Review Article

Protective effects of *Trichosanthes* on cardiovascular system

Chunjie Li1, Guanwei Fan2, Han Zhang2, Mingjun Zhu3

1Tianjin Chest Hospital, Tianjin, China; 2Tianjin State Key Laboratory of Modern Chinese Medicine, Tianjin 300193, China; 3The First Affiliated Hospital of Henan College of Traditional Chinese Medicine, Tianjin, China

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Abstract: *Trichosanthes* has had a wide range of clinical applications in traditional Chinese medicine for centuries. Trichosanthis, which is from Trichobitacin, has been clinically used in traditional Chinese medicine as a mid-term abortifacient. Moreover, *Trichosanthes* manifests a host of pharmacological properties, such as antibacterial activity and expectorant effect on cough. The clinical applications of *Trichosanthes* in the cardiovascular system have recently attired great interest because of its therapeutic effect. Researches on the relative mechanism of *Trichosanthes* in the cardiovascular system are gradually accumulated. The present article aimed to review the various cardiovascular activities of *Trichosanthes* and the protection mechanism induced by it in cardiovascular cells. The advancements in research do not only provide insights on cardiovascular research and treatment, but also reveal new pharmacological properties of this ancient yet popular Chinese medicine.

Keywords: Trichosanthes, Trichosanthis, cardiovascular system

Introduction

*Trichosanthes* is a genus of the family Cucurbitaceae. It is an annual or perennial herb that is found in tropical Asia. Its important species, such as *T. palmata*, *T. cordata*, *T. nervifolia*, *T. cucumerina*, *T. wallichiana*, *T. cuspidata*, *T. incisa*, *T. laciniosa*, and *T. kirilowii*, are found worldwide [1]. Several species of *Trichosanthes*, such as pointed gourd (*T. dioica*), are known by different names in different parts of India and Bangladesh; they are also among the most important vegetables of this region [2]. *Trichosanthes* also has widely pharmacological applications in several Asian countries. The juice from the leaves of *T. dioica* is used as tonic, febrifuge, and treatment for sub-acute cases of enlargement of the liver and spleen [3]. According to Charaka Samhita, both its leaves and fruits are used to treat alcoholism and jaundice, and the leaves are used for edema and alopecia [4]. *T. dioica* is also used as an antipyretic, diuretic, cardiotonic, and laxative agent.

The Chinese commonly use dried ripe fruits of *T. kirilowii* Maxim or *Trichosanthes rosthornii* Harms in their traditional medicine. *Trichosanthes* is mainly cultivated in Anhui, Shandong, and Henan Province, among other places in China. According to Sugababes, which is one of most famous publications on Chinese traditional medicine, *Trichosanthes* can be used to treat hyperactive cough, thick yellow phlegm, chest pain, breast abscess, lung abscess, appendicitis, and constipation. Trichosanthis or Tin Hua Fen that is obtained from the root tuber of *T. kirilowii* Maxim is a renowned traditional Chinese medicine that is still used in Chinese clinics to induce midterm abortion [5]; moreover, it has shown anti-HIV and anti-tumor properties [5-9]. Meanwhile, *Trichosanthes* has a good therapeutic effect on cardiovascular diseases; thus, its range of clinical applications continuously expands [10]. The Gualou Xiebai decoction is a famous prescription that is derived from *Trichosanthes*. It is used in dietetic therapy for cardiovascular diseases in China. The current article aimed to review the recent research progress on the effect of *Trichosanthes* in the cardiovascular system. Thus far, the discovered therapeutic effects are myocardial cell protection, antihyperglycemic/antihyperlipidemic, vascular smooth muscle cell (VSMC) prolif-
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Vascular reperfusion is the most effective treatment for myocardial infarction. Reperfusion therapy, however, can cause ischemia-reperfusion (I/R) injury in microcirculation, which is frequently accompanied by endothelial cell injury, enhanced adhesion of leukocytes, macromolecular efflux, production of oxygen free radicals, and mast cell degranulation. Microcirculatory disturbance results in organ injury, so protecting the organ after I/R is clinically important. Meanwhile, the main mechanism is closely related to the increase in the generation of oxygen-free radicals and overload of calcium [11, 12]. Malondialdehyde (MDA), which is produced through the reaction of polyunsaturated fatty acids against the cell membrane that has oxygen-free radicals, causes serious damage on the cell membrane when both myocardial ischemia and hypoxia occur. Yan et al. demonstrated that the levels of MDA, lactate dehydrogenase (LDH), and creatine kinase (CK) were significantly decreased in the serum of rats after Gualou Xiebai decoction treatment. C-Jun N-Terminal kinase (JNK), a mitogen-activated protein kinase (MAPK) protein, and the extracellular signal-regulated kinase and phosphorylation of P38 protein levels of ischemia myocardial tissue were significantly reduced [13, 14]. Trichosanthes reduces ischemic injury by scavenging oxygen-free radicals and by reducing oxidation inhibition of P38 and phosphorylation of proteins JNK. Moreover, Gualou Xiebai decoction inhibited the activity of the nitrous oxide system (NOS) and reduced the excessive production of NO on rabbit ischemic myocardium. Thus, the low-dose treatment is more effective than the high-dose treatment [15, 16]. T. dioica fruit remarkably alleviated arsenic induced myocardial oxidative stress in Wistar albino rats [17].

Besides, both mitochondria and sarcoplasmic reticulum (SR) are essential for myocardial homeostasis and cardiac function control. Myocardial ischemia slows down the opening of calcium channels on the membrane, thereby enabling the entry of Ca²⁺ into the cell and causing Ca²⁺ overload; thus, membrane stability is decreased, and mitochondrial swelling and cell necrosis are induced [18]. Therefore, the enhancement of SR Ca²⁺ loading aggravates myocardial ischemia independently from cytosolic Ca²⁺ overload. Liu et al. demonstrated that both the modified and the unmodified Gualou Xiebai Banxia (GXB) decoction could affect the changes of free calcium in rat myocardial cells and serum CK-MB as well as electrocardiogram because of ischemia. Ca²⁺ content significantly varied compared with the acute ischemia group after administering large and small doses of either modified or unmodified GXB decoction. Moreover, the content of CK-MB serum and the ST segment shift of the electrocardiogram also differed significantly. Both the modified and the unmodified GXB decoction could apparently inhibit Ca²⁺ overload in ischemic myocardial cells, reduce injury of cardiac muscles, and remarkably protect ischemic cardiac muscle tissue [19].

Accumulating studies have confirmed that the mitochondrion-mediated apoptosis pathway is involved in ischemia-related cell death, which has also been bolstered in transgenic animals. It is triggered by the activation of pro-apoptotic Bcl-2 family members like Bax [20, 21]. Bcl-2 protein is induced in salvaged apoptotic human myocytes after ischemia and/or reperfusion but the overexpression of Bax accelerated the apoptosis [22]. Meanwhile, enhanced macroautophagy also protects cardiac myocytes against I/R injury [23]. Jin et al. investigated the effects of GXB decoction on the apoptosis of cardiac myocytes and the protein expression levels of Bcl-2 and Bax of rats characterized by myocardial I/R injury. The apoptosis of cardiac myocytes was significantly suppressed by the regulation of Bcl-2 and Bax protein expressions, after GXB decoction treatment [24, 25]. Moreover, the treatment restored the activity of the specific myocardial-injury markers CK and LDH and inhibited the inflammatory response of the nuclear factor-kB (NF-kB) pathway. This process includes the down-regulation of both interleukin (IL)-1β and IL-6, and the upregulation of IL-10, which significant-
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ly reduces the myocardial impairment of the I/R model [26]. Fang et al. demonstrated that GXB decoction protects myocytes from isoproterenol-induced apoptosis by downregulating Fas/Fas-L gene expression [27], which is known as death receptor/death ligand. The modified Gualou Xiebai decoction also significantly decreases VEGF and inhibits the expressions of both P53 and Caspase-3 [28, 29]. The effect of protection on myocardial cells is shown in Table 1.

Antihyperglycemic and antihyperlipidemic attributes of Trichosanthes

The glycemic attributes of an aqueous extract of T. dioica leaves have normal and various diabetic models. A previous study orally administered normal and streptozotocin (STZ)-induced sub-diabetic and mild-diabetic rats with variable doses of 250, 500, and 750 mg/kg body weight of the T. dioica leaves extract to define their glycemic potential. The results revealed that aqueous extract of T. dioica leaves has good hypoglycemic potential and high antidiabetic profile [30]. Rai et al. showed that the traditional use of T. dioica could be adopted in diabetes management and be developed as an effective oral agent for treating diabetes mellitus and its complications [31, 32]. Pointed gourd was reported to possess a medicinal property of lowering the blood sugar level of rats [1]. Li et al. used human hepatocarcinoma cell HepG2 and the alloxan-induced diabetic mouse model to assess the hypoglycemic activity of lectin in T. kirilowii, which exhibited positive results [33, 34]. Sharmila et al. observed the cholesterol-lowering activity of aqueous T. dioica Roxb. fruit extract in both normal and STZ diabetic rats [1, 35]. The alcoholic extract of T. dioica whole fruit was demonstrated to have effects on blood sugar, serum lipids, lipoproteins, and fecal sterols of normal albino rabbits. In this experiment, normal albino rabbits were orally administrated with 2 mL/day suspension (in water) of the alcoholic extract of T. dioica whole fruit (2%) with basal diet for 4 weeks. Blood sugar, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels were reduced by the extract; it also increased high-density lipoprotein cholesterol (HDL-C), phospholipid, and fecal sterol levels [36, 37]. Wang et al. studied the effect of triangle drugs, such as ginseng, T. kirilowii Maxim, and rhubarb, on the levels of blood lipids (e.g., TC, TG, HDL-C, and LDL-C) and pro-inflammatory cytokines [e.g., intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and high-sensitive C reactive protein (hs-CRP)] during atherosclerosis treatment. Triangle drugs particularly lowered the elevated levels of both TC and LDL-C, which is beneficial for delaying the process of atherosclerosis by lowering blood lipids levels. Such drugs also decreased the level of pro-inflammatory cytokines and improved both the endothelial function and inhibition of smooth muscle proliferation [38, 39]. Wang et al. studied the clinical efficacy of danlou tablet (DT) in treating coronary heart disease angina (CHDA) patients from phlegm and stasis mutual obstruction syndrome (PSMOS) [40].

Inhibiting VSMC proliferation

Yang et al. investigated the effect of the extract of Pericarpium Trichosanthis (EPT) on the VSMC proliferation of the cell cycle of rat that was induced by platelet-derived growth factor-BB (PDGF-BB) [41]. Moreover, they specifically probed its mechanism. The addition of EPT (10, 20, and 30 mg/L) markedly inhibited PDGF-BB-induced proliferation of VSMC, decreased the S-phase cell percentage, and upgraded the GO/G1 phase cell percentage of the cell cycle. EPT was also found to suppress the elevated expressions of both c-fos and c-myc mRNA that were induced by PDGF-BB. EPT also inhibited

Table 1. Effect of myocardial cells protection

<table>
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<tr>
<th>Effect on myocardial cells</th>
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<td>Improve Clinical indicators</td>
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<td>Increase membrane stability</td>
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<td></td>
<td>Ca²⁺ entry into cell↓</td>
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<td>Suppress apoptosis of cardiac myocytes</td>
<td>Bax/bcl-2↓</td>
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<td>Caspase-3↓</td>
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<td>Inhibition of inflammatory repose in myocardial impairment</td>
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<td>VEGF↓</td>
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Malondialdehyde (MDA); lactate dehydrogenase (LDH); creatine kinase (CK); interleukin (IL); vascular endothelial growth factor (VEGF). ↓, decrease; ↑, increase.
the VSMC proliferation that was induced by PDGF-BB by preventing the transformation of the G0/G1 phase cell to S-phase cell in the cell cycle. The mechanism may be related to its downregulatory effect on both c-fos and c-myc mRNA expressions [41], the latter being part of the control mechanism for the expression of hypertrophy-related genes [42]. Yan et al. showed the effects of Gualou Xiebai decoction on integrin β1 and fibronectin that are induced by angiotensin II, especially in reversing myocardial fibrosis [43]. The integrin β1 mRNA expression showed a significant downward trend that is similar to that of fibronectin after treatment with the decoction. The model of myocardial fibrosis was intervened with different dosages of Gualou Xiebai decoction [43]. The GXB decoction could also improve myocardial fibrosis by inhibiting cardiac fibroblast proliferation, DNA, and collagen synthesis [44, 45]. *Trichosanthes* injection inhibits the proliferation of VSMC by reducing the expression of the cell nuclear antigen (PCNA) [46].

**Protection of vascular endothelium**

Tan et al. showed the protective effect of *Trichosanthes* extract on the endothelium damage that is induced by LDL [47]. The concentration of asymmetric dimethylarginine (ADMA) is closely related to endothelial dysfunction in rats. *Trichosanthes* extract protected the endothelium against the damage induced by LDL; it reduced the level of serum concentrations of ADMA, MDA, and tumor necrosis factor-α (TNF-α) and increased the level of NO [47-49]. EPT also demonstrated a protective effect on the vascular endothelium in diabetic rats [50, 51]. The VEGF level of patients with portal hypertension evidently decreased after GXB decoction powder treatment. Slight statistical differences were found between the two groups in terms of portal diameter and blood flow. However, no remarkable difference was shown in the velocity of the two groups [52]. Wu et al. evaluated the effect of extracts of Fructus Trichosanthis (EFT) on the aortic strip’s tension. EFT-induced relaxation on vascular smooth muscle is caused by its antagonistic effect to Ca2+; it inhibits both the receptor-operated channel and the potential-dependent channel [53]. Li investigated the underlying mechanism in the vasodilatory effect of GXB decoction, which exhibited a vasorelaxation effect through the NO-cGMP and cyclooxygenase signal pathway as its mechanism [54].

**Anti-platelet aggregation**

The reduction of the incidence of thromboembolic events is an important goal in the treatment of cardiovascular disease. Thrombosis and embolism are not only the leading causes of cardiovascular disease and severe sequelae, but also of poor prognosis and sudden death of patients. The number and functional properties of platelets play an important role in the occurrence of thrombosis. Zhou et al. revealed the effects of EPT injection on hemorheology in a clinical trial of a total of 650 patients characterized by cerebral infarction. They found that EPT injection can safely and effectively reduce blood viscosity, which strengthened the improvement of neurological function and stroke prognosis [55, 56]. GXB decoction can evidently decrease the level of platelet-activating factor, whereas increase the level of NO which relieves pulmonary hypertension that is induced by hypoxia at ordinary air pressure and thicken the arteriolar wall to relieve arteriolar stenosis [57]. Modified GXB decoction also demonstrated anticoagulation and fibrinolysis effects in rats [58].

**Conclusions and future perspectives**

Numerous studies have been conducted on *Trichosanthes*. Researchers have successfully extracted its fats, triterpenoids, flavonoids, and other active ingredients separately. The expectorant effect of *Trichosanthes* on cough and its impetus on cardiovascular improvement thanks to its antibacterial properties; thus, several medicines produced based on such discovery have already been put in service in clinical practice. These products include *Trichosanthes* slices and *Trichosanthes* injection.

The chemical component *Trichosanthes* is complex, and its pharmacological activity is very extensive. However, all these curative properties of *Trichosanthes* still remain cloudy even with the coming pharmaceutical progress. The pharmaceutical effects of traditional Chinese medicine are conventionally reported as the result of a substance or a combination of various substance categories working together instead of just a single chemical component. Therefore, the first step must be to identify the
chemical ingredients of *Trichosanthes*. Several ingredients discovered by compatibility studies, pharmacological effects of them, and compatibility with other herbs should be investigated, apart from studying a single component or a solitary type of pharmacologically active substance.

Pharmacological activity is used as an index with the respect of holism to evaluate the herb processing technology, extraction, purification, and preparation processes to maximize the curative property of *Trichosanthes*.

**Disclosure of conflict of interest**

None.

**Address correspondence to:** Dr. Mingjun Zhu, The First Affiliated Hospital of Henan College of Traditional Chinese Medicine, #19 Renmin Road, Zhengzhou 450000, China. E-mail: drzhumj@163.com; Dr. Guanwei Fan, Tianjin State Key laboratory of Modern Chinese Medicine, Tianjin 300193, China. E-mail: neuroman@163.com

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