



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.

Dihydromyricetin

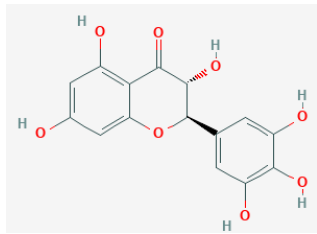
Evidence Summary

DHM has anti-inflammatory, antioxidant, pro-autophagic, and energy metabolism regulating properties due to activation of sirtuins, AMPK, and Nrf2, but poor bioavailability hinders clinical utility.

Neuroprotective Benefit: DHM shows anti-inflammatory, antioxidant, and pro-autophagy properties which reduce cognitive impairment in animal models, but a similar level of benefit to humans is unlikely due to low bioavailability.

Aging and related health concerns: DHM shows anti-inflammatory and antioxidant properties, and may favorably regulate metabolism by boosting irisin levels, improving insulin sensitivity, and enhancing lipid metabolism in animals; benefits less clear in humans.

Safety: DHM has a good safety record in short term RCTs and animal studies, which may be due to low bioavailability. Pharmacokinetic properties may differ across patient populations, and may have drug interactions due to projected CYP inhibition activity.

Availability: OTC	Dose: Therapeutic dose not established	Chemical formula: C ₁₅ H ₁₂ O ₈ MW: 320.25 g/mol
Half-life: 2 hours (in rats)	BBB: Penetrant	
Clinical trials: Type 2 diabetes (n=77, NAFLD (n=60))	Observational studies: None	
		Source: PubChem

What is it?

Dihydromyricetin (DHM), also called ampelopsin, is the major flavonoid in *Ampelopsis* plants, primarily in the species *grossedentata* [1]. It is also found in some other plant species, such as the Japanese raisin tree, *Hovenia dulcis*. These plants have been used as part of traditional Asian medicine, due to their reported anti-inflammatory, antioxidant, and anti-cancer properties, which have more recently been attributed to their high DHM content. DHM is sold as a supplement and is commonly marketed as a treatment for hangovers due to its ability to reduce blood alcohol levels and projected hepatoprotective properties. In preclinical animal models, DHM shows a variety of beneficial anti-aging properties, by reducing inflammation, oxidative stress, lipidemia, as well as regulating energy metabolism and promoting autophagy. These effects are primarily derived from its ability to activate sirtuins. However, the magnitude of the benefits seen in preclinical studies has not yet translated to the effects seen in clinical trials, likely due to the poor stability and bioavailability of currently available DHM preparations.

Neuroprotective Benefit: DHM shows anti-inflammatory, antioxidant, and pro-autophagy properties which reduce cognitive impairment in animal models, but similar level of benefit to humans is unlikely due to low bioavailability.

Types of evidence:

- Numerous laboratory studies

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:

The neuroprotective effects of DHM are primarily driven by its anti-inflammatory and antioxidant properties, as well as its ability to normalize the excitatory-inhibitory balance of neurotransmission.

Alzheimer's disease: POTENTIAL BENEFIT (Preclinical)

The neurological phenotype of Alzheimer's disease (AD), involving a loss of cognition often in combination with neuropsychiatric features, such as seizures and anxiety, suggests that there may be an underlying dysfunction in inhibitory GABAergic neurotransmission in this patient population. DHM has been identified as a positive allosteric modulator of GABA_A receptors, which may help to restore the excitatory-inhibitory balance in the AD brain [2]. In the TG-SwDI AD mouse model, DHM (2 mg/kg orally for 3 months), improved cognition based on performance on the novel object recognition task, reduced brain levels of soluble and insoluble Aβ₄₂, reduced anxiety-related phenotypes, and reduced seizure duration in aged (23-month-old) mice [2]. These phenotypic improvements were associated with a restoration of GABA_AR mediated currents, and a restoration of the level of gephyrin, a postsynaptic GABA_AR anchor protein involved in synaptic plasticity. The beneficial effects described in this study are notable, because unlike the vast majority of studies examining the protective properties of DHM, this study used aged animals and initiated treatment after the onset of pathology.

DHM (200 mg/kg i.p. for 21 days) was also found to protect cognition in rats receiving an intrahippocampal injection of Aβ₄₂ oligomers, which was accompanied by a reduction in hippocampal neuron loss, and reduction in pro-inflammatory cytokines (IL-6, IL-1β, TNFα) and NF-κB activation. DHM also increased phosphorylation of AMPK and activation of SIRT1 [3].

An anti-inflammatory phenotype was also seen in the APP/PS1 mouse model when the mice were treated with 1 mg/kg (i.p.) DHM for 2 or 4 weeks starting at 4 months of age [4]. Mice showed a reduction in microglial activation, with a shift toward more M2-like microglia, and a decrease in NLRP3 inflammasome and caspase-1 activation. The reduction in Aβ levels in the brains of the DHM treated mice may stem from the ability of DHM to delay the fibrillogenesis of amyloid in cell culture models [5].

Parkinson's disease: POTENTIAL BENEFIT (Preclinical)

DHM has been shown to exert protective effects in mouse and cell culture models of Parkinson's disease (PD) by mitigating alpha-synuclein mediated neurotoxicity and reducing oxidative stress mediated neuronal damage. In the MPTP mouse model, pretreatment with DHM (5 or 10 mg/kg) protected



against the induction of motor impairments and reduced neuronal loss via inhibition of reactive oxygen species (ROS) production [6]. In cell culture, DHM inhibits alpha-synuclein fibril formation and associated cytotoxicity [7; 8; 9]. In alpha-synuclein overexpressing mice, DHM in combination with salvianolic acid B (both 10 mg/kg/day) enhanced the lysosomal degradation of alpha-synuclein via chaperone-mediated autophagy and macroautophagy [9].

Cognitive impairment: POTENTIAL BENEFIT (Preclinical)

DHM has been shown to reduce cognitive impairment phenotypes induced by a variety of cell stressors via the preservation of mitochondrial function, reduction of oxidative stress, regulation of GABAergic neurotransmission, and reduction in pro-inflammatory mediators.

Aging (D-galactose induced): miR-34a is involved in cellular senescence, cell cycle arrest, and apoptosis, and is upregulated in the context of aging-related diseases [10]. The deacetylase SIRT1 is a positive regulator of autophagy and is a target of miR-34a. In male rats, DHM (100 mg/kg orally), prevented D-galactose-induced neuronal loss and impairment of neuronal autophagy in the hippocampus via the downregulation of miR-34a, leading to the upregulation of SIRT1 (2 to 3-fold) and inhibition of mTOR signaling [11]. DHM also partially prevented the induction of hippocampal related memory impairments in these animals, suggesting that preservation of autophagy protected neuronal integrity and function from D-galactose-induced damage.

Lead-induced: DHM treatment reduced lead-induced neuronal apoptosis, oxidative stress, neuroinflammation, and locomotor dysfunction in male mice. The protective effects were associated with the activation of AMPK and inhibition of proinflammatory NF- κ B and TLR4 signaling.

Diabetes-induced: DHM treatment improved performance on the hippocampal dependent memory task, the Morris water maze, increased hippocampal expression of BDNF, and decreased levels of oxidative stress in diabetic male mice.

Alcohol-induced: DHM is marketed as a cure for hangover, and has long been used for that purpose in the context of traditional Asian medicine. Its potential effects on acute alcohol intoxication and fetal alcohol syndrome stem from its modulation of GABA_AR plasticity. In rat pups exposed to alcohol in utero, DHM administration to the pregnant mother reduced birth deficits, such as seizures and hyperexcitability, by reducing the blood alcohol level and preventing the alcohol-induced dysregulation of GABA neurotransmission [12]. In adult male rats, DHM antagonized alcohol-induced potentiation of GABA_ARs and exposure/withdrawal-induced GABA_AR plasticity, which then reduces symptoms of withdrawal symptoms such as anxiety and seizure sensitivity [13].

APOE4 interactions: Unknown

Aging and related health concerns: *Rated C for potential and C for evidence.* DHM shows anti-inflammatory and antioxidant properties, and may favorably regulate metabolism by boosting irisin levels, improving insulin sensitivity, and enhancing lipid metabolism in animals; benefits less clear in humans.

Types of evidence:

- 2 clinical trials (Type 2 diabetes n=77; NAFLD n=60)
- 1 biomarker study (relationship between DHM intake and irisin levels in the blood)
- Numerous laboratory studies

Cardiovascular: POTENTIAL BENEFIT (Preclinical)

DHM has exhibited cardioprotective properties in preclinical models when administered near the onset of damage, suggesting that it acts primarily to prevent cellular damage rather than to treat it. Its protective properties are associated with its anti-inflammatory, antioxidant, and energy metabolism regulating effects.

DHM has been proposed to act as an exercise mimetic through its ability to stimulate production of the exercise-induced myokine, irisin [14]. Irisin is cleaved from a precursor protein in myocytes called FNDC5 that is involved in the browning of adipose tissue, which increases energy expenditure and glucose tolerance. Serum irisin levels increased approximately two-fold in sedentary rats treated with DHM (100 mg/kg), which is consistent with the increase in irisin levels in response to exercise (treadmill running) [14; 15]. The serum irisin level was positively correlated with the level of circulating DHM in both sedentary rats (treated with 100 mg/kg) ($r = 0.809$) and healthy sedentary young adult (age 20-30) humans (treated with 600 mg/day) ($r = 0.785$) [14]. Irisin production is regulated by the transcriptional coactivator PGC-1 α , which regulates genes involved in energy metabolism. DHM stimulates irisin production through the activation of PGC-1 α [14]. In this way, DHM can promote irisin in the absence of exercise, but it does not significantly further boost irisin levels in those who already engage in regular exercise [14]. While DHM can mimic several of the cardioprotective benefits of exercise in animal models, it is not as effective as exercise itself. In a rat model of myocardial infarction, DHM (100 mg/kg) reduced adverse cardiac remodeling and heart rate variability to a similar degree as an exercise regimen, but was less effective than exercise in improving cardiac contractility, carotid blood flow, stroke volume and cardiac output [15].

DHM pretreatment was protective in a mouse model of myocardial hypertrophy by decreasing ROS production and increasing antioxidant capacity through the activation of SIRT3 and FOXO3a [16]. DHM also protected against chemotherapy (adriamycin)-induced cardiotoxicity in mice when they were co-administered by inhibiting ROS production and preventing apoptosis of the cardiomyocytes [17]. DHM reduced vascular neointimal formation by inducing expression of the nuclear receptor TR3, which has a protective effect on vascular endothelial cells [18]. DHM has also been found to be protective in the context of cardiac ischemic/reperfusion injury through the induction of endogenous antioxidant programs via Nrf2 and preserving mitochondrial function via SIRT3 activation [19]. DHM reduced cardiac dysfunction and myocardial fibrosis in diabetic mice via inhibition of the pro-aging miRNA miR-34a, thereby restoring mechanisms necessary for maintaining cellular homeostasis, such as autophagy and mitophagy [20].

In male rats, DHM suppressed IL-6 mediated inflammation and induction of fibrotic pathways in a model of pulmonary hypertension [21], and improved aortic contractility during experimental sepsis by reducing oxidative stress, reducing pro-inflammatory cytokines, and normalizing potassium channel activity [22].

Atherosclerosis: POTENTIAL BENEFIT (Preclinical)

DHM has been found to be protective in mouse models (LDLr^{-/-} and ApoE^{-/-}) of atherosclerosis by inhibiting lesion formation, vascular inflammation, and oxidative stress [23; 24]. In LDLr^{-/-} mice, DHM prevented hyperlipidemia and hepatic lipid accumulation through the upregulation of PPAR α , LXR α and ABCA1, which are involved in promoting HDL biogenesis and fatty acid oxidation [23]. PPAR α also inhibits inflammatory mediators, which may contribute to the reduction in aortic inflammation in these animals. The reduction in inflammatory immune cell content may also be related to the increased production of nitric oxide (NO) via the DDAH1-ADMA-eNOS-NO pathway, as DHM was shown to inhibit a negative regulator (miR-21) of this pathway [24].

Metabolic syndrome: POTENTIAL BENEFIT (Preclinical)

In a variety of preclinical studies, DHM has shown beneficial effects on the regulation of energy metabolism by improving glucose tolerance, improving insulin sensitivity, decreasing lipid accumulation in the context of a high fat diet, and preserving mitochondrial function [25; 26; 27; 28]. These effects appear to be primarily driven by several signaling pathways that regulate metabolism with considerable cross-talk. These include sirtuin mediated activation of the kinase AMPK, which serves as a critical regulator of autophagy, lipid metabolism, and mitochondrial function, and the Nrf2 endogenous antioxidant program. Nrf2 can activate SIRT3, which in turn activates autophagic proteins such as p62,



which can then activate Nrf2. These pathways also have many overlapping functions, particularly with respect to their anti-inflammatory and antioxidant functions, thus similar phenotypic effects may be mediated by different signaling molecules in different tissue types. For example, the transcription factor Nrf2 activates the glutathione antioxidant response, while AMPK can also activate an antioxidant response through the activation of the transcription factor FOXO3a. Both Nrf2 and AMPK can reduce inflammation via inhibition of NF-κB signaling.

Obesity: POTENTIAL BENEFIT (Preclinical)

In rodent models, DHM has only marginal benefit in reducing overall weight gain during consumption of a high fat diet, but is more effective in normalizing insulin/glucose levels and preventing hyperlipidemia [25; 26; 29]. In mouse models of obesity (high fat diet and ob/ob), the plasma level of non-esterified fatty acids was found to be negatively correlated with insulin sensitivity and the proportion of slow-twitch muscle fibers [29]. Activation of AMPK by DHM improved fatty acid metabolism, thereby increasing the proportion of slow-twitch fibers and insulin sensitivity in the muscle.

Diabetes: POTENTIAL MINOR BENEFIT

A supplement of *ampelopsis grossedentata* (10 g/day) containing DHM (970 mg per 10 g) was given to participants with type 2 diabetes (n=77) in a placebo-controlled RCT for one month [30]. Compared to the placebo group, the DHM treated group showed a significant decrease in the primary outcome of the trial, the levels of fasting glucose (change from baseline DHM -0.73 ± 1.34 vs Placebo $.49 \pm 1.78$ mmol/L, $P < 0.05$), as well as in glycated albumin (-2.09 ± 1.86 vs $-1.18 \pm 1.45\%$), cystatin C (-0.09 ± 0.12 vs 0.00 ± 0.20 mg/L), and retinol binding protein-4 (-11.28 ± 11.68 vs -4.06 ± 13.39 mg/L). But there were no significant effects on the levels of fasting insulin, HOMA-IR, 2h-PG, 2h-INS, C-peptide, 2h-C-peptide, urea, creatine, uric acid, total cholesterol, triglycerides, or U-mAlb.

This study suggests there may be some marginal benefit to DHM containing supplements for regulating blood glucose, however, the potential benefits seen in this trial are inferior to what has been shown in rodent models. The discrepancy in efficacy is likely related to the poor bioavailability of DHM and timing of administration. In animal models, DHM has typically been used to prevent or mitigate the onset of metabolic dysregulation, rather than treat pre-existing metabolic problems, as is the case in the diabetic patients. In rodents, DHM-mediated improvements in insulin sensitivity were associated with increased phosphorylation of insulin receptor substrate 1 (IRS-1), Akt, and AMPK [27; 31; 32; 33; 34]. The beneficial effects on metabolism appear to require SIRT-AMPK mediated autophagy. There is currently another ongoing clinical trial assessing the effects of DHM on glucose control and insulin sensitivity in patients with type 2 diabetes ([NCT03606694](https://clinicaltrials.gov/ct2/show/study/NCT03606694)).



Fatty liver disease: POTENTIAL BENEFIT

DHM (150 mg capsules 2x/day for three months) was tested in patients with non-alcoholic fatty liver disease (NAFLD) (n=60) in a placebo-controlled RCT [35]. Compared to the placebo group, DHM treatment reduced serum levels of liver enzymes, including ALT, AST, and GGT, as well as serum levels of lipids, including LDL-c and apoB. Insulin resistance was decreased based on the HOMA-IR index, and serum pro-inflammatory mediators (TNF α) were also decreased with DHM treatment.

DHM has been shown to protect against both alcoholic and non-alcoholic associated fatty liver disease in rodent models by reducing hepatic inflammation, fibrosis, lipid accumulation, and oxidative stress [36; 37; 38]. The protective effects are primarily mediated by activation of Nrf2 mediated antioxidant capacity, AMPK mediated autophagy induction, and PPAR α mediated lipid metabolism.

DHM is primarily marketed as a 'hangover cure' and to protect against ethanol-mediated liver toxicity. In addition to providing hepatoprotection through the mitigation of ethanol-induced inflammation and oxidative stress, DHM can induce the expression of the ethanol metabolizing enzymes ADH1 and ALDH2, leading to a reduction in the concentrations of ethanol and aldehyde, and a restoration of NAD⁺ levels [38].

Acute inflammatory organ damage: POTENTIAL BENEFIT near time of injury (Preclinical)

DHM has been shown to protect against acute injury in several organ systems, including the lung, liver, and kidney, by attenuating the induction of inflammation and oxidative stress [39; 40; 41; 42]. Since DHM was typically administered in close proximity to the induction of the stressor (such as LPS), it is unclear whether its benefits require prophylactic use, and if it has meaningful benefit after the initiation of inflammatory and oxidative damage.

Cancer: POTENTIAL BENEFIT likely as an adjunct (Preclinical)

DHM has been shown to promote apoptotic cell death in a variety of cancer cell lines and rodent models. The anti-cancer activity appears to be related to the modulation of ROS generation and mitochondria dependent apoptosis [1]. Its relatively modest effects in preclinical models suggests that it is unlikely to have utility as a monotherapy, but it may be beneficial as an adjunct to other chemotherapeutic agents. Some studies have shown that its use in combination with certain chemotherapeutics may promote synergism, and/or reduce toxicity in healthy tissue. For example, DHM has synergistic anti-tumor activity when used with irinotecan in mouse models of colon cancer, but did not potentiate the anti-tumor activity of the chemotherapeutic gemcitabine [43]. DHM was also protective against cardiotoxicity without reducing anti-tumor activity when used in combination with the chemotherapeutic adriamycin [17].

Safety: Rated B for potential and C for evidence. DHM has a good safety record in short term RCTs and animal studies, which may be due to low bioavailability. Pharmacokinetic properties may differ across patient populations, and may have drug interactions due to projected CYP inhibition activity.

Types of evidence:

- 2 clinical trials (Diabetes n=77 t=1 month; NAFLD n=60 t=3 months)
- Numerous laboratory studies

The use of DHM containing supplements derived from *ampelopsis grossedentata* was not reported to have significant adverse effects in the two RCTs conducted thus far [30; 35]. However, these were relatively short duration trials of only one month and three months. DHM has also not been associated with toxicities in preclinical rodent studies [1].

The good safety profile of DHM may be related to its poor bioavailability of 4.02% in rats [44], and it is possible that new side effects may emerge with the development of more bioavailable formulations. One study in rats found that the pharmacokinetics of DHM vary in different patient populations, as the Cmax, clearance rate, and tissue distribution were significantly different between healthy and diabetic rats, suggesting that dosage may have to be carefully titrated for different populations [45].

In vitro studies in liver microsomes suggest that DHM may have significant drug interactions due to its ability to inhibit some CYP enzymes [46]. In particular, it was found to inhibit CYP3A4, CYP2E1 and CYP2D6, and thus may interfere with drugs that are metabolized by these enzymes.

Sources and dosing:

DHM is sold OTC as a supplement, and is primarily marketed as a 'hangover cure'. No clinically validated therapeutic dose has been established for any indication. DHM has low bioavailability, low solubility, poor intestinal absorption, poor permeability, poor stability, and decomposes when exposed to light or low pH [1].

Research underway:

According to Clinicaltrials.gov, there is currently one ongoing Phase 2 clinical trial ([NCT03606694](#)) testing DHM against metformin for its effects on glycemic control, insulin sensitivity and insulin secretion in type 2 diabetes mellitus, which is expected to be completed in late 2021.

There are also preclinical studies underway to try to develop a more stable, bioavailable formulation of DHM which has PK properties better suited for therapeutic use [45].

Search terms:

Pubmed, Google: Dihydromyricetin, ampelopsin

- Alzheimer's disease, Parkinson's disease, neurodegeneration, cognition, aging, cardiovascular, diabetes, liver disease, metabolism, inflammation, cancer, clinical trial, safety

Websites visited for Dihydromyricetin:

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
- [DrugBank.ca](https://drugbank.ca)

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