

# Honokiol Research Review

*A promising extract with multiple applications*

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## Abstract

Honokiol is one of two dominant biphenolic compounds isolated from *Magnolia* spp. bark, and is the most widely researched active constituent of the bark. In this literature review we discuss the accumulating body of preclinical research which shows honokiol to have wide-ranging biological and clinically relevant effects, without appreciable toxicity. In vivo studies suggest that honokiol's greatest value is in its multiple anticancer actions. In vitro research suggests honokiol has potential to enhance current anticancer regimens by inhibiting angiogenesis, promoting apoptosis, providing direct cytotoxic activity, down-regulating cancer cell signaling pathways, regulating genetic expression, enhancing the effects of specific chemotherapeutic agents, radiosensitizing cancer cells to radiation therapy, and inhibiting multidrug resistance. Honokiol also shows potential in preventative health by reducing inflammation and oxidative stress, providing neurological protection, and regulating glucose; in mental illness by its effects against anxiety and depression; and in helping regulate stress response signaling. Its antimicrobial effects demonstrate potential for partnering with antiviral/antibiotic therapy, and treating secondary infections. Honokiol may occupy a distinct therapeutic niche because of its unique characteristics: the ability to cross the blood brain barrier (BBB) and blood cerebrospinal fluid barrier (BCSFB), high systemic bioavailability, and its actions on a multiplicity of signaling pathways and genomic activity. There is a need for research on honokiol to progress to human studies and on into clinical use. Currently, honokiol is used by a growing number of practitioners in integrative treatment protocols for cancer and other conditions.

## Introduction

Magnolia bark has been extensively used in Traditional Chinese Medicine (TCM) for treating symptoms due to “stagnation of qi,” as well as stress-related symptoms, including digestive disorders arising from anxiety and emotional imbalances. It is a common ingredient in a number of TCM formulas, with detailed indications in TCM literature beyond the scope of this review. It is also widely used in Japan as an anxiolytic in the form of tea. Magnolol, the other main active phenolic compound in magnolia bark, shares some biological properties with honokiol and has been independently researched.

## Anticancer Actions

The preclinical research on honokiol's broad-ranging capabilities shows its potential as a therapeutic compound for numerous solid and hematological cancers, including its effectiveness in combating multi-drug resistance (MDR) and its synergy with other anticancer therapies. Research thus far shows no toxicity or serious adverse effects in animal models. There is currently no clinical data on the use of honokiol in humans.

### **Crosses the blood-brain barrier**

In vitro research suggests that honokiol crosses the BBB and may reach therapeutic concentrations in the brain via passage through the tight junctions formed by cerebral endothelial cells (CECs).<sup>1</sup> In the same experimental study, honokiol reached brain tissues following intravenous injection in rodents (25 mg/kg). Ultimately, this study demonstrated that honokiol was able to induce apoptotic insults to neuroblastoma cells through a Bax-mitochondrion-cytochrome c-caspase protease pathway, at concentrations that traversed the BBB. Though the exact mechanism of honokiol's ability to cross the BBB has not been fully clarified, honokiol has been shown to down-regulate P-glycoprotein, whose expression is critical to efflux pump regulation. Overexpression of P-glycoprotein is one of the primary mechanism of MDR.<sup>2</sup> In rodent models of brain tumors, honokiol showed growth inhibition when given intravenously.<sup>3</sup>

### **Promotes apoptosis**

One of the hallmarks of cancer is the failure of apoptosis (programmed cell death), which enables abnormal cells to replicate uncontrollably. Many chemotherapy drugs and natural anticancer compounds act in part by inducing apoptosis or restoring the cancer cells' ability to trigger apoptosis. Research shows honokiol induces apoptosis via multiple primary pathways involved, suggesting a therapeutic advantage over compounds that target single pathways.<sup>4</sup>

A number of studies have been published to clarify our understanding of the biochemical pathways influenced by honokiol. A comprehensive 2011 article by Xu et al in *Drug Discoveries and Therapeutics* reviewed the multiple apoptotic pathways by which honokiol exerted effects on apoptosis, and also

reviewed the multiple cells types that have shown inhibition in in vitro and in vivo studies.<sup>4</sup> Cell types include breast, prostate, colon, liver, squamous cell lung cancer, and chronic lymphocytic leukemia (CLL). A study published in PLoS One in 2011 found that honokiol arrested the cell cycle and induced apoptosis in pancreatic cancer cell lines.<sup>5</sup> In non-small cell lung cancer, honokiol suppressed cancer cell growth and induced apoptosis through influence on multiple cell-signaling pathways.<sup>6</sup> In the treatment of leukemia, honokiol induced cell cycle arrest and apoptosis through the inhibition of specific cancer cell survival signals.<sup>7</sup> A 2012 study showed honokiol's ability to stop the proliferation and spread of malignant melanoma.<sup>8</sup> In this study, honokiol induced cancer cell death and blocked proliferation by regulating cell cycle arrest through multiple signaling pathways. Another in vitro study showed that honokiol effectively induced cell cycle arrest irrespective of the androgen sensitivity status of prostate cancer cells.<sup>9</sup>

### **Inhibits angiogenesis**

Angiogenesis, another multi-pathway signaling process, becomes up-regulated in cancer cell growth and metastasis. The tumor sends out chemical signals that stimulate a transformation in endothelial cells that line nearby blood vessels, encouraging them to branch and grow toward the tumor, providing blood and nutrient supply for rapid growth. As with apoptosis, there are multiple pathways that can be targeted with specific therapies to interrupt or inhibit tumor angiogenesis. Research has elucidated that honokiol accomplishes angiogenesis inhibition through modulation of NF-kB pathway.<sup>10</sup>

Honokiol has also been shown to inhibit spread of cancer cells through the lymph system by inhibiting one of the primary pathways involved in growth stimulation related to vascular endothelial growth factor (VEGF).<sup>11</sup>

A 2012 in vivo study in PLoS One showed that honokiol, by inhibiting angiogenic pathways such as STAT-3, dampened peritoneal dissemination of gastric cancer in mice (5mg/kg delivered intraperitoneally).<sup>12</sup>

### **Direct cytotoxic effects**

A 2012 study in the journal Cancer using a mouse osteosarcoma model showed that while honokiol (150 mg/kg, intraperitoneal) was not associated with lessening the growth of the primary tumor, it was associated with a reduction in macrometastasis to the lung and liver by 69% and 80%, respectively. Using various osteosarcoma cell lines, these researchers observed that this specific anticancer mechanism did not involve self-destruction/apoptosis of cancer cells. Instead, the cytotoxic effects of honokiol appeared due to cytosolic vacuole formation and morphological changes in the endoplasmic reticulum.<sup>13</sup>

### **Influences other signaling pathways**

**P53:** Another review of research published in Antioxidants and Redox Signaling in 2009 discussed findings regarding some of honokiol's mechanisms of action.<sup>15</sup> Honokiol blocks signaling in tumors with

defective p53, a tumor suppressor protein that plays a role in conserving stability and regulating the cell cycle.<sup>14</sup> p53 function is central to preventing gene mutation and is often described as “the guardian of the genome.”<sup>15</sup> p53 also plays a role in apoptosis and inhibition of angiogenesis, interacting with more than 100 other signaling proteins. Once the protective function of p53 is no longer in effect, control mechanisms continue to unravel, leading to further mutations, which often make these types of tumors more aggressive and often more treatment resistant. Honokiol also acts by a pathway independent of p53 status to promote apoptosis by another complex signaling pathway, resulting in increased permeability of the mitochondria membrane, leading to cell death in cells with wild-type (unmutated) p53.<sup>14</sup>

**Ras:** Honokiol also blocks signaling in tumors with activated Ras, a membrane-associated guanine nucleotide-binding protein whose signaling affects many cellular functions, including cell proliferation, apoptosis, migration, and differentiation. Twenty to twenty-five percent of all human tumors and up to 90% of certain cancers, such as pancreatic, show overexpression of ras oncogenes. This mutation is also characteristic of triple negative breast cancer,<sup>16,17</sup> certain types of lung cancer, colon, and bladder cancers. Many of these tumor types show a combination of p53 and ras mutations.<sup>14,18</sup>

**NF-kB:** Like p53, NF-kB is a protein important to the cell cycle, supporting normal growth. However, excessive NF-kB activity can trigger cancer cell growth, invasion, proliferation and angiogenesis. Lessening the activity of NF-kB prevents cancer growth and metastasis, helps regulate the inflammatory response, and prevents cellular damage from oxidation. Honokiol is shown to suppress overactive NF-kB.<sup>19</sup>

## Synergistic Effects with Other Cancer Treatments

One of honokiol’s most promising benefits is its ability to synergize with other cancer treatments. Clinical trials are desperately needed to validate the potential synergy that has been demonstrated in vitro and in vivo.

### Chemotherapy

- A 2013 in vitro study published in the International Journal of Oncology showed that honokiol synergized chemotherapy drugs in multidrug resistant breast cancer.<sup>20</sup> A 2011 in vitro study published in PLoS One found that honokiol enhanced the apoptotic effects of the anticancer drug gemcitabine against pancreatic cancer.<sup>5</sup>
- In vivo research published in Oncology Letters in 2011 found honokiol enhanced the action of cisplatin against colon cancer.<sup>21</sup>
- A 2010 in vitro study from the Journal of Biological Regulators and Homeostatic Agents showed that honokiol resensitized cancer cells to doxorubicin in multidrug resistant uterine cancer.<sup>22</sup>
- A 2010 in vitro study published in Toxicology Mechanisms and Methods showed honokiol performed synergistically with the drug imatinib against human leukemia cells.<sup>23</sup>
- 2008 in vivo research published in the International Journal of Gynecological Cancer showed honokiol to potentiate the activity of cisplatin in murine models of ovarian cancer.<sup>24</sup>

- 2005 in vitro research published in Blood showed honokiol enhanced the cytotoxicity induced by fludarabine, cladribine, and chlorambucil, indicating it is a potent inducer of apoptosis in B-CLL cells.<sup>25</sup>

## Radiation treatment

- 2012 in vitro research published in Molecular Cancer Therapeutics showed that honokiol was able to sensitize cancer cells to radiation treatments.<sup>26</sup>
- A 2011 in vitro study published in American Journal of Physiology Gastrointestinal and Liver Physiology showed honokiol sensitized treatment-resistant colon cancer cells to radiation therapy.<sup>27</sup>
- Inhibition of multidrug resistance
- Honokiol has been shown to interact with genes that are involved with mechanisms of drug efflux, thus reversing MDR in experimental models. The exact mechanisms of action in this regard are thought to be related to effects of blocking of NF- $\kappa$ B activity, but other mechanisms may also be involved.<sup>2</sup>

## Anticancer Summary

Preclinical research has shown honokiol to exert anticancer effects by a multitude of mechanisms to:

- Promote and normalize apoptosis<sup>4–9, 14</sup>
- Inhibit angiogenesis<sup>10–12</sup>
- Regulate cell signaling<sup>14–19</sup>
- Induce direct cytotoxicity<sup>13</sup>
- Influence key genetic regulators<sup>4,10–19</sup>
- Enhance the effectiveness of chemotherapy regimens<sup>5,19–25</sup>
- Inhibit multi-drug resistance<sup>2</sup>
- Enhance the effects of radiation treatment<sup>26,27</sup>
- Inhibit key mechanisms that are known promoters of cancer growth and metastasis: anti-inflammatory and antioxidant effects<sup>19,28–30,34,35</sup>

Again, it is important to emphasize that honokiol has not been clinically tested in cancer care. In many of the above studies, the dose used of honokiol is much higher than can be achieved with human consumption. Definitive studies on the use and optimal dosing in humans have yet to be published.

## Additional Applications

### Anti-inflammatory effects

Honokiol demonstrates systemic anti-inflammatory effects via multiple mechanisms. Primarily, these effects relate to some of honokiol's anticancer and anti-MDR activities, including inhibition of TNF- $\alpha$  stimulated NF- $\kappa$ B activation, and NF- $\kappa$ B-regulated gene expression.<sup>28</sup> By inhibiting the NF- $\kappa$ B pathway, honokiol inhibits nitric oxide (NO) generation.<sup>29,30</sup> These effects were observed in vivo systemically as well as topically. In vitro, honokiol reversed CD40- and LMP-mediated NF- $\kappa$ B and AP-1 activation and

suppressed TNF- $\alpha$  and IL-6 production in mouse B-cell lines.<sup>31</sup> Honokiol is shown to reduce NF-kB target genes such as VEGF, ICAM-1, and COX-2. Honokiol appears to inhibit NF-kB activation through a number of stimuli.<sup>28</sup>

In a murine model of arthritis, honokiol demonstrated significant anti-inflammatory effects. Treatment with honokiol decreased clinical scores of collagen-induced arthritis in both normal and transgenic mice. Furthermore, antibody production, particularly IgG3, was diminished together with IL-12, IL-6, interferon gamma, and, notably, IL-17. These findings suggest indications for the treatment of IL-17-mediated inflammatory disorders including rheumatoid arthritis, psoriasis, and inflammatory bowel diseases.<sup>31</sup> Other studies show that honokiol also works against inflammation by inhibiting PI3k/Akt signaling pathways, as well as inhibition of downstream pathway of MEK in NF-kB signaling.<sup>32,33</sup>

### **Antioxidant and selective pro-oxidant actions**

The free radical-scavenging effects of honokiol against reactive oxygen species are documented in multiple studies.<sup>19,34,35</sup> In vivo research in a cardiac lipid peroxidation model demonstrated honokiol's free radical-scavenging abilities, helping to protect rat heart mitochondria.<sup>36</sup> Results of oxygen consumption and malondialdehyde production showed that honokiol inhibition of reactive oxygen was 1,000 times that of  $\alpha$ -tocopherol (vitamin E).<sup>37</sup> The antioxidant abilities are believed to be attributed to the allyl groups on honokiol.<sup>14</sup> The antioxidant actions of honokiol against a number of conditions, including cardiac ischemic injury and hepatic peroxidative injury, are outlined in the 2009 review "Honokiol, a multifunctional antiangiogenic and antitumor agent," by Fried and Arbiser in the *Antioxidants and Redox Signaling*.<sup>14</sup>

Honokiol also functions as a selective pro-oxidant, generating reactive oxygen against cancer cells with wild-type p53 status. It is likely a result of and triggered by p53 mutation, and HIF/mTOR-1 activation of the mitochondrial permeability transition pore.<sup>38</sup>

### **Anxiolytic effects**

Magnolia bark plays a central role traditional in Chinese medical formulas as an anxiolytic. Honokiol extracted from the bark has been studied independently to investigate its mechanisms of action on the central nervous system and has been shown to interact with neurotransmitter gamma-aminobutyric acid (GABA) receptors.<sup>39</sup> In vivo, honokiol showed similar anxiolytic effects to diazepam without a change in motor activity or muscle tone observed with diazepam. Honokiol showed no evidence of withdrawal symptoms, whereas diazepam withdrawal was characterized by hyperactivity. Diazepam also disrupted memory and learning, side effects not seen with honokiol administration.<sup>40</sup> It is also shown to increase hippocampal acetylcholine release in vivo.<sup>41</sup>

### **Neuroprotective effects**

Neuroinflammation occurs via the activation of microglia in response to inflammatory stimuli with subsequent release of proinflammatory cytokines and prostaglandins, including TNF alpha, IL-6, and

COX-2. An *in vitro* study in 2012 showed that honokiol reduces inflammation in brain tissue by down-regulating transcription factors that control the activation of overactive microglia, thus inhibiting the release of these inflammatory compounds.<sup>42</sup>

Amyloid beta peptide (A beta)–induced toxicity is a well-established pathway of neuronal cell death, which might play a role in Alzheimer’s disease. A 2010 *in vitro* study found that honokiol significantly decreased A beta–induced cell death, possibly mediated through reduced ROS production, as well as suppression of intracellular calcium elevation and inhibition of caspase-3 activity.<sup>43</sup>

Using a rodent model, honokiol was also shown to protect against damage from cerebral ischemia by reducing inflammation and oxidation in the brain.<sup>44</sup> General neuroprotective activity against cerebellar granule cell damage has also been demonstrated.<sup>45</sup>

## Additional Research

### Cardiovascular

A 2010 *in vivo* study evaluated several parameters contributing to elevated blood pressure in spontaneously hypertensive rats. Researchers found that long-term administration of honokiol significantly reduced blood pressure, possibly via vaso-relaxant and antioxidant effects. Significant reduction in elastin bands and thickness in the media layer of the aorta was also observed.<sup>46</sup>

### Kidney

Progression of renal fibrosis ultimately culminates in the development of end-stage renal disease. This often occurs in the renal tubular cells. A 2011 *in vivo* study investigated the antifibrotic and anti-inflammatory effects exerted by honokiol, focusing on renal tubular tissues. The study had *in vitro* and *in vivo* components. Honokiol slowed development of renal fibrosis both *in vivo* and *in vitro*. The *in vitro* arm showed that the antifibrotic effects occurred via a number of signaling factors. Accumulation of type 1 collagen and fibronectin were reduced in a rat ureteral obstruction model. Honokiol suppressed the expression of pro-fibrotic and proinflammatory factor and extracellular matrix proteins and shows promise as a potential therapeutic agent to prevent renal fibrosis.<sup>47</sup>

### Antimicrobial

**Oral Health Benefits:** *In vitro* studies show honokiol has significant antimicrobial activity against periodontopathic microorganisms including *Porphyromonas gingivalis*, *Prevotella intermedia*, *Micrococcus leteus*, *Bacillus subtilis*, and others.<sup>48,49</sup>

**Antiviral Activity:** Honokiol demonstrated antiviral activity against hepatitis C virus (HCV) in a 2012 *in vitro* study in Liver International. Honokiol had strong antiviral effects against HCV infection at nontoxic concentrations. Combined with interferon-alpha, honokiol's inhibitory effects were more significant than

those of ribavirin. Honokiol exerted multiple effects against the life cycle of HCV, targeting cell entry and replication, inhibiting viral replication, and thus effectively preventing it from replicating inside liver cells in a dose-dependent manner. Because of its high therapeutic index, honokiol may be a promising treatment of HCV infection, according to the authors.<sup>50</sup>

## Summary of Honokiol's Primary Properties and Actions

- Anti-inflammatory<sup>14,29–34</sup>
- Antioxidant and selective pro-oxidant<sup>14,19,34–38</sup>
- Antimicrobial<sup>48–50</sup>
- Antitumor: induces apoptosis and cell cycle arrest<sup>4–10,14</sup>
- Antiangiogenic<sup>11–14</sup>
- Anxiolytic<sup>39–41</sup>
- Neuroprotective<sup>42–45</sup>
- Cardioprotective<sup>46</sup>
- Antifibrotic<sup>47</sup>
- Synergistic with chemotherapy and radiation<sup>5,20–27</sup>
- No appreciable toxicity<sup>14</sup>

## Conclusions

A large body of preclinical research exists on honokiol. In vitro studies have investigated its multiple mechanisms of action, while in vivo studies have shown its potential benefit across a broad range of illnesses, including difficult-to-treat conditions such as MDR cancer. Honokiol's in vivo toxicity record thus far shows it to be safe. It is also shown to cross the BBB.

The preclinical research on honokiol is compelling, and its potential benefits combined with lack of toxicity are promising. Honokiol is currently being administered by a growing number of clinicians as an adjuvant therapy to address numerous pro-inflammatory and neurologic conditions, as well as multiple types of cancer. There is an urgent need to progress to clinical trials in order to validate and further clarify honokiol's diverse range of applications.

## Conflict of Interest Disclosure

*The author is owner of EcoNugenics, Inc., a dietary supplement company that sells honokiol.*

For more research involving integrative oncology, click [here](#).

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