REVIEW ARTICLE

7,8-dihydroxyflavone – a long awaited BDNF mimetic molecule with antioxidant action

Jakub Benko [1,2], Jana Klimentova [1], Stanislava Vrankova [1]

[1] Institute of Normal and Pathological Physiology, Centre of Experimental Medicine, Slovak Academy of Sciences, Sienkiewiczova 1, 813 71 Bratislava, Slovakia, [2] Faculty of Medicine, Comenius University in Bratislava, Špitálska 24, 813 72 Bratislava, Slovakia.

Correspondence to: Stanislava Vrankova, Institute of Normal and Pathological Physiology, Centre of Experimental Medicine, Slovak Academy of Sciences, Sienkiewiczova 1, 813 71 Bratislava, Slovakia
e-mail: stanislava.vrankova@savba.sk

Submitted: 2023-01-10 Accepted: 2023-03-06 Published online: 2023-03-06

Key words: **7,8-dihydroxyflavone; BDNF-TrkB system; flavonoids; antioxidants; depression**

Act Nerv Super Rediviva 2023; **65**(1): 1–7 ANSR65123R01

Abstract

7,8-dihydroxyflavone (7,8-DHF) is a small-molecule ligand of tropomyosine kinase B (TrkB) with a pharmacodynamic properties similar to brain-derived neurotrophic factor (BDNF). It occurs naturally in *Godmania aesculifolia*, *Tridax procumbens* and *Primula spp.* where it acts as an antioxidant, UV absorbent and an antimicrobial agent. During the past decade, a body of research on animal models hinted towards a potential applicability of 7,8-DHF in treatment of diseases of nervous system such as Parkinson's disease, Alzheimer's disease, major depressive disorder, and schizophrenia. In addition to neuropsychiatric disorders, 7,8-DHF was further successfully applied in the studies of cardiovascular, metabolic, and immune system related diseases and cancer. The aim of this review is to summarize key studies describing its molecular and cellular mechanisms as well as therapeutic effects.

Introduction

Brain-derived neurotrophic factor (BDNF) and tropomyosine kinase B (TrkB), a ligand and a receptor, respectively, sit at the heart of molecular processes involved in neuronal proliferation, synaptogenesis, and neuroprotection. Besides BDNF, four other neurotrophins have been identified to date - nerve growth factor (NGF), neurotrophin (NT)-3, NT-4 and NT-5. These protein ligands bind to Trk receptors Trk(A-C) with varying specificity and are most abundantly expressed in CNS (Gupta *et al.* 2013). Many neurological and psychiatric diseases such as major depression, Parkinson's or Alzheimer's lack a direct treatment acting at the site of deficiency – impaired BNDF/TrkB signalization.

Although the molecular mechanisms of neuroplasticity are relatively well understood, the search for an exogenous agonist of TrkB has been mostly unsuccessful. However, recent results showed that 7,8-dihydroxyflavone (7,8-DHF) and its derivates robustly activate TrkB and lead to molecular, cellular, and physiological changes associated with neuroplasticity (Jang *et al.* 2010; Liu *et al.* 2014). Beneficial effects outside of the context of the nervous system were also described, which can be explained by the fact that TrkB is also expressed in other tissues, and that flavones are potent antioxidants. Specifically, antihypertensive, vasodilatory, cardioprotective, anti-inflammatory,

anti-obesity, and anticancer effects were reported and are summarized below.

Mechanism of action

7,8-DHF is a selective agonist of TrkB, which is a homodimeric kinase with a trans-phosphorylation activity. It does not appear to act on other Trk (A/C) homologues and, contrary to BDNF as a natural ligand of TrkB, 7,8-DHF binds to a different site on the TrkB receptor. Following activation, two TrkB subunits undergo cross-phosphorylation at tyrosine sites Tyr515, Tyr706, and Tyr816. Tyr706 was shown to be phosphorylated most robustly and most consistently (Liu *et al.* 2014). The initial activation leads to activation of downstream pathways consisting of ERK, mitogen-activated protein kinase (MAPK), and PI3/Akt kinases. These signaling pathways are able to phosphorylate and activate the transcription factor cAMP response element-binding (CREB) protein (Jang *et al.* 2010, Liu *et al.* 2014) (Figure 1). Similar to BDNF, activation by 7,8-DHF leads to internalization of receptor complex and its ubiquitination and following degradation (Liu *et al.* 2014).

However, Boltaev *et al.* (2017) showed evidence contradicting this mechanism of action since they failed to detect any measurable downstream activation of ERK/MAPK pathway. Other studies have also reported that some effects of 7,8-DHF do not require the TrkB receptor as they occurred either in conditions in which the receptor was pharmacologically inhibited, or in cells that do not express the TrkB receptor (Huai *et al.* 2014; Ryu *et al.* 2014). It was shown that in these cases, 7,8-DHF acts through NO/cGMP and Ca^{2+} signaling pathways rather than through the TrkB receptors. 7,8-DHF blocked both intracellular Ca^{2+} release and extracellular Ca^{2+} influx. Whether 7,8-DHF can block the α-adrenoceptors or inhibit phospholipase C (PLC) remains to be elucidated (Huai *et al.* 2014).

In addition to the above-reported specific effects on the TrkB signaling pathway, 7,8-DHF as a flavonoid, had been shown to exert a direct antioxidant action (Choi *et al.* 2016).

Effect of 7,8-DHF on neurodegenerative diseases

The most important application of 7,8-DHF and the related molecules is the treatment of neuropsychiatric diseases such as major depressive disorder (MDD), Alzheimer's disease (AD), traumatic brain injury and others. Although these conditions are multicausal and seemingly unrelated, they have a common denominator – inadequate or decreased synaptic plasticity. This deficiency might be alleviated by stimulation of TrkB receptors with an endogenous or exogenous ligand. However, a direct application of BDNF is not pharmacologically feasible because it does not cross blood brain barrier. As mentioned above, a suitable exogenous ligand of TrkB was not known for several decades since the discovery of BDNF. Thus, a recognition of neurotrophic action of 7,8-DHF was greeted with a lot of enthusiasm.

The first results suggesting its neurotrophic action come from a study by Jang *et al.* (2010). In the study, the authors identified a selective affinity of 7,8-DHF to TrkB and described its ability to activate intracellular signaling via phosphorylation of Akt and ERK/MAPK both *in vitro* and *in vivo*. Furthermore, they described its therapeutic efficacy in animal models of stroke and Parkinson's disease (PD). They concluded that the therapeutic effects are most probably caused by the activation of TrkB and not to its antioxidant properties (Jang *et al.* 2010).

On a cellular level, 7,8-DHF was shown to protect PC12 cells from cell death caused by a dopaminergic neurotoxin 6-hydroxydopamine (6-OHDA) by activation of the PI3K/Akt pathway and inhibition of the JNK pathway (Han *et al.* 2014). Luo *et al.* (2016) confirmed the protective effect of 7,8-DHF in an *in vivo* model of PD, where a pretreatment with 7,8-DHF protected dopaminergic neurons in substantia nigra against 6-OHDA and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which preserved motor function. Furthermore, it was found that 7,8-DHF can repair impaired TrkB signalization in a model of AD and thus ameliorate accompanying memory deficits (Devi & Ohno, 2012; Zhang *et al.* 2014). The same effect was also demonstrated in spatial memory deficits of aged rats (Zeng *et al.* 2012). A study by Tan *et al.* (2016) demonstrated that 7,8-DHF ameliorates cognitive deficits in Apolipoprotein E knockout mice via activation of AKT/GSK-3β pathway and subsequent down-regulation of expression of abnormal tau protein. Finally, two studies showed the efficacy of 7,8-DHF in models of peripheral nervous system diseases, where it promoted neuronal survival and stimulated axon regeneration in peripheral neurons (Tsai *et al.* 2013; English *et al.* 2013).

Effect of 7,8-DHF on psychiatric diseases

Affective disorders, such as major depressive disorder (MDD) and anxiety are usually treated with antidepressants based on inhibition of monoamine reuptake, or gamma-aminobutyric acid (GABA) agonists, respectively. While widely used, these methods of treatment have several drawbacks. In the case of reuptake inhibitors, it usually takes 2–4 weeks until any effects are noticed and about a third of patients shows no response at all. On the other hand, GABA agonists pose a great risk of abuse and dependence potential similar to alcohol. As a result, the search for novel drugs of immediate action and better safety profile has been initiated. Ketamine is one of those drugs that has recently been approved by the Food and Drug Administration, as well as the European Medicines Agency for the treatment

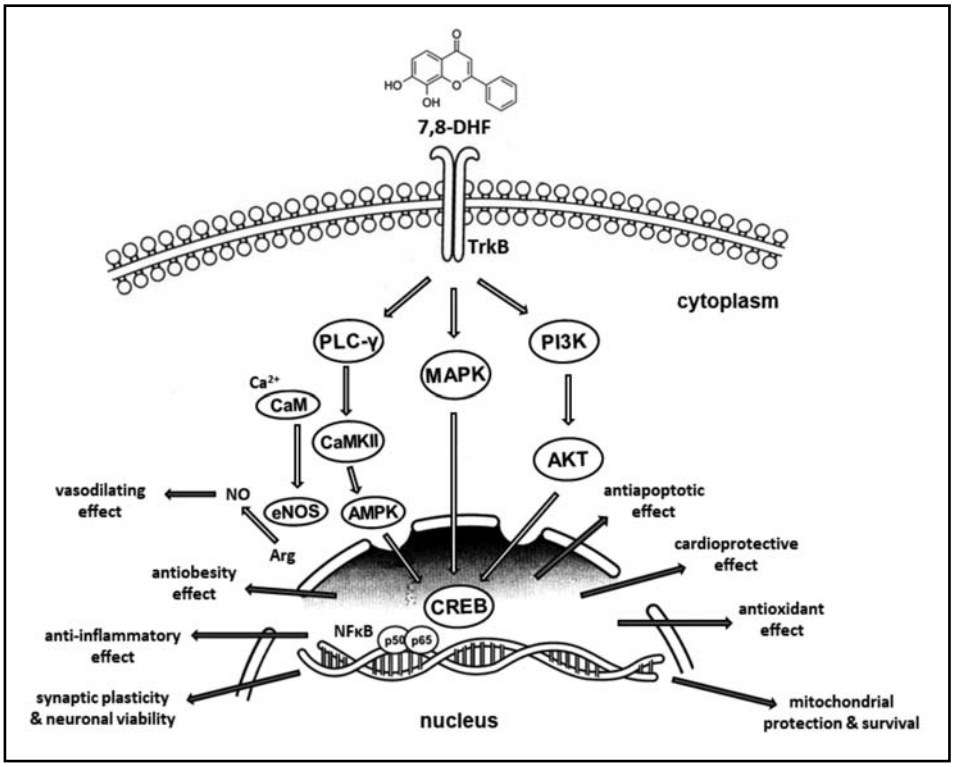

Fig. 1. Schematic picture of proposed mechanisms underlying the protective effects of 7,8-DHF
AKT, protein kinase B; AMPK, AMP-activated protein kinase; Arg, arginine; CaM, Calmodulin; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase; CREB, cAMP response element binding protein; eNOS, endothelial nitric oxide synthase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; PLC-γ, phospholipase C-γ; TrkB, tropomyosine kinase B.

of depression. As another alternative, 7,8-DHF is a suitable candidate, since depression and anxiety disorders are partially caused by inadequate synaptic plasticity. Other study comparing the effects of 7,8-DHF and non-anesthetic doses of ketamine showed immediate effects of 7,8-DHF on the depressive-like behavior in mice subjected to chronic mild stress. Notably, the effect was more sustained in comparison to the effect yielded by ketamine (Zhang *et al.* 2015a).

Similar results were obtained in other models of depression. Positive effects of 7,8-DHF were observed at the level of molecular markers, e.g. serotonin metabolism (Sinyakova *et al.* 2019), alterations of HPA-axis (Blugeot *et al.* 2011), pro-inflamatory cytokines (Park *et al.* 2014), reduction of BDNF (Blugeot *et al.* 2011), at the level of morphological changes in the brain, e.g. altered neuronal connectivity (Zhang *et al.* 2015b), decrease in hippocampal volume (Blugeot *et al.* 2011), as well as at the level of behavioral changes, e.g. fear response (Andero *et al.* 2011), anxiety (Wang *et al.* 2021), learned helplessness (Shirayama *et al.* 2015) and anhedonia (Blugeot *et al.* 2011). Moreover, 7,8-DHF appears to exert its antidepressant effect partially by attenuation of immune response (see below) in a model of depression using an injection of lipopolysaccharide (Park *et al.* 2014).

Studies exploring the use of 7,8-DHF in models of schizophrenia also found promising results – 7,8-DHF ameliorated deficits in pre-pulse inhibition, synaptic plasticity and cognition (Ren *et al.* 2013; Yang *et al.* 2014; Han *et al.* 2016). Furthermore, Han *et al.* (2016) showed that 7,8-DHF protects against molecular changes (decrease in BDNF signaling, decreased parvalbumin and PGC-1α expression) specifically in the prefrontal cortex and hippocampal formation.

Effect of 7,8-DHF on cardiovascular system

Flavonoids are well known to reduce high blood pressure and have cardiovascular protective properties (Terahara 2015). Interestingly, BDNF-TrkB signaling represents an important pathway in the cardiovascular system, which indicates a potential causal relationship (Bai *et al.* 2014; Hang *et al.* 2021).

Indeed, intravenously administered 7,8-DHF, as a BDNF mimetic, significantly reduced high blood pressure, while the oral infusion of 7,8-DHF only slightly reduced the DBP of the spontaneously hypertensive rats (Huai *et al.* 2014). The authors of the same study also assumed that a vasodilating effect of 7,8-DHF is mediated by nitric oxide/cGMP and by blocking Ca^{2+} signaling pathways rather than acting on TrkB receptors. In agreement, a specific antagonist of TrkB (ANA-12), did not block the 7,8-DHF effect in the rat aorta. Therefore, they concluded that TrkB receptors might not mediate the 7,8-DHF effect. These authors showed that the effect of 7,8-DHF was decreased when the endothelium was removed. This finding indicated that nitric oxide (NO) was involved in the 7,8-DHF effect. Administration of NO synthase inhibitor (L-NAME) significantly reduced the effect of 7,8-DHF. Thus 7,8-DHF dilated rat aortas partially via NO signaling.

On the other hand, BDNF/TrkB pathway is associated with ischemic heart diseases (Hang *et al.* 2021). Wang *et al.* (2019) showed that treatment with 7,8-DHF improved cardiac dysfunction and cardiomyocyte abnormality in myocardial ischemic mouse model. They reported that 7,8-DHF attenuated mitochondrial dysfunction of ischemic cardiomyocytes, because the impaired mitochondrial dynamics aggravated heart dysfunction during ischemia (Maneechote *et al.* 2017). The study of Wang *et al.* (2019) also showed that 7,8-DHF protects against cardiac ischemic injury by regulating optic atrophy 1 (OPA1) in H2O2-treated H9c2 cells. OPA1 is a mitochondrial inner membrane protein, that caused mitochondrial fragmentation (Wai *et al.* 2015).

Other study investigated effect of 7,8-DHF on doxorubicin-induced cardiotoxicity. The authors documented that 7,8-DHF contributed to a cardioprotective effect by activating Akt and improving mitochondrial function by upregulation of the signal transducer and activator of transcription 3 (STAT3) (Zhao *et al.* 2019). STAT3 is an important transcription factor and the key regulator involved in stress-induced heart remodelling (Haghiki *et al.*2014).

AMP-activated protein kinase (AMPK) plays a role in cellular energy balance of metabolic pathways in the hypertrophic heart (Chen *et al.* 2020). Important finding is that AMPK activity of cardiomyocyte is markedly increased in response to hypoxia and ischemia (Kim & Dyck, 2015). Zhao *et al.* 2019 and Wang *et al.* 2019 showed that 7,8-DHF inhibited AMPK activity in doxorubicin or ischemia-induced cardiac injury. On the other hand, a novel 7,8-DHF mechanism of action was documented in cardiac hypertrophy. 7,8-DHF activated AMPK/PGC-1α (biogenesis activator PGC-1) pathway and thus inhibited the progression of mitochondrial dysfunction (Hang *et al.* 2022).

Effect of 7,8-DHF on metabolic diseases

BDNF and the TrkB receptor play a key role in the regulation of body weight and energy balance (Nakagomi *et al.* 2015). It is known that BDNF reduced food intake and body weight in rats, but its short half-life hampers its clinical application (Pelleymounter *et al.* 1995; Poduslo *et al.* 1996)

Begliuomini *et al.* (2007) showed, that the plasma level of BDNF positively correlated with the estrogen level in female subjects. Chan *et al.* (2015) reported, that muscular TrkB was activated by chronic administration of 7,8-DHF, which was sufficient to prevent the development of diet-induced obesity in female mice. One of the cascades involved in the anti-diabetic and anti-obesity properties of 7,8-DHF is an increase of uncoupling protein 1 (UCP1) expression, AMPK activation and an increase in lipid oxidation, which contributes to increased systemic energy expenditure and reduced body weight gain. UCP1 is a mitochondrial regulator of thermogenesis and homeostasis in adipose tissue (Chouchani *et al.* 2018). Zhao *et al.* (2020) also confirmed the preventive and therapeutic effect of long-term 7,8-DHF administration on the development of high-fat diet (HFD)-induced obesity. The *in vitro* cellular experiments revealed a novel role of 7,8-DHF in activating tissue-specific estrogen receptor α (ERα), which are widely expressed in many cells and tissues involved in energy metabolism and glucose uptake (Ribas *et al.* 2016; Shi *et al.* 2013). 7,8-DHF treatment activated the muscular ERα (essential for the activation of muscular TrkB), increased UCP1 expression and reduced the adiposity in female mice with metabolic syndrome.

Choi *et al.* (2016) showed that 7,8-DHF has an anti-obesity effect *via* its anti-oxidant activity. 7,8-DHF treatment reduced the level of ROS and enhanced the expression of antioxidant enzymes, such as Mn-superoxide dismutase (Mn-SOD), catalase (CAT), and heme oxygenase-1 (HO-1). Administration of 7,8-DHF also down-regulated the expression of major adipogenic transcription factors, such as CCAAT/enhancer-binding protein-α (C/EBP-α), C/EBP-β, and peroxisome proliferator activated receptor-γ (PPAR-γ) in 3T3-L1 preadipocyte cells.

Wood *et al.* (2018) examined the effect of 7,8-DHF on body weight gain by enhancing mitochondrial biogenesis in skeletal muscle of obese female mice. They found out, that administration of 7,8-DHF triggered the AMPK/CREB/PGC-1α pathways which enhanced energy metabolism and thus reduced body weight gain in obese animals. Moreover, hyperlipidemia, hyperglycemia hyperinsulinemia, and ectopic lipid accumulation in skeletal muscle were reduced following 7,8-DHF treatment.

Anti-inflammatory effect of 7,8-DHF

Since flavonoids inhibit immune system related inducible enzyme activities and suppress pro-inflammatory transcription factors and cytokines, they exert anti-inflammatory action (Prasad *et al.* 2010; Yahfoufi *et al.* 2018).

It was demonstrated that 7,8-DHF attenuates the release of pro-inflammatory mediators and cytokines by suppressing the nuclear factor-κB (NF-κB) and MAPK signaling pathways. 7,8-DHF inhibited the nuclear translocation of the NF-κB (p65 subunit) and reduced the transcriptional activity of NF-κB by IκB-α degradation in BV2 microglial cells (Park *et al.* 2014). A further study also confirmed the anti-inflammatory action of 7,8-DHF via downregulation of NF-κB signaling (Ryu *et al.* 2014). In the recent study, analysis revealed that both NF-κB and iNOS expressions down-regulated significantly in the hippocampus following administration of 7,8-DHF (Amin *et al.* 2020). Other study showed that treatment with 7,8-DHF had a beneficial effect on production of pro-inflammatory cyto-

kines and proteins, specifically, 7,8-DHF reduced the levels of hepatic IL-1β, NF-kB and iNOS in rats with liver injury (Kumar *et al.* 2019). Furthermore, 7,8-DHF inhibited inflammation-induced skin aging through the reduction of matrix metalloproteinase 1 (MMP-1) synthesis. Tumor necrosis factor α (TNF-α) induced activation of the Akt and MAPK signaling pathways was suppressed after 7,8-DHF treatment (Choi *et al.* 2017). Cai *et al.* (2019) observed that 7,8-DHF down-regulated mRNA expression of TNF-α, IL-1β, IL-6, and MMP-1, MMP-3 and MMP-13 in a mouse model of osteoarthritis. The evidence for an anti-inflammatory activity of 7,8-DHF was also obtained in the recent study by Xiong *et al.* (2022). These authors demonstrated that 7,8-DHF robustly represses CCAAT/enhancer-binding protein β (C/EBPβ) expression. The transcription factor C/EBPβ is activated by proinflammatory cytokines and acts as transcription factor for these cytokines as well. Concerning BDNF/TrkB pathway, BDNF and C/EBPβ regulate each other negatively. In addition, C/EBPβ acts as repressor that blocks BDNF mRNA expression (Ahn *et al.* 2021; Li *et al.* 2022).

Anticancer effect of 7,8-DHF

It was reported that various flavone/flavonoid compounds and their derivatives have therapeutic effects in attenuating tumor development and progression. Flavonoids modulate ROS-scavenging enzyme activities, participate in arresting the cell cycle, induce apoptosis, and suppress cancer cell proliferation (Chirumbolo *et al.* 2018; Rodriguez-Garcia & Sanchez-Quesada 2019). Moreover, flavonoids decrease mitochondrial membrane potential in tumor cells, which makes them visible to cell death signaling (Abotaleb *et al.* 2018).

Treatment with 7,8-DHF effectively induced apoptosis in human leukemia U937 cells by activating the MAPK pathways and modulating B-cell lymphoma-2 (Bcl-2) family proteins (Park *et al.* 2013). Furthermore, 7,8-DHF was found to activate the nuclear factor erythroid derived 2-related factor 2/heme oxygenase 1 (Nrf2/HO-1) signaling pathway and reduce the expressions of MMP-1, MMP-3, MMP-13, IL-1β, IL-6, and TNF-α (Cai *et al.* 2019). 7,8-DHF could also alter specificity protein 1 (Sp1) transactivation and induce apoptotic cell death in oral squamous cell carcinoma (Lee *et al.* 2015). Sp1 is a transcription factor that plays important roles in the carcinogenesis by regulating growth-related signal transduction, apoptosis, tumor-suppressor genes and cell cycle control molecules (Garcia *et al.* 2008). Therefore, inhibiting Sp1 is an effective therapeutic strategy for preventing cancer. 7,8-DHF decreased Sp1, BID and Bcl-$_{xl}$ protein expression levels as well as increased Bax, and cleaved caspase-3 expressions (Lee *et al.* 2015). Other authors reported that 7,8-DHF exhibits anti-melanogenic activity through inhibition of tyrosinase activity by downregulating the α-melanocyte stimulating hormone (MSH)/cyclic adenosine monophosphate (cAMP)/microphthalmia associated transcription factor (MITF) pathway (Sim *et al.* 2016). Recently, the anti-tumor effect of 7,8-DHF/hyaluronic acid-based nanogel has been documented as one promising targeted antitumoral nanomedicine approach (Choi *et al.* 2018).

Conclusion

7,8-DHF exerts a wide range of effects which have been obtained in animal disease models or in experiments *in vitro*. Data with the TrkB specific agonist 7,8-DHF would suggest both the regenerative activity of BDNF and antioxidant efficacy as well. It can be said that these studies pointed to an important role of 7,8-DHF in the treatment strategy of various health problems. Therefore, 7,8-DHF could serve as natural compound to be tested in future clinical trials and exert benefits in numerous pathologies.

Acknowledgement

This work was supported by The European Regional Development Fund "Centrum pre biomedicínsky výskum – BIOMEDIRES — II. etapa"— ITMS2014+: 313011W428 and the Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic (project no. VEGA 2/0118/21).

Conflict of interest

The authors declare that there is no conflict of interest.

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