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Review Article

The Cardioprotective Effect of Leonurine in Hearts

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Abstract

Myocardial fibrosis is a common cardiovascular disease with a complex mechanism. Myofibroblasts and extracellular matrix play a key role in myocardial fibrosis. Leonurine, extracted from Herba Leonuri, plays a protective role in the pathogenesis and development of cardiovascular dieseses especially myocardial fibrosis. Undoubtedly, Leourine was considered as the potential therapeutic medicine of myocardial fibrosis in the future. However, the pathogenesis of leonurine on myocardial fibrosis remains unclear. The purpose of this review attempts to discuss the molecular mechanisms involved in the cardioprotective effects of Leonurine.

Keywords: Leonurine; Myocardial fibrosis; Cardioprotective effect; The molecular mechanism

1. Introduction

Leonurine (4-guanidino-n-butyl-syringate) is a bioactive alkaloid present in the traditional Chinese medicine Herba Leonuri (1). In recent years, Leonurine has been confirmed to treat cardiovascular diseases and has cardioprotective effects (2, 3), such as anti-oxidation (4), vasodilation (5), treatment of acute and chronic myocardial infarction (6) and ischemic stroke (7), anti-atherosclerosis (8). Recently, growing evidence has shown that Leonurine played a protective role in the pathogenesis and development of heart diseases such as myocardial fibrosis (9). A study reported that leonurine could prevent cardiac fibrosis

and the activation of cardiac fibroblasts partly through modulation of a NADOH Oxidase-Reactive Oxygen Species (Nox4-ROS) pathway (10). However, the mechanism of leonurine on myocardial fibrosis remains unclear. In this review, we summarize the physiological functions of Leonurine and mainly explore its mechanism in myocardial fibrosis. Furthermore, we also discuss the molecular mechanisms involved in the cardioprotective effects of Leonurine and how these might be used to overcome myocardial fibrosis.

2. Metabolisms of Leonurine

Drug metabolism refers to the process of changing the chemical structure of a drug under the action of a variety of drug-metabolizing enzymes in the body such as liver drug enzymes. Clarifying the metabolism of leonurine in vivo was beneficial to understand the pharmacological mechanism of leonurine. Qing Z et al. found that an approach of HPLC/MS/MS could apply to the identification of metabolites of leonurine in rats (11). They also reported that HPLC/MS/MS could simultaneous quantify leonurine and stachydrine, the two main bioactive components in Leonurus japonicus houtt (12). They firstly identify three metabolites including two phases Ⅱ metabolites (M1 and M2) and one phase Ⅰ metabolite (M3) in animal samples. M1 (MRM 488-312) was the main metabolites and M2 and M3 were the minor metabolites in vivo. M1 (MRM 488-312) was glucuronide metabolite of leonurine, M2 (MRM 392-312) was tentatively assigned as an O-sulfate conjugate, leonurine-10-O-sulfate. M3 (MRM 298-167) was identified as an O-demethylated leonurine and its possible structure was 4-guanidinobutyl 3,4-dihydroxy-5-methoxy benzoate (13, 14). Moreover, M1 had greater bioactivity than the prototype drug and the glucuronide metabolite could prolong the pharmacological effect of the parent drug trough an enzymatic or nonenzymatic hydrolysis (15, 16).

3. Cardioprotective Effect of Leonurine

3.1 Roles of Leonurine in Myocardial Fibrosis

Myocardial Fibrosis (MF) refers to the appearance of normal myocardial tissue with cell proliferation and excessive deposition of extracellular matrix (ECM) (17, 18). MF is a type of chronic ischemic heart disease. Myocardial cell proliferation is dominated by a variety of non-cardiac cells, and more than 90% are cardiac fibroblasts (CFBs). CFBs are also important cells regulating the synthesis and degradation of ECM. CFBs proliferate and differentiate into specific conditions, and the formation of myofibroblasts is a key link to MF (19). At the same time, myofibroblasts secrete collagen, and collagen Ⅰ and Ⅲ are important for maintaining the structure of myocardial tissue and heart function (20), and the main mechanism of MF is shown in Figure1.

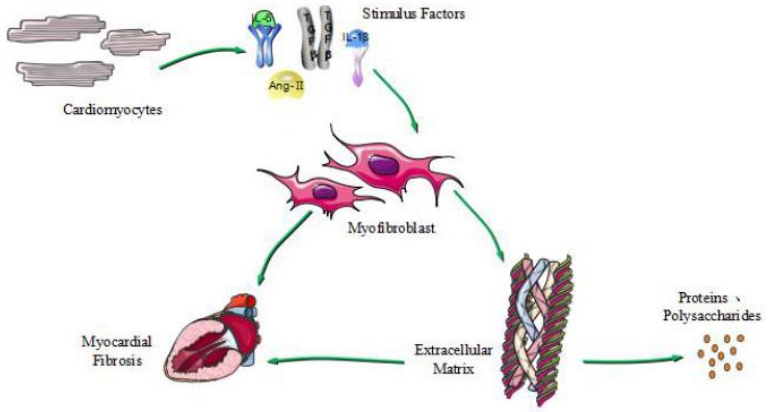

Figure 1: The main mechanism of MF. Cardiomyocytes differentiate into cardiac fibroblasts, and cardiac fibroblasts are proliferated, differentiated, or stimulated into myofibroblasts. The mainly stimulating factors are transforming growth factor-β (TGF-β), angiotensin-Ⅱ (Ang-Ⅱ), interleukin-1β (IL-1β) and interleukin-6 (IL-6). Myofibroblasts proliferate or secrete extracellular matrix, causing abnormal precipitation of extracellular matrix, and forming myocardial fibrosis.

In myocardial fibrosis models, they have been demonstrated clearly that methylation had effects on pathways of different stimulating factors (21). Pan et al. found that TGF-β inhibited DNA methyltransferase (DNMT) activity, thereby increasing collagen Ⅰ expression (22). Watson et al. also found that hypoxia-inducible factor-1α (HIF-1α) promotes the expression of DNMT1 and DNMT3, reducing the expression of collagen Ⅰ and α-smooth muscle actin (α-SMA), and also inhibiting the TGF-β profibrotic effect (23). Recently, many studies have shown that DMNTs could inhibit the activation and proliferation of CFBs. The specific mechanism is closely related to the level of DNA methylation, leading to a reduction in the generation of fibrosis. However, the mechanism of DNMTs such as DNMT1, DNMT3A, and DNMT3B on myocardial fibrosis is not clear.

3.2 Molecular Mechanisms of Leonurine in Myocardial Fibrosis

The effects of Leonurine on myocardial fibrosis are mediated by a variety of targeting proteins and signaling molecules. The main mechanisms of Leonurine against myocardial fibrosis are anti-oxidation, anti-apoptosis, anti-inflammation, stimulating stress responses, combining with target genes, regulating to stimulate factors and ion channels (Figure 2).

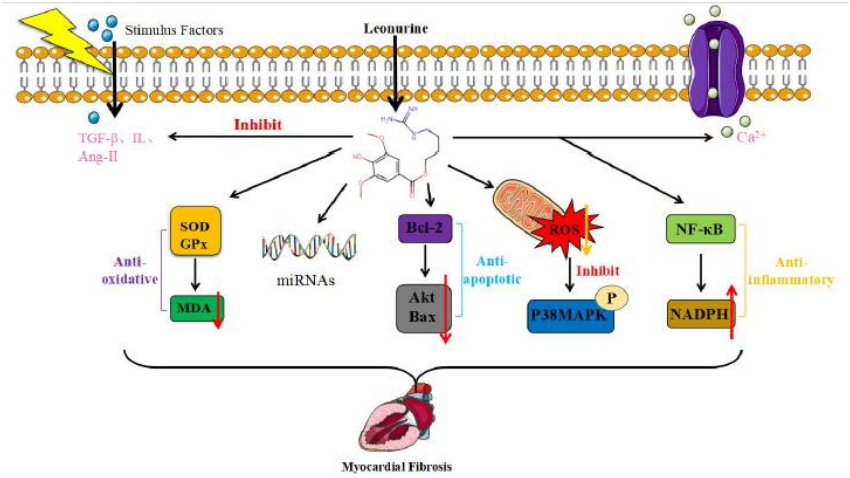

Figure 2: Different signaling proteins to show anti-myocardial fibrosis by Leonurine. Leonurine can against myocardial fibrosis via different mechanisms: Leonurine mainly against myocardial fibrosis by anti-oxidation, target genes, anti-apoptosis, stress responses, anti-inflammation, stimulate factors, and ion channels. Leonurine against oxidation by stimulating superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity to reduce malondialdehyde (MDA) expression. Leonurine plays roles by regulating the expression of microRNAs (miRNA). Leonurine against apoptosis by stimulating B-cell lymphoma-2 (Bcl-2) to reduce the expression of protein kinase (AKT) and BCL2-associated x (Bax). Leonurine activates stress responses by reducing reactive oxygen species (ROS) levels and inhibiting p38MAPK expression. Leonurine against inflammation by stimulating nuclear factor-kappa-b (NF-κB) to increase nicotinamide adenine dinucleotide phosphate (NADPH) expression. Leonurine opens ion channels such as Ca2+ channel and inhibits to stimulate factors such as TGF-β, Ang-Ⅱ and IL to produce anti-myocardial fibrosis effects.

3.2.1 Anti-oxidative Action

Oxidative stress induces cell damage through the over-production of ROS, and ROS can aggravate myocardial fibrosis. Related studies showed that Leonurine reduced ROS levels through an anti-oxidative effect to against myocardial fibrosis. Liu et al. found that Leonurine increased to SOD activity by decreasing levels of lactate dehydrogenase (LDH), creatine kinase (CK), and lipid peroxidation (3). At the same time, Zhang et al. also found that Leonurine stimulated SOD and GPx activity to reduce MDA expression, and against oxidative effect (24).

3.2.2 Anti-apoptotic Action

Anti-apoptosis is another major means of anti-myocardial fibrosis. Studies have shown that Leonurine regulated the anti-apoptotic effect against myocardial fibrosis by activating the phosphatidylinositol 3 kinase/protein kinase (PI3K/Akt) signaling pathway. Liu et al. found that Leonurine reduced Bax expression and increasing Bcl-2 expression by activating the PI3K/Akt signaling pathway, and against myocardial fibrosis (25).

3.2.3 Anti-inflammatory Action

Inflammatory is one of the most common reactions to most cardiovascular diseases. Studies have found that the most inflammatory factors had a regulatory effect

on myocardial fibrosis. Liu et al. found that Leonurine stimulated NF-κB signaling activity to reduce TNF-α, IL-6, NADPH expression and play an anti-inflammatory effect (26, 27).

3.2.4 miRNA Expression

MicroRNAs (miRNA) are the class of non-coding single-stranded RNA molecules about twenty-two nucleotides in length encoded by endogenous genes, and most microRNAs play a role in myocardial fibrosis such as microRNA-24 and micro-221/222. Yuan et al. found that microRNA-378 was cardiac-enriched and highly inhibited during cardiac remodeling (25). Wang et al. found that miR-24 was down-regulated in fibrosis after MI heart (30).

3.2.5 Ion Channels Regulation

The main ion channel for regulating myocardial fibrosis is Ca2+ channels. It had been reported that Leonurine reduced the cytosolic Ca2+ overloaded induced by hypoxia (31). Liu et al. also found that leonurine inhibited Bcl-2/Bax ration and reduced cytosolic Ca2+ overloaded against myocardial fibrosis (25).

3.3 Roles of Leonurine in Other Cardiovascular Diseases

Recently, Leonurine has long known to present as an alkaloid in Herba Leonuri and exerts several pharmacological effects shown in Table 1, such as anti-apoptosis, anti-oxidation, anti-inflammation (32, 33, 34, 35). Furthermore, Leonurine can exert its cardioprotective effects on cardiovascular diseases, such as myocardial infarction, heart failure, cardiac hypertrophy, acute myocardial ischemia, and myocardial fibrosis (Figure 3).

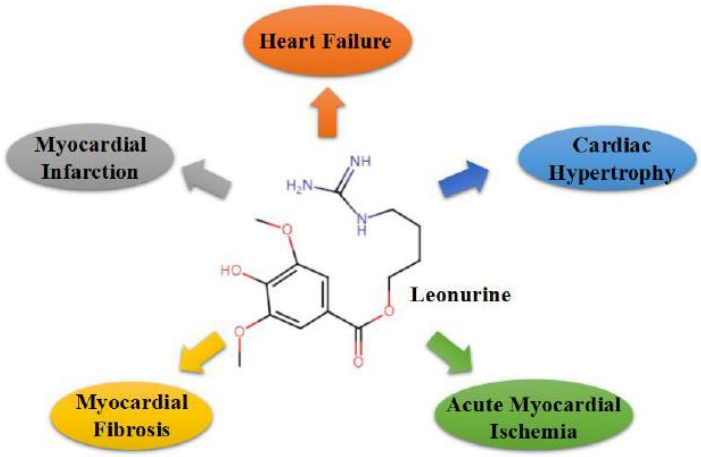

Figure 3: Cardioprotective effects of Leonurine in cardiovascular diseases. Leonurine treats heart failure, myocardial infarction, cardiac hypertrophy, acute myocardial ischemia, and myocardial fibrosis.

Table 1: The effects of Leonurine in cardiovascular diseases

Effects	Study subjects	Major findings	References
Anti-oxidation	Improving ischemia-induced myocardial injury through antioxidative activity	↓ level of LDH and CK activities	(3)
	Protecting middle cerebral artery occluded-rats from brain injury through the antioxidative mechanism and mitochondrial protection	↑ SOD activities ↓ MDA level	(24)
	Protecting ischemia-induced brain injury via modulating SOD, MDA levels	↑ SOD activities ↓ MDA level	(31)
	Protecting H9c2 rat ventricular cells from hypoxia-induced apoptosis	↑ Bcl-2 gene ↓ Bax gene ↓ the cytosolic Ca2+ overload induced by hypoxia	(25) (3)
Anti-apoptosis	Improving cardiac recovery in the rat during chronic infarction.	Akt signaling pathway ↑ Survivin and vascular endothelial growth factor expression	(30) (4)
	A mechanism through inhibition of mitochondria dysfunction in H9c2 cells	↓ ROS in H2O2 stimulated cells Apoptotic body formation and release of cytochrome c	(34)
Anti-inflammation	Exerting anti-inflammatory effect by regulating inflammatory signaling pathways	↓ TNF-α、IL-6、iNOS、COX-2、TLR4 and NF-κB ↑ IL-10	(45) (46)
	Suppressing advanced glycation endproducts-induced NADPH oxidase	↑ NF-κB ↓ NADPH	(47)
Antiplatelet aggregation	The structure and biological effect of leonurine	Guanidyl group was changed to amino, add double bonds could enhance the effect	(48) (48)
Improve coronary	Impact on blood parameters	↓ ROS	(49) (50)

flow			
Regulate the mitochondrial function	Involvement of mitochondrial function and HIF-1α dependent VEGF activation Improve the ultrastructure of mitochondrion	↓ VEGF ↓ MDA and Bax ↑ SOD、CAT and Bcl-2	(51) (52)

LDH=Lactate Dehydrogenase; CK=Creatine Kinase; SOD=Superoxide Dismutase; MDA=Malondialdehyde; Bcl-2=B cell lymphoma-2; Bax=BCL2-associated x; Ca2+=Calcium ion; Akt=Protein Kinase; ROS=Reactive Oxygen Species; TNF-α=Tumor Necrosis Factor-α; IL-6=Interleukin-6; iNOS=Inducible Nitric Oxide Synthase; COX-2=Cyclooxygenase-2; TLR4=Toll Like Receptor 4; NF-κB=Nuclear Factor Kappa-B; NADPH=Nicotinamide Adenine Dinucleotide Phosphate; HIF-1α=Hypoxia-Inducible Factor-1α; VEGF=Vascular Endothelial Growth Factor; CAT=Catalase.

3.3.1 Myocardial Infarction

Myocardial infarction (MI), one of the ischemic heart diseases, remains the leading cause of death in the world (36). It occurs when a coronary artery is occluded, leading to insufficient oxygen supply to the myocardium and the most typical feature of MI is hypoxia (37, 38, 39). Recently, there are increasing evidence shows that Leonurine is beneficial to cure MI. Leourine increased phosphorylation of AKT and expression of hypoxia-inducible factor-1 (HIF-1), surviving vascular endothelial growth factor (VEGF) in rat models (9). Leonurine significantly alleviated collagen deposition and MI size to inhibite cell apoptotic effect and improved myocardial function (40).

3.3.2 Heart Failure

Heart Failure (HF) is caused by impaired contraction and diastolic function of the heart, resulting in inadequate venous return to blood to the heart, leading to venous system stasis and insufficient blood perfusion in the arterial system, and leading to cardiac circulatory disorders. However, HF isn't an independent diseases, but the end stage of the development of heart disease. Recently, evidence show that Leonurine plays a role in relieving HF. Leonurine provided protective effects on ischemic myocardium by acting as free radicals scavengers and inhibiting the formation of ROS (41).

3.3.3 Cardiac Hypertrophy

Cardiac hypertrophy is a powerful form of compensation, but it isn't infinite. If there isn't remission, the heart function may not be able to maintain normal for a long time and eventually turning to heart failure (42). Recently, only some studies show that Leonurine has an inhibitory effect on cardiac hypertrophy. It had been reported that Leonurine may reverse cardiac muscle cell hypertrophy by regulating p38 mitogen-activated protein kinase (p38MAPK) and downstream the gene expression (43).

3.3.4 Acute Myocardial Ischemia

Myocardial ischemia refers to reduced blood perfusion of the heart, resulting in reduced oxygen supply to the heart, abnormal energy metabolism in the heart

muscle, and can not support normal heart work. Acute myocardial ischemia is a condition in which myocardial ischemia occurs in a short time. It had been reported that Leonurine-cysteine reduced MDA and ROS levels to protect certain cellular organs and related expression of apoptosis-related genes and proteins, such as Bcl-2 and Bax (44).

Conclusion and Perspectives

The article summarized the function of Leonurine in myocardial fibrosis and other cardiovascular diseases. And, the possible molecular mechanisms in myocardial fibrosis were discussed. The effects of Leonurine in anti-myocardial fibrosis are mainly through anti-oxidant, anti-apoptosis, and anti-inflammation. Furthermore, microRNAs or DNMTs interacted with proteins are also related to myocardial fibrosis in some studies. Thus, the effect of Leourine in cardiovascular diseases especially myocardial fibrosis is promised and may be helpful to reduce the risk of cardiovascular diseases in the future.

Author Contributions

Original draft preparation - Z.Y. Li with assistant from LZ Chen and YX Liu Review and PI - Y.Z. Zhu

Conflict of Interest

The authors declare no conflict of interest.

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