Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Honokiol

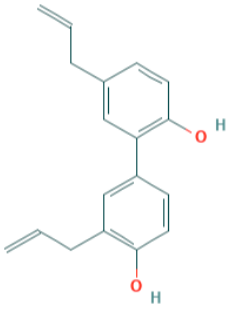
Evidence Summary

Although there is preclinical evidence for beneficial effects in neurodegenerative disease and other age-related diseases, potential beneficial effects and the bioavailability of honokiol in humans is not known.

Neuroprotective Benefit: Honokiol is beneficial in several mouse models of neurodegeneration, but specialized formulations to increase bioavailability may be needed.

Aging and related health concerns: Honokiol is beneficial in mouse models of several age-related diseases such as cardiovascular disease, but specialized formulations to increase bioavailability may be needed.

Safety: There is insufficient data in humans on whether honokiol would be safe for long-term consumption.

Availability: Available as a supplement either as purified honokiol or magnolia extract	**Dose**: Not known in humans, though individual supplements have their own recommendations	**Molecular Formula:** $C_{18}H_{18}O_2$ **Molecular weight:** 266.3g/mol  Source: Pubchem
Half-life: 290 minutes (rats)	**BBB**: Penetrant in rodents (after IV administration)	
Clinical trials: None for honokiol, but there have been two small trials for *Magnolia officinalis* extract	**Observational studies**: None	

What is it?

Honokiol is a natural compound isolated from the bark of *Magnolia officinalis*, a species of magnolia common in Japan and China, which is used as a traditional medicine in Southeast Asia. It is reported to have anxiolytic, analgesic, anti-depressant, antithrombotic, antimicrobial, anti-tumorigenic, and neuroprotective properties (Woodbury et al, 2013).

There are several mechanisms through which honokiol is suspected to act. Several studies suggests that it reduces reactive oxygen species (ROS) and increases the levels of antioxidant proteins. It may also increase the expression of SIRT3, an epigenetic enzyme important for mitochondrial function. In addition, honokiol was reported to act through PPARγ, a protein involved with glucose metabolism and fatty acid storage. Several studies also suggest it reduces inflammation (Woodbury et al, 2013).

Although available as a commercial supplement, it is not clear whether taking honokiol supplements from the store would provide benefit. Honokiol has low bioavailability, low water solubility and is rapidly metabolized by the liver. In addition, pharmacokinetic parameters vary between species. Therefore, many ongoing programs are trying to increase its bioavailability and tissue distribution by packaging it in nanoparticles, micelles, and liposomes (Ong et al, 2020).

Neuroprotective benefit: Honokiol is beneficial in several mouse models of neurodegeneration, but specialized formulations to increase bioavailability may be needed.

Types of evidence:

- Four preclinical studies in Alzheimer's disease or vascular dementia
- Four preclinical studies in stroke
- Two preclinical studies in traumatic brain injury

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

None

Human research to suggest benefits to patients with dementia:

None

Mechanisms of action for neuroprotection identified from laboratory and clinical research

Six-week-old male mice were injected in both hippocampi with a preparation of Aβ oligomers (AβO) and were treated after seven days with honokiol (0.7, 7, and 70 µg/kg, intraperitoneal, i.p.) for 14 days. Treatment with medium or high dose honokiol improved spatial learning and memory in the Morris water maze test (MWM). Treatment also reduced cell death in the hippocampus, reduced the levels of reactive oxygen species (ROS), and reduced the expression of NFκB, APP, and BACE1 (Wang et al, 2017). In another study, six-month-old AD mice ($PS1_{V97L}$-transgenic mice, at an age when AβO begin to increase) were treated with honokiol (20 mg/kg/day, i.p.) over three months. Treatment improved cognitive function on the MWM, increased SIRT3 expression in the brain, improved mitochondrial function (increased ATP), and increased antioxidant enzymes (SOD). *In vitro*, honokiol improved the viability of primary neurons exposed to AβO (Li et al, 2018). Six-week treatment of another AD mouse model (APPswe/PS1 dE9) with honokiol (20mg/kg/day, i.p.) also improved cognitive performance on the MWM, reduced hippocampal and cortical plaque load, and reduced levels of inflammatory cytokines (TNFα, IL-1β, and IL-6). It also increased the expression of Iba1 (a microglia marker) around amyloid plaques. These results were prevented by co-administration with GW9662, a PPARγ antagonist (Wang et al, 2018).

Vascular dementia

In a rat model of chronic cerebral hypoperfusion, rats were treated for four weeks with honokiol (5 mg/kg/day, i.p.). Treatment improved long-term memory on the step-down inhibitory avoidance task

and memory on the MWM. In addition, treatment increased SOD activity, reduced protein oxidation (malondialdehyde – MDA), and reduced ROS levels. Finally, treatment also reduced the levels of inflammatory cytokines (TNFα, IL-1β, and IL-6) and increased dendritic spine density (Guo et al, 2019).

Stroke

Mice were subjected to middle cerebral artery occlusion (MCAO) for 45 minutes, and honokiol (10 µg/kg, i.p.) was given 15 minutes before and 60 minutes after injury. Treatment reduced brain infarct volume (Chen et al, 2007). Another study reported that intravenous treatment with honokiol (0.01-1.0 µg/kg) in rats 15 minutes before and 60 minutes after MCAO reduced infarct volume by 20-70% in a dose-dependent manner. It also reduced lipid peroxidation (MDA) and neutrophil infiltration into the brain tissue (Liou et al, 2003). Another study reported that intravenous honokiol (0.01-1.0 µg/kg) reduced infarct volume in rats subjected to MCAO when given either before or after injury (Liou et al, 2003). Finally, Zhang et al (2012) reported that honokiol (0.7-70 µg/kg, i.p.) given 15 minutes before and after cerebral ischemia reperfusion injury in mice reduced brain water content and blood brain barrier damage.

Traumatic brain injury (TBI)

Rats were subjected to TBI and treated with honokiol (5 mg/kg/day, i.p.) for seven days. Markers of oxidative stress (MDA, myeloperoxidase – MPO, and glutathione peroxidase) were improved in the treated group and there was less evidence of blood brain barrier permeability. Treatment also reduced VEGF expression and increased GFAP expression (GFAP is expressed in astrocytes which surround the blood brain barrier) (Cetin and Deveci, 2019).

In rats subjected to TBI, honokiol (1mg/kg) given post-injury for five days improved sensorimotor function and reduced lesion size. The improvement in motor function correlated with a reduction in lesion size . In addition, honokiol prevented cell death in both the hippocampus and the cortex (Wang et al, 2014).

Aged mice

Two-month-old SAMP8 mice were treated with honokiol (0.1, 1 mg/kg/day, oral administration) over 14 days and later evaluated at four and six months. Treatment with 1 mg/kg improved cognition on the step-through passive avoidance and novel object recognition tests at six months (but not four months). It also improved the survival of cholinergic neurons in the brain (Matsui et al, 2009).

APOE4 Interactions: None reported

Aging and related health concerns: Honokiol is beneficial in mouse models of several age-related diseases, such as cardiovascular disease, but specialized formulations to increase bioavailability may be needed.

Types of evidence:

- One preclinical study in an accelerated aging mouse model
- Seven preclinical studies in mouse models of cardiovascular disease
- One preclinical study in neuropathy
- Two preclinical studies in diabetes
- One review of preclinical cancer studies

Aging

Two-month-old SAMP8 mice were treated with honokiol (0.1, 1 mg/kg/day, oral) over 14 days and later evaluated at four and six months. Treatment had no effect on survival at six months (there was not significant mortality in either group, survival was >90% for both) (Matsui et al, 2009).

Cardiovascular disease

Atherosclerosis

Atherosclerotic mice (ApoE-/- fed a Western diet) were treated with honokiol (10 or 20mg/kg/day, i.p.) or atorvastatin (10 mg/kg/day) for eight weeks. Both honokiol and atorvastatin reduced carotid atherosclerotic plaque size and reduced the collagen content in plaques. In addition, both reduced levels of inflammation (TNFα, IL-1β, and IL-6), iNOS levels, and increased SOD activity (Liu et al, 2019). In a rabbit model of atherosclerosis (vascular balloon injury), local topical application of honokiol reduced intimal thickening after 14 days. It also reduced vascular smooth muscle cell proliferation and collagen deposition and increased the expression of matrix metalloproteases (Wang et al, 2017).

Hypertension

Spontaneously hypertensive rats were treated with honokiol (200 mg/kg or 400 mg/kg, oral administration) daily over 49 days. High-dose treatment reduced blood pressure, while both doses improved endothelium-dependent, but not independent, vasodilation and reduced levels of MDA in the liver (Zhang et al, 2010).

Myocardial ischemia/reperfusion (I/R)

In a type 1 diabetes model (animals injected with streptozotocin – STZ) subjected to myocardial ischemia/reperfusion (I/R), treatment with honokiol (5 mg/kg/day, i.p.) one week prior to myocardial I/R

improved heart function after surgery and reduced infarct size. It also reduced oxidative stress (increased the expression of SOD and reduced levels of MDA) and cell death. These effects were thought to be mediated through the SIRT1 pathway, as treatment with a SIRT1 inhibitor, EX527, abolished the beneficial effects (Zhang et al, 2018).

Wang et al (2012) pre-treated rats with honokiol (5 mg/kg, i.p.) 30 minutes prior to myocardial I/R injury. Treatment with honokiol reduced infarct size and serum levels of creating kinase (CK) and lactic dehydrogenase (LDH). It also reduced levels of MDA and MPO, prevented the decrease in SOD and catalase (CAT), and reduced markers of inflammation (TNFα, IL-6, and NFκB).

Similar results were reported in WT mice subjected to myocardial M/I, where honokiol (5 or 10 mg/kg, i.p.) improved heart function, reduced the infarct size, and reduced levels of serum CK and LDH when given post-surgery (Tan et al, 2019).

Cardiac hypertrophy

In vitro, honokiol was reported to increase SIRT3 levels in neonatal rat cardiomyocytes and reduced ROS production and cell death in cardiac cells under stress. In a model of cardiac hypertrophy (transverse aortic constriction), treatment with honokiol (0.2 mg/kg/day, i.p.) for 28 days prevented an increase in heart weight and reduced collagen levels and fibrosis. Similar results were reported in mice with pre-established cardiac hypertrophy, suggesting it could reverse increased heart weight. They reported that these results required SIRT3, as honokiol was not beneficial in SIRT3-KO mice (Pillai et al, 2014).

Neuropathy

Honokiol (5 and 10 mg/kg, i.p.) did not have any effect on pain in mice on a tail-flick and hot-plate paw-shaking test. However, in another test of neuropathic pain (formalin injection in the hind paw), honokiol reduced pain in the inflammatory phase (~15 min after injection) (Lin et al, 2007).

Diabetes

In diabetic mice (*db/db*) honokiol (0.02% *w/w* in food) had no effect on body weight or fasting glucose levels, but it reduced the weight of adipose tissue, decreased HbA1c, reduced insulin resistance, and decreased plasma insulin levels. It had no effect on plasma cholesterol but reduced hepatic triglyceride levels (Kim and Jung, 2019). In another diabetes mouse model (STZ injection), treatment with honokiol reduced fasting plasma glucose levels (Sun et al, 2015).

Cancer

In vitro studies have suggested that honokiol has a variety of effects on cancer cell lines. For instance, it has been reported to prevent inflammation, induce apoptosis and necrotic cell death, induced cell cycle arrest, increase autophagy, prevent epithelial-mesenchymal transition, and suppress migration of cancer cell lines. In addition, more than 25 preclinical *in vivo* experiments with different cancer cell lines and animal models have been conducted. It was reported to prolong survival, inhibit tumor progression, prevent metastasis, induce cancer cell autophagy and apoptosis, and prevent cancer cell migration (Ong et al, 2020). Although there is significant evidence from preclinical studies that honokiol may have anti-tumor properties, there has not been significant progress in clinical development. A paper from 2018 reported that a honokiol liposome formulation will be tested in a phase 1 clinical trial (CTR20170822) in China that year (Wu et al, 2018).

Safety: There is insufficient data in humans on whether honokiol would be safe for long-term consumption.

Types of evidence:

- One review on honokiol toxicology studies
- One review on neurodegeneration

The safety of honokiol in humans is currently unknown. One toxicology study of a methanol extract of *Magnolia officinalis* (equivalent to 2 mg/day of honokiol) over three months in mice suggested some changes in clinical parameters related to kidney function and there were alterations in kidney ultrastructure morphology. Other toxicology studies in animals have not reported significant safety concerns (Sarrica et al, 2018).

Six studies have been conducted using supplements that contain *Magnolia officinalis* extract in humans. Two used a supplement which contains the equivalent of about 11.25 mg of honokiol and 0.75 mg of berberine. In total, 58 post-menopausal women were treated over six weeks. They reported possible side effects in four patients including heartburn, trembling hands, sexual dysfunction, and thyroid dysfunction, though it is not clear whether this was due to honokiol, berberine, the combination, or other compounds (the supplement contains extracts of *Magnolia officinalis* and *Phellodendron amurense* and is not purified honokiol and berberine). However, no serious adverse effects were reported. In the other studies, patients were treated with gum or mints that contain *Magnolia officinalis* extract, and no adverse effects were reported (Sarrica et al, 2018).

One theoretical concern is that honokiol has been shown to have anti-thrombotic properties. Therefore, it may be dangerous in patients who are at risk of bleeding or hemorrhage (such as those taking other blood thinning drugs, stroke patients, or those with clotting disorders) (Woodbury et al, 2013).

Drug interactions: Some studies suggest that honokiol may have anti-thrombotic properties, so it should not be used with other blood thinners (Woodbury et al, 2013). *Magnolia officinalis* extracts have been reported to have sedative effects, so they should not be taken with other drugs that may cause sedation (WebMD.com).

Dosing: Honokiol's dosing in humans is not established. Different supplements have their own dosing suggestions based on whether the supplement is a purified honokiol extract or *Magnolia officinalis* extract. For instance, one supplement suggests taking 250 mg of purified honokiol extract 1-2 times per day. Another supplement contains extracts of *Magnolia officinalis* and *Phellodendron amurense* and suggests taking 300mg two-three times per day. However, no independent testing has been conducted to confirm how much honokiol commercial supplements actually contain.

Research underway:
There are no ongoing clinical trials in clinicaltrials.gov or the EU, China, and Japan clinical trials registries.

Three active NIH-funded projects are ongoing. One study will look at the effects of honokiol in a mouse lung cancer model, one in a mouse model of breast cancer, and one in a mouse model of kidney cancer (NIH Reporter).

Search terms:
Honokiol + Alzheimer, cardiovascular, neuropathy, cognition, aging, lifespan, hypotension, atherosclerosis, ischemia, safety, apoe4

Websites visited:
Pubmed
Clinicaltrials.gov
NIH Reporter
EU Clinical Trial Registry
China Clinical Trial Registry
Japan Clinical Trial Registry
Labdoor.com

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