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Review

The Therapeutic Effects of Ligustrazine in Combination with Other Drugs in Cardiovascular Diseases

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Abstract: Chuanxiong, one of the traditional Chinese medicines (TCM), was first documented in the Tang dynasty to promote blood circulation and remove blood stasis. *Ligusticum chuanxiong Hort* was shown as the most effective portion of chuanxiong. Later chemical analysis revealed that the main chemical component of *ligusticum chuanxiong Hort* is tetramethylpyrazine. Since then, numerous explorations have been made to examine the efficiency of tetramethylpyrazine in treating different diseases and understand the underlying mechanisms of its action. Like Chuanxiong, ligustrazine (Chuan Xiong Qin) improved the functions of the circulatory and nervous systems. Ligustrazine (Chuan Xiong Qin) was also used in combination with other medicines to achieve better effects on improving cardiovascular health or alleviating the adverse effects of chemotherapies in both basic and clinical studies. The present review briefly summarizes the existing studies of the combination of ligustrazine (Chuan Xiong Qin) with other medicines in the treatment of cardiovascular diseases (CVDs) and provides valuable insights into the future research direction and better utilization of this drug.

Keywords: Ligustrazine (Chuan Xiong Qin); Salvia miltiorrhiza (Dan Shen); Berberine (Huang Lian Su); Paeoniflorin (Shao Yao Dai); Suxiao jiuxin pill; Valsartan; Doxorubicin; Cardiovascular diseases

1. Introduction

Ligustrazine (Chuan Xiong Qin), also named 2, 3, 5, 6-tetramethylpyrazine that well describes its chemical structure [1]. There are two major ways to produce ligustrazine (Chuan Xiong Qin). Briefly, the natural ligustrazine (Chuan Xiong Qin) is extracted from chuanxiong while the artificial ligustrazine (Chuan Xiong Qin) is synthesized by 3-Aminobutan-2-one hydrochloride. Ligustrazine (Chuan Xiong Qin) is now widely used to treat CVDs, mainly atherosclerosis (AS) and myocardial ischemia (MI) [2]. Ligustrazine (Chuan Xiong Qin) was found to improve cardiovascular health through promoting several beneficial physiological processes, such as the inhibition of nuclear factor kappa light chain enhancer of activated B cells (NFκB) activity against inflammation [3], the suppression of caspase-3 signaling-mediated apoptosis [4], and increasing mitochondrial and endothelial function [2]. The characteristics of lower biotoxicity and weak drug resistance contribute to its wide use in TCM clinics [5, 6]. However, like most TCM, the mechanisms responsible for ligustrazine (Chuan Xiong Qin)'s beneficial effects on cardiovascular function are still largely unexplored, even though observations are made. In this review, we mainly focus on the clinical use of ligustrazine (Chuan Xiong Qin) in combination with other medicines and the reported underlying mechanisms.

CVDs are a class of diseases involving the damage of the heart and blood vessels. According to the Word Heath Organization (WHO), CVDs are still the leading cause of mortality worldwide, taking approximately 17.9 million lives every year [7]. CVDs affecting cardiac function include heart failure, hypertensive heart disease, and cardiomyopathy. In contrast, the other CVDs associated with dysfunction of

blood vessels, mostly called coronary artery disease (CAD), are mainly caused by atherosclerosis. As a metabolic and chronic inflammatory disease, the pathogenesis of atherosclerosis is very complicated, accounting for the challenge of its prevention and treatment. Drugs, such as satins, nitroglycerin, and aspirin, targeting to improve blood lipid profile and arterial functions as well as the inhibition of inflammation, have been developed to treat CVDs [8-10]. Due to the limitation of efficiency and the side effects of these therapeutic drugs, the morbidity and mortality due to CVDs remain high in the world. Thus, new therapeutic strategies for the prevention and treatment of fatal CVDs events are in an urgent demand. The review of the therapeutic effects of ligustrazine (Chuan Xiong Qin) alone or in combination with other medicines on CVDs will provide more insights into the better use of TCM in the treatment of CVDs.

2. Ligustrazine (Chuan Xiong Qin) with Salvia Miltiorrhiza (Dan Shen) Activate the Protein Kinase B/ Endothelial Nitric Oxide Synthase Pathway to Reduce Apoptosis

To achieve better treatment efficiency, herbalists have always adopted the combined use of two or more medicinal materials. Ligustrazine (Chuan Xiong Qin) as the most widely used TCM in treating CVDs, was administered in combination with Salvia miltiorrhiza (Dan Shen) Bunge (SM), berberine (Huang Lian Su) (BBR), paeoniflorin (Shao Yao Dai) and other TCM (Table 1).

Table 1. Summary of the function of ligustrazine (Chuan Xiong Qin) in combination with other drugs in cardiovascular diseases.

Combination	Functions	Pathways	Results	References
Ligustrazine (Chuan Xiong Qin) with Salvia miltiorrhiza (Dan Shen)	Apoptosis ↓	Akt/eNOS ↑	Cardiac function ↑	[11]
Ligustrazine (Chuan Xiong Qin) with Berberine (Huang Lian Su)	Inflammation ↓	Expression of TNFα and IL-1β ↓	Cardiac function ↑	[12]
Ligustrazine (Chuan Xiong Qin) with Paeoniflorin (Shao Yao Dai)	Angiogenesis ↓	VEGF and VEGFR2 ↓ Jagged/Notch1 signaling ↓	Stability of atherosclerotic plaque ↑	[13]
Ligustrazine (Chuan Xiong Qin) with borneol (Bing Pian)	Exosome secretion ↑ Mitochondrial injury ↓ Hyperlipidemia ↓ Apoptosis ↓	PI3K/Akt/GSK3β ↑	Cardiac function ↑ Angina ↓ Atherogenesis ↓	[14,15]
Ligustrazine (Chuan Xiong Qin) with valsartan	Free radical formation ↓	CYP3A4 ↑	Hepatic metabolism of valsartan ↑	[16]
Ligustrazine (Chuan Xiong Qin) with doxorubicin	Mitochondrial function ↑ Oxidative stress ↓	14-3-3γ ↑	Chemotherapy induced-cardiovascular damage ↓	[17]

First, Danshen, also called SM, a type of TCM [18], has been used to treat CVDs and inflammatory diseases for long years on the basis of its excellent ability to improve blood circulation, which was recorded in the Compendium of Materia Medica [19]. Recently, SM (Dan Shen) has been broadly prescribed to patients with ischemic heart disease and stroke [20,21]. Similar to SM (Dan Shen), ligustrazine (Chuan Xiong Qin) has protective effects on ischemia/reperfusion (I/R) in rats [22]. The mechanisms of SM (Dan Shen) treatment against CVDs can be simply generalized by inhibiting the cardiac cell apoptosis to reduce myocardial damage [23]. Though the exact mechanisms of the beneficial effects of SM (Dan Shen) and ligustrazine (Chuan Xiong Qin) on CVDs are not fully understood, the combined use of ligustrazine (Chuan Xiong Qin) with SM (Dan Shen) shows very promising potential in the treatment of heart injury in rats. For example, a combined injection of ligustrazine (Chuan Xiong Qin) and SM (Dan Shen) significantly improved cardiac function and decreased the infarct size of I/R through activation of cardiovascular protective protein

kinase B (Akt)/Endothelial nitric oxide synthase (eNOS) signaling, surprisingly with no unexpected side effects in these treated rats [11]. However, further studies have yet to compare the therapeutic effects among individual use of these two drugs and the combination of both [24]. eNOS is an enzyme orchestrating the production of NO, which is one of the important messengers mediating vasodilatation, indicating the possible role of these two drugs in the protection of vascular function. Further investigation is needed to elucidate the advantages of this combined use and to fully understand the therapeutic effects in CVDs.

3. Ligustrazine (Chuan Xiong Qin) with Berberine (Huang Lian Su) Inhibits the Expression of Tumor Necrosis Factor-alpha and Interleukin-1 Beta to Reduce Inflammation

BBR (Huang Lian Su) is the bioactive extraction of Rhizoma coptidis, being able to suppress inflammatory response [25]. Rhizoma coptidis was first recorded as a drug in 'Shen Nong Ben Cao Jing', thousands of years ago [26]. BBR (Huang Lian Su) improves cardiovascular function in several aspects, such as reducing the levels of blood glucose and lipids together with blood pressure [25]. As an antibacterial drug, BBR (Huang Lian Su) is widely used in patients with the advantage of few side effects and low prices [27]. However, it remains a substitution treatment method only when statins do not work in clinical application. Scientists find a correlation between BBR (Huang Lian Su) and ligustrazine (Chuan Xiong Qin) because both drugs share similar mechanisms of action to certain degrees. BBR (Huang Lian Su) significantly suppressed inflammation and apoptosis by reducing the increased expression of tumor necrosis factor-alpha (TNFα) and Interleukin-1 beta (IL-1β) in I/R rats [28], thus reducing myocardial I/R injury [29]. Meanwhile, ligustrazine (Chuan Xiong Qin) also decreased apoptosis and inflammation through inhibition of TNFα and IL-1β expression, like BBR (Huang Lian Su) does [30]. Combined use of BBR (Huang Lian Su) with ligustrazine (Chuan Xiong Qin) exerted better effects on the protection of the animal models from CVDs by reducing the expression levels of proinflammatory TNFα, IL-1β, intercellular adhesion molecule 1 (ICAM-1), and regulated on activation, normal T cell expressed and secreted (RANTIES) than individual use [12]. These pre-clinical findings provide the scientific basis for applying the combination of these two drugs in patients with heart injury.

4. Ligustrazine (Chuan Xiong Qin) with Paeoniflorin (Shao Yao Dai) Decreases Oxidized Low-Density Lipoprotein-Induced Angiogenesis

Paeoniflorin (Shao Yao Dai) is an extract from Paeonia Lactiflora, usually used for relieving pain through anti-fibrosis and anti-apoptosis [31]. In CVDs, paeoniflorin (Shao Yao Dai) has been used to improve blood flow for thousands of years. Recently, it was reported that paeoniflorin (Shao Yao Dai) has antithrombotic effects by decreasing platelet aggregation [32]. Besides, paeoniflorin (Shao Yao Dai) treatment increased cardiac functions by improving mitochondrial structure and inhibiting the secretion of pro-inflammatory cytokines in rats with acute myocardial infarction [33]. In addition to cardiac protection, paeoniflorin (Shao Yao Dai) inhibits tert-butyl hydroperoxide-induced mitochondrial reactive oxygen species (ROS) production in human umbilical vein endothelial cells (HUVECs) and ROS-mediated proliferation of vascular smooth muscle cells, indicating a potential therapeutic effect on diseases related to abnormal vascular remodeling [34, 35]. Ligustrazine (Chuan Xiong Qin) improved cardiac function accompanied by decreased cell necrosis, collagen deposition, myocardial fibrosis, expression of pro-inflammatory factors, and oxidative stress in the Sprague-Dawley (SD) rats with myocardial infarction [36]. Ligustrazine (Chuan Xiong Qin) and paeoniflorin (Shao Yao Dai) are both the main components of ligusticum chuanxiong Hort, and they have a similar protective effect on cardiac injury. The combination of ligustrazine (Chuan Xiong Qin) and paeoniflorin (Shao Yao Dai) partially reversed oxidized low-density lipoprotein (ox-LDL) -induced angiogenesis via the inhibition of the expression of vascular endothelial growth factor (VEGF) and its receptor vascular endothelial growth factor receptors 2 (VEGFR2) together with the Jagged/ Neurogenic locus notch homolog protein 1 (Notch1) signaling in HUVECs, which is closely correlated to atherosclerotic plaque stability [13]. In view of the inhibitory effect of these two drugs on endothelial oxidative stress, vascular smooth muscle cell proliferation, and cardiac inflammation, which are all atherosclerotic risk

factors, it is of potential value to apply their combination to treat atherosclerotic vascular diseases, which need further studies in the future.

5. Ligustrazine (Chuan Xiong Qin) with Borneol (Bing Pian) Improves Cardiac Function

Ligustrazine (Chuan Xiong Qin) and borneol (Bing Pian) are the main components of the Suxiao jiuxin pill (SJP), being widely used in the treatment of angina in China and has been demonstrated to promote vasorelaxation while inhibit vasocontraction in human arteries [37]. The pre-clinical trial shows that SJP treatment protected cardiomyocytes from apoptosis and mitochondrial injury in the cell culture model of ischemic injury and promoted exosome secretion from mouse cardiac mesenchymal stem cells to improve cardiac homeostasis [38, 39]. Activated phosphoinositide 3-kinases (PI3K)/Akt/glycogen synthase kinase-3 beta (GSK3β) may mediate the SJP-induced suppression of apoptosis in cardiomyocytes [15]. Besides, SJP administration inhibited high cholesterol diet-induced dyslipidemia and atherogenesis in rats [14], which was also observed in patients in a randomized controlled trial [40]. The safety and efficacy of SJP on acute coronary syndrome also have been evaluated in double-blind clinical trials. It was reported that SJP might contribute to reducing major adverse cardiovascular events and improving heart function to better the life quality of patients suffering from acute coronary syndrome [41]. In addition to the acute coronary syndrome, clinal trials focusing on investigating the effects of SJP on myocardial infarction and microvascular obstruction have been launched; the results from these studies shall provide further insights into the efficacy of using this compound Chinese traditional medicine in patients.

6. Ligustrazine (Chuan Xiong Qin) Activates Cytochrome P450 3A4 to Improve Hepatic Metabolism of Valsartan

Valsartan is a blocker of angiotensin type-2 (Ang II) receptor, used alone or in combination with other therapeutic agents in the treatment of hypertension to lower cardiovascular mortality in patients with myocardial infarction [42,43]. Valsartan alleviated cardiomyopathy and improved heart function in patients, but the hepatic metabolism of this drug in the body is not ideal [44, 45]. Ligustrazine (Chuan Xiong Qin) pretreatment was proved to improve the metabolism of valsartan through activation of the hepatic enzyme Cytochrome P450 3A4 (CYP3A4) in SD rats [16]. The combination of valsartan and ligustrazine (Chuan Xiong Qin) indeed produced a better effect than either of them alone in the inhibition of cerebral ischemia-reperfusion-induced free radical formation and hippocampal neuronal loss in rats with vascular dementia [46]. It is of importance to study whether the cotreatment of ligustrazine (Chuan Xiong Qin) and valsartan will improve the therapeutic effects of valsartan on lowering blood pressure and improving heart function.

7. Ligustrazine (Chuan Xiong Qin) Activates 14-3-3γ to Reduce Cardiovascular Damage Caused by Doxorubicin

Doxorubicin (DOX) is an effective antineoplastic drug widely used in various adult and pediatric cancers [47]. However, DOX causes acute and chronic toxic adverse effects that are dosage dependent, and cardiotoxicity is a potentially fatal toxic side effect [48,49]. Moreover, arterial stiffness is induced in patients undergoing chemotherapy with DOX, serving as a monitor of cardiovascular events [50]. DOX causes cardiovascular damage through inducing cardiomyocyte death pathways, including autophagy, ferroptosis, pyroptosis, and apoptosis [51]. 14-3-3γ exerted beneficial effects on the protection of injured tissues, and increased expression of 14-3-3γ contributes to stabilizing mitochondrial function and partially reverses DOX-induced cardiotoxicity [52,53]. Furthermore, ligustrazine (Chuan Xiong Qin) inhibited DOX-induced endotheliotoxicity by increasing the expression of 14-3-3γ and mitochondrial function, and inhibiting oxidative stress[17], indicating that ligustrazine (Chuan Xiong Qin) might have the potential to be used as a supplement of DOX in patients receiving chemotherapy to reduce the adverse events in the cardiovascular system, thereby improving the survival rate and life quality of these patients.

8. Conclusions

In addition to wide usage in improving cardiac and vascular function, ligustrazine (Chuan Xiong Qin) has attracted attention for combined administration with other therapeutic agents due to its fewer and moderate side effects. Mechanistically, combined use with ligustrazine (Chuan Xiong Qin) achieves better therapeutic effects of the drugs such as SM (Dan Shen), BBR (Huang Lian Su), paeoniflorin (Shao Yao Dai), and borneol (Bing Pian) on cardiac and vascular injury through inhibiting the expression of inflammatory cytokines, apoptosis and angiogenesis. Furthermore, ligustrazine (Chuan Xiong Qin) administration improves the metabolic efficiency of drugs, for example, valsartan, by activating the hepatic enzyme CYP3A4, thereby improving the therapeutic effects of valsartan on hypertensive diseases. Cancer remains one of the leading causes of global death. Chemotherapy is an important therapeutic strategy in silencing tumor cells but inducing acute and chronic toxic adverse effects affecting the life quality of patients. Ligustrazine (Chuan Xiong Qin) was proven to alleviate the life-threatening cardiotoxicity induced by DOX-mediated chemotherapy via increasing 14-3-3γ and stabilizing mitochondrial function. With the strengths of lower side effects and effective functions in protecting cardiac and vascular functions, ligustrazine (Chuan Xiong Qin) shows great potential in the treatment of CVDs and protection of the heart and arteries from toxicity induced by other drugs during the treatment of other diseases.

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