



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.

7,8-Dihydroxyflavone (7,8-DHF)

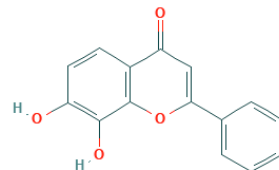
Evidence Summary

7,8-DHF is neuroprotective in many animal models, and there is a biological rationale for increasing BDNF signaling through TrkB. However, no human studies have been conducted.

Neuroprotective Benefit: 7,8-DHF is neuroprotective in many different animal models, but there are no studies in humans.

Aging and related health concerns: N/A

Safety: No human studies have examined the safety of 7,8-DHF.

Availability: Available as a supplement	Dose: No currently established dose	Chemical formula: C ₁₅ H ₁₀ O ₄ MW: 254.241g/mol  Source: Pubchem
Half life: 134 minutes (mice)	BBB: penetrant in animals	
Bioavailability: ~5% (mice)		
Clinical trials: None	Observational studies: None	

What is it?

Brain-derived neurotrophic factor (BDNF) is a growth factor that binds to TrkB and p75 to regulate neuronal survival, differentiation and plasticity. 7,8-dihydroxyflavone (7,8-DHF) is a naturally occurring flavone found in the tree *Godmania aesculifolia* and the weed *Tridax procumbens* that was reported to be a potent TrkB agonist ([Jang et al, 2010](#)). Although BDNF is an attractive target for Alzheimer's disease, it does not cross the blood brain barrier and has a short half-life. 7,8-DHF was found to both cross the blood brain barrier and activate TrkB receptors in the brain.

Although 7,8-DHF was found to activate TrkB and prevent glutamate-induced toxicity in neurons, but not neurons lacking the TrkB receptor ([Jang et al, 2010](#)), there is some controversy whether 7,8-DHF really activates the TrkB receptor. Using multiple *in vitro* cell-based assays, [Boltaev et al \(2017\)](#) and [Todd et al \(2014\)](#) reported that 7,8-DHF failed to activate the TrkB receptor or downstream signaling pathways (e.g. AKT and ERK1/2). In fact, at higher concentrations (>20uM), [Todd et al \(2014\)](#) reported that 7,8-DHF was neurotoxic in a cortico-striatal cell culture system. Previous studies used Western blotting to confirm *in vivo* activation of the TrkB receptor after 7,8-DHF treatment, and the authors speculate that the processing involved in Western blotting preparation may have led to inaccurate results. They recommend using multiple assays to confirm TrkB activation. Additionally, they reported that commercially available TrkB antibodies are non-specific. Alternatively, since 7,8-DHF is heavily metabolized, they also suggested that a 7,8-DHF metabolite may activate TrkB, a result that would not be seen in an *in vitro* assay.

More work needs to be done to confirm that 7,8-DHF is truly a TrkB agonist.

Neuroprotective Benefit: 7,8-DHF is neuroprotective in many different animal models, but there are no studies in humans.

Types of evidence:

- Multiple preclinical studies in different models of neurodegeneration

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

None

Human research to suggest benefits to patients with dementia:

No human studies have examined whether 7,8-DHF is beneficial for Alzheimer's patients. However, BDNF mRNA levels were reported to be reduced in postmortem samples from patients with Alzheimer's disease and mild cognitive impairment (MCI) and correlated with cognitive function. Additionally, BDNF levels were decreased in the temporal cortex correlated with Braak staging (an indicator of tau pathology) and were decreased in patients with non-Alzheimer's tauopathies. However, there are mixed reports on whether TrkB levels, serum BDNF, and BDNF SNPs are associated with Alzheimer's disease ([Tanila 2017](#)).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Preclinical studies suggest that 7,8-DHF is beneficial for Alzheimer's disease through its action as an agonist for the BDNF receptor (TrkB). It was reported to cross the blood brain barrier ([Liu et al, 2013](#)), and although it did not increase the number of new neurons in aged animals, it did increase dendritic length of newborn neurons in the hippocampus ([Wang et al, 2017](#)).

Healthy animals

Acute treatment of 7,8-DHF in healthy young rats was reported to improve performance on an object discrimination task ([Bollen et al, 2013](#)).

Prevention paradigms

Treatment of Alzheimer's mice with 7,8-DHF for two months reduced A β 42-containing plaques and protected from increased levels of choline-containing compounds and prevented the reduction of glutamate. Although there were no significant differences in soluble A β 40 or A β 42, A β 40-containing plaques, dendritic spine density or neurogenesis, all of the results trended in a direction that would indicate a benefit ([Aytan et al, 2018](#)). However, in another prevention study, treatment of 7,8-DHF in an



Alzheimer's mouse model for four months increased phosphorylated TrkB (pTrkB) and downstream signaling pathways, reduced amyloid plaques (but not total A β 42), prevented synaptic loss, increased LTP, and improved cognition ([Zhang et al, 2014](#)). Additionally, treatment of ApoE knockout mice with 7,8-DHF from five weeks of age for 25 weeks improved cognition and reduced tau pathology ([Tan et al, 2016](#)).

Treatment paradigms

Early disease: Acute treatment of early disease Alzheimer's mice and wild type (WT) mice with 7,8-DHF was reported to improve performance on an object discrimination task ([Bollen et al, 2013](#)). Another study reported no effect of 7,8-DHF on cognition or amyloid plaques, but it was conducted in a model that begins plaque formation and memory deficits before a mouse is fully mature (6 weeks), so it is not clear if the failure to recapitulate the results might be due to a different type of animal model rather than the drug being ineffective ([Zhou et al, 2015](#)).

Mid-disease: Treatment of middle-aged Alzheimer's mice with 7,8-DHF for four weeks improved cognition, increased spine density, increased expression of GluA1 and GluA2, increased phosphorylation of TrkB and downstream signaling (pAKT, pCREB, pERK, and pCaMKII) but did not change A β 40 or 42 levels. The increased expression of GluA1 and GluA2 were dependent on pTrkB downstream signaling ([Gao et al, 2016](#)).

In models of neuronal death or scopolamine-induced cognitive impairment, 7,8-DHF treatment improved cognition, increased LTP, increased the density of thin spines in the hippocampus, reduced A β 40 and A β 42, reduced oxidative stress, and increased the expression of anti-oxidant enzymes ([Castello et al, 2014](#); [Chen et al, 2014](#)).

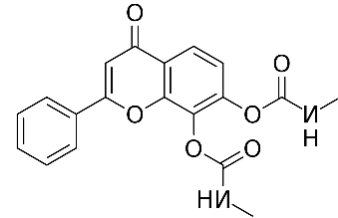
Late-disease: Treatment of old Alzheimer's mice with 7,8-DHF for 10 days improved cognition, increased pTrkB (without changing BDNF levels), reduced BACE1 expression and reduced A β 40 and A β 42 ([Devi and Ohno, 2012](#)).

In addition to its beneficial effects in Alzheimer's disease, 7,8-DHF has also been reported to improve outcomes in models of ALS, depression, Rett syndrome, Parkinson's, Multiple Sclerosis, and Huntington's disease ([Aytan et al, 2018](#), [Makar et al, 2016](#)).



R13

7,8-DHF was reported to have low bioavailability (4.6%) and suboptimal brain exposure due to the fact that its catechol group (a benzene ring with two OH) makes it subject to metabolism from glucuronidation, sulfation, and methylation. However, the catechol group is an essential pharmacophore, so [Chen et al \(2018\)](#) synthesized a number of compounds to increase bioavailability of 7,8-DHF and developed R13 (figure right). R13 is a prodrug with an increased bioavailability of 7,8-DHF from 4.6% to 10.5% and an increased half-life from 134 minutes to 219.6 minutes. R13 half-life in the brain was 4 hours.



Source: [Wikipedia](#)

In a prevention paradigm, treatment of Alzheimer's mice with R13 for three months increased phosphorylation of TrkB, prevented synaptic loss, increased long-term potentiation (LTP), reduced amyloid plaques in the hippocampus and frontal cortex, reduced A β 40 (but not 42) levels, reduced inflammatory cytokines (IL-6, TNF α , IL-1 β), and improved cognition.

Potential Harm

Neurotrophins have been reported to induce neuronal death in certain *in vitro* conditions. [Kim et al \(2010\)](#) reported that prolonged exposure (10 days) of cultured cortical neurons to BDNF induced necrosis through activation of the NMDA receptor. Consistent with this, [Koh et al \(1995\)](#) reported that BDNF induced necrosis in cultured neurons exposed to oxygen-glucose deprivation or NMDA, and [Mcdonald et al \(2002\)](#) reported that BDNF increased damage in iron-induced spinal cord injury. Whether these results may be recapitulated when there may be increased glutamate excitotoxicity *in vivo* (as in Alzheimer's disease) is not known.

APOE4

No information

Aging and related health concerns: N/A.

Types of evidence:

- None

7,8-DHF has not been investigated for any age-related diseases.



Safety: No human studies have examined the safety of 7,8-DHF.

Types of evidence:

- *Preclinical studies*

Preclinical studies have not reported any toxicity. However, no human studies have been conducted.

Cancer

Whether or not 7,8-DHF has an impact on cancer is unknown. The BDNF/TrkB pathway is cytoprotective, and expression of BDNF/TrkB is upregulated in many types of cancers and can make cancer chemotherapeutic-resistant. Therefore, there TrkB antagonists are currently in the clinic for oncology. However, BDNF overexpression in the hypothalamus in mice can stimulate the immune system which can protect against cancer ([Radin and Patel, 2017](#)). Therefore, there is a hypothetical risk that 7,8-DHF may accelerate cancer growth. However, the only studies conducted so far suggest that 7,8-DHF may suppress proliferation and induce apoptosis of cancer cells *in vitro* ([Sim et al, 2016](#); [Lee et al, 2015](#)). More work needs to be done to understand how 7,8-DHF may impact cancer risk.

Drug interactions:

7,8-DHF has not been studied in humans and drug interactions are unknown.

Sources and dosing:

A human dose for 7,8-dihydroxyflavone is not established. Online stores sell it in 25mg capsules.

Research underway:

None

Search terms:

- 7,8-dihydroxyflavone

Websites:

- Clinicaltrials.gov



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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit [Cognitive Vitality's Rating page](#).