kinases and serine/threonine kinases. Because of its pharmacological safety, honokiol can either be used alone or in combination with other chemotherapeutic drugs for the prevention and treatment of cancer. The current review describes in detail the various reports supporting these anti-cancer studies documented with this promising agent.

1. Introduction

The fight with cancer has been waged for several years; however, this frightful disease still remains one of the prime reasons for death globally. The World Health Organization reports that millions of people across the globe are diagnosed with cancer every year. Although the war against cancer is not yet over, people have learnt a great deal about the biology, diagnosis, and prognosis of this disease [1–4]. However, the conventional chemotherapeutics used for the treatment and prevention of cancer are often associated with adverse side effects and development of chemoresistance. Thus, unearthing a novel cure with low cost, minimal side effects, and easy accessibility is of utter importance and requisite for the better management of this life-threatening disease [5–15].

Recently, emphasis has been put on research of traditional medicines that have been used for the prevention and treatment of cancer for hundreds of years. Approximately 70% of the drugs used for the treatment of cancer are either derived from natural products or imitate natural products in one form or another; however, this huge reserve of unidentified phytochemicals and chemotherapeutics agents needs to be further explored [16–33]. Several phytochemicals (*viz.* alkaloids, diterpenoids, flavonoids, polyphenolic compounds, and sesquiterpenes) attained from various medicinal plants, fruits, and vegetables possess immense anti-cancer potential [20,25,34–38]. Furthermore, these

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https://doi.org/10.1016/j.phrs.2019.04.004
Received 21 January 2019; Received in revised form 18 March 2019; Accepted 2 April 2019
Available online 17 April 2019
1043-6618/

phytochemicals acquired from botanicals regulate various molecular targets, which includes regulation of apoptotic and anti-apoptotic proteins, different transcription factors, chemokines, cell surface adhesion molecules, inflammatory enzymes, and activity of protein kinases. Therefore, the holistic approach of traditional medicine is now being assimilated into modern medical systems to complement the flaws of existing conventional medical care [26,39–46].

Traditional Chinese medicines include rich sources of biologically active ingredients that have been commonly used in clinical practices in many countries. Several Chinese herbal formulas and pleiotropic natural products possess potent anti-cancer activity and act by targeting diverse molecular networks involved in the disease. Thus, these herbal formulations are promising candidate drugs that can be developed for the prevention and treatment of cancer [47]. Honokiol (HNKL) is a vital bioactive biphenolic compound found in the bark and leaf extracts of *Magnolia officinalis, Magnolia obovate*, and *Magnolia grandiflora.* It has been extensively used as a folk remedy for centuries in traditional Chinese medicines for the treatment of gastrointestinal disorders, cough, anxiety, stroke, and allergic diseases, and also used as an antithrombotic, anti-depressant, anti-emetic, and antibacterial agent [48–54]. Several *in vitro* and *in vivo* studies over a period of time have proven the efficacy of HNKL to act against tumors of different types, such as lung cancer, prostate cancer, breast cancer, gall bladder cancer, colon cancer, skin cancer, and hepatocarcinoma [55]. The broad aim of this article is to provide an overall framework describing the chemistry, biological activities, molecular targets, and preclinical studies performed with HNKL against different cancers.

2. Chemistry of HNKL

Neolignans are large class of phenols commonly present as a phytochemical in the plant kingdom. HNKL (a phenylpropanoid compound) belongs to the class of neolignans and its synthesis takes place in the shikimic acid pathway. It is characterized by the presence of para-allyl-phenol and an ortho-allyl-phenol, which are joined together with the help of ortho-, para-C-C-coupling. The degree of side chain oxidation and substitution of the aromatic moieties has resulted in the availability of a large number of natural derivatives of HNKL [56–59]. The molecular mass and the monoisotropic mass of HNKL ($C_{18}H_{18}O_2$) are 266.34 g/mol and 266.131 g/mol respectively (Fig. 1). The International Union of Pure and Applied Chemistry (IUPAC) name of HNKL is 2-(4-hydroxy-3-prop-2-enylphenyl)-4-prop-2-enylphenol and it is commonly known as 35354-74-6; 5,3′-Diallyl-2,4′-dihydroxybiphenyl; NSC 293100; 3,5′-Diallyl-4,2′-dihydroxybiphenyl. The melting temperature and boiling point of Honokiol are 86–86.5 °C and 400 °C

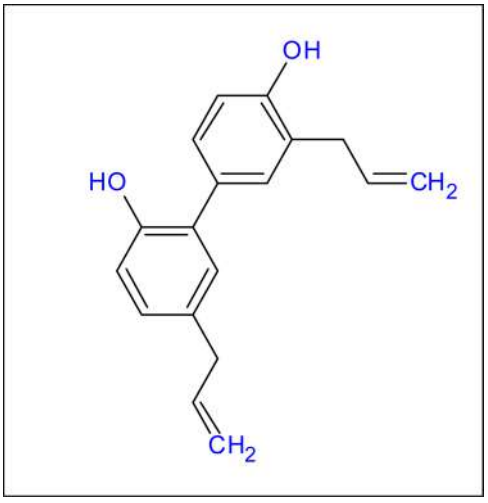

Fig. 1. Structure of Honokiol.

respectively. HNKL is insoluble in water and the heat of vaporization is 67.7 kJ/mol. Furthermore, several derivatives based on the basic structure of HNKL, such as 3-formyl-honokiol, 5-formyl-honokiol, 3,5-diformyl-honokiol, 4-O-Methylhonokiol, H2-P and 3,5-diallyl-2,40-dihydroxy-[1,10-biphenyl]-3,50-dicarbaldehyde, have been developed that possess potent anti-cancer activities [60–63] (Fig. 2). HNKL and its structural analog, magnolol, both possess a fragrant and spicy odor. Aromaticity is common in most of the anesthetics available, such as lidocaine, propofol, and etomidate. However, only propofol has a phenol ring like HNKL, and its structural homology explains its related biological activities [64–67].

3. Biological activities of HNKL

The cones, leaves, and bark of magnolia tree possess different biologically active phytochemicals such as obovatol, magnolol, HNKL, 4-O-methylhonokiol, and other neolignan compounds. HNKL displays a wide range of biological activities such as anti-oxidative [68–70], anti-arrhythmic [71], anti-inflammatory [72], anti-cancer, neuroprotective [72–89], anti-angiogenesis [90,91], anti-thrombocytic [92], anxiolytic [93–96], anti-nociceptive [97], anti-depressant [98,99], anti-spasmodic [100], and gamma-aminobutyric acid (GABA) modulating properties *in vitro* and in preclinical models. It has been also found to exert wide variety of other biological activities such as anti-microbial [101–103], anti-fungal [104], and anti-HIV (human immunodeficiency viruses) [105]. Although several pharmacokinetics studies have established the fact that HNKL acts as a potent anti-cancer agent, this biological activity is yet to be defined clinically [87]. Because of its increasing popularity in modern medical research, several derivatives of HNKL have been synthesized and developed for delivery through oral, intravenous, liposomal, and transdermal preparations [106–108]. Some benefits of HNKL have also been observed in the peri-operative period, not only for its analgesic, anti-microbial, and anxiolytic effects, but for its potent role in oncogenic and neurologic procedures.

4. Molecular targets of HNKL

HNKL exerts its effect on multiple molecular targets that modulate the expression of genes controlling the different hallmarks of cancer (Fig. 3). In addition, it has also been found to be effective in overcoming chemoresistance and displays remarkable chemosensitization ability when used with well-known chemotherapeutics.

4.1. Effect of HNKL on apoptosis

The programmed cell death or apoptosis is an evolutionarily conserved and highly controlled form of cell death that is crucial for homeostasis and development of multicellular organisms. Apoptosis is an important strategy to control the progression of cancer [109–114]. Preclinical studies on different cancer cell lines and animal models have shown that HNKL enhances the expression of pro-apoptotic proteins such as Bcl-2-associated X protein (Bax), BH3 interacting-domain death agonist (Bid), and Bcl-2 homologous antagonist/killer (Bak), and reduces the expression of anti-apoptotic proteins such as B-cell lymphoma protein-2 (Bcl-2) and Bcl-x_L. Furthermore, HNKL also triggers the release of mitochondrial cytochrome c (Cyt-c) to the cytosol and activation of caspase cascades, which play a vital role in apoptosis-mediated cancer cell death and poly (adenosine diphosphate-ribose) polymerase (PARP) cleavage [115–124].

4.2. Effect of HNKL on EGFR signaling

The epidermal growth factor receptor (EGFR) level is found to be frequently deregulated in different types of tumors [125,126]. Mutation or overexpression of EGFR triggers abnormal metabolism, ultimately leading to enhanced cell survival and proliferation [127–132]. HNKL

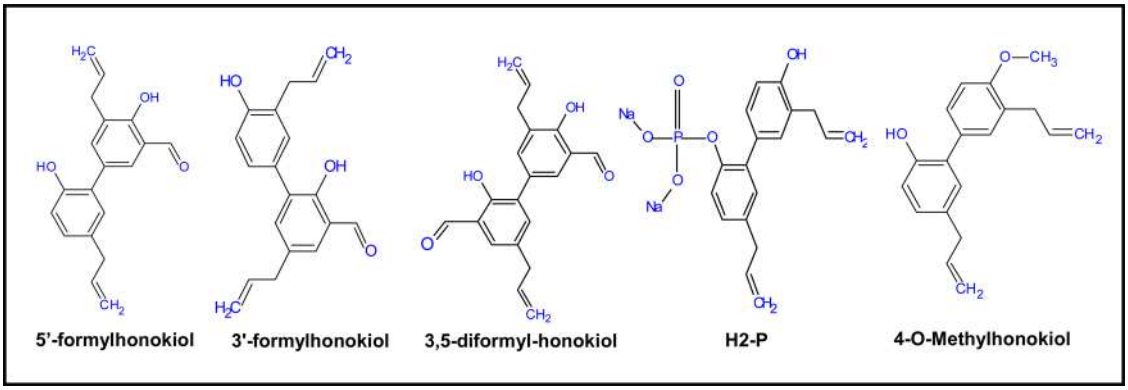

Fig. 2. Different derivatives of Honokiol.

regulates the EGFR signaling pathway *via* inhibition of EGFR expression and its phosphorylation [117,132–134]. HNKL suppresses EGFR expression both in *in vitro* and *in vivo* xenograft mouse models in head and neck squamous cell carcinoma (HNSCC). Molecular docking analysis displayed that HNKL inhibits EGFR and possesses better binding affinity than the clinically applied gefitinib (EGFR tyrosine kinase inhibitor) [133].

4.3. Effect of HNKL on STAT3 activation cascade

STAT3 is a ubiquitously expressed transcription factors regulating the expression of a wide range of genes involved in diverse physiological processes such as differentiation, development, metabolism, immunity and cancer [86]. Receptor tyrosine kinases (RTKs), G-protein-coupled receptors (GPCR), and interleukin (IL) families regulate the expression of signal transducer and activator of transcription 3 (STAT3) oncogene [135,136]. Upon phosphorylation, STAT3 undergoes dimerization and translocation to the nucleus and modulates the action of major downstream proteins involved in tumorigenesis [137–142]. Studies have shown that HNKL can downregulate the expression of STAT3 in both *in vitro* and *in vivo* settings [143,144].

4.4. Effect of HNKL on the mTOR pathway

Various cellular processes such as cell growth, proliferation, and metabolism are controlled by the protein kinase, mammalian target of rapamycin (mTOR). In cancer, the PI3K–Akt pathway gets activated through a variety of molecular mechanisms, which in turn aberrantly activate the mTOR pathway [145–150]. HNKL inhibits the activation of mTOR *via* deregulation of the extracellular signal-regulated kinase (ERK) pathway. Furthermore, HNKL also suppressed the mTOR signaling mediators 4E-BP1 and p70 S6 kinase by enhancing the expression of Phosphatase and Tensin homolog (PTEN). Rapamycin, an inhibitor of mTOR, in combination with HNKL synergistically induced

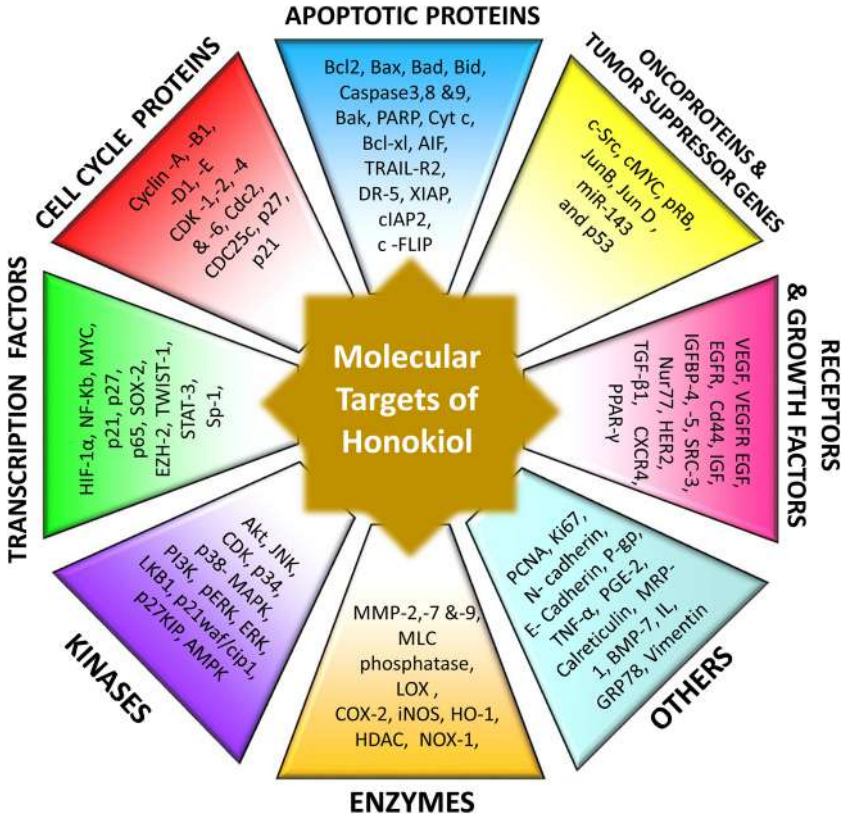

Fig. 3. Various molecular targets modulated by Honokiol treatment.

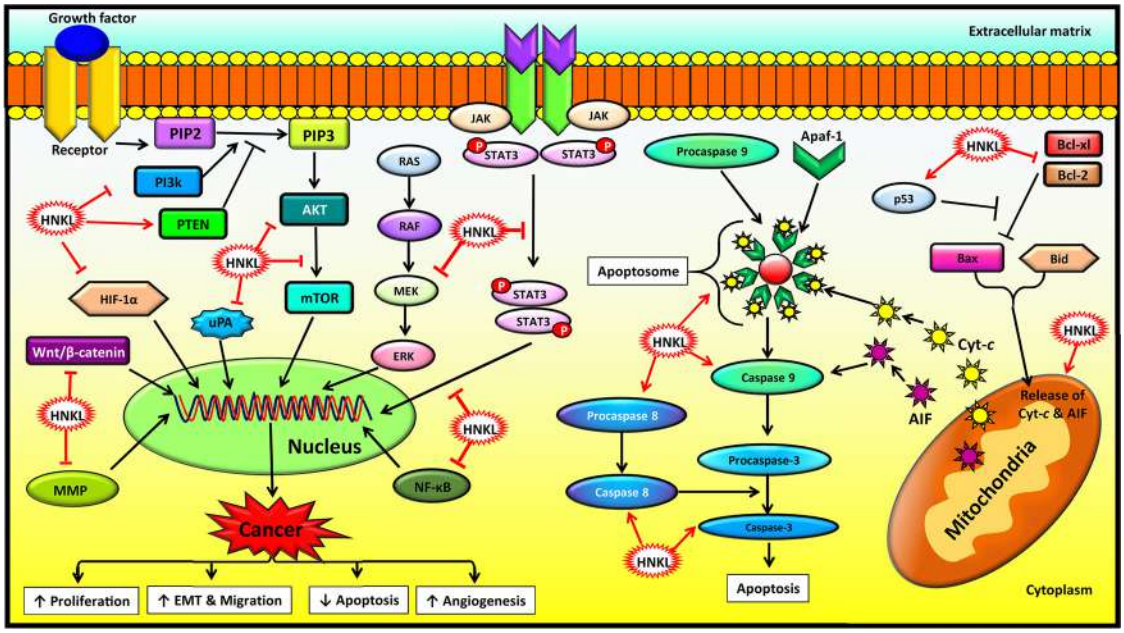

Fig. 4. Honokiol regulates various signaling pathways involved in cancer progression. Honokiol: HNKL; T: Inhibition/Downregulation; T: Inhibition/Downregulation by HNKL; ↑: Upregulation/Activation; ↑: Upregulation/Activation by HNKL.

apoptosis in breast cancer cells [117,151]. In addition, HNKL has also been found to reduce the immunoresistance of breast, glioblastoma, and prostate cancer in *in vitro* settings *via* downregulation of the PI3K/mTOR pathway [152].

4.5. Effect of HNKL on NF-κB signaling

Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) is constitutively expressed in many malignancies and is involved in several physiological processes such as development, differentiation, immunity, metabolism, and in early and late developmental stages of cancer [153–160]. Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα) binds to NF-κB and does not allow its transcriptional activation and translocation to the nucleus [161,162]. HNKL inhibits the activation of IKK (inhibitor kinase), which further does not allow phosphorylation of NF-κB, resulting in reduction of IκBα degradation. Moreover, HNKL can also inhibit NF-κB activation through suppression of the Akt signaling pathway [161,163]. HNKL inhibits invasion, induces apoptosis, and reduces osteoclastogenesis through modulation of the NF-κB pathway [164].

4.6. Effect of HNKL on autophagy

Autophagy is a naturally controlled mechanism of the cell that disassembles unwanted or dysfunctional components which allows orderly degradation and recycling of different cellular components. Autophagy counteracts different malignancies by favoring cancer cell death, making it a promising target for cancer therapy [165,166]. Several preclinical studies have proved the efficacy of HNKL for the induction of autophagy in cancer models. HNKL activates autophagic cell death *via* the reactive oxygen species (ROS)/ERK1/2 and PI3K/Akt/mTOR signaling pathways in human osteosarcoma cells [167,168]. Furthermore, HNKL induces autophagy in KRAS mutant lung cancer cells by regulating the AMPK-mTOR signaling pathway [169]. HNKL induces autophagy of neuroblastoma cells by activation of the PI3K/Akt/mTOR and ERK1/2 signaling pathways [170,171]. All these observations clearly demonstrate that HNKL mediates the induction of autophagy and has a multifaceted impact on the development and progression of tumors.

4.7. Effect of HNKL on cell cycle proteins

Cell-division cycle or the cell cycle, involves a series of events that take place in a cell which causes DNA duplication/DNA replication and organelles and cytoplasmic division to generate two daughter cells. Cell cycle has different checkpoints for the proper regulation and monitoring of the progression of the cell cycle. Various proteins are involved in the progression of the cell cycle [172]. HNKL displays anti-cancer activity by modulating various proteins involved in the cell cycle [69,173]. HNKL suppressed the expression of cyclin-B1, CDC2, and CDC25C, whereas it upregulated the expression of p-CDC2 and p-CDC25 in human gastric carcinoma and human neuroglioma cells [121,174]. Huang K.J. et al., reported that, when exposed to HNKL, human oral squamous cell carcinoma (OSCC) cells demonstrated reduced cell proliferation due to downregulation of cyclin dependent kinase (CDK)-2 and CDK-4 and the upregulation of cell cycle suppressors, p21 and p27; thereby arresting the cell cycle at the G1 stage [175]. Further, treatment of prostate cancer cells with HNKL induced cell cycle arrest at the G0-G1 phase by downregulating the expression of c-Myc [176].

5. Role of HNKL in cancer prevention and treatment

The therapeutic potential of HNKL against different cancers is well evidenced by the enormous amount of preclinical studies that implicate its role in the regulation of the different hallmarks of cancer, *i.e.* survival, proliferation, angiogenesis, invasion, and metastasis (Fig. 4) (Table 1). The effects of HNKL upon the regulatory mechanisms of diverse proteins associated with different malignancies are briefly summarized below.

5.1. Bladder cancer

Bladder cancer or the cancers of the urinary tract affect both males and females, and in males, its frequency is four times higher compared to females [177]. Zhang Q, et al., reported that treatment of urinary bladder cancer cells with HNKL inhibited their cell proliferation, survival, migration, and invasion by reducing the expression of matrix metalloproteinase (MMP)-9, CD44, Sox2, and Enhancer of Zeste

Table 1
Honokiol and its mechanism of action against different cancers.

Cancer	*In vitro/ In vivo*	Mechanism of action	Reference
Bladder cancer	*In vitro*	↓MMP9, CD44, Sox2, EZH2	[178]
	In vivo	↓Tumor growth, tumor stemness	[178]
	In vitro	↑E-cadherin, ↓SRC-3, MMP-2, Twist1, N-cadherin	[179]
Breast cancer	*In vitro*	↑LKB1, ↓STAT3	[183]
	In vitro	↓Cell growth	[184]
	In vitro	↑Apoptosis, cell cycle arrest	[185]
	In vivo	↑Apoptosis	[185]
	In vitro	↓P-glycoprotein	[186]
	In vitro	↑Apoptosis, ↓TNF-α, Nur77	[115]
	In vitro	↓STAT3, ↑E-cadherin	[143]
	In vitro	↑LKB1, miR-143, ↓Wnt1, β-catenin	[187]
	In vitro	↑Apoptosis, DNA fragmentation	[116]
	In vitro	↑Apoptosis, necrosis ↓Chemoresistance	[189]
	In vitro	↑LKB1, pAMPK ↓Metastasis, cell proliferation	[190]
	In vitro	↓Metastasis, NO, COX-2, PGE2	[191]
	In vitro	↓Cell growth, PI3K	[152]
	In vitro	↓c-Src, EGFR, CDK-4, &-2, Akt, pRb, cyclin-D1&-E, c-Myc, Bcl-2 ↑Cleavage of PARP, caspase-3,-8 & -9, Bid	[117]
	In vitro	↓PLD↑Apoptosis	[192]
	In vitro	↓PI3K, Akt, mTOR, EGFR2, HER-2, erbB2, c-erbB2, cyclin-D1,-E, CDK-2, c-myc	[151]
	In vivo	↓Tumor growth ↑apoptosis	[118]
	In vitro	↓MUC1, MRP1	[193]
Colon cancer	*In vitro*	↑Apoptosis	[195]
	In vitro	↑Apoptosis	[119]
	In vitro	↑BMP 7, p53	[196]
	In vitro	↓Notch	[197]
	In vivo	↓HIF-1α, tumor growth	[198]
	In vitro	↓Calreticulin	[199]
	In vivo	↓Tumor growth	[199]
	In vitro	↓Survivin, ↑apoptosis, p53	[200]
	In vivo	↓Tumor growth	[201]
	In vitro	↑Caspase-3, ↓COX-2, PGE2, VEGF phosphorylation of Akt, ERK1/2, NF-κB	[202]
	In vitro	↓γ-secretase, Notch	[203]
	In vitro	↓cyclin- A1, -D1	[204]
	In vitro	↓Radioresistance	[205]
	In vivo	↓Tumor growth, Metastasis	[206]
	In vitro	↑Apoptosis	[206]
Gastric cancer	*In vitro*	↑Apoptosis, ↓GRP94	[120]
	In vivo	↓Tumor growth	[120]
	In vitro	↑LOX, ↓PPAR-gamma, COX-2	[210]
	In vivo	↑LOX, ↓PPAR-gamma, COX-2	[210]
	In vitro	↑SHP-1, STAT-3 dephosphorylation	[211]
	In vivo	↓Tumor growth	[212]
	In vitro	↑Apoptosis ↓vimentin, Snail, Tpl2	[212]
	In vitro	↑p53, p21, Bax ↓cyclin-B1, CDC2, CDC25C, Bcl-2	[121]
Glioblastoma	*In vitro*	↑Apoptosis	[170]
	In vivo	↑Apoptosis	[170]
	In vitro	↑Autophagy, ROS ↓PI3K/Akt pathway	[214]
	In vitro	↑Apoptosis, cell cycle arrest caspase-8,-9,&-3 activation, p21 p53phosphorylation ↓ CDK-6,-4, cyclin-D1, pRb, E2F1	[215]
	In vivo	↓Tumor growth	[73]
	In vitro	↑Apoptosis, Bax, Ca^{2+}	[216]
	In vitro	↓ICAM-1, VCAM-1, Bcl-2 ↑Apoptosis, Bax	[217]
	In vitro	↑Apoptosis, PARP, Bcl-x_L ↓Rb protein	[218]
	In vitro	↑Apoptosis, p38 MAPK, Cell cycle arrest ↓STAT3 signaling	[219]
	In vitro	↑Apoptosis, Ca^{2+}	[220]
	In vitro	↓PI3K/mTOR pathway	[152]
	In vitro	↓Notch3, ↑Apoptosis	[221]
	In vitro	↑Apoptosis, cleavage of caspase-3 DNA fragmentation, cell cycle arrest at G1 phase	[222]
	In vitro	↑Apoptosis ↓cell proliferation	[223]
Kidney cancer	*In vitro*	↓Metastasis	[236]
	In vivo	↓Tumor, growth metastasis	[237]
	In vivo	↓HO-1, VEGF & tumor growth	[238]
	In vivo	↓Tumor growth & c-Met, HO-1	[239]
	In vitro	↓IL-1β, IL-18, TNF-α, PGE2, NO, &TGF-β1	[240]
	In vitro	↓metastasis↑RhoA/ROCK/MLC	[241]
	In vitro	↓mTOR signaling	[147]
Leukemia	*In vitro*	↑Anti-proliferative	[242]
	In vitro	↑Anti-proliferative	[243]
	In vitro	↑DNA fragmentation	[244]
	In vitro	↑p27 (Kip1)	[246]
	In vitro	↓AML1-ETO	[248]
	In vivo	↓AML1-ETO	[248]
	In vitro	↑Apoptosis, Bax, Bak & survivin ↓Bcl-2 and XIAP	[249]
	In vitro	↑SHP1 ↓STAT3	[250]
	In vitro	↑caspase-3,-8,-9 & Cleavage of PARP	[251]
	In vitro	↑Cell cycle arrest at G0/G1, p53, p21, caspase-3, -9, Bax ↓cyclin-D1,-A & E, CDK-2,-4 &-6, Bcl-2, Bcl-x_L	[252]
	In vitro	↓cyclin-D1,-D2,-E, CDK-2, C4 &- 6 and c-Myc, cIAP-2, XIAP, survivin, JunB, JunD ↑Apoptosis, cell cycle arrest, caspases-3 &-9	[123]
	In vitro	↓class I HDACs ↑Apoptosis	[253]
	In vitro	↑Paraptosis, ROS	[124]
	In vitro	↓Angiogenesis, VEGF, VEGFR1, MMP-9	[254]
	In vitro	↑paraptosis, apoptosis	[255]
	In vitro	↑Necrosis, CypD	[256]
Liver cancer	*In vitro*	↓Cell proliferation, STAT3 , c-Src kinases, JAK1 ↑SHP-1	[144]
	In vitro	↑Apoptosis, MAPK, caspase-3 Cyt-c, ↓Bcl-x_L, Bcl-2	[262]
	In vitro	↓Metastasis, EGFR	[263]
	In vivo	↓Metastasis, EGFR	[263]
	In vitro	↑Cell cycle arrest at G0/G1 phase, p21, ↓cyclin D1, E1	[264]
Lung cancer	*In vitro*	↓Metastasis, c-FLIP	[266]
	In vitro	↓p-EGFR, p-Akt, p-STAT3	[267]
	In vivo	↓p-EGFR, p-Akt, p-STAT3 & tumor growth	[267]
	In vitro	↑Cell apoptosis ↑TRAIL-R2 (DR5), Bax caspase-3, & cleaved PARP	[268]
	In vitro	↑Cell death & Autophagy	[269]
	In vitro	↑Apoptosis ↓proliferation	[206]
	In vivo	↓Tumor growth, angiogenesis ↑Apoptosis	[206]
	In vitro	↑Cell cycle arrest at G1-S & apoptosis ↓Cell proliferation	[270]
	In vivo	↓mitochondrial function	[270]
	In vitro	↓COX-2, PGE2, β-catenin MMP-2 & 9, NF-κB/p65	[271]
	In vitro	↑Cell cycle arrest at G1 ↓cyclin-D1,-D2, CDKs & HDACs	[272]
	In vitro	↑Cell cycle arrest at G0-G1 phase ↓CDK-1, cyclin B1	[273]
	In vivo	↓Metastasis & angiogenesis	[274]
	In vitro	↓Lyn Kinase ↑Apoptosis	[275]
	In vivo	↓Tumor growth & metastasis STAT3 Activation	[276]
	In vitro	↑Autophagy, Apoptosis & cell cycle arrest at G1	[169]

(*continued on next page*)

Table 1 (*continued*)

Cancer	*In vitro/ In vivo*	Mechanism of action	Reference
	In vitro	↓pAkt, Erk1/2 & EGFR signaling Hsp90 client proteins ↑Autophagy	[277]
	In vivo	↓pAkt, Erk1/2, Hsp90 client proteins	[277]
	In vitro	↓c-FLIP ↑TRAIL	[278]
	In vitro	↑Apoptosis, caspase-3, Cyt.c	[74]
	In vivo	↑Apoptosis, anti-tumor	[279]
	In vivo	↓Metastasis, angiogenesis	[91]
	In vitro	↓CDK-2, -4, cyclin-E, - D1 ↑Apoptosis, PARP cleavage, caspase-3 ↓Tumor growth	[173]
Lymphoma	*In vitro*	↑ROS ↓NF-κB	[280]
	In vitro	↑Apoptosis, caspase-8, Bad	[281]
	In vitro	↑Apoptosis, Cell cycle arrest at G0/G1 Phase ↓Bcl-2	[282]
Multiple myeloma	*In vitro*	↑Cytotoxicity, AIF activation of caspases-3,-7,-8,&-9	[283]
	In vivo	↑Cytotoxicity, AIF activation of caspases-3,-7,-8,&-9	[283]
Nasopharyngeal carcinoma	*In vitro*	↓Cell proliferation ↑cell cycle arrest at G1	[233]
	In vivo	↓Tumor growth	[233]
Oral cancer	*In vitro*	↓Sp1, p27, p21, Mcl-1, survivin ↑Apoptosis, p27, p21	[228]
	In vitro	↓Wnt/β-catenin, c-Myc, cyclin-D1, survivin, Bcl-2 ↑apoptosis, caspase-3	[229]
	In vitro	↑DNA fragmentation, apoptosis	[227]
	In vitro	↑Apoptosis	[89]
	In vitro	↓iNOS & ERp44 ↑Apoptosis	[122]
	In vitro	↑anti-proliferative	[133]
	In vitro	↓CDK-2,-4 ↑p21, p27	[175]
	In vivo	↓Tumor growth	[230]
	In vitro	↑Apoptosis	[230]
	In vitro	↓JAK2/STAT3 signaling	[231]
Ovarian cancer	*In vitro*	↑cytotoxicity	[287]
	In vitro	↑Apoptosis, ↓cell proliferation	[288]
	In vivo	↓Tumor growth	[288]
	In vitro	↑Chemotherapy efficacy	[290]
	In vivo	↑Apoptosis	[291]
Osteosarcoma	*In vitro*	↑Cell death, cell proliferation	[285]
	In vivo	↓Metastasis	[285]
	In vitro	↑Apoptosis, Autophagy, GRP-78 ROS, & Cell cycle arrest at G0/G1 phase	[167]
	In vitro	↓miR-21, PI3K/Akt, Bcl-2 ↑Apoptosis, Cleavage of caspase -3 PARP, Bax	[286]
	In vivo	↓miR-21, PI3K/Akt, Bcl-2 ↑Apoptosis, Cleavage of caspase -3 PARP & Bax	[286]
	In vitro	↑Apoptosis, LC3II protein Bcl-2-like protein 4, caspase-3, p53 ↓PI3K, p-Akt, p-mTOR, cyclin D1	[168]
Pancreatic cancer	*In vitro*	↓SHH, CXCR4	[293]
	In vivo	↓Tumor growth, metastasis & desmoplasia	[293]
	In vitro	↑Cell cycle arrest at G1, p21, p27, Bax ↓cyclin-D1,-E, CDK-2, -4, NF-κB	[294]
Prostate cancer	*In vitro*	↑Apoptosis, caspases-3,-8 & -9 PARP cleavage	[299]
	In vitro	↓c-Myc ↑arrest cell cycle at G0-G1	[176]
	In vivo	↓Tumor growth ↑ Apoptosis	[300]
	In vitro	↓Cell viability, AR activity	[301]
	In vitro	↑Autophagy, ROS	[302]
	In vivo	↓LC3BII	[302]
	In vitro	↑T cell immunotherapy ↓PI3K/mTOR signaling	[152]
	In vitro	↑cell cycle arrest at G0-G1 ↓pRb, E2F1, CDK -4&-6, cyclin-D1&-E	[303]
Skin cancer	*In vitro*	↑Apoptosis, cell cycle arrest ↓cell viability, proliferation	[305]
	In vivo	↓Tumor growth	[305]
	In vitro	↑Apoptosis, caspase activation & Cyt-c release↓cyclin-D1, mTOR, γ-secretase & Akt phosphorylation	[306]
	In vitro	↑Apoptosis, cell cycle arrest& Cyt-c release↓cyclin-D1, mTOR, γ-secretase & Akt phosphorylation	[307]
	In vitro	↑Apoptosis ↓Notch-2 signaling & proliferation	[308]
	In vitro	↑p-AMPK	[309]
	In vivo	↑p-AMPK	[309]
	In vitro	↑p-AMPK	[310]
	In vivo	↑p-AMPK	[310]
	In vivo	↓tumor growth	[311]
	In vitro	↑Apoptosis	[311]
	In vitro	↑Apoptosis, cell cycle arrest p21, p27& DNA fragmentation ↓cyclin-D1,-D2 &-E & CDK-2,-4,-6	[312]
	In vivo	↓cyclin-D1,-D2 &-E, CDK-2,-4,-6 , p-Akt, COX-2, PGE-2, PCNA, PI3K, TNF-α, IL-1β & IL-6 ↑Cip/p21, Kip/p27	[313]
	In vitro	↑Apoptosis ↓cell viability	[314]
	In vivo	↓Tumor growth	[315]
	In vitro	↓Nox1	[316]
	In vivo	↓Metastasis	[316]
Thyroid cancer	*In vitro*	↑Apoptosis & cell cycle arrest	[317]
	In vivo	↑Apoptosis & cell cycle arrest ↑Cellular cytotoxicity	[317] [318]

Homologue2 (EZH2), and inducing the expression level of tumor suppressor miR-143. Similar effects were also observed in a T24 tumor xenograft animal model upon treatment with HNKL, accompanied by suppression of tumor growth and tumor stemness [178]. Furthermore, HNKL inhibited metastasis and epithelial-mesenchymal transition (EMT) in urinary bladder cancer through downregulation of expression of steroid receptor coactivator-3 (SRC-3), MMP-2, Twist1, and N-cadherin, and upregulation of E-cadherin [179].

5.2. Breast cancer

Breast cancer is the foremost cause of cancer-related death among women. The incidence and mortality due to breast cancer is increasing at an alarming rate [180–182]. *In vitro* and *in vivo* models of breast cancer demonstrated that HNKL had anti-proliferative and anti-tumor effects by increasing the expression of Liver kinase B1 (LKB1) and inhibition of STAT3 [183]. Godugu C. et al., reported that HNKL nanomicellar formulation (size range of 20–40 nm) displayed potent anticancer effects against highly aggressive triple negative breast cancer cells both in *in vitro* and the *in vivo* settings [184]. Moreover, HNKL treatment induced massive cellular apoptosis and cell cycle arrest *in vitro* and profound tumor regression *in vivo* [185]. HNKL reduced multidrug resistance by downregulation of P-glycoprotein (P-gp) in MCF-7/ADR breast cancer cells [186].

Xie L. et al., identified that HNKL treatment has the ability to induce apoptosis by inhibiting tumor necrosis factor alpha (TNF-α)-induced Nur77 expression in breast cancer cells [115]. Avtanski D.B. et al., demonstrated that treatment with HNKL diminished EMT by targeting STAT3/Zeb1/E-cadherin in breast cancer in both *in vitro* and *in vivo* models [143]. Further, the same group of scientists revealed that HNKL inhibited leptin induced cancer cell proliferation through upregulation of LKB1 and miR-34a expression, and downregulation of the Wnt1-MTA1-β-catenin signaling pathway [187,188]. HNKL treatment induced apoptosis and augmented DNA fragmentation in highly invasive MDA-MB231 breast cancer cells [116]. Furthermore, HNKL reduced chemoresistance and enhanced apoptosis and necrosis in multidrug

resistant breast cancer cells [189].

Two different studies conducted by two different groups of scientists revealed that HNKL inhibits metastasis in breast cancer cells and increases cell death by increasing LKB1 expression and AMP-activated protein kinase (AMPK) phosphorylation, and reduces the levels of nitric oxide (NO), cyclooxygenase-2 (COX-2), and prostaglandin (PG) E2 [190,191]. HNKL treatment augmented T cell-mediated cancer immunotherapy through downregulation of the PI3K/mTOR pathway in breast cancer cells [152]. Another study conducted by Park E.J. et al., demonstrated that HNKL downregulated the expression of c-Src, c-Myc, EGFR, Akt signaling, CDK-2,-4, cyclin-D1, cyclin-E, and phosphorylation of retinoblastoma protein (pRb). It further induced apoptosis by diminishing the level of Bcl-2, enhancing PARP cleavage and activation of caspase-3, -8, and -9, upregulation of Bid and DNA fragmentation, which ultimately triggered apoptosis and cell cycle arrest in MDA-MB231 breast cancer cells [117]. HNKL treatment downregulated the phospholipase D (PLD) level and promoted apoptosis [192]. HNKL in combination with lapatinib or rapamycin showed a decrease in EGFR2, HER-2, erbB2, c-erbB2 expression level. It further attenuated PI3K/Akt/mTOR cell signaling by reducing the phosphorylation of Akt and upregulation of PTEN, and promoted G1-phase cell cycle arrest by downregulating cyclin-D1, -E, CDK-2, as well as c-myc and induction of caspase dependent apoptosis in different breast cancer cell lines [151]. *In vivo* studies showed HNKL treatment in combination with Adriamycin decreased tumor growth and induced apoptosis [118]. Further, HNKL displayed chemosensitizing ability by increasing the efficacy of doxorubicin through suppression of Mucin 1(MUC1) and multidrug resistance proteins (MRP1) in mammary carcinoma cells [193].

5.3. Colon cancer

According to the global cancer statistics 2012, colorectal cancer is the third most common malignancy occurring globally, with a five year survival less than 10% in the advanced stage of disease [194]. HNKL showed potent anti-cancer activity *in vitro* and *in vivo* where it induced apoptosis in the treated colon cancer cells [195]. In another study using colorectal carcinoma RKO cells, treatment with HNKL showed increased apoptosis through activation of caspase independent of p53 [119]. Interestingly, HNKL showed anti-cancer activity in the human colon cancer cell line HCT116 by upregulation of expression of bone morphogenetic protein (BMP)-7 and activation of p53 [196]. A reverse engineering logic-based method and published western blot data analysis study conducted by Wynn M.L. et al., demonstrated that HNKL exhibited its effect by inhibiting the Notch signaling pathway in SW480 colon cancer cells [197]. Lan K.L. et al., reported that HNKL acts as an inhibitor of Hypoxia-inducible factor-1α (HIF-1α), which ultimately leads to a reduction in tumor growth [198]. Studies conducted on both *in vitro* and *in vivo* models of colon cancer indicated that HNKL treatment promoted endoplasmic reticulum (ER) stress and led to downregulated expression of calreticulin, which eventually caused regression of tumor progression and metastasis [199].

Furthermore, Lai Y.J. et al., reported that HNKL mediated its anticancer effects by decreasing the concentration of survivin protein and increasing the expression of p53 [200]. Diverse chemosensitization and radiosensitization effects of HNKL have been studied and it was found that HNKL enhances the therapeutic potential of different drugs and radiotherapy. For instance, Cheng N. et al., demonstrated that *in vivo* treatment with liposomal HNKL along with cisplatin synergistically inhibited the proliferation of CT26 cells *via* apoptosis and inhibited subcutaneous tumor growth [201]. Likewise, the combination of HNKL and oxaliplatin treatment increased the expression of caspase-3, decreased the level of COX-2, prostaglandin E2 (PGE2), and vascular endothelial growth factor (VEGF), and inhibited phosphorylation of Akt, ERK1/2, NF-κB, and p65 in HT-29 cells [202]. HNKL, along with ionizing radiation, potentially inhibited the growth of colon cancer tumor stem cells by inhibiting the formation of the γ-secretase complex and inhibiting the Notch signaling pathway [203].

Moreover, He Z. et al., in 2011, demonstrated that HNKL improved radiosensitization of HCT116 cell line (which has a mismatch repair system mutation) by increasing p53 phosphorylation and decreasing the expression of cyclin-A1 and -D1 proteins [204]. A different study conducted by the same group of scientists showed that HNKL enhanced radiosensitization and decreased the radioresistance developed in patients with colorectal cancer [205]. HNKL in combination with gene therapy displayed enhanced apoptosis in the *in vitro* setting and regression in tumor growth and reduced metastasis in the *in vivo* setting [206].

5.4. Gastric cancer

Gastric cancer is the third leading cause of cancer-related deaths in the world [207–209]. *In vitro* studies on human gastric cancer cell lines AGS, MKN45, N87, and SCM-1 demonstrated that HNKL induced apoptosis by cleavage of glucose-regulated protein-94 (GRP-94) by calpain protein (m-calpain), and as a consequence, it affected the expression and the effect of GRP94 in tumor progression. Moreover, *in vivo* studies on a MKN45 xenograft mice model treated with HNKL displayed a significant reduction of tumor growth and development [120]. Liu S.H. et al., demonstrated that HNKL augmented the expression of 15-lipoxygenase (LOX)-1 and enhanced production of 13-S-hydroxyoctadecadienoic acid, which in turn resulted in deregulation of proteins involved in tumor growth, such as peroxisome proliferator-activated receptor-gamma and COX-2 in gastric cancer cells and a xenograft tumor mice model [210]. In another study, treatment with HNKL against human gastric tumor cells in a xenograft mice model showed inhibition of peritoneal dissemination and angiogenesis [211]. In addition, HNKL promoted dephosphorylation of STAT-3, which significantly reduced its DNA binding efficacy that is coordinated *via* upregulation of Src homology 2 (SH2)-containing tyrosine phosphatase-1 (SHP-1) expression [211].

In vivo studies carried out by Pan H.C. et al., showed HNKL promoted anti-tumor activity along with a decrease in peritoneal dissemination and organ metastasis of orthotopically implanted MKN45 cells in a mouse model. Further, it was also concluded that HNKL could enhance apoptosis induced by ER stress and reduce the expression of vimentin, snail, and tumor progression locus 2 (Tpl2), which inhibited EMT in HNKL treated gastric tumor cells [212]. Yan B. et al., reported that HNKL induced apoptosis and cell cycle arrest by activation and upregulation of p53 and p21, and notably increasing the expression of the pro-apoptotic protein Bax. At the same time it also downregulated the expression of cyclin-B1, CDC2, CDC25C, and increased the expression of the pro-apoptotic Bax level and reduced the anti-apoptotic protein Bcl-2 level [121].

5.5. Glioblastoma

Brain cancer constitutes approximately 2% of all cancer cases in the world [213]. Preclinical investigations on the effects of HNKL on human glioma using *in vitro* and *in vivo* models revealed that HNKL mediated its anti-tumor effects *via* induction of autophagy [170]. Moreover, HNKL induced autophagy in U87 MG by ROS production and downregulated the expression of PI3K, p-Akt, and p- mTOR in the *in vitro* and *in vivo* setting [214]. The same group showed that HNKL inhibited human glioma growth in both *in vitro* and *in vivo* models by induction of apoptosis and cell cycle arrest by increasing the expression levels of caspase-8, -9, and -3, p21, activation of p53 phosphorylation, and suppressing the levels of CDK-4, -6, cyclin-D1, pRB, and E2F1 [215]. HNKL displayed potent anti-tumor activity as depicted by the *in vivo* studies using an intracerebral gliosarcoma model and human U251 xenograft glioma murine model [73]. Lin J.W. et al., reported that HNKL can cross the blood brain barrier and promote apoptosis in neuroblastoma cells by increasing the release of calcium from

mitochondria and augmenting the expression of Bax protein [216]. An *in vitro* study on T98G human glioblastoma cells showed HNKL's potent anti-cancer effect *via* downregulation of expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and anti-apoptotic protein Bcl-2, and upregulation of pro-apoptotic protein Bax [217]. Chang K.H. et al., reported apoptosis mediated cell cytotoxicity in the glioblastoma multiforme (GBM) cell line, as evidenced by decreased expression of Rb protein and an upsurge of PARP cleavage and Bcl-x_L [218].

Furthermore, Zhang Y. et al., showed HNKL induced cell cycle arrest and apoptosis in glioblastoma cells by inhibition of STAT3 signaling and activation of p38 MAPK mediated apoptosis [219]. Enhanced release of Ca^{2+} from the ER can induce apoptosis in human glioma cancer cells following treatment with HNKL [220]. Different studies have shown the chemosensitization potential of HNKL against glioblastma. HNKL treatment augmented T cell-mediated cancer immunotherapy through downregulation of the PI3K/mTOR pathway [152]. In addition, HNKL eliminated the cancer stem-like cells and potentiated temozolomide sensitivity in GBM cells through enhanced apoptosis *via* downregulation of Notch3 expression [221]. Following treatment with HNKL, Temozolomide (TMZ) drug-sensitive and tolerant glioma cells exhibited an increase in apoptosis by caspase-3 activation, DNA fragmentation, and cell-cycle arrest at the G1 phase [222]. HNKL in combination with lauroyl-gemcitabine (Gem-C_{12}) chemotherapy against GBM showed a reduction in cell proliferation and increase in cell death mediated through apoptosis [223]. Crane C. et al., reported that HNKL improved the T cell-mediated cancer immunotherapy in glioma without affecting critical pro-inflammatory T cell functions *via* decreasing the activity of the PI3K/mTOR pathway [152].

5.6. Head and neck squamous cell carcinoma

The incidence of HNSCC is increasing at a very rapid rate with every passing year and with very poor prognosis [224–226]. HNKL promoted DNA fragmentation and inhibition of cell proliferation, and increased cell death by amplifying the level of apoptosis in OSCC cells and HNSCC cell lines [89,133,227]. Two different studies showed that HNKL induced apoptosis-mediated cytotoxicity in different OSCC cell lines. In a former study, Kim D.W. et al., demonstrated that HNKL induced apoptosis by inhibition of transcription factor specificity protein 1 (Sp1), upregulation of p27 and p21 expression, and downregulation of Mcl-1 and survivin in HN-22 and HSC-4 cell lines [228]. Growth inhibitory and apoptotic effects were also observed in the latter investigation on SAS cells upon treatment with HNKL, where it was found to involve the inhibition of the Wnt/β-catenin signaling pathway, downregulation of c-Myc, cyclin-D1, Survivin, and Bcl-2, and upregulation of cleaved caspase-3 expression [229].

Furthermore, treatment of OSCC cell lines with HNKL induced apoptosis and decreased the expression of inducible NO synthase (iNOS) and ER resident protein 44 (ERp44) [122]. Likewise, *in vitro* and *in vivo* models of OSCC displayed downregulated expression of CDK-2 and -4, and upregulated expression of p21 and p27,resulting in cell cycle arrest following treatment with HNKL [175]. The combination of HNKL and 5-Fluorouracil (5-FU) synergistically stimulated apoptosis and enriched the clinical therapeutic efficacy of 5-FU without its toxicity both *in vitro* and *in vivo* [230]. In an *in vitro* study using SAS, OECM-1, and cancer stem cell-like side population (SP) cells showed induction of apoptosis *via* Bax/Bcl-2 and caspase-3-dependent pathway, and suppression of JAK2/STAT3, Akt, and ERK signaling pathways upon treatment with HNKL. Furthermore, in the SAS SP xenograft model, HNKL inhibited the survival or proliferation signaling pathways as well as angiogenesis [231]. Cetuximab-resistant HNSCC patient-derived xenografts (PDX), upon treatment with the combination of Cetuximab and HNKL, exhibited a significantly reduced tumor growth by downregulation of active MAPK, Akt, and dynamin-related protein (DRP)-1 signaling [232]. HNKL loaded nanoparticles inhibited tumor growth and proliferation and promoted cell-cycle arrest at the G_1 phase in nasopharyngeal carcinoma [233].

5.7. Kidney cancer

Renal carcinoma comprises of tumors arising from the renal pelvis and renal parenchyma [234,235]. Studies have shown that HNKL potentially suppresses invasion, metastasis, and colony formation of 786-0 renal cell carcinoma cells *via* targeting Kisspeptin (KISS)1/KISS1R signaling [236]. Furthermore, Li W. et al., demonstrated that A-498 cell line upon treatment with HNKL regulated the miR-141/ZEB2 signaling, which in turn assisted in dual-blocking EMT and cancer stem cell properties, and ultimately triggering inhibition of cancer metastasis. Additionally, subcutaneous injection of HNKL into BALB/c nude mice resulted in significant inhibition of tumor growth and size by decreasing the expression levels of ZEB2, vimentin, and fibronectin, and increasing the expression of E-cadherin [237]. Calcineurin inhibitors (CNI) such as cyclosporine A used as an immunosuppressant for avoiding allograft rejection, promotes renal tumor growth *via* induction of proto-oncogene Ras, VEGF signaling, and overexpression of cytoprotective enzyme heme oxygenase 1(HO-1). However, HNKL reverted the effects of cyclosporine A and inhibited its activities by repressing Ras-mediated survival of 786-0 and Caki-1 cancer cells through the suppression of VEGF and HO-1 [238].

Another recent study on the effect of HNKL on CNI-induced renal cancer revealed that HNKL significantly decreased c-Met phosphorylation and Ras activation and inhibited the expression of both c-Met- and CNI-induced HO-1, and ameliorated cancer cell apoptosis in the *in vitro* setting. It also displayed regression of tumor growth *via* downregulation of phospho-c-Met and HO-1 and scaling down the blood vessel density in the *in vivo* setting [239]. HNKL is also responsible for the marked inhibition of high glucose-induced expression of inflammatory cytokines such as interleukin (IL)-1β, IL-18, TNF-α, PGE2, NO, and transforming growth factor (TGF)-β1, and chemokines such as monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, and regulated on activation, normal T cell expressed and secreted (RANTES) in a dose-dependent manner in human renal mesangial cells [240]. Cheng S. et al., reported that treatment of 786-0 renal cancer cells upon with HNKL diminished the migration of highly metastatic cells through activation of RhoA/Rho-associated protein kinase (ROCK)/myosin light chain (MLC) signaling pathways [241].

5.8. Leukemia

HNKL exhibits potent anti-proliferative and cytotoxic effects against a wide range of leukemia cell lines, *viz.* SUP-B15, K562, CEM, HL-60, CCRF-CEM, and NB4 [242–247]. Zhou B. et al., affirmed that HNKL induced cellular apoptosis, inhibited cell proliferation, reduced angiogenesis and migration, and curtailed tumor growth in a xenograft leukemia mouse model and in a murine C1498 acute myeloid leukemia (AML) model by increasing the degradation of AML1-ETO protein [248]. HNKL/triphenylmethane analogs synthesized by Mędra A. et al., acted as inducers of apoptosis by suppressing the expression of Bcl-2 and XIAP, and enhancing the Bax, Bak and survivin protein expression in *ex vivo* chronic lymphocytic leukemia, and in Burkitt lymphoma, diffuse large B-cell lymphoma, and multiple myeloma cells *in vitro* [249]. Furthermore, HNKL treatment upregulated the expression of protein tyrosine phosphatase SHP1, which inhibited the activation of STAT3, resulting in diminished progression of AML [250]. HNKL induced apoptosis of B-cell chronic lymphocytic leukemia *via* activation of caspase-3,-8,and -9, and PAPR cleavage [251].

Additionally, HNKL exerted its effect against AML HL60 cells by promoting cell cycle arrest at the G0/G1 phase *via* downregulation of cyclin-D1, -A, and–E, and CDK-2,-4, and -6. It also further induced apoptosis by reducing the expression of Bcl-2 and Bcl-x_L, increasing the expression of Bax, p53, and p21, and activation of caspase-3 and -9

[252]. HNKL promoted cell cycle arrest T-cell leukemia cells at the G-1 stage, which was mediated through reduced expression of cyclins-D1,-D2, and -E, CDK-2,-4, and -6, and c-Myc; while apoptosis was induced *via* downregulated expression of cIAP-2, XIAP, survivin, JunB and JunD, and enhanced activation of caspases-3 and -9 [123]. Li H.Y. et al., reported that HNKL induced apoptosis in treated AML cells *via* suppression of expression of histone deacetylases (class I HDACs) [253].

HNKL predominantly induced cell death and apoptosis *via* caspase-independent paraptosis mediated through increased reactive oxygen species production in NB4 and K562 leukemia cells [124]. Moreover, HNKL inhibited the invasion and angiogenesis of U937 cells through downregulation of VEGF, VEGFR1, and MMP-9 expression [254]. Furthermore, HNKL in combination with imatinib-induced paraptosis and apoptosis, and exhibited schedule-dependent synergy against human leukemia cells [255]. HNKL induced necrotic cell death and loss of mitochondrial membrane potential *via* upregulation of cyclophilin D (CypD) in HL-60 cells [256]. HNKL inhibited the production of LTC4 and LTB4, which is stimulated by the Ca^{2+} ionophore A23187, in rat basophillic cells [257].

5.9. Liver cancer

Liver cancer is the fifth most commonly occurring cancer in men and seventh among women [258–261]. Various studies have shown the efficacy of HNKL against liver cancer. HNKL could inhibit proliferation and induce apoptosis of hepatocellular carcinoma (HCC) cells by inhibiting the STAT3 signaling pathway by inducing the expression of tyrosine phosphatase SHP-1, inhibiting the activation of upstream c-Src kinases, and JAK-1 and -2. Additionally, it potentiated the anti-cancer effects of paclitaxel and doxorubicin in HCC cells [144]. HNKL inducted apoptosis in the HepG2 cell line *via* activation of caspase-3, an increased release of Cyt-c from mitochondria, downregulation of Bcl-x_L and Bcl-2, and modulation of the p38 MAPK pathway [262]. *In vitro* and *in vivo* studies conducted by Chen H.C. et al., demonstrated that liposomal HNKL inhibits metastasis of Hep G2 cells by destabilizing EGFR and its downstream targets. In addition, liposomal HNKL repressed the motility, migration, and lamellipodia formation in the *in vitro* setup and lessened extravasation of HepG2 cells in a metastasis model of transgenic zebrafish [263]. HNKL in combination with rosiglitazone synergistically promotes cell cycle arrest at the G0/G1 phase by regulation of p21, cyclin-D1, and cyclin-E1 proteins. However, combined treatment of HNKL (20 μM) with rosiglitazone (50 μM and 100 μM) resulted in induced growth inhibition in SK-Hep1 cells but the same effect was not observed in Mahlavu hepatoma cell line [264]. The nanoparticles of Epigallocatechin-3-gallate and chitin loaded with HNKL induced anti-proliferative activity in HepG2 cells by arresting the cells at the G2/M phase and decreasing mitochondrial membrane potential in the *in vitro* setting, and reduced tumor growth significantly in the *in vivo* setting [265].

5.10. Lung cancer

Several reports have also highlighted the potential therapeutic effects of HNKL against lung cancer, which remains as one of the leading causes of mortality worldwide. HNKL reduced the migration and EMT-mediated motility of human non-small cell lung cancer (NSCLC) cell lines A549 and H460 by decreasing the expression of c-FLIP, N-cadherin, snail, and p-Smad2/3, and increasing the expression of IκB levels in the cells [266]. Tumorigenic bronchial cells, upon treatment with HNKL, displayed suppressed proliferation, and increased apoptosis *in vitro* through downregulation of p-EGFR, p-Akt, p-STAT3, and cell cycle-related proteins. Furthermore, similar effects were also observed in a murine lung tumor model, along with regression of tumor growth, size, and multiplicity. Interestingly, HNKL also sensitized tumorigenic bronchial cells and erlotinib resistant H1650 and H1975 cells to erlotinib [267]. *In vitro* treatment of NSCLC cells with HNKL promoted apoptosis by upregulating the expression of TRAIL-R2 (DR5), Bax, caspase-3, cleaved caspase-3, and cleaved PARP [268].

The combination of HNKL with chloroquine induced cell death and autophagy in NSCLC cells by cathepsin D and caspase-dependent pathways [269]. HNKL augmented PNAS-4 gene therapy and inhibited proliferation of Lewis lung carcinoma LL2 cells by induction of apoptosis. In addition, systemic administration of plasmids encoding mPNAS-4 *in vivo* along with a low concentration of HNKL showed repression of tumor growth *via* induction of apoptosis and inhibition of angiogenesis [206]. *In vitro* studies conducted by Pan J. et al., revealed that lung squamous cell carcinoma (SCC), upon treatment with HNKL, changed their redox status in the mitochondria, which in turn led to inhibition of cell proliferation, induction of cell cycle arrest at the G1-S phase checkpoint, and triggered cellular apoptosis. Moreover, using HNKL in an *in vivo* murine model of SCC resulted in a significantly decreased percentage of bronchus that displayed abnormal lung SCC histology [270].

A group of scientists unraveled the role of HNKL against A549, H1299, H460, and H226 NSCLC cells and showed that HNKL mediates its anti-cancer activity by downregulating the levels of COX-2, PGE2, β-catenin, NF-κB/p65, and MMP-2 and -9 [271]. Another study conducted by Singh T. et al., revealed that HNKL also augmented G-1 phase cell cycle arrest by decreasing the levels of cyclin-D1,-D2, and CDKs, and inhibited the activity of HDACs [272]. Lin J.M. et al., designed and synthesized HNKL analogs that displayed higher growth inhibitory activity in A549 cells and considerably arrested the cells at the G0-G1 phase of the cell cycle. These anti-cancer activities were associated with a reduction of both CDK-1 and cyclin-B1 protein levels in A549 cells [273]. Wen J. et al., developed liposomal HNKL that inhibited metastasis and angiogenesis in a lung cancer murine model [274]. Recent studies on the effect of HNKL on human lung adenocarcinoma cells showed that HNKL induced apoptosis, and inhibited cellular proliferation and invasion of the cancerous cells by targeting Lyn kinase expression [275]. HNKL treatment inhibited lung cancer tumor growth and metastasis by inhibition of the STAT3 signaling pathway [276]. Furthermore, HNKL promoted apoptosis, cell cycle arrest at G1 stage, and autophagy in KRAS mutant lung cancer cells [169].

Yang J. et al., reported that liposomal HNKL, when used on both gefitinib-sensitive and gefitinib-resistant NSCLC cells, inhibited the Akt and ERK1/2 signaling pathways by increased lysosomal degradation of Hsp90 client proteins and enhanced protective autophagy in both *in vitro* and *in vivo* conditions [277]. Moreover, treatment with HNKL downregulated cellular FLICE-inhibitory protein (c-FLIP) and induced apoptosis mediated by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [278]. HNKL induced apoptosis in CH27 cells and promoted release of mitochondrial Cyt-c and activation of caspase-3 [74]. HNKL treatment induced apoptosis and anti-tumor activity in a human lung cancer A549 xenograft model [279]. The combination of HNKL with radiotherapy synergistically inhibited tumor growth and angiogenesis [91].

5.11. Lymphoma and multiple myeloma

HNKL significantly increased the ROS level, reduced the NF-κB activity, p-65, and Nrf2 expression levels, and ultimately elicited cell death through apoptosis in Raji and Molt4 lymphoma cell lines and BALB/C mice that had subcutaneous administration of Raji cells [280]. Chen W. et al., revealed that HNKL provoked apoptosis and cell death in a dose-dependent manner by significantly enhancing the expression of caspase-8 and Bad and inducing cell cycle arrest at the G0/G1 phase in Raji cells [281]. HNKL in combination with Gemcitabine stimulated cell cycle arrest at the G0/G1 phase and induced apoptosis *via* downregulation of the expression of Bcl-2 protein in human Burkitt lymphoma cells [282].

Ishitsuka K. et al., reported that HNKL drastically induced cell cytotoxicity in human multiple myeloma (MM) cell lines and tumor cells

from patients with MM. HNKL activated caspase-3, -7, -8, and -9, and apoptosis inducing factor (AIF) from mitochondria. Thus, suggesting that HNKL mediated apoptosis *via* both caspase-dependent and caspase-independent pathways. Furthermore, it reduced tube formation by endothelial cells, indicating the role of HNKl in the regulation of neovascularization in the bone marrow microenvironment [283].

5.12. Osteosarcoma

Osteosarcoma is a malignant bone tumor characterized by uncontrolled cell growth in tissues of the bone [284]. *In vitro* and *in vivo* studies by Steinmann P. et al., showed HNKL treatment induced cell death and inhibited cell proliferation and metastasis in osteosarcoma [285]. Recent study on the effect on HNKL on HOS and U2OS osteosarcoma cells has shown that HNKL induced cell cycle arrest at the G0/G1 phase and elicited autophagy and apoptosis by upregulation of glucose-regulated protein (GRP)-78 and intracellular ROS production [167]. Yang J. et al., reported that HNKL displays its anti-cancer effects by significantly downregulating miR-21, the PI3K/Akt signaling pathway, and anti-apoptotic Bcl-2 protein expression; inducing apoptosis by upregulating proapoptotic Bax protein expression and increasing the levels of cleaved-caspase-3 and PARP cleavage in both *in vitro* and *in vivo* models of osteosarcoma [286]. HNKL treatment of osteosarcoma cells augmented apoptosis by upregulating the expression of proteins such as LC3II protein associated with autophagy, Bcl-2-like protein 4, caspase-3, and p53 protein, and reducing the PI3K, p-Akt, p-mTOR, and cyclin-D1 protein expression [168].

5.13. Ovarian cancer

Treatment with HNKL exhibited strong cytotoxic effects against OVCAR-3 human ovarian adenocarcinoma cells [287]. In 2008, Li Z. et al., revealed that HNKL promoted apoptosis and significantly reduced cell proliferation in SKOV3 and COC1 human ovarian cancer cells and further treatment of tumor-bearing animals with HNKL diminished the microvessel densities and resulted in inhibition of tumor growth and development [288]. HNKL downregulated the expression of P-gp in NCI/ADR-RES cells in a concentration- and time-dependent manner, resulting in 2.5- to 4.1-fold decrease in P-gp expression [289]. HNKL showed apotent chemosensitization ability and augmented the therapeutic efficacy of cisplastin against ovarian carcinoma [290]. Furthermore, liposomal HNKL reduced cisplatin chemoresistance in nude mice bearing A2780s and A2780cp subcutaneous tumors and prolonged the survival of the treated mice by decreasing the intratumoral microvessel density and increasing the tumor apoptosis [291].

5.14. Pancreatic cancer

The rate of mortality due to pancreatic cancer is almost similar to its rate of incidence, and is the seventh most common cause of deaths due to cancer globally [292]. *In vitro* and *in vivo* studies showed that treatment with HNKL diminished pancreatic tumor growth, metastasis, and desmoplasia by interfering with bidirectional tumor-stromal crosstalk by decreasing the expression of mediators such as sonic hedgehog (SHH) and CXCR4 proteins [293]. Furthermore, HNKL arrested the cell cycle at the G1 stage and induced apoptosis in MiaPaCa and Panc-1 cells by downregulating of expression of cyclin-D1,-E and CDK-2,-4, and upregulating the expression of CDK inhibitors (*i.e.* p21 and p27), and increasing the levels of Bax proteins. Additionally, HNKL potently decreased the NF-κB level in the nucleus and downregulated the transcriptional activity of NF-κB responsive promoter [294]. HNKL in combination with bleomycin displayed a synergistic effect against Panc-1 cells by inhibiting DNA polymerase-β and -λ [295].

5.15. Prostate cancer

Approximately 1.1 million new cases of prostate cancer have been reported by GLOBOCAN 2012 all across the world [194,296–298]. Several studies reported that HNKL exhibited potent anti-cancer efficacy against prostate cancer both in *in vitro* and in *in vivo*. An analysis of the apoptotic potential of HNKL has revealed its cytotoxic effects against prostate cancer cells and it has been shown to induce apoptosis mediated through the activation of caspases-3, -8, and -9, and enhanced cleavage of PARP [299]. PC-3 and 22Rv1 cells, upon treatment with HNKL, displayed reduced c-Myc expression, which led to cell cycle arrest at the G0-G1 phase of the cell cycle [176]. An *in vivo* study carried out by Hahm E.R. et al., disclosed that HNKL exhibited antitumor activity in a PC-3 xenograft animal model by induction of apoptosis [300]. Furthermore, Hahm E.R. et al., reported that HNKL and its dichloroacetate analog effectively reduced cell viability and androgen receptor (AR) protein level in LNCaP, C4-2, and TRAMP-C1 cells by inhibiting the nuclear translocation, transcriptional repression, and proteasomal degradation of the AR [301]. Another study showed that HNKL induced ROS mediated autophagy in PC-3, LNCaP, and Myc-CaP cells *in vitro* and increased the levels of LC3BII protein in a PC-3 murine tumor xenograft model [302]. Also it was depicted in PC-3 and LNCaP cells that HNKL causes cell cycle arrest at the G0-G1 phase accompanied by a decreased phosphorylated Rb level, E2F1 transcriptional activity, as well as cyclin-D1,-E, and CDK-4, -6 levels [303].

5.16. Skin cancer

The white population of the world is highly susceptible to melanoma and it is a serious global health issue [304]. *In vitro* treatment of SKMEL-2 and UACC-62 melanoma cells with HNKL resulted in decreased cell viability and proliferation, and promotion of cell cycle arrest and apoptosis. In addition, HNKL displayed regression of tumor growth in SKMEL-2 and UACC-62 melanoma xenograft animal models [305]. Studies have shown that HNKL treatment induced apoptosis in malignant melanoma cells by increasing caspase activation and release of Cyt-c from the mitochondria. In addition, HNKL augmented cell cycle arrest by downregulating the level of cyclin-D1, mTOR, and phosphorylation of Akt, and inhibiting the expression of γ-secretase complex proteins [306,307]. HNKL treatment decreased cellular proliferation and induced apoptosis in melanoma stem cells by suppressing the Notch-2 signaling pathway [308]. HNKL affects melanoma cell growth *in vitro* and reduced tumor growth *in vivo* by increasing the level of phosphorylated AMPK [309,310].

HNKL induced apoptosis in an UV-B induced skin cancer mouse model, ultimately resulting in diminished tumor progression and regression of tumor growth [311]. Treatment of A431 cells with HNKL enhanced cell cycle arrest at the G0/G1 phase by deregulating the expression of cyclin-D1, - D2, and CDK-2, -4 and -6 proteins, and increasing the expression of CDK inhibitors p21 and p27. Moreover, HNKL also induced apoptosis by augmenting DNA fragmentation in the treated cells [312]. HNKL significantly inhibited the expression of COX-2, PGE-2, PCNA, and pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6 in an UV radiation-induced skin cancer mouse model. It also induced cell cycle arrest, which was mediated through inhibition of cyclin-D1, -D2, and–E, CDK-2,-4, and -6, and upregulation of Cip/p21 and Kip/p27. It further inhibited the levels of PI3K and phosphorylation of Akt at Ser(473) in UVB-induced skin tumors [313]. The combination of HNKL, magnolol, and α-santalol synergistically attenuated cell viability and proliferation, and increased apoptosis in human epidermoid carcinoma A431 cells [314]. *In vivo* studies carried out by Guillermo R.F. et al., showed that HNKL reduced tumor multiplicity and volume in an UV-B induced skin cancer model in a dose-dependent manner [315]. Prasad R. et al., revealed that HNKL inhibited the migratory potential of human melanoma cell lines A375, Hs294t, SK-Mel119, and SK-Mel28 by decreasing oxidative stress and Nox 1 expression. Furthermore, oral

gavage of HNKL in nude mice inhibited the growth, migration or extravasation of intravenously injected melanoma cells in different internal body organs, such as the lung, kidney and liver, through inhibition of Nox1 activity in these internal organs [316].

5.17. Thyroid cancer

HNKL treatment can promote cell cycle arrest and augment the induction of caspase-dependent apoptosis *in vitro* and *in vivo* in human thyroid cancer cells [317]. Proteomic analysis of HNKL against thyroid cancer cells showed that HNKL significantly changed the expression levels of 178 proteins associated with glycolysis, the cytoskeleton, and transcription control, and induced cellular cytotoxicity [318].

6. Toxicological studies

The magnolia extract containing HNKL and magnolol upon treatment in both *in vitro* and *in vivo* settings, showed no mutagenic and genotoxic potential. Subchronic study conducted as per the Organization for Economic Co-operation and Development guidelines stated no adverse effect level for concentrated Magnolol bark extract (MBE) > 240 mg/kg b.w/d [319]. Numerous studies have declared HNKL to exhibit low toxicity *in vivo* [59,75,90,319–321]. A Study has shown that intravenous administration of HNKL at a dose of 20–80 mg/kg body weight/day for 2 weeks in Sprague–Dawley rats did not induce any signs of toxicity such as body weight loss, reduction of mean daily food intake decrease, change in hematological and serum biochemical values, and tissue pathologic changes [70]. *In vitro* and *in vivo* studies have also revealed that honokiol microemulsion induced no prominent genotoxicity [322]. Moreover, with the increasing popularity of Magnolia extracts (herbal products) and its easy availability on the internet may lead to abuse/misuse of magnolia extract and its main constituents HNKL and magnolol, which may interfere with pharmacological treatments, especially those required for chronic disease management [323]. However, the intake of HNKL has been modeled for use as a functional ingredient in mints and chewing gums and as a flavoring agent is considered safe against the reported no adverse effect level [324].

7. Conclusion

HNKL is a natural, organic compound that exhibits substantial chemopreventive and therapeutic potential against different cancers in both *in vitro* and *in vivo* settings. It has been extensively studied for its diverse biological activities against gastrointestinal disorders, cough, anxiety, stroke, and allergic diseases, and has also been used as an antithrombotic, anti-depressant, anti-emetic, and antibacterial agent. HNKL affects multiple molecular and cellular targets, leading to regression of tumor growth. HNKL in combination with existing chemotherapeutic agents improves their efficacy, reduces toxicity, and helps to overcome chemoresistance. The preclinical studies on HNKL is enthralling, and its potential benefits combined with lack of toxicity and no adverse side effects are promising, thus making it a potential clinical candidate. HNKL inhibits the regression of different cancers *via* the induction of apoptosis through modulation of Ca^{+2} channels, up-regulation of pro-apoptotic proteins, and suppression of anti-apoptotic proteins and affecting mitochondrial-dependent pathways. It also displays anti-metastatic effects by the inhibition of MMPs, PI3K/Akt/mTOR, epithelial to mesenchymal transition, NF-κB, STAT3, and Wnt signaling pathways. Furthermore, HNKL regulates the EGFR signaling pathway *via* suppression of either EGFR expression or EGFR phosphorylation. As the source of HNKL is from botanicals, therefore it could significantly reduce the expenses incurred to cure cancer. HNKL is currently being used by many clinicians as an adjuvant therapy to address several pro-inflammatory and neurologic conditions, as well as different types of cancer. Nevertheless, more preclinical and clinical investigations are essential to claim the potential of HNKL, which would help to bring this compound to the clinic for the welfare of mankind.

Abbreviations

AMPKAMP-activated protein kinaseARAndrogen receptor activityAIFApoptosis-inducing factorAML1Acute myeloid leukemia 1 proteinBaxBcl-2-associated X proteinBcl-2B-cell lymphoma 2BADThe Bcl-2-associated death promoter proteinBMP-7Bone morphogenetic protein 7COX-2Cyclooxygenase 2CRCalreticulinCypDCyclophilin DCDKCyclin Dependent KinaseCyt-ccytochrome complexc-FLIPCellular FLICE inhibitory proteinCXCRchemokine receptor typeERp44Endoplasmic reticulum resident protein 44EZH2Enhancer of Zeste Homologue 2EGFREpidermal growth factor receptorERKExtracellular signal-regulated kinase 2GRPGlucose-regulated proteinHDACsHistone deacetylases class-1HIF-1αHypoxia-inducible factor-1αHO-1Heme oxygenase 1HER-2human epidermal growth factor receptor 2ICAM-1Intercellular adhesion molecule-1iNOSInducible nitric oxide synthaseILInterleukinJAK1Janus-activated kinase 1LKB1Liver kinase B1LOX-115-lipoxygenaseMAPKp38mitogen-activated protein kinaseMMPMatrix metalloproteinaseMRP-1Multidrug resistance proteinsMUC-1Mucin 1miRmicro RNAmTORmechanistic target of rapamycinMcl-1Induced myeloid leukemia cell differentiation proteinNONitric oxideNox1NADPH oxidase 1Nur77nuclear receptorNF-κBNuclear factor kappa-light-chain-enhancer of activated B cellsPARPPoly adenosine diphosphate-ribose polymerase-PLDPhospholipase-DPPAR-gammaPeroxisome proliferator-activated receptor-gammapRbPhosphorylated retinoblastoma proteinp-AMPKPhosphorylated AMP-activated protein kinasePGE2Prostaglandin E2PI3KPhosphatidylinositol-4,5-bisphosphate 3-kinasep-EGFRPhosphorylated Epidermal growth factor receptorPCNAProliferating cell nuclear antigenROSReactive oxygen speciesRbRetinoblastoma proteinROCKRho-associated protein kinaseSHHSonic hedgehogSHP-1Src homology 2-SH2-containing tyrosine phosphatase-1Sp1Transcription factor specificity protein 1SRC-3Steroid receptor coactivator-3Sox-2Sex determining region Y-box 2STAT3Signal transducer and activator of transcription 3Tpl-2Tumor progression locus 2TNF-αtumor necrosis factor alphaTGF-β1Transforming growth factor beta 1VCAM-1Vascular cell adhesion molecule-1VEGFVascular endothelial growth factorXIAPX-linked inhibitor of apoptosis protein

Author Contributions

GS and AKB conceived the project; KB, AMR, VD, GP, DV, BLS, SPN reviewed the literature and wrote the manuscript, LF, FA, GS, and AKB edited and finalized the article.

Conflict of interest statement

The authors declare no conflict of interests related to this study.

Acknowledgements

This work was supported by BT/556/NE/U-Excel/2016 grant awarded to AK by Department of Biotechnology (DBT), Government of India. The authors Abhishek Manoj Ranaware and Kishore Banik acknowledge UGC, New Delhi, India for providing their fellowship. The author Bethsebie Lalduhsaki Sailo acknowledges DST INSPIRE, India for providing her fellowship.

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