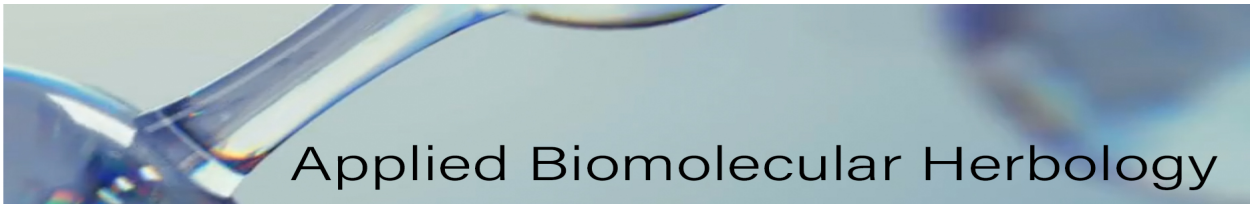
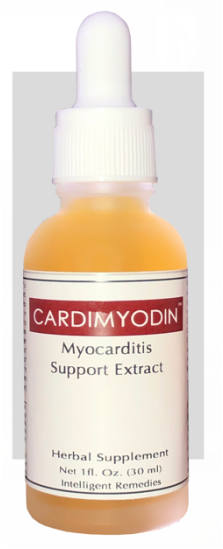


CARDIMYODIN

Product Information



Cardimyodin Formula is designed to attenuate inflammation of the heart muscle from viral myocarditis, caused by the S-Spike protein found in the Covid virus and other inoculation-based sources. Contains phytotherapeutic extracts of ***Crocus autumnale, Panax quintifolius, Astragalus membracanus, Zingiber officinalis, Ganoderma lucidum and Cinnamomum verum.*** This is a synergistic herbal formula known to alleviate heart inflammation.

Myocarditis Inflammation is common after acute myocardial infarction (AMI). The massive loss of myocardium through cell necrosis, apoptosis, and autophagy activates a strong inflammatory response that develops due to recruitment of inflammatory cells and induction of the expression of inflammatory cytokines and chemokines. Myocardial necrosis with subsequent endogenous inflammation, leads to myocardial damage, ventricular dilation, and dysfunction.

Crocus autumnale, Contains Colchicine, a well-established anti-inflammatory drug that is commonly used to treat gout, and it also targets the inflammasome. Colchicine is also used as a treatment for pericarditis. It may exert multipotent anti-inflammatory effects, particularly by inhibiting neutrophils migration, and may also have direct anti-inflammatory effects by inhibiting key inflammatory signaling networks called inflammasomes and proinflammatory cytokines.

Panax quintifolius, ginseng is widely used in Asia to treat cardiovascular diseases (CVD)3. Studies have shown that ginseng can inhibit cardiomyocyte hypertrophy and heart failure (HF)4 and prevent cardiac dysfunction.

Ganoderma lucidum G. lucidum possess antioxidative, antihypertensive, hypoglycemic, lipid-lowering, and anti-inflammatory properties. In particular triterpenoids and polysaccharides, exhibit antioxidant activity, reducing power, scavenging and chelating abilities.

Astragalus membracanus, contains life-prolonging compounds for human use and is associated with a significant effect in the immune system. Total Flavonoids of Astragalus attenuates CVB3 induced down-regulation of calumenin in a mouse model of viral myocarditis.

Zingiber officinalis, Gingerols (found in fresh extracted root) increases the uptake of calcium by the myocardium and enhance the force of contractions (cardiotonic). It is hepatoprotective, anti-inflammatory, antioxidant, antiseptic, and promote gastric secretions.

Cinnamomum verum, Cinnamon health benefits are attributed to its content of a few specific types of antioxidants, including polyphenols, phenolic acid and flavonoids.
Cardimyodin is uniquely extracted from select organic herbs, organic cane alcohol and deep ocean mineral water, as the extraction solvent. Utilizing advanced all-glass apparatus **Cardimyodin**'s ingredients undergoe hours of reflux extraction that applies heat and hydroalcohol to enhance the bioavailability of the resultant extraction.

- **Highly bio-available due to heat and hydro-alcohol reflux extraction**
- **Organic**, Non-GMO, Gluten free
- Extracted with **Maui-grown organic sugarcane alcohol** and deep ocean mineral water

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Study Protocol Systematic Review

Medicine

OPEN

Efficacy and safety of colchicine in the treatment of acute myocardial infarction

A protocol for systematic review and meta-analysis

Hui Xiong, MM[a], Xianli Huang, MM[a], Lingzhang Rao, MM[a], Jinhe Zhao, MM[b,*]

Abstract

Background: There are no meta-analyses evaluating the efficacy and safety of colchicine in the treatment of acute myocardial infarction (AMI). Our protocol is conceived to evaluate the efficacy and safety of colchicine in comparison of placebo and test the hypothesis that a short course of treatment with colchicine could lead to reduced infarct size in patients presenting with AMI.

Methods: We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines and the recommendations of the Cochrane Collaboration to conduct this meta-analysis. Reviewers will search the PubMed, Cochrane Library, Web of Science, and EMBASE online databases for all English-language cohort studies published up to April, 2021. The cohort studies focusing on assess the efficacy and safety of colchicine in the treatment of AMI will be included in our meta-analysis. At least one of the following outcomes should have been measured: reduced infarct size, C-reactive protein (CRP) level, adverse events, death and major cardiovascular events. Review Manager software will be used for the meta-analysis. All outcomes are pooled on random-effect model. A P value of $<.05$ is considered to be statistically significant.

Results: Our protocol is conceived to evaluate the efficacy and safety of colchicine in comparison of placebo and test the hypothesis that a short course of treatment with colchicine could lead to reduced infarct size in patients presenting with AMI.

Registration number: 10.17605/OSF.IO/NTU5F.

Abbreviations: AMI = acute myocardial infarction, CRP = C-reactive protein, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Keywords: acute myocardial infarction, colchicine, meta-analysis, protocol, review

1. Introduction

Inflammation is common after acute myocardial infarction (AMI). The massive loss of myocardium through cell necrosis, apoptosis, and autophagy activates a strong inflammatory response that develops due to recruitment of inflammatory cells and induction of the expression of inflammatory cytokines and chemokines.[1–3] The most commonly used circulating biomarker clinically is C-reactive protein (CRP), with a peak frequently observed around day 3 after AMI. In the case of AMI, inflammation is closely associated with the pathophysiology of ischemia-reperfusion injury and fibrosis.[4,5] As mentioned previously, inflammation plays a deleterious role at the onset of reperfusion. It can lead to infarct size and the process of heart remodeling, which can lead to heart failure.[6] Inflammatory status is a major predictor of adverse events after AMI. Therefore, inflammation seems to be a promising therapeutic target for patients with AMI. Several anti-inflammatory therapies appear to be potential candidates, but so far, there has been little research in this area.[7,8]

Colchicine is a well-established anti-inflammatory drug that is commonly used to treat gout, and it also targets the inflammasome. Colchicine is also used as a treatment for pericarditis. It may exert multipotent anti-inflammatory effects, particularly by inhibiting neutrophils migration, and may also have direct anti-inflammatory effects by inhibiting key inflammatory signaling networks called inflammasomes and proinflammatory cytokines.[8,9] In addition, colchicine has been shown to have anti-atherosclerosis effects and has been proposed to reduce inflammation in patients with stable coronary heart disease.[10] Recently, colchicine has been shown to decrease infarct size, with a reduction in the concentration of creatine kinase muscle-brain fraction and infarct size on cardiac magnetic resonance imaging in patients with AMI.[11,12]

Currently, there are no meta-analyses evaluating the efficacy and safety of colchicine in the treatment of AMI. Our protocol is conceived to evaluate the efficacy and safety of colchicine in comparison of placebo and test the hypothesis that a short course

HX and XH equally contributed to the study.

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The authors have no conflicts of interests to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Herbal medicines for viral myocarditis

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Abstract

Background—Herbal medicines are being used for treating viral diseases including viral myocarditis, and many controlled trials have been done to investigate their efficacy.

Objectives—To assess the effects of herbal medicines on clinical and indirect outcomes in patients with viral myocarditis.

Search methods—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* Issue 3, 2009, MEDLINE (January 1966 - July 2009), EMBASE (January 1998 - July 2009), Chinese Biomedical Database (1979 - 2009), China National Knowledge Infrastructure (1979 - 2009), Chinese VIP Information (1989 - 2009), Chinese Academic Conference Papers Database and Chinese Dissertation Database (1980 - 2009), AMED (1985 - 2009), LILACS accessed in July 2009 and the trials register of the Cochrane Complementary Medicine Field. We handsearched Chinese journals and conference proceedings. No language restrictions were applied.

Selection criteria—Randomised controlled trials of herbal medicines (with a minimum of seven days treatment duration) compared with placebo, no intervention, or conventional interventions were included. Trials of herbal medicine plus conventional drug versus drug alone were also included. Only trials that reported adequate description of allocation sequence generation were included.

Data collection and analysis—Two review authors independently extracted data and evaluated trial quality. Adverse effects information was collected from the trials.

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Contributions of authors: Jianping Liu: defined the review question, developed the protocol and search strategy, selected studies, assessed quality, extracted data, analysed data, developed the final review.
Zhaolan Liu: searched for trials, selected studies, assessed quality of trials, extracted data, analysed data, and updated the review.
Zhijun Liu: searched for trials, selected studies, assessed quality of trials, extracted data.
Min Yang: selected studies and extracted data.
Joey Kwong: interpretated data and their analyses; provided methodological perspective and general advice on this review update.

Declarations of interest: None known.

Differences between protocol and review: During the updating of the published review, we applied a more strict inclusion criteria regarding the study design. We restricted all randomised trials to adequate description of the generation of allocation sequence. Therefore, some RCTs included in original review were excluded due to unclear method for generation of the allocation sequence. This resulted in 40 trials (43 references) that were included in the previous version of the review being excluded from this update. Searches were updated and 14 new trials were identified.

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REVIEW ARTICLE

OPEN ACCESS Check for updates

The beneficial effects of *Ganoderma lucidum* on cardiovascular and metabolic disease risk

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ABSTRACT

Context: Various herbal medicines are thought to be useful in the management of cardiometabolic disease and its risk factors. *Ganoderma lucidum* (Curtis) P. Karst. (Ganodermataceae), also known as Lingzhi, has received considerable attention for various indications, including some related to the prevention and treatment of cardiovascular and metabolic disease by ameliorating major cardiovascular risk factors.

Objective: This review focuses on the major studies of the whole plant, plant extract, and specific active compounds isolated from *G. lucidum* in relation to the main risk factors for cardiometabolic disease.

Methods: References from major databases including PubMed, Web of Science, and Google Scholar were compiled. The search terms used were *Ganoderma lucidum*, Lingzhi, Reishi, cardiovascular, hypoglycaemic, diabetes, dyslipidaemia, antihypertensive, and anti-inflammatory.

Results: A number of *in vitro* studies and *in vivo* animal models have found that *G. lucidum* possesses antioxidative, antihypertensive, hypoglycaemic, lipid-lowering, and anti-inflammatory properties, but the health benefits in clinical trials are inconsistent. Among these potential health benefits, the most compelling evidence thus far is its hypoglycaemic effects in patients with type 2 diabetes or hyperglycaemia.

Conclusions: The inconsistent evidence about the potential health benefits of *G. lucidum* is possibly because of the use of different *Ganoderma* formulations and different study populations. Further large controlled clinical studies are therefore needed to clarify the potential benefits of *G. lucidum* preparations standardised by known active components in the prevention and treatment of cardiometabolic disease.

ARTICLE HISTORY
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KEYWORDS
Antihypertensive; antioxidant; dyslipidaemia; hypoglycaemic; Lingzhi; Reishi

Introduction

Cardiovascular disease (CVD) is highly prevalent, with ischaemic heart disease and stroke being the two leading causes of mortality throughout the world (World Health Organization 2021). Metabolic syndrome is characterised by a cluster of conditions including insulin resistance, central obesity, hypertension, dyslipidaemia, and low-grade chronic inflammation (Eckel et al. 2005). Several drug treatments for CVD have been derived from plant sources, such as digoxin and reserpine. Herbal medicines are now becoming more popular, representing a potentially cost-effective class of substances for combating CVD if safe and effective therapies can be identified. The common herbal medicines used in the West include Asian ginseng, astragalus, flaxseed oil, garlic, ginkgo, grape seeds, green tea, hawthorn, milk thistle, and soy (Liperoti et al. 2017). Herbal formulae are widely used in the clinic in China for hypertension, dyslipidaemia, coronary heart disease, and heart failure (Liu and Huang 2016).

Ganoderma (Ganodermataceae) is a kind of woody mushroom that can be found all over the world. Individual members of the species are identified according to different characteristics, such as shape and colour (red, black, blue/green, white, yellow, and purple) of the fruiting bodies, host specificity, and geographical origin (Upton 2000; Wachtel-Galor et al. 2011). *Ganoderma lucidum* (Curtis) P. Karst. (Curtis 1781), known as Lingzhi in China and Reishi in Japan, has been used in traditional Chinese medicine (TCM) for over 2000 years for a broad range of indications including improving general health, well-being, and longevity (Bishop et al. 2015; Klupp et al. 2015).

A variety of commercial products from *G. lucidum*, such as powders, dietary supplements, and tea (Wachtel-Galor et al. 2011), are available. They have been shown to possess a range of activities against CVD, including effects on lipids, blood pressure, obesity, diabetes, and antioxidant and radical scavenging properties (Liu and Tie 2019; Meng and Yang 2019; Winska et al. 2019). However, scientific evidence supporting the beneficial medical properties of *G. lucidum* is still inconclusive (Hapuarachchi et al. 2016). Many of the commercial products from *G. lucidum* may not have undergone effective standardisation, so it is difficult to compare results from different studies with different products. Many different herbal supplements or nutraceutical commercial products bearing the names Lingzhi, Reishi, or *Ganoderma*, etc., contain extracts from various parts of *G. lucidum*, often in combination with other herbal components. Ganopoly™ (Encore Health), which is a product

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20 pages

Review Article

Associated Targets of the Antioxidant Cardioprotection of *Ganoderma lucidum* in Diabetic Cardiomyopathy by Using Open Targets Platform: A Systematic Review

Fahmi Shaher,[1] **Hongbin Qiu**,[1] **Shuqiu Wang**,[1] **Yu Hu**,[1] **Weiqun Wang**,[2] **Yu Zhang**,[3] **Yao Wei**,[1] **Hisham AL-ward**,[4] **Mahfoudh A. M. Abdulghani**,[5] **Sattam Khulaif Alenezi**,[5] **Salem Baldi**,[6] **and Shaobo Zhou**[7]

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Even with substantial advances in cardiovascular therapy, the morbidity and mortality rates of diabetic cardiomyopathy (DCM) continually increase. Hence, a feasible therapeutic approach is urgently needed. *Objectives*. This work is aimed at systemically reviewing literature and addressing cell targets in DCM through the possible cardioprotection of *G. lucidum* through its antioxidant effects by using the Open Targets Platform (OTP) website. *Methods*. The OTP website version of 19.11 was accessed in December 2019 to identify the studies in DCM involving *G. lucidum*. *Results*. Among the 157 cell targets associated with DCM, the mammalian target of rapamycin (mTOR) was shared by all evidence, drug, and text mining data with 0.08 score association. mTOR also had the highest score association 0.1 with autophagy in DCM. Among the 1731 studies of indexed PubMed articles on *G. lucidum* published between 1985 and 2019, 33 addressed the antioxidant effects of *G. lucidum* and its molecular signal pathways involving oxidative stress and therefore were included in the current work. *Conclusion*. mTOR is one of the targets by DCM and can be inhibited by the antioxidative properties of *G. lucidum* directly via scavenging radicals and indirectly via modulating mTOR signal pathways such as Wnt signaling pathway, Erk1/2 signaling, and NF-κB pathways.

1. Introduction

Cardiovascular complications are associated with diabetes and lead to high mortality [1, 2]. Diabetic cardiomyopathy (DCM) is one of the main causes of heart injury and death in patients with diabetes. A total of 1.6 million deaths worldwide are directly attributed to diabetes every year [3]. Independent of coronary artery disease, DCM has increased prevalence during the last two decades and is experienced by 55% of patients with diabetes [4]. With diabetes being a global epidemic, the number of patients with DCM has increased. For the last two decades, the number of people with diabetes worldwide has increased from 151 million in 2000 to 425 million in 2017 and is estimated to increase to 629 million by 2045 [5]. The risk of developing DCM is higher for patients with diabetes than that for those without diabetes [6] and increases 2 to 4 times for those with more than a 10-year span of diabetes [7, 8]. Once DCM has developed, reducing its morbidity and mortality is difficult even with pharmacological improvement in terms of

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Heart function and thoracic aorta gene expression profiling studies of ginseng combined with different herbal medicines in eNOS knockout mice

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Yuchen Qian[1], Pan Li[1], Bin Lv[1], Xiaoqing Jiang[1], Ting Wang[1], Han Zhang[1], Xiaoying Wang[1,2] & Xiumei Gao[1]

Ginseng, a popular herbal remedy, is often used in combination with other drugs to achieve the maximum therapeutic response. Shenfu (SFI) and Shenmai injection (SMI) have been widely used to treat cardiovascular disease in China. Our study explored the cardiovascular protection of SFI and SMI in eNOS knockout mice to investigate the differences and similarities of the two ginseng-combinations. Transthoracic echocardiography was performed to evaluate the left ventricular structure and function at baseline and 3, 7, and 14 days after drug administration. Agilent Gene Expression microarrays were used to demonstrate the gene expression profiling of the thoracic aorta. Ingenuity Pathway Analysis was performed to evaluate the mechanism improved by SFI and SMI in eNOS knockout mice. Both SFI and SMI could modulate Gadd45 Signaling from TOP15 canonical pathways. Moreover, SFI showed a better effect in the early treatment stage and improved myocardial function via GATA4, GATA6 and COL3A1. Meanwhile, SMI exerted better protective effects at the chronic stage, which may be related to endothelium protection by VEGFA and ACE. The advantage of multi-target by drug combination in progression of complex diseases should be noticed. The appropriate adjustment of drug combination could lead to a better accurate medical care in clinic.

Ginseng (Panax ginseng C.A. Meyer), which belongs to the genus Panax of the family *Araliaceae*, was first recorded in the oldest Chinese medical material *Shen Nong Ben Cao Jing* dating back to the 2nd century AD[1]. Ginseng has been used for health-related purposes for at least 2,000 years and has been among the top 10 selling herbal supplements in the United States over the past decade[2]. Ginseng is used to improve general well-being and relieve various health problems, such as cardiovascular disorders, respiratory disorders, and depression. Today, ginseng is widely used in Asia to treat cardiovascular diseases (CVD)[3]. Studies have shown that ginseng can inhibit cardiomyocyte hypertrophy and heart failure (HF)[4] and prevent cardiac dysfunction[5]. Experimental studies have also revealed that ginseng can improve ischemic and reperfusion injury to the heart in a variety of animal models[6]. However, many complex physiological processes, such as inflammation[7], oxidative stress[8], and apoptosis are involved in CVD[9]. Medical science has long realized that the pathogenesis and progression of diseases are too complex for single drug treatment[10]. Therefore, herbal combination should be used to enhance curative effects, reduce toxicity, expand therapeutic range, adapt to complex disease, and prevent drug poisoning. Through a flexible combination, it can adjust the dynamic balance of the body in many ways, moreover, the advantages of adapting to the diversity of pathological changes are very prominent[11,12]. In China, ginseng is often used in combination with other herbal medicines to achieve maximum therapeutic response. In Chinese Pharmacopoeia (2015 edition), two ginseng-based injections are used to treat CVD; one is Shenfu Injection (SFI),

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General Cardiology

Total Flavonoids of Astragalus Plays a Cardioprotective Role in Viral Myocarditis

Xiaomin Zhou, Qing Xin, Yilin Wang, Yajun Zhao, Hua Chai, Xia Huang, Xiexin Tao and Ming Zhao

Background: Viral myocarditis is initiated by viral infection of myocardial tissue leading to dilated cardiomyopathy and congestive heart failure. Recent studies have linked viral myocarditis with dysfunctions in endoplasmic reticulum (ER) mediated Ca^{2+} homeostasis and the unfolded protein response (UPR). Currently there are no effective treatments for this viral infection.

Methods: We employed the use of a well-characterized pathogen coxsackievirus B3 (CVB3) to induce mouse viral myocarditis. After intraperitoneal administration of total flavonoids of Astragalus (TFA), we examined the protective effect of TFA on CVB3-induced heart function impairment and decreased calumenin mRNA levels. Furthermore, calumenin protein level was studied *in vivo* and *in vitro* with CVB3 infection in the presence or absence of TFA. The interaction between calumenin and the sarco/endoplasmic reticulum Ca^{2+}-ATPase 2 (SERCA2) was also tested in HL-1 cells.

Results: Whereas customarily we would expect that CVB3 infection would decrease mRNA and protein levels of the Ca^{2+} binding ER chaperone calumenin, here TFA treatment prevented this decline in both CVB3 infected mice and in an *in vitro* system of infected HL-1 cardiomyocytes. CVB3 infection in HL-1 cells prevented the association of calumenin with the calcium mobilizing protein SERCA2, and TFA treatment rescued this interaction.

Conclusions: This study identified that CVB3 infection promotes cardiomyocyte dysfunction by effecting expression levels and activity of the cardio protective ER chaperone calumenin. For the first time, TFA was shown to prevent loss of mRNA and protein levels of calumenin and also rescued the association of this protein with SERCA2.

Key Words: Calumenin • Sarco/endoplasmic reticulum Ca^{2+}-ATPase • Total flavonoids of Astragalus • Viral myocarditis

INTRODUCTION

Viral myocarditis is a worldwide cause of cardiac disease particularly in infants, children and young adults, and the incidence of these cases continues to rise.[1] Viral infection of cardiomyocytes promotes the characteristic inflammation and cellular dysfunction that defines this inflammatory disease.[2] Prolonged inflammation of these structural cells has been shown to be responsible for dilated cardiomyopathy (DCM) and congestive heart failure.[3] Much of the pathophysiology of this process remains unknown. However, multiple pathogens have been linked to this dysfunction, the most well-studied of these being the single-stranded RNA enterovirus, coxsackievirus B3 (CVB3).[4]

Recently, CVB3 infection of cardiomyocytes was observed to induce endoplasmic reticulum (ER) stress and cardiomyocyte apoptosis.[5] The specific proteins involved in viral myocarditis are just beginning to be identified and much attention is being paid to ER resident proteins. Viral-induced cardiomyopathies have been linked to dysfunctions within this organelle whereby changes

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