

Review

# The Emerging Role of BDNF/TrkB Signaling in Cardiovascular Diseases

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**Abstract:** Brain-derived neurotrophic factor (BDNF) is one of the most abundant neurotrophins in the central nervous system. Numerous studies suggest that BDNF has extensive roles by binding to its specific receptor, tropomyosin-related kinase receptor B (TrkB), and thereby triggering downstream signaling pathways. Recently, growing evidence highlights that the BDNF/TrkB pathway is expressed in the cardiovascular system and closely associated with the development and outcome of cardiovascular diseases (CVD), including coronary artery disease, heart failure, cardiomyopathy, hypertension, and metabolic diseases. Furthermore, circulating BDNF has also been revealed as a new potential biomarker for both diagnosis and prognosis of CVD. In this review, we discuss the current evidence of the emerging role of BDNF/TrkB signaling and address the challenges that remain in translating these discoveries to novel therapeutic strategies for CVD.

**Keywords:** brain-derived neurotrophic factor; tropomyosin-related kinase receptor B; cardiovascular diseases; biomarker



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## 1. Introduction

The neurotrophin (NT) family is generally reserved for four structurally related factors: neuronal growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT-3, and NT-4/5 [1]. Among them, BDNF is a protein isolated and firstly purified from pig brain in 1982 [2]. Subsequently, the expression of BDNF was also detected in the cardiovascular system [3]. Nowadays, it has been well recognized that BDNF is the most abundant endogenous neurotrophic factor in the body [4]. Studies have shown that BDNF is a master regulator of synaptic transmission and plasticity at adult synapses in many regions of the central nervous system. The NT actions are mediated by interacting with two transmembrane receptors with different affinity. Generally, all members of the NT family bind to pan-NT receptor p75NTR with low affinity, whereas mature NTs bind to different tropomyosin-related kinase (Trk) receptors, including TrkA, TrkB, and TrkC, with high affinity according to ligand selectivity. TrkA has been identified as the preferred receptor for NGF, and TrkB for BDNF [5]. The TrkB family comprises several isoforms such as TrkB full-length (TrkB-FL), truncated TrkB.T1, and TrkB.T2. The intracellular region of TrkB has intrinsic tyrosine kinase activity. In contrast, TrkB.T1 lacks a tyrosine kinase

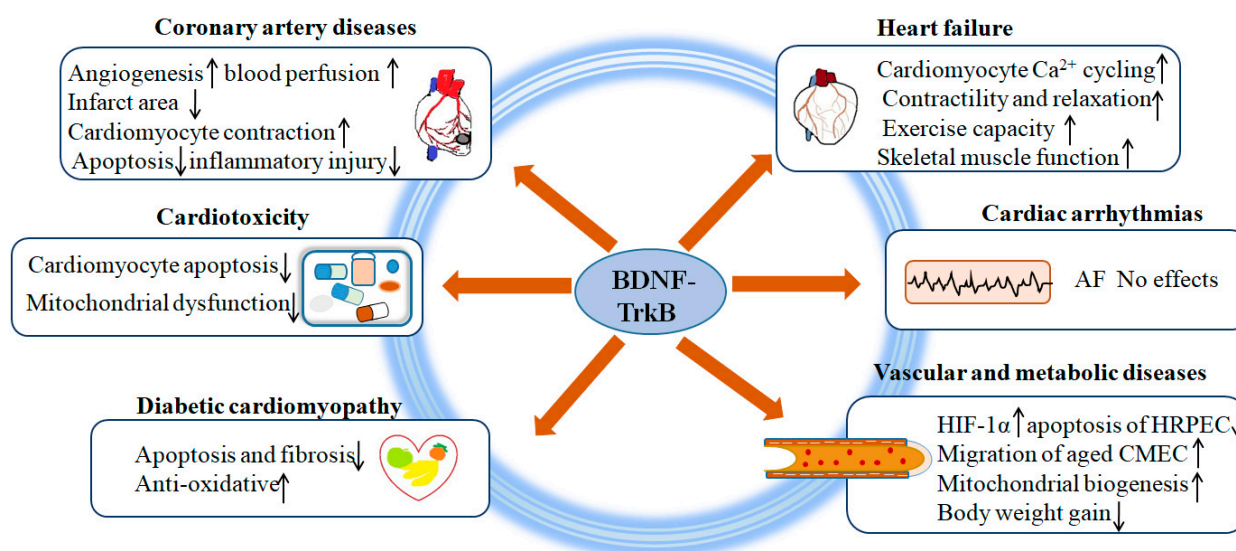
domain and negatively regulated TrkB-FL [6]. BDNF plays essential roles in neuromuscular function. It was found that expression of BDNF, but not other members of the NT family, is perturbed in muscle from patients with Kennedy's disease (KD). It was also reported that BDNF rescued synaptic and muscle function in a muscle-type specific manner in KD mice model [7]. Here, we summarize the progresses of BDNF/TrkB-related signaling pathways and the critical roles in cardiovascular diseases (CVD) and discuss the potential therapeutic role of targeting BDNF/TrkB.

## 2. BDNF/TrkB-Related Signaling Pathways

To date, a variety of signaling pathways have been found to be regulated by BDNF/TrkB, such as PI3K/Akt, mitogen-activated protein kinase (MAPK), PLC $\gamma$ , nuclear factor  $\kappa$ B (NF- $\kappa$ B), and so forth [4]. Theoretically, activation of TrkB simulates BDNF activity, including TrkB receptor phosphorylation and dimerization, as well as activating Akt and MAPK pathways. For example, Gupta et al. reported that BDNF mimetic 7,8-dihydroxyflavone (7,8-DHF) activated the TrkB signaling and protected the retinal ganglion cells from excitotoxic and oxidative stress by activating the downstream cell survival Akt and extracellular-regulated protein kinase (ERK)1/2 pathways [8]. Similarly, Kang et al. found that 7,8-DHF repressed hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>)-induced damage of C2C12 myoblasts by scavenging reactive oxygen species (ROS) and activating the PI3K/Akt and ERK signaling pathways [9]. Huang et al. found that early systemic 7,8-DHF treatment protected immature retinas against hypoxic-ischemic injury by modulating the MAPK/ERK signaling pathway [10]. In contrast, it was found that ERK signals were not affected after 7,8-DHF treatment [11], which contradicts previous studies. Moreover, other studies also reported inhibition of MAPK during the protection of 7,8-DHF. For instance, Park et al. found that 7,8-DHF inhibited lipopolysaccharide-induced inflammation by negatively regulating NF- $\kappa$ B and MAPK activation [12]. Likewise, another study supported that 7,8-DHF protected PC12 cells against the neurotoxin 6-OHDA-induced cytotoxicity via activating PI3K/Akt and inhibiting c-Jun N-terminal kinase (JNK) pathways [13]. However, it should be noted that the majority of current findings are in the neurons, and mechanistic evidence regarding the potential role of BDNF/TrkB in the cardiovascular system is limited. Our recent study indicated that 7,8-DHF activated the TrkB receptor and protected against cytotoxic anthracycline antibiotic doxorubicin (DOX)-induced cardiotoxicity by activating Akt and inhibiting ERK [14]. Moreover, we also demonstrated that 7,8-DHF attenuated ischemic myocardial injury by activating Akt and inhibited mitochondrial excessive fission [15]. More work should be done to comprehensively elucidate the role of 7,8-DHF in the cardiovascular system, which would help us to better clarify the molecular mechanisms of 7,8-DHF in both cardiac and vascular cells.

## 3. Role of BDNF/TrkB in Coronary Artery Diseases

Because BDNF is a widely existing neurotrophic factor in brain tissue and peripheral nerves, it can affect nerve development, survival, and postinjury repair. Previous studies mainly focused on its role in neurological diseases and found that BDNF had protective effects against cerebral ischemic injury. Currently, more and more studies suggest that the BDNF/TrkB axis plays an important role in cardiovascular function. Here, we summarize current advancements of the critical role of BDNF/TrkB in common CVD (Figure 1).



**Figure 1.** Schematic representation of BDNF/TrkB in cardiovascular diseases. AF, atrial fibrillation; HIF-1 $\alpha$ , hypoxia inducible factor 1 alpha; HRPEC, human retinal pigment epithelial cells; CMEC, cardiac microvascular endothelial cells.

Several previous studies firstly paid attention to the effects of BDNF on myocardial infarction (MI). It was found that intramyocardial injection of BDNF post-MI induced angiogenesis in the infarct area and the peripheral area. The study also found that simultaneous injection of basic fibroblast growth factor (bFGF) and BDNF significantly increased microvascular density in a canine infarct model and improved blood perfusion and cardiac function compared with bFGF applied alone [16]. In fact, early studies mainly focused on the role of BDNF in neurological diseases and found that BDNF had protective effects on cerebral ischemic injury. For example, Schabitz et al. found that intracerebral injection of BDNF could effectively reduce the infarct area in ischemic rats [17]. Since BDNF and its receptor TrkB are also distributed in myocardial tissue, the role of BDNF in myocardial tissue has been gradually emphasized by researchers in recent years, and there is evidence that it has an obvious myocardial protective effect. Hiltunen et al. found that after myocardial ischemia–reperfusion for 2 and 5 h in rats, the expression of BDNF in the left ventricular myocardium increased by twofold, and the mRNA expression of BDNF could be detected in the ischemic marginal area [18]. Ejiri et al. found that BDNF significantly improved coronary heart disease, and the study found that the content of BDNF in plasma was significantly increased in patients with unstable angina pectoris [19]. Likewise, studies by Okada et al. confirmed that the plasma level of BDNF in myocardial ischemic mice increased significantly, which puts forward the central nervous system-mediated signal transduction mechanism to protect ischemic myocardium: when there is cardiac ischemic damage, myocardial cells through efferent nerve feedback to the central nervous system increase the expression of BDNF in the nerve cells, so as to increase the level of BDNF in peripheral blood, activating the angiogenesis-related molecular mechanism of inhibiting myocardial reconstruction and repair of ischemic myocardium [20]. Recently, a new study also uncovered serum BDNF was differentially expressed in plaque tissues in patients with coronary heart disease compared with normal intimae in healthy subjects using microarray profiling analysis and qRT-PCR validation [21]. Recent studies have revealed that BDNF regulates cardiomyocyte contraction and directly affects cardiac function of mice [22,23]. Consistently, our previous studies found that exogenous BDNF attenuated myocardial ischemia by inhibiting apoptosis of rat cardiomyocytes [24]. However, other studies reported that BDNF may aggravate the inflammatory injury in the hearts of aging rats [25–27]. However, why BDNF plays different roles between young and old remains not fully understood. So, more work is needed to further explore the role of BDNF/TrkB in cardiac inflammation and senescence. Based on these findings, the potential role of BDNF

in ischemic myocardium is attracting more and more attention. However, the molecular mechanism of BDNF in protecting ischemic myocardium should be clarified by more solid evidence.

#### 4. Role of BDNF/TrkB in Heart Failure (HF)

A study found that BDNF enhanced normal cardiomyocyte  $\text{Ca}^{2+}$  cycling, contractility, and relaxation via regulating  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II (CaMKII) signals. However, TrkB.T1 was increased in the failing rodent myocytes, which is insensitive to BDNF due to lack of tyrosine kinase activity [22]. Moreover, the majority of recent studies focused on the association of BDNF level in peripheral blood with progress and prognosis of HF (summarized below). Lately, studies found that BDNF was relevant to exercise in heart diseases. For example, Zhang et al. reported that exercise training ameliorated HF-induced muscle atrophy by activating BDNF and adenosine monophosphate-activated protein kinase-proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (AMPK-PGC1 $\alpha$ ) signaling pathway [28]. Exercise training after MI increased mature BDNF protein in both skeletal muscle and the noninfarct area of the left ventricles, and improved muscle dysfunction and cardiac function post-MI [29]. On the other hand, BDNF treatment also improved exercise capacity in HF mice [30]. A very recent study proved that the protective effects of BDNF on the exercise capacity of mice with HF were due to the enhancement of fatty acid oxidation via the activation of the AMPK $\alpha$ -PGC1 $\alpha$  pathway in skeletal muscle [31]. Serum BDNF levels were associated with exercise capacity and skeletal muscle function, but not with muscle mass in patients with HF. BDNF production was controlled by muscle function and activity and consequently regulated exercise capacity [32]. Exercise training post-MI increased mature BDNF in the paraventricular nucleus (PVN), but not in the rostral ventrolateral medulla (RVLM). Exercise decreased Akt activity in the PVN and p-CaMKII $\beta$  expression in the RVLM, but BDNF-TrkB signaling only mediated the effect of exercise on p-CaMKII $\beta$  in the RVLM, but not of Akt in the PVN [33].

#### 5. Role of BDNF/TrkB in Cardiotoxicity

We previously found that BDNF/TrkB signaling was impaired in DOX-induced cardiotoxicity. Cardiac BDNF protein expression was lower in DOX-treated mice than control mice. Intravenous injection of recombinant human BDNF inhibited cardiac dysfunction and cardiomyocyte apoptosis by activating Akt signals [34]. Similar effects were found in pancreatic  $\beta$  cells. It was observed that DOX significantly inhibited BDNF production with a dose-dependent manner, while BDNF prevented apoptosis and restored the antioxidant levels in rat insulinoma cells [35]. Furthermore, our study further uncovered that BDNF mimetic, 7,8-DHF, activated the TrkB receptor and attenuated DOX-induced cardiotoxicity and mitochondrial dysfunction in a mouse model [14]. Consistently, Liao et al. reproduced that neurotrophic signaling including both BDNF/TrkB and NGF/TrkA was affected by DOX [36]. Besides, there is now consensus that a number of chemotherapy drugs such as arsenic trioxide cause cardiotoxicity. Arsenic trioxide has been confirmed to induce a long QT interval and cardiomyocyte apoptosis [37,38]. However, the effects of the BDNF/TrkB pathway in arsenic trioxide-induced cardiotoxicity were unknown. So, it is worth studying the potential role of BDNF/TrkB in this drug-induced cardiotoxicity and further investigating the therapeutic implications.

#### 6. Role of BDNF/TrkB in Diabetes

Studies have clarified that circulating BDNF level is decreased in type 2 diabetic patients. Replenishing BDNF or enhancing its downstream signaling pathway may be beneficial for diabetes [39]. Cardiac levels of BDNF and TrkB receptor were reduced in type 2 diabetic rats. *L. plantarum* and insulin supplementation inhibited cardiac apoptosis and fibrosis by modulating BDNF and enhancing TrkB expression [40]. In addition, caveolin-3 overexpression was reported to protect diabetic rat cardiomyocytes against acute MI/reperfusion injury by enhancing BDNF/TrkB signaling pathways [41]. It was

documented that NTs play important roles in the regulation of energy balance and body weight [42,43]. In particular, BDNF treatment enhanced energy expenditure in db/dbmice by acting directly on the hypothalamus [44]. BDNF ameliorated glucose metabolism by enhancement of glucose utilization in muscle and brown adipose tissue of diabetic mice, via modulating the central and peripheral nervous systems [45].

### 7. Role of BDNF/TrkB in Cardiac Arrhythmias

Studies have demonstrated that BDNF/TrkB signaling is required for normal cardiac contraction and relaxation. Fulgenzi et al. reported that cardiac BDNF maintained heart contraction force and long-term homeostasis through TrkB.T1. Deletion of TrkB.T1 in the cardiomyocytes caused dysregulated calcium signaling and cardiomyopathy [23]. In contrast, few studies reported a relationship between BDNF and cardiac arrhythmias. In a prospective study, Rahman et al. explored whether BDNF was associated with incidence of atrial fibrillation (AF). They found that serum BDNF level was not statistically related with AF occurrence [46]. However, the roles of BDNF in ventricular arrhythmias are still largely unknown.

### 8. Role of BDNF/TrkB in Vascular and Metabolic Diseases

It was reported that intravenous treatment of 7,8-DHF produced an antihypertensive effect in spontaneously hypertensive rats due to its vasodilation role [47]. Another study by Helan et al. reported that human pulmonary artery endothelial cells expressed and secreted BDNF in response to hypoxia, which induced expression of hypoxia inducible factor 1 alpha (HIF-1 $\alpha$ ) [48]. Wood et al. demonstrated that BDNF mimetic 7,8-DHF treatment increased cellular respiration of skeletal muscle cells by facilitating mitochondrial biogenesis, thereby reduced body weight gain in obese mice [49]. Consistently, Chan et al. found that activation of the muscular TrkB receptor regulated energy metabolism in diet-induced obese mice [50]. Moreover, other studies also found that activation of the TrkB receptor alleviated complication of diabetes. For instance, Allen et al. reported that the TrkB signaling pathway is indispensable in the protective effects of exercise against the diabetic retina complication [51]. Agrimi et al. reported cardiac dysfunction characterized by apoptosis, fibrosis, and oxidative stress in obese mice exposed to psychosocial stress. Simultaneously, lower BDNF/TrkB level was observed in mouse ventricles [52]. However, the authors did not provide direct causal evidence supporting BDNF/TrkB contributed to cardiac remodeling. Lately, another study found that 7,8-DHF protected neurons from high glucose-induced oxidative stress [53]. However, the potential role of 7,8-DHF in high glucose-induced cardiomyocyte injury and diabetic cardiomyopathy is undetermined. Yu et al. reported that activation of the TrkB receptor by 7,8-DHF repressed apoptosis of human retinal pigment epithelial cells [54]. Recent studies also found that the truncated TrkB-T1 is the unique isoform expressed in aged cardiac microvascular endothelial cells (CMECs). Meanwhile, BDNF activated TrkB.T1 and thereby induced migration of aged CMECs by recruiting the Willin–Hippo pathway [55].

### 9. Role of BDNF/TrkB in Noncardiac Cells

It should be noted that BDNF and TrkB are expressed in various cell types such as cardiomyocytes, endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and fibroblasts in the cardiovascular system, thus the potential role of BDNF/TrkB in noncardiac cells should also be seriously considered. In particular, it was noticed that BDNF/TrkB participated in the activities of fibroblasts. For example, Cherubini and colleagues found that TrkB was expressed in lung fibroblasts, and activation of BDNF/TrkB axis promoted the epithelial–mesenchymal transition in idiopathic pulmonary fibrosis [56]. Similarly, BDNF/TrkB was associated with pathologic changes of other types of fibroblasts such as airway [57] and human dermal fibroblast cells [58]. Accordingly, whether BDNF/TrkB is involved in cardiac interstitial fibrosis is interesting to further investigate. In addition, BDNF is also expressed in pulmonary artery endothelial cells (PAECs) and gastric smooth

muscle cells. Helan et al. reported that PAECs expressed and secreted BDNF in response to hypoxia via an HIF-1-regulated pathway [48]. Activation of the BDNF/TrkB axis accelerated epithelial–mesenchymal transition in idiopathic pulmonary fibrosis [56]. In addition, recent studies found that 7,8-DHF enhanced cholinergic contraction of rat gastric smooth muscle via upregulating muscarinic M<sub>3</sub> receptor expression [59]. The detailed role of BDNF/TrkB in these cells will be uncovered in the future.

### 10. Role of Circulating BDNF in CVD

Several clinical studies paid attention to the association of circulating BDNF in either plasma or serum with CVD, including coronary artery disease, angina, HF, and diabetes. In 2005, Ejiri et al. firstly reported that coronary sinus and aorta BDNF level was significantly higher in the unstable angina group than the stable effort angina and noncoronary artery disease groups [19]. It was reported that serum BDNF was significantly lower in individuals with CAD than controls [60]. Higher serum BDNF is associated with a decreased risk of CVD and mortality [61]. Moreover, serum BDNF was found correlated with HF. For example, Takashio et al. found that plasma BDNF levels were decreased in patients with HF and associated with HF severity [62]. Studies demonstrated that decreased serum BDNF levels were significantly associated with adverse outcomes in HF patients [63,64]. Recent studies also found that the serum BDNF level at discharge may be a useful biomarker of the prognosis in patients with HF [65]. They proposed that serum BDNF can be a useful prognostic biomarker to predict adverse clinical outcomes in patients with HF. Besides, decreased serum BDNF levels are correlated with exercise intolerance in patients with HF [66]. Further studies found that BDNF levels were associated with exercise capacity and skeletal muscle function, but not with muscle mass [32]. In contrast, no significant association of serum BDNF levels and the risk of incident AF was found [46]. In addition, plasma BDNF was decreased in aged rats compared to young rats, which could be increased by regular exercise [67]. Interestingly, a recent study reported that serum BDNF, as well as irisin and adropin, is correlated with the occurrence of depression in coronary heart disease patients [68]. A recent study also found that circulatory BDNF was decreased in patients with type 2 diabetes and depression [69]. Taken together, circulating BDNF may be a candidate biomarker for some cardiac diseases (summarized in Table 1). More studies are needed to compare the sensitivity, specificity, accuracy, and correlation with currently used markers to better evaluate its feasibility in clinical diagnosis and treatment.

**Table 1.** Circulating BDNF as a potential biomarker in cardiovascular diseases.

Diseases	Source	Description	References
Unstable angina	Plasma	Higher in unstable angina compared with the stable effort angina and noncoronary artery disease groups	Ejiri J et al. 2005 [19]
Coronary artery disease	Serum	BDNF was significantly lower in patients with coronary artery disease than control	Monisha K et al. 2020 [60]
Myocardial ischemia	Plasma	BDNF was markedly increased after myocardial ischemia	Okada S et al. 2012 [20]
Cardiovascular diseases	Serum	Higher BDNF level is associated with a decreased risk of cardiovascular diseases and mortality	Kaess B et al. 2015 [61]
Depression in coronary heart disease	Plasma	Plasma BDNF was associated with occurrence of depression in coronary heart disease	Han W et al. 2019 [68]
Heart failure	Plasma	Low BDNF level is associated with the severity of heart failure	Takashio S et al. 2015 [62]
Heart failure	Serum	BDNF predicts adverse clinical outcomes in patients with heart failure	Fukushima A et al. 2015 [63]
Heart failure	Serum	Low BDNF level is independently associated with an increased risk of cardiac events	Kadowaki S et al. 2015 [64]
Heart failure	Serum	BDNF level at discharge may be a useful biomarker of the prognosis in patients with heart failure	Shibata A et al. 2018 [65]
Heart failure	Serum	Decreased BDNF is correlated with exercise intolerance in patients with heart failure	Fukushima A et al. 2013 [66]
Heart failure	Serum	BDNF levels were associated with exercise capacity and skeletal muscle function, but not with muscle mass	Nakano I et al. 2020 [32]
Atrial fibrillation	Serum	No statistically significant association was found between serum BDNF levels and risk of incident atrial fibrillation	Rahman F et al. 2016 [46]
Aging	Plasma	Regular exercise improves aging-induced decrease in the cardiac, hepatic, and plasma BDNF	Belviranli M et al. 2018 [67]
T2DM with depression	Serum	Decreased levels of circulatory BDNF in patients with type 2 diabetes and depression	Prabu P et al. 2020 [69]

## 11. Concluding Remarks

At present, studies on BDNF structure, molecular morphology, action, and mechanism have achieved stage achievements. The emerging role of BDNF/TrkB in CVD was paid more and more attention. Several clinical applications of BDNF have been developed, which can treat common neuropsychiatric diseases, such as Parkinson's disease, Alzheimer's disease, depression, schizophrenia, and so forth [70–73], and can also be used as a reference indicator for early diagnosis and prognosis of certain tumors [74]. However, BDNF itself has the following limitations: (1) short half-life, low tissue content, rapid metabolism after entering the body, and difficulty in reaching sufficient drug concentration and maintenance time; (2) production technology requirements and the high cost and low yield limit its use as a clinical conventional drug. However, gene engineering technology can transfer the gene fragment expressing BDNF to the expression cells through vectors, so as to achieve the effect of local sustained release of BDNF and avoid a lot of inconvenience such as drug administration. Recent studies have also linked a segment of highly charged, alkaline amino acid transactivator of transcription (TAT) encoded by human immunodeficiency virus type 1 (HIV-1) to the BDNF to improve its transmission through the blood–brain barrier, and the results show that TAT-BDNF can effectively target the brain and improve cognitive function in animals with Alzheimer's disease [75]. In addition, several BDNF mimics/TrkB agonists (e.g., 7,8-DHF) have been discovered to simulate BDNF action. Meanwhile, numerous derivatives of TrkB agonists have been developed to examine their efficacy [76]. With the deepening of research and the continuous development of new technologies, the technical bottleneck in the BDNF translation is expected to be overcome [77,78].

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## Abbreviations

BDNF	brain-derived neurotrophic factor
CVD	cardiovascular diseases
DOX	doxorubicin
7,8-DHF	7,8-dihydroxyflavone
ERK	extracellular regulated protein kinase
HF	heart failure
MAPK	mitogen-activated protein kinase
MI	myocardial infarction
NF- $\kappa$ B	nuclear factor $\kappa$ B
NGF	neuronal growth factor
NT	neurotrophin
TrkB	tropomyosin-related kinase receptor B

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