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•Special topic•

Honokiol: A naturally occurring lignan with pleiotropic bioactivities

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[ABSTRACT] Honokiol is the dominant biphenolic compound isolated from the *Magnolia* tree, and has long been considered as the active constituent of the traditional Chinese herb, '*Houpo*', which is widely used to treat symptoms due to 'stagnation of *qi*'. Pharmacological studies have shown that honokiol possesses a wide range of bioactivities without obvious toxicity. Honokiol protects the liver, kidneys, nervous system, and cardiovascular system through reducing oxidative stress and relieving inflammation. Moreover, honokiol shows anti-diabetic property through enhancing insulin sensitivity, and anti-obese property through promoting browning of adipocytes. *In vivo* and *in vitro* studies indicated that honokiol functions as an anti-cancer agent through multiple mechanisms: inhibiting angiogenesis, promoting cell apoptosis, and regulating cell cycle. A variety of therapeutic effects of honokiol may be associated with its physiochemical properties, which make honokiol readily cross the blood brain barrier and the blood-cerebrospinal fluid barrier, with high bioavailability. In the future, more clinical researches on honokiol are needed to fully authenticate its therapeutic values.

[KEY WORDS] Honokiol; Natural sources; Ethnopharmacological uses; Physicochemical properties; Bioactivities; Clinical trials
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Introduction

Magnolia barks have been commonly used as traditional alternative medicines for treating stress-related symptoms due to anxiety and emotional imbalances, especially in China and Japan. Honokiol (HK, Fig. 1) is a lignan which has been considered as one of main biological active compounds in the *Magnolia* tree, along with magnolol, 4-*O*-methylhonokiol, and obovatol. HK was initially isolated from *Magnolia obovata*, which is a component of herbal tea, including *Houpo* and *Saiboku-tu* [1]. The compound exhibits multifunctional activities, such as anti-oxidation, anti-inflammation, kidney protection, liver protection, neuroprotection, cardiovascular protection, anti-obesity, anti-diabetes and anti-cancer (Table 1). Because of its physical properties, HK can readily cross the blood brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCFB), acting as a potent candidate with high bioavailability. Interestingly, HK is identified as an activator of sirtuin 3 (SIRT3), an NAD^+-dependent deacetylase, in cardiomyocytes [2]. The current review is aimed to summarize the natural sources, traditional uses and physicochemical properties of HK, discuss the pharmacological properties and clinical trials of HK in the recent years, and evaluate its therapeutic potential in the future.

Natural Sources and Traditional Uses of HK

HK is widely distributed in the barks, seed cones, and leaves of the *Magnolia* tree in many parts of the world [3, 4]. For traditional herbal medicine, especially in China and Japan, *M. biondii*, *M. obovata*, and *M. officinalis* are commonly used, which are the major natural sources of HK [4]. *M. grandiflora*, a native species of South American, and *M. dealbata*, a Mexican species, have also been reported as the

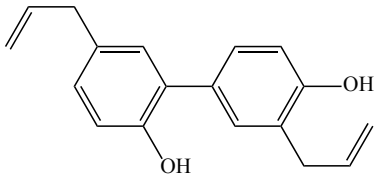

Fig. 1 Chemical structure of HK

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Table 1 Pharmacological activities of HK *in vivo* and in *vitro*

Disease model/ Pharmacological activity	Model	Regulated substances/receptors	Reference
Inflammation	HRMCs	Inflammatory cytokines (IL-1β, IL-18, TNF-α, PGE2, TGF-β1, NO and ROS)	[16]
Glomerulonephritis (GN)	Wistar rats	ICAM-1 and MCP-1 mRNA	[20]
Inflammation	Macrophages	MAPKs, PKC-α, and NF-κB pathways	[21]
Inflammatory pain	NMRI mice	C-Fos protein in the superficial (I-II) laminae of the L4-L5 lumbar dorsal horn	[24]
Eccentric exercise-induced skeletal muscle damage	Wistar rats	NF-κB	[23]
Collagen-induced arthritis	DBA/1J mice	Inflammatory cytokines (IL-17, IL-1β and TNF-α), matrix metalloproteinases (MMP-3, MMP-9 and MMP-13)	[18]
Oxidative damage	AML12 hepatocytes	SIRT3	[13]
Liver oxidative injury	C57BL/6 mice	SIRT3	[13]
Acute cytotoxicity	Renal epithelial cells	ROS and cytoskeletal protein (actin and tubulin)	[26]
Renal fibrosis	NRK-52E cells	TGF-β1/Smad signaling pathway, extracellular matrix Type I (α1) collagen and fibronectin	[28]
Alcoholic fatty liver	Wistar rats	SREBP-1c	[86]
NAFLD	C57BL/6J mice	PPAR-γ	[37]
Oxidative stress induced neurotoxicity	PC12 cells	Keap1/Nrf2/ARE pathway	[43]
Cerebral ischemia	ICR mice	Na^+, K^+-ATPase activity and mitochondrial functions	[41]
AD	PC12 cells	ROS, intracellular calcium, and caspase-3	[44]
CUMS	ICR mice	5-HT	[47]
MI/R	SD rats	SIRT1-Nrf2 pathway	[50]
Spontaneously hypertension	SHR	NO, and RhoA/Rho-kinase pathway	[52]
Atherosclerosis	RASMCs	ERK-NF-κB pathway	[55]
HG and IT	INS-1 cells	Nrf2/ARE pathway	[58]
Type 2 diabetes	KKAy mice	PPAR-γ	[60]
Obesity	3T3-L1 preadipocytes	Ras/ERK1/2 and PI3K/Akt pathways	[61]
Anti-angiogenesis	Human retinal pigment epithelial cells (D407)	HIF pathway	[78]
Anti-angiogenesis	Mouse D_3 ES cells	MAPK/mTOR signaling pathway	[80]
Anti-proliferation	ER-negative human breast adenocarcinoma MDA-MB-231 cells	c-Src/EGFR-mediated signaling pathway	[67]
Anti-proliferation	PC-3 and LNCaP cells	Protein levels and/or phosphorylation of Rb and E2F1	[69]
Cell migration	HepG2 cells	Ras GTPase-activating-like protein (IQGAP1), Cdc42/Rac1	[87]
Apoptosis	HepG2 cells	MAPK, procaspase-3 and -9, caspase-3	[74]
Lymphangiogenesis and metastasis	C57BL/6 mice	VEGFR-3	[88]
Apoptosis	Human NSCLC cells	cellular FLICE-inhibitory protein (c-FLIP)	[89]

sources of HK. Furthermore, many HK derivatives have been isolated, including 8′, 9′-dihydroxymagnaldehyde E (**1**), 8′, 9′-dihydroxyhonokiol (**2**), erythro-7-*O*-methylhonokitriol (**3**), erythro-honokitriol (**4**), threo-7-*O*-methylhonokitriol (**5**), threo-honokitriol (**6**), magnaldehyde E (**7**), magnotriol B (**8**), magnaldehyde B (**9**), and magnolol (**10**) (Fig. 2) [5].

In China, *Magnolia* bark is called *Houpo*, which has been widely used in traditional Chinese medicine (TCM) formulas, such as *Banxia Houpo Tang*, *Xiao Zhengai Tang*, *Pingwei San* and *Shenmi Tang* [4, 6]. *Houpo* is traditionally used in Eastern Asia as an analgesic in the treatment of anxiety and mood disorders [6, 7]. In Japan, *Hange-koboku-to* (*Banxia-houpo-tang*) and *Saiboku-tu*, two prescriptions containing *Magnolia* barks, are still used in clinical setting [8].

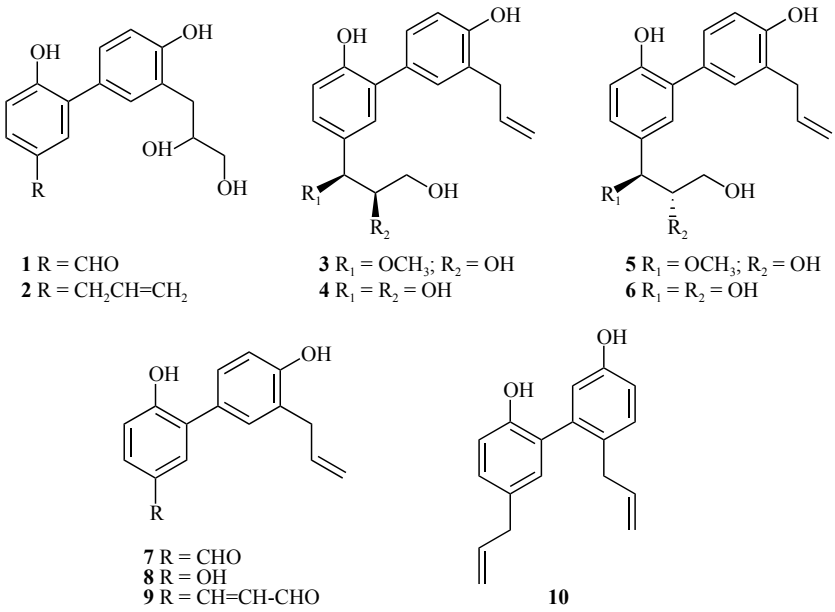

Fig. 2 Examples of HK derivatives from traditional Chinese herbs, 8′, 9′-dihydroxymagnaldehyde E (1), 8′, 9′-dihydroxyhonokiol (2), erythro-7-*O*-methylhonokitriol (3), erythro-honokitriol (4), threo-7-*O*-methylhonokitriol (5), threo-honokitriol (6), magnaldehyde E (7), magnotriol B (8), magnaldehyde B (9), and magnolol (10)

Notably, *Hange-koboku-to* is generally used to treat symptoms such as hoarseness and foreign body sensation in the throat.

Physicochemical Properties of HK

HK belongs to the class of neolignan biphenols and can be synthesized in the shikimic acid pathway [9]. The molecular mass of HK ($C_{18}H_{18}O_2$) is 266.34 g·mol^{-1}. The International Union of Pure and Applied Chemistry (IUPAC) name of HK is 2-(4-hydroxy-3-prop-2-enylphenyl)-4-prop-2-enylphenol. HK is a fine white powder with an aromatic smell. The monomer is colorless scale-like crystals. The melting temperature and boiling point of HK are 86–86.5 °C and 400 °C, respectively. It is soluble in common organic solvents, easily soluble in benzene, ether, chloroform, and ethanol, but insoluble in water.

Pharmacological Activities of HK

Anti-oxidation

Generally, phagocytes (such as neutrophils, eosinophils and monocytes) produce reactive oxygen species (ROS) when being stimulated, and excessive accumulation of ROS causes oxidative stress [10]. It was reported that HK reduces the activity of assembled-nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is the major ROS producing enzyme in neutrophils [11]. Further studies indicated that HK is a pharmacological activator of SIRT3 in the mitochondria, and can increase oxygen consumption rate and reduce ROS production [12]. Oxidative stress is a critical cause of liver damage. A recent study found that HK protects *tert*-butyl hydroperoxide (*t*-BHP)-injured AML12 hepatocytes and chloroform-induced liver damage in mice through activating SIRT3. HK weakens the acetylation of superoxide dismutase 2 (SOD2) and peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) to decrease ROS accumulation and promote mitochondrial biogenesis, respectively. Through regulating the Ku70 dynamic-related protein 1 axis, HK attenuates *t*-BHP-induced mitochondrial destruction [13]. By scavenging free radicals and regulating active oxygen levels, HK directly or indirectly participates in various regulations of oxidative stress, which might be due to its phenolic core structure [2, 14]. Coupled with its high fat solubility, the anti-oxidative property of HK might be one of the major reasons for HK's versatility. The traditional functions of *Houpo* are to warm the middle, lower the *qi*, dry dampness and resolve phlegm, which might be attributable to the anti-oxidative property of HK.

Anti-inflammation

Inflammation is the response of the body's immune system to pathogenic factors and their damage. Many diseases are accompanied with inflammation, such as neurodegenerative diseases, cancer, pain, and metabolic disorders. Due to adverse reactions, many anti-inflammatory agents are not suitable for long-term use. In contrast, traditional herbal medicines have long been used for treatment of acute or chronic inflammation; more and more researchers confine their attention to natural compounds.

HK exerts anti-inflammatory effects through regulating a variety of inflammatory mediators. In human renal mesangial cells (HRMCs), HK inhibits the expression of high glucose (HG)-induced pro-inflammatory cytokines, for instance interleukin (IL)-1β, IL-17, IL-18, tumor necrosis factor-α (TNF-α), prostaglandin E2 (PGE2), transforming growth factor-β1 (TGF-β1) and nitric oxide (NO), in a dose-depend-

ent manner [15-18]. Oral administration of HK inhibits the progression of collagen-induced arthritis by reducing the expression of matrix metalloproteinases (MMP-3, MMP-9, and MMP-13) and oxidative stress [18].

Moreover, HK markedly inhibits the expression of chemokines, such as monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), and RANTES, which are essential in the pathogenesis of diabetic nephropathy (DN) and non-diabetic nephropathy (NDN) [16, 19]. In rats with anti-Thy1 disease, HK attenuates proteinuria, reduces the accumulation of glomerular macrophages, suppresses the proliferation of mesangial cells, and ameliorates glomerular sclerosis through suppressing intracellular adhesion molecule-1 (ICAM-1) and MCP-1 mRNA in the early phase [20].

The inflammation-related signaling pathways are also involved in the anti-inflammatory effect of HK. In macrophages, HK inhibits lipopolysaccharide (LPS)-induced phosphorylation of extracellular signal regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase 1/2 (JNK1/2), and p38. Furthermore, HK suppresses the membrane translocation of protein kinase C (PKC)-α, and the activation of nuclear transcription factor κ-B (NF-κB) [21, 22]. Through inactivating NF-κB, HK downregulates the expression for cyclooxygenase-2 (COX-2), inducible NO synthase (iNOS) and proinflammatory cytokine genes, and protects Wistar rats against skeletal muscle damage caused by inflammation [23]. In an inflammatory pain model of NMRI mice induced by glutamate, HK exerts analgesic effects through reducing the expression of c-Fos protein in the superficial (I-II) layer of the L4-L5 low back horn [24].

Both *in vivo* and *in vitro* results suggest the potent anti-inflammatory property of HK, mainly through down-regulation of pro-inflammatory factors, which indicate the potential role of HK in the treatment of inflammation-related diseases. In traditional Chinese medicine, *Houpo* is used as an analgesic, which might be related with the anti-inflammatory effect of HK.

Kidney protection

Many studies reported the protective effect of HK on the kidneys [25, 26]. This function is closely related to its anti-oxidative activity. HK alleviates aristolochic acid-mediated nephrotoxicity by reducing ROS level and maintaining cell redox balance and anti-oxidative capacity [25, 26]. By increasing the levels of actin and tubulin, HK stabilizes the cytoskeletal morphology, thereby maintaining the polarity and morphology of renal epithelial cells [26]. Overexpression of extracellular matrix (ECM) is an important feature of the pathogenesis of fibrosis [27]. The TGF-β1 signaling pathway can activate tubulointerstitial fibrosis. TGF-β1 and connective tissue growth factor (CTGF)-induced phosphorylation of Smad-2/3 in renal tubular cells was inhibited by HK [28, 29]. HK also decreases the mRNA expression of MCP-1 and ICAM-1, as well as the accumulation of ECM (type I collagen and fibronectin) in renal fibrosis rats [28]. HK might represent a therapeutic agent to treat renal fibrosis. The above bioactivities of HK might contribute to traditional application of *Houpo* in treating water poisoning syndrome.

Liver protection

In rat and human liver, the main metabolic pathways of HK include glucuronidation and sulfation [30]. HK has a great influence on the activity of human liver microsome cytochrome P (CYP) 450 enzymes and uridine diphosphate-glucuronic acid-glucuronosyltransferase (UGT) enzymes [31–33]. CYP450 enzyme isoforms show different impacts on the metabolism of HK in rat liver microsomes: CYP2E1 subtype enzyme is responsible for the oxidation of HK terminal double bonds to epoxy metabolites, CYP3A4 subtype enzyme is responsible for further hydrolytic metabolism, and CYP1A2 promotes the cleavage of the carbonyl groups [32]. In rats treated with HK, the pharmacokinetic parameters of theophylline and tolbutamide were changed, which may be due to inhibition of CYP1A2 and CYP2C11 [33]. Actually, HK strongly inhibited CYP1A2-mediated phenacetin *O*-deethylation, CYP2C8-mediated amodiaquine *N*-deethylation, CYP2C9-mediated diclofenac 4-hydroxylation, CYP2C19-mediated *S*-mephenytoin 4-hydroxylation, and UGT1A9-mediated propofol glucuronidation [31]. These studies suggest that HK may affect the metabolism of other drugs when administered together. During clinical application, pharmacovigilance should be done to prevent adverse reactions.

Long-term alcohol consumption is an important cause of liver fibrosis. Alcohol abuse promotes the secretion of pro-inflammatory cytokines (TNF-α, IL6 and IL8), oxidative stress and lipid peroxidation, which in turn result in inflammation, apoptosis and fibrosis. In ethanol-treated RAW264.7 cells, extracts containing HK reduces the production of TNF-α, ROS and superoxide anion free radicals, the activation of NADPH oxidase, and ultimately cell death [34]. When liver injury occurs, serum indicators increase, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Treatment with HK not only reduces ALT and AST in serum, but also reduces the levels of liver malondialdehyde (MDA), one of the important products of lipid peroxidation [35-37]. Glutathione (GSH) is an important antioxidant participating in ROS scavenging in many organelles. HK treatment restored hepatic GSH content and inhibited TNF-α secretion in chronic ethanol-fed rats [34]. Moreover, HK was reported to ameliorate alcoholic steatosis through blocking sterol regulatory element-binding protein-1c (SREBP-1c)-mediated fatty acid synthesis [34]. Liver macrophages, both pro-inflammatory M1 type and anti-inflammatory M2 type, play a key role in the pathogenesis of hepatitis [38]. HK has a protective effect on nonalcoholic fatty liver disease (NAFLD), possibly through polarizing macrophages to M2 phenotype through peroxisome proliferator-activated receptor (PPAR)-γ activation [35, 37]. In China, *Houpo* is often prescribed to treat hangover, which may be partly verified by the above bioactivities of HK.

Neuroprotection

Houpo is reported to relieve headache and irritability, thus the regulatory effect of HK on the nervous system has been widely investigated. HK possesses neuroprotective property, mainly due to its ability to across the BBB and BSCB [39, 40]. The brain and nerves have a high oxygen consumption rate, with a large amount of lipids as energy source, which are vulnerable to oxidative stress. By inhibiting the production of ROS and maintaining mitochondrial function and Na^+, K^+-ATPase activity, HK protects the brain against ischemia-reperfusion injury in mice [41]. Though elevation of GSH level and upregulation of cytoprotective molecules, including heme oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), thioredoxin (Trx1) and Trx1 reductase (Trx1R), HK alleviates oxidative stress induced neurotoxicity via the Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor (erythroid-derived 2)-like 2 (Nrf2)/antioxidant response element (ARE) pathway [42, 43].

Actually, HK decreases amyloid β peptide (Aβ)-induced PC12 cells death through suppression of intracellular calcium elevation and inhibition of caspase-3 activity, which provides new evidence for the treatment of Alzheimer's disease [44]. Moreover, HK prevents learning and memory impairment and cholinergic deficit in SAMP8 mice [45]. It was reported that the extract from the barks of *M. officinalis*, containing HK as the major constituent, shortened the immobility time of mice in the forced swimming test and tail suspension test, reduced 5-hydroxytryptamine (5-HT) turnover in some brain regions (the frontal cortex, hippocampus, striatum, hypothalamus and nucleus accumbens), and reversed chronic unpredictable mild stress (CUMS)-induced deficit in sucrose intake to prevent anhedonia in rats [46–48].

The above studies showed that HK is involved in protecting cerebral ischemia, and possesses the effects of anti-learning and memory disorders, anti-Alzheimer's disease, and anti-anxiety. However, the underlying mechanisms are complex. For better practical applications of HK in neuroprotection, further clinical trials are needed to verify its safety and effectiveness.

Cardiovascular protection

In traditional Chinese medicine, *Houpo* is used to eliminate tightness in the chest and abdomen, and invigorate blood circulation, which might be correlated with the strong protective effect of HK on the heart [49]. In recent years, the role of oxidative stress on cardiovascular diseases and the underlying mechanisms have received widespread attentions. It is generally believed that oxidative stress is involved in atherosclerosis, hypertension, upset tremor, myocardial ischemia/reperfusion injury, and cardiomyopathy. HK ameliorates myocardial ischemia/reperfusion injury in type 1 diabetic rats through activating the SIRT1/Nrf2 signaling pathway [50]. During this process, HK activated SIRT1, enhanced Nrf2 nuclear translocation, increased anti-oxidative capacity, and decreased apoptosis [49, 50]. Additionally, HK has a therapeutic window of at least 5 h after the onset of cerebral ischemia or 3 h after reperfusion in rats, which may partly result from the disruption of postsynaptic density protein 95 (PSD95)-NO production by activating neuronal NO synthase (nNOS) interaction, leading to the inhibition of neurotoxic NO production [51].

HK can dilate blood vessels, which may be achieved through inhibiting the RhoA/Rho-kinase signaling pathway [52, 53]. HK inhibits vascular contraction in response to U46619 and sodium fluoride by inhibiting the activation of RhoA and the subsequent phosphorylation of myosin phosphatase targeting subunit 1 (MYPT1) PKC-potentiated inhibitory protein for heterotrimeric myosin light-chain phosphatase of 17 kDa (CPI17), and the phosphorylation of 20 kDa myosin light chains (MLC_{20}) [53]. Long-term administration of HK to spontaneously hypertensive rats (SHR) decreased systolic blood pressure through increasing NO production [52]. With the release of NO, HK inhibits platelet aggregation and thus suppresses arterial thrombosis [54]. For atherosclerosis, HK effectively suppressed TNF-α-induced cell migration and MMP expression in rat aortic smooth muscle cells through inhibition of the ERK/NF-κB pathway [55].

In terms of cardiovascular diseases, HK can relieve myocardial ischemia/reperfusion injury, lower blood pressure, and produce anti-atherosclerosis effects.

Anti-diabetes and anti-obesity

Houpo is reported to have hypoglycemic effect and commonly prescribed for the treatment of diabetes, such as *Houpo-sanwu-tang*. As the major ingredient, HK has attracted increasing attentions as a potential anti-diabetic drug [56]. Diabetic complications (such as diabetic nephropathy, liver disease, cardiomyopathy and other cardiovascular diseases) are very harmful to the human body and even lead to death. Oxidative stress and inflammation play important roles in the pathogenesis of diabetes complications [57]. In light of anti-inflammatory and anti-oxidative properties, HK has high potential in the treatment of diabetes. HK acts as a potent ROS scavenger *via* the Nrf2/ARE pathway, so as to effectively attenuate oxidative stress and improve pancreatic β cell function of DM rats under HG and intermittent hypoxia (IH) treatment [58]. In murine 3T3-F442A adipocytes, HK induces the 2-deoxy-2-[(7-nitro-2, 1, 3-benzoxadiazol-4-yl)amino]-D-glucose (2-NBDG) uptake by 50% under insulin stimulation and these changes were abolished by selective inhibitors of the insulin signaling pathway, which suggests that HK stimulates glucose uptake in insulin-sensitive adipocytes by activating the insulin signaling pathway [1]. The agonists of the nuclear receptor PPAR-γ are used to treat hyperglycemia in patients with metabolic syndrome or type 2 diabetes [59]. According to computer simulation, HK does directly bind to the purified PPAR-γ ligand binding domain and act as a partial agonist [59, 60]. Oral administration of HK lowers blood sugar level and suppresses weight gain in diabetic KKAy mice [60].

Adipocytes are considered to be the main drug target in the treatment of obesity and obesity-mediated metabolic syndrome. By increasing the expression of PPARc2 mRNA and

enhancing the insulin signaling pathways such as Ras/ERK1/2 and phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt), HK promotes adipocyte differentiation and induces large adipocytes apoptosis [61]. Through the activation of ERK, HK induces adipocyte browning by elevating the levels of brown adipocyte-specific genes such as cell death-inducing DFFA-like effector a (Cidea), cytochrome c oxidase subunit8 (Cox8), fibroblast growth factor21 (FGF21), PGC-1α, and uncoupling protein 1 (UCP1). HK promotes the apoptosis of 3T3-L1 white adipocytes and inhibits the apoptosis of HIB1B brown adipocytes through reverse regulation of the pro-apoptotic protein B-cell lymphoma-2-associated X protein (BAX) and anti-apoptotic protein B-cell lymphoma (Bcl)-2 [62]. These results indicate the potential of HK as an anti-obesity agent. It was also reported that HK lowered the weight of white adipose tissue (WAT), decreased adipocyte size and protected against insulin resistance in high-fat diet (HFD)-fed mice [63]. Through regulating the balance of WAT and brown adipose tissue (BAT), HK effectively improves obesity.

Anti-tumor

Due to their efficacy and safety, herbal medicines are widely used in cancer treatment. Many anti-cancer drugs have been found from herbal medicines, such as maytansine, taxol and triptolide. In traditional Chinese medicine, *Houpo* is used to remove dampness and reduce phlegm, which indicates its potential to treat tumors. HK is reported to have therapeutic effects on many cancers, including skin cancer [64, 65], breast cancer [66, 67], esophageal cancer [68], prostate cancer [69], gastric cancer [70], ovarian cancer [71], brain cancer [72], lung cancer [73], and liver cancer [74].

Tumor growth is inseparable from the material supply of blood vessels, and abnormal structure and function of blood vessels will promote tumor deterioration [75]. Therefore, the level of vascular endothelial growth factor (VEGF) in serum is closely associated with tumor growth and serves as a marker of cancer diagnosis [76]. Blocking VEGF expression inhibits tumor growth and prevents metastasis [77]. HK is reported to inhibit tumor angiogenesis. HK decreases hypoxia-inducible-factor (HIF)-mediated expression of pro-angiogenic genes under hypoxic conditions [78]. The activation, proliferation, invasion, migration, and tube formation of endothelial cells (ECs) are the fundamental steps for angiogenesis [79]. HK inhibits the vascular formation of mouse embryonic stem (mES) cells on 3-D collagen gel and decreases the expression of endothelial biomarkers VEGF receptors (VEGFR)2 and platelet endothelial cell adhesion molecule (PECAM) in the differentiated embryoid body-derived endothelial cells through blocking the mitogen-activated protein kinase (MAPK)/mammalian target of rapamycin (mTOR) signaling pathways [80].

Several proteins function as the potential targets for the anti-tumor effect of HK. HK blocks signaling in p53 defective tumors and activates ras through directly blocking the activation of phospholipase D [81, 82]. In addition, HK causes the death of wild-type p53 cells by inducing cyclophilin D to enhance the mitochondrial permeability transition pore. In MDA-MB-231 human breast cancer cells, HK exerted antiproliferative activity with the cell cycle arrest at the G_0/G_1 phase and sequential induction of apoptotic cell death by down-regulating the activation of the c-Src/epidermal growth factor receptor (EGFR)-mediated signaling pathway [67].

Till now, most of the studies have been conducted on cancer cells, and there is a lack of clinical data. In addition, tumor treatment usually requires high selectivity. The clinical application of HK urgently requires more research on targeted preparations.

Clinical Trials of HK

There are a few clinical trials related to HK. The effects of proprietary substitutes of Magnolia Bark and Phellodendron Bark Extract (Relora®) on worries, stress and sleep in healthy premenopausal women have been evaluated, which demonstrates that Relora can relieve mild transient anxiety in premenopausal women [83]. Another study found that during a six-month period of use, men who used a dentifrice containing 0.3% *Magnolia* extract significantly improved gingivitis than the control group [84]. Two studies indirectly revealed HK's great potential in anti-inflammatory and anti-anxiety.

Conclusion

In summary, recent studies have confirmed that HK is a pleiotropic compound, suggesting it functions through a number of pathways, with great clinical potential (Fig. 3). The broad pharmacological activity of HK may be related to its numerous metabolites *in vivo* [85]. Because of its physical properties, HK can readily cross the BBB and the BCFB. As a result, HK is a potent candidate with high bioavailability. However, we must recognize the following points: 1) Although HK has been identified to modulate many targets, its anti-oxidative property is the most fundamental pharmacological basis. 2) For practical clinical applications, it is of great significance to develop highly selective targeted preparations of HK. 3) The current pharmacological research on HK is still based on pre-clinical studies, which is still difficult to determine the actual action and mechanism of HK in the human body, thus many of its pharmacological effects need to be further verified by random and controlled clinical trials with large-scale samples. 4) Like many herbal ingredients, evidence-based medicine should be used as a guide to establish a complete drug quality control system to ensure the quality and safety of drugs. Precision medicine advances rapidly, so more pharmaceutical studies should be carried out to develop highly selective targeted preparations of HK and enhance the oral bioavailability of HK. On the other hand, more pharmacological studies are needed to identify and verify the direct targets of HK, which may facilitate the structure optimization of HK and even its clinical application. Till now, no clinical trial was performed on HK alone, but as an ingredient of herbal medicine extract. Therefore, more in-depth re-

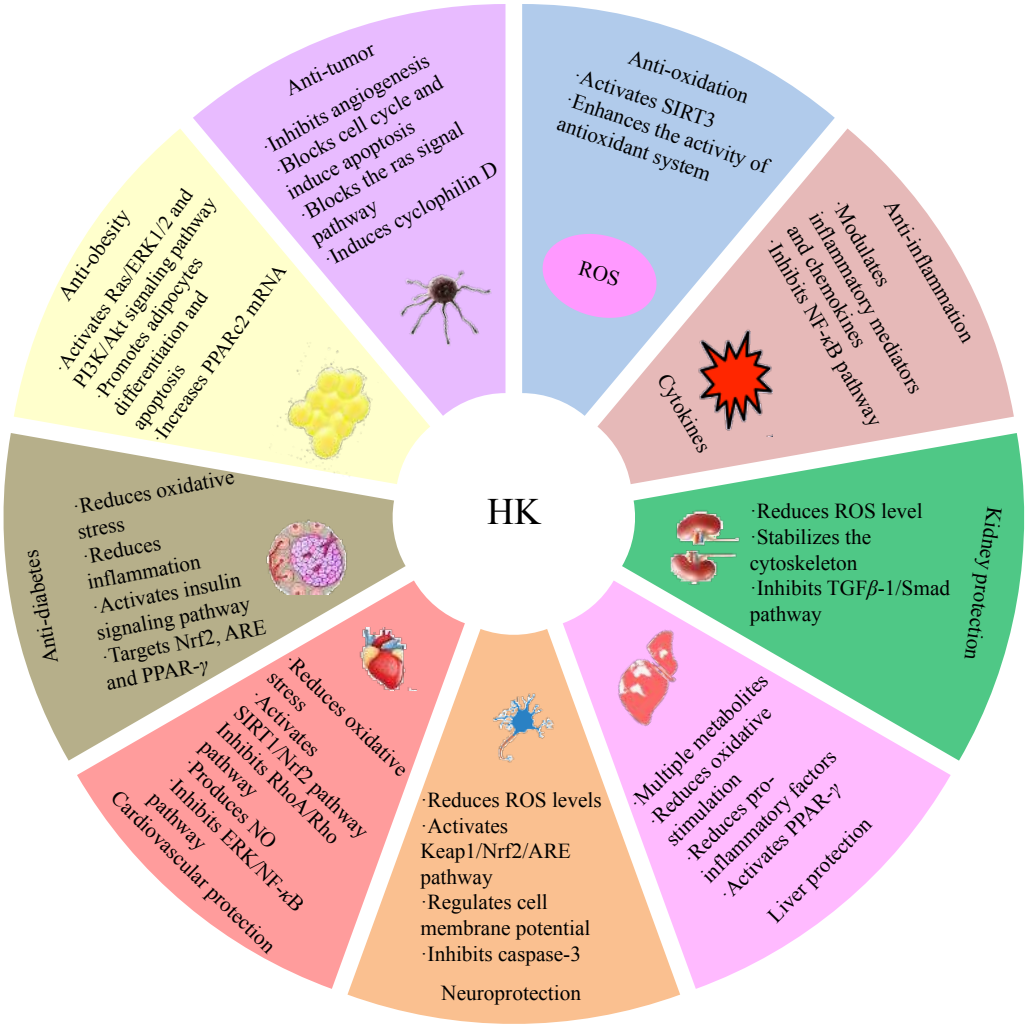

Fig. 3 A summary of the pharmacological activities and the underlying mechanisms of HK

search and clinical trials on HK are necessary for its future clinical application.

Abbreviations

Aβ, amyloid β peptide; AD, Alzheimer's disease; ALT, alanine aminotransferase; Akt, protein kinase B; ARE, antioxidant response element; AST, aspartate aminotransferase; α1, accumulation of type I; BAT, brown adipose tissue; BAX, B-cell lymphoma-2-associated X protein; BBB, blood brain barrier; Bcl, B-cell lymphoma; BCSFB, blood cerebrospinal fluid barrier; Cidea, cell death-inducing DFFA-like effector a; CL, high cholesterol and high fat; COX-2, cyclooxygenase-2; Cox8, cytochrome c oxidase subunit 8; CPI17, PKC-potentiated inhibitory protein for heterotrimeric MLCP of 17 kDa; CTGF, connective tissue growth factor; CUMS, chronic unpredictable mild stress; CYP, cytochrome P; DN, diabetic nephropathy; EB, embryoid body; ECs, endothelial cells; ECMS, extracellular matrix components; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal regulated kinase 1/2; Fgf21, gene encoding fibroblast growth factor21; FST, forced swimming test; GSH, glutathione; HFD, high-fat diet; HG, high-glucose; HIF, hypoxia-inducible-factor; HK, Honokiol; HO-1, hemeoxygenase-1; HRMCs, human renal mesangial cells; ICAM-1, glomerularintracellular adhesion molecule-1; IH, intermittent hypoxia; IL, interleukin; iNOS, inducible nitric oxide synthase; IUPAC, International Union of Pure and Applied Chemistry; JNK1/2, c-Jun *N*-terminal kinase 1/2; Keap1, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; mES, mouse embryonic stem; MIP-1α, macrophage inflammatory protein-1α; MLCP, myosin light-chain phosphatase; MLC_{20}, phosphorylation of 20 kDa myosin light chains; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; MYPT1, myosin phosphatase targeting subunit 1; NADPH, nicotinamide adenine dinucleotide phosphate; NAFLD, non-alcoholic fatty liver disease; NDN, non-diabetic nephropathy; NF-κB, nuclear transcription factor κ-B, nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NQO1, NAD(P)H quinone oxidoreductase 1; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PARP, poly-ADP-ribose-polymerase; PE-

CAM, platelet endothelial cell adhesion molecule; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; PGE2, prostaglandin E2; PI3K, phosphoinositide-3-kinase; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; PSD95, postsynaptic density protein 95; RASMCs, rat aortic smooth muscle cells; ROS, reactive oxygen species; SD, Sprague-Dawley; SHR, spontaneously hypertensive rats; SIRT, sirtuin; SOD2, superoxide dismutase 2; SREBP-1c, sterol regulatory element-binding protein-1c; *t*-BHP, *tert*-butyl hydroperoxide; TGF-β1, transforming growth factor-β1; TNF-α: tumor necrosis factor-α; Trx, thioredoxin; TrxR, Trx reductase; TST, tail suspension test; UCP1, uncoupling protein 1; UGT, uridine diphosphateglucuronic acid-glucuronosyltransferase; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptors; WAT, white adipose tissue; 2-NBDG, 2-Deoxy-2-[(7-nitro-2, 1, 3-benzoxadiazol-4-yl) amino]-D-glucose; 5-HT, 5-hydroxytryptamine.

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