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# An Overview of Cardiotonic Medicinal Plants from the Perspective of Iranian Traditional Medicine

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## Abstract

**Context:** Cardiovascular disorders are a leading cause of mortality and morbidity worldwide, especially in people with diabetes. Due to synthetic drugs' adverse effects, new medicines are needed.

**Evidence Acquisition:** Iranian traditional medicine (ITM) is one of the oldest medical systems. In this article, we first introduce a list of cardiotonic medicinal plants based on ITM. Then we review the cardio-related effects of these plants based on electronic databases.

**Results:** Among the introduced medicinal plants from ITM, *Phyllanthus emblica* L., *Rosa canina* L., *Ocimum basilicum* L., and *Melissa officinalis* L. have cardiotonic effects. Also, *P. emblica*, *O. basilicum*, *M. officinalis*, *Citrus medica* L., *Malus domestica* Borkh., *Elettaria cardamomum* (L.) Maton, and *R. canina* have cardioprotective effects and possess several biological activities that reduce cardiovascular disease risk factors.

**Conclusions:** The cardiotonic medicinal plants based on ITM have excellent value; several pharmacological studies have proved some of their cardioprotective and cardiotonic effects. The other plants' potential for improving the heart's contractile power as a cardiotonic drug must be evaluated in further pharmacological and clinical studies.

*Keywords:* Medicinal Plants, Cardiovascular Disease, Cardiotonic Agents, Iranian Traditional Medicine, Persian Medicine

## 1. Context

Cardiovascular disease (CVD) is a prominent cause of morbidity and mortality worldwide, especially in people with diabetes (1). Diabetes increases reactive oxygen species (ROS) production, insulin resistance, hyperglycemia, cardiac inflammation, and endothelial dysfunction, which can lead to cardiac dysfunction (2-5). These events produce structural and functional cardiac changes that reduce blood flow (3-5). Hyperlipidemia, hypertension, and obesity raise the risk of complications associated with this disease (6). Cardiotonic enhances heart contractility and cardiac function, increasing blood flow to all organs and tissues (7).

Despite advances in CVD treatments, new drugs are needed due to synthetic drug adverse effects. Research on medicinal plants that can be added to diets to minimize CVD risk is also crucial (8). Cardiovascular disease risk factors can be decreased by medicinal plants' biological effects, such as their antioxidant, anti-inflammatory, sugar-lowering, and lipid-lowering properties (9). Additionally, various plant cardiotonic substances, including digoxin and ouabain, have been identified (10). Overall, the study of medicinal plants' effectiveness in CVD is recommended to manage the disease (9).

Iranian traditional medicine (ITM) is one of the oldest medical systems using medicinal plants to treat various diseases, including heart disease (11). Tonic medicine was one of the ITM's recommendations for improving an organ's physiological activities and increasing its resistance to pathological conditions. In this study, we introduce medicinal plants described as cardiotonic from the perspective of ITM.

## 2. Evidence Acquisition

To identify medicinal plants having tonifying effect on the heart, this study used six books, including Al-Qanoon fi al-Tibb (The Canon of Medicine) by Avicenna (11), Al-

Havi (The Liber Continens) by Rhazes (12), the Makhzan-ol-Adviah, by Aghili Khorasani (13), Al-abniye an- Hagha'egh-al- Adviah written by Heravi (14), Tohfat-al- Mo'menin written by Hakim Mo'men (15) and Al-Shamel fe-Sena'at-e- Tabiee by Gharashi (16). Keywords such as "moghavi-e-ghalb" and "moghavi-e-del," which mean cardiotonic, were chosen. The matching and translation of medicinal plants' traditional names into scientific terms were done using the following three books: Encyclopedia of Traditional Medicine (Medicinal Plants) (17), Comparative description of ancient medicinal plants (18), and Scientific names of medicinal plants used in traditional medicine (19). The medicinal plants' scientific names were searched in electronic databases, including PubMed, Scopus, and Science Direct. Data were collected from inception until November 2022. Only English language articles that full text was available were included. The search terms were the scientific name and common name of each plant combined with "cardiac," "heart," "inotrope," "cardiac dysfunction," "systolic dysfunction," "diastolic dysfunction," "heart failure," and "cardiomyopathy". The study in electronic databases for each plant was performed as follows: "scientific name" [Title/Abstract] or "common name" [Title/ Abstract] and "cardiac" [Title/Abstract] or "heart" [Title/Abstract]) or "inotrope" [Title/Abstract]) or "cardiomyopathy" [Title/Abstract]) or "cardiac dysfunction" [Title/ Abstract] or "systolic dysfunction" [Title/Abstract] or "diastolic dysfunction" [Title/Abstract]) or "heart failure" [Title/Abstract]). We have considered in vitro, in vivo, and clinical studies.

## 3. Results

The selected medicinal plants were ranked based on the frequency of expression of their cardiotonic effect in the nominated books. Rankings 3 and above are listed in Table 1.

The cardioprotective effects of selected medicinal plants described as cardiotonic from Persian medicine/ITM retrieved from electronic databases are summarized in Table 2.

## 4. Discussion

Cardiovascular diseases are a leading cause of death globally (57). Diabetes, especially type 2, increases CVD risk (1). Insulin resistance leads to hyperglycemia and dyslipidemia. Hyperglycemia causes inflammation, oxidative stress, endothelial dysfunction, and hypertension (58, 59). Besides, insulin resistance decreases cardiomyocytes' metabolic flexibility, resulting in lipid accumulation and lipotoxicity in the heart (58). On the other hand, endothelial dysfunction and dyslipidemia contributing to atherosclerosis. Normalizing oxidative stress, hyperlipidemia, and hyperglycemia prevent cardiac dysfunction caused by diabetes (60).

In this study, we reviewed cardiotonic medicinal plants from ITM and their cardioprotective benefits. According to the results, 16 medicinal plants were the most commonly mentioned cardiotonics in prominent ITM books (Table 1). Amla, basil, lemon balm, and dog rose are cardiotonic among these plants. They enhanced heart contractility. Several pharmacological studies have demonstrated lemon balm and amla's cardioprotective effects, which are related to flavonoids and phenolic compounds, including emblicanin-A and B, ellagic acid, caffeic acid, and gallic acid (45, 61-63).

Seven plants in Table 2 exhibit cardioprotective properties. Reactive oxygen species and oxidant/antioxidant imbalance contribute to CVD. All these plants scavenge free radicals and boost antioxidant enzymes, including SOD, CAT, and GSH. Also, amla, citron, and dog rose are rich in vitamin C, an exogenous antioxidant (47, 64-66). These plants with anti-inflammatory properties improve CVD (62, 63, 67-72). Cardiac damage raises LVEDP. Lemon balm and amla minimized this impact (33). Also, amla, basil, and apple decreased heart hypertrophy, which is evident in cardiac dysfunction. Hyperglycemia, hyperlipidemia, and hypertension are CVD risk factors. Based on several studies, the plants in Table 2 improve these risk factors (62, 63, 67-72).

Diet is vital for cardiovascular health (3). Diet adjustment is one of the most straightforward strategies to lower heart disease risk factors (3). Some studies link vegetable and fruit consumption with a lower risk of cardiovascular disease (73). Medicinal herbs, especially amla, apple, and citron, are widely used worldwide, proving their safety; they can be incorporated into cardiovascular patients' diets.

Iranian traditional medicine recommends aromatherapy (74). Smelling apple, citron, dog rose, myrtle, and eaglewood were advised for heart health. In line with ITM, several studies have shown the health benefits of aromatherapy (75).

Other medicinal plants listed in Table 1, Persian willow, myrtle, elecampane, common pear, and eaglewood, have flavonoids and antioxidant activity, which may protect the heart from cardiac damage (76-81).

### 4.1. Conclusions

In conclusion, several pharmacological studies have proven cardioprotective and cardiotonic benefits of ITM-based medicinal plants. *Melissa officinalis*, *P. emblica*, *R. canina*, and *O. basilicum* are cardiotonic. Further pharmacolog-

**Table 1.** Medicinal Plants Described as Cardiotonic Based on Iranian Traditional Medicine

| Traditional Name | Scientific Name | Common Name | Family | Administration | Part Used | Reference |
|---|---|---|---|---|---|---|
| **Ood** | *Aquilaria malaccensis* Lam. | Eaglewood | Thymelaeaceae | Oral/ Inhalation | Wood | (11, 13-15) |
| **Tabashir** | *Bambusa bambos* (L.) Voss (Syn: *Bambusa arundinacea* Willd.) | Giant thorny bamboo | Poaceae | Oral | Stem | (11, 15, 16) |
| **Bahman** | *Centaurea behen* L. | White Behen | Asteraceae | Oral | Root | (11, 14, 15) |
| **Otroj** | *Citrus medica* L. | Citron | Rutaceae | Oral/ Inhalation | Fruit | (13, 15, 16) |
| **Daronaj** | *Doronicum pardalianches* L./ *Doronicum columnae* Ten. | Great leopard's bane; Eastern leopard's bane | Asteraceae | Oral | Root | (11, 14, 15) |
| **Ghagheleh** | *Elettaria cardamomum* (L.) Maton | Green cardamom | Zingiberaceae | Oral | Fruit | (13, 15, 16) |
| **Rasan** | *Inula helenium* L. | Elecampane | Asteraceae | Oral | Root | (11, 13, 15) |
| **Toffah/ Sib** | *Malus domestica* Borkh. | Apple | Rosaceae | Oral/ Inhalation | Fruit | (11, 13-16) |
| **Badranjboye** | *Melissa officinalis* L. | Lemon balm | Lamiaceae | Oral | Leaf | (13-15) |
| **As/ Mord** | *Myrtus communis* L. | Myrtle | Myrtaceae | Oral/ Inhalation | Leaf, fruit | (11-13, 15, 16) |
| **Baderoj** | *Ocimum basilicum* L. | Basil | Lamiaceae | Oral | Leaf | (11, 14-16) |
| **Amlaj** | *Phyllanthus emblica* L. | Amla/ Indian gooseberry | Phyllanthaceae | Oral | Fruit | (11, 13, 15) |
| **Kamsari** | *Pyrus communis* L. | Common pear | Rosaceae | Oral | Fruit | (13, 15, 16) |
| **Nasrin** | *Rosa canina* L. | Dog rose | Rosaceae | Oral/ Inhalation | Flower | (13, 15, 16) |
| **khelaf** | *Salix aegyptiaca* Fors. | Persian willow | Salicaceae | Oral | Leaf | (13-15) |
| **Satakhis** | *Stachys germanica* L. | German hedgenettle | Lamiaceae | Oral | Leaf | (13, 15, 16) |

ical and clinical studies must investigate other plants' cardiotonic potential.

## Footnotes

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**Table 2.** Cardioprotective Effects of Selected Medicinal Plants Described as Cardiotonic from Iranian Traditional Medicine

| Scientific Name | Part | Preparation | Method | Dosage/Duration | Results | Reference |
|---|---|---|---|---|---|---|
| | | | **Cardioprotection** | | | |
| ***Elettaria cardamomum* (L.) Maton** | Fruit | Aqueous extract | Doxorubicin-induced cardiotoxicity in rats, 2.5 mg/kg, i.p., every other day for two weeks | 200 mg/kg, p.o., 3 weeks | ↓ Cardiotoxicity, oxidative stress, apoptosis, LDH, CK, cTnT, MDA, NF-$\kappa$B, caspase 3; ↑ angiogenesis, VEGF, SOD, CAT, GPx | (20) |
| ***Elettaria cardamomum* (L.) Maton** | Fruit | Aqueous extract | Isoproterenol-induced myocardial infarction in rats | 100 and 200 mg/kg, p.o., 30 days | ↑ HR, SAP, DAP, MAP; ↑ GSH, SOD, CAT, GSH-Px; ↓ MDA; Protection from myocardial injury: ↓ Myonecrosis, edema, inflammation | (21) |
| ***Citrus medica* L.** | Fruit | Ethanol extract | Isoproterenol-induced cardiomyopathy in rats | 250 and 500 mg/kg, p.o., 15 days | ↓ LDH, CK, AST, ALT, LDL, TC, TG, VLDL, MDA, HR; ↑ HDL; 500 mg/kg: No inflammation, ↓ muscle fiber damage | (22) |
| ***Malus domestica* L.** | Fruit | Vinegar | High-fat diet-induced obese rats | 3.5, 7, 14 ml/kg, p.o., 18 weeks | ↓ Body weight, visceral adipose tissue, TG, LDL, TC, CK-MB, LDH, CRP, fibrinogen, leptin, TNF-$\alpha$, cardiac hypertrophy, myocardial fibrosis | (23) |
| ***Melissa officinalis* L.** | Aerial parts | Hydro alcohol extract | The effect on human umbilical vein endothelial cells under oxidative stress induced by $H_2O_2$ | 25 - 500 $\mu$g/mL | Antioxidant, cytoprotective effects | (24) |
| ***Melissa officinalis* L.** | Leaf | Ethanol extract | Experimental autoimmune myocarditis in rats | 50, 100, or 200, p.o., mg/kg, 3 weeks | Improved echocardiographic parameters and cardiac function; ↓ inflammatory infiltrate, collagen content in the; heart tissues; ↓ prooxidants production; ↑ GSH, SOD, CAT | (25) |
| ***Melissa officinalis* L.** | Leaf | Ethanol extract | Myocardial I/R injury in rats | 50, 100, or 200, p.o., mg/kg, 1 week | ↓ Prooxidants, fibrosis; 200 mg/kg: ↑ Coronary flow, SOD, CAT; ↑ myocardial contractile function | (26) |
| ***Melissa officinalis* L.** | Aerial parts | Aqueous extract | - | 50, 100, or 200, p.o., mg/kg, 1 week | Significant ECG alterations | (27) |
| ***Melissa officinalis* L.** | Leaf | Ethanol extract | $CaCl_2$-induced arrhythmias in rats, 140 mg/kg, i.v. | 100 and 200 mg/kg, p.o., 2 weeks | ↓ HR, VPB, VT, VF | (28) |
| ***Melissa officinalis* L.** | Aerial part | Aqueous extract | Ventricular arrhythmias following ischemia-reperfusion in rats | 50, 100, 200 and 400 mg/kg, i.p. | Mild protective effect against ventricular arrhythmias | (29) |
| ***Melissa officinalis* L.** | Leaf | Aqueous extract | Isolated hearts of rats | 0.077, 0.77, 7.7, 77 mg/mL | No changes in contractile force; ↓ cardiac rate | (30) |
| ***Melissa officinalis* L.** | Aerial part | Ethanol extract | Doxorubicin-induced cardiotoxicity in rats, 15 mg/kg, i.p. | 250, 500 and 750 mg/kg, p.o., 10 days | ↓ Cardiac damage: ↓ AST, CK, CK-MB; ↓ inflammation: ↓ mRNA levels of NF-kB, COX-2, TNF-$\alpha$, edema, MPO; ↓ oxidative stress: ↑ SOD, potent free radical scavenging activity; ↓ apoptosis: ↓ Bax, caspase-3 | (31) |
| ***Melissa officinalis* L.** | Leaf | Ethanol extract | Ischemia-induced arrhythmia in rats | 25, 50 and 100 mg/kg, p.o., 2 weeks | Improvement of I/R induced myocardial dysfunction; ↓ ventricular tachycardia, ventricular ectopic beats, MDA, LDH, CTnI; ↑ SOD; free radical scavenging activity | (32) |
| ***Melissa officinalis* L.** | Aerial part | Aqueous extract | Isoproterenol induced myocardial injury in rats | 50, 100 and 200 mg/kg, p.o., 1 week | 50, 100 mg/kg: ↓ MDA, LVSP; 200 mg/kg: ↑ Contractility, speed of left ventricular relaxation; All doses: ↓ HR, LVEDP | (33) |

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| ***Melissa officinalis* L.** | Leaf | Infusion 5% | Methimazole induced hypothyroidism in rats | Instead of drinking water, 1 week | ↓ Post ischemic recovery of heart | (34) |
| ***Melissa officinalis* L.** | Leaf | Capsule: 500 mg of lyophilized aqueous extract | A double-blind randomized placebo-controlled clinical trial, adults with benign palpitations | 500 mg, BD, 2 weeks | ↓ Palpitation | (35) |
| ***Melissa officinalis* L.** | Leaf | Capsule: 350 mg of hydro alcohol extract | A double-blind randomized placebo-controlled clinical trial in patients with type 2 diabetes | 350 mg, BD, 12 weeks | ↓ FBS, HbA1c, $\beta$-cell activity, TG, hs-CRP, SBP; ↑ HDL-c; no significant change: Total cholesterol, LDL-c, insulin, and HOMA-IR | (36) |
| ***Melissa officinalis* L.** | Leaf | Capsule: 500 mg of extract | A randomized double-blinded controlled clinical trial in patients with type 2 diabetes | 500 mg, BD, 3 months | No significant metabolic changes compared to the control group | (37) |
| ***Melissa officinalis* L.** | Leaf; stem | Essential oil | A double-blinded controlled clinical trial in patients with acute coronary syndrome in the emergency department. | Inhalation 2 drops in two aromatherapy phases for 10 min with 90-min intervals | ↓ Stress, HR, MAP | (38) |
| ***Ocimumbasilicum* L.** | Leaf | Ethanol extract | Isoproterenol induced myocardial infarction in rats | 10, 20 and 40 mg/kg, BD, p.o., 2 days | ↓ MDA, myocardial necrosis and fibrosis; ↑ LVSP; inhibition of the elevation of ST-segment; improvement of myocardial contractility | (39) |
| ***Ocimumbasilicum* L.** | Leaf | Aqueous extract | Reno vascular hypertensive rats | 100, 200 and 400 mg/kg, p.o., 4 weeks | ↓ SBP, DBP, cardiac hypertrophy | (40) |
| ***Phyllanthus emblica* L.** | Fruit | Ethanol extract | In vitro assay for evaluating extract on doxorubicin toxicity | 1, 10 and 100 $\mu$g/mL | The protective effect on cardiotoxicity at concentration of 100 $\mu$g/mL; antioxidant activity | (41) |
| ***Phyllanthus emblica* L.** | -[a] | Isolated compound (Corilagin) and its analog Dgg16 | Anti-atherogenic effect on human umbilical vein endothelial cells | 0.0001 - 1 mmol/L | ↓ MDA; inhibition of ox-LDL-induced VSMC proliferation | (42) |
| ***Phyllanthus emblica* L.** | Fruit | Ethanol extract | Rats fed with high fat diet | 100 mg/kg, p.o., 3 weeks | ↓ HR, sympathetic function, LDL; ↑ parasympathetic function | (43) |
| ***Phyllanthus emblica* L.** | -[a] | Isolated sesquiterpen glycoside; (phyllaemblicin B) | Coxsackie virus B3 induced apoptosis and myocarditis in mice | 4, 8 and 12 mg/kg, i.v., 1 week | ↓ LDH, CK; ↓ myocardium damage: ↓ Necrosis, inflammatory infiltrates; ↓ apoptosis: ↓ caspase-3, ↑ Bcl-2 | (44) |
| ***Phyllanthus emblica* L.** | Fruit | Emblicanin-A and B enriched fraction | I/R-induced cardiotoxicity in rat | 100 and 200 mg/kg, BD, p.o., 2 weeks | ↑ Cardiac SOD, CAT, GSH-Px; ↓LPO | (45) |
| ***Phyllanthus emblica* L.** | -[a] | Aqueous extract | I/R-induced cardiotoxicity in rat | 100 mg/kg, p.o., 30 days | Upregulation of PI3K/Akt/GSK3b/b-catenin; ↑ Bcl-2, eNOS phosphorylation | (46) |
| ***Phyllanthus emblica* L.** | Fruit | Fresh fruit homogenate | I/R-induced cardiotoxicity in rat | 250, 500 and 750 mg/kg, p.o., 30 days | ↑Cardiac SOD, CAT, GSH-Px; ↓LPO; myocardial adaptation | (47) |
| ***Phyllanthus emblica* L.** | Fruit | Juice | STZ-induced diabetic myocardial dysfunction in rat | 1 ml/kg, p.o., 8 weeks | ↓ VLDL, LDL, TG, glucose, LDH, CK-MB, BP; ↑ HDL, HR, force of contraction; antioxidant activity: ↑ SOD, CAT, GSH, ↓ MDA; restoration of hemodynamic parameters; ↓ LV collagen and protein content: ↓ cardiac stiffness and fibrosis | (48) |
| ***Phyllanthus emblica* L.** | -[a] | Powder | High cholesterol diet induced atherosclerosis in rat | 100 mg/kg, p.o., 30 days | ↓ VLDL, LDL, LDH, AST, ALT; ↑ HDL; antioxidant activity: ↓ Oxidative stress, ↑ SOD, CAT, GPx | (49) |
| ***Phyllanthus emblica* L.** | Fruit | Ethanol extract | Rat fed with high fat diet | 100 and 200 mg/kg, 3 weeks | ↓ MDA; cardiac protection | (50) |

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|---|---|---|---|---|---|---|
| ***Phyllanthus emblica* L.** | Fruit | Powder (2.5% of powdered chow food) | 2K1C rats | Rats fed with food supplemented amla powder, 4 weeks | ↓ MDA, NO, APOP; ↑ antioxidant activity; ↓ inflammation, fibrosis | (51) |
| ***Phyllanthus emblica* L.** | Fruit | Hydro alcohol extract | Isoproterenol-induced; cardiotoxicity in rats | 100, 250 and 500 mg/kg, p.o., 30 days | 250, 500 mg/kg: ↑ SAP, DAP, MAP, HR, SOD, CAT, GPx, GSH; 250, 500 mg/kg: Myocardial protection: ↓ Inflammation, myonecrosis; ↓ LVEDP, LPO; restoration of hemodynamic parameters and cardiac function | (52) |
| ***Phyllanthus emblica* L.** | -[a] | Capsule 250, 500 mg | A randomized, double-blind, controlled study, patients with type 2 diabetes mellitus | 1 and 2 capsule, BD, 12 weeks | ↓ RI, MDA, CRP, LDL, TG, TC, $HbA_{1C}$; ↑GSH, HDL; improvement of endothelial function | (53) |
| ***Rosa canina* L.** | Flower | Aromatic water | Ischemia-reperfusion injuries in the isolated rat heart | 0.416%, 1.25%, 2.5% and 4.16% | Negative chronotropic effect; Positive inotropic effect; ↑ LVDP, contractile force | (54) |
| ***Rosa canina* L.** | Fruit | Methanol extract | Heat shock-induced cardiomyocyte injury in rats | 250, 500 and 1000 mg/mL, p.o., 2 weeks | 500 and 1000 mg/mL: ↓ ROS, cleaved caspase 8, cardiac injury; 500 and 1000 mg/mL: ↑ Pro-caspase 8; inhibition of PERK/eIF2$\alpha$/CHOP signaling | (55) |
| ***Rosa canina* L.** | Fruit | Juice | A randomized, double-blind, cross-over clinical study, obese and non-diabetic patients | 40 g, 6 weeks | ↓ SBP, TC, LDL, LDL/HDL | (56) |

Abbreviations: ECG, electrocardiogram; L-NAME, N-nitro-L-arginine methyl ester; cTnT, cardiac troponin T; LDH, lactate dehydrogenase; CK, creatine kinase; NF-$\kappa$B, nuclear factor kappa B; MDA, malondialdehyde; SOD, superoxide dismutase; I/R, ischemia-reperfusion; VEGF, vascular endothelial growth factor; VPB, ventricular premature beats; VT, ventricular tachycardia; VF, ventricular fibrillation; LVSP, left ventricular systolic pressure; RI, reflex index; CRP, C-reactive protein; HbA1c, hemoglobin A1c; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CAT, catalase; GSH, glutathion; GPx, glutathione peroxidase; AST, aspartate aminotransferase; CK-MB, creatine kinase-MB; TNF-$\alpha$, tumor necrosis factor-$\alpha$; COX-2, cycloxygenase-2; MPO, myeloperoxidase; Bax, Bcl-2-associated X protein; CTnI, serum cardiac troponin I; LVEDP, left ventricular end-diastolic pressure; ALT, alanine amino transferase; AST, aspartate amino transferase; ROS, reactive oxygen species; LPO, lipid peroxidation; VSMC, vascular smooth muscular cells; ox-LDL, oxidized low-density lipoprotein; NF-kB, nuclear factor kappa B; BD, twice a day; TDS, three times a day; TC, total Cholesterol; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride; PERK, PKR-like endoplasmic reticulum kinase; CHOP, CCAAT enhancer-binding protein homologous protein; LVDP, left ventricular developed pressure; NO, nitric oxide; APOP, advanced protein oxidation product; 2K1C, two-kidneys-one-clip

[a] Not mentioned