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A Prospective Medication for the Treatment of Illnesses of the Cardiovascular and Neurological Systems is Stachydrine

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Abstract

In terms of effective medical treatment, cardiovascular disease (CVD), which is the leading cause of death worldwide, presents a significant obstacle. Traditional Chinese herb *Leonurus japonicus Houtt* is widely used in China to treat obstetrical and gynecological conditions like menstrual disorders, dysmenorrhea, amenorrhea, blood stasis, postpartum bleeding, and blood-related diseases like cardiovascular disease. It has been demonstrated that stachydrine, the primary alkaloid in Leonurus, has a wide range of biological activities, including antioxidant, anti-coagulant, anti-apoptotic, vasodilator, and angiogenic promoter. Also, it has been shown to enjoy remarkable benefits in the avoidance and treatment of CVD through guideline of different illness related flagging pathways and sub-atomic targets. In this exhaustive audit, we analyze the most recent pharmacological impacts and atomic components of Stachydrine in treating cardiovascular and cerebrovascular illnesses. We want to establish a solid scientific foundation for the creation of new CVD drug formulations.

Keywords: Cardiovascular disease • Cerebrovascular disease • Stachydrine • *Leonurus japonicus Houtt*

Introduction

It is well known that the leading cause of death worldwide is cardiovascular and cerebrovascular disease. Cardiovascular framework infections essentially incorporate atherosclerosis, myocardial localized necrosis, cardiovascular breakdown, and vasospasm. On the other hand, brain injury diseases like ischemic stroke and traumatic brain injury are considered cerebrovascular diseases, as are diseases of the central nervous system like depression and Alzheimer's disease. Human bodies are thought to be incomplete without the brain and heart. The heart is regarded as the sign of life in traditional Chinese medicine and is referred to as "the official of the sovereign and the great master of the five organs and six bowels." In contrast, modern medicine considers brain death to be the end of life and regards the brain as the core of the human body. Pathological changes in the heart and brain are fundamentally interconnected and mutually reinforcing, making them the greatest threats to human health and the most common causes of morbidity and mortality in both developed and developing nations [1].

Currently, nitrates, statins, beta-blockers, clopidogrel, aspirin, and ACE-I/angiotensin receptor blockers (ARBs) are the primary medications used in western medicine to treat cardiovascular disease. Patients with stable cardiovascular disease (CVD) have seen their clinical prognosis significantly improved by these medications. However, there are significant difficulties associated with the treatment burden, feasibility, and side effects of long-term use of these drugs. 60–70 percent of patients with cardio-cerebrovascular diseases still suffer from serious sequelae, such as aphasia, paralysis, and changes in facial expressions, which significantly impact the patients' quality of life. This is despite significant advancements in diagnosis and treatment over the past two decades. As a result, finding effective complementary and alternative treatments for cardio-cerebrovascular diseases is essential [2].

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Literature Review

The motherwort, *Leonurus japonicus Houtt*, is a species of the genus *Leonurus* (family Lamiaceae) that has long been used in traditional medicine in Asia, Europe, North Korea, Japan, and the United States. *Leonurus* has been used to treat obstetrical and gynecological diseases like dysmenorrhea, amenorrhea, and postpartum bleeding in traditional Chinese medicine for more than two thousand years. *Leonurus* has been found to have anti-inflammatory, antioxidant, anti-apoptotic, anti-platelet, and pro-angiogenic properties in recent pharmacological studies. These properties may be beneficial to the cardiovascular system, brain tissue, and central nervous system [1].

The primary alkaloid in *Leonurus heterophyllus* is stachydrine(STA), also known as proline betaine or N, N-dimethyl-L-proline. Its molecular structure is (2S)-1,1-dimethylpyrrolidine-2-carboxylic acid. When compared to Leonurine, its content is approximately ten times higher. Studies in recent years have demonstrated that STA has biological properties comparable to those of Leonurus, including anti-thrombotic, anti-inflammatory, and anti-oxidant, anti-apoptotic, anti-thrombotic, and cardio protective properties. As a result, STA has the potential to be a novel cardio protective agent or a cardiovascular disease adjuvant therapy [3].

It is common knowledge that proper blood flow throughout the body is dependent on the health of blood vessels. Vascular endothelial cells participate in the exchange of fluids, nutrients, and metabolites as a semipermeable barrier, as well as the release of factors associated with vasodilation and contraction, coagulation, and inflammation. They are in charge of sustaining normal circulation and vascular homeostasis. Atherosclerosis, diabetes, and hypertension are just a few of the conditions that can develop when the integrity of the vascular endothelium is compromised. As a result, endothelial dysfunction is linked to vasoconstriction, thrombosis, and inflammatory states, making it a characteristic of numerous cardio-cerebrovascular diseases. As a result, improving the function of vascular endothelial cells is an important target for the treatment of cardiovascular diseases and for expanding our knowledge of how these diseases develop [4].

By increasing the expression of GTPCH1 and DHFR, studies have demonstrated that STA could effectively improve endothelial dysfunction by reversing Hcy-induced endothelial dysfunction and preventing eNOS uncoupling. By regulating the interaction between the AMPK and Akt pathways in endothelial cells, STA can also improve the homeostasis of the intravascular environment by causing eNOS phosphorylation and vasorelaxation. By

suppressing the expression of P16INK4A (a protein involved in the senescence program) and SIRT1, STA can also prevent high glucose-induced endothelial cell senescence. This promotes enzymatic activity, increases endothelial cell survival, and enhances endothelial function [5].

Present day medication has distinguished heart hypertrophy, cardiomyocyte fibrosis, and cardiomyocyte apoptosis as normal neurotic changes in cardiovascular disease, which are free and prescient gamble factors for unfriendly cardiovascular occasions. As a result, maintaining the function of cardiomyocytes is crucial to both the prevention and treatment of cardiovascular diseases. Fortunately, significant biological activity of STA in cardiovascular disease has been demonstrated by recent pharmacological findings [4].

Although it is a potent form of compensation, myocardial hypertrophy is not unlimited. The hypertrophied myocardium's function cannot be sustained over time, resulting in heart failure. STA has been shown in studies to increase cardiomyocyte hypertrophy, which may have cardio protective effects. STA treatment significantly reduced the heart weight/body weight, cross-sectional areas, and mRNA expression of myocardial hypertrophy markers (like ANP, BNP, and -MHC) associated with cardiac hypertrophy in a rat model of norepinephrine-induced cardiac hypertrophy. The inhibition of the NF-B and JAK/STAT signaling pathways may be responsible for the reduction in cardiac hypertrophy. Moreover, in a cross over aortic choking prompted cardiovascular breakdown model, STA essentially worked on heart hypertrophy and reduced heart brokenness by hindering ROS creation and NOX_2 action, as well as by restraining enactment of the TGF-β/Smad flagging pathway, consequently further developing hemodynamic and heart diastolic capability [6].

STA has been shown to reduce cardiomyocyte surface area, the /-MHC ratio, and the expression of cardiomyocyte hypertrophy-related factors and phospholamban in in vitro experiments. Additionally, it may increase cardiomyocyte hypertrophy by lowering the Protein/DNA ratio and the amount of oxygen consumed by the myocardium. In addition, STA maintains intracellular calcium homeostasis by inhibiting the over activation of sympathetic adrenergic receptors, decreasing the expression of PLN proteins, increasing SERCA activity and SR calcium uptake, and ultimately enhancing NE-induced cardiomyocyte hypertrophy [7].

In a similar vein, in vitro experiments have shown that by inhibiting the CaN/NFAT pathway, STA can improve the phenylephrine-induced cardiomyocyte hypertrophy by reducing cardiomyocyte surface area and biomarkers of cardiac hypertrophy (ANP, BNP, -MHC/-MHC). By inhibiting the ROS/NF-B signaling pathway, it can also reduce the cellular inflammatory response and apoptosis, thereby reducing cardiomyocyte hypertrophy in neonatal rats. Through the CaMKII/HDAC4/MEF2C signaling pathway, it has also been shown to regulate p-CaMKII to inhibit nuclear output or promote nuclear input of HDAC4, enhance inhibition of MEF2C, and alleviate pressure overload-induced cardiac hypertrophy. A solid foundation has been laid by these research findings for additional STA clinical trials [8].

Cardiomyocyte fibrosis is a significant worldwide wellbeing worry that is connected to practically all types of coronary illness. The extracellular matrix's homeostasis is maintained by cardiac fibroblasts, a key type of heart cell. These cells will become myofibroblasts when they are activated, continuing to produce fibrotic properties like an excessive amount of collagen synthesis and secretion, which promotes cardiac fibrosis. Cardiomyocyte hypertrophy, apoptosis, and ventricular dilation are just a few of the pathological changes that will occur as a result of this, which will ultimately result in heart failure.

STA treatment significantly reduced the fibrotic area/total area ratio and the mRNA levels of collagen I and collagen III in the NE-induced cardiomyocyte cardiac hypertrophy model, indicating that STA has potent anti-cardiomyocyte fibrosis effects. Additionally, it prevented diastolic heart failure and improved cardiomyocyte fibrosis by inhibiting the TGF-/Smad pathway, which reduced TAC-induced interstitial and perivascular fibrosis in rat hearts. STA was also found to prevent cardiac rationale fibrosis by inhibiting the ACE/AngII/AT1R-TGF-1 pro-fibrotic axis in a model of pressure overload and angiotensin II-induced cardiac fibroblasts (CFs). This prevented cardiac fibroblast (MFs) transformation [9].

Discussion

The main part of the human nervous system is the Central Nervous System (CNS), which is made up of nerve centers in different places and doing different things. Ischemic stroke, brain injury, multiple sclerosis, Alzheimer's disease, Parkinson's disease, depression, and cerebral ischemia are just a few of the CNS-related illnesses that have emerged as a significant threat to human life and health in recent years. As the CNS is made out of various nerve cells, and these cells are fundamental for the transmission of data and the working of the CNS. In this way, safeguarding the nerve cell capability is a pivotal objective for the treatment of cerebrovascular illnesses. With a half-life of 32 minutes in the distribution phase and 190 minutes in the elimination phase, the pharmacokinetics of STA after intravenous administration to rabbits are consistent with a two-compartment model, according to studies [7].

They suggested that STA had a faster metabolism or excretion rate and was distributed from the central compartment to the peripheral compartment. *Leonurus japonicus* extract was administered orally to normal rats, and the plasma concentrations of STA and leonurine shared a similar half-life. However, the plasma concentration of STA was three times higher than that of leonurine. In a similar vein, the plasma concentration of STA was found to be higher than that of other components in the oral solution in the study of Shenyanyihao. This suggests that STA is more bioavailable than other components. In addition, pharmacokinetic studies on STA have shown that it has a high bioavailability and is absorbed and metabolized faster. In cold-stagnation and blood-stasis primary dysmenorrhoea (CSBS-PD) rats, STA also had a longer half-life (t1/2), a longer mean residence time (MRT), and a larger volume of distribution (Vd), pointing to a possible target-area distribution of STA [10].

Conclusion

To produce their therapeutic effects, modern drugs typically target a single target, which can be affected by the patient's genotype or co-morbidities. Many drugs, like aspirin and clopidogrel, have been shown to have adverse effects that depend on the patient's drug metabolism rates in clinical applications. Natural products and their derivatives, in contrast to the single targets of modern drugs, have been the focus of research. They are regarded as a valuable source of therapeutic drugs and have demonstrated unique advantages in treating a variety of intractable diseases around the world, including cardiometabolic diseases, chronic liver diseases, and chronic kidney diseases. Leonurus japonicus Houtt is one of these natural products that are used in China to improve blood flow, regulate menstruation, reduce swelling, treat fever, and detoxify.

As a result, it is referred to as "The blood's miracle drug" and "Good remedy for menstruation and obstetrics." *Leonurus heterophyllus* is used to treat anxiety disorders in Europe. Leonurine and STA are the main bioactive components in recent pharmacological studies, confirming their extensive cardio-cerebrovascular protective effects. Because of its great water dissolvability, high happy and boundless presence in different plants, STA, which has slight water solvency, low satisfied, and is just tracked down in Leonurus, is more important for innovative work than leonurine. As a result, the pharmacological effects and mechanisms of STA on the cardio-cerebrovascular system are examined in this paper. Further in-depth research is required to accelerate its comprehensive development and utilization, as well as to provide a rational scientific foundation for cardio-cerebrovascular prevention and treatment due to STA's remarkable pharmacological activities and unclear mechanisms.

Acknowledgement

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Conflicts of Interest

None.

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