Pharmacological advances of honokiol: Mechanisms, targets and therapeutic potential (Review)

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Abstract. Honokiol (HKL), a bioactive biphenolic lignan isolated from the bark of *Magnolia officinalis*, possesses diverse pharmacological properties, including neuroprotective, antitumor, anti-inflammatory and metabolic regulatory effects. Despite its therapeutic promise, the clinical application of HKL is severely restricted by its hydrophobicity and low oral bioavailability. The present review systematically summarized 99 studies (90 original articles and nine reviews) on the pharmacological profile of HKL. It detailed HKL's molecular interactions with key signaling targets, such as sirtuin 3, NOD-like receptor family pyrin domain containing 3-cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes, Yes-associated protein/transcriptional coactivator with PDZ-binding motif, adenosine monophosphate-activated protein kinase and signal transducer and activator of transcription 3, which underly its efficacy against cancer (ovarian, liver, breast, colorectal, and lung), neurodegeneration (Alzheimer's and Parkinson's disease), metabolic disorders (diabetes, nonalcoholic fatty liver disease and obesity) and inflammatory and infectious diseases. Furthermore, the present review critically evaluated recently developed strategies to overcome its pharmacokinetic limitations. The present review offered an updated theoretical basis for understanding the structure-activity relationship of HKL and provided insights into its translation from bench to bedside.

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1. Introduction

Magnolia bark has been utilized in traditional Chinese and Japanese medicine for a long history to treat conditions such as gastrointestinal dysfunction, and anxiety. The active constituents, honokiol (HKL; 5,3'-diallyl-biphenyl-2,4'-diol), a regioisomer of magnolol, was first isolated in 1972 (1), yet its full pharmacological potential remained underexplored for decades and systematic reviews consolidating its molecular mechanisms remain scarce. Previous studies have confirmed that HKL is favorable for the treatment of a variety of diseases, including anti-inflammatory, antioxidant, neuroprotective and antitumor effects, rendering it favorable for the treatment of a wide spectrum of diseases (2-5). Recent resurgence of interest, driven by its multitarget pharmacology and favorable toxicity profile, has positioned HKL as a lead compound for rational drug design, although clinical translation remains hampered by formulation challenges (2). Concurrently, advances in structural modification and drug delivery strategies have begun to address the inherent limitations of HKL, such as poor aqueous solubility and suboptimal bioavailability. As a result, the present review synthesized recent advances in the mechanistic understanding, pharmacology and translational research of HKL, benchmarks it against other natural-product derivatives and outlined an evidence-based developmental pipeline for future investigations.

2. Method

For the present review, a comprehensive literature search was conducted across multiple electronic databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.scopus.com/). Keywords such as ‘honokiol’, ‘Alzheimer's disease’, ‘cancer’, ‘metabolic disorders’, ‘infectious diseases’, and ‘pharmacology’ were used in the search.

The present review systematically reviewed all relevant *in vitro*, *in vivo* and clinical studies investigating the therapeutic effects of HKL. The present review synthesized original research published between 2023 and 2025 to provide an updated profile of the direct molecular targets, signaling mechanisms, and nano-enabled delivery strategies of HKL.

3. Structural considerations

HKL possesses two phenolic hydroxyls flanked by ortho-allyl substituents. This structure is ideal for membrane permeation but problematic for oral absorption. Recent total synthesis of HKL utilized a phosphonium ylide-mediated cascade reaction and natural product isomerization processes, providing a novel alternative approach to unite *Illicium*-derived neolignans under a common precursor, chavicol (6). It has poor water solubility, which leads to high hepatic first-pass clearance and results in a low oral bioavailability of only 0.7% in rats, thereby limiting its clinical application. To address this limitation through structural modification, the two phenolic hydroxyl groups (C2'-OH and C4-OH) in the HKL molecule are key sites. Among them, the C2'-OH group is considered the 'critical pharmacophore' for most of its activity, while chemical modification at the C4-OH position serves as a potential site for enhancing efficacy and reducing toxicity. For instance, introducing additional pharmacophores (such as 1,3,4-thiadiazole, metformin) via a linker at C4-OH can increase antitumor activity by 10 to 100-fold while reducing toxicity to normal cells (2,7). The ortho-allyl substituent also plays an important role in its antitumor activity (7).

Several studies have reported more active and targeted HKL derivatives: Zhong *et al* (3) conjugated HKL with metformin via a 1,3,5-triazine ring to obtain the derivative HM568. In an MPTP-induced Parkinson's disease mouse model, HM568 markedly improved motor performance, attenuated neuroinflammation, restored the number of tyrosine hydroxylase-positive neurons and reduced α-synuclein aggregation, while the safety profile was favorable (LD_{50} >2,000 mg/kg). Sasia *et al* (8) reported that a hexafluorinated HKL derivative (claisened hexafluoro; CH) and the parent HKL (3 μmol/l) both exhibited antisenescence effects in BV-2 microglia intermittently stimulated with LPS, and reduced the expression of senescence-associated markers and inflammatory factors, showing efficacy comparable to that of the γ-secretase inhibitor DAPT. Among the 22 HKL-thioether-1,3,4-oxadiazole derivatives synthesized by Yang *et al* (9), compound 3k exhibited superior inhibitory activity against HCT116 colon cancer cells (IC_{50}=6.1 μmol/l) compared with that of 5-fluorouracil. It effectively induced cell cycle arrest and apoptosis by suppressing Yes-associated protein (YAP) signaling. Among the 28 mitochondria-targeted HKL derivatives designed by Miao *et al* (5), compound 2E-3-F16 induced ROS-mediated mitochondrial dysfunction in NCI-H446 lung cancer cells in a concentration-dependent manner. It demonstrated higher tumor selectivity and lower toxicity in *Caenorhabditis elegans* than did the parent HKL. In a cerebral ischemia/reperfusion model study, HH-A, the derivative with markedly improved water solubility, markedly reduced infarct volume and cerebral edema by activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) signaling pathway, with efficacy surpassing that of edaravone dexborneol (4).

In conclusion, these studies demonstrate that rational structural modification of HKL can simultaneously increase its water solubility, target specificity and therapeutic index while preserving its multimodal anti-inflammatory and cytoprotective effects.

4. Molecular targets and systems pharmacology

Traditional Chinese medicine has attracted intense research interest in recent years and its therapeutic potential is now recognized worldwide. Among its bioactive constituents, HKL stands out as a pleiotropic agent that concurrently modulates multiple validated targets across several signaling cascades (Fig. 1).

HKL exerts pharmacological effects through a hierarchy of direct binding targets and downstream signaling cascades. Experimentally validated direct targets, including sirtuin 3 (SIRT3) (10), OTU deubiquitinase, ubiquitin aldehyde binding 2 (OTUB2) (11), NOD-like receptor protein 3 (NLRP3) (12), solute carrier family 3 member 2 (SLC3A2) (13), oligomycin sensitivity-conferring protein (OSCP) (14), histone deacetylase 3 (15), heat shock protein 27 (HSP27) (16), platelet glycoprotein VI (GP6) (17), fibroblast growth factor receptor 1 (FGFR1) (18), adenosine monophosphate-activated protein kinase (AMPK) (19), initiate primary pathways that converge on mitochondrial quality control and cystine-dependent redox homeostasis. Indirectly regulated components, including YAP/transcriptional coactivator with PDZ-binding motif (TAZ), signal transducer and activator of transcription 3 (STAT3), and peroxisome proliferator-activated receptor gamma (PPARγ), may amplify or dampen these core signals in a disease-specific manner (Fig. 1).

SIRT3-mitochondrial quality control. SIRT3 is a highly conserved NAD^+-dependent deacetylase that is predominantly localized in mitochondria and plays crucial roles in regulating oxidative stress, metabolism, inflammation, apoptosis and autophagy (20). HKL alleviates mitochondrial dysfunction and reduces oxidative stress by binding and activating SIRT3 (10,20). In Alzheimer's disease (AD) models, HKL upregulates SIRT3 expression, promotes mitophagy and attenuates β-amyloid (Aβ) deposits (21). A similar mechanism was observed in myocardial ischemia-reperfusion injury (22) and diabetic nephropathy (23). This SIRT3-dependent protection was further confirmed in sodium fluoride-induced mitochondrial damage in porcine oocytes, where HKL restored superoxide dismutase 2 (SOD2) activity via SIRT3-mediated deacetylation, alleviating mitochondrial reactive oxygen species (mtROS) accumulation and improving developmental competence (24). Similarly, in cigarette smoke-exposed airway epithelial cells, HKL activated the SIRT3/SOD2 signaling pathway to suppress ROS generation, inflammatory cytokine release, and apoptosis (25). HKL was shown to ameliorate diabetes-associated cognitive dysfunction by upregulating SIRT3, which limited excessive mitochondria-associated endoplasmic reticulum membrane formation, and preserved neuronal survival (26). Collectively, these findings underscore HKL as a potent SIRT3 activator capable of counteracting

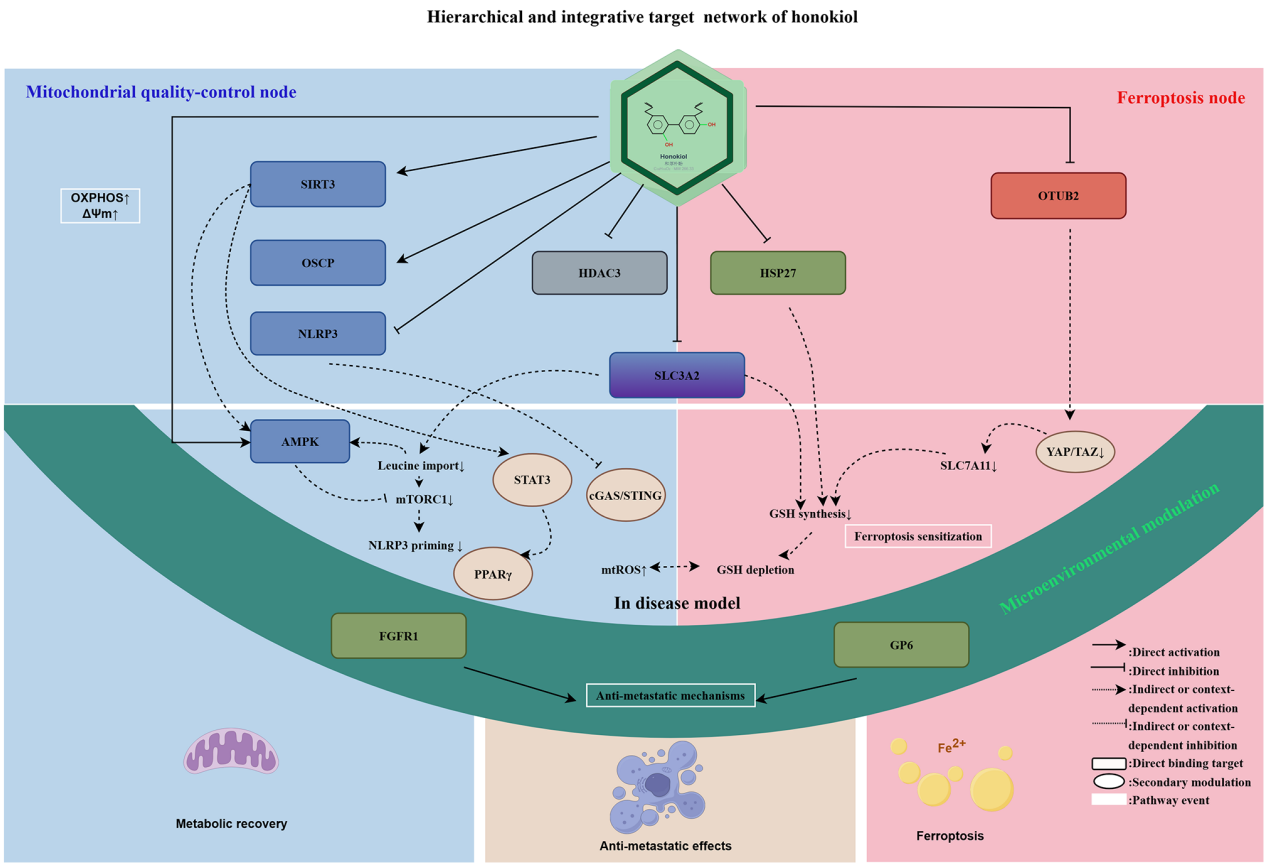

Figure 1. The targets and pathways of honokiol. Direct binding targets (SIRT3, OTUB2, SLC3A2, OSCP, NLRP3, HDAC3, HSP27, GP6 and FGFR1) initiate primary pathways associated with mitochondrial quality control and cystine metabolism. Secondary modulators (cGAS-STING, YAP/TAZ, STAT3, AMPK and PPARγ) amplify or suppress these signals in a disease-specific manner. Dashed arrows indicate indirect action and context dependent crosstalk. SIRT3, sirtuin 3; OTUB2, OTU domain-containing ubiquitin aldehyde-binding protein 2; SLC3A2, solute carrier family 3 member 2; OSCP, oligomycin sensitivity-conferring protein; NLRP3, NOD-like receptor protein 3; HDAC, histone deacetylase; HSP27, heat shock protein 27; GP6, platelet glycoprotein VI; FGFR1, fibroblast growth factor receptor 1; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; YAP, Yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; STAT3, signal transducer and activator of transcription 3; AMPK, adenosine monophosphate-activated protein kinase; PPARγ, peroxisome proliferator-activated receptor gamma; HSP, heat shock protein.

mitochondrial oxidative injury across multiple organs and disease contexts.

NLRP3-cGAS-STING Axis. The NLRP3 inflammasome acts as a central hub driving numerous inflammatory diseases. HKL suppresses NLRP3 inflammasome activation through context-dependent mechanisms. In lupus nephritis models, it binds NLRP3 directly and inhibited its activation, thereby downregulating the interleukin-33 (IL-33)/interleukin 1 receptor-like 1 (ST2) axis (12). In sepsis/colitis models, it indirectly blocked NLRP3 assembly and caspase-1 activation by promoting degradation of SLC3A2, decreasing L-leucine uptake and suppressing mechanistic target of rapamycin complex 1 (mTORC1) signaling (13). In Neisseria gonorrhoeae-infected macrophages, dual-action HKL inhibited NLRP3/caspase-1 pyroptosis while exerting direct bactericidal effects (27). HKL also mitigated cGAS-STING activation through mitochondrial homeostasis. It promoted SIRT3-mediated SOD2 deacetylation and attenuated mtDNA damage (28). In hepatic fibrosis, HKL interrupted the NLRP3-pyroptosis-cGAS-STING feedback loop, reducing liver damage and collagen deposition (29). In models of acute peritonitis and lupus nephritis, HKL not only inhibited the NLRP3/IL-1β axis but also activated the Sirt1-autophagy pathway or suppressed IL-33/ST2 signaling, markedly decreasing TNF-α and IL-6 levels and alleviating organ injury (30,12). In lung injury, it inhibited silica-induced cGAS-STING signaling and macrophage pyroptosis (31). In summary, HKL provides a broad-spectrum and safe intervention for NLRP3-driven infections, metabolic disorders and autoimmune inflammation.

YAP/TAZ transcriptional hub. YAP and TAZ are key transcriptional coactivators of the Hippo pathway and play important roles in controlling organ size and tissue malignant transformation (32). In CNE1 nasopharyngeal carcinoma cells, HKL arrested cells in G_0/G_1 phase and promoted apoptosis by decreasing the mitochondrial membrane potential and inducing YAP phosphorylation via the Hippo pathway; these effects could be reversed by an MST1/2 inhibitor (XMU-MP-1) (33). In ovarian cancer, HKL antagonized OTUB2 to destabilize YAP, suppressed SLC7A11, triggered lipid ROS-mediated ferroptosis and reduced Ki67 expression (11). Concurrently, it suppressed proliferation and invasion, downregulated YAP/TAZ signaling, triggered apoptosis and restrained tumor growth *in vivo* (34).

FGFR. PEAQ-ITC data show that HKL binds the FGFR1 kinase domain ATP-binding pocket, blocking downstream signaling. In FGFR1-expressing cancer cells, HKL abolished FGF1-mediated protection against the microtubule poison taltobulin, restoring cytotoxicity. While prolonged taltobulin exposure selected for dual-resistant clones with upregulated FGFR1 and cyclin D expression, cotreatment with HKL or a ligand trap prevented this resistance (18). Thus, targeting the FGF1/FGFR1 axis with HKL overcomes intrinsic taltobulin resistance and suppresses acquired resistance, suggesting a strategy to enhance the efficacy of microtubule-directed chemotherapy.

STAT3. Across independent disease models, HKL converges on a single druggable node, STAT3 Tyr705 phosphorylation, to reprogram pathological gene expression. In reserpine-induced fibromyalgia, oral HKL (8 mg/kg) downregulated Janus kinases (JAK)/STAT3 transcription in spinal tissue, inhibiting calcitonin gene-related-peptide expression and alleviating mechanical allodynia (35). In addition, HKL upregulated the endogenous STAT3 inhibitor protein inhibitor of activated stat protein 3, selectively suppressed STAT3 Tyr705 phosphorylation, downregulated Bcl-2 and drove caspase-3-mediated apoptosis both *in vitro* and in xenografts (36). HKL activated SIRT3 to deacetylate STAT3, thereby suppressing STAT3/retinoic acid receptor-related orphan receptor γ t signaling, curbing Th17 differentiation and IL-17/IL-21 production and consequently ameliorating colitis in both DSS-induced and IL-10-deficient mouse models (37). Similarly, during chronic cerebral hypoperfusion, HKL increased SIRT3 activity, blocked STAT3 nuclear translocation and prevented astrocyte A1 polarization, preserving hippocampal neurons and memory (38). Thus, whether the pathology is chronic pain, cancer, colitis or vascular dementia, HKL acts as a context-specific STAT3 gatekeeper, representing a pleiotropic yet mechanistically unified therapeutic agent.

AMPK. HKL is a direct AMPK activator that docks onto the AMPKγ1 subunit, bypassing classical upstream kinases and robustly switching on the AMPK signaling axis (19). In metabolic, hypertensive, renal and fatty-liver disorders, this interaction restored energy homeostasis: it blocked atrial fibrosis and lipid accumulation in atrial tissue (39), suppressed the expression of profibrotic α-smooth muscle actin and collagen IV in the kidney (40), inhibited Ang-II-induced cardiac hypertrophy via Nur77-liver kinase b1 (LKB1)-AMPK (41) and mitigated oxidative stress in aged laying hens (42). HKL (5 mg/kg, 4 weeks) attenuated adenine-induced chronic kidney disease in rats by curbing Bcl-2-interacting protein 3 (BNIP3)/BNIP3-like (NIX)- and FUN14 domain-containing 1 (FUNDC1)-driven excessive mitophagy and reversing AMPK activation, thereby improving renal function and limiting fibrosis and apoptosis (40). Thus, targeting AMPKγ1 with HKL offers a unified, nontoxic strategy against metabolic syndrome and related end-organ damage.

PPARγ. HKL activates the PPARγ signaling pathway, resulting in increased uncoupling protein 1 expression, increased heat production in adipose tissue and anti-obesity effects. Magnolol or HKL alleviated nonalcoholic fatty liver disease (NAFLD), promoted adipose-tissue browning and counteracted obesity through dual activation of PPARα/γ (43).

Hierarchical and integrative regulation. It is hypothesized that the pharmacological effects of HKL may be conceptualized through two principal functional modules, mitochondrial quality control and ferroptotic regulation, with additional microenvironmental modulation, whose relative dominance depends on cellular context and disease-specific vulnerabilities.

Mitochondrial quality-control node. Direct binding of SIRT3 and OSCP promotes oxidative phosphorylation and restores membrane potential. Direct NLRP3 binding provides parallel inflammasome suppression. Concurrent SLC3A2 inhibition restricts leucine import, attenuating mTORC1 activation and suppressing NLRP3 inflammasome priming. These inputs position this node as the dominant effector in metabolic and neurodegenerative diseases, where bioenergetic restoration is the primary therapeutic objective.

Ferroptosis node. Direct OTUB2 antagonism accelerates YAP proteasomal degradation, leading to the transcriptional suppression of SLC7A11. This is compounded by direct SLC3A2 inhibition, resulting in a dual-hit disruption of cystine uptake. The resulting depletion of glutathione sensitizes cells to ferroptosis, particularly in YAP-hyperactive malignancies. HSP27 inhibition may further impair oxidative stress defenses, although this requires additional validation.

In disease models, cross-nodal amplification is mediated by shared secondary effectors mtROS from OXPHOS perturbation and amplifies ferroptotic sensitivity when glutathione defense is simultaneously compromised. AMPK activation reinforces mTORC1 suppression, establishing a self-reinforcing metabolic brake. PPARγ and STAT3 modulation provides additional contextual tuning.

Microenvironmental effects. FGFR1 inhibition attenuates growth factor-driven signaling, whereas GP6 antagonism may disrupt platelet-tumor interactions. These effects are less well characterized but suggest complementary antimetastatic mechanisms.

This proposed architecture may help explain the broad preclinical spectrum of HKL: metabolic recovery appears to predominate in nonmalignant disease models, sensitivity to ferroptosis may prevail in cancers with high YAP/SLC7A11 vulnerability, and microenvironmental effects could contribute to its antimetastatic activity.

5. Disease-focused pharmacodynamics

Cancer. HKL exerts multiple anticancer effects by inducing apoptosis, cell cycle arrest and autophagy in cancer cells. Its mechanisms have been extensively studied because of its ability to target multiple pathological pathways (Fig. 2).

Ovarian cancer. HKL physically occupies the deubiquitinase OTUB2, silencing YAP/TAZ signaling and inducing a lipid-ROS burst, Fe^{2+} overload and classical ferroptotic death (11). ROS-cleavable micelles (RC-PH-Ms) loaded with both HKL and paclitaxel, switched tumor-associated macrophages from the M2 phenotype to the M1 phenotype and inhibited metastatic cells from using the vascular supply (44). Glutathione-sensitive HKL polyprodrug nanoparticles

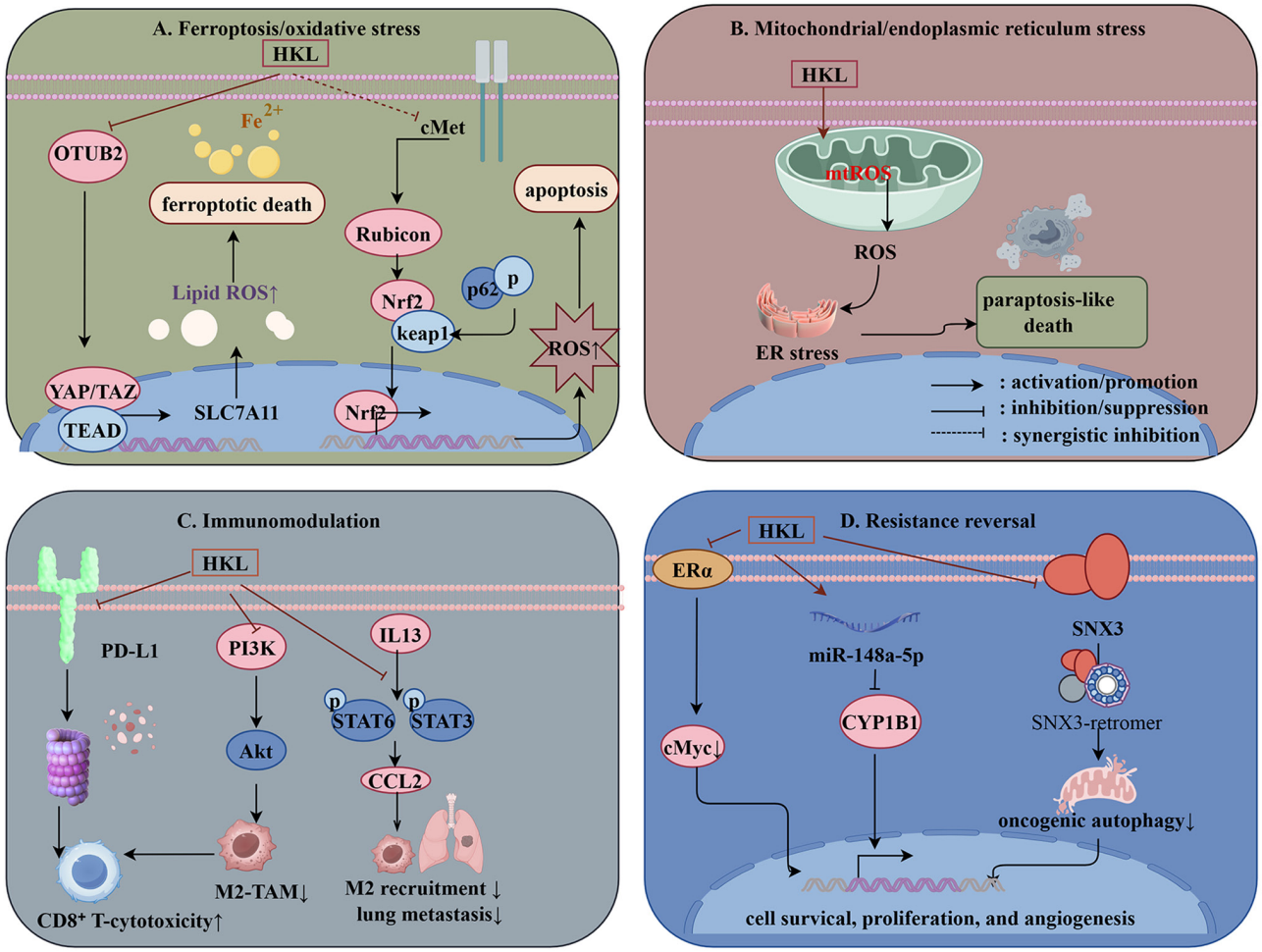

Figure 2. Functional classification of honokiol anticancer mechanisms. HKL modulates four molecular hubs: (A) Ferroptosis/oxidative stress: (OTUB2-YAP/TAZ axis, c-Met-Rubicon-p62-Nrf2 axis) (B) Mitochondrial/endoplasmic reticulum stress: (paraptosis-like death) (C) Immunomodulation: (PD-L1, gasdermin E, PI3K, IL-13) (D) Resistance reversal: (ERα, miR-148a-5p, SNX3). HKL, honokiol; OSCP, oligomycin sensitivity-conferring protein; YAP, Yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; Nrf2, nuclear factor erythroid 2-related factor 2; PD-L1, programmed death-ligand 1; PI3K, phosphatidylinositol 3-kinase; IL, interleukin; ERα, estrogen receptor alpha; miR, microRNA; SNX3, sorting nexin 3.

(A/P-PHK NP40) bearing EpCAM aptamers achieved 15% drug loading and tumor-specific release, outperformed free HKL in cell and xenograft models, and demonstrated greater inhibitory effects on the growth of ovarian cancer cells (45).

Hepatocellular carcinoma. An amphiphilic Angelica-polysaccharide-berberine conjugate, ASP-BBR-PM@HKL, exhibited a high rate of cell inhibition and an excellent antiHCC effect in subsequent *in vivo* experiments (46). HKL-generated mtROS accumulate and diffuse to the endoplasmic reticulum, initiating endoplasmic reticulum stress and culminating in the paraptosis-like death of Hep3B cells, an alternative death route bypassing classical apoptosis resistance (47).

Breast cancer. Du *et al* (48) developed CD44-targeting MPDA nanoparticles loaded with HKL and surface-coated with hyaluronic acid and then combined them with low-dose metformin and near-infrared photothermal therapy. The nanosystem showed high stability, biocompatibility, potent *in vitro* cytotoxicity and significant *in vivo* tumor suppression via activation of cleaved caspase-3/poly ADP ribose polymerase-mediated apoptosis, offering a promising nanomedicine platform for breast cancer therapy. By binding to and downregulating estrogen receptor alpha (ERα), HKL restored trastuzumab sensitivity in HER2^{+}/ERα^{+} trastuzumab-resistant HCC1954 cells (49). HKL transcriptionally upregulated tumor-suppressive miR-148a-5p, downregulated cytochrome p450 1B1 and potentiated paclitaxel-induced apoptosis in MDA-MB-231 cells (50). HKL blocked IL-13/signal transducer and activator of transcription 6 (STAT6) signaling, reduced chemokine (C-C motif) ligand-2 (CCL2) secretion and thereby decreased the ratio of M2/M1 macrophages in triple-negative breast tumors, markedly reducing pulmonary metastasis *in vivo* (51).

Colorectal cancer. A triple combination of HKL + magnolol + baicalin triggered GSDME-dependent pyroptosis, converted 'cold' tumors to 'hot' tumors and outperformed FOLFIRI when partnered with antiprogrammed cell death 1 (PD-1) therapy (52). HKL disrupted the sorting nexin 3 (SNX3)-retromer complex, impaired oncogenic autophagy and macropinocytosis and sensitized KRAS(G13D)-mutant colorectal cancer to cetuximab (53).

Lung cancer. Liposomal HKL suppressed phosphatidylinositol 3-kinase/Akt signaling, decreased M2-TAM and MDSC infiltration and increased CD8^{+} T-cell activity in lung cancer, indicating superior antiPD-1 efficacy (54). HNK interrupted

the IL-1β-triggered nuclear factor kappa-B (NF-κB)-vascular endothelial growth factor forward loop and suppressed human umbilical vein endothelial cell tube formation and tumor angiogenesis *in vitro* and *in vivo* (55). Direct physical engagement of HKL with PD-L1 accelerated its degradation, reinvigorated T-cell cytotoxicity and suppressed tumor growth in C57BL/6 mice (56).

Other malignancies. In nasopharyngeal carcinoma, the HKL derivative 1g downregulated HIF-1α, MMP-2 and Bcl-2 expression and suppressed CNE-2Z cell invasion and xenograft expansion (57). In anaplastic thyroid cancer, ROS-dependent EMT blockade underlies the HKL-mediated inhibition of KMH-2 and ASH-3 cell proliferation and migration (58). HKL combined with cabozantinib inhibited the c-Met-Rubicon-p62-Nrf2 antioxidant axis, elevated ROS and triggered renal cell carcinoma (RCC) death (59).

Together, the capacity of HKL to engage oxidative, apoptotic, immunologic and resistance-related hubs endows it with a unique polypharmacologic signature. Coupling these mechanistic insights with rationally engineered nanocarriers or combination regimens paves the way toward precision, low-toxicity cancer therapeutics.

Neurodegeneration. AD is characterized by β-amyloid (Aβ) overproduction, τ hyperphosphorylation, neuroinflammation and mitochondrial collapse. HKL crosses the blood-brain barrier and affects these underlying factors through a coordinated, multilevel mechanism.

Aβ generation and aggregation. In streptozotocin-icv rats, HKL reduced the number of hippocampal $A\beta_{1-42}$ plaques and neurofibrillary tangles while restoring memory function in the Morris-water and elevated-plus mazes. HKL downregulated NF-κB (p65) and reduced AchE and neuro-inflammatory markers (IL-1β and IL-6), indicating that HKL interrupted the NF-κB pathway to curb amyloidogenic processing (60). *In silico* docking and cell-free assays revealed that HKL is a nanomolar-to-micromolar dual inhibitor of β-site amyloid precursor protein cleaving enzyme 1, AChE, glutaminyl cyclase and glycogen synthase kinase-3β. These results indicate that HKL suppresses Aβ generation, aggregation and pyro-Glu modification, establishing HKL as a multienzyme blocker for AD intervention (61).

SIRT3-centered mitochondrial quality control HKL (20 mg/kg) elevated SIRT3 expression in the hippocampi and livers of APP/PS1 mice. This was associated with increased levels of insulin-degrading enzyme and SOD2, whereas hepatic LDL receptor-related protein 1 expression decreased, collectively reducing Aβ deposition, decreasing aspartate aminotransferase/alanine aminotransferase ALT levels and restoring albumin levels. These findings suggest that reinforcement of the hepatic 'Aβ-sink' contributes to central clearance (62). In a hippocampal neuronal AD model, HKL triggered mitochondrial autophagy, reduced ROS levels and mitochondrial membrane depolarization and protected against Aβ-oligomer-induced apoptosis; all these benefits were abolished by the selective SIRT3 inhibitor 3-TYP or by cyclosporine-A (21).

Neuro-inflammation. Chronic cerebral hypoperfusion (CCH) rats treated with 1 mg/kg HKL for 21 days presented restored SIRT3 activity and inhibited STAT3 nuclear translocation and A1 polarization in the hippocampi. Moreover, the neuronal and synaptic loss were prevented and spatial memory was recovered, indicating that HKL ameliorated CCH-induced neurological damage, at least in part, by modulating the SIRT3-STAT3 axis (38). Conjugation of HKL to the mitochondria-targeting peptide XJB produced conjugates that are less toxic than the parent compound and provide protection on neuronal injury *in vitro* and *in vivo*. These beneficial effects coincide with elevated SIRT3 activity, upregulation of the mitochondrial fusion protein mitofusin-1 (Mfn-1), and induction of autophagy. Thus, mitochondria-directed delivery amplifies the SIRT3-dependent bioactivity of HKL and offers a promising avenue for the drug development of drugs for AD (63). Similarly, supplementation with HKL promotes the survival and growth of iPSC-derived neurons from a sporadic-AD patient, supporting its potential to promote neuronal viability in a human disease genotype (64).

From enzyme inhibition to SIRT3-mediated mitochondrial autophagy and glial modulation, HKL offers a contiguous, low-toxicity chain of actions that restrains Aβ genesis, promotes clearance and alleviates neuroinflammation.

Parkinson's disease (PD). HKL affects PD mainly at three checkpoints. First, HKL-butyrate and related short-chain-fatty-acyl esters reversibly decrease the abundance of *Enterococcus faecalis*, the gut bacterium that converts oral levodopa to dopamine, thereby increasing central dopamine bioavailability (65). Second, the mitochondria-targeted derivative Mito-ortho-HNK amplifies this microbial brake by suppressing *Enterococcus faecalis* proliferation, thereby reducing gut levodopa metabolism and enhancing brain dopamine levels in levodopa-d3-treated mice (66). Third, the hybrid analog HM568 suppresses microglial M1 polarization; downregulates NF-κB pathway markers; lowers the levels of IL-1β, IL-6 and TNF-α; protects tyrosine-hydroxylase-positive neurons and reverses motor deficits in MPTP-PD mice (3). Thus, HKL and its pro-drugs act as gut-brain axis modulators that simultaneously suppress peripheral levodopa metabolism, alleviate neuroinflammation and preserve nigrostriatal function.

Metabolic disorders

Nonalcoholic steatohepatitis (NASH). HKL alleviates NAFLD through multiple mechanisms. It docks onto AMPKγ1, switching on AMPK signaling to suppress lipogenesis and fibrogenesis in hepatocytes (19). HNK alleviates oxidative stress and inflammation in metabolic dysfunction-associated fatty liver disease (MAFLD) by activating the Nrf2 pathway. Nrf2 signaling and receptor interacting protein kinase 3 (RIPK3)-mediated necroptosis form a negative feedback axis, playing a key role in MAFLD progression (67). HKL also restructures the gut-liver axis, increasing the abundance of *Ruminococcaceae, Caulobacteraceae* and *Brevundimona*, normalizing serum bile acid and lipid levels, thereby attenuating steatohepatitis in methionine-choline-deficient C57BL/6 mice (68). HKL (40 mg/kg) attenuated liver injury, decreased the activity of the cholesterol-induced NLRP3-cGAS-STING feed-forward loop and alleviated hepatic fibrosis (29).

Diabetes syndrome. Obesity is a chronic metabolic disorder characterized by excessive accretion of adipose mass that results from the complex interplay of genetic susceptibility

and environmental cues. HKL exerts anti-obesogenic effects through a polypharmacologic mode of action that simultaneously engages multiple validated molecular targets and intersecting signaling pathways, thereby attenuating adiposity and its downstream complications. HKL alleviated diabetic nephropathy in high fat diet (HFD)-fed streptozotocin (STZ)-treated rats by suppressing endoplasmic reticulum-stress signaling (glucose-regulated protein 78, C/EBP homologous protein, activating transcription factor 4 and tribbles homolog 3) and Rho-kinase 1/2, which subsequently reduced oxidative stress and albuminuria and restored creatinine clearance (69). In diabetic mice, HKL recapitulated the cardioprotective effects of semaglutide by restoring Raf kinase inhibitor protein (RKIP) through a SIRT3-dependent mechanism, which suppressed TANK-binding kinase 1-NF-κB signaling, thereby reducing cardiac inflammation in an RKIP-dependent manner (70). Retinal microvascular injury was blocked when HKL promoted SIRT3-mediated mitochondrial fusion and decreased ROS levels and endothelial apoptosis in db/db mice (71). Periodontal ligament stem cells rescued by HKL induced SIRT3-driven deacetylation of leucine rich pentatricopeptide repeat-containing (LRPPRC), restoring oxidative phosphorylation and alveolar bone regeneration under high glucose conditions (72). Cognitive decline was reversed as HKL disassembled the pathological voltage dependent anion channel 1-glucose regulated protein 75-inositol 1,4,5-trisphosphate receptor complex and reduced mitochondria-endoplasmic reticulum contacts in the diabetic mouse hippocampus via SIRT3 (26), whereas network pharmacology of HKL revealed additional retinoid X receptor alpha/vitamin D receptor heterodimer activation that restored autophagy and alleviated depression-like behavior in HFD-fed diabetic mice (73). Testicular oxidative stress and polyol-pathway hyperactivity were normalized by oral HKL (25 mg/kg^{-1}) in HFD-fed STZ-treated rats, with no change in testicular weight and a decrease in serum estradiol (74). In diabetic cardiorenal co-injury, transcriptomic mining revealed hemoglobin subunits (hemoglobin subunit α 1/2, hemoglobin subunit β) and proliferation and apoptosis adaptor protein as shared diabetic signatures; HKL was predicted to modulate hemoglobin subunits via molecular docking, pending experimental validation (75). In Dahl salt-sensitive rats, intraperitoneal administration of HKL at 5 mg/kg/day for 12 weeks improved the ejection fraction and fractional shortening without altering blood pressure, heart rate, or body weight; this effect required SIRT3 and was accompanied by reduced acetylation of MPC1 and increased mitochondrial pyruvate oxidation (76).

Infectious and inflammatory diseases. HKL has been increasingly recognized for its broad-spectrum anti-inflammatory activities. Recent studies have shown that HKL exerts its anti-inflammatory effects through multiple molecular pathways, including inhibition of the NLRP3 inflammasome, suppression of NF-κB signaling, and modulation of SIRT3-dependent mitochondrial function. For instance, Hua *et al* (27) demonstrated that HKL markedly inhibited NLRP3 inflammasome activation in *Neisseria gonorrhoeae*-infected macrophages, reducing IL-1β secretion and caspase-1 activity, while preserving mitochondrial integrity and suppressing ROS production. Similarly, Zhou *et al* (28) reported that HKL attenuated silica-induced lung fibrosis by inhibiting macrophage pyroptosis via the cGAS-STING pathway, highlighting its potential in treating chronic inflammatory diseases (31). Moreover, Zhou *et al* (28) reported that HKL activates SIRT3, a mitochondrial deacetylase that regulates the activity of anti-oxidant enzymes such as SOD2, thereby reducing mtROS levels and preventing inflammasome activation. This SIRT3-mediated mechanism is also involved in the protective effects of HKL against endothelial dysfunction and fibrosis in models of pulmonary and renal inflammation. Additionally, Niu *et al* (77) demonstrated that HKL inhibits transient receptor potential vanilloid 4 (TRPV4) channels by targeting the ankyrin repeat domain, contributing to its anti-inflammatory profile by modulating calcium signaling and endothelial permeability in inflammatory bowel disease.

HKL has emerged as a broad-spectrum, anti-infective natural product. Sun *et al* (78) reported potent synergistic bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *E. faecium* (VRE) when combined with β-lactam antibiotics; mechanistic work revealed that HKL disrupted FtsZ GTPase activity while enhancing its polymerization, blocked septum formation and ultimately caused cell death, whereas *Galleria mellonella* larvae infected with *S. aureus* showed markedly improved survival with minimal systemic toxicity. Ren *et al* (79) demonstrated that HKL decreased *Streptococcus mutans* survival at 30 μg/ml minimum inhibitory concentration, yet at 15 μg/ml suppressed EPS synthesis, lactic-acid production and biofilm biomass and downregulated the expression of the virulence genes *gtfB/C/D*, *comD/E* and *ldh* without harming human gingival fibroblasts, indicating its potential as an anticaries agent. Sophorolipid micelles encapsulating HKL (HKL-SLMs) developed by Lin *et al* (80) disrupted *S. aureus* biofilms *in vitro* by destroying extracellular polysaccharides, proteins and DNA; reducing planktonic counts by 6.42 $\log_{10}$ CFU/ml; and preventing early biofilm reformation. In a murine pneumonia model, these micelles decreased pulmonary bacterial load and inflammation, suggesting that they are promising formulations for refractory lung infections. Zheng *et al* (81) reported that the combination of HKL with resveratrol exerted synergistic antibiofilm effects against *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, reducing the levels of matrix polysaccharides and DNA while downregulating the expression of biofilm formation genes.

In viral infections, HKL showed promising antiviral activity against both RNA and DNA viruses. Zhao *et al* (82) identified HKL as a key antiviral component in Zhengqi tablets, a traditional Chinese medicine formulation, by targeting the 3CL/M^{Pro} of SARS-CoV-2, thereby inhibiting viral replication. Furthermore, Yang *et al* (83) evaluated the antiviral efficacy of HKL against *Micropterus salmoides* rhabdovirus, a pathogen that affects aquaculture. The authors reported that HKL markedly reduced viral load and cytopathic effects in infected cells and improved survival rates in infected fish, suggesting its potential as a natural antiviral agent in veterinary medicine. HKL protected Vero E6 and human A549-ACE2/TMPRSS2 cells from SARS-CoV-2-induced cytopathic effects, reducing viral RNA and infectious titers by up to ~1,000-fold. It acted at the post-entry step, inhibited multiple SARS-CoV-2 variants including Omicron and blocked the replication of MERS-CoV

Table I. Some delivery systems for the increasing of the Honokiol bioavailability.

First author/s, year	Category	Delivery system	Targeting mechanism	Key advantage	Major limitation	(Refs.)
Sampieri-Morán *et al*, 2025	Nano-formulation	SNEDDS	Lymphatic transport; bypass first-pass	High oral bioavailability	High surfactant content; GI irritation	(85)
Liu *et al*, 2025	Nano-formulation	Pt/HKL-NMs	Passive EPR	Synergistic antitumor potential	Complex preparation; batch variability	(86)
Thakur *et al*, 2024	Nano-formulation	Flunarizine-HKL NPs	Dual-drug co-delivery	Synergistic vascular targeting	Complex optimization; scale-up difficulty	(87)
He *et al*, 2024	Stimuli-responsive	CD-MOF	GSH-triggered disulfide cleavage	High loading; homologous targeting	pH-dependent stability; complex coating	(88)
Liao *et al*, 2025	Stimuli-responsive	Polycyclophosphazene Nano-HKL	GSH-responsive covalent bond cleavage	High plasma stability; precise release	Potential degradation toxicity	(89)
Wang *et al*, 2025	Stimuli-responsive	ASP-SS-BBR/HKL	GSH-responsive; dual-delivery	Berberine-HKL synergy	Unclear metabolic pathway	(46)
Miao *et al*, 2024	Mitochondrial	TPP-HKL	ΔΨm-driven accumulation	Potent mitochondrial toxicity	Hemolysis risk; platelet toxicity	(5)
Liu *et al*, 2025	Mitochondrial	XJB-HKL	mitochondrial inner membrane affinity	Low cytotoxicity; SIRT3 activation	Peptide enzymatic degradation	(63)

HKL, honokiol; SNEDDS, self-nano-emulsifying systems; Pt/HKL-NM, Platinum/HKL nanomedicines; EPR, enhanced permeability and retention; CD-MOF, cyclodextrin metal organic framework; ASP-SS-BBR, *Angelica sinensis* polysaccharide-berberineamphiphilic polymer; TPP, triphenylphosphonium; XJB-HKL, XJB peptide-conjugated honokiol; STAT3, signal transducer and activator of transcription 3; SIRT3, sirtuin 3; ΔΨm, mitochondrial membrane potential; GSH, glutathione.

and SARS-CoV, demonstrating broad-spectrum anticoronavirus activity combined with anti-inflammatory properties, warranting further animal and clinical evaluation (84).

In summary, HKL exerts anti-inflammatory effects and protects mitochondria by inhibiting the NLRP3, cGAS-STING and NF-κB pathways and activating SIRT3; it kills drug-resistant bacteria such as MRSA by blocking FtsZ and disrupting biofilms; additionally, it targets 3CLpro, which inhibits COVID-19 and its variants, resulting in broad-spectrum anti-infective activity with low toxicity.

6. Pharmacokinetics and delivery innovation

The clinical promise of HKL is hampered by low aqueous solubility and poor oral bioavailability. To overcome this, a succession of nano- and chemical strategies has been developed (Table I).

Nanoformulations. Lipophilic active compounds can be dissolved in the oil core of nanoemulsions (NEs) and be passively transported into the cells that absorb the NEs. Building on this concept, Sampieri-Morán *et al* (85) prepared both high-energy NE and low-energy self-nanoemulsifying drug delivery systems (SNEDDS) to orally deliver Magnolia bark extract; the formulations increased HKL bioavailability 3.47- and 3.98-fold, respectively, with the SNEDDS ((21.7±0.65 nm) and NEs (119.7±0.47 nm) both showing good stability. Liu *et al* (86) co-assembled HKL and Pt^{4+} into nanomicelles (Pt/HKL-NMs; 70% encapsulated) that simultaneously scavenged radicals, suppressed inflammation, killed bacteria and reduced drug toxicity. Thakur *et al* (87) used a QbD-CCD approach to engineer flunarizine-HKL coloaded cross-linked hybrid nanoparticles (>75% encapsulation) embedded in a thermoresponsive gel that released both drugs steadily for at least one month; combined administration protected zebrafish lateral-line neuromasts from cisplatin-induced hair-cell loss, outperforming either drug alone or the approved rescue agent sodium thiosulfate, and offered a new intratympanic strategy to prevent cisplatin ototoxicity.

Stimuli-responsive carriers. Various drug delivery systems have been developed to overcome the limitations of platinum-based chemotherapy. Among them, stimuli-responsive nanocarrier systems, recognized as one of the most promising

strategies, have attracted increasing attention. For instance, a glutathione-responsive cyclodextrin metal-organic framework (CD-MOF) loaded with HKL and indocyanine green achieved 94.08% breast tumor suppression in transplanted tumor-bearing mice under synergistic photochemotherapy (88). In addition, Liao *et al* (89) developed ~160 nm GSH-responsive polyphosphazene Nano-HKL particles by covalently linking HKL to hexachlorocyclotriphosphazene via a disulfide-containing linker. The construct remained stable in plasma and gradually released HKL in the glutathione-rich tumor microenvironment through disulfide bond reduction. Its redox-mediated delivery markedly suppresses A375 melanoma xenograft tumor growth, outperforming free HKL through inducing G_2/M cell cycle arrest and apoptosis and showing no observable systemic toxicity in major organs. The polysaccharide-berberine amphiphilic polymer (ASP-SS-BBR) loaded with HKL can achieve effective glutathione-responsive release. *In vitro* and *in vivo* evidence have both shown that this polymer can effectively target and inhibit the activity of hepatocellular carcinoma cells (46). Together, these studies demonstrate that pH- or GSH-gated HKL nanosystems can safely amplify therapeutic indices across kingdoms, from soil-borne bacteria to malignant melanoma.

Mitochondrial targeting. Mitochondrial targeting has emerged as a powerful strategy to amplify both the anticancer and neuroprotective actions of HKL. Miao *et al* (5) synthesized triphenylphosphonium-HKL conjugates (TPP-HKL) that accumulated 10-fold in isolated mitochondria and decreased the IC_{50} in cisplatin-resistant A549/DDP cells, while simultaneously reducing systemic hemolysis. In addition, Liu *et al* (63) coupled HKL to the mitochondria-directed XJB peptide; the resulting nanocojugate retained SIRT3-activating capacity, increased autophagy and upregulated the expression of the fusion protein Mfn-1, thereby conferring superior protection against neuronal injury *in vitro* and in zebrafish models of Alzheimer's disease at markedly lower concentrations than those of native HKL. Together, these studies demonstrate that mitochondrial targeting, whether via TPP^+ or XJB peptide, converts HKL into a more potent, selective and safer therapeutic for both cancer and neurodegeneration.

The evolution of HKL delivery systems reflects a trajectory from basic solubilization to sophisticated targeting. Nanoformulations (SNEDDS, Pt/HKL-NMs) primarily address the physicochemical limitations of HKL, enhancing bioavailability but lacking active targeting. CD-MOF, polyphosphazene, ASP-SS-BBR) introduce tumor microenvironment-triggered release, improving the therapeutic index but lacking widespread efficacy. Mitochondrial-targeted systems represent the current frontier: TPP-HKL achieves the greatest mitochondrial accumulation but is associated with hemolysis and platelet dysfunction, whereas XJB-HKL offers a safer alternative with peptide-mediated targeting; however, its efficacy is currently validated only in neurodegenerative models and its peptide stability *in vivo* remains to be optimized. No singular system currently offers a panacea across all the metrics; rational selection depends on the specific disease context, acceptable toxicity profile, and administration route.

7. Potential clinical applications

HKL is a low-molecular-weight biphenolic compound that readily crosses the blood-brain barrier (BBB) and exhibits pleiotropic bioactivities, conferring translational potential in several therapeutic areas. It has demonstrated antitumor effects against lung cancer, breast cancer, prostate cancer and glioblastoma. Its BBB permeability makes it a particularly promising candidate for brain malignancies. HKL also has neuroprotective effects that are relevant to neurodegenerative diseases, is beneficial for cardiovascular and metabolic disorders, and possesses anti-inflammatory and analgesic effects that are applicable to arthritis and periodontitis treatment and nonopioid pain management.

Several features favor clinical translation. HKL is derived from a medicinal and edible plant (*Magnolia officinalis*), with a relatively favorable toxicity profile. Advances in nanoformulations, including liposomes, polymeric micelles and nanoparticles, have substantially improved its bioavailability despite poor aqueous solubility. Additionally, HKL acts as a chemosensitizer alongside cisplatin and doxorubicin and can reverse multidrug resistance. Preliminary evidence from humans supports some of effects: a randomized, double-blind, placebo-controlled trial demonstrated that Relora®, a standardized proprietary extract combining HKL-containing *M. officinalis* bark extract with *Phellodendron amurense*, markedly reduced salivary cortisol exposure and anxiety symptoms in moderately stressed adults over a four-week intervention period (90), Furthermore, early-phase clinical investigation has progressed beyond preclinical stages in China, where a Phase I trial (CTR20170822) has been conducted to evaluate the efficacy of HKL in cancer patients and an additional registered trial (CTR20240113) is being conducted to examine its application in a broader therapeutic context, collectively representing the most advanced clinical development of HKL as an investigational agent to date.

However, challenges remain. Its short plasma half-life, rapid metabolism, and poor water solubility create difficulties in its formulation, particularly for intravenous administration. Large-scale good laboratory practice (GLP)-compliant toxicological data are also lacking. A zebrafish study revealed that 0.6 mg/l HKL caused gill bleaching, liver hemorrhage and 46% mortality, whereas 0.2 mg/l was largely nontoxic. High-dose HKL upregulated the expression of apoptosis-related genes (*Bax, caspase-3, caspase-9* and *P53*), elevated hepatic TNF-α and ROS levels, and increased the activity of antioxidant enzymes (catalase), leading to oxidative stress and tissue necrosis. Low doses, by contrast, triggered adaptive antioxidant responses with increased mitochondrial membrane potential. These findings confirm dose-dependent toxicity and highlight the need for rigorous safety evaluation (91). Stringent purity and quality control standards for large-scale manufacturing must also be established.

Despite encouraging preclinical findings, a substantial translational gap remains. Typically, in murine studies, 20-200 mg/kg HKL is administered via intraperitoneal or intravenous routes, achieving plasma concentrations that may not be readily attainable in humans at tolerable doses. Much of the mechanistic evidence has been derived from murine studies. The transition from DMSO-solubilized preparations

to GMP-grade nanoformulations introduces bioequivalence uncertainties yet to be characterized in humans. The classification of HKL as a nutraceutical may complicate investigational new drug filing strategies, potentially slowing formal clinical development. These factors may contribute to the limited human pharmacokinetic data, validated biomarkers, and target engagement evidence currently available from immortalized cell lines or xenograft models, which may not fully recapitulate human disease complexity.

Currently, most HKL research remains preclinical and registered human clinical trials are limited. A systematic search of ClinicalTrials.gov and the Chinese Clinical Trial Registry (accessed April 2026) revealed five trials. These trials cover oncology, neurology, psychiatry and oral health, yet they all share fundamental limitations that preclude the establishment of HKL-specific efficacy. Among trials registered on ClinicalTrials.gov, NCT06566443 (registered 2024, not yet recruiting) was conducted to evaluate a HKL-containing dietary supplement in early-stage non-small cell lung cancer patients with an open-label, preoperative design and safety and quality-of-life endpoints; its dietary-supplement framing and confounding constituents preclude the attribution of any efficacy signal to HKL alone. NCT06672965 (completed 2024) was performed to investigate an oral HKL formulation for anxiety in a randomized, double-blind, placebo-controlled trial; however, it was positioned as an antistress dietary supplement rather than a pharmaceutical intervention, with HKL doses likely below pharmacologically active thresholds. NCT00966953 (completed 2008, unpublished) was conducted to examine an oral health HKL formulation for gingival conditions in a randomized parallel-group design; this trial assessed local, topical action rather than systemic absorption, providing no pharmacokinetic or efficacy data relevant to internal indications.

In China, a phase I trial (CTR20170822; registered 2017) of liposomal HKL in advanced solid tumors completed initial enrollment. Full results from this cohort have not appeared in peer-reviewed literature. Efficacy claims in subsequent papers rely on indirect citations, making independent verification impossible. Notably, the indication shifted from broad solid tumors in this early trial towards recurrent glioblastoma in a subsequently registered phase II trial (CTR20240113, 2024), suggesting a strategic pivot toward central nervous system malignancies where the blood-brain barrier permeability of HKL confers a mechanistic advantage rather than robust efficacy signals in systemic cancers.

Collectively, these trials reflect the multi-indication exploratory potential of HKL but underscore the absence of large-scale phase III evidence, the predominance of nutraceutical-framed development and the lack of dose-optimization studies achieving pharmacologically relevant systemic exposure. No phase III randomized controlled trial evaluating HKL as a primary oncologic or neuroprotective intervention has been conducted. Approval as a standalone prescription drug therefore remains a distant prospect under current evidence standards. Near-term applications are likely restricted to premium nutraceuticals with validated bioavailability enhancement, adjunctive therapeutics in combination with established chemotherapeutic agents and nanodelivery-based formulations for CNS indications where blood-brain barrier permeability provides a distinct, mechanistically grounded advantage.

Advancing HKL toward clinical validation requires a phased evidence-building approach (92). Priorities include rigorous human pharmacokinetic characterization of GMP-grade formulations to address dose translatability uncertainties, identification of clinically feasible biomarkers for patient enrichment and mechanistic early-phase trials with paired biomarker assessments to confirm target engagement. Only upon completion of these steps would comparative effectiveness studies against standard-of-care regimens be informative and cost-effective.

8. Limitations and evidence gaps

Publication bias and selective reporting. The narrative synthesized in the present review is predominantly derived from studies reporting positive pharmacological outcomes, reflecting a well-documented publication bias in natural product research (93). This bias is not merely theoretical: Direct evidence exists that HKL inhibited bend3 hemangioma growth *in vitro* but failed to affect proliferation in nude mice, with the authors explicitly noting this negative result as unpublished data (94). Such selective publication of positive *in vitro* findings while omitting negative *in vivo* outcomes artificially inflates the perceived translational potential.

Dose-dependent toxicity and narrow therapeutic window. Although HKL has favorable safety profiles at therapeutic doses, converging evidence from *in vitro*, *in vivo* and limited clinical data suggests that its therapeutic window is critically narrow, raising important concerns for translational and clinical applications.

In vitro cytotoxicity thresholds vary considerably across cell lines, complicating the establishment of a universal safe concentration range. Yang *et al* (95) demonstrated that liposomal HKL (LH) did not induce cytotoxicity in hepatocellular carcinoma cell lines (HepG2, SK-HEP1, and SMCC7721) or normal liver cells (LO2) at concentrations <40 μmol/l, whereas it did induce cytotoxicity >60 μmol/l after 24 h of exposure. By contrast, Salgado-Benvindo *et al* (84) reported substantial cytotoxicity in HuH-7 cells at much lower concentrations, with a 50% reduction in viability (CC_{50}) at ~20 μmol/l. The two- to threefold variation in these thresholds reflects inherent cell line differences. It also complicates any direct translation of *in vitro* data to *in vivo* or clinical settings.

In vivo data add further constraints. A rat developmental toxicity study reported a NOAEL of 600 μg/kg/day and embryo-fetal toxicity at 2,000 μg/kg/day, yielding a 3.3-fold margin (96). In a separate chronic study, mice given *Magnolia officinalis* extract equivalent to 2 mg/day HKL for three months showed HKL accumulation in serum, urine and kidneys, with elevated serum creatinine and blood urea nitrogen levels and ultrastructural renal damage (97; and references therein). Notably, similar nephrotoxicity was not reported in 21- or 90-day subchronic studies (97). Whether this reflects duration-dependent toxicity, species differences, or formulation effects remains to be clarified.

Intravenous HKL has been administered to cancer patients at doses ≤50 mg/kg (98). In beagle dogs, lethality was reported

at 66.7-100.0 mg/kg (99); in pregnant rats, developmental toxicity appeared at 2,000 μg/kg/day (96). These values are not normalized for species differences in metabolism or body surface area. Direct comparison is therefore not supported by available pharmacokinetic data.

Oral *Magnolia* bark extract containing combined magnolol and HKL at 1-10 mg has been studied in volunteers over periods ranging from single doses to one year, with no reported adverse effects attributed to the neolignans (97). The route, formulation, and indication differ markedly from those in the intravenous oncological setting.

Safety appears to depend on dose, duration, route and population. Cumulative nephrotoxicity in rodents emerged only after three months of exposure (97). Formal dose-escalation trials in humans are lacking. The maximum tolerated dose remains undefined.

9. Conclusions

The 2023-2025 research corpus positions HKL as a prototypical multitarget nutraceutical transitioning toward pharmaceutical credibility. Mechanistically, HKL can directly bind to targets such as NLPR3, FGFR1, the AMPK1 subunit, ERα and PD-L1 and exerts its pharmacological effects at the nexus of mitochondrial homeostasis, inflammasome restraint, and oncogenic signaling, offering broad-spectrum utility. Contemporary nanotechnology and medicinal-chemistry efforts have rectified historical PK liabilities, enabling first-in-human trials. A coordinated precision-medicine framework that integrates predictive biomarkers and AI-assisted drug design, will be pivotal for the success of HKL in modern therapeutics.

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Authors' contributions

WJ conceived and designed the review structure; performed the literature search and data extraction; drafted the original manuscript; prepared the figures and tables and reviewed and edited the final version. Data authentication is not applicable. The author read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The author declares that they have no competing interests.

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