Research Progress on the Treatment of Cardiovascular Diseases with Traditional Chinese Medicine *Hirudo*

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Abstract This paper systematically summarizes the main active components, pharmacological mechanisms, clinical effects, safety considerations, and precautions of *Hirudo*, aiming to provide insights and methods for its clinical application in cardiovascular disease treatment.

Key words *Hirudo*, Cardiovascular diseases, Heart disease, Traditional Chinese medicine treatment

1 Introduction

Hirudo, also known as leech, is the dried whole body of the animal *Whitmania pigra* Whitman. It has a long medicinal history, with records dating back to *Shennong's Classic of Materia Medica* which states: "It mainly expels stagnant blood and blood stasis, treats amenorrhea (recorded as water obstruction in *Imperial Readings*), breaks blood stasis and accumulations, treats infertility, benefits water passages and grows in ponds and marshes." It is classified as a lower-grade (toxic) herb due to its potent nature and slight toxicity[1]. The 2020 edition of the *Pharmacopoeia of the People's Republic of China* (Part I) specifies that *Hirudo* medicinal materials are the dried whole bodies of *W. pigra* Whitman, *H. nipponica* Whitman, or *W. acranulata* Whitman from the Hirudinidae family, possessing functions of breaking blood stasis, promoting menstruation, eliminating blood stasis, and resolving masses. *Hirudo* has an affinity for blood and particularly excels in "expelling blood stasis," demonstrating excellent effects in promoting blood circulation and dredging collaterals. Zhang Xichun once commented on its efficacy: "While excelling at breaking stagnant blood, it does not harm fresh blood. Although specialized in treating blood-related disorders, it causes no damage to the qi system." As a classic blood-breaking and stasis-removing worm-derived drug, *Hirudo* shows remarkable clinical effects and has been widely used in clinical treatments.

In recent years, with deepening understanding of modern pharmacological action, the application value of *Hirudo* in cardiovascular diseases has gained increasing attention. It has been involved in treating coronary heart disease, dilated cardiomyopathy, myocardial infarction, heart failure, *etc.* Cardiovascular diseases, as one of the high-incidence and high-mortality conditions, pose serious threats to life. Traditional treatment regimens have certain limitations, imposing significant psychological pressure and economic burdens on patients. *Hirudo* has become a research hotspot due to its unique pharmacological activity. This paper aims to systematically review current research status of *Hirudo* in treating cardiovascular diseases, providing insights and methods for its clinical application.

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2 Main active components

Hirudo contains various bioactive substances, with main therapeutic components including macromolecular active substances such as hirudin, heparin, analgesic enzymes, and hemolysins. These are single-chain polypeptides composed of 65 amino acid residues[2]. The primary antithrombotic active substances are hirudin and hemokinin[3].

As a highly effective natural thrombin-specific inhibitor, hirudin demonstrates multiple pharmacological effects including anticoagulation, antithrombosis, promotion of microvascular generation, anti-fibrosis, anti-tumor activity, anti-hyperuricemia, improvement of cerebral hemorrhage, anti-atherosclerosis, and amelioration of diabetic complications, making it applicable for clinical treatment of various diseases[4]. Chemically synthesized hirudin peptides have clear indications for diseases such as acute coronary syndrome. They are safer and more effective than heparin, showing advantages even in low-risk individuals[5].

Beyond hirudin, hyaluronidase can decompose hyaluronic acid to promote drug penetration and interstitial substance diffusion; histamine-like substances can dilate blood vessels and improve local blood circulation; protease inhibitors regulate inflammatory responses. The synergistic effects of these components form the foundation of *Hirudo*'s multifaceted pharmacological activity. Notably, differences in active component content and proportions exist among *Hirudo* varieties, origins, and processing methods, which directly affect clinical efficacy.

3 Main pharmacological effects in cardiovascular disease treatment

The main pharmacological effects related to cardiovascular disease treatment include antiplatelet aggregation, anticoagulation, and antithrombosis. Platelet aggregation is one of the causes of cardiovascular and cerebrovascular diseases. Cui Meiyue *et al.* [6] demonstrated through research that hirudin from traditional Chinese medicine significantly activates blood circulation, improves hyper-

viscosity in blood stasis model rabbits induced by high-molecular-weight dextran, and inhibits platelet aggregation. *Hirudo* shows significant effects in improving hemorheology and inhibiting platelet aggregation, holding important positive implications for treating cardiovascular and cerebrovascular diseases. Hirudin is currently the most potent anticoagulant active substance. It exerts antithrombotic effects by directly acting on thrombin to decompose and inhibit thrombus growth. As a blood-breaking and stasis-resolving Chinese medicine, it has been widely used in treating stroke, pulmonary embolism, and other diseases[7]. Chemical structure is the most influential factor in anticoagulation effects, primarily through antithrombin binding to thrombin's active site to prevent coagulation factor binding. Meanwhile, active components in *Hirudo* can also reduce platelet activity through competitive inhibition pathways[8]. Additionally, an experimental study confirmed that hirudin can exert antioxidant stress responses and protect ischemic myocardium[9].

4 Clinical applications in cardiac-related diseases

4.1 Empirical formulas for heart disease treatment

4.1.1 Coronary heart disease with angina pectoris. In the treatment of coronary heart disease with angina pectoris, Wang Yanmin conducted a controlled clinical trial comparing *Hirudo*-integrated therapy with conventional Western medicine alone. The results demonstrated that combining *Hirudo* improved clinical symptoms and enhanced therapeutic efficacy, suggesting its potential for widespread application[10]. Liu Junli[11] performed cluster analysis through data mining on core medications for coronary heart disease treatment, identifying *Hirudo* as a representative drug for resolving blood stasis and dredging collaterals.

Professor Liu Hongxu from the Cardiovascular Department of Beijing Hospital of Traditional Chinese Medicine affiliated with Capital Medical University proposed the "Yiqi Poxue" (Qi-tonifying and blood-breaking) therapy based on the "chronic disease entering collaterals" theory. His empirical formula "Shenyuan Dan," featuring the core herb pair "*Astragalus-Hirudo*" for qi-tonifying and stasis-removing, has proven effective in treating qi deficiency and blood stasis-type coronary heart disease[12-13].

Huang Haiyan[14] demonstrated through a controlled clinical trial that the self-designed Shenfu Shuizhi Decoction shows superior efficacy compared to conventional blood-activating and stasis-resolving medications in treating coronary heart disease with angina pectoris. It effectively alleviates symptoms, reduces drug side effects, and improves patients' quality of life.

National TCM Master Professor Wang Xinlu applied the "blood turbidity" theory to the syndrome differentiation treatment of coronary heart disease[15]. His prescription "Huazhuo Xingxue Decoction" consists of nine herbs: lotus leaf, cassia seed, charred hawthorn, red peony root, processed *Hirudo*, wine-processed rhubarb, *Liquidambaris fructus*, giant knotweed rhizome, and fleeceflower root, with modifications based on symptoms[16].

National TCM Master Professor Lei Zhongyi proposed the "phlegm-stasis-toxin intermingling" theory for coronary heart disease based on decades of clinical experience. His empirical formula "Danqu Fang"[17] (composed of *salvia* root, red yeast rice, *Panax notoginseng*, *Ginkgo biloba* leaves, red peony root, *Hirudo*, tree peony bark, snakegourd peel, macrostemon bulb, *pueraria* root, honey-fried *astragalus*, *coptis* root, and processed *pinellia*) employs *Hirudo* and *G. biloba* leaves for blood activation and stasis resolution. Fan Hong *et al.*[18] confirmed through clinical trials that Danqu Fang safely and effectively treats phlegm-stasis-toxin intermingling type coronary heart disease with angina pectoris, demonstrating anti-thrombotic, anti-inflammatory, lipid-regulating, and plaque-stabilizing effects while significantly improving clinical symptoms and preventing disease progression.

4.1.2 Dilated cardiomyopathy. Professor Li Qinghai developed the Guanmai Ningtong Formula for treating dilated cardiomyopathy based on the classical prescription Gualou Xiebai Banxia Decoction from *Synopsis of the Golden Chamber* (*Jin Gui Yao Lue*) and his clinical experience. This formula incorporates *P. notoginseng* (Sanqi) and *Hirudo* to activate blood circulation, remove stasis, and relieve collateral pain[19].

4.1.3 Myocardial infarction. Ouyang Jiahui *et al.*[20] employed network pharmacology to conclude that *Hirudo* may exert therapeutic effects on acute myocardial infarction (AMI) through multi-component, multi-target, and multi-pathway mechanisms, providing a theoretical foundation for its clinical application and pharmaceutical development in AMI treatment. An Xiaojun *et al.*[21] demonstrated through clinical trials that long-term low-dose administration of *Hirudo* and *Pueraria* instant granules effectively improves myocardial metabolism and enhances cardiac function. This regimen is applicable in the follow-up treatment of old myocardial infarction, showing clinical value in improving therapeutic efficacy and preventing recurrence of myocardial infarction.

4.1.4 Heart failure. Fu Qibo conducted a randomized parallel-controlled trial demonstrating that Xinbi Decoction combined with Western medicine significantly improves chronic heart failure due to coronary heart disease (characterized by qi deficiency, blood stasis, and fluid retention). Xinbi Decoction includes: *Astragalus* (Huangqi) and *Codonopsis* (Dangshen) to tonify qi; *Atractylodes* (Baizhu) and *Poria* (Fuling) to promote diuresis and calm the heart; *Carthamus tinctorius* (Honghua), *S. miltiorrhiza* (Danshen), and *Angelica sinensis* root tail (Dangguiwei) to activate blood circulation and resolve stasis; *Hirudo* (Shuizhi) to break blood stasis; *Glycyrrhiza* (Gancao) to harmonize the formula. The combined formula promotes blood circulation, resolves stasis, and revitalizes heart yang[22].

Professor Pei Zhengxue proposed that the pathogenesis of chronic congestive heart failure involves root patterns of heart qi deficiency, weakened heart yang, and qi deficiency with blood stasis, with blood stasis and fluid retention as secondary manifestations. Clinically, modified Linggui Zhugan Decoction and Gualou Xiebai

Banxia Decoction—augmented with Cinnamomi Ramulus (Guizhi), Aconiti Lateralis Praeparata (Fuzi), ginseng (Renshen), *S. miltiorrhiza* (Danshen), *Hirudo* (Shuizhi), and *C. tinctorius* (Honghua)—have shown remarkable therapeutic effects[23].

Fan Lezhi *et al.*[24] compared cases of chronic systolic heart failure treated with integrated Chinese – Western medicine over two years against those treated with Western medicine alone. The TCM regimen, incorporating blood-activating herbs like *S. miltiorrhiza* (Danshen) and *Hirudo* (Shuizhi), demonstrated effects including inhibition of cardiomyocyte apoptosis, dilation of microvessels, and reduction of blood viscosity, thereby alleviating cardiac afterload. The study concluded that integrated therapy yields superior outcomes compared to Western medicine alone[24].

4.1.5 Post-PCI applications. Bivalirudin is a 20-amino acid synthetic derivative of hirudin, designed based on the protein sequence of leech anticoagulant. It exerts its anticoagulant effect by inhibiting thrombin[25]. Bivalirudin is applicable in percutaneous coronary transluminal angioplasty (PCTA) for unstable angina, percutaneous coronary intervention (PCI), thrombolytic therapy for myocardial infarction, peripheral vascular interventions, cardiac surgeries, and heparin-induced thrombocytopenia[26-28].

4.1.6 Other applications. Professor Shang Yun, a renowned TCM expert in Shanghai, advocates the theory of "internal spleen-stomach injury with phlegm-stasis pathogenesis." He developed Huangqi Decoction as a core formula for treating cardiac disorders, including Huangqi Baoxin Decoction for asymptomatic myocardial ischemia in coronary heart disease, Huangqi Shuxin Decoction for stable angina, and Huangqi Maitong Decoction for post-stent coronary heart disease. All formulas incorporate *Hirudo* (Shuizhi) to break stasis and unblock collaterals[29].

4.2 Related Chinese patent medicines

4.2.1 Maixuekang Capsules (Enteric – Coated Tablets). Maixuekang Capsules/Tablets contain *Hirudo* (Shuizhi) sourced from *H. nipponia*. It is the only TCM product labeled with antithrombin activity units—14 units per capsule/tablet. It is used for stable angina, acute coronary syndrome, cerebral infarction, and atherosclerosis[30].

4.2.2 Danqu Capsules. Master of Traditional Chinese Medicine Lei Zhongyi developed the Danqu formula based on clinical experience to treat coronary heart disease angina pectoris with phlegm-stasis-toxin intermingling patterns. In 2015, Shaanxi Provincial Hospital of Traditional Chinese Medicine standardized it as the hospital preparation Danqu Capsules. Chen Jinfeng *et al.*[31-32] demonstrated through animal studies that Danqu Capsules are safe and effective for patients with coronary heart disease complicated by hypertension and tachycardia. They also highlighted that most components of the formula enhance immunity, improve cardiocerebral and vascular endothelial functions, and exert anti-inflammatory effects.

4.2.3 Shuizhi Tongluo Capsules. Shuizhi Tongluo Capsules are a hospital preparation from Shijiazhuang Hospital of Traditional Chinese Medicine for coronary heart disease, based on the empirical formula of senior TCM experts. Professor Li Yongxin posits that recurrent unstable angina post-PCI aligns with the pathogenesis of "root deficiency with superficial excess". The treatment principle of "tonifying qi, activating blood, resolving stasis, and unblocking collaterals" is applied, often using Shuizhi Tongluo Capsules[33].

4.2.4 Shenzhi Tongxin Capsules. Professor Zhang Shiliang developed Shenzhi Tongxin Capsules to treat chest obstruction and heart pain of qi deficiency and blood stasis patterns. Qi Luyao *et al.*[34] utilized network pharmacology to reveal that the core herb pair (Ginseng – *Hirudo*) acts through multi-component, multi-target, and multi-pathway mechanisms to inhibit dilated cardiomyopathy pathogenesis. It prevents and treats cardiac enlargement, arrhythmias, and thromboembolism, reducing sudden death risk.

4.2.5 Compound Shuizhi Powder Capsules. Li Genpei clinically formulated Compound Shuizhi Powder Capsules (containing *Hirudo*, Bear Bile, Bovis Calculus, Arisaema cum Bile, and Ginseng). Clinical observations on patients with qi stagnation and blood stasis-type coronary heart disease angina showed that the formula tonifies qi, activates blood, resolves phlegm, opens orifices, and unblocks vessels, thereby enhancing myocardial contractility[35].

5 Safety and precautions of *Hirudo* therapy

Zhou Yufeng[36] investigated the mechanism, efficacy, and safety of Gancao Decoction combined with processed *Hirudo* (Shuizhi) in treating chest obstruction and heart pain. The study found that the experimental group (Zhigancao Decoction plus low-dose processed *Hirudo*) showed superior improvements in TC, LDL-C, CRR, and LVEF indices, along with higher clinical efficacy. This indicates a synergistic effect of processed *Hirudo* in enhancing therapeutic outcomes without increasing adverse reactions. Yuan Xiaohuan *et al.*[37] conducted animal experiments demonstrating that *Hirudo* injection, prepared from *Hirudo* medicinal materials, meets pharmacopeial safety standards and holds clinical potential. Additionally, studies suggest that hirudin, compared to heparin, is a safer anticoagulant for patients undergoing PTCA due to unstable angina or post-infarction angina, reducing bleeding risks[38].

Despite the advantages of *Hirudo* therapy in treating cardiac diseases, its safety concerns should not be overlooked. Major adverse reactions include bleeding tendency, localized allergic reactions, and gastrointestinal discomfort. Bleeding is the most critical complication, particularly when used concomitantly with other anticoagulants, which increases the risk. Therefore, clinical application requires strict adherence to indications and contraindications, regular monitoring of coagulation function, and timely dose adjustments.

To mitigate risks, the following principles are recommended: start with a low initial dose and gradually increase it; avoid concurrent use with antiplatelet agents such as aspirin and clopi-

dogrel; discontinue the medication sufficiently before surgeries; and closely monitor for signs of bleeding. Special populations, including the elderly and patients with hepatic or renal impairment, should use it with caution. Additionally, standardized breeding, processing, and quality control of *Hirudo* are critical to ensuring drug safety.

6 Conclusion

As a classic worm-derived traditional Chinese medicine for "breaking blood stasis and unblocking collaterals," *Hirudo* holds significant potential in treating cardiovascular diseases. Its potent thrombolytic and collateral-activating effects effectively resolve existing thrombi, prevent recurrence, and alleviate cardiovascular symptoms. However, challenges remain. Future research should focus on: developing novel hirudin derivatives with enhanced targeting and stability; conducting large-scale multicenter clinical trials for robust efficacy evidence; optimizing combination therapies with other TCM or Western drugs; and establishing comprehensive quality standards and adverse reaction monitoring systems. With the modernization and globalization of TCM, *Hirudo* may emerge as a breakthrough in the "disease-syndrome integrated" approach for cardiovascular care, offering novel paradigms to address complex diseases.

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(From page 86)

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