NARRATIVE REVIEW

A narrative review on the role of traditional Chinese medicine (TCM) in treating coronary artery disease

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Abstract

Coronary artery disease is one of the leading types of cardiovascular disorders globally, and is a significant contributor to mortality. Its prevalence is increasing annually, underscoring the need for innovative therapeutic strategies to enhance patient outcomes and quality of life. Despite the availability of numerous pharmacological treatments, there remains a critical need for novel interventions. Traditional Chinese medicine, with its centuries-old history, offers promising alternatives. The current narrative review was planned to examine 10 prominent Chinese herbal medicines currently in use, including Salvia miltiorrhiza, Hawthorn, Schisandra berry, Ginseng, Ginkgo biloba, Astragali radix, Reishi mushroom, Licorice root, Dang gui, and Cinnamon bark. While each of these traditional medicines holds potential for managing coronary artery disease, further large-scale clinical trials are warranted to draw more definitive conclusions.

Keywords: Traditional drugs, Traditional Chinese medicine, TCM, Coronary artery disease.

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Introduction

In 2019, there were about 120.33 million Chinese had some cardiovascular disease (CVD), and the number was higher than in any other country.[1] Among these CVDs, coronary artery disease (CAD) stood out as the most frequent, caused by a reduction in blood flow to the heart due to atherosclerotic plaque deposition.[2] Moreover, the rupture of the atherosclerotic plaque may initiate a sequence of events, including myocardial infarction (MI), arrhythmia, cardiogenic shock, and heart failure (HF).[3] The complications associated with CAD highlight the necessity for early prevention. Nevertheless, pharmacological interventions are often required in most cases.[4] Despite ongoing advancements in medication efficacy, the global CVD-related mortality rate has escalated from 12.1 million in 1990 to 20.5 million in 2021.[5] This fact, together with an increase in aging population and an unhealthy lifestyle, stresses the importance of finding new cures to this old disease. In this context, the remedies provided by the traditional Chinese medicine (TCM) could prove beneficial. TCM has a deep historical tradition in China and other East Asian countries. In the Western world, cultural evolution has also led to a greater interest in holistic medicine in general, and TCM in particular.[6] However, significant challenges persist in standardising and classifying the available Chinese herbal medicines, even though research, registration and expansion efforts have been underway over the last decade.[6]

Given that scientific evidence for many of these drugs is sparse, the current narrative review was planned to summarise the known TCMs used in the treatment of CAD, and to enumerate their possible mechanisms of action and side effects while discussing future directions in terms of the development of new drugs.

Salvia miltiorrhiza (Danshen)

Salvia miltiorrhiza, also called Danshen or red sage, is a plant growing extensively in most parts of China. It is a member of the Salvia family, and has been used for medical purposes since the days of the Han Dynasty. It is one of about a thousand members of the Salvia genus.[7]

Salvia miltiorrhiza contains about 50 biologically active elements[8] the best known being osmarinic acid, salvianolic acid, tashinones, ursolic acid, oleanolic acid and chlorogenic acid.[9] There is a general consensus that Salvia miltiorrhiza extracts, teas or decocts or droplet pills, have antidiabetic, antihypertensive, anti-inflammatory and anti-atherosclerotic properties, but the exact responsible components and the mechanism of action remain elusive.[10]

Multiple studies have focussed on the effects of Salvia miltiorrhiza extracts on several CVDs, and have found therapeutic effects, like decreasing vascular resistance, protecting against atherosclerosis, and improving the cardiac function.[7] Such effects appear to be the consequence of multiple components acting through different mechanisms, as salvianolic acid activates pAKT

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and STAT3 pathways, whereas tashinones' actions involves p38/NF-κB.[11] In contrast to other popular TCMs, Salvia miltiorrhiza has been subjected to a few clinical trials. A meta-analysis of 9 clinical studies found that the addition of Danshen decoction to typical HF treatment improved several parameters, including left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic diameter (LVESD), and brain natriuretic peptide levels. While no adverse reactions were reported in these studies, the limitations, like the short duration of treatment, small sample size, and the inclusion of Chinese population only, cannot be ignored.[7] However, a small clinical study comprising 20 patients treated with Salvia miltiorrhiza root reported one serious adverse case of peripheral facial nerve paralysis.[12]

Hawthorn (Shan Zha)

This plant is known by many names, including Crataegus pinnatifida, mountain Hawthorn, Chinese haw, Chinese Hawthorn or Chinese hawberry. Hawthorn species grow as shrubs or trees in the temperate zones of Europe, Asia and North America.[13]

There are over 250 phytochemical compounds present in the extract of Hawthorn, which include lignans, phenylpropanoids, flavonoids, triterpenoids and their glycosides, from fruits, leaves and seeds of Hawthorn.[14] Flavanoids and oligomeric procyanidins are considered the major constituents, and there have been attempts to standardise Hawthorn's extracts based on these compounds.[15] Other biologically active constituents are amines like phenylethylamine, O-methoxy-phenylethylamine, and tyramine and triterpene compounds, like ursolic, oleanolic and crategolic acids.[14]

Hawthorn is one of the most commonly used herbal medicines worldwide for the treatment of cardiac problems.[16] Its extracts were reported to stimulate coronary vasodilation through endothelial release of nitric oxide.[17] These observations in vitro were also translated by positive outcomes in clinical settings. For instance, standardised Hawthorn extracts demonstrated an improvement in the clinical symptoms of patients with New York Heart Association (NYHA) class II or III congestive heart failure (CHF) when combined with typical cardiac medications.[18] However, a possible pro-arrhythmic effect was also observed.[18] Therefore, caution should be practised in using Hawthorn extracts together with other coagulation medication.[14]

Schisandra Berry (Wu Wei Zi)

Schisandra berry (Wu Wei Zi) is a perennial woody vine plant growing in forests in northern China, South Korea, Japan and far-eastern parts of Russia. The fruit of Schisandra berry is also called magnolia berry, or five-flavour fruit, and has a long history of use as nutritional and fatigue-fighting food supplement.[19]

Several active constituents have been identified in Schisandra berry, the most important being lignans. The lignans present in Schisandra berry are schisandrin, (schisandrol A, wuweizisu A), schisandrin B (gomisin, wuwezisu B, γ-schisandrin), schisantherin A (gomosin C, schisandrer A), schisantherin B (gomosin B, schisanrer B), schisanhenol (gomosin K3), deoxyschisandrin (schisandrin A) and gomisin A (schisandrol B), each having distinct biological actions.[20] Like many other Chinese herbs, Schisandra berry also contains flavonoids that contribute to its biological activity.[21]

Among these lignans, Schisandrin A has been shown to have anti-inflammatory properties, can reduce reactive oxygen species (ROS), prevent development of obesity, and improve myocardial ischaemia-reperfusion injury through the activation of NRF2 and by increasing adenosine monophosphate-activated protein kinase phosphorylation in animal models.[20] Similar effects were found with deoxyschizandrin, and it has been suggested that these compounds exert their biological effects by binding to farnesyl X receptor (FXR) and G protein-coupled bile acid receptor 1.[22] Moreover, Schisandrin B has cardioprotective actions by inhibition of oxidative stress (OS) and apoptosis by decreasing the cleavage of caspase-3 stimulating Akt phosphorylation.[20] Furthermore, Schisantherin A may protect neuronal, cardiac and hepatic functionality through NRF2 and AKT pathway.[23] Despite the relative broad experimental evidence on the biological actions of Schisandra berry, there are very few clinical trials confirming its curative effects.[24] Due to the paucity of human studies, there is limited knowledge about the side effects of Schisandra sphenanthera, but changes in the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported by a study comprising 20 patients.[25]

Ginseng (Ren Shen)

Ginseng is a highly valued and popular herb with many claims regarding its potential health benefits. It has been used for centuries in traditional Chinese, Korean and native American medicine. Ginseng belongs to the Panax genus within the Araliaceae family. There are several species of Ginseng, but the most well-known are iPanax Ginseng (Asian or Korean Ginseng) and Panax quinquefolius (American Ginseng).[26]

The major bioactive components of Ginseng are the ginsenosides, a group of saponins with dammarane triterpenoid structure.[27] Other components with biological

activity present in Ginseng are polysaccharides, alkaloids, volatile oils, lignans and flavonoids. Although there is a general consensus that ginsenosides are responsible for the unique health effects of Ginseng, the role of each individual compounds still needs to be investigated. Similarly, although Ginseng extracts are credited to improve health on many aspects, like cardiovascular activity, cognitive function, energy and fatigue reduction, immune activity and diabetes management,[26] the detailed overall outcome in general population still needs further studies.

At the cellular level, ginsenosides upregulate and increase the phosphorylation of AKT and PI3 kinase,[28] inhibit RhoA signalling,[29] stimulate adenosine monophosphate-activated protein kinase[30] and reduce NF-κB activity.[31] The effect of Ginseng extracts to improve cardiac function and reducing cardiac fibrosis can be attributed to these cellular effects, restoration of cardiac/mitochondrial function, increase in glucose uptake and protection against cardiac remodelling, and alleviation of myocardial injury by inhibiting cardiomyocyte apoptosis.[22] In addition, Ginseng has an anti-atherosclerotic effect and improves plasma lipid profile.[32]

As with other TCMs, translational studies in humans for Ginseng are few and mostly inconclusive. As of 2020, a total of 152 Ginseng clinical trials had been registered, with 119 trials published. However, the vast majority of these trials were conducted at single centres, involved fewer than 200 participants, and utilised various forms of Ginseng over periods shorter than 3 months.[33]

Ginkgo biloba (Yin Xing)

Ginkgo biloba, also known as ginkgo, ginko, silver fruit, silver peach, or maidenhair tree, is the oldest tree species on Earth (about 200 million years old) and the only surviving species of the Ginkgoaceae family from Gymnospermae.[34] It has been historically used for senility, asthma, bronchitis, kidney and bladder disorders.[35] Based on this practice, Gingko has a widespread acceptance in the general population as an over-the-counter (OTC) self-medication for cognitive function, vertigo, intermittent claudication, and peripheral vascular disease.[36]

The biological and pharmacological actions of ginkgo extracts are mainly due to the ginkgolides, bilobalide, ginkgolic acids, alkyl coumarins, 1-hydroxypyrenes, zeatin, flavonoids, triterpenes, carotenoids, polyprenols, aromatic acids (p-hydroxybenzoic acid, protocatachuic acid, vanillic acid), ascorbic acid, D-glucaric acid, quinic acid, shikimic acid, 6-hydroxykynuric acid, pentadiene-1,5-diphenol, tannins, and the toxic compound ginkgotoxin.[37]

Ginkgolides have multiple actions in the cell[38] but most important appear to be the inhibition of platelet active factor actions, which is a powerful mediator of inflammation and pain.[39] Ginkgolides (with Ginkgolide B being the most powerful) are irreversible antagonists of G protein-coupled receptors, and block its actions.[38] Further, ginkgolides modulate glutamate γ-aminobutyric A release in the central nervous system (CNS), and changes the synaptic plasticity.[40] Moreover, it also modulates catecholaminergic and serotoninergic transmission. In addition, it has antioxidant effect in the cells that is mediated by AKT, NF-κB and MAPK pathways.[40]

Astragali radix (Huang Qi)

Astragali radix, also known as Astragalus propinquus, Astragalus root or Huang Qi, is found in western and northern China, far-eastern parts of Russia, and in Mongolia. The putative therapeutic properties of this plant were mentioned as early as 200BCE.[41] The active pharmacological components of this plant are flavonoids, saponins and polysaccharides.[42] Among these, astragalosides, calycosin-7-glucoside, and ononin are considered to be responsible for its curative effects.[42]

The extracts of Astragali radix as water decoctions or powder were proposed to enhance the activity of immune system, are neuroprotective and anti-glycaemic agents, and prevent apoptosis and inflammation. The molecular mechanisms activated by Astragali radix components appear to involve activation of PI3K/AKT/NRF2 pathway , inactivation of p38 and Erk1/2, and inhibition of NF-κB-mediated transcription.[43] Based on these observations, Astragali radix food supplements and extracts were suggested to be useful in the treatment of atherosclerosis.[44] However, the putative pharmacological activities need to be proven in clinical trials by using a standardised extract or its individual chemical constituents.

Reishi mushroom (Ling Zhi)

Reishi mushroom (Ling Zhi), or Ganoderma lucidum, has been long viewed by TCM as a therapeutic mushroom with credited curative properties, like enhancing vital energy, anorexia, improving cardiac function, increasing memory, and preventing aging.[45]

There are about 400 compounds in Reishi mushroom, but the main components are triterpenoids, polyglycans and protein (LZ-8). Based on in vitro studies, these compounds were proposed during the last 10 years as remedies in many diseases, including the CVDs.[46]

The triterpenoidic compounds, which are partly different compared to the ones present in Hawthorn, appear to have a plethora of cellular actions, like regulating Sterol

regulatory element-binding proteins (SREBPs), have anti-tumour activity via multiple pathways like inactivating PI3K/AKT signalling, inhibiting cellular senescence through 14-3-3ε and activating the calcium (Ca2+) calmodulin (CaM)/CaM-dependent protein kinase II, or downregulation in Notch-1 messenger ribonucleic acid (mRNA) expression.[47] On the other hand, ganoderic acid inhibit the differentiation of mesenchymal via inhibiting both TGF-β/Smad and MAPK signalling pathways.[48] Moreover, in spontaneously hypertensive rats, its own proteases auto-digested Reishi mushroom extract decreased blood pressure, perhaps through the inhibition of angiotensin converting enzyme (ACE).[49]

In the literature, there have been attempts to systematise the chemical content of Reishi mushroom for use in humans as injections, powders,[46] dietary supplements and tea.[50] However, the results of these studies were contradictory and confusing. Nevertheless, these mushroom extracts were generally well-tolerated by most participants, and no major toxicity was observed across the studies.[46]

Licorice root (Gan Cao)

Licorice root (Gan Cao), or Glycyrrhiza glabra, belongs to the Leguminosae family, and grows in zones with mild temperate climate in Asia and Europe. The various historical uses of Licorice involve respiratory and gastrointestinal illnesses, skin lesions, CVDs and kidney diseases.[51]

The biologically active elements present in Licorice root are primary glycyrrhizin, its metabolites glycyrrhetinic acid and glabridin, quercetin, and other minor flavonoids.[52]

The beneficial effects of Licorice extracts in CAD can be attributed to its anti-diabetic and lipid-lowering properties. Like in the other cases, the anti-glycaemic effects are due to the modulation of multiple cellular mechanisms, including PI3K/Akt, AMPK, AGE-RAGE, MAPK, NF-κB and NLRP3, leading to upregulation of glucose transporters, and inhibition of gluconeogenesis.[53] Similarly, glycyrrhizin and its metabolites decrease the serum and hepatic FFA, triglycerides (TGs), total cholesterol (TC), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) levels, and increases the high-density lipoprotein (HDL) level.[53] Despite the evidence, future clinical trials are warranted to validate the putative positive effects of Licorice extract in CAD treatment.

The main side effect of Licorice extract is pseudoaldosteronism, that can lead to hypertension, oedema, hyperkalaemia, metabolic alkalosis, hyporeninaemia and myalgia, which sometimes can be life-threatening. These side effects are due to the formation of 18β-glycyrrhetyl-3-O-sulfate, and, therefore, the determination of the serum level of this compound can serve as a biomarker for individuals who should avoid Licorice.[54]

Angelica root (Dang Gui)

Angelica sinensis, commonly known as Dong Quai, Dang Gui or female Ginseng, belongs to the herbal family of Apiaceae, and grows in the mountain regions of eastern Asia. The root extract of the plant has been used in the TCM for more than a thousand years for the regulation of menstruation and menopausal support, as well as in the treatment of high blood pressure, heart disease, anaemia, constipation, psoriasis and allergies.[55]

The main biological active components of Angelica sinensis are phthalides, organic acids and their esters, and polysaccharides. Among the different compounds, ferulic acid and Z-ligustilide are considered to be responsible for the main biological activity of this plant.[55]

Ferulic acid is recognised as having multiple biological effects, such as antioxidant, anti-inflammatory, antimicrobial, antiallergic, hepatoprotective, anticarcinogenic, antithrombotic, antiviral and vasodilatory actions.[56] At the cellular level, ferulic acid has multiple effects on signal transduction, particularly on the inhibition of AKT and MAPK pathways.[57] Through this mechanism, ferulic acid was shown in cellular and animal studies to reduce the levels of ROS, increase the production of nitric oxide, increase monoamine neurotransmitters in the hippocampus and frontal cortex, and stimulate insulin production.[56] Based on this evidence, the compound was proposed to treat high blood pressure, atherosclerosis, CAD and diabetes mellitus (DM). However, clinical trials to support these uses are currently lacking. While a systematic review of 36 studies (with 3,207 patients) showed some improvement in clinical symptoms of CAD in conjunction with typical medication, but a firm conclusion needs further research.[58]

The effects of Z-ligustilide at the cellular level appear to involve the suppression of the NF-κB pathway, cellular protection by induction of Heat Shock Protein 70 through the activation of MAPK and p38, prevention of vascular smooth muscle migration by inhibiting MMP2 and ROCK/JNK, improvement in mitochondrial function in neurons, and inhibition of angiotensin II-mediated cardiac hypertrophy through the restoration of expression levels of p53, Bcl-2 and Bax.[59] Based on these cellular mechanisms, it can be inferred that Z-ligustilide has the potential to treat atherosclerosis and cardiac hypertrophy, but future clinical studies are warranted to support these uses.

There are multiple other therapeutic actions of Angelica sinensis extracts in vivo that cannot be explained only by the effects of ferulic acid or Z-ligustilide, and, thus, the actions of its other constituents should be explored in the future.

Cinnamon bark (Rou Gui)

There are four main species of Cinnamon: Cinnamon cassia (cassia or Chinese Cinnamon), Curcuma burmanni (Korintje, Padang cassia or Indonesian Cinnamon), Curcuma loureiroi (Saigon Cinnamon, Vietnam cassia or Vietnamese Cinnamon), and Curcuma verum, which is also known as Curcuma zeylanicum (Sri Lanka Cinnamon or Ceylon Cinnamon). It belongs to the Lauraceae family, and the Cinnamon cassia is grown in the Fujian province of south-eastern China.[60]

All species of Cinnamon contain different concentrations of terpenes, phenylpropenes, eugenol, linalool, β-caryophyllene and eugenol. However, cinnamaldehyde (trans-cinnamaldehyde or 3-phenyl-2-propenal) is the main constituent (60-80%) of Cinnamon bark.[61]

Cinnamaldehyde pre-treatment may have cardioprotective effects against ischaemia/reperfusion injury, attenuated pressure overload-induced cardiac hypertrophy, and blocked adrenergic-mediated hypertrophy in isolated cardiac myocytes.[62] The water extract of Cinnamon were also able to reduce blood pressure in healthy rats through an endothelial-dependent relaxation.[63] In addition, a potential positive effect of Cinnamon extracts on atherosclerotic plaque development was also demonstrated in a study.[64] Overall, these results support the use of Cinnamon derivatives as adjuvant medication for the treatment of CAD and other CVDs. However, the limited number of clinical trials published thus far have shown conflicting results, including a very modest effect on blood pressure after Cinnamon supplementation.[65] However, Cinnamon and its derivatives appear to be effective in reducing TC, TGs and LDL levels at doses lower than the ones affecting blood pressure.[66]

Cinnamon is generally safe when used in moderation as a spice in food. However, the use of Cinnamon supplements, especially Cinnamomum cassia, can cause potential side effects that can vary from individual to individual and concurrent medications. Cinnamaldehyde, a major component of Cinnamon, can prolong the coagulation times by modulating the platelet aggregation and thrombosis, probably by inhibiting thromboxane A2 receptor.[60] Similarly, the coumarins can also cause liver toxicity when consumed in large quantities.[67]

Conclusion

The narrative review summarised the effects of 10 prominent TCMs on CAD, drawing from centuries of usage with both observational and anecdotal evidence. These herbal medicines have been utilised for millennia not only for CVDs, but also for various other health disorders. However, these herbal drugs cannot replace clinical medications due to several limitations, including variations in the chemical composition of extracts, the complexity of their multi-compound mixtures, and the inadequate characterisation of their effects in both in vitro and in vivo studies. Additionally, there is a notable deficiency of large, representative clinical trials. Thus, addressing these challenges is crucial to fully harness the therapeutic potential of these TCMs in CAD.

Elaborations:
pAKT: Phosphorylated Akt.
STAT3: Signal Transducer and Activator of Transcription 3.
p38/NF-κB: p38 Mitogen-Activated Protein Kinase /Nuclear Factor-kappa B.
NRF2: Nuclear Factor Erythroid 2-Related Factor 2.
PI3K: Phosphoinositide 3-Kinase.
RhoA: Ras Homolog Family Member A.
MAPK: Mitogen-Activated Protein Kinase.
Erk1/2: Extracellular Signal-Regulated Kinase 1/2.
TGF-β/Smad: Transforming Growth Factor Beta.
AMPK: AMP-Activated Protein Kinase.
AGE-RAGE: Advanced Glycation End Products.
NLRP3: NOD-like Receptor Family Pyrin Domain Containing 3.
FFA: Free Fatty Acids.
MMP2: Matrix Metalloproteinase 2.
ROCK/JNK: Rho-Associated Protein Kinase / c-Jun N-terminal Kinase.
p53: Tumour Protein 53.
Bcl-2: B-cell lymphoma 2.
Bax: Bcl-2-Associated X Protein.

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Author Contribution:
AZ, XL: Data collection and interpretation.
XL: Data curation and acquisition.
ND: Helped in mining, visualisation and data analysis.
BH: Visualised, review and editing.