REVIEW
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The chemical composition, quality control and pharmacological effects of Gualou-Xiebai-Banxia Decoction: a review

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Author contributions

All authors participated in the preparation of this review. Wang YT, Lai YY, Wang L contributed to literature review and data analyses. Zheng XL and Li HJ contributed to figures and tables. Chen SH and Xiang Z were major contributors in designing and writing the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

GXBD, Gualou-Xiebai-Banxia Decoction; TCM, traditional Chinese medicine; TF, *Trichosanthis Fructus*; AMB, *Allii Macrostemonis Bulbus*; PR, *Pinelliae Rhizoma*; CHD, coronary heart disease; CVD, cardiovascular disease; ChP, *Chinese Pharmacopoeia*; Q-markers, quality markers; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PHD, pulmonary heart disease; TG, triglycerides; LDL, low-density lipoprotein; ox-LDL, oxidized low-density lipoprotein; VEGF, vascular endothelial growth factor; PI3K, phosphoinositide 3-kinase; AMPK, AMP-activated protein kinase; AKT, protein kinase B; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; SREBP1c, Sterol regulatory element binding protein; NF-κB, nuclear factor kappaB; eNOS, endothelial nitric oxide synthase; SCD1, stearoyl-CoA Desaturase 1; AMI, acute myocardial infarction; ROS, reactive oxygen species.

Citation

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Abstract

Gualou-Xiebai-Banxia Decoction (GXBD) is a traditional Chinese herbal formula including four traditional Chinese medicines: Gualou (*Trichosanthis Fructus*, TF), Xiebai (*Allii Macrostemonis Bulbus*, AMB), Banxia (*Pinelliae Rhizoma*, PR) and yellow wine. It is a classical therapy for chest stuffiness and pain syndrome and is widely used in the clinical treatment of coronary heart disease. It also shows significant therapeutic effects on pulmonary heart disease, hyperlipidemia, and arrhythmia. This study conducted a literature review and collected information on GXBD from databases such as PubMed, Web of Science, China National Knowledge Infrastructure, and ScienceDirect. The result indicated that the main active ingredients of GXBD are steroids, flavonoids, terpenoids, alkaloids, amino acids, and organic acids. Trigonelline, macrostemonoside and cucurbitacin B can provide reference for its quality control. GXBD may exert therapeutic effects on coronary heart disease through AMPK, PI3K-AKT, oxLDL, VEGF, and NF-κB signal pathways. This review provides a comprehensive analysis and summary of the chemical composition and in vivo metabolism of three traditional Chinese medicines (TF, AMB, and PR), along with an evaluation of the chemical composition, quality control, pharmacological effects, and clinical application of GXBD. Based on these, areas requiring further research on GXBD have been proposed to provide a reference for its further development and new drug research.

Keywords: Gualou-Xiebai-Banxia Decoction; chemical composition; chest stuffiness; quality control; pharmacological mechanism

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Highlights

Gualou-Xiebai-Banxia Decoction (GXBD) has good therapeutic effects on coronary heart disease. The active components are steroids, flavonoids, terpenoids, alkaloids and organic acids. This formula can regulate multiple pathways including AMPK, P13K-AKT, and NF-κB. This review provides references for the drug development and clinical application of GXBD.

Medical history of objective

GXBD, a classical formula used for chest stuffiness and pain syndrome, is derived from Zhang Zhongjing's "*The Golden Chamber*" (Eastern Han Dynasty). Since ancient times, GXBD has been mainly used for chest tightness pain. Modern clinical studies have found that GXBD has the effects of improving myocardial ischemia, regulating blood lipids, protecting myocardium and anti-inflammation.

Background

Gualou-Xiebai-Banxia Decoction (GXBD) is a traditional Chinese herbal formula that traces its roots back to the classic medical book of *The Golden Chamber*, authored by Zhang Zhongjing, a renowned physician in the Eastern Han Dynasty. GXBD consists of *Trichosanthis Fructus* (TF), *Allii Macrostemonis Bulbus* (AMB), *Pinelliae Rhizoma* (PR), and yellow wine (Figure 1). TF is the dried ripe fruit of *Trichosanthes kirilowii* Maxim. or *Trichosanthes rosthornii* Harms, plants of the *Cucurbitaceae* family. AMB is the dried bulb of *Allium macrostemon* Bge. or *Allium chinense* G. Don, plants of the *Liliaceae* family. PR is the dried tuber of *Pinellia ternata* (Thunb.) Breit., a plant of the *Araceae* family. In *The Golden Chamber*, it is recorded that GXBD includes TF, AMB, PR and "Baijiu". "Baijiu" has been verified to be modern yellow wine [1]. GXBD is one of the classic formulas listed in the *Catalogue of Ancient Classical Formulas* (*First Batch*), published by the National Administration of Traditional Chinese Medicine in 2018 [2].

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, responsible for 32% of all global deaths [3, 4]. Coronary heart disease (CHD), as a type of CVD, is resulted from atherosclerosis (plaque accumulation) in the coronary arteries that narrow or blocks the blood vessels, further causing ischemia (lack of oxygen), hypoxia (low oxygen), or necrosis (death) of the heart muscle. From the early to the mid-20th century, the mortality from heart disease increased due to the growing number of CHD patients caused by the increased prevalence of coronary artery atherosclerosis [5]. The data from the China Health and Wellness Statistical Yearbook 2020 showed that the death rate of CHD among urban dwellers in China was 121.59 per million in 2019, while that among rural residents was 130.14 per million [6]. CHD has become a major public health problem that threaten people's physical health. China has a large population of CHD patients, and the mortality rate of CHD has been increasing yearly. The medical burden and economic burden of CHD are hefty for both the country and individuals [7, 8]. Typically, CHD patients undergo extended periods of medication as a prevailing approach in modern clinical treatment. Nevertheless, this method often presents significant challenges, resulting in unfavorable encounters for individuals receiving the treatment. However, serious side effects, poor compliance, low quality of life, and high re-occlusion rate are important challenges faced by CHD treatment. On the other hand, traditional Chinese medicine (TCM) provides a novel and valuable therapy for CHD and similar symptoms.

In addition, GXBD can be modified with *Mori Cortex*, *Acorus Calamus* L., *Descurainiae Semen*, *Lepidii Semen*, *Poria* and other herbs to treat pulmonary heart disease (PHD) [9]; adding *Glycyrrhizae Radix Et Rhizoma*, *Ephedrae Herba*, *Pseudostellariae Radix* and other herbs to treat chronic PHD [10]; adding *Salviae Miltiorrhizae Radix et Rhizoma* and *Astragalus* and other herbs that can treat coronary atherosclerotic heart disease and diabetes caused by liver and kidney yin deficiency [11]; adding *Arisaema*, *Platycodon*, *Mori Cortex*, *Houttuyniae Herba*, *Lonicerae Japonicae Flos*, *Scutellariae Radix*, *Aurantii Fructus*, winter melon seed, *Armeniacae Semen Amarum* and other herbs to treat acute exacerbation of chronic PHD [12]; adding *Aurantii Fructus Immaturus*, *Salviae Miltiorrhizae Radix Et Rhizoma*, *Santali Albi Lignum* and other herbs to treat angina pectoris of coronary atherosclerotic heart disease, etc. [13, 14]. In addition to GXBD, Zhishi-Xiebai-Guizhi Decoction (ZXGD) and Dan-Lou prescription are also derived from the two herbs of TF and AMB. Modern clinical studies have shown that ZXGD also has good therapeutic effects in treating CVDs [15, 16]. Dan-Lou prescription is a formula composed of TF, AMB, and other herbs such as *Puerariae Lobatae Radix*, *Chuanxiong Rhizoma*, and *Astragali Radix*. The Chinese patent medicine Dan-Lou tablet is made from it and has been widely used in clinical practice [17, 18]. The above studies show that the modified formula of GXBD can be used to treat atherosclerotic heart disease, PHD, chronic cardiogenic heart disease and other diseases.

To develop TCM and better serve people's health, profound research on GXBD is essential. Therefore, the article reviews the chemical constituents, metabolism, pharmacological effects, and clinical applications of GXBD, aiming to provide references for the new drug development and in-depth research of it.

Material and method

Using Chinese or English as the retrieval language, search PubMed, Web of Science, China National Knowledge Infrastructure, and ScienceDirect databases for the source, composition, chemical constituents, pharmacological effects, mechanism of action, and clinical application of GXBD. The search keywords include GXBD, chemical constituents, CHD, metabolites, signaling pathways, quality standards, and clinical applications. All references in this work are from experimental studies published before April 2023.

Compound constituents and metabolites

According to the literature reports, the main active ingredients of GXBD are steroidal compounds, flavonoids, nitrogen compounds, terpenoids, alkaloids, amino acids and organic acids. Li et al. detected the components of GXBD by UPLC-ESI-LTQ-Orbitrap-MS, identified 88 chemical constituents, including 11 flavonoids, 11 amino acids, 18 alkaloids and nitrogen compounds, 19 organic acids, 9 volatile oils and lipids, 3 sugars, 5 cyclic peptides, 3 steroidal saponins, 2 terpenoids, and 7 other compounds [19]. Xiang et al. and Wang et al. analyzed the components of GXBD using UPLC-Q-TOF/MS [20, 21]. Xiang et al. identified 49 chemical constituents, including 7 terpenoids, 6 flavonoids, 5 alkaloids, 17 organic acids, 8 steroids and

Figure 1 Formulation of Gualou Xiebai Banxia Decoction

steroidal saponins, 2 nucleosides, and 4 other compounds. Among them, adenosine, cucurbitacin B, quercetin, ephedrine, scutellarein, chrysoeriol, and prostaglandin A1 were confirmed by standard comparison. Wang et al. identified 28 constituents, including 5 nucleosides, 10 alkaloids, 3 flavonoids, 3 amino acids and 7 other compounds. The detailed components and the structures are shown in Supplementary Table S1 [19–23].

Some metabolites in TCM may also play a therapeutic role as active substances. The phase I metabolic reactions of GXBD mainly include dehydration, deglycosylation, dehydrogenation, hydroxylation, and hydrolysis. Phase II metabolic reactions mainly involve acetylation, taurine regulation, hydroxymethylation, and sulfate regulation pathways [23]. Li et al. and Xiang et al. identified the metabolites of GXBD by detecting the plasma, urine and feces of SD rats. Li et al. detected 12 metabolites, namely paeonol-sulfation, apigenin-sulfation, luteolin-sulfation, apigenin-methylation, luteolin-methylation, pinellianamide-sulfation, nicotinic acid-glucuronic acid conjugation, 4-hydroxynicotinic acid-sulfation, pinellianamide-dehydroxylation, cucurbitic acid-methylation, chrysosplenol D-methylation, (-)-secoisolariciresinol-dehydroxylation. These metabolites are produced by both phase I and phase II metabolism. In addition to plasma, urine and feces samples, Xiang et al. also analyzed the bile samples of SD rats, and found 129 metabolites, of which 83 in plasma samples, 39 in urine samples, 25 in bile samples, and 9 in feces samples. Steroids and steroidal saponins were detected in plasma, urine and feces samples; terpenoid metabolites were mainly present in plasma and bile, and were metabolized by phase II metabolism; nucleoside components were detected in urine and feces. In summary, the in vivo metabolic process of GXBD is a result of the combined activity of phase I and phase II metabolism.

Quality control

Quality control is a critical factor for the clinical efficacy of TCM [24]. However, GXBD and its preparations have not been included in the *Chinese Pharmacopoeia* (ChP), and the index components of single herbs have yet to be listed in the 2020 edition. In the 2020 edition of the ChP, thin-layer chromatography was used to identify TF, AMB, and PR qualitatively in GXBD. TF and AMB used the comparator product to prepare reference solutions, and PR's reference solution was prepared with comparator product as well as a mixture of alanine, valine, and leucine reference solutions as another reference solution. ChP requires spots of the same color to appear in the chromatogram of the test substance at the corresponding position to the chromatogram of the reference substance.

To improve the quality and quality control level of Chinese medicine products in China, Academician Liu Changxiao introduced a new concept of quality markers (Q-markers) for TCM in 2016 [25]. Q-markers are chemical substances inherent in TCM materials and products or formed during the preparation process; they are closely related to the functional properties of TCM. Q-markers consider the characteristics of TCM system, such as biological attributes, manufacturing process, and compatibility theory, and create a new model of TCM quality research. Since 1977, 46 terpenoids, 29 steroids, 22 flavonoids, 28 nitrogen compounds, 8 lignans and 29 other compounds have been identified from TF [26]. Among them, terpenoids, steroids, and nitrogen compounds may be the main active ingredients, with important biological characteristics. From the analysis of the specificity of the components, the tetracyclic and pentacyclic triterpenoids in TF are located downstream of the biosynthetic pathway, with strong specificity. Triterpenoids are useful for identifying the quality of TF since they are significant chemical indicators for Cucurbitaceae plants [27]. On the other hand, flavonoids are also active components of TF. Although some certain flavonoids are found in various plants and therefore not suitable as Q-markers for TF, some flavonoids with limited occurrence, such as luteolin-3'-O-β-glucoside, quercetin-3-O-[α-L-rhamnosyl-(1→2)-β-D-glucosyl]-5-O-β-D-glucoside, 4',6-dihydroxy-4-methoxyisoaurone, can be regarded as potential Q-markers of TF [28]. Steroidal saponins, flavonoids, alkaloids, volatile oils, polysaccharides, organic acids, and amino acids are the main constituents of AMB. Among them, steroidal saponins, sulfur-containing compounds and nitrogen compounds are the most active [29]. The current research on Q-markers of AMB mainly focuses on detecting furostanol saponins, adenosine and other components [30, 31]. It has also been shown that GC-MS analysis revealed the presence of sulfur-containing compounds as the major volatile oil components in AMB [32].

PR mainly contains nucleosides, alkaloids, organic acids, proteins, amino acids, polysaccharides, volatile oils and other components. The components reported to be related to the efficacy and quality of PR are mainly nucleosides, alkaloids, and organic acids [33–35]. In 1999, Wu et al. used acid-base titration to determine the content of calcium oxalate crystals in PR. They proposed that this could be used as an indicator to control the degree of processing, and combined with the traditional experience of slight or no pungent sensation in the mouth to control the quality of processed products [36]. Yang et al. identified five characteristic peaks in establishing the HPLC fingerprint of PR, namely inosine, guanosine, adenosine, succinic acid and ephedrine hydrochloride [37]. Zhang et al. developed a molecular detection method based on species-specific nucleotide markers and primers, using PCR technology to identify the specific nucleotide sequences in PR, aiming to identify the authenticity of PR [38]. PR total alkaloids have various pharmacological activities, and are closely related to the main effects of PR. Some studies used ultraviolet spectrophotometry to calculate the content of PR total alkaloids with ephedrine hydrochloride as the reference substance [39]. The content of PR total alkaloids or a specific alkaloid can be used as one of the detection items for quality control of PR.

At present, some works of literature have indicated that the pharmacological activities of some compounds in GXBD are consistent with the main efficacy of this formula such as adenosine, which dilates blood vessels and reduces blood pressure [40]; alliin plays an important role in anti-CVDs; macrostemonoside has significant platelet activity [41, 42]; nicotinamide can effectively prevent oxidative stress damage of cardiac vascular endothelial cells [43]; trigonelline has the effect of lowering cholesterol [44]; cucurbitacin B can effectively prevent myocardial hypertrophy and fibrosis, and enhance myocardial contractility and relaxation [45]. These compounds can provide reference for the quality control of GXBD.

Pharmacodynamics and mechanism of action

Pharmacodynamics

As the main formula of TCM treatment, GXBD has also attracted more and more attention with the gradual increase in the incidence of CHD. The research on the efficacy and mechanism of GXBD is also increasing year by year. The reported effects include improving myocardial ischemia, regulating blood lipids, protecting myocardium, and anti-inflammation. The experimental subjects include Wistar rats, SD rats, ApoE$^{-/-}$ mice, CHD patients, and myocardial ischemia patients. The administration methods vary according to the experimental subjects. When the experimental subjects are rats or mice, the administration methods usually adopt gavage; when they are humans or miniature swine, oral administration is adopted. The administration dose of mice, rats or miniature swine ranges from 2.68 to 20 g/kg/d or 10–20 mL/kg/d, while the oral dose for human patients is usually one dose per day. In the study of myocardial protection effect, sometimes myocardial cells are chosen as experimental subjects (Table 1) [46–68].

Mechanism of action

The signal pathways that GXBD can regulate have been reported mainly include AMPK signal pathway, PI3K-AKT signal pathway, oxLDL signal pathway, VEGF signal pathway, NF-κB signal pathway [46, 47, 52, 68–74]. The crosstalk among various pathways is shown in Figure 2.

Table 1 The pharmacodynamics of GXBD

Pharmacodynamics	Experimental subjects	Administration methods	Experimental result	References
Improve myocardial ischemia	Male Wistar rats	10 mL/kg, 7 days i.g.	GXBD mitigated endothelial progenitor cells apoptosis.	[46]
	Male Wistar rats	20 g/kg/d i.g.	GXBD regulated the mobilization of bone marrow endothelial progenitor cells.	[47]
	Patients with transient myocardial ischemia	1 dose per day, taken orally for 4 weeks	GXBD improved patient cardiac function and alleviated clinical conditions.	[48]
	Patients with acute myocardial ischemia	1 dose per day, taken orally for 30–45 days	GXBD improved symptoms of myocardial ischemia in patients.	[49]
Regulating blood lipids	Male Wistar rats	5 g/kg, 7 days i.g.	GXBD improved P407-induced hyperlipidemia, including increased plasma triglycerides (TGs), aspartate aminotransferase elevation, and lipid accumulation.	[50]
	ApoE$^{-/-}$ male mice	20 mL/kg, 8 weeks i.g.	GXBD can significantly improve lipid metabolism and oxidative stress on AS mice.	[51]
	Patients with CHD and angina pectoris	1 dose per day, taken orally for 30 days	GXBD can improve oxidative stress indexes and adjust the levels of endothelin-1, nitric oxide, cardiac troponin I, and von Willebrand Factor.	[52]
Regulating blood lipids	Patients with CHD and angina pectoris	1 dose per day, taken orally for 4 weeks	GXBD has a significant effect on improving the patients' clinical conditions and maintaining the balance of the blood lipid level.	[13]
	Patients with CHD and dyslipidemia	2 dose per day, taken orally for 8 weeks	GXBD is a useful and potent therapy for CHD patients with dyslipidemia.	[53]
	Patients with CHD and angina pectoris	1 dose per day, taken orally for 30 days	GXBD can efficiently lower the occurrence and length of angina episodes, regulate blood lipid levels, and improve prognosis.	[54]
	Patient with CHD	1 dose per day, taken orally for 4 weeks	GXBD can efficiently lower the values of blood lipids and hemorheology markers.	[55]
	Patients with CHD and angina pectoris	1 dose per day, taken orally for 30 days	GXBD can significantly improve the values of blood lipids and hemorheology.	[56]
Myocardial protection effect	Cardiac myocytes of the neonatal rats within 3 days	GXBD with a series of concentrations	GXBD has a significant protective effect on myocardial cells injured by ischemia and hypoxia, and the protective effect is dose-dependent.	[57]
	Cardiac myocytes of the neonatal rats within 3 days	GXBD with a series of concentrations	GXBD have significant protective effects on myocardial cells injured by ischemia and hypoxia.	[58]
	Male SD rats	2.68 g/kg/d, 8 weeks i.g.	GXBD can enhance heart function, lower myocardial fibrosis and delay the progression of heart failure.	[59]
	Chinese Experimental miniature swine	3 g/kg/d, taken orally for 8 weeks	GXBD exhibits a remarkable anti-apoptotic effect on the myocardium in miniature swine with phlegm and blood stasis type CHD model.	[60]
Lower blood pressure	Patients with hypertension and CHD	1 dose per day, taken orally for 4 weeks	GXBD reduces blood pressure and blood lipid levels, and regulates immune function.	[61]
	Patients with hypertension and CHD	1 dose per day, taken orally for 4 weeks	GXBD can improve patients' blood pressure levels and lower blood lipid levels.	[62]
	Patients with hypertension and CHD	1 dose per day, taken orally for 4 weeks	GXBD can significantly improve patients' blood lipid and blood pressure levels, and regulate their heart rate.	[63]
	Patients with hypertension and CHD	1 dose per day, taken orally for 4 weeks	GXBD can lower blood pressure and enhance blood lipid levels.	[64]
Anti-inflammatory	Unstable angina pectoris	1 dose per day, taken orally for 2 weeks	GXBD can reduce patients' inflammatory response.	[65]
	SD rats	12.48 mg/g, 4 weeks	GXBD can suppress the inflammation of CAG rats by downregulating JAK2/STAT3 pathway and upregulating Hh signal pathway.	[66]
	Patients with CHD and angina pectoris	1 dose per day, taken orally for 1 month	GXBD can lower the amounts of inflammatory agents in patients, thus alleviating the signs of angina.	[67]
	Patients with stable angina pectoris	1 dose per day, taken orally for 2 weeks	GXBD can efficiently relieve the symptoms and signs of patients, adjust coronary microcirculation and blood rheology, reduce inflammatory responses.	[68]

GXBD, Gualou-Xiebai-Banxia Decoction; CHD, coronary heart disease; TGs, triglycerides.

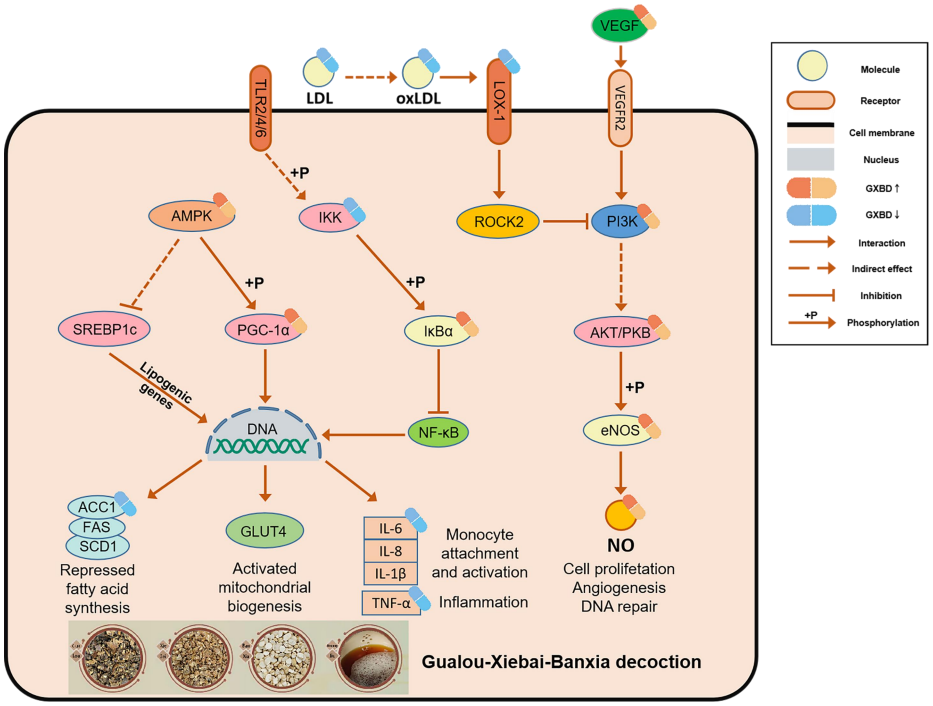

Figure 2 Regulatory mechanism network of GXBD. LDL, low-density lipoprotein; ox-LDL, oxidized low-density lipoprotein; VEGF, vascular endothelial growth factor; PI3K, phosphoinositide 3-kinase; AMPK, AMP-activated protein kinase; AKT, protein kinase B; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; SREBP1c, Sterol regulatory element binding protein; NF-κB, nuclear factor kappaB; eNOS, endothelial nitric oxide synthase; GXBD, Gualou-Xiebai-Banxia Decoction; GLUT4, glucosetransporter4; FAS, fatty acid synthase; ACC1, acetyl coA carboxylase 1; SCD1, stearoyl-CoA desaturase 1; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8.

AMPK pathway. AMP-activated protein kinase (AMPK) is a key enzyme that controls cellular energy homeostasis. Besides maintaining intracellular energy balance, it can also regulate systemic energy metabolism [75]. AMPK can maintain energy balance by stimulating metabolic pathways that produce adenosine triphosphate and suppressing metabolic pathways that consume adenosine triphosphate in reaction to binding adenosine monophosphate and adenosine diphosphate. Sterol regulatory element binding protein (SREBP1c) is a crucial transcription factor in lipid formation, which can activate key enzymes of lipid synthesis such as fatty acid synthase (FAS), acetyl coA carboxylase 1 (ACC1), and stearoyl-CoA Desaturase 1 (SCD1), leading to lipid accumulation. AMPK can indirectly inhibit the activity of SREBP1c. RT-qPCR and Western blot analysis showed that GXBD could reduce the mRNA expression of *SCD1*, *ACC1*, and *FAS* [50]. *SCD1* is involved in the last step of TG synthesis in the liver. Thus, the lipid-lowering effect of GXBD can be explained by suppressing these lipogenic genes.

Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a crucial cellular signal that regulates energy and nutrient balance. It can strongly regulate gene expression upon activation, stimulate mitochondrial oxidative metabolism in brown adipose tissue, and AMPK can directly enhance the expression of PGC-1α by phosphorylation [76]. The reduction of *PGC-1α* transcriptional expression and activity can lead to dysfunction of energy metabolism in cardiomyocytes, which is also thought to be one of the causes of cardiac dysfunction after myocardial damage [77–79]. Western blot analysis results showed that GXBD could upregulate the expression of AMPK, PGC-1α and other proteins in myocardial tissue, improve mitochondrial dysfunction, and provide experimental basis for exploring the mechanism of prevention and treatment of myocardial injury by GXBD [69].

PI3K-AKT pathway. PI3K-AKT is a key signal pathway for maintaining cell survival, which is widely present in various cells and involved in regulating cell proliferation, differentiation, apoptosis and other physiological processes [80]. Activated PI3K can transform phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3). As a second messenger, PIP3 can activate protein kinase B (AKT) by protein kinase D1 (PKD1) phosphorylation, which then induces the phosphorylation of downstream endothelial nitric oxide synthase (eNOS) [80]. eNOS can catalyze NO production in the activated state, and the generated NO can participate in cell proliferation and angiogenesis processes. Under excessive oxidative stress, eNOS will be inactivated and catalyze the production of O_2^- instead of NO, leading to cell apoptosis [81]. RT-PCR and Western blot analysis results showed that GXBD may stimulate PI3K-AKT signal pathway and increase the expression and phosphorylation levels of phosphoinositide 3-kinase (PI3K), AKT, eNOS proteins in rat myocardial tissue, increase the mRNA expression levels of *PI3K*, *AKT* and *eNOS* genes, significantly reduce myocardial pathological injury, and exert protective effect on type 2 diabetes mellitus-acute myocardial infarction (AMI), indicating that the efficacy of GXBD is closely related to PI3K-AKT signal pathway [46, 70].

ox-LDL pathway. Atherosclerosis is a long-term inflammatory condition that involves the accumulation of fats and immune cells in the artery wall. Oxidative stress increases when there is an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant ability, which causes endothelial dysfunction, a major factor in the formation of atherosclerosis [82]. Conditions such as hypertension, diabetes, dyslipidemia and others can lead to increased ROS generation in the vascular wall [83]. Increased ROS can turn low-density lipoprotein (LDL) into oxidized low-density lipoprotein (ox-LDL), an important factor in causing atherosclerosis. ox-LDL acts on various cells, such as endothelial cells, macrophages, fibroblasts, and others, through the transmembrane glycoprotein LOX-1, causing these cells to produce ROS [84, 85]. Elevated ROS can act as second messengers, directly affect endothelial cells, causing NO inactivation and nuclear factor kappaB (NF-κB) activation, membrane lipid peroxidation [86, 87]. ox-LDL interacts with vascular endothelial cells, causing endothelial cell damage and endothelial dysfunction, which is an important pathological process that triggers atherosclerosis. Western blot and RT-PCR analysis showed that after treatment with GXBD, the serum ox-LDL level of $ApoE^{-/-}$ mice was

significantly reduced, and the protein and mRNA expression levels of *Lox-1* in the aorta were decreased [51, 71]. These results indicate that GXBD can interfere with the ox-LDL pathway, inhibit Lox-1-mediated ox-LDL-induced oxidative stress damage, and play an anti-atherosclerotic mechanism.

VEGF pathway. Vascular endothelial growth factor (VEGF), also called vascular permeability factor (VPF), has a crucial function in forming new blood vessels. In 1983, Senger et al. described a factor secreted by tumors that increased vascular permeability and named it "VPF" [88]. Later, it was found that it could affect the mitosis of endothelial cells and proposed the name VEGF. Endothelial cells, macrophages, fibroblasts and others can produce VEGF [89]. VEGF is a growth factor that targets vascular endothelial cells exclusively, which increases vascular permeability, promoting endothelial cell migration, proliferation and angiogenesis. The receptors that have a high affinity for vascular endothelial growth factors are known as vascular endothelial growth factor receptors (VEGFR), which are mainly classified into VEGFR-1, VEGFR-2 and VEGFR-3. VEGFR-2 is present in vascular and lymphatic endothelium and others and can directly or indirectly activate the PI3K-AKT pathway for cell proliferation and angiogenesis under the action of VEGF. Zheng et al. found that GXBD may regulate the mobilization of bone marrow EPCs by up-regulating the expression or secretion of VEGF, eNOS and NO in the plasma of Wistar rats through the VEGF pathway [47]. Promoting EPC mobilization manifests GXBD's efficacy at the progenitor cell level.

NF-κB pathway. NF-κB is a major controller of immune response, inflammation and cancer. NF-κB is the hub protein of this pathway, which regulates gene expression by receiving various cytokine stimuli [90]. Various cytokines (such as ox-LDL) participate in signal transduction and phosphorylate inhibitor of kappa B kinase (IKK), which further phosphorylates recombinant inhibitory subunit of NF-κB alpha (IκBα). The latter is degraded by proteasome through ubiquitination after phosphorylation, thus activating NF-κB. Activated NF-κB increases the production of inflammatory factors (such as TNF-α, IL-1β, IL-6, IL-8), thus triggering inflammation. In addition, ROS can also indirectly act on Src, affecting the signal transduction of downstream pathways and indirectly activating NF-κB. Research has shown that GXBD can lower the levels of inflammatory factors TNF-α, IL-8, IL-1β, IL-6, decrease the expression of IKK protein and increase the expression level of IκBα, and suppress the activation of NF-κB and inflammation [68, 73, 74].

Clinical application

GXBD is a classical formula from Zhang Zhongjing's the *The Golden Chamber*, recorded as the main formula for treating chest stuffiness and pain syndrome. In addition to its application in treating CHD in modern clinical practice, GXBD is also used for PHD, hyperlipidemia, viral myocarditis, arrhythmia, gastritis, cholecystitis, mammary gland hyperplasia, and other diseases. On Chinese Clinical Trial Registry website (www.chictr.org.cn/), we can retrieve two registration information relating to GXBD, as shown in Table 2.

CHD

CHD is categorized as chest stuffiness and pain syndrome in TCM system, and GXBD also has a positive effect on treating modern CHD. He et al. randomly divided 110 patients with CHD angina pectoris into treatment group and control group. The treatment group received GXBD, and the control group received Xiaoxintong (a nitrate anti-angina drug) [91]. The results indicated that the total effective rate of GXBD treatment group was about 20% more than that of the control group, reaching 86.21%, with good effect and no apparent toxic and side effects. Du et al. divided 68 patients with CHD complicated with carotid artery plaque into groups for treatment. The control group got conventional western medicine treatment, and the treatment group got GXBD on top of that [92]. After treatment with GXBD, the plaque area, pulse wave velocity and blood lipid level of the treatment group were improved compared with those of simple western medicine treatment, which confirmed the clear therapeutic effect of GXBD on CHD. Tian et al. randomly assigned 86 patients with recurrent angina after PCI to two groups: the control group (43 cases), which received standard western medicine therapy, and the treatment group (43 cases), which received modified GXBD in addition to the control group therapy [93]. The results showed that modified GXBD significantly improved TCM symptoms, angina attack times, degree, and electrocardiogram indicators of patients with recurrent angina after PCI. Zhu et al. randomly allocated 60 patients with CHD angina to two groups of 30 cases each. Both groups received standard western medicine therapy, and the treatment group also received modified GXBD for a duration of four weeks [94]. Both groups showed improvement in the symptoms of chest tightness, chest pain and palpitation after therapy, and the improvement was more pronounced in the GXBD intervention group, with a statistically significant difference. The above studies showed that GXBD had significant therapeutic effect on CHD.

PHD

PHD is a cardiac disorder mainly caused by pulmonary arterial hypertension due to bronchopulmonary or pulmonary vascular lesions. According to the onset and course of the disease, it can be divided into acute and chronic types, with the latter being more common in clinical practice. PHD develops slowly and clinically with various symptoms and sins of the original pulmonary or thoracic diseases. It mainly manifests as progressive pulmonary and cardiac failure and damage to other organs. Zhao Yingyun treated patients with PHD according to different stages of onset (ventilation disorder stage, ventilation disorder stage and circulation disorder stage), and stopped using western medicine during this period. The total effective rate reached 96% [9]. Among them, 18 patients were followed up for more than five years and their condition was stable without recurrence. Wang et al. selected 93 patients with acute onset of PHD and gave them the same western medicine treatment. The treatment group was administrated GXBD [95]. Both groups showed significant improvement in the indicators after therapy and the treatment group was superior to the control group, which demonstrated the definite therapeutic effect of GXBD on the acute onset of PHD.

Hyperlipidemia

Hyperlipidemia is a common and heterogeneous disease in middle-aged and elderly people. It is one of the primary causes of atherosclerosis, CHD, and cerebrovascular disease. It also serves as the pathological basis for the emergence and evolution of CHD and cerebrovascular disease. The main manifestation of hyperlipidemia is the elevation of cholesterol or TG levels in plasma. Most of them have no typical symptoms. It is prone to occur in people who drink alcohol,

Table 2 Clinical trial registration information of GXBD

Registration number	Public title	Study type	Date of registration
ChiCTR2300073548	Based on "phlegm-stasis and collateralization" to explore the efficacy of Gualou-Xiebai-Banxia Decoction in the treatment of COPD related pulmonary hypertension and the study of intestinal bacteria-metabolism.	Interventional study	2023-07-14
ChiCTR-INR-16009944	Clinical observation on treatment of carotid artery atherosclerosis with Gualou Xiebai Banxia Decoction and Hongqu.	Interventional study	2016-11-21

smoke, are overweight, obese, and have diabetes. Wang et al. selected 100 patients, including 41 cases of simple hyperlipidemia, 22 cases of hypertension, 3 cases of fatty liver, 15 cases of CHD, and 12 cases of cerebral arteriosclerosis [96]. The patients took GXBD and modified herbs, one dose per day, for two consecutive months. After treatment, the plasma levels of cholesterol (TC) and TG were decreased in the patients, and the total effective rate was 98%, 17% higher than that of the control group. Wang et al. and Wang Min et al. also found that GXBD could lower the plasma levels of TC, TG, and low-density lipoprotein cholesterol, enhance the blood rheology of the patients [56, 97].

Arrhythmia

Arrhythmia is an irregular heartbeat caused by abnormal electrical conduction system of the heart, which influences the initiation and (or) conduction of cardiac activity, leading to abnormal frequency and (or) rhythm of the heart. Arrhythmia patients often have palpitations, dyspnea or chest tightness symptoms, which belong to the category of palpitations in TCM system. Cui et al. studied the efficacy of GXBD combined with amiodarone in the therapeutic effect of treating ventricular arrhythmia complicated by AMI [98]. 78 patients with AMI complicated by ventricular arrhythmia were randomly and averagely divided into two groups. The control group was administrated conventional western medicine plus amiodarone, and the observation group was administrated orally GXBD plus or minus administration on the top of the control group. After treatment, the heart rate variability indexes, inflammatory factor levels and total effective rate of the observation group were remarkably higher than those of the control group. The total effective rate was 92.31%, and 20.5% higher than that of the control group. Yang et al. also selected 68 patients for the study. After two weeks of treatment, 61.7% of the patients had no palpitation symptoms and 29.4% had reduced symptoms [99].

Other diseases

In addition to the above clinical applications, GXBD has also been used to treat chronic obstructive pulmonary disease, chronic atrophic gastritis, depression, ischemic stroke, pulmonary interstitial fibrosis, chronic heart failure, chest rib injury, etc. [100–106]. Still, in modern clinical practice, the primary clinical research is on the treatment of CHD.

Advantages and potential challenge

The toxicity of TCM is an essential aspect of quality control research. GXBD consists of TF, AMB, PR, and yellow wine. PR, a toxic TCM, can cause severe oral irritation and throat pain when ingested directly. For safety reasons, clinicians often use processed forms of PR in clinical practice. Although the addition of Alumen during processing can reduce the toxicity of PR, it does not completely eliminate it. Therefore, the toxicity control of processed PR is the challenge facing the clinical application of GXBD. In addition, the permissible limit of Alumen in the processed PR is also an important consideration for quality control.

Although there is extensive research on the clinical treatment of GXBD, the administered dosage form for participants remains traditional decoction. Traditional decoction are inconvenient for transportation and storage. If a new dosage form, such as tablets, granules, or other formulations, could be developed, patient compliance would significantly improve. This development would play a crucial role in advancing the clinical application of GXBD.

Conclusion

GXBD is a main formula for treating chest stuffiness and pain syndrome, consisting of TF, AMB, PR and yellow wine. The main active ingredients include steroidal compounds, flavonoids, nitrogen compounds, terpenoids, alkaloids, amino acids, and organic acids, among which cucurbitacin B, adenosine, macrostemonoside, vanillic acid, alliin, nicotinamide, trigonelline and others may be quality control markers. In addition to treating CHD, GXBD also significantly affects on chronic obstructive pulmonary disease, chronic atrophic gastritis, depression, ischemic stroke, pulmonary interstitial fibrosis, chronic heart failure, chest rib injury, and other diseases. At present, the main clinical research is still on the treatment of CHD. So far, the reported pathways involved in the mechanism of action of GXBD include AMPK signaling pathway, PI3K-AKT signaling pathway, oxLDL signaling pathway, VEGF signaling pathway, NF-κB signaling pathway, but which specific components are involved still need more in-depth research. New dosage forms of GXBD have not been developed, which hinder its clinical application. If it is made into tablets, granules, or other dosage forms, the patient's compliance will significantly improve. In addition, there is no record of the content determination standards of TF, AMB and PR single herbs in ChP, which leads to the lack of quality standards for GXBD formula. In summary, this article reviews the chemical components, quality control, pharmacological mechanisms and clinical applications of GXBD, aiming to provide reference for its future development and research.

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